UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

School of Chemistry

Towards the Enantioselective Total Synthesis of Luminacin D

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Abstract

Doctorate of Philosophy

TOWARDS THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF LUMINACIN D

By Helen Jane Gale

A proposed strategy for the enantioselective total synthesis of luminacin D, one of a family of 14 structurally similar compounds extracted from *Streptomyces species* which have been shown to possess anti-angiogenic properties, has been devised and tested. The luminacins are structurally similar, and for synthetic purposes are composed of an aromatic fragment linked to an aliphatic fragment.

The aromatic fragment has been synthesised in 5 steps from resorcinol in 19% overall yield. Acylation of resorcinol and subsequent reduction proceeds smoothly. The bismethoxymethyl protection was carried out in a two-step procedure. Optimal conditions for the hydroxymethylation reaction use 3 equivalents of *s*-butyl lithium and gave a 6:1 ratio of regioisomers. Protection of the resulting primary alcohol as a silyl ether proceeded smoothly. A trial coupling reaction of the aromatic fragment with 2.0 equivalents of acetaldehyde, 1.1 equivalents of *s*-butyllithium and tetramethylethylene diamine, provided the expected and desired racemic product in 77% yield.

Synthesis of the aldehyde fragment for the Nagao acetate-aldol reaction was carried out smoothly in 6 steps from propionaldehyde and methyl acrylate. Triethylsilyl protection gave 36% overall yield; *p*-methoxybenzyl protection gave 42% overall yield; and triisopropylsilyl protection gave 60% overall yield. The Nagao acetate aldol produced a single diastereoisomer in 67% yield when using triisopropylsilyl protection. With triethylsilyl protection, the Nagao product was isolated as a single diastereomer in 44% yield. With *p*-methoxybenzyl protection, the Nagao product was isolated as gave a mixture of diastereomers in 51% yield. Silyl protection of the Nagao product proceeded smoothly in 95% yield. Transformation to aldehyde for the Evans aldol reaction proceeded smoothly in 82% yield on a large scale. The Evans aldol reaction mediated by Bu_2BOTf gave a single diastereomer in 90% yield. Reduction of the Evans product to the 1,3-diol was carried out in 94% yield. Protection of the primary alcohol as a pivaloyl ester provided 63% yield, but protection of the remaining secondary alcohol in the fragment has not been possible. Protection of the 1,3-diol as a benzylidine acetal was unsuccessful. Protection of the secondary alcohol in the Evans aldol product as a silyl ether smoothly resulted in 90% product yield.

Tin mediated acetate β-ketoimide aldol reactions have been carried out using our aldehyde with both silyl and *p*-methoxybenzyl protection. Acetate β-ketoimide aldol reactions using propionaldehyde have been much faster, but selectivity was poor. Repeating Evans' work using propionoate derived reagents have given single diastereomers in good yields.

The synthesis of a fragment suitable for coupling to the aromatic fragment through the Nagao/Evans or β-ketoimide methodologies has so far been elusive.

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Abbreviations

aq.	aqueous
Bn	benzyl
BnTCA	benzyl trichloroactimidate
BOMO	Benzyloxymethylether
m-CPBA	*m*-chloroperbenzoic acid
CSA	camphor sulfonic acid
DABCO	1,4-diazabicyclo(2.2.2)octane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAl-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMD	dimethyldioxirane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
equiv.	equivalents
IBX	*o*-iodoxybenzoic acid
MOMO	methoxymethylether
NIS	*N*-iodosuccinamide
NMO	4-methyl morpholine-*N*-oxide
PMB	*p*-methoxybenzyl
PMBTCA	*p*-methoxybenzyl trichloroacetimidate
PMP	*p*-methoxybenzylidine
PPTS	pyridinium *p*-toluenesulfonate
sp	septet
sx	sextet
TBAF	tetrabutyl ammonium fluoride
TBS	*t*-butyldimethylsilyl
TBHP	*t*-butyl hydroperoxide
TCA	trichloroacetimidate
TEA	triethylamine
TEMPO	(2,2,6,6)-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N,N,N',N'*-tetramethylethylene diamine
TMS	trimethylsilyl
TPAP	tetrapropyl ammonium perruthenate
Ts	*p*-toluenesulfonyl

Acknowledgements

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Chapter 1: Introduction

Luminacin D is the most active of a family 14 angiogenesis inhibitors isolated from the *Streptomyces* bacterium. Inhibition of angiogenesis has relevance in the treatment of many pathological diseases and as such the luminacins are interesting synthetic targets. Angiogenesis and its inhibition are discussed in Chapter 1, section 1.1. Structural elucidation has shown the luminacins to contain both aromatic and aliphatic moieties. The isolation and initial structural elucidation are discussed in Chapter 1, section 1.1.4. Previous syntheses of the luminacins are discussed in Chapter 1, section 1.2.

A synthetic route based on a strategic disconnection to give an aromatic fragment and an aliphatic fragment was conceived, discussed in Chapter 1, section 1.3. A discussion of the stereoselective reactions used in the synthetic route is contained in Chapter 1, section 1.4. The synthesis of the aromatic fragment is discussed in Chapter 2, with experimental details contained in Chapter 6, section 6.1. The synthesis of the aliphatic fragment through the Nagao/Evans methodology is discussed in Chapter 3, with experimental details contained in Chapter 6, section 6.2. A second route towards the aliphatic fragment, the β-ketoimide methodology is discussed in Chapter 4, with experimental details contained in Chapter 6, section 6.3. A summary of the present synthetic strategy and additional related research towards luminacin D is discussed in Chapter 5, with experimental details in Chapter 6, section 6.4.

1.1 Angiogenesis

1.1.1 What is angiogenesis?

Angiogenesis is the process by which new blood vessels develop within living organisms. Capillaries are made up of two types of cell, endothelial cells and pericytes, which contain all the genetic material necessary to form capillary networks.[1] Angiogenesis consists of several stages:

- Endothelial cells are stimulated to produce matrix metalloproteases (MMPs);
- The MMPs cause breakdown of the extra cellular matrix;
- Breakdown of the extra cellular matrix allows endothelial cell migration;
- Endothelial cells undergo proliferation and differentiation to organise themselves into tubes and branches which develop into new blood vessels.

Angiogenesis *in vivo* is an extremely complex process with many controlling factors. So-called "angiogenic molecules" act to accelerate blood vessel growth when required and "antiangiogenic molecules" act to terminate this process when growth is no longer called for.

Antagonistic molecules limit blood vessel formation to specific periods. Blood vessel formation occurs in a controlled manner during normal growth, in the reproductive cycle and in wound healing. The growth of new blood vessels is inhibited at the end of these concise periods.

When cells in the body are damaged, such as in a wounded area, cell lysis results. This allows the release of a range of polypeptides known as fibroblast growth factors (FGFs), stimulating endothelial cells to produce MMPs. This gives rise to new blood vessel formation allowing repair of the damaged area. FGFs have been shown to cause *in vitro* endothelial cell migration and proliferation resulting in new blood vessel formation. FGFs have a strong affinity for heparin and binding *in vivo* is known to enable biological activity. Binding also allows transport throughout the body and gives protection from damage (via heat, proteases or extremes of pH).[1]

To facilitate repair of a wound lymphocyte cells are recruited. These lymphocyte cells secrete angiogenin, a polypeptide that initiates angiogenesis by stimulating other cells to produce angiogenic molecules. In addition, macrophage cells are recruited to allow removal of any foreign bodies from the wounded area. Upon activation, the macrophage cells secrete the protein tumour necrosis factor-alpha. This polypeptide has a wide range of effects on endothelial cells, initiating angiogenesis, again by stimulating other cells to produce angiogenic molecules.[2] When the body has carried out the repair, the angiogenic molecules are no longer secreted and no further blood vessel growth occurs.

During the female menstrual cycle angiogenesis occurs in a controlled manner. Follicle stimulating hormone produced by the pituitary gland causes the Graafian follicle to develop. The ovum begins to secrete oestrogen, which initiates blood vessel growth in the endometrial wall. Ovulation results in damage to the membrane that contained the follicle, allowing migration of ovarian cells into the cavity, now called the corpus luteum. Angiogenic molecules produced by the migrating cells allow blood vessel growth in the corpus luteum. The blood enables supply of the large amounts of nutrients and hormone precursors needed in the ensuing stages. The corpus luteum produces luteinising

hormone and progesterone, which continue to stimulate blood vessel growth in the endometrial lining. If the ovum remains unfertilised then blood vessels in the corpus lutem recede. This results in the reduction in the amount of progesterone and luteinising hormone produced, causing breakdown of the endometrial wall in menstruation.[2]

Uncontrolled angiogenesis is often associated with pathological diseases. A tumour must stimulate blood vessel formation in order to grow beyond the size limited by the diffusion path of oxygen. In diabetic retinopathy new capillaries grow into the vitreous cavity. The resulting leakage of blood is one of the major causes of blindness in this and many other diseases of the eye. In arthritis, blood vessels enter into the joints, destroying cartilage and causing severe pain.[1]

Targeting the individual stages of blood vessel development could result in treatment of diseases where angiogenesis is a contributing factor.

1.1.2 Inhibition of angiogenesis as a strategy for cancer treatment

At an undetermined point in tumour progression angiogenic activity is induced. It is thought that tumour cells may activate macrophages and mast cells into the production of angiogenic molecules.[2] Simultaneously, some tumour cells also secrete tumour necrosis factor-alpha, which is known to initiate angiogenesis. The development of a new blood supply causes a dramatic acceleration of tumour growth due to an increase in available nutrients. The new blood vessels also open up direct access to the whole body, facilitating metastasis. The use of antiangiogenic molecules could prove a valuable method in the containment of cancer. The pharmaceutical industry is currently investigating potential drugs based on this principle.[3]

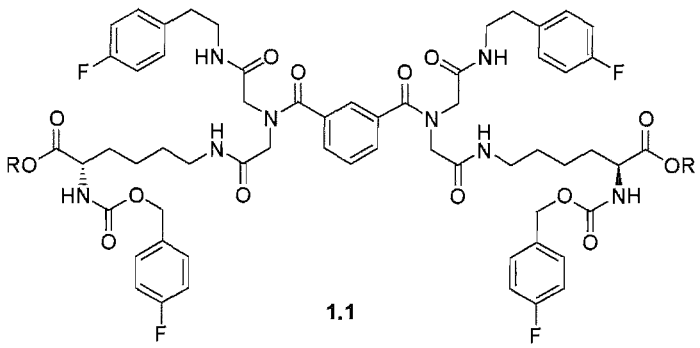
1.1.3 Existing angiogenesis inhibitors

Antiangiogenic molecules have been isolated from a wide range of organisms, and libraries of structurally similar compounds have been synthesised. Owing to the complex nature of blood vessel formation, they work with a variety of mechanisms, targeting different stages in angiogenesis.

Thrombospondin is a glycoprotein found in platelet alpha granules and is proposed to participate in the stabilisation of platelet aggregates. It has shown inhibitory effects on the migration of endothelial cells, thus reducing angiogenesis. Platelet factor IV is a tetrameric protein also found in platelet alpha granules and has been shown to exhibit

antiangiogenic effects and inhibit the growth of solid tumours. Protamine is a protein isolated from sperm with a high affinity for heparin and has been shown to inhibit angiogenesis *in vivo*.[2]

It is known that during blood vessel formation the protein MMP2 interacts with the $\alpha_V\beta_3$ integrin protein on the surface of endothelial cells stimulating angiogenesis. Small molecule mimics for MMP2, such as **1.1**, Figure1.1, block this interaction. Prevention of this link has been shown to inhibit angiogenesis *in vivo*. $\alpha_V\beta_3$ Integrin protein facilitates interaction between cells in the extra cellular matrix, but this function is not affected by binding of the mimic.[4]



1.1

Figure 1.1: Mimic for MMP2.

Eponemycin, **1.2**, Figure 1.2, isolated from *Streptomyces hygroscopicus*, has been shown to inhibit cell proliferation and migration *in vitro*, whilst preventing angiogenesis *in vivo*. Vitamin D_3, **1.3**, and some of its analogues have been shown to inhibit cell differentiation and prevent angiogenesis.[5] Fumagillin, **1.4**, isolated from *Aspergillus fumigatus* inhibits endothelial cell proliferation *in vitro* and angiogenesis *in vivo*. Proliferation can only occur when cells are elongated; when fumagillin was present endothelial cells became rounded. Growth of other cells in the body was also inhibited, resulting in weight loss.[6] A synthetic analogue of fumagillin, AGM1470, **1.5**, shows selective inhibition of endothelial cell proliferation alone.[7] Many of the known antiangiogenic molecules show promising results, and further studies may yet result in drugs based on these principles being used for treatment of pathological disease.

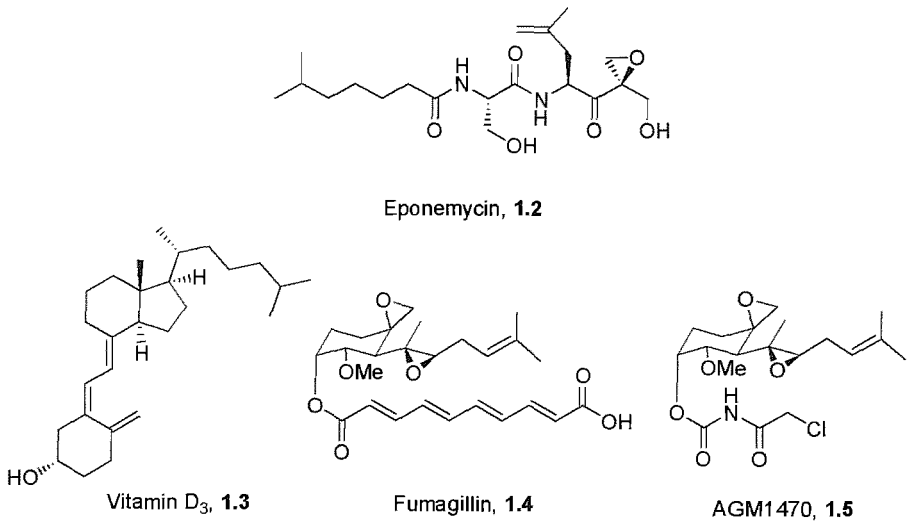


Figure 1.2: Exisiting angiogenesis inhibitors.

1.2 Luminacins

The luminacins are a family of 14 compounds with similar structures, isolated from the *Streptomyces* species, strain Mer-VD1207, which exhibit antiangiogenic properties. The most active angiogenic inhibitor was found to be luminacin D, **1.6**, Figure 1.3.[8] The IC_{50} value (median inhibition concentration) for luminacin D was reported as 0.017 μg/mL, compared to its nearest competitor, luminacin E_1, **1.7**, with an IC_{50} value of 0.047 μg/mL.[8] The luminacins have structural variations at the positions marked with arrows in Figure 1.3, as determined by NMR studies. The first structural elucidation failed to reveal both the absolute stereochemistry and in addition the relative stereochemistry at C2'.[9]

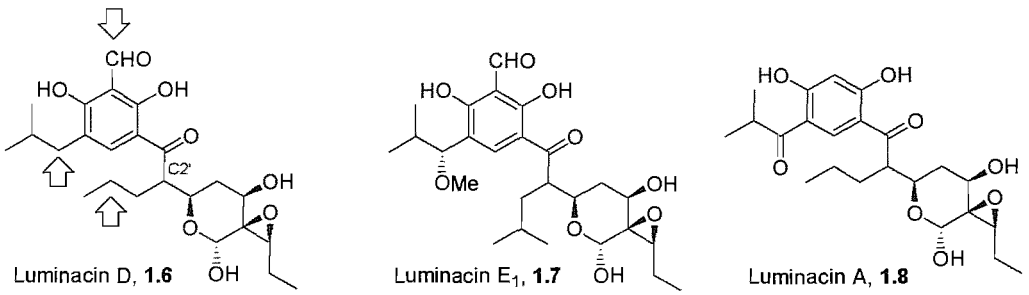


Figure 1.3: Some of the Luminacins.

Luminacin D contains an epoxide functionality (also present in other known angiogenesis inhibitors), although the aromatic aldehyde functionality appears to be more important for activity. Luminacin A, **1.8**, for example, does not have an aromatic aldehyde and has poor antiangiogenic properties. Luminacin D appears to have a different mode of action to all current angiogenesis inhibitors, which inhibit proliferation and migration. Luminacin D

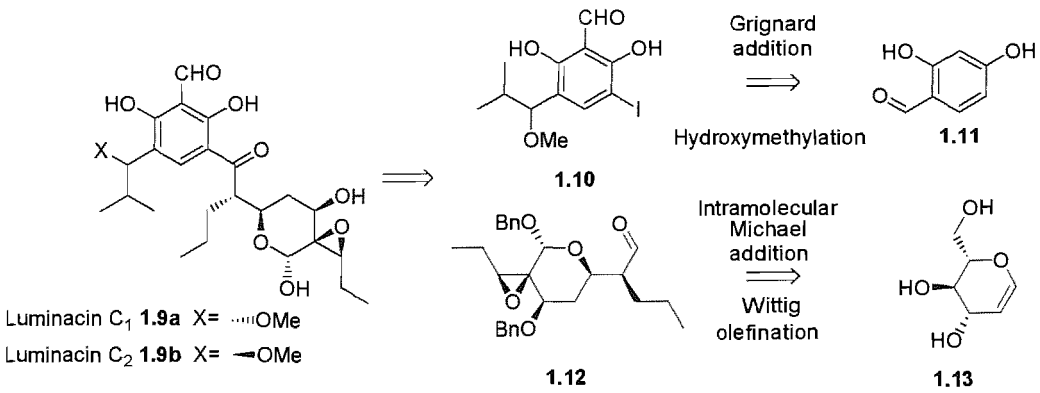
selectively inhibits endothelial proliferation and, crucially, tube formation, resulting in a decreased number of capillaries. Importantly, luminacin D also showed no cytotoxicity.[9] Further investigation into the chemical functionalities required for optimal activity is necessary.

1.2.1 Previous syntheses of luminacins

1.2.1.1 The Tatsuta synthesis of luminacins C_1 and C_2[10]

(a) Retrosynthetic analysis

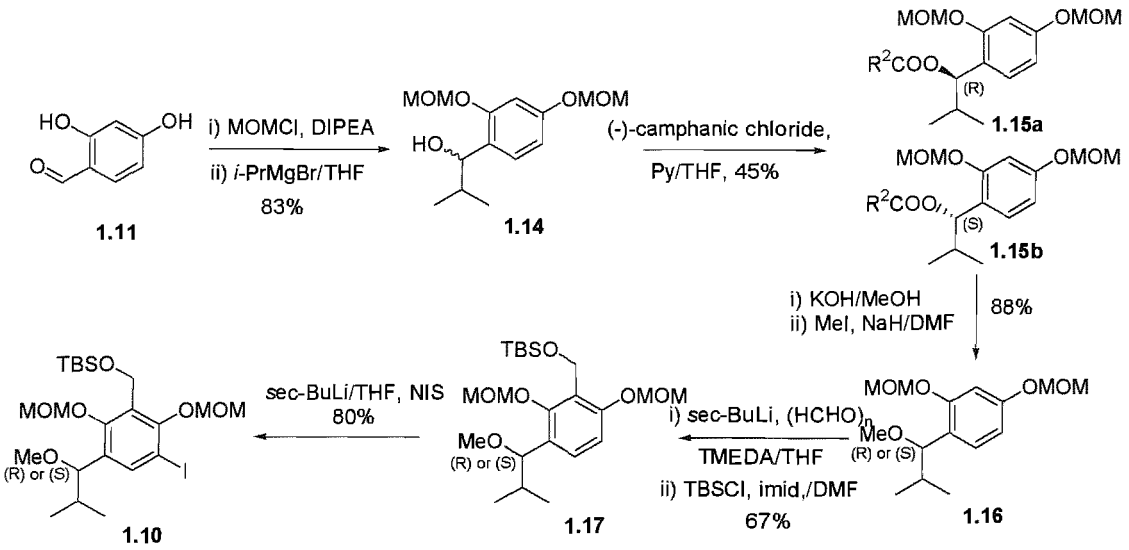
Tatsuta and co workers carried out the first total synthesis of luminacins C_1, **1.9a**, and C_2, **1.9b**. Isolation of all possible diastereomers was carried out in order to establish the absolute stereochemistry of this group of angiogenesis inhibitors. Unsurprisingly, the retrosynthetic analysis centres on a strategic disconnection leading to aromatic fragment **1.10** and aliphatic fragment **1.12**, Scheme 1.1.



Scheme 1.1: Retrosynthetic analysis proposed by Tatsuta and co-workers.

(b) Synthesis of aromatic fragment **1.10**

The aromatic fragment was synthesised from 2,3-dihydroxybenzaldehyde, **1.11**, Scheme 1.2. Protection as the methoxymethyl ether using chloromethyl methyl ether and Grignard addition using *iso*propyl magnesium bromide gave a racemic mixture of alcohols, **1.14**. Treatment with (–)-camphanic chloride gave the diastereomeric esters **1.15a** and **1.15b**, which were separated by recrystallisation. Each enantiopure fragment underwent an ester hydrolysis and transformation to the corresponding methyl ethers **1.16**. An *ortho*-directed hydroxymethylation was carried out using paraformaldehyde, and the resulting primary alcohol was protected as a silyl ether, **1.17**. A second *ortho*-directed lithiation followed by iodination gave the desired fragment **1.10** in overall 18% yield.



Scheme 1.2: Tatsuta aromatic fragment synthesis.

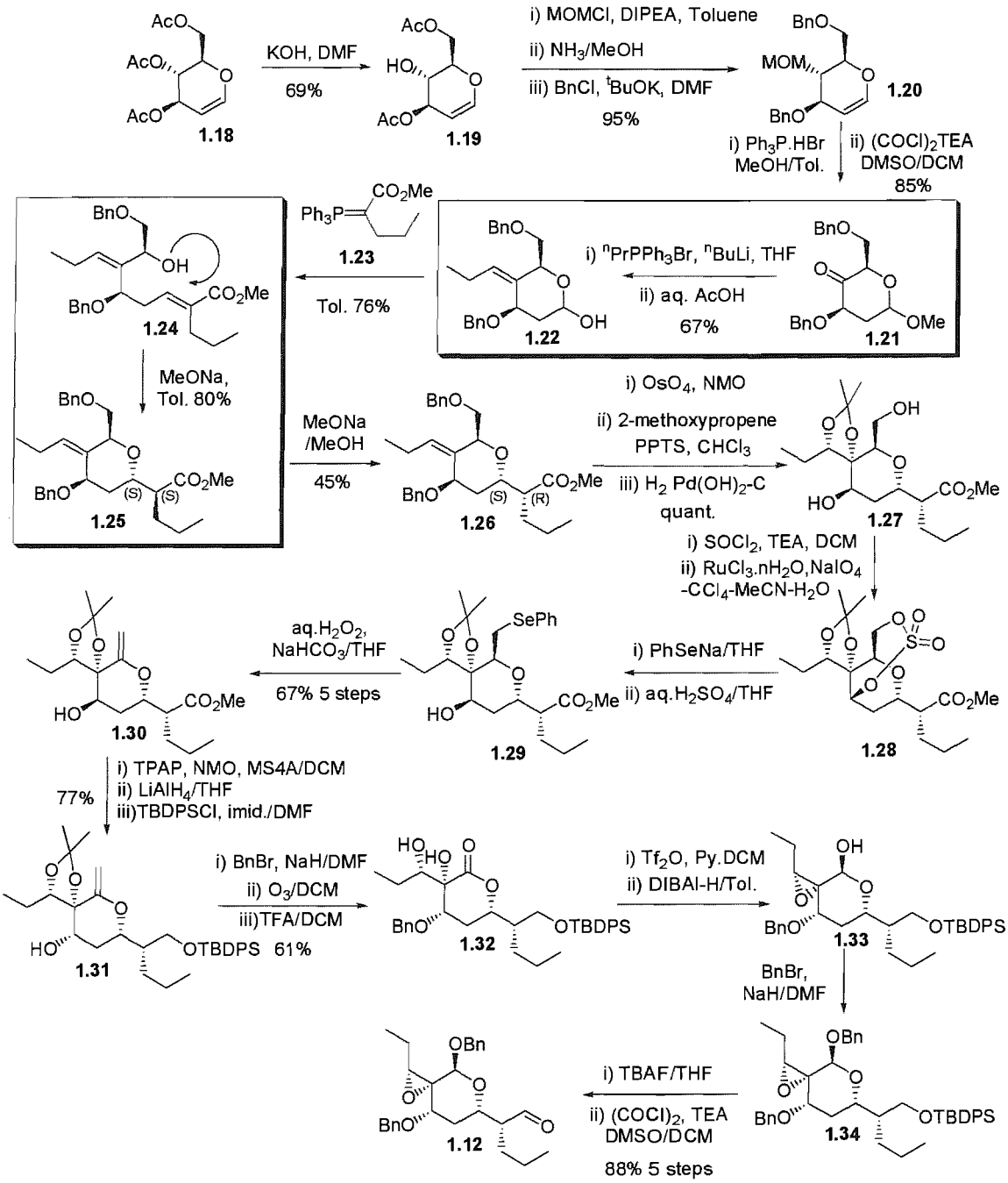
(c) Synthesis of aliphatic fragment **1.12**

The use of (D)-glucal gave access to *epi*-luminacins C_1 and C_2 after the coupling and deprotection steps. The same synthesis was carried out using (L)-glucal to give luminacins C_1 and C_2.

(D)-Glucal was peracetylated to give **1.18**, Scheme 1.3. A selective acetate deprotection led to **1.19**. A methoxymethyl protection, deacylation and benzylation sequence afforded **1.20**. Methanolysis of glycal **1.20** effected deprotection of the methoxymethyl group. The resulting alcohol underwent oxidation to give the ketone **1.21**. A Wittig olefination was carried out using *n*-propyl triphenylphosphonium bromide and *n*-butyl lithium, and hydrolysis of the anomeric methoxy group yielded **1.22**. The non-stabilised ylide was used to give access to the *Z* alkene. Thus, the first key step in the synthesis was complete. A second Wittig reaction using "stabilised" ylide **1.23** yielded the *E* alkene geometry in **1.24**.

A stereoselective intramolecular Michael addition is the second key step and yielded the *exo*-olefin **1.25**. The propyl group was epimerised using sodium methoxide to give the relative stereochemistry in the luminacins **1.26**. This was followed by a dihydroxylation and the resulting 1,2-diol underwent protection with acetone. The benzyl protection was removed by hydrogenolysis, leading to **1.27**. Synthesis of the cyclic sulfate allowed the introduction of the primary phenylselenide group **1.29**, which underwent an oxidation to give the *exo*-olefin **1.30**. The free secondary alcohol in **1.30** underwent epimerisation through an oxidation/reduction sequence and the resulting free hydroxyl group was protected as a benzyl ether **1.31**. Ketone **1.32** was isolated after ozonolysis and

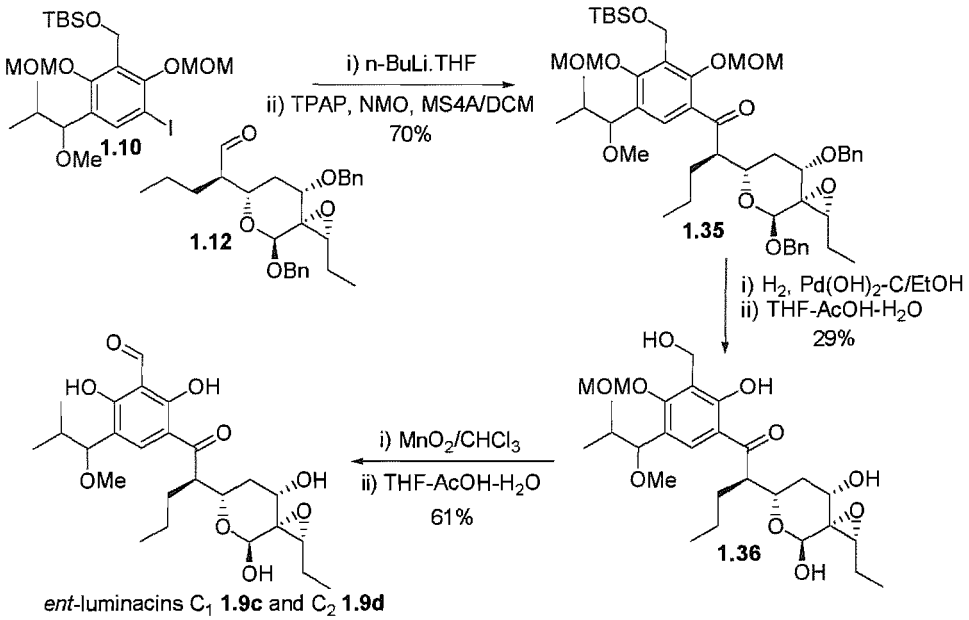
acetonide deprotection. The sensitive epoxide was introduced at this late stage, however, notably before the coupling step, through an S_N2 displacement. The ketone was reduced using di*iso*butyl aluminium hydride giving **1.33**. The resulting secondary alcohol underwent benzyl protection leading to **1.34**. Finally the silyl protection was removed and an oxidation gave the desired aldehyde **1.12** for coupling.



Scheme 1.3: Tatsuta aliphatic fragment synthesis.

(d) Coupling and final steps

The aromatic fragment **1.10** was subjected to a halogen-lithium exchange and the resulting anion attacked the aliphatic fragment **1.12**, Scheme 1.4. The secondary alcohol was oxidised to give **1.35**. Hydrogenolysis of the benzyl groups was followed by hydrolysis giving mono methoxymethylated **1.36**. The primary alcohol was then oxidised and the remaining methoxymethyl group removed using aqueous acetic acid/THF to give *ent*-luminacins C_1, **1.9c**, and C_2,**1.9d**.



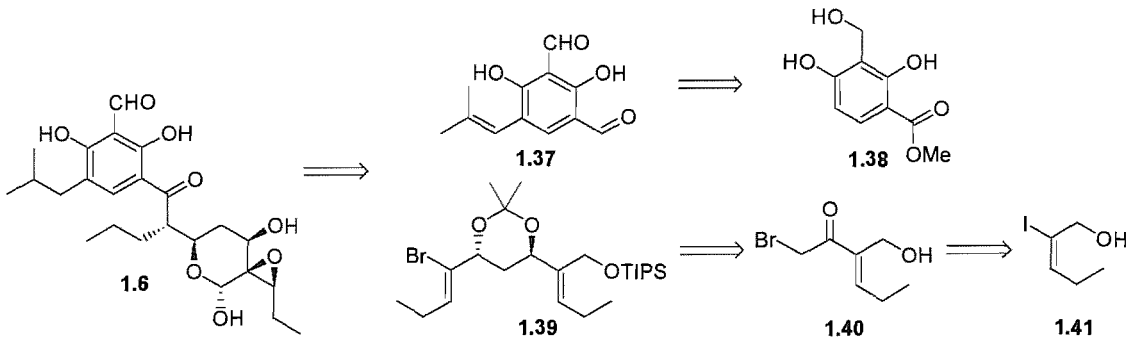
Scheme 1.4: Tatsuta coupling and final synthetic steps.

Analytical data for **1.9c** and **1.9d** matched that of the natural compounds, with the exception of the optical rotations, for which the signs were opposite. Synthesis of luminacins C_1 and C_2 was then carried out from (L)-glucal. The absolute stereochemistry of the luminacins was confirmed through precisely matching analytical data.

1.2.1.2 The Wood synthesis of luminacin D[11]

(a) Retrosynthetic analysis

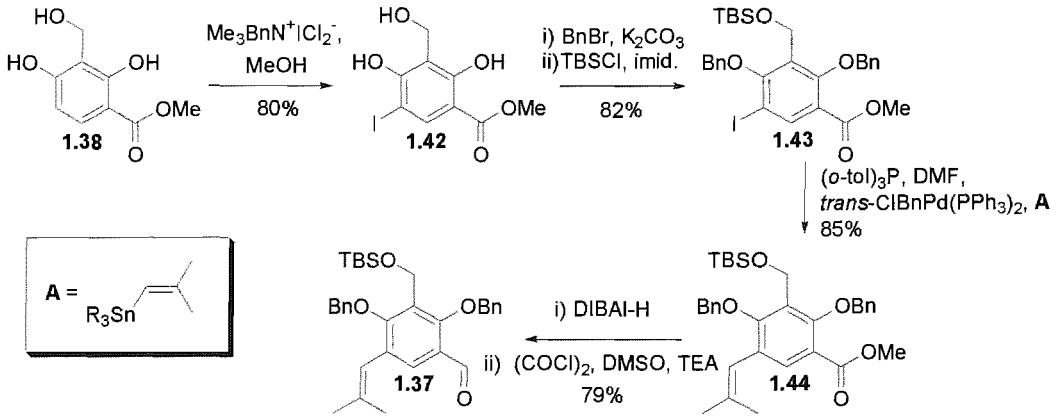
Wood and co workers carried out a racemic synthesis of luminacin D. Within the synthesis was the potential to allow derivatisation to potentially active analogues. The retrosynthetic analysis again focuses on a disconnection towards an aromatic fragment, **1.37**, and an aliphatic fragment, **1.39**, Scheme 1.5.



Scheme 1.5: Retrosynthetic analysis proposed by Wood and co-workers.

(b) Synthesis of aromatic fragment **1.37**

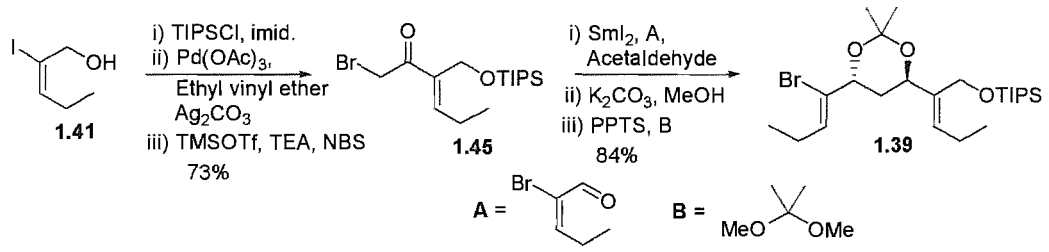
The aromatic fragment was synthesised from known triol **1.38**, Scheme 1.6. This underwent an iodination to give **1.42**, it should be noted that bromination reactions resulted in over-halogenation. The phenolic oxygens were protected as benzyl ethers and the benzylic alcohol as a silyl ether, **1.43**. The protected iodide then underwent a Stille cross-coupling reaction with (tributyl)-*iso*butenylstannane to introduce the 4-carbon side chain in **1.44**. The final step was reduction of the ester to aldehyde **1.37** for coupling.



Scheme 1.6: Wood aromatic fragment synthesis.

(c) Synthesis of aliphatic fragment **1.39**

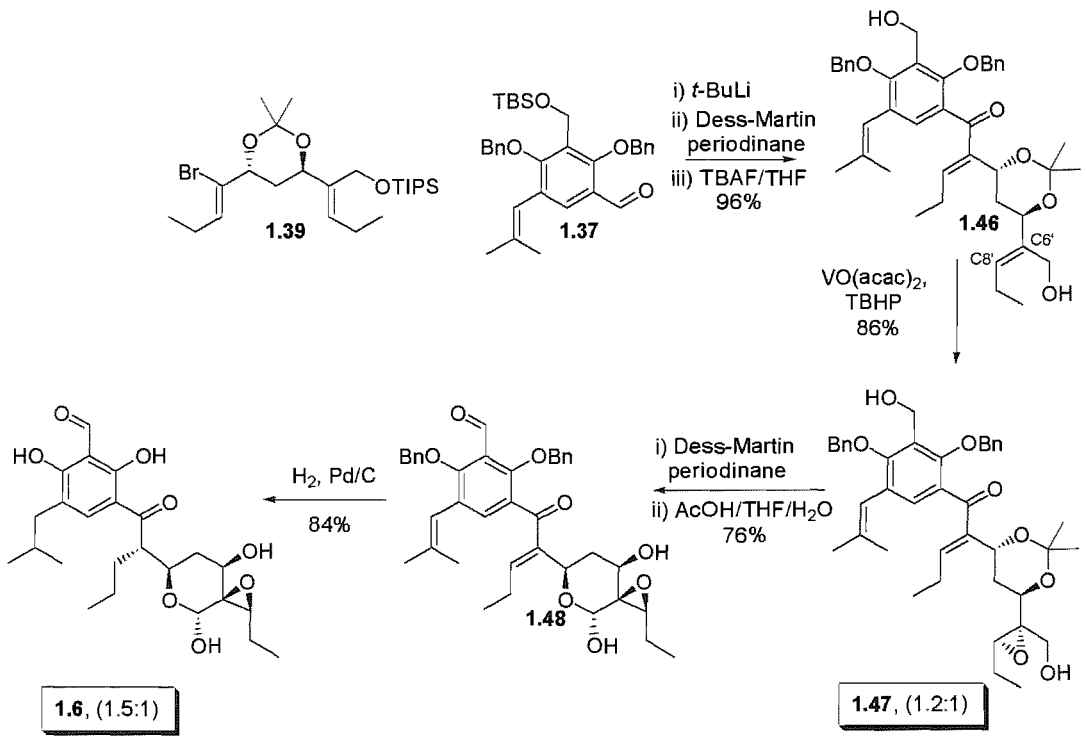
The synthesis of the aliphatic fragment, Scheme 1.7, began from the known vinyl iodide **1.41**. A silyl protection was carried out, followed by an acylation using ethyl vinyl ether and α-bromination to give **1.45**. Formation of the samarium enolate and addition of (*E*)-2-bromo-2-pentenal followed by acetaldehyde gave the desired 1,3-diol. This tandem aldol Evans-Tishchenko-type reaction is the first application of this chemistry to the smooth reaction of two different aldehydes (acetaldehyde and **A** in Scheme 1.7) via a sequential addition sequence. Protection of the 1,3-diol as the acetonide gave the coupling precursor **1.39**.



Scheme 1.7: Wood aliphatic fragment synthesis.

(d) Coupling and final steps

The aromatic fragment **1.37** and acyclic aliphatic fragment **1.39** were coupled via a halogen-lithium exchange reaction (using *t*-butyl lithium); the resulting alcohol was oxidised and the silyl protection removed to give **1.46**, Scheme 1.8. In this case, the two fragments were coupled prior to the installation of the epoxide and the cyclisation step. It was found that cyclisation prior to epoxidation caused problems with isomerisation of the C6'-C8' trisubstituted alkene. It should also be noted that coupling with the unsaturated precursor **1.39** was used to eliminate any potential problems with retro aldol reactions in **1.46**. The epoxide was introduced using $VO(acac)_2$/TBHP, giving a relatively poor selectivity of 1.2:1 in favour of the desired diastereomer, yielding **1.47**. Oxidation of the primary alcohols allowed cyclisation to proceed smoothly giving **1.48**.



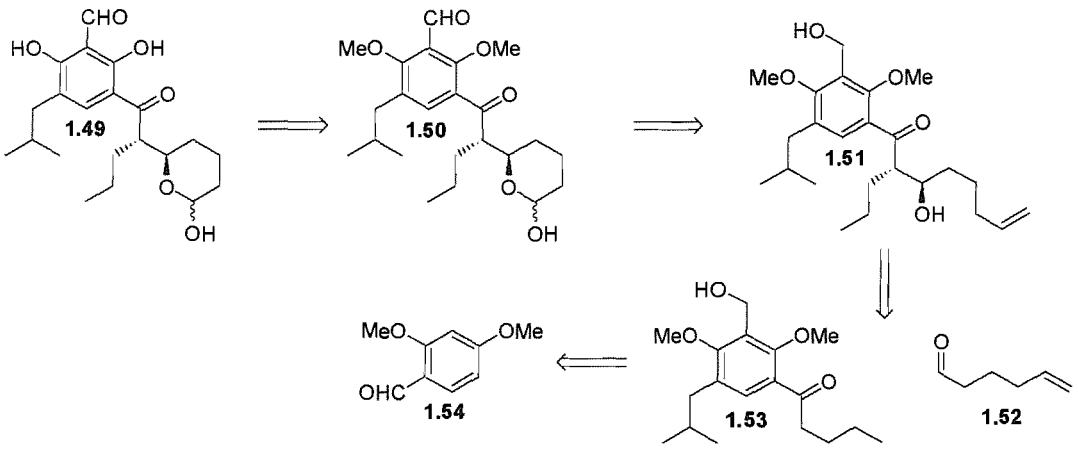
Scheme 1.8: Wood coupling and final synthetic steps.

The aromatic and aliphatic alkene side chains were reduced in a two-step hydrogenation giving racemic luminacin D, **1.6** (1.5:1), in 5.3% overall yield.

1.2.1.3 The Shipman synthesis of a simplified analogue of luminacin D[12]

(a) Retrosynthetic analysis

The synthesis was based on an alkylation of 2,4-dimethoxybenzaldehyde **1.54**, Scheme 1.9. A stereoselective aldol reaction of **1.53** was investigated to introduce the C2'–C3' stereochemistry. A *syn*-selective aldol reaction with the aldehyde **1.52** would give the desired fragment **1.51** for lactol formation. An oxidative cleavage of the alkene to the aldehyde would give the desired lactol **1.50**.



Scheme 1.9: Retrosynthetic analysis proposed by Shipman and co-workers.

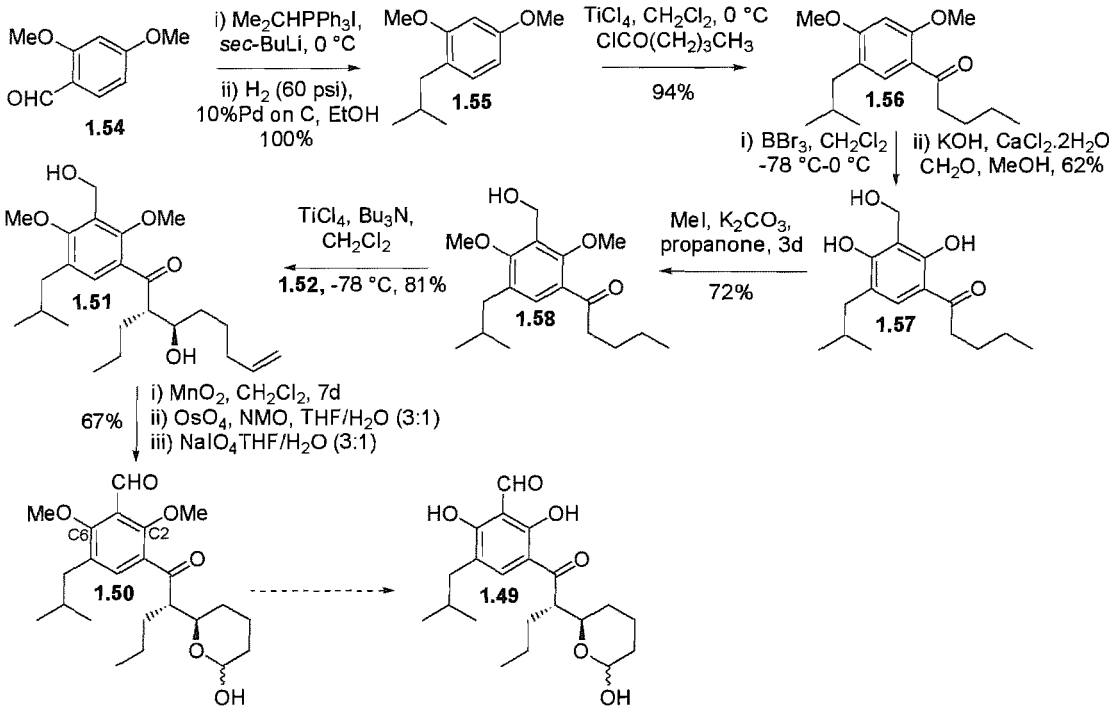
(b) Synthesis

The focus of this synthesis was the investigation of a stereoselective aldol reaction to allow introduction of the C2'–C3' bond. A Wittig olefination followed by hydrogenation was used to introduce the *sec*-butyl chain in **1.55**. Acylation using valeroyl chloride gave the ketone **1.56** as a single regioisomer, in 94% yield. The methyl ethers were removed by the use of boron tribromide and the subsequent hydroxymethylation gave **1.57** in 62% yield. The methyl ethers were re-introduced, **1.53**, and a *syn*-aldol reaction with **1.52** gave **1.51** as a single stereoisomer in 81% yield. Oxidation of the benzylic alcohol was effected using manganese(IV) oxide. Cleavage of the alkene under oxidative conditions gave the aldehyde, which immediately gave the lactol **1.58**, Scheme 1.10.

The removal of both methyl ethers to give **1.49** with a range of Lewis acids was unsuccessful, and the protection strategy was therefore revised. It was shown that the C2

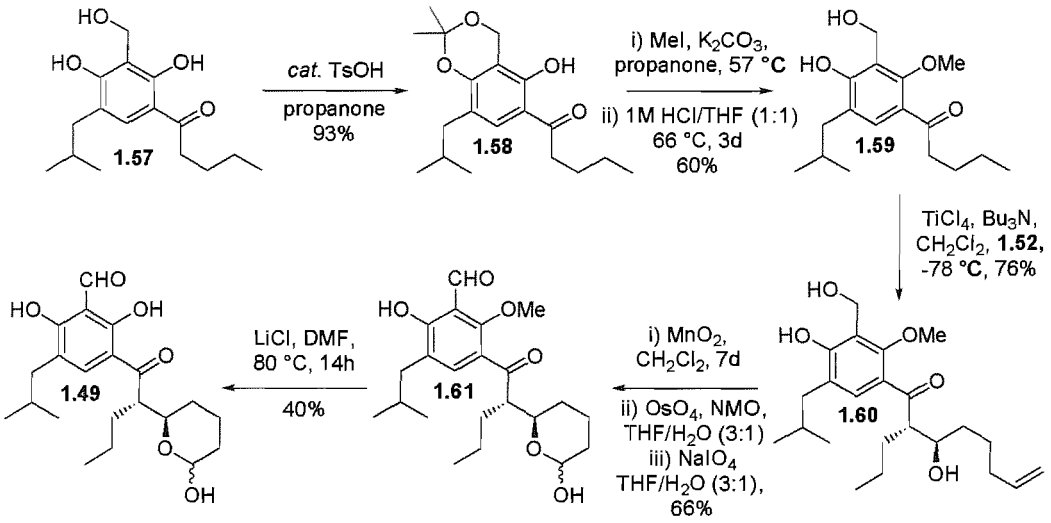
methyl ether was relatively easy to remove with the C6 methyl ether being problematic. Fragment **1.57** was protected as the acetonide, **1.58**, in 93% yield, Scheme 1.11.

The C2 hydroxyl group is more active towards deprotection due to hydrogen bonding to the adjacent carbonyl functionality. The C2 alcohol was protected as the methyl ether and the acetonide was removed to give **1.59** in 60% yield. This underwent a *syn*-selective aldol reaction with **1.52** to give **1.60** in 76% yield (diastereomeric ratio 87:13). Oxidation of the benzylic hydroxymethyl group to the aldehyde and oxidative cleavage of the alkene gave **1.61** in 66% yield. The removal of the methyl ether was carried out using lithium chloride to give **1.49** in 40% yield.



Scheme 1.10: Synthesis of luminacin D analogue, *bis*-methoxy protection.

Luminacin D analogue **1.49** has been synthesised in 6% overall yield from 2,4-dimethoxybenzaldehyde, **1.54**. The analogue exhibits antiangiogenic activity, reinforcing the proposal that in this family of compounds the epoxide moiety is less important for activity when compared to the aromatic aldehyde.



Scheme 1.11: Synthesis of luminacin D analogue, acetonide-methoxy protection.

1.2.2 Summary of previous luminacin syntheses

Tatsuta and co-workers carried out syntheses of all possible diastereomers of luminacins C_1 and C_2. This allowed confirmation of the absolute stereochemistry by comparison of analytical data to the natural products. Their drawn out synthesis of the aliphatic fragment begins with chiral centres already *in-situ* by the use of (L)-glucal. Their synthesis of the aromatic fragment provides a concise route to the substitution pattern required in luminacins C_1 and C_2. Coupling occurs successfully with the sensitive epoxide in place.

Wood's synthesis gave access to racemic luminacin D (the C2' epimers produced were separable by preparative TLC). The hydrogenation of the alkene in gave the natural diastereomer in 1.5:1 ratio. The introduction of the epoxide was carried out after coupling before intramolecular lactol formation. The epoxidation while unselective was carried out with a small bias towards the desired diastereomer (1.2:1).

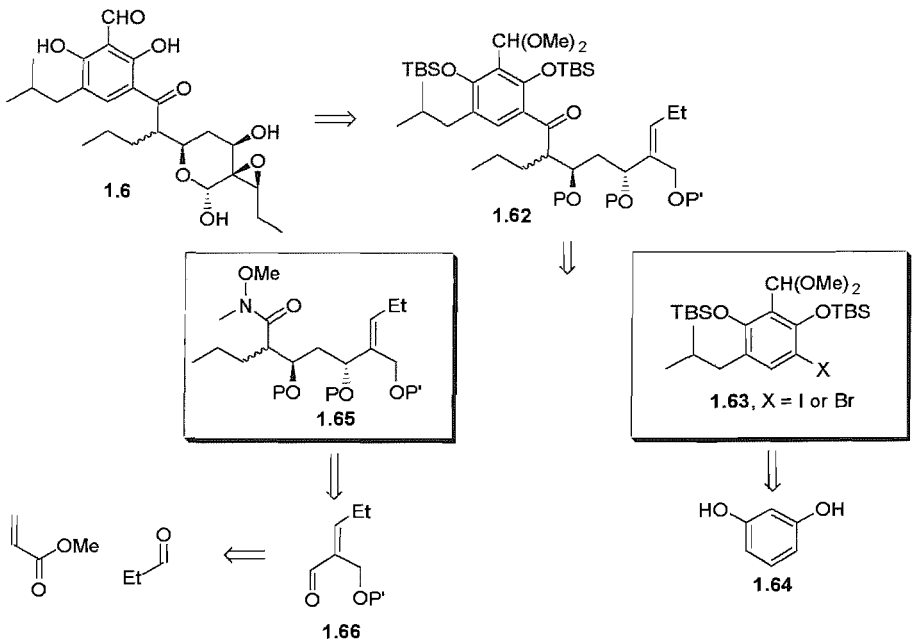
Shipman has carried out a synthesis of an active analogue of luminacin D. The absence of the epoxide functionality in the fragment has not affected activity. It has been shown that aldol chemistry can be used effectively to introduce the desired relative stereochemistry for luminacin D.

1.3 Proposed synthetic strategy towards luminacin D

1.3.1 Retrosynthetic analysis

This project was conceived and commenced prior to the publication of Tatsuta's structural confirmation of the luminacins,[10] with the absolute stereochemistry and the relative stereochemistry at C2' undetermined. The aim was to confirm the structure of luminacin D within the synthesis. It was envisaged that the use of auxiliary controlled aldol reactions would allow the synthesis of all possible diastereoisomers of **1.6**, allowing comparison of analytical data to those of the natural product. The initial retrosynthetic analysis is shown in Scheme 1.12. Hemiacetal and epoxide formation would be carried out at the final stages of the synthesis from the intermediate **1.62**. Strategic disconnections of **1.62** lead back to aromatic component **1.63** and aliphatic component **1.65**. The two fragments would be coupled via a lithiation reaction. Should the formation of the Weinreb amide prove difficult, the coupling can be carried out from the corresponding aldehyde. A planned series of 6 steps converts resorcinol **1.64** into the aromatic fragment **1.63**.

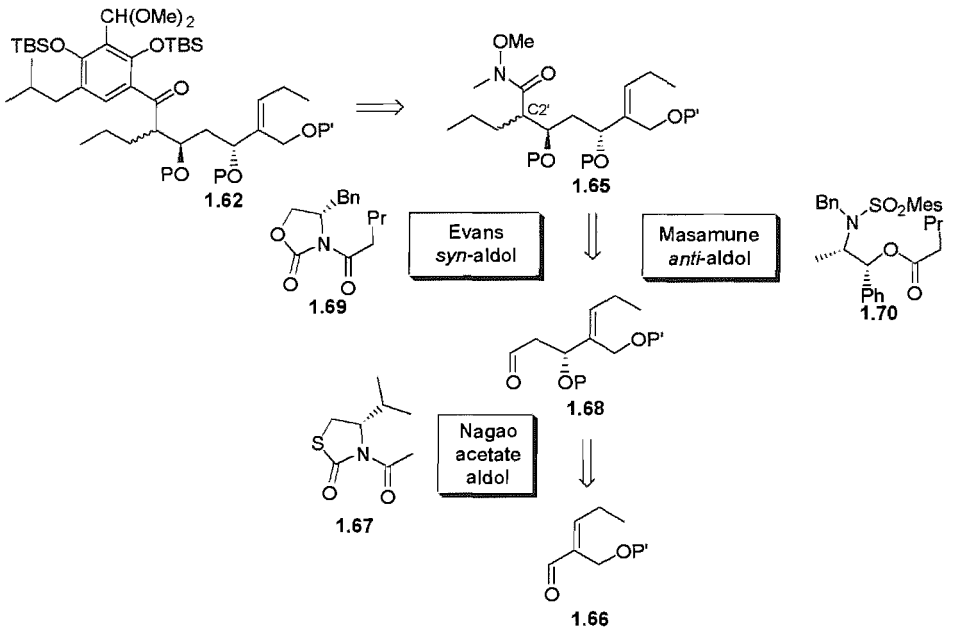
Further disconnections of the aliphatic fragment **1.65** lead to α,β-unsaturated aldehyde **1.66**. This is the substrate for the first in a series of asymmetric aldol reactions introducing the chiral centres in a stereoselective way. Aldehyde **1.66** would be synthesised from propionaldehyde and methyl acrylate in 6 steps.



Scheme 1.12: Our retrosynthetic analysis.

1.3.2 Synthesis of aliphatic fragment **1.65**

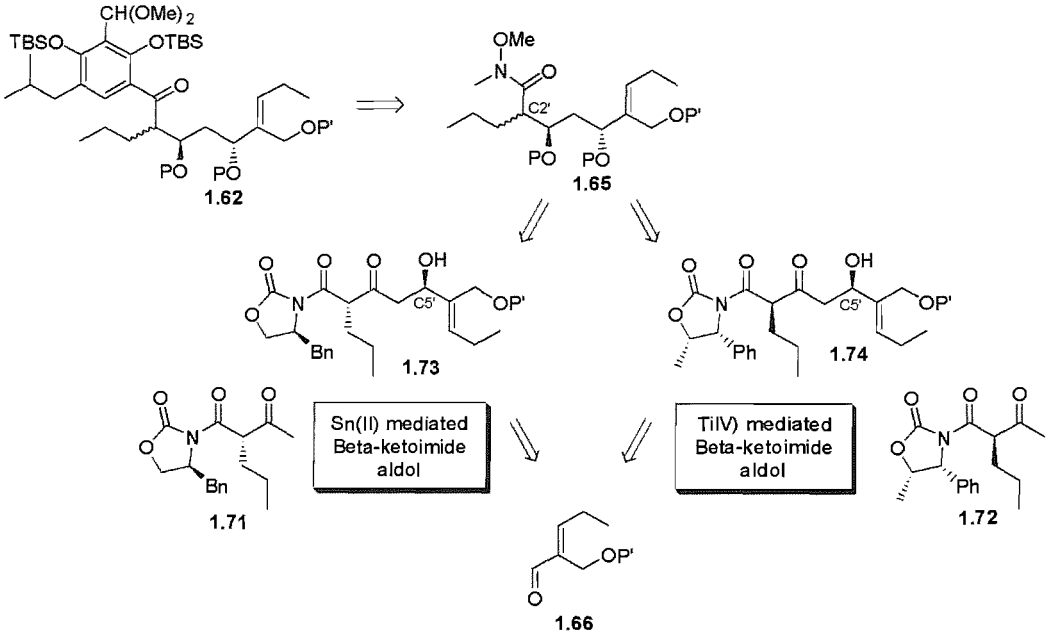
In order to carry out structural confirmation of the luminacins, routes to the two possible C2' epimers were devised. A synthesis scheme using a series of stereoselective aldol reactions formed the primary route, Scheme 1.13. A Nagao acetate aldol reaction with aldehyde **1.66** would install the first stereocentre for **1.65**. Subsequent removal of the Nagao auxiliary leads to **1.68**, the precursor aldehyde to the C2' epimers. This aldehyde would be subjected to an Evans-*syn* and a Masamune-*anti* aldol reaction using **1.69** and **1.70**, giving the C2'epimers, which would subsequently be manipulated to give the Weinreb amide **1.65**, or aldehyde needed for coupling. This route uses reactions for which the stereochemical outcomes are well documented, allowing a reliable determination of the absolute stereochemistry of **1.6**.



Scheme 1.13: Retrosynthetic analysis of aliphatic fragment via Nagao-Evans/Masamune methodology.

A route involving acetate β-ketoimide aldol reactions between aldehyde **1.66** and β-ketoimides **1.71** and **1.72** was also considered. The same C5' stereochemical outcome as the Nagao acetate-aldol reaction would be achieved through the use of the Lewis acids Ti(IV) and Sn(II). An *anti* selective reduction of the β carbonyls in **1.73** and **1.74** would lead to C2' epimers, Scheme 1.14. The aldol products can be manipulated to give the fragments suitable for coupling. This synthetic route would provide a more concise route to the aliphatic fragment; however the stereochemical outcome of these acetate β-ketoimide aldol reactions is unprecedented. β-Ketoimide aldol reactions have been carried out using propionoate-derived reagents with extremely good diastereoselectivities.

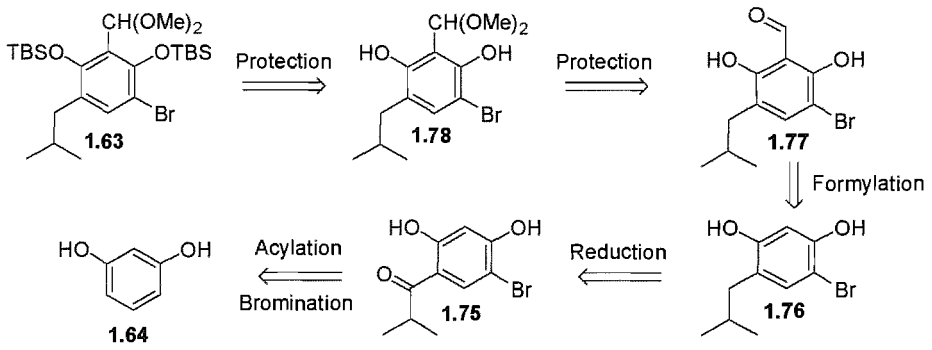
It was hoped to confirm the stereochemical outcome of the acetate β-ketoimide reaction using the more reliable route described above.



Scheme 1.14: Retrosynthetic analysis of aliphatic fragment via beta-ketoimide methodology.

1.3.3 Synthesis of aromatic fragment **1.63**

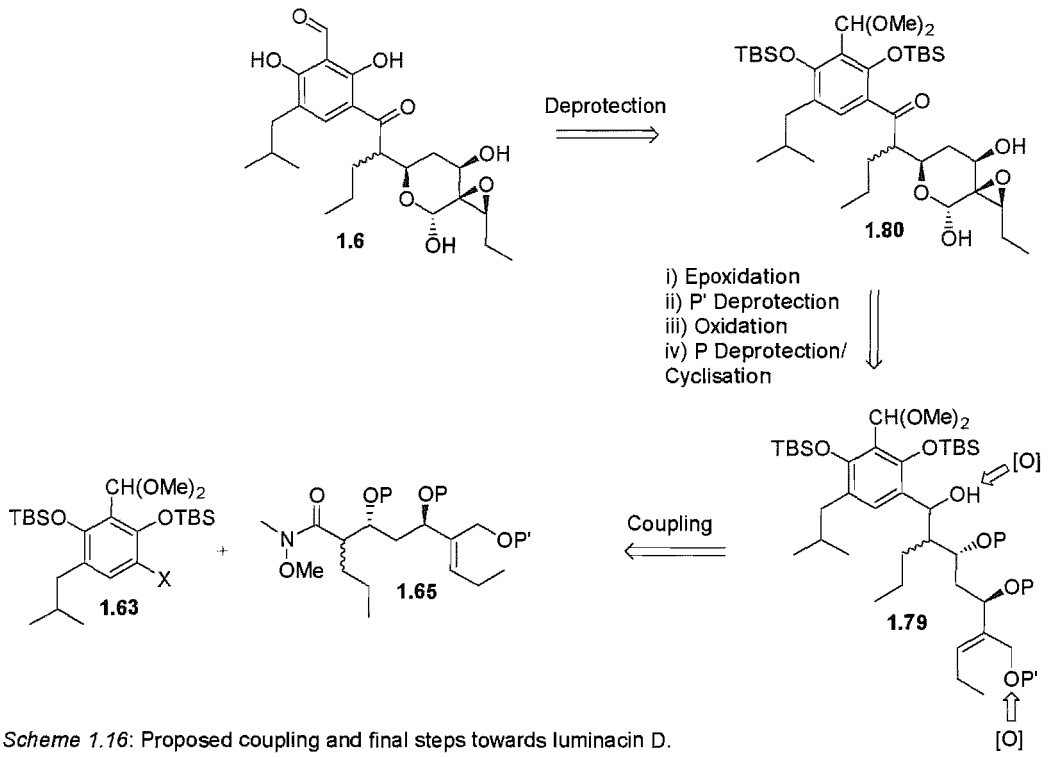
A synthetic route based on the acylation and bromination of resorcinol would lead to our desired aromatic fragment, Scheme 1.15. The bromination of resorcinol **1.64** is well documented in the literature[13 14 15] and should allow facile installation of the halogen in **1.75**. An acylation reaction followed by reduction would allow installation of the *sec*-butyl chain in **1.77**. The introduction of the aldehyde between the phenolic functionalities in **1.76** would be through a formylation reaction. Protection of the aldehyde with trimethyl orthoformate yielding **1.78** and the phenols as *t*-butyldimethylsilyl ethers will give the completed fragment **1.63**.



Scheme 1.15: Retrosynthetic analysis of aromatic fragment.

1.3.4 Coupling and final steps

The coupling reaction between the two fragments **1.63** and **1.65** would be carried out using an alkyl lithium base. Initially, coupling would be carried out without the epoxide in place, yielding **1.79**; however, should it prove advantageous, coupling on the fully functionalised fragment would be investigated. Within the aliphatic fragment, protection of the primary alcohol must be orthogonal to that of the secondary alcohols to allow independent removal. This will allow oxidation of selected alcohols in a single step, before the remaining protection is removed facilitating cyclisation leading to **1.80**. Finally, removal of the remaining protecting groups would provide access to **1.6**, Scheme 1.16.



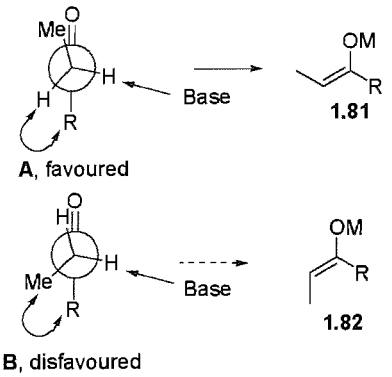
Scheme 1.16: Proposed coupling and final steps towards luminacin D.

1.4 Aldol reactions

Aldol reactions were chosen as the basis of the proposed stereocontrolled synthesis, as they are both reliable and versatile. They can be used with a range of highly functionalised aldehydes and auxiliary based stereocontrol can, in turn, be affected by the choice of Lewis acid.

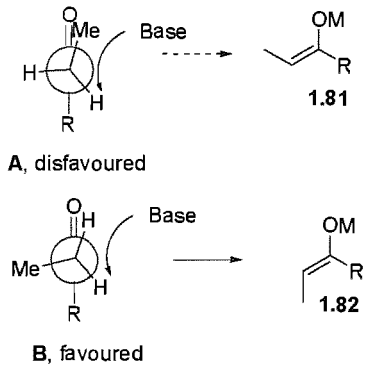
The stereochemical outcome of an aldol reaction is related to the geometry of the pre-formed enolate used in the reaction. Conformer **A** is sterically favoured as the gauche

interactions are minimised when compared to conformer **B**, Scheme 1.17.[16] As the size of the R group increases this effect becomes more marked thus amides and ketones form *Z*-enolates, **1.81**.



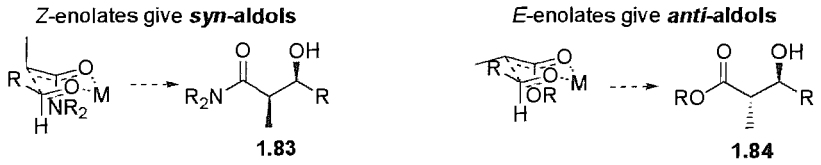
Scheme 1.17: *Z*-enolate formation.

However lithium bases are known to favour formation of *E* enolates, **1.82**, when R small. For this to occur there must be an unfavourable interaction between the base and the methyl group in conformation **A**. Heathcock et.al. proposed the approach of the base was not along the axis of the C–H bond but over the plane of the enolate to be formed, Scheme 1.18.[17]



Scheme 1.18: *E*-enolate formation

Transition metal mediated aldol reactions generally occur through a cyclic six membered Zimmerman-Traxler transition state. *Z* Enolates give *syn*-aldols, **1.83**, and *E* enolates give *anti*-aldols, **1.84**, Scheme 1.19. The two faces of an achiral enolate are not sterically distinguished, thus two enantiomers are produced in these reactions.



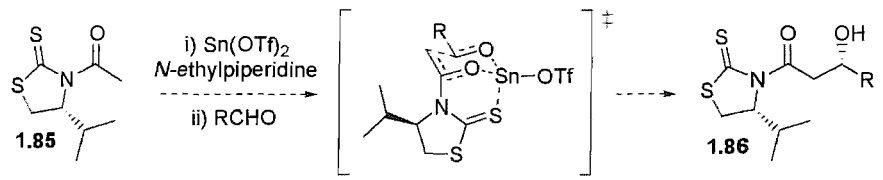
Scheme 1.19: Products resulting from *syn* and *anti* aldol reactions of achiral enolates.

The presence of a chiral centre in the enolate R group through the use of chiral auxiliaries creates two diastereotopic enolate faces. The direction of attack will be from the least sterically hindered face of the enolate. Chelation to a metal or Lewis acid can be used to lock the geometry of the enolate, resulting in increased stereoselectivity. The auxiliary can be removed reductively at the end of the synthesis and recycled.

1.4.1 The Nagao acetate-aldol reaction

The use of acetate-derived Evans oxazolidinone substrates is known to be poorly selective.[18] A control group, such as bromine[19] or thiomethyl,[20] could be introduced, but this would require removal at the end of the synthesis. A second factor is that aldol reactions with oxazolidinone auxiliaries and α,β-unsaturated aldehydes (such as **1.66** in the proposed synthesis) are known to be problematic. Sensitivity towards both acidic and basic conditions means there is a risk of dehydration and epimerisation.

Acetate-derived thiazolidinethione substrates, **1.85**, are known to give good diastereoselectivity with unsaturated aldehydes.[21] $Sn(OTf)_2$ and *N*-ethylpiperidine allow formation of the enolate which then undergoes reaction with the aldehyde to give **1.86**, Scheme 1.20. The use of either enantiomer of the chiral auxiliary gives access to both diastereomers. The stereochemical outcome of these reactions is dictated by attack on the least sterically hindered face of the enolate. Tin is sulfophilic and has labile ligands, locking the geometry of the transition state, favouring approach of the aldehyde to one side of the enolate. The auxiliary can be reductively removed and recycled by a range of reducing conditions to give chiral compounds ranging from amides to 1,3-diols.

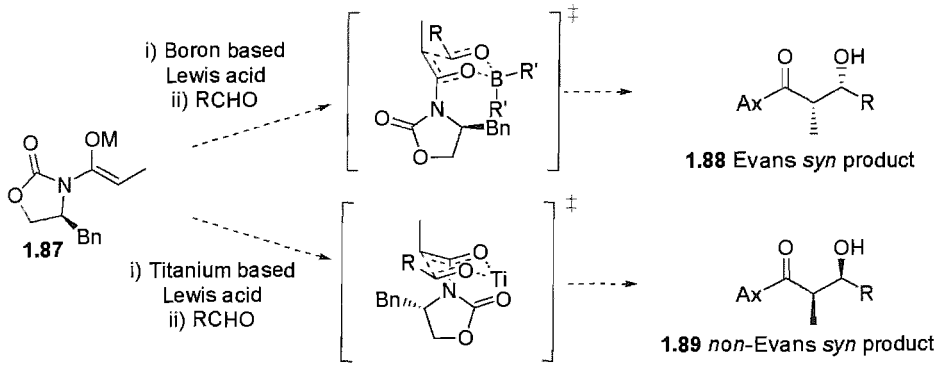


Scheme 1.20: The Nagao acetate-aldol reaction.

Diastereoselectivity and yields are highly sensitive to the stoichiometry of the reagents used. 1.2 equivalents of aldehyde, base and Lewis acid (relative to the chiral reagent), typically produces yields of 80%, with 94% diastereomeric excess. With increasing amount of base, a reduction in the selectivity is obtained, most likely due to the coordination of the base to the tin on the less hindered face, preventing the aldehyde approaching from this direction.

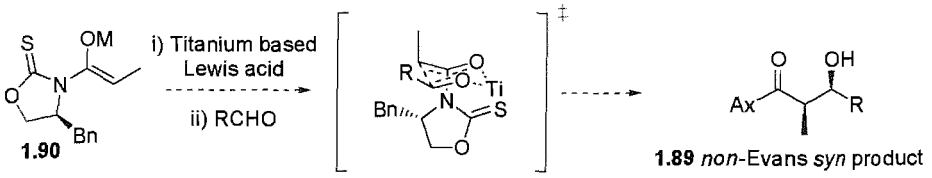
1.4.2 The Evans *syn*-aldol reaction

Evans *syn*-aldol reactions use chiral oxazolidinone auxiliaries, which are known to form exclusively *Z*-enolates, **1.87**. The use of Bu_2BOTf gives access to the Evans *syn*-aldol product **1.88**, whereas $TiCl_4$ gives access to the *non*-Evans aldol product **1.89**, Scheme 1.21. These Lewis acids have different affinities for oxygen, changing the orientation of the auxiliary in the transition state.[22]



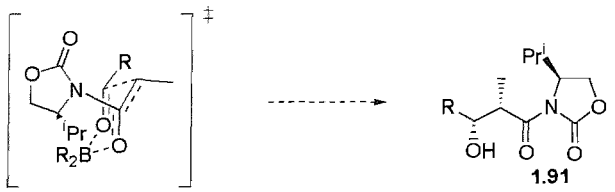
Scheme 1.21: The Evans *syn*-aldol reaction and *non*-Evans *syn*-aldol reaction.

Bu_2BOTf has only one labile ligand, allowing coordination to two heteroatoms, the remaining carbonyl group aligning to minimise dipole repulsions. $TiCl_4$ has four labile ligands giving the potential to coordinate to more heteroatoms in the transition state. Titanium also has a greater affinity for oxygen than that of boron. Coordination to three heteroatoms can occur in the transition state resulting in the opposite stereochemistry. The use of $TiCl_4$ and oxazolidinones gives slightly lower diastereoselectivities compared to Bu_2BOTf. This can be overcome by the use of oxazolidinethione auxiliaries such as **1.90**, Scheme 1.22. Reactions using oxazolidinethiones are more selective due to titanium's greater affinity for sulfur. These reactions are highly selective using a wide range of aldehydes and mild reducing conditions are able to efficiently recycle the auxiliaries.

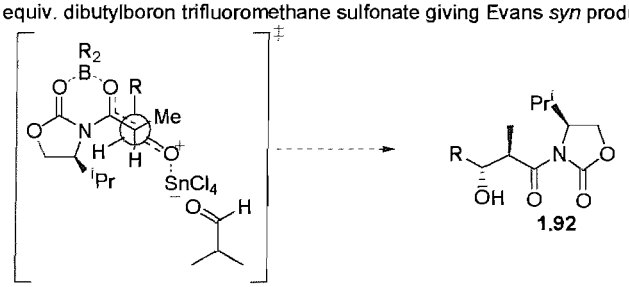


Scheme 1.22: The Evans *syn*-aldol reaction with **1.90**.

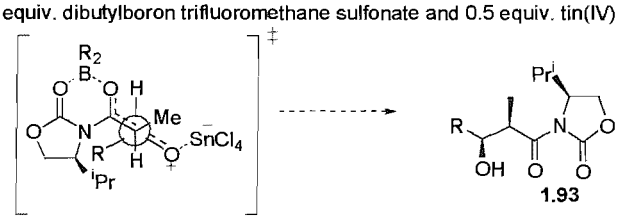
These reactions are sensitive to manipulation of the stoichiometry of Lewis acid in the reaction, resulting in other products with a reduction in distereoselectivity. The origin of the marked effect of the Lewis acid stoichiometry on the product obtained is unclear. It is proposed to be a result of external aldehyde activation giving rise to open transition states, Scheme 1.23.[16] When one equivalent of Bu_2BOTf is used, the Evans *syn*-product **1.91** (96% diastereomeric excess) predominates, due to attack of the *re*-face of the enolate in a closed transition state, as shown in Scheme 1.23 A. The use of 1 equivalent of Bu_2BOTf with the addition of 0.5 equivalents of Sn(IV) chloride gives the *anti*-product, **1.92** (with some non-Evans *syn*-product, 90% diastereomeric excess), Scheme 1.23 B. The increased effective size of the aldehyde results in the open transition state. Reactions with aromatic aldehydes gave the *anti*-product, whereas simple aldehydes gave the Evans *syn*-product. An extra 2 equivalents of Sn(IV) chloride used to externally activate the aldehyde gives access to the *non*-Evans *syn*-product **1.93** (with some *anti*-product, 66% diastereomeric excess) in the presence of 1 equivalent of Bu_2BOTf, as shown in Scheme 1.23 C.



A: 1 equiv. dibutylboron trifluoromethane sulfonate giving Evans *syn* product.



B: 1 equiv. dibutylboron trifluoromethane sulfonate and 0.5 equiv. tin(IV) chloride giving *anti* product.



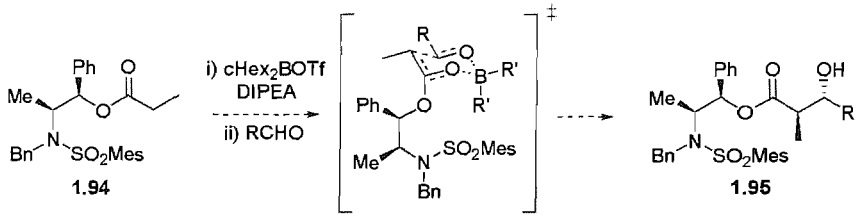
C: 1 equiv. dibutylboron trifluoromethane sulfonate 2 equiv. tin(IV) chloride giving *non*-Evans *syn* product.

Scheme1.23: Proposed transition states resulting from increasing amount of Lewis acid.

The rate of these reactions was accelerated when 1.1 equivalent of (–)-sparteine was employed as base. It should be noted that there was no observed stereo induction from the use of this chiral base, and results were comparable when either isomer of auxiliary was used.[22]

1.4.3 The Masamune *anti*-aldol reaction[23]

Selective access to the *anti*-products can be achieved in high diastereomeric excess by the use of chiral ester derivatives, which are known to give exclusively *E*-enolates. The use of chiral norephedrine derivatives such as **1.94** have been shown to give access to the *anti*-product **1.95** when using 1.2 equivalents dicyclohexyl boron trifluoromethanesulfonate and di*iso*propylethylamine, Scheme 1.24.

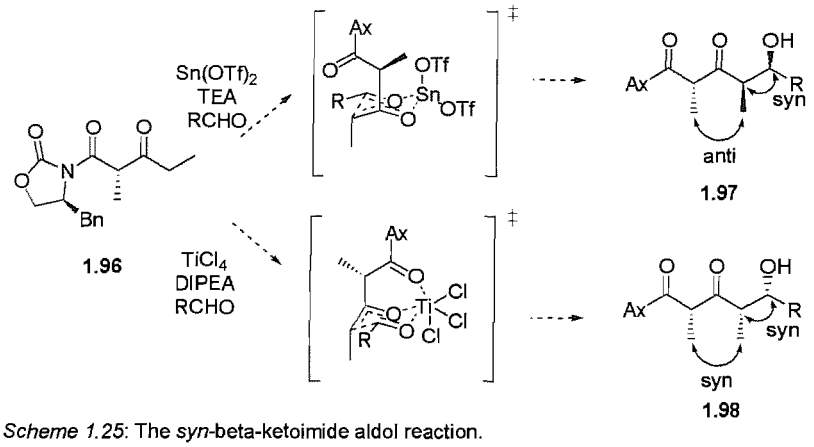


Scheme 1.24: The Masamune *anti*-aldol reaction.

The reactions are highly selective when using a range of electrophiles including α,β-unsaturated aldehydes with typical diastereomeric excesses of 96%. The auxiliary can be recycled by reductive methods giving either the carboxylic acid or 1,3-diol. The stereochemical outcome of the reactions is sensitive to the reaction conditions. The use of other boron reagents and amine bases reduced the diastereomeric excess due to formation of the *syn*-product. Using Bu_2BOTf and DIPEA the *syn* product was isolated with 70% diastereomeric excess.

1.4.4 The β-ketoimide aldol reaction

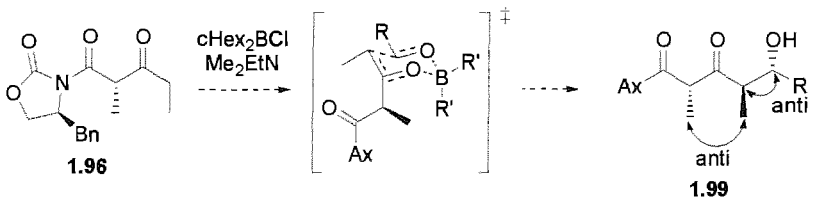
Propionoate-derived β-ketoimide reagents, **1.96**, are made up of a stereocentre α to two carbonyl bonds. They are much more stable than expected due to an internal non-bonding interaction. This minimises allylic strain and prevents the orbitals of the carbonyl functionality aligning with the α-C–H bond, preventing elimination and problems regarding racemisation. These types of aldol reaction have been carried out with good selectivity with α,β-unsaturated aldehydes with typical de's of 90-98%.[24] However, the acetate-derived analogous aldol reactions have not been investigated.



Scheme 1.25: The *syn*-beta-ketoimide aldol reaction.

The formation of the enolate using $Sn(OTf)_2$ /TEA and $TiCl_4$/DIPEA gave exclusively the *Z*-enolate, Scheme 1.25. The stereocontrol in these *syn*-aldol reactions comes from the orientation of the alkyl group with the stereocentre in the auxiliary having minimal effect, Scheme 1.24. Sn(II) coordinates to two heteroatoms in the transition state and the remaining carbonyl group aligns to minimise dipole interactions resulting in the *anti-syn* aldol product **1.97**. Ti(IV) coordinates to three heteroatoms in the transition state, which would result in the *syn-syn* aldol product **1.98**.

Formation of the enolate using $cHex_2BCl/Me_2EtN$ in diethyl ether gave the *E*-enolate. These reactions gave access to *anti-anti* **1.99** aldol products with good yields and reasonable diastereomeric excess of 70%, Scheme 1.26.[25]

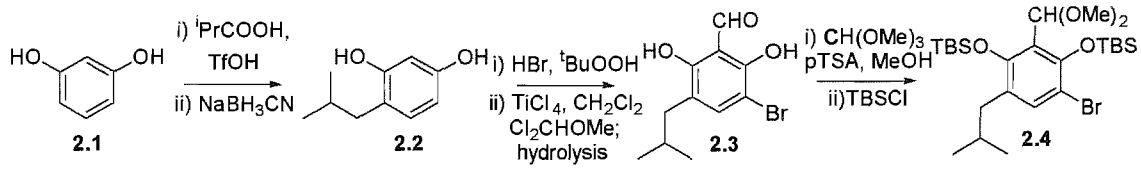


Scheme 1.26: The *anti*-beta-ketoimide aldol reaction.

Chapter 2: Aromatic fragment synthesis

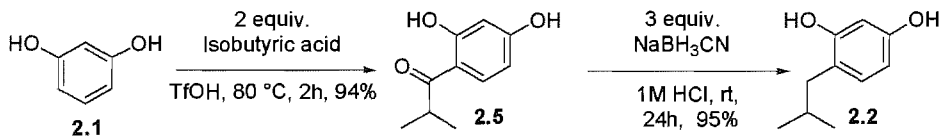
2.1 Initial synthetic route

The proposed synthetic route was based on the acylation and bromination of resorcinol, **2.1**, Scheme 2.1. Acylation by triflic acid and *iso*butyric acid would introduce the *sec*-butyl group to resorcinol. Reduction of the benzylic ketone to methylene group using sodium cyanoborohydride would be expected to produce **2.2**. Bromination of **2.2**, followed by formylation, is expected to yield **2.3**. Protection of the aldehyde as a dimethyl acetal would allow mild deprotection conditions in the final steps of the synthesis. Final protection of the hydroxyl groups as *t*-butyldimethylsilyl ethers is expected to give the fully protected aromatic fragment **2.4**.



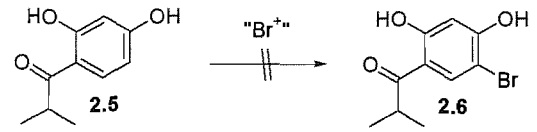
Scheme 2.1: Synthesis based on bromination of resorcinol.

The acylation of resorcinol[26] as shown in Scheme 2.2 occurred smoothly, yielding **2.5** in 94% yield. The toxic nature of cyano compounds prompted experimentation with reduction reactions using sodium borohydride[27] and sodium triacetoxyborohydride,[28] but ketone or methylene derivatives were absent after aqueous workup. Using sodium cyanoborohydride[29] in 1M hydrochloric acid gave **2.2** smoothly in 95% yield.



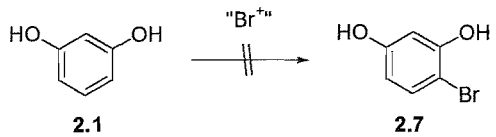
Scheme 2.2: Acylation of Resorcinol and reduction to methylene.

Work carried out within our laboratory showed poly bromination to occur when subjecting **2.2** to a range of bromination conditions. It was thought that bromination prior to reduction would allow access to the desired brominated product. However, bromination of **2.5**, Scheme 2.3, using *N*-bromopiperidine[30] and sodium bromide failed, whereas *N*-bromosuccinamide[13] resulted in poly bromination.



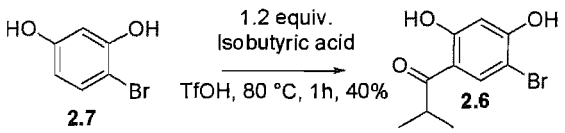
Scheme 2.3: Bromination of **2.5**.

Therefore, installation of bromine before acylation was investigated. Bromination of resorcinol, Scheme 2.4, following a literature procedure using both 0.5 and 1.0 equivalents of diethyldibromomalonate[15] did not go to completion after heating for 4 days, and separation of **2.7** from resorcinol was not possible. These experiments were also conducted in a microwave reactor, to encourage reaction completion, but the same problems resulted. A procedure using 1 equivalent of sodium bromide and dimethyldioxirane[14] was carried out, but, again, isolation of **2.7** from resorcinol was not possible.



Scheme 2.4: Bromination of resorcinol.

Accordingly, a small commercial sample (Aldrich) of the expensive 4-bromoresorcinol **2.7** was purchased, and the acylation using *iso*butyric acid and triflic acid carried out on a small scale, Scheme 2.5. Brominated product **2.6** was isolated in 40% yield, and trace amounts of the regioisomer (resulting from acylation at the *ortho* position) were seen by ^{1}H NMR.



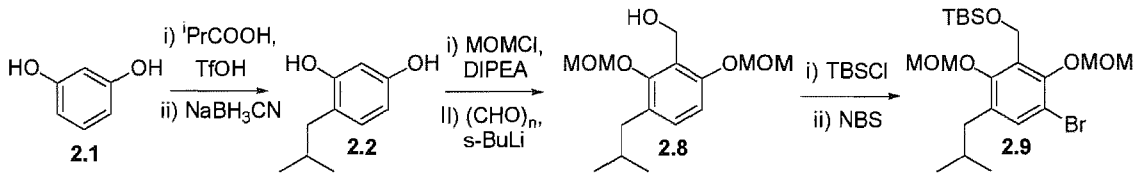
Scheme 2.5: Acylation of 4-Bromoresorcinol.

Bromination of resorcinol and its derivatives have shown limited success in our hands. Acylation and reduction steps have been carried out smoothly giving **2.2**.[26, 27]

2.2 Application of the Tatsuta aromatic fragment synthesis

The Tatsuta synthesis[10] of the aromatic fragment for luminacins C_1 and C_2 (discussed in Chapter 1) can be readily applied to our synthetic strategy, as shown in Scheme 2.6.

bis-Methoxymethyl protection of the hydroxyl groups in **2.2** would allow an *ortho*-directed hydroxymethylation between the two protected alcohols, giving **2.8**. Protection of the free hydroxyl group followed by a second *ortho*-directed reaction would introduce the chosen halogen giving the desired aromatic fragment **2.9**.



Scheme 2.6: Application of the Tatsuta methodology to our synthesis.

This methodology uses a hydroxymethylation reaction to introduce a primary alcohol group at the *ortho* position, which must be oxidised to the aldehyde in luminacin D. The protecting group used for the primary alcohol in **2.8** must be removed after coupling, to allow a single oxidation step (as discussed in Chapter 1), Figure 2.1. Results from the present investigations into the Nagao acetate-aldol reaction (discussed in Chapter 3, 3.2.4.1) showed the best protecting group for our aldehyde to be a tri*iso*propylsilyl ether. The *t*-butyldimethyl silyl group was therefore chosen to protect this primary alcohol in the aromatic fragment.

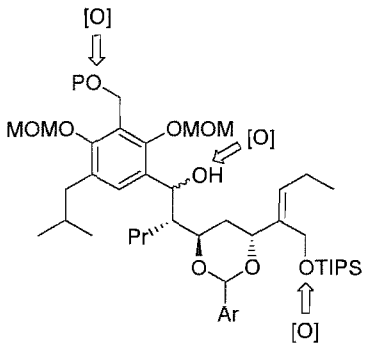
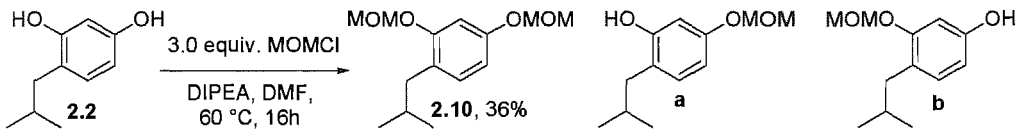


Figure 2.1: Sites to be simultaneously oxidised after coupling

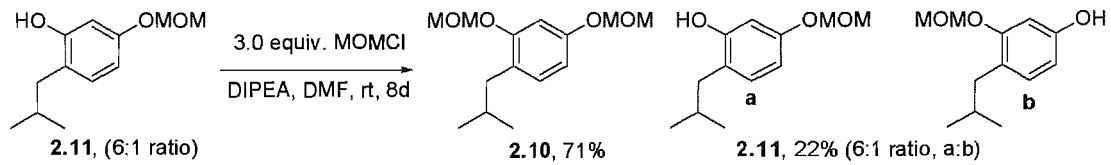
2.2.1 Di-protection of aromatic alcohols

Orthogonal protection of the aromatic fragment is important for the subsequent stages in the synthesis. The use of a methoxymethyl ether would allow an *ortho*-directed hydroxymethylation reaction, and can be deprotected in the presence of other groups. Phenolic protection was carried out using 3.0 equivalents of chloromethyl methyl ether and di*iso*propylethylamine.[31] Stirring at room temperature in dimethylformamide for 7 days gave 34% diprotection, **2.10,** with 38% monoprotection, **2.11**, as a 6:1 ratio of **a:b**. A reaction was then carried out in the presence of a catalytic amount of tetrabutylammonium iodide, with the intention of forming iodomethylmethyl ether in order to accelerate the reaction; however the ratio of **2.10:2.11** was not improved. Heating the reaction to 60 °C in dimethylformamide for 16 hours gave **2.10** in 36% yield, with 67% of the mono protected **2.11** again in a 6:1 ratio, Scheme 2.7.



Scheme 2.7: Methoxymethyl protection of **2.2**.

Resubmission of **2.11** to the reaction conditions allowed isolation of **2.10** in 71% yield, with 22% of **2.11** (6:1 ratio) returned after 8 days at room temperature, Scheme 2.8.



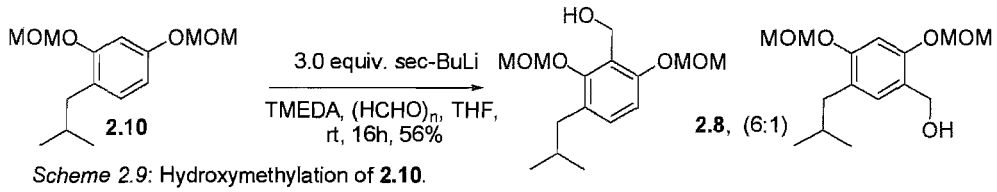
Scheme 2.8: Methoxymethyl protection of **2.11**.

Use of a stronger base to encourage the reaction towards completion was investigated. Using 2.0 equivalents of chloromethyl methyl ether and sodium hydride,[32] stirring **2.2** for 8 days at room temperature gave 38% of **2.10** and 19% of **2.11**. This did not improve the product yield and some loss of material was evident.

2.2.2 The hydroxymethylation reaction

The hydroxymethylation reaction of **2.10** was carried out using *sec*-butyl lithium, tetramethylethylene diamine and paraformaldehyde (1:1:1).[33] Optimisation of the stoichiometry of the reagents was carried out, as shown in Table 2.1.

The use of 3.0 equivalents of reagents gave **2.8** in 56% yield, Scheme 2.9. Analysis of the ^{1}H NMR spectrum of **2.8** indicated the existence of a 6:1 ratio of inseparable regioisomers.



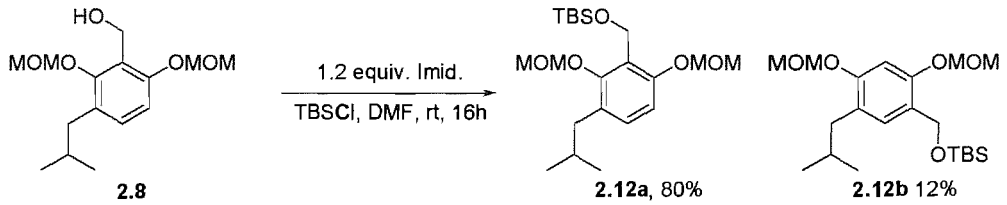
Scheme 2.9: Hydroxymethylation of **2.10**.

Equivalents of BuLi	Yield %
2.0	39
2.1	41
2.4	51
2.8	52
3.0	**56**
3.5	44

Table 2.1: The effect of stoichiometry of *sec*-butyl lithium on the yield for the hydroxymethylation reaction.

2.2.3 Protection of primary alcohol

Protection of **2.8** proceeds smoothly with 1.2 equivalents of imidazole/*t*-butyldimethyl silylchloride,[34] Scheme 2.10. The regioisomers generated in the hydroxymethylation step could now be separated, with **2.12a** obtained in 80% yield and **2.12b** in 12% yield (6.7:1 ratio).

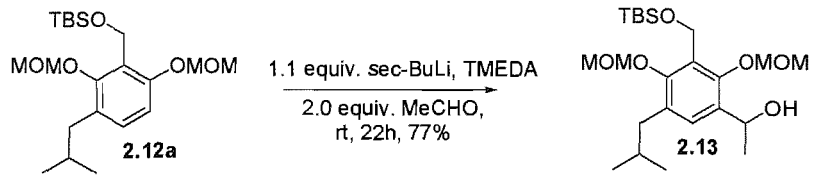


Scheme 2.10: Protection of **2.8** as a t-butyldimethyl silyl ether.

2.3 Trial coupling reaction

With the completion of the aromatic fragment, attention was given to the coupling step. Tatsuta et al.[10] performed a second *ortho*-directed lithiation and quenched the anion produced with *N*-iodosuccinamide, isolating the iodo compound. This was then subjected to a lithium-halogen exchange reaction and then quenched with their aliphatic fragment.

Problems in brominating our derivatives prompted investigation into the need for isolating the halogenated species. The removal of this extra step would also improve efficiency of the synthetic route. Therefore, an *ortho*-lithiation reaction on **2.12a**, using 1.1 equivalents of *sec*-butyl lithium and tetramethylethylene diamine,[33] was conducted, followed by quenching the anion with 2.0 equivalents of acetaldehyde, Scheme 2.11.



Scheme 2.11 Trial coupling reaction with acetaldehyde.

The desired racemic product, **2.13**, was isolated in 77% yield. The execution of a halogen-lithium exchange sequence would seem unnecessary, however acetaldehyde is an extremely simple aldehyde and the aliphatic fragment may not be expected to react in the same way.

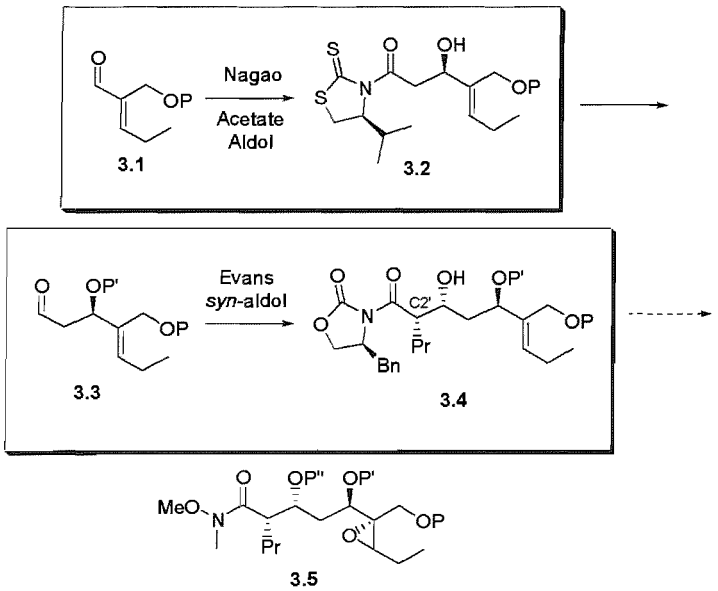
2.3 Summary

The aromatic fragment from the proposed synthetic scheme has been synthesised in 5 steps from resorcinol in 19% overall yield. The *bis*-methoxymethyl protection and hydroxymethylation steps have proven to be a synthetic challenge. Tatsuta's good yields as discussed in Chapter 1 have not been reproducible with our aromatic fragment for luminacin D. Acylation of resorcinol proceeds smoothly in 94% yield and the subsequent reduction in 95% yield. Methoxymethyl protection was carried out in a two-step procedure giving *bis*-methoxymethyl product in 46% yield. Optimal conditions for the hydroxymethylation reaction use 3 equivalents of *sec*-butyl lithium and yielded product in just 56% yield as a 6:1 ratio of regioisomers. Protection of the resulting primary alcohol as the silyl ether allowed separation of these regioisomers and gave the desired isomer in 80% yield. A trial coupling reaction with acetaldehyde proceeded smoothly giving the racemic alcohol in 77% yield, although coupling with the luminacin D aliphatic fragment has not been possible.

Chapter 3: Aliphatic fragment synthesis: Nagao/Evans methodology

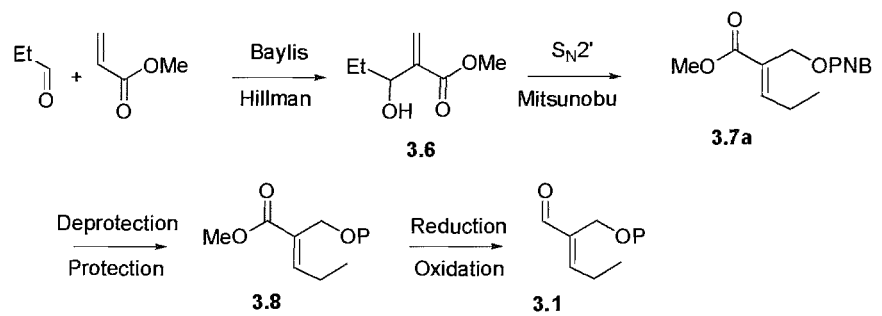
3.1 Introduction

The absolute stereochemistry of the luminacins had not been established at the outset of this work. As discussed in Chapter 1, a series of stereoselective aldol reactions was envisaged to allow access to the desired diastereomer for luminacin D, Scheme 3.1.



Scheme 3.1: Proposed synthesis via Nagao-Evans methodology.

The required aliphatic fragment would be constructed by a Nagao acetate-aldol reaction with aldehyde **3.1**, followed by an Evans *syn*-aldol reaction. These reactions are expected to efficiently allow access to the desired compound. The chiral fragment **3.4** would subsequently be manipulated to give fragments such as **3.5** suitable for coupling to the aromatic fragment. The primary synthetic target of the present work was aldehyde **3.1**, which has been synthesised from methyl acrylate and propionaldehyde through a series of well-documented reactions, Scheme 3.2.



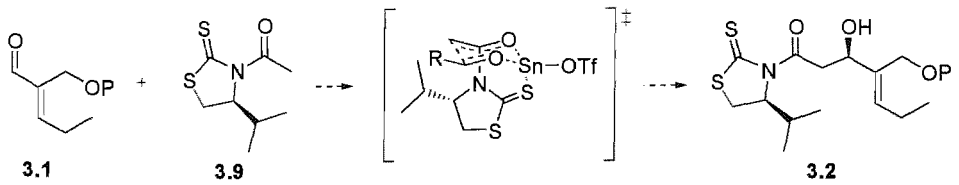
Scheme 3.2: Proposed synthesis of aldehyde **3.1**.

3.2 The Nagao acetate-aldol reaction

3.2.1 Introduction

For the present synthesis of luminacin D an acetate-aldol reaction with aldehyde, **3.1** is necessary. Acetate-derived thiazolidinethione auxiliaries, such as **3.9**, are known to give good diastereoselectivity with unsaturated aldehydes.[21] The use of $Sn(OTf)_2$ and *N*-ethylpiperidine allows formation of the enolate which then undergoes reaction with the unsaturated aldehyde. Diastereoselectivity and yields are highly sensitive to the stoichiometry of the reagents used. Optimal conditions using 1.2 equivalents of aldehyde, base and Lewis acid (relative to the chiral reagent) typically produce yields of 80% with 94% diastereomeric excess.

The stereochemical outcome of these reactions is dictated by attack on the least sterically hindered face of the enolate, shown in the transition state, Scheme 3.3. Tin is sulfophilic and has labile ligands, locking the geometry of the transition state, favouring approach of the aldehyde to one side of the enolate.

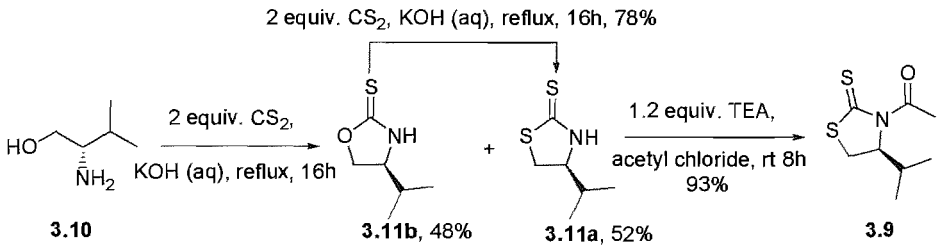


3.1 **3.9** **3.2**

Scheme 3.3: Nagao acetate-aldol reaction.

3.2.2 Synthesis of the acylated auxiliary

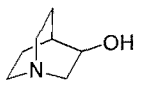
The chiral thiazolidinethione substrate **3.9** was synthesised from commercially available (2*S*)-amino-3-methyl-butan-2-ol, **3.10**. Refluxing with 2 equivalents of carbon disulfide in 1N aqueous potassium hydroxide for 16 hours,[21] gave **3.11a** as a white crystalline solid in 52% yield (after trituration with DCM/hexane), with 48% of the undesired **3.11b** as a waxy solid. The undesired oxazolidinethione **3.11b** can be resubmitted to the reaction conditions[35] to give **3.11b** in 78% yield. Acylation of **3.11a** was carried out using 1.2 equivalents of TEA and acetyl chloride,[36] giving **3.9** as a yellow oil in 93% yield, Scheme 3.4.



Scheme 3.4: Synthesis of chiral auxiliary for Nagao actetate-aldol reaction.

3.2.3 Synthesis of the aldehyde substrates

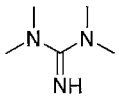
The Baylis-Hillman reaction between aldehydes and activated alkenes results in highly functionalised products. These reactions are catalysed by tertiary amine bases and are often characterised by low reaction rates. Many studies have been documented in which reaction catalysts, solvents and temperature for different substrates are manipulated. Four commonly used catalysts are 3-quinuclidinol, **3.12**, diazabicyclo[2,2,2]octane, **3.13**, quinuclidine, **3.14**, and tetramethyl guanidine, **3.15**, *Figure 3.1*.



3-Quinuclidinol, **3.12**

1,4-diazabicyclo[2.2.2]octane, **3.13**

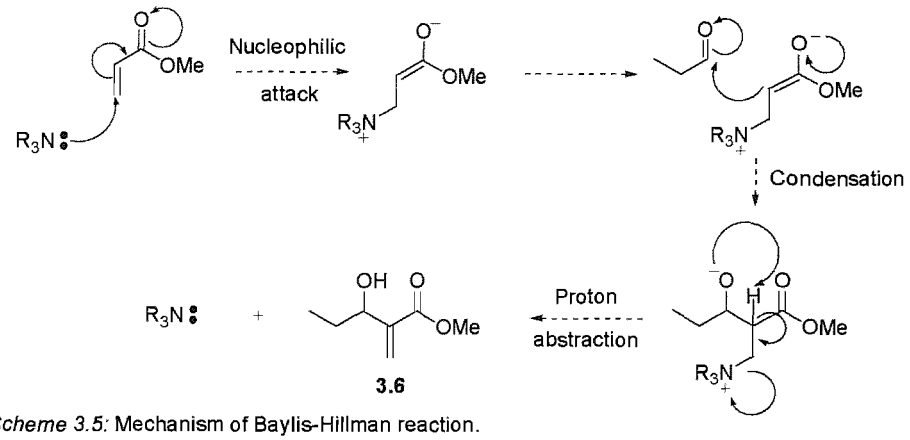
Quinuclidine, **3.14**



1,1,3,3-tetramethylguanidine, **3.15**

Figure 3.1: Common catalysts for the Baylis-Hillman reaction.

The alkene moiety in methyl acrylate is activated towards nucleophilic attack due to the presence of the electron withdrawing ester functionality. The nucleophilic amine attacks the alkene at the positively polarised carbon atom. The resulting bipolar intermediate undergoes an aldol-type reaction with propionaldehyde. The negatively charged oxygen atom produced abstracts a proton internally. The tertiary carbon atom stablises the anion allowing elimination of the amine catalyst, Scheme 3.5.



Scheme 3.5: Mechanism of Baylis-Hillman reaction.

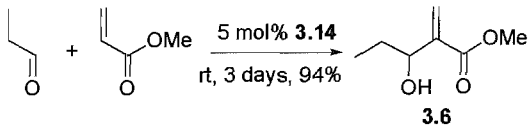
Work by Drewes[37] has shown **3.12** to be the optimum catalyst for the Baylis-Hillman reaction between methyl acrylate and propionaldehyde, giving **3.6** in 61% yield (in solvent free conditions). In our hands 1.3 equivalents of methyl acrylate, 1.0 equivalents of propionaldehyde and 5 mol% **3.12** in dichloromethane gave **3.6** in 14% yield after stirring at room temperature for 7 days. When the reaction time was increased to 14 days, **3.6** was accessed in 61% yield. The extended reaction times needed to gain access to **3.6** made large-scale synthesis difficult. The use of formamide is known to accelerate the rate of reaction[38] and this has been met with some success with the present system. Carrying out a reaction with 5 mol% **3.12** in formamide achieved a 31% yield in 16 hours. Aqueous based solvents such as 1,4-dioxane/water, have been shown to accelerate the rate of reaction.[39] In our hands a reaction using 2 equivalents of **3.13** in 1,4-dioxane/water (1:1, v/v) gave **3.6** in 33% yield at room temperature after 36 hours. Leahy has shown that an increase in rate can be seen at 0 °C in dioxane.[40] However, in the present case, 10 mol% **3.13** stirring in dioxane at 0 °C for 8 hours gave none of the desired product. The use of 1,1,3,3-tetramethyl guanidine **3.15** has good activity when using simple aldehydes.[41] A reaction using 0.5 equivalents of **3.15** only produced 8% of **3.6**. In an attempt to increase the efficiency of our synthesis procedure, the stoichiometry of the reagents was changed. Previously, 1.3 equivalents of acrylate and 1.0 equivalents of aldehyde were used, but changing to 1.5 equivalents of aldehyde and 1.0 equivalents of acrylate gave no improvement in yield.

With the reaction yield being so capricious, an array of reactions were carried out with analysis by liquid chromatography and ultraviolet detection. The four catalysts (all at 5 mol%) were screened against six solvent systems at room temperature for 16 hours, the results being summarised in Table 3.1.

	3-Quinuclidinol, **3.12**	1,4-Diazabicyclo [2.2.2]octane, **3.13**	Quinuclidine, **3.13**	1,1,3,3-Tetramethyl guanidine, **3.14**
Neat	1:4.9	2.7:1	**1:1011**	2.5:1*
Methanol	1:2.6*	2.2:1	1:5.2*	0:0*
Dioxane:Water	2087:0.1	0:0	1.8:1	1926:0.1
THF:Water	1755:0.1	2518:1	2.5:1	1680:0.1
CH_2Cl_2	1.3:1	1555:1	1:1.6	0:0*
Acetonitrile	1.2:1	940:1	1:2.9	5.1:1*

Table 3.1: Results from Baylis Hillman optimisation.

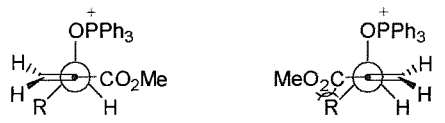
The percentage areas of each absorbance peak at 230 nm were calculated. The results are then given as a ratio of methyl acrylate:product, corrected to allow for their differing response factors. Reactions marked with an asterisk gave an uncharacterised side product as the major component. These results clearly show that the best system for the present substrates uses quinuclidine in the absence of solvent, bold in Table 3.1. A large scale (477 mmol) reaction was thus carried out using 5 mol% **3.14** stirring at room temperature for three days, resulting in **3.6** being produced in 94% yield, Scheme 3.6.



3.6

Scheme 3.6: Optimised Baylis-Hillman reaction.

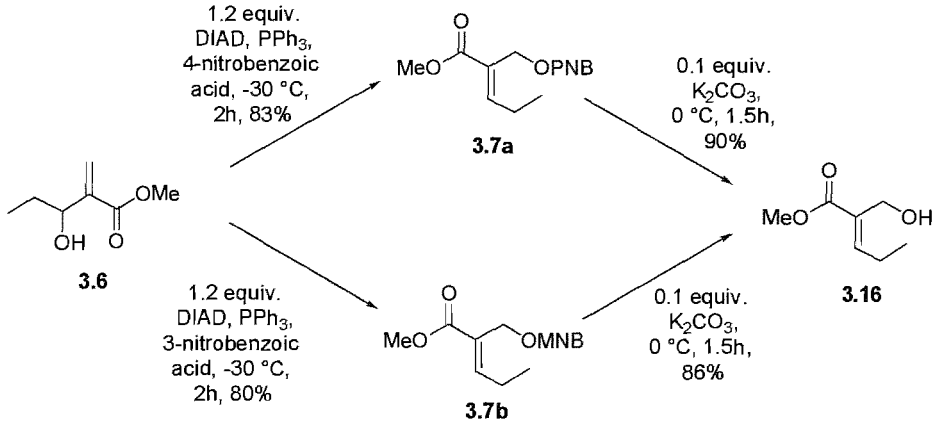
The classic Mitsunobu conditions would be applied to **3.6**. [42] The α,β-unsaturated nature of the phosphonium salt derived from **3.6** means that the S_N2' reaction is preferred. *p*-Nitro benzoic acid and diethylazodicarboxylate were used in the literature procedure, giving **3.7a** in 85% yield, deprotection was then carried out using K_2CO_3 and methanol giving **3.16** in 87% yield. The *E* alkene isomer was obtained exclusively as predicted by the transition state shown in Figure 3.3. The oxophosphonium group aligns to maximise interactions between its σ^* orbital and the π system of the alkene. The R group is aligned to minimise interactions with the ester functionality. *Anti* attack gives the *E* isomer.



Favoured: *E* alkene Disfavoured: *Z* alkene

Figure 3.3: Transition states for *E* and *Z* alkene formation.

Initial reactions were carried out using 1.2 equivalents of *m*-nitrobenzoic acid and di*iso*propylazodicarboxlate, giving **3.7b** in 80% yield, Scheme 3.7. Some problems with stirring occurred due to the viscosity of the reaction at –30 ° C and the reaction was therefore carried out at higher dilution when compared to the literature procedure.



Scheme 3.7: Synthesis of known hydroxy ester **3.16**.

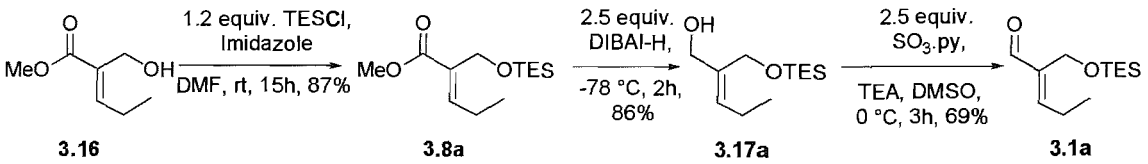
Deprotection of the *m*-nitrobenzoate group was carried out in the presence of 0.1 equivalent of potassium carbonate in methanol at 0 °C, giving **3.16** in 86% yield. A reaction using 1.2 equivalents of *p*-nitrobenzoic acid and di*iso*propylazodicarboxylate again gave similar yields to those attained in the literature procedure, Scheme 3.7. The inversion step gave **3.7a** in 83% yield and the deprotection resulted in **3.16** in 90% yield.

For large-scale reactions, considerable amounts of triphenylphosphine oxide are produced. Trimethylsilyl trifluoromethanesulfonate and acetic anhydride have been used with aromatic aldehydes,[43] yielding the desired inversion and reducing the amount of waste. The procedure also allows deprotection to be carried out in a one-pot procedure, thereby increasing time efficiency. However these conditions were unsuccessful with propionaldehyde.

Having successfully produced hydroxy-ester **3.16**, the next step involved the synthesis of the aldehyde substrates for the Nagao acetate-aldol reaction. The proximity of the alcohol functionality to the reacting centre in this vital step was of concern when choosing its protecting group. To ensure the optimum conditions for the Nagao acetate-aldol reaction, reactions were planned with a range of protecting groups in place.

The protection of **3.16** as a triethylsilyl ether, Scheme 3.8, was carried out by stirring with 1.2 equivalents of triethysilyl chloride with imidazole overnight,[34] giving **3.8a** in 87% yield.

The reduction of **3.8a** using di*iso*butyl aluminium hydride was carried out at –78 °C for 2 hours. Initially, it was hoped to produce the aldehyde **3.1a** in one step, using 1.4 equivalents of di*iso*butyl aluminium hydride, added drop-wise over 15 minutes. The reaction yielded 56% of the alcohol **3.17a** and the remaining starting material was recovered. Using 2.5 equivalents of di*iso*butyl aluminium hydride produced the alcohol **3.17a** in 86% yield, again with remaining starting material returned.



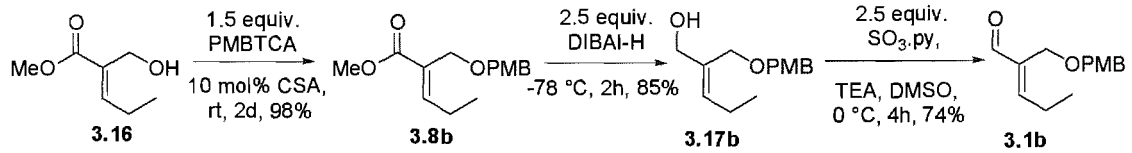
Scheme 3.8: Conversion to aldehyde **3.1a**.

A well-known method for the oxidation of allylic alcohols uses manganese(IV) oxide in DCM.[44] Using 20 equivalents of manganese(IV) oxide added in portions over 24 hours and stirring for 3 days at room temperature gave **3.1a** in 36% yield (63% of starting material was regained); stirring for 7 days in total produced **3.1a** in 82% yield. However, for a large-scale synthesis, such a long reaction time is undesirable. The reaction was carried out with sonication in the hope of improving the reaction time. Initially, sonication for 15 minutes yielded 48% of **3.1a** with 47% of the starting material regained. Some deconjugation of the product occurred. Sonicating for 45 minutes produced **3.1a** in a lower yield, 46%, with just 6% of starting material regained with a large proportion of the deconjugated product. Lastly, sonicating for 12 minutes produced **3.1a** in a yield of 30% with 32% of starting material regained. With these reactions showing limited scope with our system, further conditions were therefore investigated.

Using 1.0 equivalent of IBX reagent in dimethylsulfoxide,[45] stirring for 3 hours gave **3.1a** in a poor (16%) yield, again returning starting material (34%). A Swern oxidation[46] failed, giving polar side products, which were inseparable. None of the required aldehyde was observed and no starting material was regained. Next, an oxidation using TEMPO[47] was tried. Stirring **3.17a** with trichloro*iso*cyanuric acid, followed by TEMPO addition, resulted in removal of the triethylsilyl protection. Stirring alcohol **3.17a** with TEMPO and then adding the trichloro*iso*cyanuric acid gave a 22% yield of aldehyde **3.1a**. Oxidations using 0.05 equivalents of TPAP and 3 equivalents of NMO[48] produced **3.1a** in 50% yield, after stirring at room temperature for 3 hours. The Parik-Doering conditions[49] proved to be the most successful with the present system, however. Oxidation was carried out with 2.5 equivalents of sulfur trioxide/pyridine complex, and **3.1a** was obtained in 69% yield after

stirring at 0 °C for 4 hours. This gave access to the primary synthetic target in 36% overall yield from methyl acrylate and propionaldehyde.

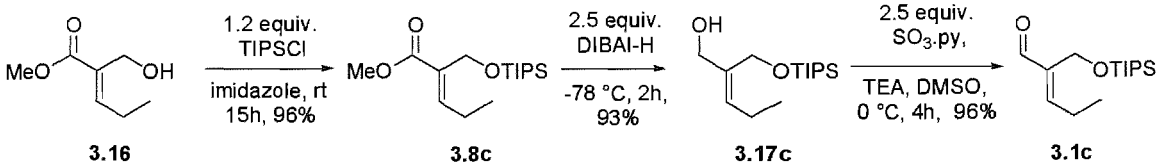
Protection as a *p*-methoxy benzyl ether was carried out, Scheme 3.9. Protection of **3.16** using 1.1 equivalents of *p*-methoxybenzyl bromide and sodium hydride was unsuccessful. As could be expected, **3.16** was not stable under the strongly basic reaction conditions.



Scheme 3.9: Synthesis of aldehyde **3.1b**.

Protection of alcohol **3.16** with 1.5 equivalents of *p*-methoxybenzyl trichloroacetimidate in the presence of 10 mol% camphor sulfonic acid[50] gave **3.8b** in 98% yield. Following an identical procedure as for **3.1a**, reduction to the alcohol **3.17b** in 85% yield and subsequent reoxidation gave aldehyde **3.1b** in 74% yield. This gave access to the second aldehyde in 42% overall yield from methyl acrylate and propionaldehyde.

The tri*iso*propysilyl protecting group was the next choice in the search for a suitable protection strategy. Thus, **3.16** was protected using 1.2 equivalents of tri*iso*propylsilyl chloride and imidazole,[34] giving **3.8c** in 96% yield. This was followed by a reduction to **3.17c** in 93% yield. Conversion to the aldehyde using the Parik-Doering conditions gave **3.1c** in 96% yield, Scheme 3.10. This has given access to the third aldehyde in 60% overall yield from methyl acrylate and propionaldehyde.



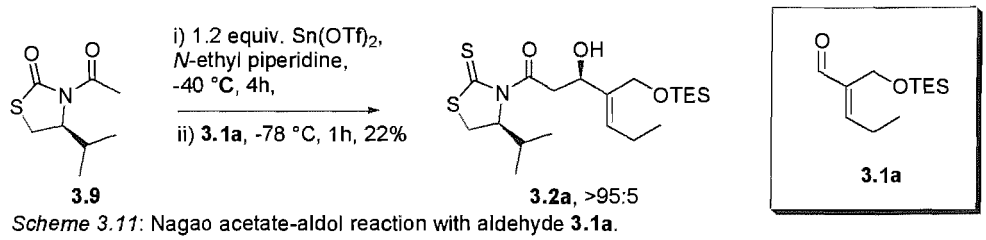
Scheme 3.10: Synthesis of aldehyde **3.1c**.

3.2.4 Optimisation of the Nagao acetate-aldol reaction

a) Establishing the optimal protecting group for **3.1**

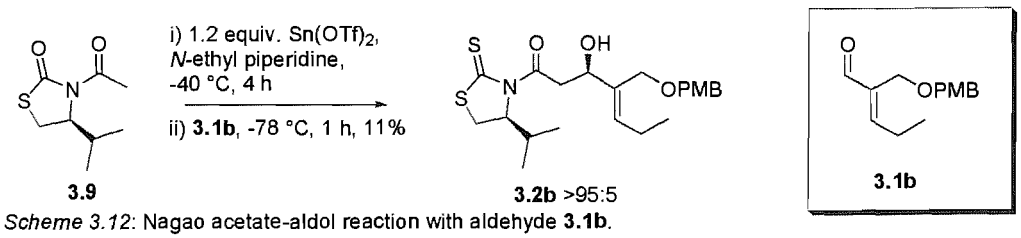
N-Ethylpiperidine was added dropwise to a suspension of $Sn(OTf)_2$ followed by the dropwise addition of a solution of **3.9** in CH_2Cl_2. Enolisation was effected in 4 hours at –40 °C, whereupon the reaction was cooled to –78 °C whereupon a solution **3.1a** in CH_2Cl_2

added drop-wise.[21] The reaction was quenched after 1 hour at –78 °C, giving **3.2a** as a yellow oil in only 22% yield, Scheme 3.11. A single diastereoisomer, predicted by the transition state model in Scheme 3.3, was seen by ^{13}C NMR. Stirring the auxiliary under enolising conditions for a longer period of time had no effect on the yield. Increasing the amount of base to 1.3 equivalents caused silyl deprotection of **3.1a**. The reaction returns aldehyde **3.1a** in 68% yield, and Nagao reagent **3.9** in 57% yield.



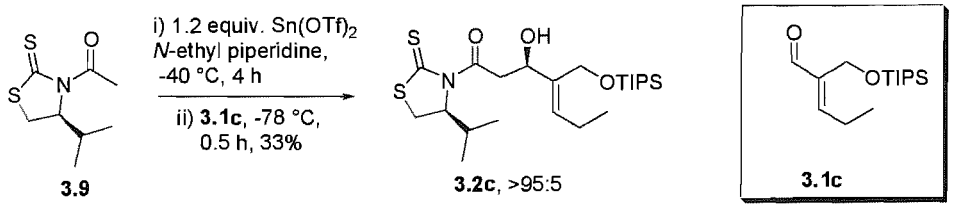
Scheme 3.11: Nagao acetate-aldol reaction with aldehyde **3.1a**.

The Nagao acetate-aldol reaction using **3.1b** also resulted in a poor yield, Scheme 3.12. The best yield of **3.2b** was 11%, a single diastereoisomer, predicted by the transition state model in Scheme 3.3, was seen by ^{13}C NMR. Again, starting materials were isolated as the major components from the reaction, with **3.1b** in 72% yield and **3.9** in 79% yield. Increasing the reaction time did not increase the yield.



Scheme 3.12: Nagao acetate-aldol reaction with aldehyde **3.1b**.

The Nagao acetate-aldol reaction using **3.1c** as the substrate gave **3.2c** in 33% yield, a single diastereoisomer, predicted by the transition state model in Scheme 3.3, was seen by ^{13}C NMR, Scheme 3.13. Aldehyde **3.1c** was recovered in 57% yield and Nagao reagent **3.9** was produced in 56% yield.

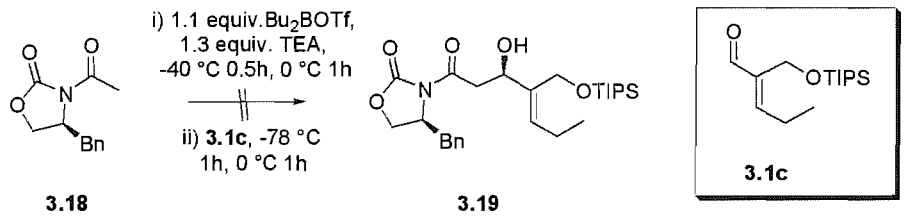


Scheme 3.13: Nagao acetate-aldol reaction with aldehyde **3.1c**.

Increasing the timescale of the reaction step, stirring the enolate and aldehyde at –78 °C for 20 hours, gave **3.2c** in 45% yield. Increasing the temperature of the reaction gave variable yields, although starting materials were always recovered. It should be noted that the product was always a single diastereoisomer, as shown by NMR.

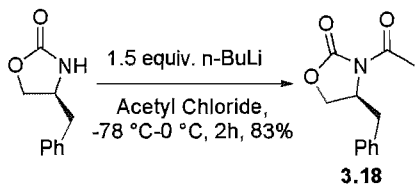
b) Control experiment

In order to establish whether problems with reaction rates of the Nagao acetate aldol reaction were due to the hindered aldehyde, a trial reaction using Evans-type auxiliary **3.18** was carried out, Scheme 3.15. It is known that enolisation is not a problem in this case, as other reactions using boron Lewis acids have been successful in our hands (see Chapter 3, section 3.4.3). The aldol reaction between **3.18** and **3.1c** using standard conditions showed no products, returning only starting materials. This indicates that the hindered nature of the aldehyde is indeed the problem leading to low reaction rates.



Scheme 3.14: Use of oxazolidinone auxiliary and boron Lewis acid.

The acetate-derived oxazolidinone **3.18** was synthesised from (4*S*)-benzyloxazolidione[51] using 1.5 equivalents of *n*-butyl lithium and acetyl chloride in 83% yield, Scheme 3.15.



Scheme 3.15: Synthesis of chiral reagent for Evans acetate-aldol reaction.

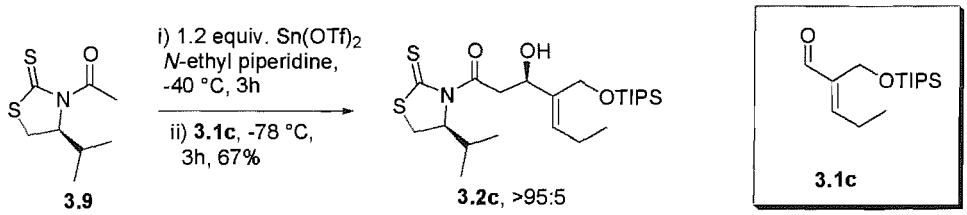
c) Investigating the effect of reactant concentration

An investigation into the effect of reactant concentration was carried out. A series of reactions in which the amount of solvent was reduced was carried out, and the resulting yields correlated to concentration, as summarised in Table 3.2. All reaction conditions were kept constant, with enolisation of **3.11** occurring at –40 °C for 3 hours followed by cooling to –78 °C and reaction with **3.1c** for 3 hours.

Concentration, M	Yield, %
0.27	35
0.4	51
0.58	**67**
0.7	63
0.84	64

Table 3.2: The effect of concentration on the yield of the Nagao acetate-aldol reaction.

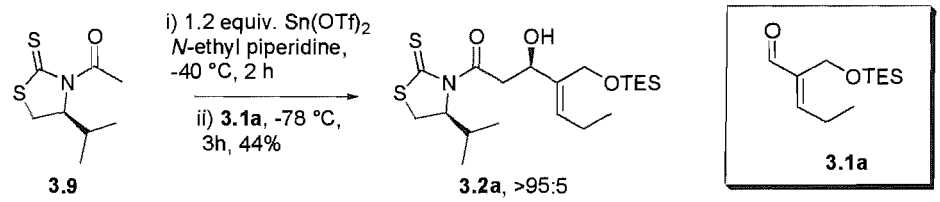
Increasing the concentration produced the desired product as a single diastereoisomer, with isolated yields consistently in the mid-sixtieth percentile. The highest yield of 67% was from a Nagao acetate-aldol reaction carried out at 0.6M, Scheme 3.16. The increase in concentration gave no visible signs of a reduction in stereoselectivity, with a single diastereoisomer visible in the ^{13}C NMR spectrum.



Scheme 3.16: Optimised Nagao acetate-aldol reaction with aldehyde **3.1c**.

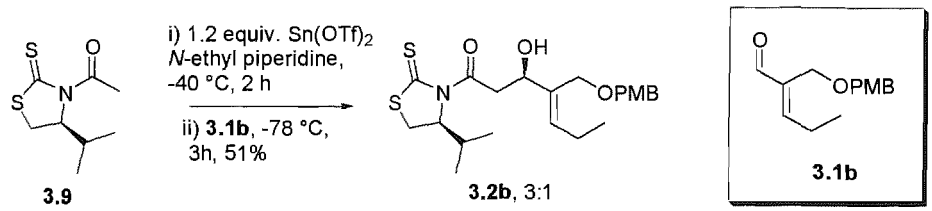
d) Application of optimal Nagao acetate-aldol conditions to aldehydes **3.1a** and **3.1b**

Nagao acetate-aldol reactions using the optimised conditions were carried out with the other protected aldehydes. The triethylsilyl protected aldehyde **3.1a** produced the desired product **3.2a** in 44% yield, Scheme 3.17. This product was isolated as a single diastereoisomer (determined by NMR).



Scheme 3.17: Optimised Nagao acetate-aldol reaction with aldehyde **3.1a**.

The *p*-methoxybenzyl protected aldehyde **3.1b** produced the desired product **3.2b** in 51% yield, Scheme 3.18, although a mixture of diastereoisomers was seen (3:1 ratio based on isolated yields after HPLC).



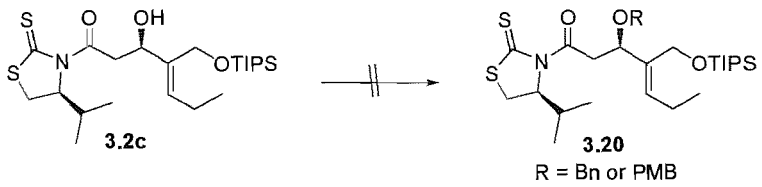
Scheme 3.18: Optimised Nagao acetate-aldol reaction with aldehyde **3.1b**.

These results show that tri*iso*propylsilyl protection in the aldehyde produces the best yields and stereoselectivity in the acetate aldol reaction.

3.3 Conversion to the aldehyde substrate for the Evans aldol reaction

3.3.1 Orthogonal protection of **3.2c**

An optimal synthetic strategy requires orthogonal protection of the free secondary alcohol in **3.2c** (as discussed in Chapter 1). With a tri*iso*propylsilyl ether protecting the primary alcohol, protection of the secondary alcohol as a benzyl ether is an obvious choice.



Scheme 3.19: Benzylation of Nagao product **3.2c**.

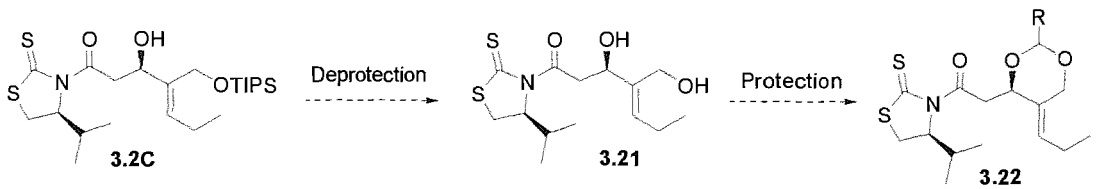
It is known that basic conditions can lead to retro aldol reactions, and acid catalysed reactions using trichloroacetimidates were therefore proposed. The reaction between benzyl trichloroacetimidate and **3.2c** was catalysed by 10 mol% triflic acid,[50] giving a complex mixture of products. None of the desired product was observed and **3.2c** was not returned. 5 Mol % triflic acid also proved to be too concentrated, resulting in another complex mixture, whereas 1 mol % triflic acid was not concentrated enough and returned starting material. Using 10 mol% camphor sulfonic acid catalyst returned **3.2c**, which is not surprising, as benzyl trichloroacetimidate is less reactive than *p*-methoxybenzyl trichloroacetimidate for which protections have been shown to be successful in the presence of this mild acid.[50]

Protections using *p*-methoxybenzyl trichloroacetimidate and 10 mol% camphor sulfonic acid[50] were carried out, again with a complex mixture of products resulting, and **3.2c** was

not returned. A protection using 5 mol% Sc(III) trifluoromethanesulfonate and 1.5 equivalents of *p*-methoxybenzyl trichloroacetimidate[52] was unsuccessful, returning starting material.

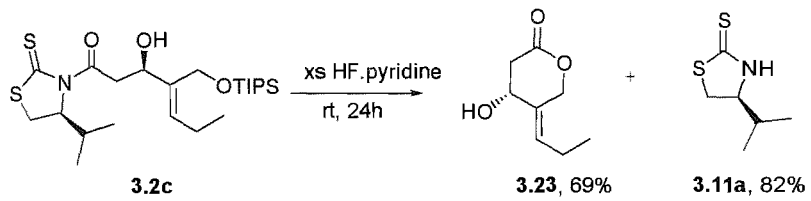
3.3.2 Silyl deprotection of **3.2c**

With orthogonal protections unsuccessful, the removal of the silyl protection from **3.2c** to produce the 1,3-diol **3.21** was considered. This would allow formation of a cyclic acetal, Scheme 3.20. Formation of the 1,3-dioxolane would create a rigid 6-membered ring structure which was envisaged as a suitable substrate for the epoxidation step.



Scheme 3.20: Proposed route towards a substrate for epoxidation.

Upon removal of the silyl protection in **3.2c**, the lactone **3.23** was exclusively produced. When tetrabutyl ammonium fluoride[53] at 0 °C was used, **3.23** was produced in 46% yield with 8% of auxiliary **3.11a**. At room temperature, auxiliary **3.11a** was isolated in 83% yield with 35% of lactone **3.23**. Increasing the temperature to 50 °C, produced **3.23** in 18% yield with just 23% of **3.11a**. The use of 2.5 equivalents of tris(dimethylamino)sulfur (trimethylsilyl)dilfluoride[54] produced only **3.11a** in 55% yield with no other products isolated. An excess of hydrogen fluoride in pyridine[55] gave **3.23** in 69% yield, returning 82% of **3.11a**, Scheme 3.21. Using acetic acid, THF and water (3:1:1) gave 12% of **3.11a** and 31% of **3.23**.



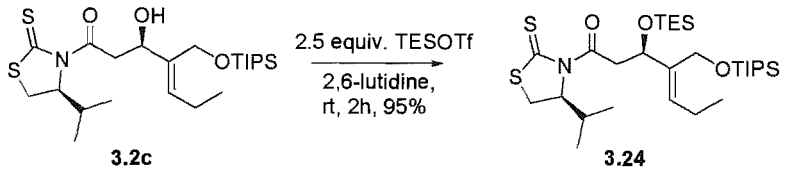
Scheme 3.21: Silyl deprotection giving lactone **3.23**.

The deprotection of compounds similar to **3.2c** is known to give cyclic ester products even when using oxazolidinone auxiliaries.[56] Analysis of **3.23** showed that the allylic alcohol is in an axial orientation. While the lactone route may prove useful synthetically in

a directed epoxidation reaction, it is expected that the reduction of the lactone and subsequent ring opening steps will be problematic in the presence of the sensitive epoxide.

3.3.3 Protection of **3.2c** as a triethylsilyl ether

Protection as a silyl ether would allow a single deprotection step later in the synthesis and the possibility of accessing the 1,3-dioxolane, as discussed above. A protection was carried out using 2.5 equivalents of triethylsilyl trifluromethane sulfonate in the presence of 3 equivalents of 2,6-lutidine[57] giving **3.24** in 95% yield, Scheme 3.22.

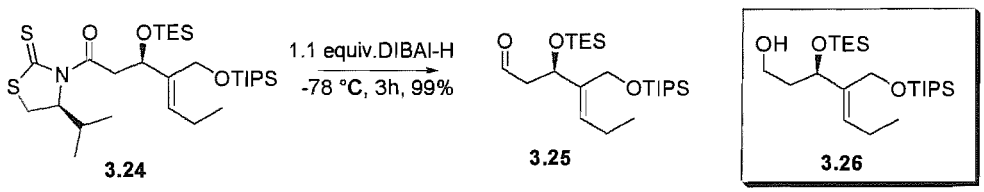


3.2c **3.24**

Scheme 3.22: Silyl protection of Nagao product **3.2c**.

3.3.4 Synthesis of aldehyde **3.25**

Having obtained **3.24** on large scale, it was then necessary to access the desired aldehyde for the Evans *syn*-aldol reaction to complete the stereochemical framework required in luminacin D. Nagao product **3.24** was reduced using 1.1 equivalents of di*iso*butylaluminium hydride[58] giving the desired aldehyde **3.25** in 99% yield, Scheme 3.23. Traces of **3.24** have been encountered in larger scale synthesis (3 mmol). The use of 2.5 equivalents of di*iso*butylaluminium hydride directly gave pure **3.25** in 82% yield, without over-reduction to **3.26**.



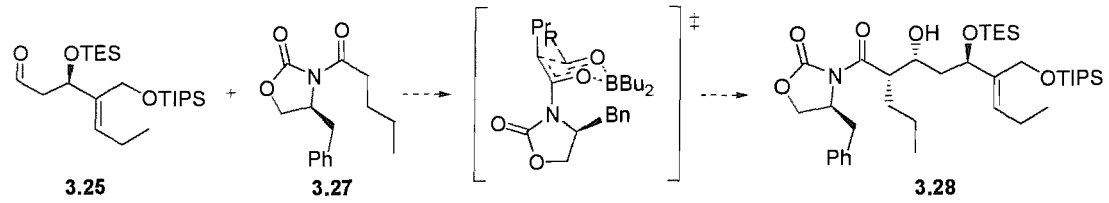
3.24 **3.25** **3.26**

Scheme 3.23: Reduction of **3.24** to give aldehyde for Evans aldol reaction.

3.4 The Evans *syn*-aldol reaction

3.4.1 Introduction

The Evans *syn*-aldol reaction would allow installation of the next two stereocentres for the synthesis of luminacin D. These reactions use acylated oxazolidinone auxiliaries, such as **3.27**. With 1.1 equivalents of Bu_2BOTf they form the *Z*-enolate exclusively,[16] allowing *syn*-selective reactions with the aldehyde, Scheme 3.24. These reactions are also sensitive to the stoichiometry of reagents used. Optimal conditions using 1.1 equivalents of Bu_2BOTf and 1.3 equivalents of TEA typically produce yields in the mid-ninetieth percentile with de's of similar values.[59]

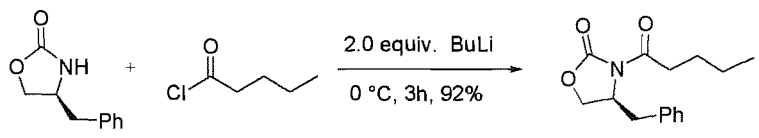


3.25 **3.27** **3.28**

Scheme 3.24: Proposed Evans aldol reaction with **3.25**.

3.4.2 Synthesis of the acylated auxiliary

For the proposed synthesis, the chiral reagent **3.27** is required, and this can be accessed in a simple acylation reaction from commercially available auxiliaries.[51] The acylation of (4*S*)-benzyl oxazolidinone was therefore carried out following the literature procedure using 2.0 equivalents of *n*-butyl lithium and valeroyl chloride to give **3.27** in 92% yield, Scheme 3.25.

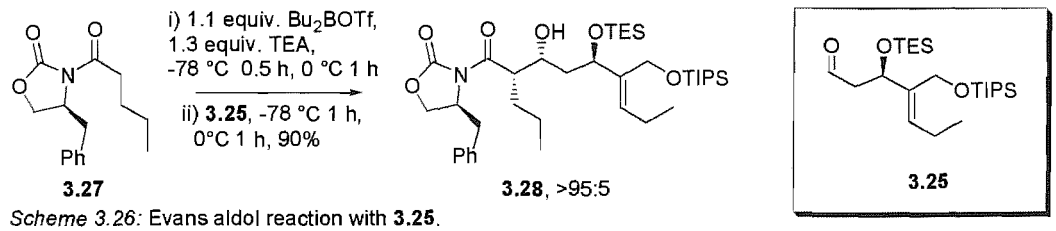


3.27

Scheme 3.25: Synthesis of chiral reagent for Evans *syn*-aldol reaction.

3.4.3 The Evans *syn*-aldol reaction

The Evans aldol reaction using 1.1 equivalents of Bu_2BOTf and 1.3 equivalents of TEA[60] produced **3.28** in 90% yield, as a single diastereoisomer, predicted by the transition state model in Scheme 3.24, was seen by ^{13}C NMR, Scheme 3.26.

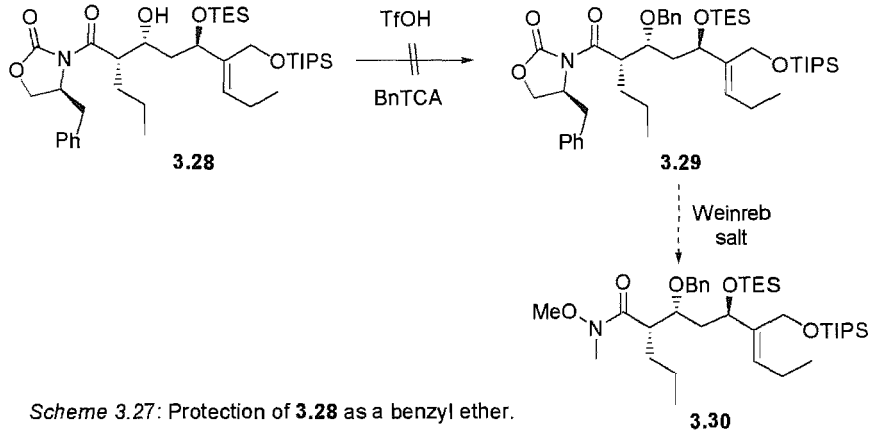


Scheme 3.26: Evans aldol reaction with **3.25**.

3.5 Further manipulation

3.5.1 Orthogonal protection of secondary alcohol in **3.28**

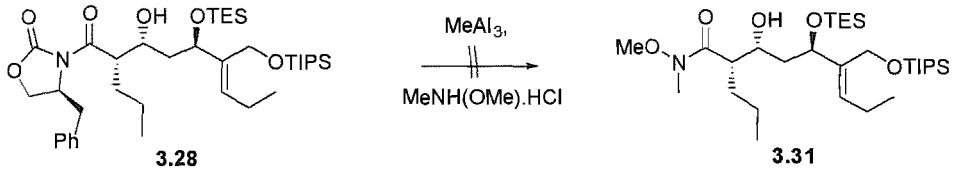
Orthogonal protection is desired for the free secondary alcohol in **3.28**, and a benzyl group was chosen for this purpose. Conversion into the Weinreb amide **3.30**, Scheme 3.27, would allow our chosen coupling/epoxidation sequence.



Scheme 3.27: Protection of **3.28** as a benzyl ether.

Using benzyltrichloroacetimidate and triflic acid[50] catalyst loadings ranging from 5 mol % to 2 mol % were unsuccessful. No benzylated product **3.28** was seen and starting material was lost in all cases.

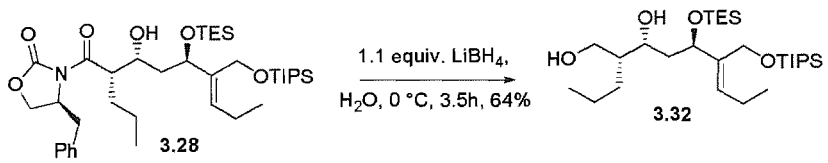
Conversion directly to the Weinreb amide **3.31** was attempted using trimethyl aluminium and Weinreb salt,[61] Scheme 3.28. It was hoped to carry out a selective protection after this well-known transformation. Various conditions were used, ranging from 18 °C for 16 hours to 0 °C for 2 or 4 hours. All reactions gave a complex mixture of products from which neither starting material nor desired product was seen.



Scheme 3.28: Formation of the Weinreb amide **3.31**.

3.5.2 Reductive removal of auxiliary from **3.28**

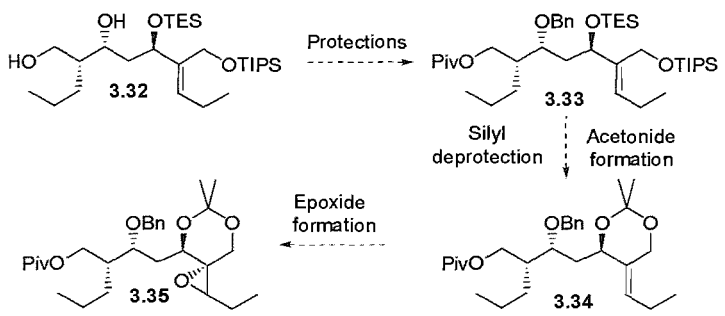
Following the lack of success in manipulating **3.28** it was decided to reductively remove the auxiliary giving 1,3-diol **3.32**. The reduction has been carried out smoothly using 1.0 equivalents of lithium borohydride,[22] giving **3.32** in 94% yield, Scheme 3.29. With removal of the carbonyl functionality α to the propyl group, the risk of epimerisation in **3.32** is minimal when compared to **3.27**, maintaining the integrity of the selectively introduced stereocentres.



Scheme 3.29: Reduction of **3.28** to the 1,3-diol.

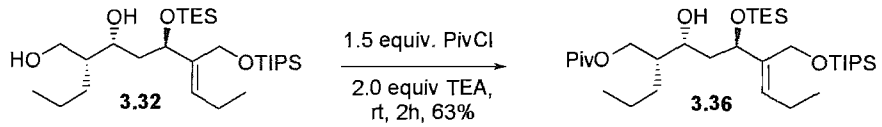
3.5.3 Protection of 1,3-diol **3.32**

The next steps in the synthesis towards dioxolane **1.34** are outlined in Scheme 3.30. A selective protection of the primary alcohol in **3.32** is desired. The aim was to introduce a pivaloyl group to the primary alcohol and to protect the secondary alcohol as a benzyl ether, giving **3.33**. Then the two silyl ethers will be removed, allowing formation of acetal **3.34**. A selective epoxidation should then be possible giving **3.35**. Upon obtaining epoxide **3.35**, the pivaloyl protection can be removed and an oxidation of the resulting primary alcohol will give a fragment suitable for the coupling reaction.



Scheme 3.30: Proposed protection strategy and route towards selective epoxidation

Protection of the primary alcohol in **3.32** as the pivaloate ester[62] has been carried out, Scheme 3.31. The reaction was carried out initially at 0 °C using 1.5 equivalents of trimethylacetyl chloride and 2.0 equivents of TEA, due to concerns about protecting the secondary alcohol. This resulted in 51% of **3.36** being produced, with 31% of **3.32** returned. The reaction was then carried out at room temperature for 2 hours giving **3.36** in 63% yield. An apolar side product (which was not bis-protected) was seen, but characterisation was not possible. Reducing the amount of trimethylacetyl chloride caused starting material to be returned and increasing reaction time caused a degradation of the reaction.



Scheme 3.31: Protection of primary alcohol in **3.32** as a pivaloate ester.

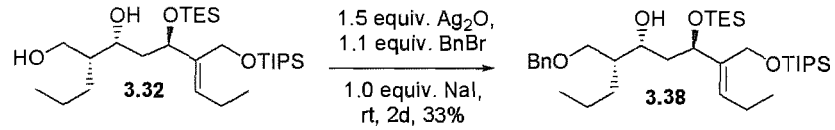
Protection of the secondary alcohol in **3.36** as a benzyl ether, Scheme 3.32, has proven to be problematic. Protections using 2 mol% triflic acid with benzyl trichloroacetimidate[50] and those using sodium hydride with benzyl bromide were unsuccessful.

Scheme 3.32: Protection of **3.36** as a benzyl ether.

Protection of the primary alcohol in **3.32** as a benzyl ether was then investigated. Both acidic and basic methods for the introduction of a benzyl group would cause problems for this highly functionalised fragment.

A neutral method using dibutyltin oxide is known to selectively protect primary alcohols.[63] However, this procedure was unsuccessful in our hands. The reaction mixture was refluxed in toluene for 3 days, with only starting material returned and no product seen. Increasing the reaction time to 6 days caused degradation of the starting material, and no product was isolated.

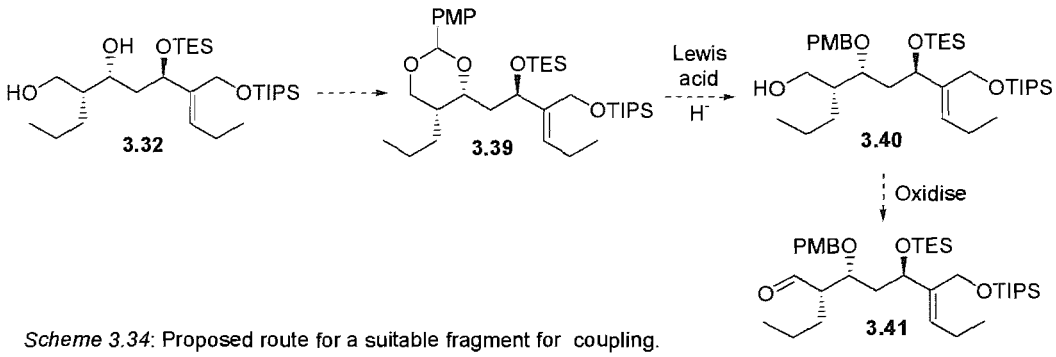
The use of silver oxide[64 65] has been more promising. Stirring at room temperature for 48 hours with benzyl bromide and sodium iodide gave **3.38** in 33% yield, Scheme 3.33.



Scheme 3.33: Protection of primary alcohol in **3.32** as a benzyl ether.

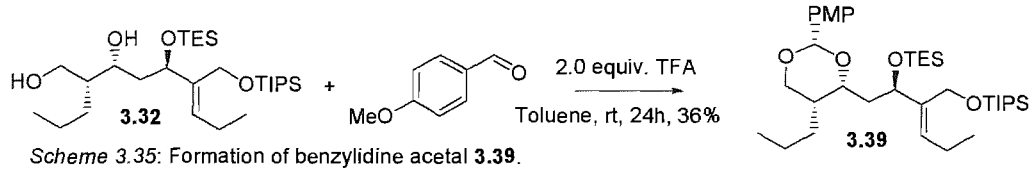
Attempts to optimise this reaction met with limited success. Changing the solvent showed that DMF is better than CH_2Cl_2 or toluene. However the yields of product in these parallel experiments were lower due to a change in iodide source, from sodium iodide to potassium iodide (which is more generally used). When using DMF and potassium iodide **3.38** was isolated in 25% yield. When using toluene as solvent, no reaction occurred, and when using CH_2Cl_2 a yield of 17% was achieved. Tetrabutylammonium iodide has also been used, but is a poor catalyst, resulting in a 10% reduction in yield. Heating the reaction to 50 °C overnight in DMF caused breakdown of the starting material and no product was isolated.

With increasing problems in the protection strategy, a route involving formation of the benzylidene acetal was conceived, scheme 3.34. Formation of **3.39** followed by reduction would enable access to the primary alcohol **3.40**. Formation of aldehyde **3.41** would allow coupling to the aromatic fragment.



Scheme 3.34: Proposed route for a suitable fragment for coupling.

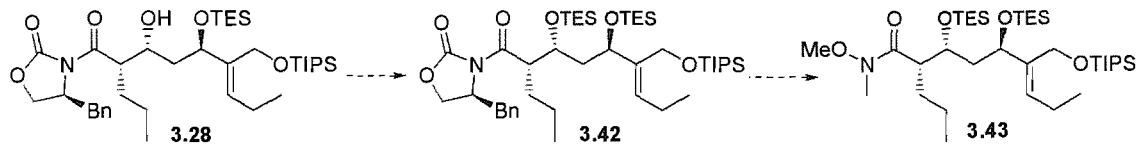
Several conditions were investigated to access **3.39**, with limited success. Mono *p*-methoxybenzylation of **3.32**, followed by reaction with DDQ would give **3.39**. A reaction using 5 mol% Sc(III) trifluoromethanesulfonate and 1.5 equivalents of *p*-methoxy benzyltrichloroacetimidate[52] failed, but starting material was not returned. Formation of the acetal directly using 5 equivalents of *p*-anisaldehyde dimethyl acetal in the presence of 0.1 equivalents of *p*-toluenesulfonic acid[66] returned **3.32**. The use of 2 equivalents of *p*-anisaldehyde and trifluoroacetic acid gave **3.39** in 36% yield, with no starting material returned after 24 hours at room temperature, Scheme 3.35.



Scheme 3.35: Formation of benzylidine acetal **3.39**.

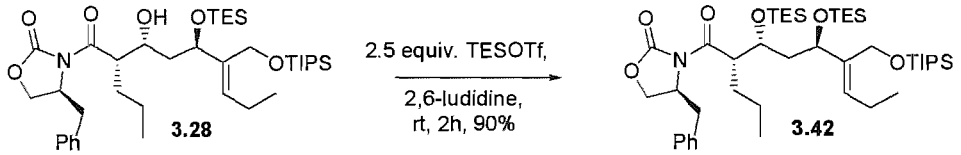
3.5.4 Silyl protection of **3.28**

Triethylsilyl protection of **3.28** was envisaged, as in Scheme 3.36. Transformation to the Weinreb amide **3.43** would allow coupling to our aromatic fragment.



Scheme 3.36: Proposed Tri silylated fragment for coupling.

A protection using 2.5 equivalents of triethylsilyl trifluoromethanesulfonate and 2,6-lutidine[57] was carried out giving **3.42** in 90% yield, Scheme 3.37.



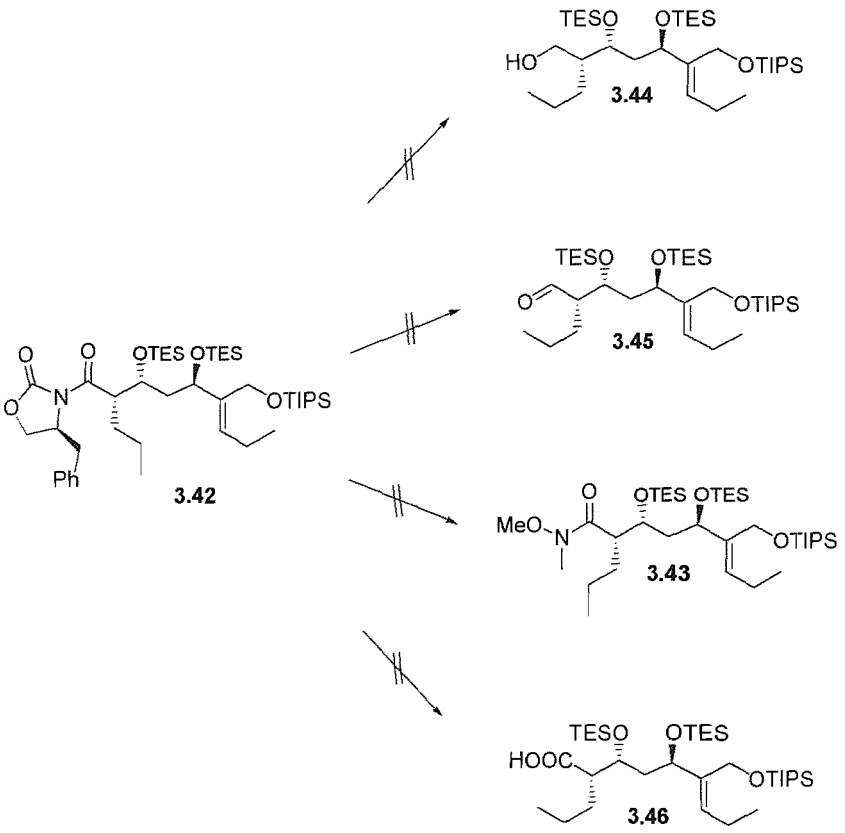
Scheme 3.37: Protection of **3.28** as a triethylsilyl ether.

3.5.5 Reductive removal of auxiliary from **3.42**

To gain access to an appropriate fragment for coupling, reducing conditions were applied to **3.42**. Access to the alcohol **3.44**, aldehyde **3.45**, Weinreb amide **3.43** or carboxylic acid **3.46** is desired, Scheme 3.38.

Access to alcohol **3.44** would be achieved through the use of 4 equivalents of sodium borohydride or lithium borohydride and water; however, application of these reducing agents was unsuccessful and starting materials were returned. The use of 1.0 equivalent of lithium aluminium hydride caused reaction degradation, with no starting materials returned. The use of 2.5 equivalents of di*iso*butylaluminium hydride[58] to give aldehyde **3.45** was also unsuccessful returning starting material. Formation of the Weinreb amide[58] **3.43** using 3.0 equivalents of Weinreb salt and trimethylaluminium also returned starting

material. Formation of carboxylic acid[58] **3.46** using 10 equivalents of aqueous hydrogen peroxide and 2.0 equivalents of lithium hydroxide returned starting material.



Scheme 3.38: Manipulation of protected Evans aldol product **3.42**.

3.6 Summary

Synthesis of the aldehyde substrate for the Nagao acetate-aldol reaction has been carried out smoothly in 6 steps from propionaldehyde and methyl acrylate. Three different protecting groups have been used. With triethylsilyl protection the aldehyde was obtained in 36% overall yield; with *p*-methoxybenzyl protection the aldehyde was synthesised in 42% overall yield; and with tri*iso*propyl protection the aldehyde was produced in 60% overall yield. The Nagao acetate aldol reaction has been extensively investigated. The concentration of the reagents was increased relative to the literature procedure, and when using tri*iso*propyl protected aldehyde, product was isolated in 67% yield as a single stereoisomer. Application of the optimised conditions to aldehyde with *p*-methoxybenzyl protection gave a mixture of diastereomers in 51% yield. The use of aldehyde with triethylsilyl protection gave the Nagao product in a reduced 44% yield, with the product

again isolated as a single diastereomer.

Orthogonal protection of the resulting secondary alcohol proved problematic, although silyl protection proceeded in good 95% yield. Transformation to aldehyde for the Evans aldol reaction proceeded smoothly in 82% yield. The Evans aldol reaction, mediated by Bu_2BOTf, gave a single stereoisomer in 90% yield.

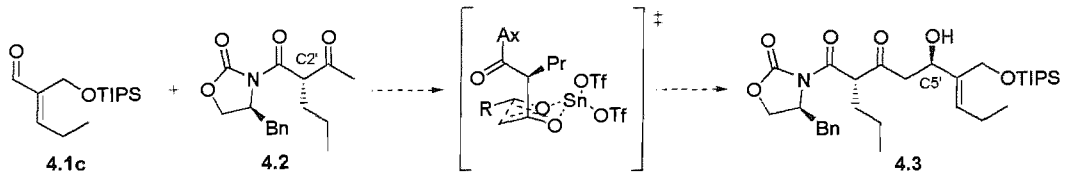
Protection of the secondary alcohol in the Evans aldol product also proved difficult, although reductive removal of the chiral auxiliary gave the1,3-diol in 94% yield. Protection of the free primary alcohol within this 1,3-diol as a pivaloyl ester has been carried out in 63% yield, but protection of the secondary alcohol was not possible. Protection of the 1,3-diol as a benzylidene acetal was unsuccessful.

Protection of the secondary alcohol in the Evans aldol product as a silyl ether was carried out smoothly in 90% yield. Further conversion to a fragment for coupling has not been possible.

Chapter 4: Aliphatic fragment synthesis: β-ketoimide methodology

4.1 Introduction

The β-ketoimide derivatives of Evans-type auxiliaries have a 1,3-dicarbonyl stereogenic centre (C2'), which is not susceptible to racemisation.[24] Aldol reactions with α,β-unsaturated aldehydes, such as **4.1c**, are known to be highly selective when using propionoate derived reagents with typical yields and de's in the ninetieth percentile. However the stereochemical outcome of the acetate aldol is unprecedented. The stereocontrol in the β-ketoimide aldol reaction originates from the orientation of the alkyl group, with the chiral auxiliary having minimal effect.



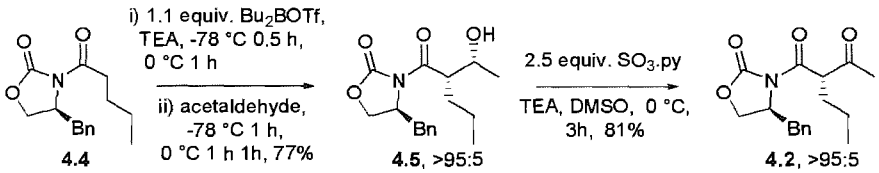
4.1c **4.2** **4.3**

Scheme 4.1: Synthesis of aliphatic fragment through beta-ketoimide aldol methodology.

With the absolute stereochemistry of luminacin D now established, the Sn(II) mediated β-ketoimide aldol reaction with reagent **4.2** will be used to give access to derivative **4.3** with the desired stereochemistry at C5', Scheme 4.1.

4.2 Synthesis of the acetate β-ketoimide substrate

Synthesis of the acetate β-ketoimide reagent **4.2** was from commercially available (4*S*)-benzyl oxazolidinone, following the protocol used by Evans[25,59] for the propionoate derived reagents. Acylation using valeroyl chloride gave **4.4** which underwent an Evans *syn*-aldol reaction with acetaldehyde using 1.1 equivalents of Bu_2BOTf and 1.3 equivalents of TEA giving **4.5** in 77% yield, Scheme 4.2. The resulting free alcohol underwent an oxidation using the Parik-Doering conditions, giving β-ketoimide **4.2** in 81% yield. Overall yield from (4*S*)-benzyl oxazolidinone was 57%.



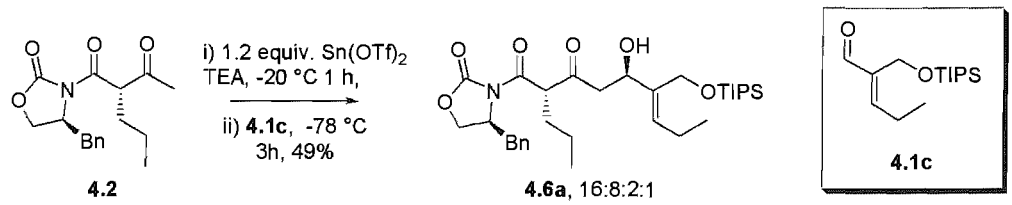
4.4 **4.5**, >95:5 **4.2**, >95:5

Scheme 4.2: Synthesis of chiral reagent for acetate beta-ketoimide aldol.

4.3 Tin mediated acetate β-ketoimide aldol reaction

4.3.1 The effect of concentration

The β-ketoimide aldol reaction between **4.2** and **4.1c** was carried out using 1.2 equivalents of $Sn(OTf)_2$/TEA, Scheme 4.3. The hindered nature of the α,β-unsaturated aldehyde caused problems with reaction rate and optimisation of concentration was required.



4.2 **4.6a**, 16:8:2:1

Scheme 4.3: Tin mediated acetate beta-ketoimide aldol reaction with aldehyde **4.1c**.

Initial work on increasing the reaction concentration was carried out, as shown in Table 4.1. Enolisation of **4.2** was effected at −20 °C for 1 hour, followed by reaction with **4.1c** at −78 °C for 3 hours. The increase in yield seen by increasing the concentration shows a similar trend to those seen with the Nagao acetate-aldol reaction.

Concentration, M	Yield, %
0.32	41
0.22	**49**
0.13	31
0.07	7

Table 4.1: The effect of concentration on the yield of the acetate β-ketoimide aldol reaction.

The optimum concentration of 0.2M gave **4.6a** in 49% yield as a mixture of 4 inseparable components (in the ratio 16:8:2:1). These 4 components are seen from the expansion of alkene CH signal (expected to be a triplet) in the ^{1}H NMR spectrum, Figure 4.1. The spectrum comprises a series of overlapping triplets, with the major component predicted by the transition state model in Scheme 4.1. Here, it is proposed that the second component is the C5' diastereomer and the minor components may result from alkene isomerisation, though this cannot be definitively proven as the diastereomeric mixture has not been separated.

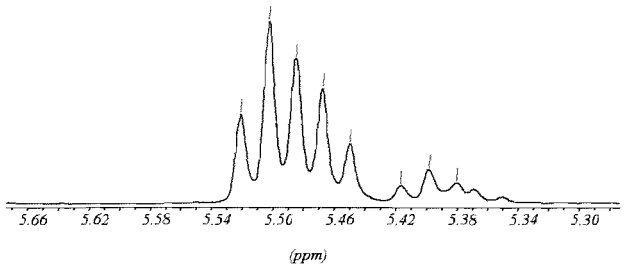
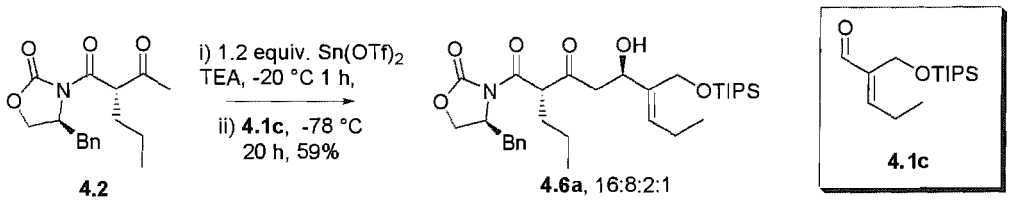


Figure 4.1: Expansion of the alkene CH proton NMR spectrum of **4.6a**, indicating the presence of 4 components.

4.3.2 Increasing reaction time

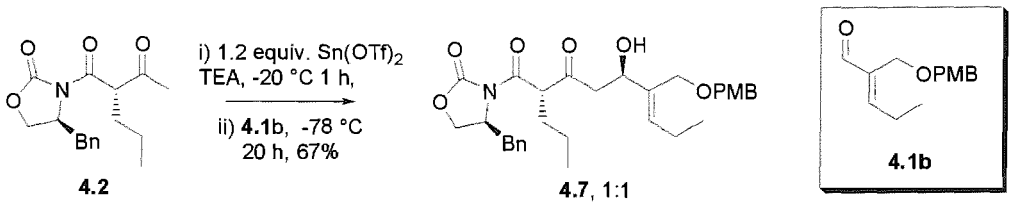
The reaction time at this optimal concentration was increased from 3 hours to 20 hours, giving **4.6a** in a yield of 59%, again as a mixture of inseparable components in the same ratio (16:8:2:1), Scheme 4.4.



Scheme 4.4: Oprimised tin mediated acetate beta-ketoimide aldol reaction with aldehyde **4.1c**.

4.3.3 β-Ketoimide aldol reaction with **4.1b**

Access to a single diastereoisomer from the acetate β-ketoimide aldol reaction was desired. A reaction between aldehyde **4.1b** and chiral reagent **4.2** was carried out at the optimised conditions, giving **4.7** in 67% isolated yield, Scheme 4.5. However, **4.7** was isolated as an inseparable 1:1 mixture of diastereoisomers, as seen in the expansion of the alkene CH signal in the 1H NMR spectrum, Figure 4.2.



Scheme 4.5: Tin mediated acetate beta-ketoimide aldol reaction with aldehyde **4.1b**.

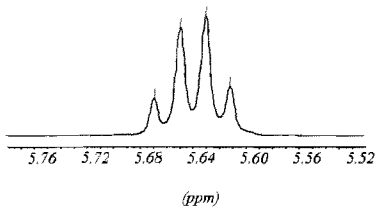
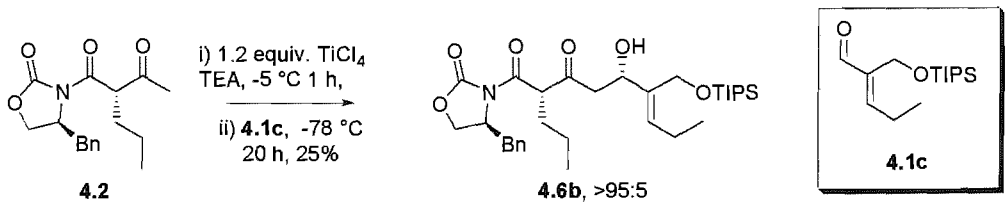


Figure 4.2: Expansion of the alkene CH proton NMR spectrum of **4.7**, indicating the presence of 2 components.

4.4 Further investigation of the acetate β-ketoimide aldol reaction

4.4.1 Titanium mediated β-ketoimide aldol reaction

Results for the acetate β-ketoimide aldol reaction using Sn(II) were disappointing, with poor yields and selectivity. It was anticipated that using Ti(IV) may reduce the selectivity and rate problems. A reaction was therefore carried out between **4.2** and **4.1c** using Ti(IV), which was expected from transistion state models to give the opposite C5' diastereomer, Scheme 4.6.



Scheme 4.6: Titanium mediated acetate beta-ketoimide aldol reaction with aldehyde **4.1c**.

Using the optimal reaction conditions (above), **4.6b** was isolated in 25% yield, as a single stereoisomer according to Scheme 4.6, however the stereochemical outcome has not been proven. This can be seen from the expansion of the alkene CH signal in the proton NMR spectrum shown in Figure 4.3. The chemical shift of the alkene proton in **4.6b** matches that of one of the triplets in **4.6a**. This suggests that the bulky nature of the aldehyde may cause reaction rate problems. Selectivity of the acetate derived β-ketoimide-aldol reaction is improved when using Ti(IV), but conversion is poor.

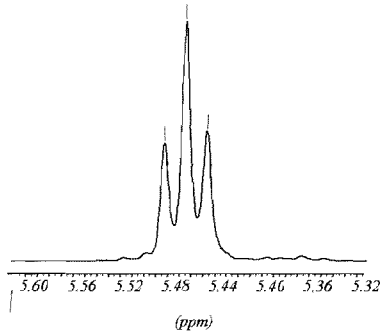
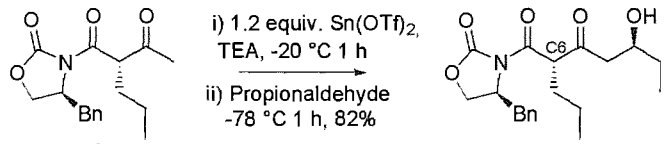


Figure 4.3: Expansion of the alkene CH proton NMR spectrum of **4.6b**, showing >95% diastereoisomeric purity.

4.4.2 Acetate β-ketoimide aldol reactions with propionaldehyde

In order to establish that the bulky aldehyde is indeed the cause of poor yields, analogous reactions were carried out with propionaldehyde. A reaction was carried out mediated by 1.2 equivalents of $Sn(OTf)_2$ and TEA, giving **4.8** in 82% yield, Scheme 4.7. The reaction rate with this unhindered aldehyde is much faster, and the reaction was complete in 2 hours. The product was isolated as a 3.4:1 ratio of diastereoisomers, Figure 4.4. Increasing the reaction time to 20 hours reduced the selectivity to 1.5:1. This indicates that the long reaction time necessary when using the bulky aldehyde contributes to the reduced selectivity in the acetate β-ketoimide aldol reaction with **4.1c**.



4.2 **4.8**, 3.4:1

Scheme 4.7: Tin mediated acetate beta-ketoimide aldol reaction with propionaldehyde.

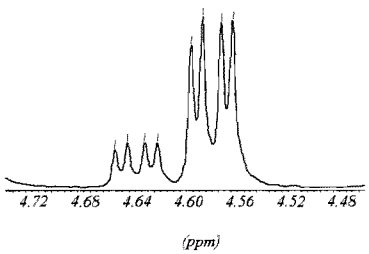
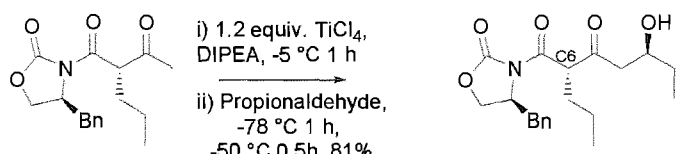


Figure 4.4: Expansion of the C6 proton NMR spectrum of **4.8** from tin mediated reaction, indicating the presence of 2 components.

The analogous reaction using 1.2 equivalents of $TiCl_4$ and DIPEA gave **4.8** in 81% yield, Scheme 4.8. The product was isolated as a 6.5:1 ratio of diastereoisomers, Figure 4.5. This ratio is improved when compared to Sn(II), confirming that Ti(IV) mediated reactions are more selective (potentially due to degradation of the tin reagent). However, the same C3 epimer was the major component when using both Sn(II) and Ti(IV).



4.2 **4.8**, 6.5:1

Scheme 4.8 Titanium mediated acetate beta-ketoimide aldol condensation with propionaldehyde.

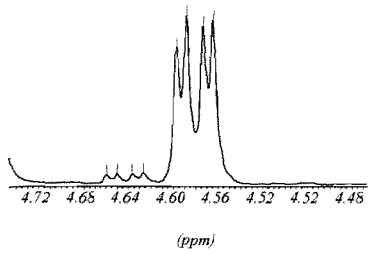
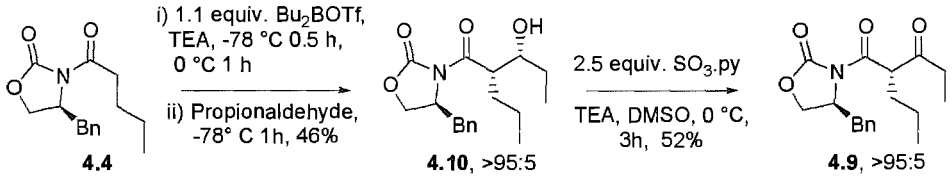


Figure 4.5: Expansion of the C6 proton NMR spectrum of **4.8** from titanium mediated reaction, indicating the presence of 2 components.

4.4.3 Repeating Evans' work[59]

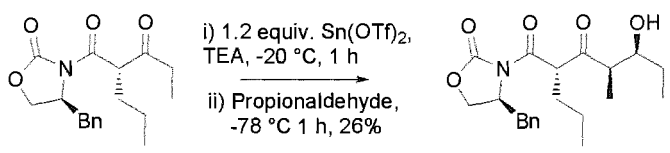
To determine unequivocally that acetate β-ketoimide aldol reactions lead to product mixtures, it was necessary to carry out reactions analogous to Evans' work.[59] It should be noted that Evans carried out reactions with a methyl group in the position where we have a propyl group in the β-ketoimide reagent. Synthesis of β-ketoimide reagent **4.9** also started from (4S)-benzyl oxazolidinone, following Evans' protocol.[25 59] Acylation using valeroyl chloride gives **4.4** which underwent an Evans aldol reaction with propionaldehyde using 1.1 equivalents of Bu_2BOTf and 1.3 equivalents of TEA, producing **4.10** in 46% yield, Scheme 4.9. The resulting alcohol underwent an oxidation using the Parik-Doering conditions, giving β-ketoimide **4.9** in 52% yield. These reactions remained unoptimised.



4.4 **4.10**, >95:5 **4.9**, >95:5

Scheme 4.9: Synthesis of chiral reagent for propionoate beta-ketoimide aldol.

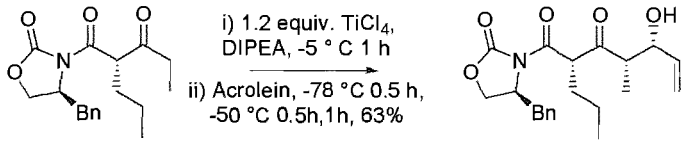
An aldol reaction between **4.9** and propionaldehyde was mediated by 1.2 equivalents of $Sn(OTf)_2$ and TEA, Scheme 4.10. Aldol product **4.11** was isolated in 26% yield as a single diastereoisomer. The low yield is a result of a short reaction time and this reaction also remained unoptimised.



4.9 **4.11**, >95:5

Scheme 4.10: Tin mediated propionoate beta-ketoimide aldol reaction with propionaldehyde.

An aldol reaction between **4.9** and acrolein was carried out using 1.2 equivalents of $TiCl_4$ and DIPEA, Scheme 4.11. The use of titanium gives access to the opposite *syn* isomer, because coordination to three heteroatoms is possible in the transition state. The aldol product **4.12** was isolated in 63% yield as a single diasteroisomer.



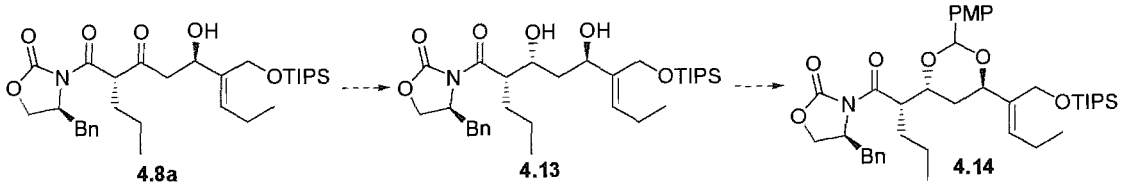
4.9 **4.12**, >95:5

Scheme 4.11: Titanium mediated propionoate beta-ketoimide aldol reaction with acrolein.

4.5 Further manipulation

4.5.1 Selective reduction

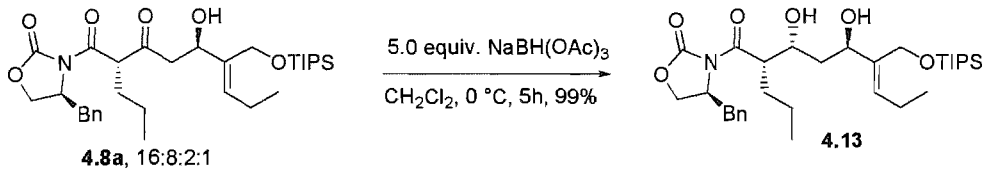
β-Ketoimide aldol products can be subjected to *syn* or *anti* reductions by the choice of reagents with good diastereomeric excesses. The use of sodium triacetoxyborohydride would give access to the *anti*-1,3-diol **4.13**. The two secondary alcohols produced will be protected as the benzylidene acetal **4.14**. The auxiliary would be removed to give a suitable fragment for coupling, Scheme 4.12.



4.8a **4.13** **4.14**

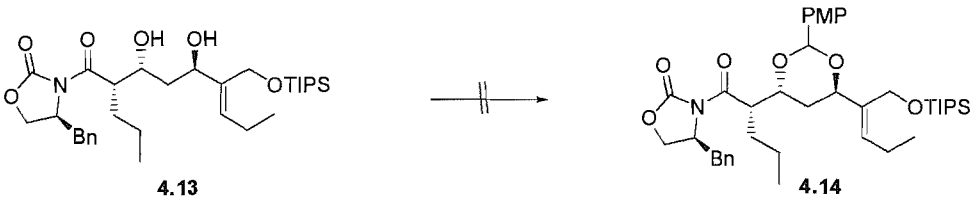
Scheme 4.12: Synthesis and protection of 1,3-diol.

As it was not possible to isolate pure **4.8a**, the reduction was carried out on the diastereomeric mixture, with a view to separation after protection. Using 5 equivalents of sodium triacetoxyborohydride in acetic acid[59] gave **4.13** in 83% yield (determined by mass balance). As acetic acid can potentially cause problems with isomerisation of the alkene functionality, the reaction was carried out in CH_2Cl_2 to eliminate this risk, and **4.13** was obtained in an improved 99% yield (determined by mass balance), Scheme 4.13. The product was immediately subjected to protection conditions to minimise any loss of stereochemical purity.



Scheme 4.13: Selective reduction of **4.8a** using sodium triacetoxyborohydride.

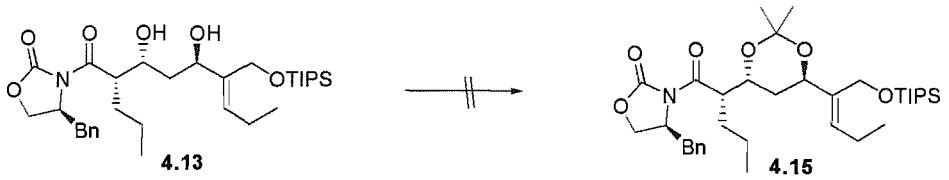
4.5.2 Protection of 1,3-diol **4.13**



Scheme 4.14: Protection of **4.13** as a benzylidine acetal.

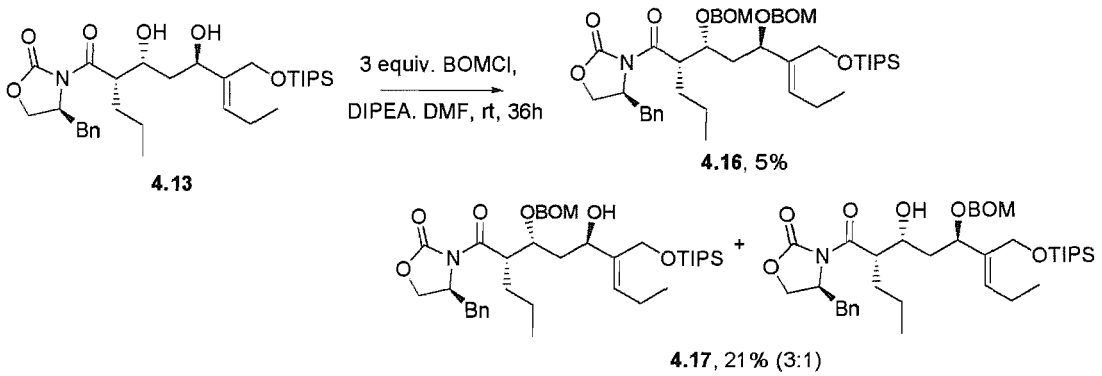
Synthesis of the benzylidene acetal **4.14** has proven problematic, Scheme 4.14. The use of 2.0 equivalents of *p*-anisaldehyde and trifluoroacetic acid (which showed some success with the terminal 1,3-diol) returned starting material after 3 days. Similarly, the use of 5 equivalents of *p*-anisaldehyde dimethyl acetal in the presence of 0.1 equivalent of camphorsulfonic acid[67] at room temperature returned starting material after 16 hours. Likewise, 5 equivalents of *p*-anisaldehyde dimethyl acetal in the presence of 0.1 equivalent of *p*-toluenesulfonic acid[66] returned starting material after 4 days. Refluxing 5 equivalents of *p*-anisaldehyde dimethyl acetal in the presence of 0.1 equivalent of *p*-toluenesulfonic acid in tetrahydrofuran was also unsuccessful. The use of 10 mol% pyridinium-*p*-toluene sulfonate under reflux in tetrahydrofuran for 18 hours was unsuccessful, but starting material was not returned. The use of the Lewis acids Sn(II) chloride and Zn(II) chloride at room temperature was also unsuccessful, with no products or starting materials isolated.

Work towards formation of acetonide **4.15** was carried out, Scheme 4.15. Reactions using 10 mol% camphor sulfonic acid in acetone, and stirring at room temperature for 48 hours, followed by refluxing for 18 hours, only returned starting material. The use of 10 mol% pyridinium-*p*-toluene sulfonate also returned starting material after refluxing in acetone for 18 hours.



Scheme 4.15: Protection of **4.13** as an acetonide.

It was then decided to carry out protection as a *bis*-benzyloxymethyl ether, which should be easily removed at the end of the synthesis at the same time as the methoxymethyl ethers in the aromatic fragment. The reaction was carried out using 3 equivalents of benzylchloromethylether and di*iso*propylethylamine, and stirring in dimethylformamide for 36 hours, Scheme 4.16. This reaction gave the bis-protected **4.16** in 5% yield and the mono-protected **4.17** in a combined yield of 21% (3.1:1 mixture of regioisomers). However, no starting material was returned. Positive ion electrospray mass spectrometry and infra red spectroscopy indicated the desired products had been formed. However, analysis of the proton and carbon NMR spectra showed a complex mixture of diastereoisomers, although the expected signals were all present. Separation of the mixture by HPLC to allow full characterisation was not possible.



Scheme 4.16: Protection of **4.13** as a benzyloxymethyl ether.

4.6 Summary

Tin mediated acetate β-ketoimide aldol reactions have been carried out using aldehydes protected with *p*-methoxybenzyl, in 67% yield, and tri*iso*propylsilyl groups, in 59% yield. The reaction rates have been reduced due to the bulky nature of the aldehyde substrates, and the products were isolated as diastereomeric mixtures. Acetate β-ketoimide aldol reactions using propionaldehyde were much faster with improved yields of around 80%, but selectivity remained poor. Repeating Evans' work using propionoate derived reagents have given β-ketoimide aldol products as single diastereomers, indicating the acetate

derived reactions are less selective.

Anti selective reduction of the acetate β-ketoimide product was carried out in 99% yield. The protection of the resulting 1,3-diol has proven problematic, however, and isolation of a single diastereoisomer has not been possible. Protection as the benzylidene acetal and acetonide has proven unsuccessful and formation of the bisbenzyloxymethyl ether has been poor yielding. Therefore a fragment suitable for coupling to our aromatic fragment has not been synthesised through this methodology.

Chapter 5: Review of the present synthetic strategy and additional related research towards luminacin D

5.1 Review of the synthetic strategy

The aromatic fragment from the proposed synthetic scheme has been synthesised in 5 steps from resorcinol. Acylation of resorcinol and subsequent reduction proceeds smoothly. The methoxymethyl protection and hydroxymethylation steps have proven a synthetic challenge. The bismethoxymethyl protection was carried out in a two-step procedure and optimal conditions for the hydroxymethylation reaction use 3 equivalents of reagents. Protection of the resulting primary alcohol as the silyl ether allowed separation of the regioisomers produced in the hydroxymethylation reaction. A trial coupling reaction with acetaldehyde proceeded smoothly giving the desired racemic alcohol.

Synthesis of the aldehyde substrate for the Nagao acetate-aldol reaction has been carried out smoothly in 6 steps from propionaldehyde and methyl acrylate, with three different protecting groups. The Nagao acetate aldol reaction has been extensively investigated. The concentration of the reagents was increased relative to the literature procedure, and when using tri*iso*propylsilyl protected aldehyde, product was isolated as a single stereoisomer. Application of the optimised conditions to aldehyde with *p*-methoxybenzyl protection gave a mixture of diastereomers. Application of the optimised conditions to aldehyde with triethylsilyl protection gave the Nagao product as a single diastereomer.

Orthogonal protection of the resulting secondary alcohol proved problematic, although silyl protection proceeded smoothly. It was hoped that the silyl protection might be removed allowing formation of an acetal for a selective epoxidation, as discussed below. Transformation to aldehyde for the Evans aldol reaction proceeded smoothly. The Evans aldol reaction, mediated by Bu_2BOTf, gave a single stereoisomer.

Protection of the secondary alcohol in the Evans aldol product also proved difficult, although reductive removal of the chiral auxiliary gave the1,3-diol. Protection of the free primary alcohol within this 1,3-diol as a pivaloyl ester has been carried out, but protection of the secondary alcohol was not possible. Protection of the 1,3-diol as a benzylidene acetal was also unsuccessful. Protection of the secondary alcohol in the Evans aldol product as a silyl ether was carried out smoothly, however further conversion to a fragment for coupling has not been possible.

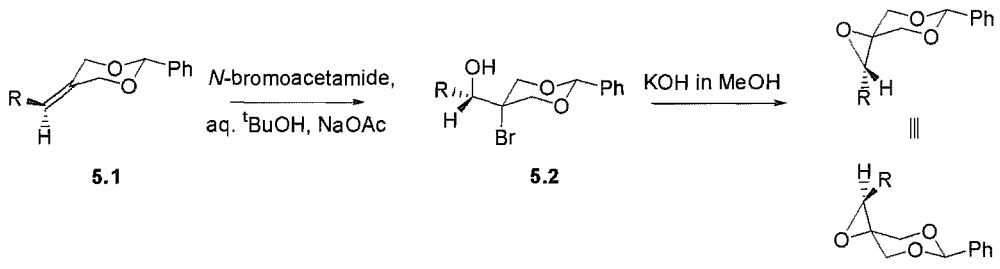
Tin mediated acetate β-ketoimide aldol reactions have been carried out using aldehydes protected with *p*-methoxybenzyl and tri*iso*propylsilyl groups. The reaction rates have been reduced due to the bulky nature of the aldehyde substrates, and the products were isolated as diastereomeric mixtures. Acetate β-ketoimide aldol reactions using propionaldehyde were much faster, but selectivity remained poor. Repeating Evans' work using propionoate derived reagents have given β-ketoimide aldol products as single diastereomers in good yields, indicating the acetate derived reactions are unselective and that the present aldehyde substrate does inhibit reaction rates.

Anti selective reduction of the acetate β-ketoimide product was carried out, however protection of the resulting 1,3-diol has proven problematic and isolation of a single diastereoisomer has not been possible. Protection as both the benzylidene acetal and acetonide has proven unsuccessful. It was hoped the protection groups could be moved along the chain to produce a suitable fragment to investigate selective epoxidation, as discussed below. Formation of the bisbenzyloxymethyl ether has also been poor yielding. Therefore a fragment suitable for coupling to our aromatic fragment has not been synthesised through this methodology.

5.2 Work towards selective epoxidation

In the total synthesis of luminacin D by Wood and co-workers, the allylic epoxidation was carried out with poor diastereoselectivity (1.2:1) using vanadyl acetoacetate and *t*-butyl hydroperoxide.[11] Although Wood's two diastereomers were separable, it was considered that other reactions could be envisaged, resulting in epoxidation with improved diastereoselectivity. For example, it has been shown that the formation of cyclic 1,3-acetals can allow extremely selective epoxidation reactions that favour attack on the axial face, Scheme 5.1.

Thus, *hypo*bromination[68 69] of **5.1** gave only bromohydrin **5.2** and epoxidation gave the β-epoxide **5.3** as a single diastereomer. It was hoped that applying this type of epoxidation reaction in the present synthesis would avoid problems protecting the hindered secondary alcohol.

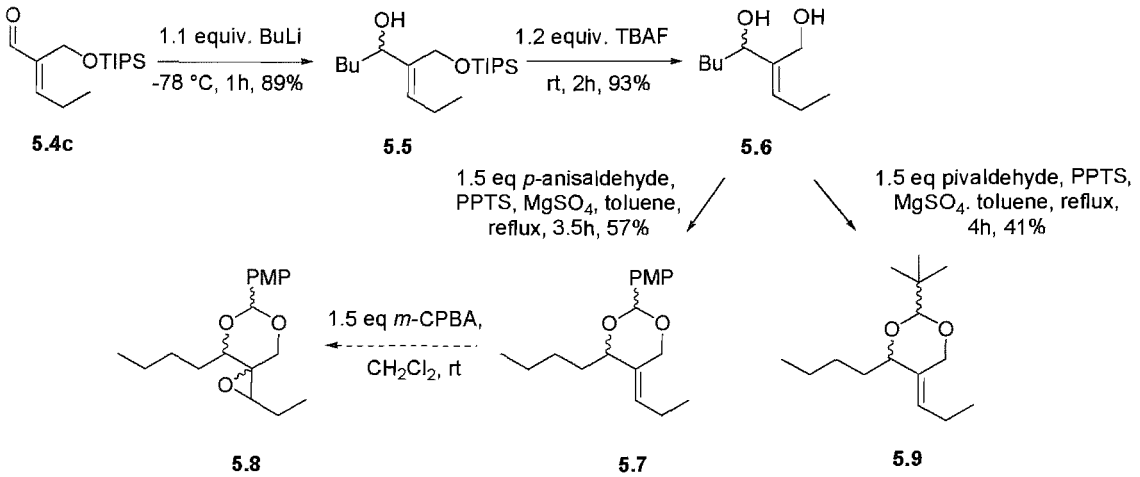


Scheme 5.1: Selective epoxidation via bromohydrin **5.2**.

In model reactions carried out according to Scheme 5.2, aldehyde **5.4c** undergoes an alkylation reaction with 1.1 equivalents of *n*-butyl lithium, forming racemic alcohol **5.5** in 89% yield. The alkyl chain introduced provides a model for the auxiliary terminus in our aliphatic fragment of interest. The 1,3-diol **5.6** was accessed in 93% yield using 1.2 equivalents of tetrabutylammonium fluoride. Formation of acetal **5.7** was carried out with 1.5 equivalents of *p*-anisaldehyde, under reflux in toluene, in 57 % yield, with only 5% of starting material being returned. Benzylidene acetal **5.7** was isolated as a 3:1 mixture of inseparable diastereomers.

Protection of the 1,3-diol was also carried out using 1.5 equivalents of pivaldehyde. The resulting acetal **5.9** was isolated in just 41% yield (as a 5:1 mixture of diastereoisomers which were unable to separate) with 10% of starting material returned.

Epoxidation of **5.7** was carried out using 1.5 equivalents of *m*-chloroperbenzoic acid. The reaction mixture was a complex mixture of diastereoisomers and epoxide **5.8** was not isolated.



Scheme 5.2: Model studies for selective epoxidation.

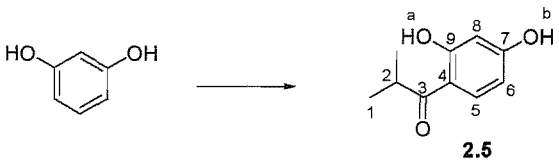
Chapter 6: Experimental

General

Unless otherwise stated, all reactions were carried out in flame-dried glassware cooled under N_2. THF and Et_2O were distilled from sodium/benzophenone. CH_2Cl_2, triethylamine, di*iso*propylethylamine and *N*-ethylpiperidine were distilled from CaH_2. DMSO was distilled from CaH_2 and stored over molecular sieves. Propionaldehyde and methyl acrylate were distilled from $CaCl_2$ and stored over molecular sieves. MeOH and EtOH were distilled from $Mg(OMe)_2$ and $Mg(OEt)_2$, respectively. Toluene was distilled from sodium. All compounds that were purified by preparative HPLC (BioRad Biosil D 90-10 250x22 mm column, with a refractive index detector, at a flow rate of 20 mL/min), first underwent flash column chromatography with the quoted solvent system. All NMR spectra were run in $CDCl_3$ on Bruker AC300 or DPX400 MHz spectrometer. CIMS were run in CH_2Cl_2 on ThermoQuest TraceMS and ESMS were run in methanol on Waters ZMD or acetonitrile on Micromass Platform II. High resolution MS were run on Bruker Apex III. All IR spectra were run as films on a Matheson FTIR, unless otherwise stated. All optical rotations were taken on a PolAAar100 spectrometer.

6.1 The aromatic fragment (Chapter 2)

2,3-Dihydroxy*iso*butyrophenone (2.5)



2.5

Triflic acid (100.0 g, 666 mmol) was added in one portion to resorcinol (24.8 g, 225 mmol) in *iso*butyric acid (41.0 mL, 444 mmol). The reaction mixture was heated at 80 °C for 2 h. The reaction mixture was then cooled to 30 °C before diluting with CH_2Cl_2 (300 mL) and pouring slowly into cold water (150 mL). The phases were separated and the aqueous layer was then extracted with CH_2Cl_2 (3×75 mL). The organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Ketone **2.5** (37.7 g, 209 mmol, 94%) was isolated as a colourless oil by flash chromatography (40-60 petrol /EtOAc 88:12). Spectral data matches the literature.[70]

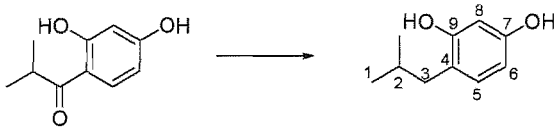
Mw 181.21 ($C_{10}H_{12}O_3$);

Rf 0.30 (hexane/EtOAc 80:20);

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.03 ($1H_{OHa}$, s), 7.70 ($1H_8$, d, J = 9.6 Hz), 6.42–6.39 ($2H_{5,6}$, m), 6.10 ($1H_{OHb}$, s, br), 3.52 ($1H_2$, sp, J = 6.8 Hz), 1.24 ($6H_1$, d, J = 6.8 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1 (C3), 165.8 (C7), 162.5 (C9), 132.1 (C5), 112.6 (C4), 107.6 (C8), 103.7 (C6), 34.6 (C2), 19.4 (C1).

1,3-Dihydroxy-4-*iso*butyl benzene (2.2)



2.2

Sodium cyanoborohydride (40.0 g, 637 mmol) was added in one portion to a solution of **2.5** (37.7 g, 209 mmol) and methyl orange indicator (71 mg) in MeOH (450 mL) in a flask equipped with a dropping funnel and a bleach bubbler. 1.0M Hydrochloric acid was added at a rate to maintain the indicator's red colour. The reaction was stirred at room temperature for 24 h. The reaction was diluted with water (150 mL) and the product extracted with CH_2Cl_2 (8×100 mL). The combined organic fractions were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Alkylated benzene derivative **2.2** (33.1 g, 199 mmol, 95%) was isolated as a white crystalline solid after passing through a silica plug (40-60 petrol/EtOAc 80:20).

Mw 166.12 ($C_{10}H_{14}O_2$);

m.p. 66 °C (hexane/EtOAc);

Rf 0.3 (40-60 petrol/EtOAc 80:20);

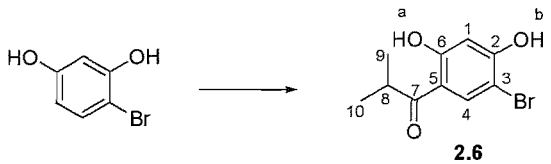
IR (cm^{-1}) 3350 (OH), 1605, 1516, 1454 (C=C);

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 ($1H_5$, d, J = 8.0 Hz), 6.36 ($1H_6$, dd, J = 8.0, 2.5 Hz), 6.34 ($1H_8$, d, J = 2.3 Hz), 5.93 ($1H_{OH}$, s), 5.49 ($1H_{OH}$, s), 2.38 ($2H_3$, d, J = 7.3 Hz), 1.85 ($1H_2$, sp, J = 6.8 Hz), 0.89 ($6H_1$, d, J = 6.8 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4 (C7,9), 131.8 (C5), 120.1 (C4), 107.5 (C8), 102.9 (C6), 38.5 (C3), 28.9 (C2), 22.4 (C1);

ES–MS m/z 165 $(M-H)^-$.

2,3-Dihydroxy-4-bromo *iso*butyrophenone (2.6)

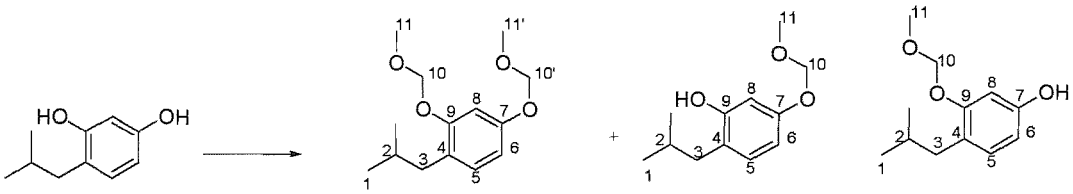


2.6

Triflic acid (819 μL, 9.26 mmol) was added in one portion to a solution of 4-bromoresorcinol (Aldrich, 509 mg, 2.69 mmol) in *iso*butyric acid (294 μL, 3.17 mmol). The reaction mixture was heated to 80 °C for 1 h. The reaction mixture was then cooled to room temperature and diluted with CH_2Cl_2 (20 mL) before pouring slowly into cold water (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (2×20 mL). The organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Ketone **2.6** (366 mg, 1.41 mmol, 40%) was isolated by preparative HPLC (hexane/EtOAc 80:20).

Mw 259.1 ($C_{10}H_{11}BrO_3$);
Rf 0.26 (hexane/EtOAc 80:20);
IR (cm^{-1}) (solution in CH_2Cl_2) 3054, 2983 (O–H), 1417, 1266, 879, 736;
^{1}H NMR (300 MHz, $CDCl_3$) δ 12.78 ($1H_{OHa}$, s), 7.91 ($1H_1$, s), 6.63 ($1H_4$, s), 5.94 ($1H_{OHb}$, s), 3.49 ($1H_8$, sp, J = 6.8 Hz), 1.24 ($6H_{9,10}$, d, J = 6.8 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4 (C7), 165.0 (C6), 158.3 (C2), 133.4 (C1), 113.9 (C5), 104.7 (C3), 100.2 (C4), 34.8 (C8), 19.4 (C9,10);
CIMS m/z [%] 261, 259 [100] $(M)^+$, 217, 215 [45] $(M–[C_3H_7])^+$, 181 [60] $(M–Br+H)^+$, 137 [30] $(M–[C_3H_7Br])^+$;

1,3-Bis(methoxymethyloxy)-4-*iso*butyl-benzene (2.10), 2-*iso*butyl-5-methoxymethyloxy-phenol (2.11a), 3-methoxymethyloxy-4-*iso*butyl-phenol (2.11b)



2.10 **2.11a**, major **2.11b**, minor

Di*iso*propylethylamine (28.0 mL, 157 mmol) was added dropwise to a solution of **2.2** (8.8 g, 52.4 mmol) in DMF (40 mL) at 0 °C. Chloromethyl methyl ether (12.0 mL, 157 mmol) was added dropwise and the reaction stirred at room temperature for 7 d, followed by quenching by 2N NaOH (50 mL). The products were extracted with CH_2Cl_2 (3×200 mL). The combined organic fractions were washed with water (100 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Bisprotected **2.10** (4.57 g, 18.0 mmol, 34%) and monoprotected **2.11** (4.19 g, 19.9 mmol, 38%, were obtained as a 6:1 ratio in favour of the least sterically hindered regioisomer) were isolated as colourless oils by flash chromatography (40-60 petrol/EtOAc 85:15). The regioisomers in **2.11** were separable by HPLC (hexane/EtOAc 85:15) to allow confirmation of analytical data.

Di*iso*propylethylamine (27 mL, 151 mmol) was added dropwise to a solution of **2.11** (10.32 g, 49.1 mmol) in dry DMF (40 mL) at 0 °C. Chloromethyl methyl ether (12 mL, 158 mmol) was added dropwise and the reaction stirred at 0 °C for 1 h before warming to room temperature and stirring for 8 d. The reaction was quenched by 2N NaOH (30 mL) and the products extracted with CH_2Cl_2 (3×100 mL), the combined organic fractions were washed with water (50 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. **2.10** (8.90 g, 35.0 mmol, 71%) and **2.11** (2.32 g, 11.0 mmol, 22%) as a 6:1 ratio in favour of the least sterically hindered isomer) were isolated as colourless oils by flash chromatography (40-60 petrol/EtOAc 85:15).

Data for 2.10

Mw 254.32 ($C_{14}H_{23}O_4$);

Rf 0.54 (40-60 petrol/EtOAc 85:15);

IR (cm^{-1}) 1610, 1587, 1503 (C=C), 1003 (C–O);

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 ($1H_5$, d, J = 8.0 Hz), 6.78 ($1H_8$, d, J = 2.3 Hz), 6.64 ($1H_6$, dd, J = 8.3, 2.3 Hz), 5.16 ($2H_{10'}$, s), 5.14 ($2H_{10}$, s), 3.48 ($6H_{11,11'}$, s), 2.44 ($2H_3$, d, J = 7.0 Hz), 1.88 ($1H_2$, sp, J = 6.8 Hz), 0.90 ($6H_1$, d, J = 6.5 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4 (C7), 156.0 (C9), 131.1 (C5), 124.3 (C4), 108.3 (C8), 103.3 (C6), 94.7 (C10), 94.4 (C10'), 56.0 (2C11, 11'), 38.9 (C3), 29.0 (C2), 22.5 (C1);

CIMS m/z 255 [100] $(M+H)^+$;

HRMS (ES+) for $C_{14}H_{23}O_4$ $(M+Na)^+$ calcd. 277.1410, found 277.1408.

Data for 2.11a (major isomer)

Mw 210.27 ($C_{12}H_{18}O_3$);

Rf 0.37 (40-60 petrol/EtOAc 85:15);

IR (cm^{-1}) 3403 (OH), 1616, 1596, 1515 (C=C), 1010 (C–O);

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 ($1H_5$, d, J = 8.3 Hz), 6.58 ($1H_6$, dd, J = 8.3, 2.5 Hz), 6.54 ($1H_8$, d, J = 2.5 Hz), 5.45 ($1H_{OH}$, s br), 5.15 ($2H_{10}$, s), 3.48 ($3H_{11}$, s), 2.44 ($2H_3$, d, J = 7.3 Hz), 1.91 ($1H_2$, sp, J = 6.8 Hz), 0.93 ($6H_1$, d, J = 6.5 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 (C9), 154.4 (C7), 131.6 (C5), 121.3 (C4), 108.1 (C8), 103.7 (C6), 94.5 (C10), 55.9 (C11), 38.6 (C3), 28.9 (C2), 22.4 (C1);

ES+MS m/z 211 [30] $(M+H)^+$;

HRMS (EI) for $C_{12}H_{18}O_3$ $(M)^+$ calcd. 210.12559, found 210.1254.

Data for 2.11b (minor isomer)

Mw 210.27 ($C_{12}H_{18}O_3$);

Rf 0.31 (40-60 petrol/EtOAc 85:15);

IR (cm^{-1}) 3403 (OH), 1616, 1596, 1515 (C=C), 1010 (C–O);

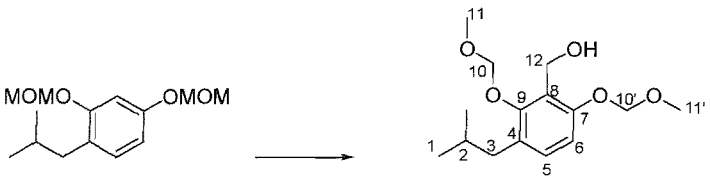
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 ($1H_5$, d, J = 8.3 Hz), 6.63 ($1H_8$, d, J = 2.5 Hz), 6.43 ($1H_6$, dd, J = 8.0, 2.5 Hz), 5.16 ($2H_{10}$, s), 3.49 ($3H_{11}$, s), 2.43 ($2H_3$, d, J = 7.3 Hz), 1.86 ($1H_2$, sp, J = 6.8 Hz), 0.90 ($6H_1$, d, J = 6.5 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0 (C7), 154.6 (C9), 131.4 (C5), 122.9 (C4), 108.0 (C6), 101.9 (C8), 94.3 (C10), 55.9 (C11), 38.8 (C3), 29.0 (C2), 22.5 (C1);

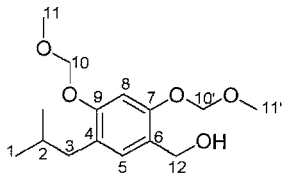
CIMS m/z 211 [40] $(M+H)^+$, 210 [75] $(M)^+$;

HRMS (EI) for $C_{12}H_{18}O_3$ $(M)^+$ calcd. 210.12559, found 210.1252.

1,3-Bismethoxymethyloxy-2-hydroxymethyl-4-*iso*butyl benzene (2.8a), 1,3-bismethoxymethyloxy-4-*iso*butyl-6-hydroxymethyl benzene (2.8b)



2.8a



2.8b

Tetramethylethylene diamine (3.0 mL, 14.2 mmol) was added dropwise to a solution of *bis*-methoxymethyl protected **2.10** (1.2 g, 4.7 mmol) in THF (10 mL) at –78 °C. *sec*-Butyl lithium, 1.4M in cyclohexane, (10.0 mL, 14.0 mmol) was added dropwise and the reaction stirred at –78 °C for 1 h before the addition of paraformaldehyde (460 mg, 15.3 mmol) in one portion. The reaction was stirred for a further hour at –78 °C before warming to room temperature and stirring for 16 h. The reaction was quenched by water (30 mL) and the product extracted with CH_2Cl_2 (3×100 mL). The combined organic fractions were washed with water (30 mL) and dried over $MgSO_4$ before the solvent was removed under reduced pressure. Hydroxymethylated **2.8** (753 mg, 2.64 mmol, 56%) was isolated as a colourless oil (6:1 ratio of inseparable regioisomers from NMR analysis) by flash chromatography (40-60 petrol/EtOAc 70:30).

Data for 2.8a (major regioisomer)

Mw 284.35 ($C_{15}H_{25}O_5$);

Rf 0.15 (40-60 petrol/EtOAc 70:30)

IR (cm^{-1}) 3479 (OH), 1600, 1483 (ar C=C), 1035 (C–O);

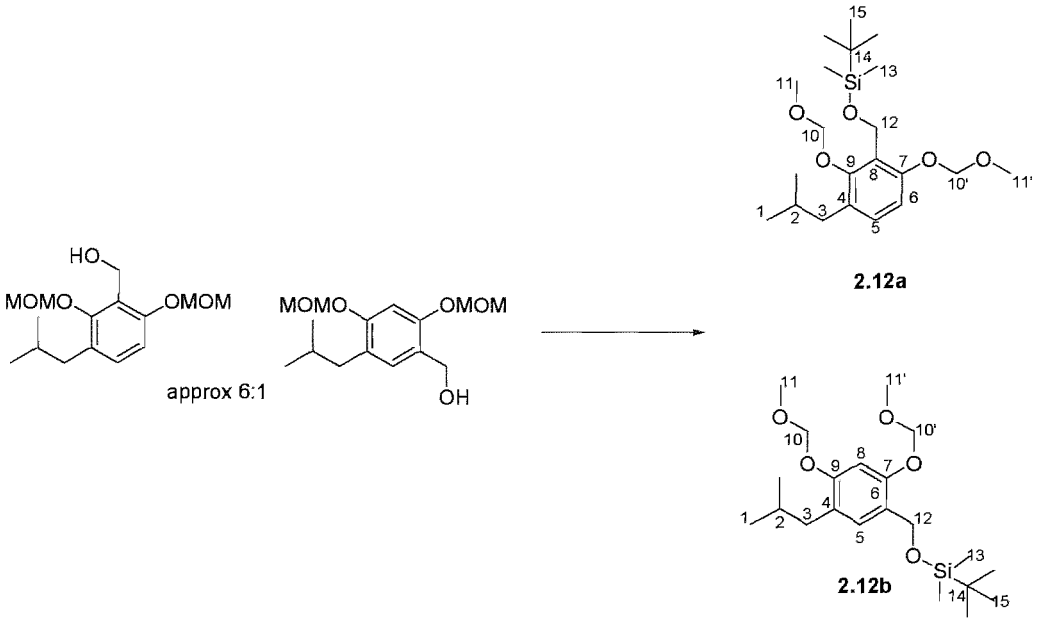
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 ($1H_5$, d, J = 8.5 Hz), 6.86 ($1H_6$, d, J = 8.3 Hz), 5.20 ($2H_{10'}$, s), 4.99 ($2H_{10}$, s), 4.70 ($2H_{12}$, s), 3.62 ($3H_{11'}$, s), 3.48 ($3H_{11}$, s), 2.40 ($2H_3$, d, J = 7.3 Hz), 1.88 ($1H_2$, sp, J = 6.8 Hz), 0.88 ($6H_1$, d, J = 6.8 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9 (C7), 154.7 (C9), 130.7 (C5), 128.2 (C8), 124.2 (C4), 111.0 (C6), 100.2 (C10), 95.0 (C10'), 57.4 (C11), 56.3 (C11'), 55.0 (C12), 39.4 (C3), 29.1 (C2), 22.5 (C1);

CIMS m/z 267 [70] $(M–OH)^+$, 284 [40] $(M)^+$;

HRMS (ES+) for $C_{15}H_{25}O_5$ $(M+Na)^+$ calcd. 307.1516, found 307.1513.

(3-*iso*butyl-1,3-Bismethoxymethyloxy-2-(t-butyldimethyl silanyl)-oxymethyl-4-*iso*butyl benzene (2.12a), t-Butyl(5-*iso*butyl-1,3-bismethoxymethyloxy-4-*iso*butyl-6-(t-butyldimethyl silanyl)-oxymethyl benzene (2.12b)



Imidazole (220 mg, 3.23 mmol) was added in one portion to a solution of **2.8** (753 mg, 2.64 mmol) in dry DMF (10 mL) at 0 °C. Tetrabutyldimethylsilyl chloride (478 mg, 3.17 mmol) was added in one portion and the reaction was stirred at 0 °C for 1 h. The reaction was warmed to room temperature and stirring continued for a further 16 h. The reaction mixture was poured into cold water (30 mL) and the products extracted with CH_2Cl_2 (3×50 mL). The combined organic fractions were dried over $MgSO_4$ before the solvent was removed under reduced pressure. Silyl products **2.12a** (845 mg, 2.12 mmol, 80%) and **2.12b** (126 mg, 0.32 mmol, 12%) were isolated as colourless oils by flash chromatography (40-60 petrol/EtOAc 95:5).

Data for 2.12a

Mw 398.25 ($C_{21}H_{38}O_5Si$);

Rf 0.43 (40-60 petrol/EtOAc 95:5);

IR (cm^{-1}) 1614, 1593, 1501, 1464 (ar C=C), 1278 (Si–C), 1254 (Si–O), 1151, 1115, 1078, 1040, 1004 (C–O);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 ($1H_5$, d, J = 8.5 Hz), 6.87 ($1H_6$, d, J = 8.5 Hz), 5.19 ($2H_{10'}$, s), 5.13 ($2H_{10}$, s), 4.74 ($2H_{12}$, s), 3.63 ($3H_{11'}$, s), 3.50 ($3H_{11}$, s), 2.52 ($2H_3$, d, J = 7.4 Hz), 1.93 ($1H_2$, sp, J = 6.8 Hz), 0.92-0.88 ($9H_{15}$, $6H_1$, m), 0.13 ($6H_{13}$, s);

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8 (C7), 155.1 (C9), 130.75 (C5), 128.5(C8), 123.1 (C4), 110.3 (C6), 101.1 (C10), 94.7 (C10'), 57.4 (C11), 56.0 (C11'), 55.4 (C12), 39.4 (C3), 29.2 (C2), 25.9 (C15), 22.5 (C1), 18.4 (C14), –5.3 (C13);

CIMS m/z 284 [40] $(M–TBDMS)^+$, 267 [75] $(M–TBSOH)^+$;

HRMS (ES+) for $C_{21}H_{39}O_5Si$ $(M+Na)^+$ calcd. 421.2381, found 421.2382.

Data for 2.12b

Mw 398.25 ($C_{21}H_{38}O_5Si$);

Rf 0.21 (40-60 petrol/EtOAc 95:5);

IR (cm^{-1}) 1602, 1589, 1485, 1465 (ar C=C),1252 (Si–O), 1155, 1043 (C–O);

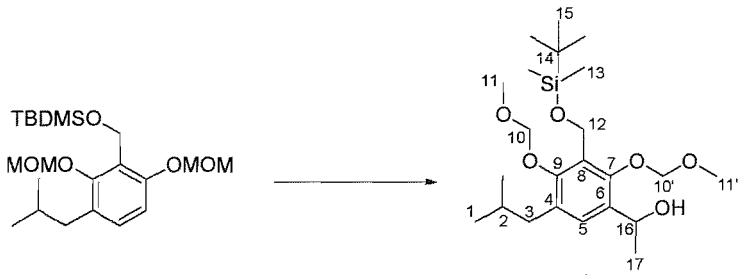
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 ($1H_5$, s), 6.84 ($1H_8$, s), 5.17 ($2H_{10'}$, s), 5.16 ($2H_{10}$, s), 4.73 ($2H_{12}$, s), 3.49 ($6H_{11,11'}$, s), 2.46 ($2H_3$, d, J = 7.2 Hz), 1.89 ($1H_2$, sp, J = 6.8 Hz), 0.96 ($9H_{15}$, s), 0.92 ($6H_1$, d, J = 6.8 Hz), 0.11 ($6H_{13}$, s);

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7 (C7), 152.6 (C9), 129.6 (C5), 123.8 (C6), 123.1 (C4), 101.3 (C8), 94.8 (C10, 10'), 60.0 (C11, 11'), 56.0 (C12), 38.9 (C3), 29.9 (C2), 26.0 (C15), 22.5 (C1), 18.4 (C14), –5.3 (C13);

CIMS m/z 267 [70] $(M–TBDMSOH)^+$;

HRMS (ES+) for $C_{21}H_{39}O_5Si$ $(M+Na)^+$ calcd. 421.2381, found 421.2385.

1,3-Bismethoxymethyloxy-2-(*t*-butyldimethylsilanyl)-oxymethyl-4-*iso*butyl benzene (2.13)



2.13

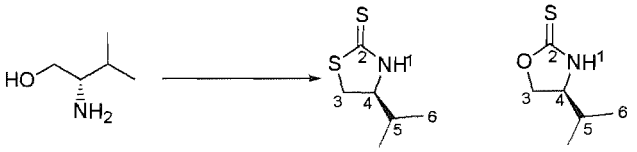
Tetramethylethylene diamine (60 μL, 0.28 mmol) was added dropwise to a solution of **2.12a** (103 mg, 0.25 mmol) in THF (1 mL) at –78 °C. *sec*-Butyl lithium, 1.4M in cyclohexane, (200 μL, 0.28 mmol) was added dropwise and the reaction stirred at –78 °C for 1 h. Acetaldehyde (30 μL, 0.50 mmol) was added dropwise and the reaction stirred at –78 °C for 1 h before warming to room temperature. The reaction was stirred at 0 °C before quenching by water (1 mL). The product was extracted with CH_2Cl_2 (3×10 mL).

The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Racemic **2.13** (85 mg, 0.19 mmol, 77%) was isolated as a colourless oil by flash chromatography (40-60 petrol/acetone 80:20).

Mw 442.66 ($C_{23}H_{42}O_6Si$);
Rf 0.43 (40-60 petrol/acetone 80:20);
IR (cm^{-1}) 3456 (O–H)1586, 1466, 1383 (ar), 1254 (Si–O), 1158, 1052, 1029 (C–O);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 ($1H_5$, s), 5.19 ($1H_{16}$, q, J = 6.5 Hz), 5.12 ($2H_{10}$, s), 5.08 ($1H_{10'}$, d, J = 5.5 Hz), 5.04 ($1H_{10'}$, d, J = 5.5 Hz), 4.64 ($2H_{12}$, s), 3.59 ($6H_{11}$, s), 3.25 ($1H_{OH}$, s br), 2.62 ($1H_3$, dd, J = 13.4, 7.0 Hz), 2.47 ($1H_3$, dd, J = 13.4, 7.5 Hz), 1.93 ($1H_2$, sp, J = 6.8 Hz), 1.51 ($3H_{17}$, d, J = 6.6 Hz), 0.94-0.88 ($6H_1$, $9H_{15}$, m), 0.16 ($3H_{13}$, s), 0.15 ($3H_{13}$, s);
^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5 (C7), 154.0 (C9), 134.3 (C6), 131.7 (C5), 128.0 (C8), 126.7 (C4), 101.6 (C10), 101.2 (C10'), 63.6 (C16), 57.3 (C11), 55.8 (C12), 39.6 (C3), 29.1 (C2), 25.8 (C15), 22.5 (C1), 22.3 (C17), 21.9 (C17), 18.0 (C14), –5.5 (C13);
ES+MS m/z 908.8 [10] $(2M+Na)^+$, 507.3 [100] $(M+MeCN+Na)^+$, 443.2 [40] $(M+H)^+$;
HRMS (ES+) for $C_{23}H_{42}O_6Si$ $(M+Na)^+$ calcd. 465.2643, found 465.2653.

6.2 The aliphatic fragment (Chapter 3)

(4*S*)-*t*-Butyl-1,3-thiazolidine-2-thione (3.11a), (4*S*)-*t*-butyl-1,3-oxazolidine-2-thione (3.11b)



3.11a **3.11b**

Carbon disulfide (12.0 mL, 199 mmol) was added to a solution of (2*S*)-amino-3-methyl butan-1-ol (10.0 g, 97 mmol) in 1N aqueous potassium hydroxide (100 mL). The reaction was heated to 90 °C for 16 h. The products were extracted with CH_2Cl_2 (3×50 mL) and the combined organic fractions washed with water (50 mL) before drying over $MgSO_4$. The solvent was removed under reduced pressure and thiazolidinethione **3.11a** (8.7 g, 54 mmol, 52%) as a white crystalline solid and oxazolidinethione **3.11b** (8.0 g, 55 mmol, 48 %) as a waxy solid were isolated by flash chromatography (hexane/EtOAc 80:20). Spectral data match the literature.[35]

3.11a

Carbon disulfide (3.9 mL, 64.5 mmol) was added to a solution of **3.11b** (2.7 g, 18.3 mmol) in 1N aqueous potassium hydroxide (45 mL). The reaction was heated to 90 °C for 16 h, before cooling to room temperature. The products were extracted with CH_2Cl_2 (3×30 mL) and the combined organic fractions washed with water (50 mL) before drying over $MgSO_4$. The solvent was removed under reduced pressure and thiazolidinethione **3.11a** (2.7 g, 16.8 mmol, 78%) as a white crystalline solid and oxazolidinethione **3.11b** (666 mg, 4.6 mmol, 21%,) as a waxy solid were isolated by flash chromatography (hexane/EtOAc 75:25). Spectral data match the literature.[35]

Data for 3.11a

Mw 161.29 ($C_6H_{11}NS_2$);

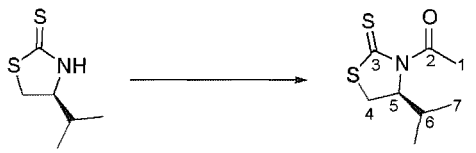
Rf 0.21 (hexane/EtOAc 80:20);

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 ($1H_1$, s, br), 4.06 ($1H_4$, ddd, J = 15.6, 8.0, 0.8 Hz), 3.52 ($1H_3$, dd, J = 8, 11 Hz), 3.31 ($1H_3$, dd, J = 8, 11 Hz), 1.99 ($1H_5$, m), 1.02 ($3H_6$, d, J = 6.7 Hz), 1.00 ($3H_6$, d, J = 6.7 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9 (C2), 70.0 (C3), 35.8 (C4), 31.9 (C5), 18.8 (C6), 18.2 (C6);
CIMS m/z [%] 162 [100] $(M+H)^+$, 118 [55] $(M-{}^i Pr+H)^+$.

Data for 3.11b

Mw 145.16 ($C_6H_{11}NOS$);
Rf 0.23 (hexane/EtOAc 70:30);
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 ($1H_1$, s, br), 4.69 ($1H_4$, app t, J = 9.2 Hz), 4.37 ($1H_3$, dd, J = 9.2, 6.8 Hz), 3.85 ($1H_3$, dd, J = 9.2, 6.6 Hz), 1.85 ($1H_5$, sx, J = 6.8 Hz), 0.98 ($3H_6$, d, J = 6.6 Hz), 0.93 ($3H_6$, d, J = 6.8 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4 (C2), 73.4 (C3), 62.4 (C4), 32.1 (C5), 17.9 (C6), 17.8 (C6);
CIMS m/z [%] 146 [30] $(M+H)^+$, 114 [100] $(M-S)^+$.

3-Acetyl-(4*S*)-*t*-butyl-1,3-thiazolidine-2-thione (3.9)



3.9

Acetyl chloride (5.0 mL, 66.0 mmol) was added to a solution of **3.11a** (8.8 g, 55.0 mmol) in CH_2Cl_2 (130 mL). Triethylamine (9.2 mL, 65.5 mmol) was added dropwise and the reaction stirred for 8 h at room temperature. The reaction mixture was washed with water (100 mL). The aqueous wash was extracted with CH_2Cl_2 (3×100 mL). The combined organic fractions were dried over $MgSO_4$ before the solvent was removed under reduced pressure. Nagao reagent **3.9** (10.4 g, 50.9 mmol, 93%) was isolated as a yellow oil by flash chromatography (40-60 petrol/EtOAc 90:10). Spectral data match the literature.[36]

Mw 203.28 ($C_8H_{13}NOS_2$);
Rf 0.28 (hexane/EtOAc 90:10);
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 ($1H_5$, ddd, J = 8.0, 6.2, 1.1 Hz), 3.50 ($1H_4$, dd, J = 11.5, 8.0 Hz), 3.03 ($1H_4$, dd, J = 11.5, 1.1 Hz), 2.78 ($3H_1$, s), 2.38 ($1H_6$, m), 1.07 ($3H_7$, d, J = 7

Hz), 0.99 ($3H_7$, d, J = 7 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2 (C3), 170.7 (C2), 71.2 (C5), 30.7 (C4), 30.4 (C6), 26.9 (C1), 19.0 (C7), 17.7 (C7);

CIMS m/z [%] 203 [100] $(M)^+$, 162 [60] $(M–Ac+2H)^+$, 118 [70] $(M–Ac–iPr+H)^+$.

Methyl 2-(1-hydroxypropyl)acrylate (3.6)

3.6

Quinuclidine (2.7 g, 5 mol%) was placed in a flask and propionaldehyde (25.0 mL, 19.4 g, 348.7 mmol) was added. Methyl acrylate (39.0 mL, 37.1 g, 430.3 mmol) was added in 10 mL portions over 20 minutes. The reaction vessel was wrapped in aluminium foil and stirred at room temperature for 3 days. The reaction mixture was poured into 2M HCl (50 mL) and CH_2Cl_2 (20 mL). The aqueous fraction was extracted with CH_2Cl_2 (3×50 mL). The combined organic fractions were dried over Na_2SO_4, the solvent and volatile starting materials were removed under reduced pressure giving Baylis Hillman product **3.6** (45.4 g, 315 mmol, 94%) as a colourless oil (used crude in the next reaction). Spectral data match the literature.[37]

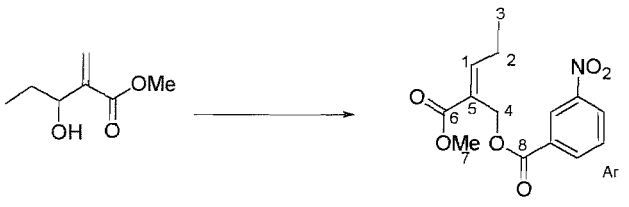
Mw 144.17 ($C_7H_{12}O_3$);

Rf 0.26 (hexane/EtOAc 70:30);

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 ($1H_4$, s), 5.80 ($1H_4$, s), 4.33 ($1H_3$, t, J = 6.3 Hz), 3.78 ($3H_7$, s), 1.77-1.61 ($2H_2$, m), 0.95 ($3H_1$, t, J = 7.4 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0 (C6), 125.2 (C5), 73.1 (C4), 51.9 (C3), 29.0 (C7), 15.3 (C2), 10.1 (C1).

Methyl-2-(3-nitrobenzoyl)oxymethyl-pent-2*E*-enoate (3.7a)

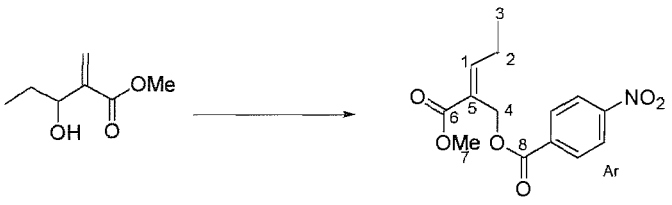


3.7a

Triphenylphosphine (6.2 g, 23.8 mmol) and *m*-nitrobenzoic acid (4.0 g, 24.1 mmol) were added to a solution of **3.6** (2.8 mg, 19.4 mmol) in THF (40 mL). The reaction mixture was cooled to –40 °C whereupon di*iso*propylazodicarboxylate (14.8 mL, 23.0 mmol) was added dropwise. The reaction was stirred for 1.5 h before warming to room temperature. The reaction mixture was diluted with diethyl ether (20 mL) and water (15 mL). The organic layer was separated and washed with water (10 mL) and 2N NaOH (2×10 mL). The aqueous layer was extracted with diethyl ether (4×20 mL). The combined organic fractions were washed with conc.$NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude reaction mixture was dissolved in hexane/diethyl ether (95:5) and the precipitated triphenylphosphine oxide was removed by filtration. Nitrobenzoate **3.7a** (4.6 g, 15.5 mmol, 80%) was isolated as a pale yellow oil by flash chromatography (hexane/Et_2O 70:30). Spectral data match the literature.[42]

Mw 293.28 ($C_{14}H_{15}O_6N$);
Rf 0.16 (hexane/Et_2O 70:30);
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 ($1H_{Ar}$, ddd, J = 7.2, 2.2, 1.1 Hz), 8.37-8.34 ($2H_{Ar}$, m), 7.65 ($1H_{Ar}$, t, J = 8.0 Hz), 7.17 ($1H_1$, t, J = 7.7 Hz), 5.22 ($2H_4$, s), 3.79 ($3H_7$, s), 2.47-2.37 ($2H_2$, m), 1.19 ($3H_3$, t, J = 7.5 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 180.4 (C8), 166.5 (C6), 164.2 (Ar), 151.6 (C5), 135.3 (Ar), 128.6 (C1), 127.8 (Ar), 124.8 (Ar), 59.5 (C7), 52.1 (C4), 22.5 (C2), 13.1 (C3).

Methyl-2-(4-nitrobenzoyl)oxymethyl-pent-2*E*-enoate (3.7b)



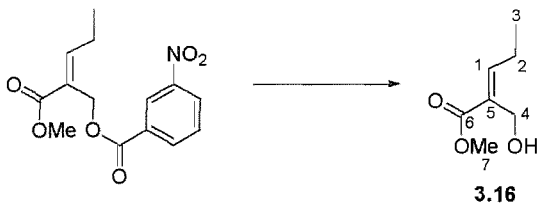
3.7b

Triphenylphosphine (12.1 g, 46.0 mmol) and *p*-nitrobenzoic acid (7.8 g, 46.4 mmol) were added to a solution of **3.6** (4.4 g, 30.7 mmol) in THF (250 mL). The reaction mixture was cooled to –40 °C whereupon di*iso*propylazodicarboxylate (9.1 mL, 46.0 mmol) was added dropwise. The reaction was warmed to –30 °C over 1 h, stirred at –30 °C for 1 h. The reaction was warmed to room temperature and the solvent was removed under reduced pressure. The reaction mixture was dissolved in diethyl ether (150 mL), washed with

water (10 mL) and 2N NaOH (2×10 mL). The aqueous layer was extracted with Et_2O (2×25 mL). The combined organic fractions were washed with conc.$NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude reaction mixture was dissolved in hexane/diethyl ether (95:5) and the precipitated triphenylphosphine oxide was removed by filtration. Nitrobenzoate **3.7b** (6.1 g, 21.4 mmol, 83%) was isolated as a pale yellow solid by flash chromatography (hexane/EtOAc 90:10). Spectral data match the literature.[42]

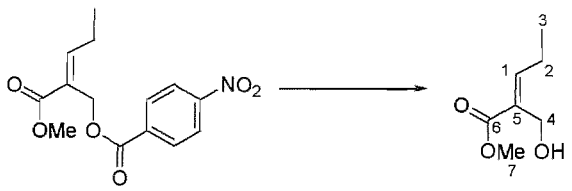
Mw 293.28 ($C_{14}H_{15}O_6N$);
m.p. 54-55 °C (methanol);
Rf 0.19 (hexane/EtOAc 90:10);
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30-8.27 ($2H_{Ar}$, m), 8.21-8.17 ($2H_{Ar}$, m), 7.16 ($1H_1$, t, J = 7.8 Hz), 5.10 ($2H_4$, s), 3.80 ($3H_7$, s), 2.46-2.36 ($2H_2$, m), 1.12 ($3H_3$, t, J = 7.5 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C6), 164.4 (C8), 151.9 (C5), 135.5 (C1), 130.8 (Ar), 125.9 (Ar), 123.5 (Ar), 59.3 (C4), 52.1 (C7), 22.3 (C2), 13.2 (C3).

Methyl-2-(hydroxymethyl)-pent-2*E*-enoate (3.16)



3.16

Potassium carbonate (158 mg, 1.1 mmol) was added to a solution of **3.7a** (2.6 g, 8.9 mmol) in methanol (30 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h. The reaction was diluted with water (5 mL) and diethyl ether (20 mL). The phases were separated and the aqueous fraction extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were washed with brine (10 mL) and dried over $MgSO_4$ before the solvent was removed under reduced pressure. Alcohol **3.16** (1.3 g, 8.8 mmol, 86 %) was isolated as a colourless oil by flash chromatography (hexane/EtOAc 80:20).

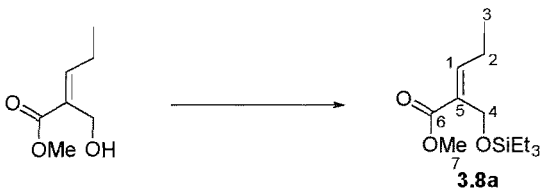


3.16

Potassium carbonate (428 mg, 3.1 mmol) was added to a solution of **3.7b** (9.1 g, 31.0 mmol) in methanol (350 mL) at 0 °C. The reaction was stirred at 0 °C for 1.5 h. Approximately half of the solvent was removed under reduced pressure and water (100 mL) was added to dissolve the K_2CO_3. The product was extracted with CH_2Cl_2 (6×100 mL) and the combined organic fractions were dried over $MgSO_4$. The solvent was removed under reduced pressure and alcohol **3.16** (4.0 g, 90%, 27.8 mmol) was isolated as a colourless oil by flash chromatography (40-60 petrol/EtOAc 80:20). Spectral data match the literature.[42]

Mw 144.17 ($C_7H_{12}O_3$);
Rf 0.16 (hexane/EtOAc 80:20);
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.9 ($1H_1$, t, J = 7.7 Hz), 4.29 ($2H_4$, s), 3.75 ($3H_7$, s), 2.35-2.25 ($2H_2$, m), 1.08 ($3H_3$, t, J = 7.5 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3 (C6), 147.3 (C5), 130.1 (C1), 57.2 (C4), 51.8 (C7), 21.7 (C2), 13.3 (C3).

Methyl-2-(triethylsilyl)oxymethyl-pent-2*E*-enoate (3.8a)



3.8a

Triethylsilyl chloride (2.3 mL, 16.1 mmol) was added dropwise over 15 minutes to a solution of **3.16** (1.9 g, 13.5 mmol) and imidazole (1.2 g, 17.9 mmol) in DMF (20 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h before warming to room temperature. The reaction was stirred at rt for a further 15 h. The reaction mixture was poured into ice-cold water (20 mL). The aqueous fraction was extracted with CH_2Cl_2 (3×50 mL). The combined organic fractions were washed with water (20 mL) and brine (20 mL) then dried over $MgSO_4$ before the solvent was removed under reduced pressure. Silyl product **3.8a** (3.1 g, 11.8 mmol, 87%) was isolated as a colourless oil by flash chromatography (hexane/EtOAc 95:5).

Mw 258.43 ($C_{13}H_{26}O_3Si$);
Rf 0.33 (hexane/EtOAc 95:5);

IR (cm^{-1}) 2956 (C–H), 1717 (C=O), 1649 (C=C), 1459, 1435, 1414 (C–C), 1378, 1311, 1287, 1237 (C–O);

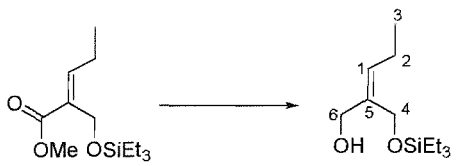
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 ($1H_1$, t, J = 7.5 Hz), 4.40 ($2H_4$, s), 3.75 ($3H_7$, s), 2.34 ($2H_2$, app qn, J = 7.5 Hz), 1.05 ($3H_3$, t, J = 7.5 Hz), 0.95 ($9H_{TESCH3}$, t, J = 3.3 Hz), 0.61 ($6H_{TESCH2}$, q, J = 3.3 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.8 (C6), 148.2 (C5), 130.8 (C1), 56.6 (C4), 51.6 (C7), 21.9 (C2), 13.3 (C3), 6.7 ($TESCH_2$), 4.3 ($TESCH_3$);

CIMS m/z [%] 259 [68] $(M+H)^+$, 229 [100] $(M–MeO+H)^+$;

HRMS (CI) for $C_{11}H_{21}O_3Si$ $(M–Et)^+$ calcd. 229.12600, found 229.12704.

2-(Triethylsilyl)oxymethyl-pent-2*Z*-enol (3.17a)



3.17a

Di*iso*butyl aluminium hydride, 1.0M in hexanes, (35.0 mL, 35.0 mmol) was added dropwise over 20 minutes to a solution of **3.8a** (3.3 g, 12.7 mmol) in diethyl ether (30 mL) at –78 °C. The reaction was stirred at –78 °C for 2 h followed by quenching by water (4 mL), 2N NaOH (10 mL) and water (5 mL). The reaction was then warmed to room temperature. The aqueous layer was extracted with diethyl ether (3×30 mL) and the organic fractions were washed with brine (50 mL) before drying over $MgSO_4$ the solvent was removed under reduced pressure. Alcohol **3.17a** (2.5 g, 11.0 mmol, 86%) was isolated as a colourless oil by flash chromatography (hexane/EtOAc 85:15).

Mw 230.42 ($C_{12}H_{26}O_2Si$);

Rf 0.65 (hexane/EtOAc 85:15);

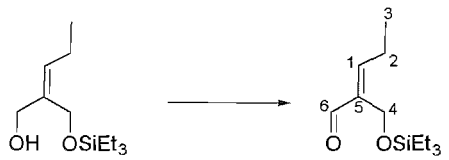
IR (cm^{-1}) 3398 (O–H), 3051, 2956, 2907, 2869, 2734 (C–H), 1670, 1459, 1414 (C=C), 1266, 1239 (C–O);

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.49 ($1H_1$, t, J = 7.4 Hz), 4.35 ($2H_4$, s), 4.15 ($2H_6$, s), 2.05 ($2H_2$, app qn, J = 7.5 Hz), 0.99 ($3H_3$, t, J = 7.5 Hz), 0.99 ($9H_{TESCH3}$, t, J = 8.1 Hz), 0.61 ($6H_{TESCH2}$, q, J = 8.1 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1 (C5), 131.2 (C1), 67.5 (C6), 60.6 (C4), 20.7 (C2), 14.1 (C3), 6.7 ($TESCH_2$), 4.2 ($TESCH_3$);

CIMS m/z [%] 231 [46] $(M+H)^+$, 213 [100] $(M-OH_2)^+$, 201 [28] $(M-CH_2OH+H)^+$, 132 [46] $(HOTES)^+$;
HRMS (EI) for $C_{10}H_{21}O_2Si$ $(M-Et)^+$ calcd. 201.13108, found 201.13107.

2-(Triethylsilyl)oxymethyl-pent-2*E*-enal (3.1a)

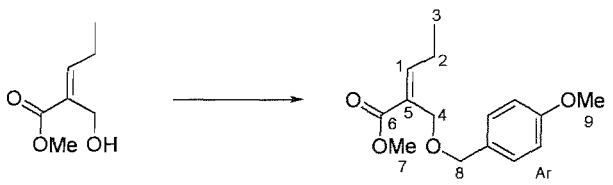


3.1a

Sulfur trioxide-pyridine complex (439 mg, 2.76 mmol) was dissolved in CH_2Cl_2 (2 mL), DMSO (4 mL) and triethylamine (300 μL, 4.08 mmol) was added dropwise. The pale yellow solution was added dropwise to a solution of **3.17a** (265 mg, 1.15 mmol) in 1:1 CH_2Cl_2/DMSO (10 mL) at 0 °C. The reaction was stirred at 0 °C for 3 h followed by pouring into 2M NH_4Cl (5 mL). The organic fraction was separated and washed with water (5 mL) and the aqueous washings were extracted with CH_2Cl_2 (3 ×10 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent removed under reduced pressure. Aldehyde **3.1a** (170 mg, 0.74 mmol, 69%) was isolated by flash chromatography (hexane/EtOAc 90:10).

Mw 228.27 ($C_{12}H_{24}O_2Si$);
Rf 0.5 (hexane/EtOAc 90:10);
IR (cm^{-1}) 2922, 2956, 2912, 2877, 2813 (C–H), 1689 (C=O), 1646 (C=C), 1459, 1413, 1382, 1239 (C–O), 1207, 1081 (Si–O);
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 ($1H_6$, s), 6.61 ($1H_1$, t, J = 7.5 Hz), 4.37 ($2H_4$, s), 2.55 ($2H_2$, app qn, J = 7.5 Hz), 1.15 ($3H_3$, t, J = 7.5 Hz), 0.96 ($9H_{TESCH3}$, t, J = 8.1 Hz), 0.62 ($6H_{TESCH2}$, t, J = 8.1 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9 (C6), 160.1 (C5), 141.2 (C1), 54.3 (C4), 22.6 (C2), 13.1 (C3), 6.7 ($TESCH_2$), 4.2 ($TESCH_3$);
CIMS m/z [%] 229 [65] $(M+H)^+$, 199 [100] $(M-CHO)^+$;
HRMS (ES+) for $C_{12}H_{24}O_2Si$ $(M+H)^+$ calcd. 229.16195, found 229.16238.

Methyl-2-(*p*-methoxybenzyl)oxymethyl-pent-2*E*-enoate (3.8b)

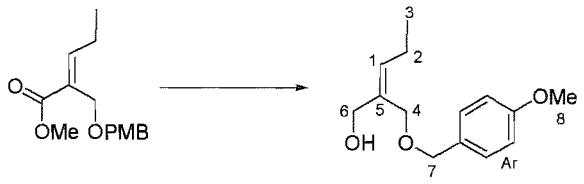


3.8b

p-Methoxybenzyltrichloroacetimidate (1.51 g, 5.34 mmol) in CH_2Cl_2 (4 mL) was added dropwise to a solution of **3.16** (498 mg, 3.45 mmol) in CH_2Cl_2 (4 mL). Camphor sulfonic acid (91 mg, 10 mol%) was added in one portion. The reaction was stirred at room temperature for 48 h followed by quenching by c.$NaHCO_3$ (4 mL). The organic fraction was separated and washed with water (4 mL) and the aqueous fractions were extracted with CH_2Cl_2 (3×10 mL). The organic fractions were dried over $MgSO_4$ before the solvent was removed under reduced pressure. *p*-Methoxy benzyl ether **3.8b** (893 mg, 3.38 mmol, 98%) was isolated as a colourless oil by flash chromatography (hexane/EtOAc 85:15).

Mw 264.32 ($C_{15}H_{20}O_4$);
Rf 0.30 (hexane/EtOAc 85:15);
IR (cm^{-1}) 2952, 2874, 2837 (C–H), 1717, 1613, 1514 (ar C=C), 1463 (C=C), 1437, 1303 (ar C=C), 1247, 1173, 1150, 1077, 1035 (C–O);
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.25 ($2H_{Ar}$, m), 7.01 ($1H_1$, t, J = 7.5 Hz), 6.93-6.83 ($2H_{Ar}$, m), 4.47 ($2H_4$, s), 4.23 ($2H_8$, s), 3.81 ($3H_7$, s), 3.77 ($3H_9$, s), 2.27 ($2H_2$, app qn, J = 7.5 Hz), 1.07 ($3H_3$, t, J = 7.5 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0 (C6), 159.1 (Ar), 150.0 (C5), 130.3 (C1), 129.4 (Ar), 128.3 (Ar), 113.7 (Ar), 72.1 (C8), 63.0 (C9), 55.2 (C4), 51.8 (C7), 22.1 (C2), 13.2 (C3);
ES+MS m/z [%] 551.4 [15] $(2M+Na)^+$, 328.3 [20] $(M+Na+MeCN)^+$, 287.2 [20] $(M+Na)^+$, 282.3 [25] $(M+NH_4)^+$, 265.2 [30] $(M+H)^+$;
HRMS (ES+) for $C_{15}H_{20}O_4$ $(M+Na)^+$ calcd. 287.1254, found 287.1255.

2-(*p*-Methoxybenzyl)oxymethyl-pent-2*Z*-enol (3.17b)

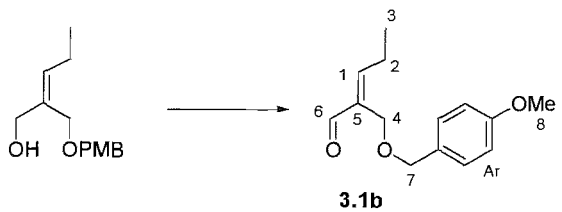


3.17b

Di*iso*butyl aluminium hydride, 1.0M in hexanes, (4.0 mL, 3.98 mmol) was added dropwise to a solution of **3.8b** (418 mg, 1.58 mmol) in diethyl ether (8 mL) at –78 °C. The reaction was stirred at –78 °C for 2 h, followed by quenching by water (2 mL) and 2N NaOH (5 mL). The reaction was then warmed to room temperature. The organic layer was separated and washed with water (10 mL) and the aqueous fractions were extracted with diethyl ether (3×10 mL). The organic fractions were washed with brine (20 mL) before drying over $MgSO_4$ and removing the solvent under reduced pressure. Alcohol **3.17b** (302 mg, 1.28 mmol, 85%) was isolated as a colourless oil by flash chromatography (hexane/EtOAc 80:20→hexane/EtOAc 60:40).

Mw 236.31 ($C_{14}H_{20}O_3$);
Rf 0.16 (hexane/EtOAc 80:20);
IR (cm^{-1}) 3407 (O–H), 2962, 2933, 2871 (C–H), 1613, 1586, 1514 (ar C=C), 1463(C=C), 1302, 1249, 1147, 1074, 1035 (C–O);
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.26 ($2H_{Ar}$, m), 6.91-6.88 ($2H_{Ar}$, m), 5.63 ($1H_1$, t, J = 7.4 Hz), 4.46 ($2H_4$, s), 4.15 ($2H_6$, $2H_7$, s), 3.82 ($3H_8$, s), 2.07 ($2H_2$, app qn, J = 7.5 Hz), 0.99 ($3H_3$, t, J = 7.5 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0 (C5), 134.3 (Ar), 133.5 (Ar), 130.0 (C1), 129.4 (Ar), 113.8 (Ar), 72.2 (C7), 67.2 (C6), 66.7 (C8), 55.3 (C4), 20.9 (C2), 14.1 (C3);
ES+MS m/z [%] 495.5 [10] $(2M+Na)^+$, 300.3 [5] $(M+Na+MeCN)^+$, 254.3 [10] $(M+NH_4)^+$, 219.1 [10] $(M-H_2O)^+$;
HRMS (ES+) for $C_{14}H_{20}O_3$ $(M+Na)^+$ calcd. 259.1310, found 259.1305.

2-(*p*-Methoxybenzyl)oxymethyl-pent-2*E*-enal (3.1b)



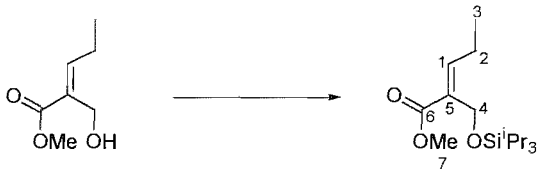
3.1b

Sulfur trioxide-pyridine complex (521 mg, 3.28 mmol) was dissolved in DMSO (3 mL) and triethylamine (500 μL, 3.30 mmol) was added dropwise. This solution was added dropwise to a solution of **3.17b** (310 mg, 1.31 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction was stirred at 0 °C for 4 h, followed by quenching by pouring into 2M NH_4Cl (10

mL). The phases were separated and the aqueous fraction was extracted with pentane (4×20 mL). The organic fractions were dried over $MgSO_4$ before the solvent was removed under reduced pressure. Aldehyde **3.1b** (282 mg, 1.20 mmol, 74%) was isolated as a colourless oil by flash chromatography (hexane/EtOAc 65:35).

Mw 234.29 ($C_{14}H_{18}O_3$);
Rf 0.58 (hexane/EtOAc 65:35);
IR (cm^{-1}) 2969, 2931, 2874, 2837 (C–H), 1682 (C=O), 1649, 1607, 1526, 1460 (C=C), 1299, 1247, 1172, 1077, 1025 (C–O);
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 ($1H_6$, s), 7.28-7.25 ($2H_{Ar}$, dt, J = 8.6, 2.4 Hz), 7.24-6.85 ($2H_{Ar}$, dt, J = 8.6, 2.6 Hz), 6.70 ($1H_1$, t, J = 7.4 Hz), 4.44 ($2H_4$, s), 4.20 ($2H_7$, s), 3.81 ($3H_8$, s), 2.47 ($2H_2$, app qn, J = 7.5 Hz), 1.13 ($3H_3$, t, J = 7.5 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9 (C6), 161.1 (Ar), 159.2 (C5), 139.0 (Ar), 130.2 (C1), 129.4 (Ar), 113.7 (Ar), 72.5 (C7), 60.6 (C8), 55.2 (C4), 22.6 (C2), 13.0 (C3);
ES+MS m/z [%] 252.1 [10] $(M+NH_4)^+$,
HRMS (ES+) for $C_{14}H_{18}O_3$ $(M+Na)^+$ calcd. 257.1148, found 257.1148.

Methyl-2-(tri*iso*propylsilyl)oxymethyl-pent-2*E*-enoate (3.8c)



3.8c

Tri*iso*propylsilyl chloride (6.3 mL, 29.5 mmol) was added dropwise over 15 minutes to a solution of **3.16** (3.6 g, 24.6 mmol) and imidazole (2.1 g, 31.3 mmol) in DMF (20 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h before warming to room temperature. The reaction was stirred for a further 16 h at rt followed by quenching by pouring into ice-cold water (100 mL). The products were extracted with CH_2Cl_2 (3×50 mL). The combined organic fractions were dried over $MgSO_4$ before removing the solvent under reduced pressure. Silyl product **3.8c** (7.2 g, 24.0 mmol, 96%) was obtained as a colourless oil by flash chromatography (hexane/EtOAc 98:2).

Mw 300.51 ($C_{16}H_{32}O_3Si$);
Rf 0.51 (hexane/EtOAc 95:5);
IR (cm^{-1}) 2944, 2867 (C–H), 1720, 1649 (C=O), 1462, 1436 (C=C), 1311, 1286, 1238

(Si–O), 1086, 1065, (C–O);

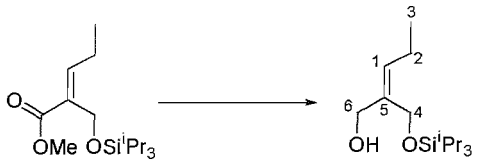
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 ($1H_1$, t, J = 7.5 Hz), 4.47 ($2H_4$, s), 3.48 ($3H_7$, s), 2.35 ($2H_2$, app qn, J = 7.5 Hz), 1.10–1.06 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, $3H_3$, m);

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9 (C6), 147.9 (C5), 131.0 (C1), 57.3 (C4), 51.6 (C7), 22.0 (C2), 17.9 ($TIPSCH_2$), 13.3 ($TIPSCH_3$), 12.0 (C3);

CIMS m/z [%] 301 [52] $(M)^+$, 257 [100] $(M–iPr–H)^+$;

Anal. $C_{16}H_{32}O_3Si$: calcd. C, 63.95; H, 10.73, found C, 63.72; H, 11.0.

2-(Tri*iso*propylsilyl)oxymethyl-pent-2*Z*-enol (3.17c)



3.17c

Di*iso*butyl aluminium hydride, 1.0M in hexanes, (44.0 mL, 44.0 mmol) was added dropwise over 1 h to a solution of **3.8c** (5.2 g, 17.4 mmol) in diethyl ether (150 mL) at –78 °C. The reaction was stirred at –78°C for 2 h, followed by quenching by water (8 mL) and 2N NaOH (15 mL). The reaction was warmed to room temperature and the organic phase was separated and washed with water (50 mL). The combined aqueous washings were extracted with diethyl ether (3×50 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Alcohol **3.17c** (4.4 g, 16.1 mmol, 93%) was isolated as a colourless oil by flash chromatography (EtOAc/40-60 petrol 10:90). Spectral data match the literature.[42]

Mw 272.50 ($C_{15}H_{32}O_2Si$);

Rf 0.27 (hexane/EtOAc 90:10);

IR (cm^{-1}) 3364 (O–H), 2961, 2943, 2866 (C–H), 1463 (C=C), 1384 (Si–O), 1085, 1066, 1013 (C–O);

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 ($1H_1$, t, J = 7.4 Hz), 4.46 ($2H_4$, s), 4.18 ($2H_6$, s), 2.04 ($2H_2$, app qn, J = 7.5 Hz), 1.13–1.07 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, m), 0.99 ($3H_3$, t, J = 7.5 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2 (C5), 130.8 (C1), 67.6 (C6), 61.6 (C4), 20.8 (C2), 17.9 (TIPSCH), 14.1 (C3), 11.8 ($TIPSCH_3$);

CIMS m/z [%] 273 [25] $(M+2H)^+$, 255 [100] $(M–2H–OH_2)^+$, 229 [40] $(M–^iPr+H)^+$.

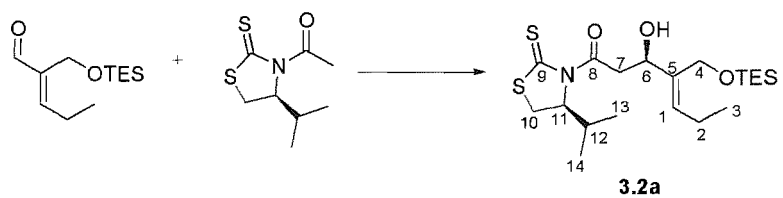
2-(Tri*iso*propylsilanyl)oxymethyl-pent-2*E*-enal (3.1c)

3.1c

Sulfur trioxide-pyridine complex (6.7 g, 40.2 mmol) was dissolved in 1:1 CH_2Cl_2/DMSO (50 mL) and triethylamine (6.2 mL, 44.1 mmol) was added dropwise. This solution was added dropwise to a solution of **3.17c** (4.4 g, 16.1 mmol) in 1:1 CH_2Cl_2/DMSO (50 mL) at 0 °C. The reaction was stirred at 0 °C for 4 h, followed by quenching by pouring into 2M NH_4Cl (50 mL). The organic fraction was separated and washed with water (50 mL) and the combined aqueous fractions were extracted with pentane (3×30 mL). The organic fractions were dried over $MgSO_4$ before the solvent was removed under reduced pressure. Aldehyde **3.1c** (4.2 g, 96%, 15.4 mmol) was isolated as a colourless oil by flash chromatography (EtOAc/40-60 petrol 5:95).

Mw 269.31 ($C_{15}H_{30}O_2Si$);
Rf 0.64 (hexane/EtOAc 90:10);
IR (cm^{-1}) 2943, 2867, 2711 (C–H), 1690 (C=O), 1646, 1463 (C=C), 1383, 1207 (Si–O), 1090, 1068, 1014 (C–O);
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 ($1H_6$, s), 6.61 ($1H_1$, t, J = 7.5 Hz), 4.46 ($2H_4$, s), 2.58 ($2H_2$, app qn, J = 7.5 Hz), 1.17–1.03 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, $3H_3$, m);
^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9 (C6), 160.1 (C5), 143.2 (C1), 55.1 (C4), 22.8 (C2), 17.9 (TIPSCH), 13.1 (C3), 11.9 (TIPSCH3);
CIMS m/z [%] 271 [85] $(M+H)^+$, 227 [80] $(M-{}^iPr)^+$;
HRMS (EI) for $C_{15}H_{29}O_2Si$ $(M-H)^+$ calcd. 269.19368, found 269.1928.

(4*S*)-*Iso*propyl-3-(3-hydroxy-4-(triethylsilanyl)oxymethyl-hept-4-enoyl)-thiazolidine-2-thione (3.2a)

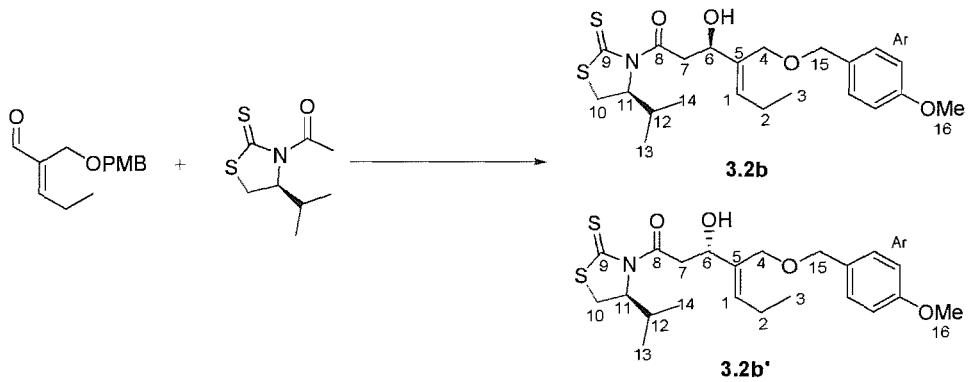


3.2a

Tin(II) trifluoromethanesulfonate (394 mg, 0.89 mmol) was suspended in CH_2Cl_2 (0.5 mL) between –40 °C and –50 °C and *N*-ethylpiperidine (124 μL, 0.89 mmol) was added dropwise. A solution of **3.9** (152 mg, 0.75 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise and the reaction stirred between –40 °C and –50 °C for 2 h. The reaction mixture was cooled to –78 °C whereupon a solution of **3.1a** (205 mg, 0.89 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise. The reaction was stirred at –78 °C for 3 h followed by quenching by 2M NH_4Cl (5 mL). The reaction was then warmed to room temperature and the organic layer was separated and washed with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The organic fractions were dried over $MgSO_4$ and the solvent removed under reduced pressure. Nagao acetate aldol product **3.2a** (144 mg, 0.33 mmol, 44%) was isolated as a yellow oil by flash chromatography (hexane/EtOAc 85:15), remaining starting materials were returned. NMR analysis showed a single diastereoisomer.

Mw 431.73 ($C_{20}H_{37}NO_3S_2Si$);
Rf 0.19 (hexane/EtOAc 80:20);
$[\alpha]_D$ +254 (*c* 1.70, $CHCl_3$, 22 °C);
IR (cm^{-1}) (solution in CH_2Cl_2) 3380 (O–H), 2955, 2931, 2902, 2879 (C–H), 1697 (C=O),1470 (C–C), 1361 (Si–O), 1233 (C–O), 1167 (C=S);
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 ($1H_1$, t, *J* = 7.3 Hz), 5.17 ($1H_{11}$, app t, *J* = 6.5 Hz), 4.76 ($1H_6$, m), 4.39 ($1H_4$, d, *J* = 11.8 Hz), 4.33 ($1H_4$, d, *J* = 11.8 Hz), 3.66 ($1H_7$, dd, *J* = 17.0, 9.0 Hz), 3.57 ($1H_2$, dd, *J* = 17.3, 3.5 Hz), 3.52 ($1H_{12}$, dd, *J* = 10.5, 7.0 Hz), 3.44 ($1H_{OH}$, d, *J* = 5.8 Hz), 3.01 ($1H_{10}$, d, *J* = 11.5 Hz), 2.39 ($1H_{10}$, m), 2.16-2.01 ($2H_2$, m), 1.07 ($3H_{13}$, d, *J* = 6.7 Hz), 1.02–0.97 ($9H_{TESCH3}$, $3H_{14}$, $3H_3$, m), 0.65 ($6H_{TESCH2}$, q, *J* = 7.8 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8 (C9), 172.4 (C8), 136.8 (C5), 131.0 (C1), 72.1 (C6), 71.6 (C101), 59.4 (C4), 44.9 (C7), 30.9 (C12), 30.7 (C10), 20.7 (C2), 19.1 (C3), 17.8 (C13), 14.1 (C14), 6.8 ($TESCH_2$), 4.3 ($TESCH_3$);
ES+MS m/z [%] 495 [100] $(M+MeCN+Na)^+$, 454 [15] $(M+Na)^+$, 414 [20] $(M-H_2O+H)^+$;
HRMS (ES+) for $C_{20}H_{37}NO_3S_2Si$ $(M+Na)^+$ calcd. 454.1876, found 454.1881.

4*S*-*Iso*propyl-3-(3*R*-hydroxy-4-(*p*-methoxybenzyl)oxymethyl-hept-4-enoyl)-thiazolidin-2-thione (3.2b), 4*S*-*Iso*propyl-3-(3*S*-hydroxy-4-(*p*-methoxybenzyl)oxymethyl-hept-4-enoyl)-thiazolidin-2-thione (3.2b)



Tin(II) trifluoromethanesulfonate (275 mg, 0.66 mmol) was suspended in CH_2Cl_2 (1 mL) between –40 °C and –50 °C and *N*-ethylpiperidine (90 μL, 0.66 mmol) was added dropwise. A solution of **3.9** (125 mg, 0.61 mmol) in CH_2Cl_2 (2 mL) was added dropwise and the reaction stirred between –40 °C and –50 °C for 4 h. The reaction mixture was cooled to –78 °C whereupon a solution of **3.1b** (149 mg, 0.64 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction was stirred at –78 °C for 30 minutes followed by quenching by 2M NH_4Cl (5 mL). The reaction was warmed to room temperature and the organic layer was separated and washed with water (5 mL). The aqueous fractions were extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were dried over $MgSO_4$ before the solvent was removed under reduced pressure. Nagao acetate aldol product **3.2b** (28 mg, 0.06 mmol, 11%) was isolated as a yellow oil by flash chromatography (hexane/EtOAc 85:15), remaining starting materials were returned. NMR analysis showed a single diastereoisomer.

Tin(II) trifluoromethanesulfonate (502 mg, 1.20 mmol) was suspended in CH_2Cl_2 (0.5 mL) between –40 °C and –50 °C and *N*-ethylpiperidine (165 μL, 1.20 mmol) was added dropwise. A solution of **3.9** (211 mg, 0.90 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise and the reaction stirred between –40 °C and –50 °C for 2 h. The reaction mixture was cooled to –78 °C whereupon a solution of **3.1b** (282 mg, 1.20 mmol) in CH_2Cl_2 (0.8 mL) was added dropwise. The reaction was stirred at –78 °C for 3 h, followed by quenching by 2M NH_4Cl (5 mL). The reaction was then warmed to room temperature and the organic layer was separated and washed with water (10 mL). The aqueous fractions were

extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were dried over $MgSO_4$ before the solvent was removed under reduced pressure. Nagao acetate aldol product **3.2b** and **3.2b'** (221 mg, 0.51 mmol, 51%) were isolated as a yellow oil by flash chromatography (hexane/EtOAc 85:15), remaining starting materials were returned. HPLC analysis showed a 3:1 ratio of diastereoisomers **3.2b:3.2b'**.

Data for 3.2b

Mw 437.62 ($C_{22}H_{31}NO_4S_2$);

Rf 0.12 (hexane/EtOAc 80:20);

$[\alpha]_D$ +271 (*c* 0.95, $CHCl_3$, 23 °C);

IR (cm^{-1}) (solution in CH_2Cl_2) 3474 (O–H), 2963 (C–H), 1692 (C=O), 1606, 1512, 1465, 1365, 1242 (C–O), 1167 (C=S);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 ($2H_{Ar}$, m), 6.90-6.85 ($2H_{Ar}$, m), 5.74 ($1H_1$, t, *J* = 7.4 Hz), 5.15 ($1H_{11}$, t, *J* = 6.8 Hz), 4.64 ($1H_6$, m), 4.45 ($2H_{15}$, s), 4.15 ($1H_4$, d, *J* = 11.3 Hz), 4.10 ($1H_4$, d, *J* = 11.3 Hz), 3.81 ($3H_{16}$, s), 3.69 ($1H_7$, dd, *J* = 16.8, 9.3 Hz), 3.52 ($1H_2$, dd, *J* = 17.0, 3.5 Hz), 3.48 ($1H_{12}$, dd, *J* = 11.2, 7.7 Hz), 3.41 ($1H_{OH}$, s br), 3.02 ($1H_{10}$, d, *J* = 7.9 Hz), 2.38 ($1H_{10}$, m), 2.13-2.04 ($2H_2$, m), 1.06 ($3H_{13}$, d, *J* = 6.8 Hz), 0.99 ($3H_3$, t, *J* = 7.4 Hz), 0.98 ($3H_{14}$, d, *J* = 6.8 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9 (C9), 172.6 (C8), 159.2 (Ar), 134.9 (C5), 133.7 (Ar), 129.9 (Ar), 129.4 (C1), 113.8 (Ar), 72.3 (C15), 71.7 (C6), 71.5 (C11), 65.4 (C16), 55.2 (C4), 44.4 (C7), 30.8 (C12), 30.6 (C10), 20.9 (C2), 19.1 (C3), 17.7 (C14), 14.1 (C13);

ES+MS m/z [%] 460.3 [20] $(M+Na)^+$; 438.2 [10] $(CH_2PhMe)^+$;

HRMS (ES+) for $C_{22}H_{31}NO_4S_2$ $(M+H)^+$ calcd. 438.1767, found 438.1763.

Data for 3.2b' (C6 epimer)

Mw 437.62 ($C_{22}H_{31}NO_4S_2$);

Rf 0.12 (hexane/EtOAc 80:20);

$[\alpha]_D$ +197 (*c* 1.25, $CHCl_3$, 23 °C);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 ($2H_{Ar}$, m), 6.90-6.85 ($2H_{Ar}$, m), 5.74 ($1H_1$, t, *J* = 7.4 Hz), 5.15 ($1H_{11}$, t, *J* = 6.8 Hz), 4.64 ($1H_6$, m), 4.45 ($2H_{15}$, s), 4.15 ($1H_4$, d, *J* = 11.3 Hz), 4.10 ($1H_4$, d, *J* = 11.3 Hz), 3.81 ($3H_{16}$, s), 3.68 ($1H_7$, dd, *J* = 17.5, 12.1 Hz), 3.53 ($1H_7$, dd, *J* = 17.3, 5.04 Hz), 3.49 ($1H_{12}$, dd, *J* = 15.6, 10.8 Hz), 3.02 ($1H_{10}$, d, *J* = 7.9 Hz), 2.38 ($1H_{10}$, m), 2.13-2.04 ($2H_2$, m), 1.06 ($3H_{13}$, d, *J* = 6.8 Hz), 0.99 ($3H_3$, t, *J* = 7.4 Hz), 0.98 ($3H_{14}$, d, *J* = 6.8 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9 (C9), 172.6 (C8), 159.2 (Ar), 134.9 (C5), 133.7 (Ar), 129.9 (Ar), 129.4 (C1), 113.8 (Ar), 72.3 (C15), 71.7 (C6), 71.5 (C11), 65.4 (C16), 55.2 (C4), 44.4 (C7), 30.8 (C12), 30.6 (C10), 20.9 (C2), 19.1 (C3), 17.7 (C14), 14.1 (C13);
ES+MS m/z [%] 460.3 [20] $(M+Na)^+$; 438.2 [10] $(CH_2PhMe)^+$;

4*S*-*Iso*propyl-3-(3R-hydroxy-4-(tri*iso*propylsilanyl)oxymethyl-hept-4-enoyl)-thiazolidine-2-thione (3.2c)

3.2c

Tin(II) trifluoromethanesulfonate (5.0 g, 12.0 mmol) was suspended in CH_2Cl_2 (8 mL) between –40 °C and –50 °C, *N*-ethylpiperidine (1.7 mL, 12.0 mmol) was added dropwise. A solution of **3.9** (2.0 g, 10.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise and the reaction stirred between –40 °C and –50 °C for 3 h. The reaction mixture was cooled to –78 °C whereupon a solution of **3.1c** (3.2 g, 12.0 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction was stirred at –78 °C for 3 h, followed by quenching by 1M $NaHSO_4$ (10 mL). The reaction was warmed to room temperature and the organic layer was separated and washed with c.$NaHCO_3$ (30 mL). The aqueous washings were extracted with CH_2Cl_2 (4×20 mL). The organic fractions were dried over $MgSO_4$ before the solvent was removed under reduced pressure. Nagao acetate aldol product **3.2c** (3.0 g, 6.4 mmol, 67%) was isolated as a yellow oil by flash chromatography (hexane/EtOAc 90:10), remaining starting materials were returned. NMR analysis shows a single diastereoisomer.

Mw 473.81 ($C_{23}H_{42}NO_3S_2Si$);
Rf 0.09 (hexane/EtOAc 90:10);
[α]$_D$ +239 (*c* 0.90, $CHCl_3$, 25 °C);
IR (cm^{-1}) (solution in CH_2Cl_2) 3489 (O–H), 2965, 2936, 2865 (C–H), 1694 (C=O),1469 (C=C), 1370 (Si–O), 1256 (C–O), 1152 (C=S);
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 ($1H_1$, t, *J* = 7.5 Hz), 5.16 ($1H_{11}$, app t, *J* = 6.8 Hz), 4.79 ($1H_6$, m), 4.48 ($1H_4$, d, *J* = 12.0 Hz), 4.45 ($1H_4$, d, *J* = 12.0 Hz), 3.66 ($1H_7$, dd, *J* = 17.0, 8.7 Hz), 3.58 ($1H_7$, dd, *J* = 16.8, 3.8 Hz), 3.52 ($1H_{OH}$, d, *J* = 9.0 Hz), 3.50 ($1H_{12}$, dd, *J* = 8.0, 4.2 Hz), 3.02 ($1H_{10}$, dd, *J* = 0.8, 11.3 Hz), 3.38 ($1H_{10}$, m), 2.11-1.99 ($2H_2$, m), 1.14–0.96

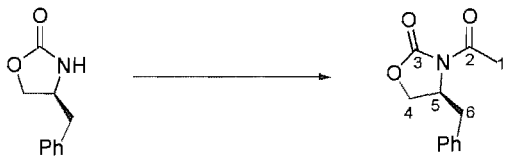
($18H_{TIPSCH3}$, $3H_{TIPSCH}$, $3H_3$, $3H_{13}$, $3H_{14}$, m);

^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8 (C9), 172.3 (C8), 136.8 (C5), 130.5 (C1), 71.9 (C6), 71.6 (C11), 60.4 (C4), 44.9 (C7), 30.8 (C12), 30.7 (C10), 20.8 (C2), 19.1 (C3), 18.0 ($TIPSCH_3$), 17.8 (C14), 14.1 (C13), 11.8 (TIPSCH);

ES+MS m/z [%] 596.4 [15] $(M+2H+Na)^+$, 474.4 [20] $(M+2H)^+$;

Anal. $C_{23}H_{42}NO_3S_2Si$: calcd. C, 58.31; H, 9.15; N, 2.95, found C, 58.51; H, 9.43; N, 2.77.

3-Acetyl-(4*S*)-benzyl oxazolidin-2-one (3.18)



3.18

n-Butyl lithium, 2.5M in hexanes, (3.4 mL, 8.5 mmol) was added dropwise to a solution of (4*S*)-benzyloxazolidinone (1.2 g, 6.5 mmol) in THF (10 mL) at –78 °C. Acetyl chloride (602 μL, 8.5 mmol) was added dropwise and the reaction was warmed to 0 °C over 2 h. The reaction was quenched by 2M NH_4Cl (15 mL) before warming to room temperature. The organic phase was separated and washed with water (10 mL), the aqueous washings were extracted with CH_2Cl_2 (3×20 mL). The combined organic fractions were dried over $MgSO_4$ before the solvent was removed under reduced pressure. Evans reagent **3.18** (1.0 g, 4.6 mmol, 83%) was isolated as a white solid by flash chromatography (hexane/EtOAc 80:20).

Mw 219.24 ($C_{12}H_{13}NO_3$);

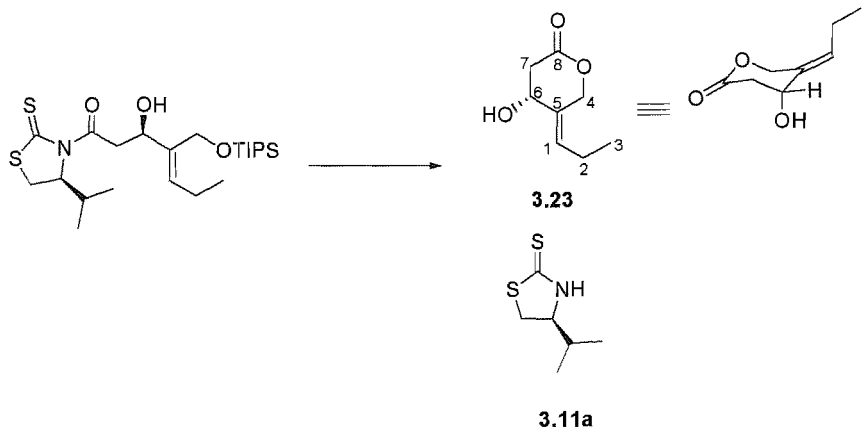
Rf 0.4 (hexane/EtOAc 80:20);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.20 ($5H_{Ar}$, m), 4.69 ($1H_5$, m), 4.25–4.16 ($2H_6$, m), 3.32 ($1H_4$, dd, J = 13.4, 3.3 Hz), 2.79 ($1H_4$, dd, J = 13.4, 9.6 Hz), 2.57 ($3H_1$, s);

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (C2), 135.6 (C3), 135.2 (Ar), 129.4 (Ar), 128.9 (Ar), 127.3 (Ar), 66.1 (C4), 55.0 (C5), 37.8 (C6), 23.8 (C1);

CIMS m/z [%] 237 [38] $(M+NH_4)^+$, 220 [100] $(M)^+$.

Lactone (3.23)



3.23

3.11a

Hydrogen fluoride-pyridine complex (200 μL, 0.50 mmol) was added dropwise to a solution of **3.2c** (97 mg, 0.21 mmol) in THF (2.0 mL) at room temperature. The reaction was stirred at rt for 24 h before the addition of ethyl acetate (2.0 mL) and conc.$NaHCO_3$ (2.0 mL). The organic fraction was separated and washed with c.$NaHCO_3$ (10 mL) and the combined aqueous washings were extracted with CH_2Cl_2 (3×10 mL). The organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Products **3.11a** (27 mg, 0.17 mmol, 82%) and **3.23** (22mg, 0.14 mmol, 69%) were isolated by flash chromatography (hexane/EtOAc 80:20).

Data for 3.23

Mw 156.18 ($C_8H_{13}O_3$);

Rf 0.18 (40-60 petrol/acetone 80:20);

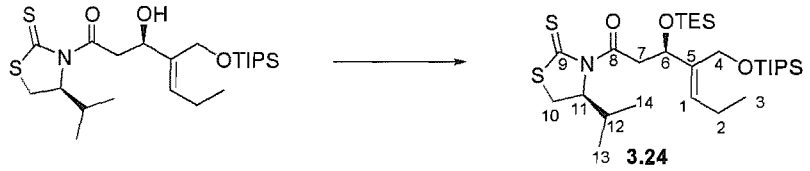
IR (cm^{-1}) 3419 (O–H), 1725 (C=O), 1460, 1396 (C=C), 1258, 1208, 1142, 104, 1024.6 (C–O);

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 ($1H_1$, td, J = 7.7, 1.0 Hz), 5.04 ($1H_7$, d, J = 14.3 Hz), 4.86 ($1H_7$, d, J = 14.1 Hz), 4.55 ($1H_6$, t, J = 4.5 Hz), 2.80 ($1H_4$, s), 2.79 ($1H_4$, s), 2.08 ($2H_2$, app qn, J = 7.5 Hz), 1.04 ($3H_3$, t, J = 7.5 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (C8), 132.3 (C5), 130.8 (C1), 68.1 (C6), 65.5 (C7), 39.3 (C4), 20.8 (C2), 13.7 (C3);

CIMS m/z [%] 156 (M^+), 139 $(M-H_2O)^+$.

4*S*-*Iso*propyl-3-(3*R*-(triethylsilanyl)oxy-4-(tri*iso*propylsilanyl)oxymethyl-hept-4-enoyl)-thiazolidine-2-thione (3.24)

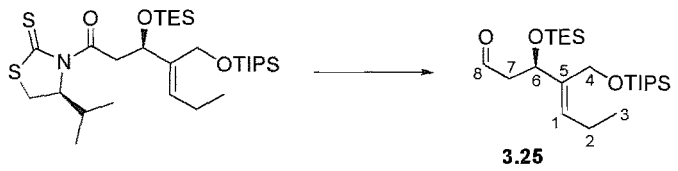


3.24

2,6-Lutidine (2.3 mL, 19.5 mmol) was added dropwise to a solution of **3.2c** (3.7 g, 7.8 mmol) in CH_2Cl_2 (40 mL) at 0 °C. Triethylsilyl trifluoromethanesulfonate (4.4 mL, 19.5 mmol) was then added dropwise and the reaction was stirred at 0 °C for 1 h. The reaction was warmed to room temperature. The reaction was stirred at room temperature for 1 h before quenching by water (40 mL). The organic phase separated and washed with water (80 mL) and the combined aqueous washings extracted with CH_2Cl_2 (3×50 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Protected Nagao product **3.24** (4.4 g, 7.41 mmol, 95%) was isolated as a yellow oil by flash chromatography (hexane/EtOAc 98:2).

Mw 588.07 ($C_{29}H_{57}NO_3S_2Si_2$);
Rf 0.6 (hexane/EtOAc 90:10);
[α]$_D$ +171.5 (c 0.65, $CHCl_3$, 25 °C);
IR (cm^{-1}) 2956 (alkene C–H), 2870 (C–H), 1699 (C=O), 1462 (C=C), 1280, 1250 (Si–O), 1159 (C=S), 1045 (C–O), 1006 (C–O);
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 ($1H_1$, t, J = 7.2 Hz), 5.02 ($1H_{11}$, app t, J = 6.7 Hz), 4.93 ($1H_6$, m), 4.34 ($1H_4$, d, J = 12.0 Hz), 4.27 ($1H_4$, d, J = 11.8 Hz), 3.62 ($1H_7$, dd, J = 17.1, 9.2 Hz), 3.48 ($1H_{12}$, dd, J = 11.3, 7.8 Hz), 3.25 ($1H_7$, dd, J = 17.1, 2.4 Hz), 3.03 ($1H_{10}$, d, J = 11.4 Hz), 2.41 ($1H_{10}$, m), 2.14-2.03 ($2H_2$, m), 1.11–0.90 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, $3H_3$, $3H_{13}$, $3H_{14}$, m), 0.63–0.49 ($6H_{TESCH2}$, $9H_{TESCH3}$, m);
^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0 (C9), 172.1 (C8), 139.4 (C5), 129.4 (C1), 71.8 (C6), 70.8 (C10), 59.3 (C4), 46.8 (C7), 31.3 (C11), 30.9 (C12), 20.9 (C2), 19.2 (C13, 14), 18.3 ($TIPSCH_3$), 14.4 (C3), 12.1 (TIPSCH), 7.1 ($TESCH_3$), 4.9 ($TESCH_2$);
ES+MS m/z [%] 588 [10] $(M)^+$;
Anal. $C_{29}H_{57}NO_3S_2Si_2$: calcd. C, 66.2; H, 10.26; N, 2.50, found: C, 66.18; H, 10.51; N, 2.13.

3*R*-(Triethylsilanyl)oxy-4*R*-(tri*iso*propylsilanyl)oxymethyl-hept-4-enal (3.25)

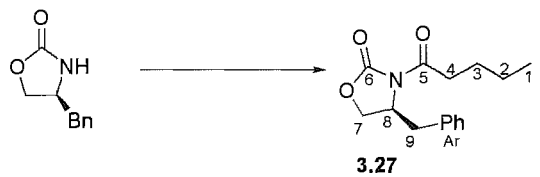


3.25

Di*iso*butyl aluminium hydride, 1.0M in hexanes, (2.77 mL, 2.77 mmol) was added dropwise to a solution of **3.24** (1.48 g, 2.52 mmol) in diethyl ether (40 mL) at –78 °C. The reaction was stirred at –78 °C for 3 h followed by quenching by water (15 mL) and 2N NaOH (15 mL). The reaction was warmed to room temperature. The organic phase was separated and washed with water (15 mL) and the aqueous washings were extracted with CH_2Cl_2 (3×50 mL). The organic phase was dried over $MgSO_4$ before the solvent was removed under reduced pressure. **3.25** (1.07 g, 2.49 mmol, 99%) was isolated as a colourless oil by flash chromatograph (EtOAc/40–60 petrol 2:98→5:95).

Mw 428.80 ($C_{23}H_{48}O_3Si_2$);
Rf 0.21 (EtOAc/hexane 2:98);
$[\alpha]_D$ +8.6 (c 1.05, $CHCl_3$, 25 °C);
IR (cm^{-1}) 1727 (C=O), 1462 (C=C), 1384,1242 (Si–O), 1086 (C–O), 1063 (C–O);
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 ($1H_8$, t, J = 2.6 Hz), 5.63 ($1H_1$, t, J = 7.4 Hz), 4.80 ($1H_6$, t, J = 5.6 Hz), 4.39 ($1H_4$, d, J = 11.8 Hz), 4.26 ($1H_4$, d, J = 11.8 Hz), 2.68–2.64 ($2H_7$, m), 2.09-2.03 ($2H_2$, m), 1.13–0.98 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, m), 0.99 ($9H_{TESCH3}$, t, J = 7.7 Hz), 0.94 ($3H_3$, t, J = 7.7 Hz), 0.59 ($6H_{TESCH2}$, q, J = 7.9 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1 (C8), 138.4 (C5), 129.5 (C1), 69.6 (C6), 58.7 (C4), 50.7 (C7), 20.6 (C2), 18.0 ($TIPSCH_3$), 14.2 (C3), 11.9 (TIPSCH), 6.8 ($TESCH_3$), 4.7 ($TESCH_2$);
ES+ m/z [%] 897.3 [25] $(2M+MeCN)^+$, 429.4 [15] $(M+H)^+$;
HRMS (ES+) for $C_{23}H_{48}O_3Si_2$ $(M+Na)^+$ calcd. 451.3034, found 451.3035.

***N*-Valeroyl-(4*S*)-benzyl oxazolidinone (3.27)**

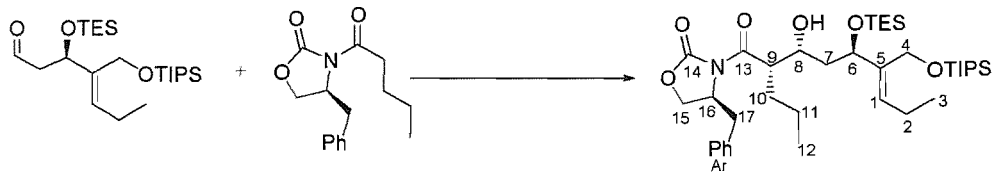


3.27

n-Butyl lithium, 2.5M in hexanes, (23.0 mL, 57.5 mmol) was added dropwise to a solution of (4S)-Benzyl oxazolidinone (5.0 g, 28.2 mmol) in THF (25 mL) at –78 °C. The reaction was stirred at –78 °C for 1 h when valeroyl chloride (6.7 mL, 56.4 mmol) was added dropwise. The reaction was warmed to 0 °C over 1 h. The reaction was stirred at 0 °C for 2 h followed by quenching by 2M NH_4Cl (30 mL). The reaction mixture was warmed to room temperature and washed with water (50 mL). The products were extracted with CH_2Cl_2 (3×100 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Evans reagent **3.27** (6.8 g, 26.1 mmol, 92 %) was isolated as a colourless oil by flash chromatography (hexane/acetone 85:15). Spectral data matches that in the literature[51].

Mw 261.32 ($C_{15}H_{20}NO_3$);
Rf 0.33 (hexane/acetone 85:15);
^{1}H NMR 300MHz, $CDCl_3$ δ 7.30–7.21 ($5H_{Ar}$, m), 4.69 ($1H_8$, m), 4.24–4.15 ($2H_7$, m), 3.31 ($1H_9$, dd, J = 13.2, 3.3 Hz), 3.04–2.85 ($2H_4$, m), 2.77 ($1H_9$, dd, J = 13.2, 9.5 Hz), 1.74–1.64 ($2H_3$, m), 1.48–1.36 ($2H_2$, m), 0.98 ($3H_1$, t, J = 7 Hz);
^{13}C NMR 300 MHz, $CDCl_3$ δ 173.6 (C5), 152.3 (C6), 135.5 (Ar), 129.6 (Ar), 129.1 (Ar), 127.5 (Ar), 66.3 (C7), 55.3 (C8), 38.1 (C9), 35.4 (C4), 26.5 (C3), 22.4 (C2), 14.0 (C1).

4S-Benzyl-3-(3*R*-hydroxy-2*S*-propyl-5*R*-(triethysilanyl)oxy-6-(tri*iso*propylsilanyl)oxymethyl-non-6-enoyl)oxazolidin-2-one (3.28)



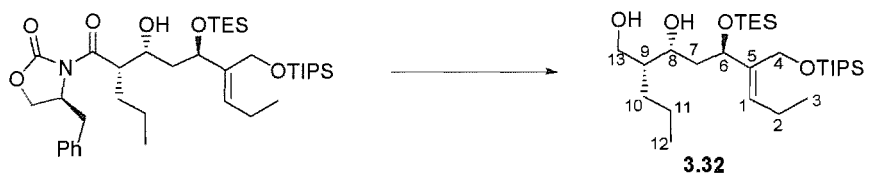
3.25 **3.27** **3.28**

Dibutylboron trifluoromethanesulfonate, 1.0M in CH_2Cl_2, (3.40 mL, 3.40 mmol) was added dropwise to a solution of **3.27** (811 mg, 3.10 mmol) in CH_2Cl_2 (20 mL) at –78 °C. Triethylamine (559 μL, 4.02 mmol) was added dropwise and the reaction stirred at –78 °C for 30 minutes. The reaction was then warmed to 0 °C and stirred for 1 h. The reaction was recooled to –78 °C whereupon **3.25** (1.06 g, 2.48 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The reaction was stirred at –78 °C for 1 h when it was warmed to 0 °C for 1 h. The reaction was quenched by pH 7.2 phosphate buffer (20 mL), methanol (20

mL) and 25% aq. H_2O_2 (10 mL) before stirring at 0 °C for 1 h. The reaction was warmed to room temperature and the organic phase separated and washed with water (15 mL). The aqueous washings were extracted with CH_2Cl_2 (3×50 mL). The organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Evans *syn*-aldol product **3.28** (1.54 g, 2.23 mmol, 90%) was isolated as a colourless oil by flash chromatography (acetone/40–60 petrol 10:90). NMR analysis shows a single distereoisomer.

Mw 690.11 ($C_{38}H_{67}NO_6Si_2$);
Rf 0.29 (acetone/hexane 10:90);
$[\alpha]_D$ +51.0 (c 0.89, $CHCl_3$, 22 °C);
IR (cm^{-1}) 3520 (O–H), 1783, 1694 (C=O), 1462 (C=C), 1383, 1349 (ar C=C), 1239, 1026 (Si–O), 1080, 1062, 1006 (C–O);
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.22 ($5H_{Ar}$, m), 5.61 ($1H_1$, t, J = 7.4 Hz), 4.77 ($1H_6$, t(br)), 4.67 ($1H_{16}$, m), 4.48 ($1H_4$, d, J = 12.1 Hz), 4.14–4.03 ($1H_4$, $1H_8$, $1H_9$, $2H_{15}$, m), 3.88 ($1H_{OH}$, s), 3.34 ($1H_{17}$, dd, J = 13.2, 3.0 Hz), 2.69 ($1H_{17}$, dd, J = 13.2, 10.1 Hz), 2.17-1.52 ($2H_2$, m), 1.84–1.80 ($3H_{7,10}$, m), 1.58 ($1H_{10}$, m), 1.40–1.26 ($2H_{11}$, m), 1.10–1.05 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, m), 1.00–0.91 ($9H_{TESCH3}$, $3H_3$, $3H_{12}$, m), 0.59 ($6H_{TESCH2}$, q, J = 7.7 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3 (C13), 153.4 (C14), 137.5 (C5), 135.7 (Ar), 129.5 (Ar), 129.1 (Ar), 128.8 (Ar), 127.4 (C1), 72.3 (C6), 69.9 (C8), 65.9 (C15), 59.1 (C4), 55.9 (C16), 48.2 (C9), 38.2 (C17), 38.1 (C7), 30.3 (C10), 20.8 (C2), 20.7 (C11), 18.2 ($TIPSCH_3$), 14.5 (C3, 12), 12.1 (TIPSCH), 7.0 ($TESCH_3$), 4.7 ($TESCH_2$);
ES+MS m/z [%] 712.5 [45] $(M+Na)^+$, 690.5 [75] $(M)^+$;
HRMS (ES+) for $C_{38}H_{67}NO_6Si_2$ $(M+Na)^+$ calcd. 712.4399, found 712.4401.

2*R*-Propyl-5*R*-(triethylsilanyl)oxy-6-(tri*iso*propylsilanyl)oxymethyl-non-6-ene-1,3*R*-diol (3.32)



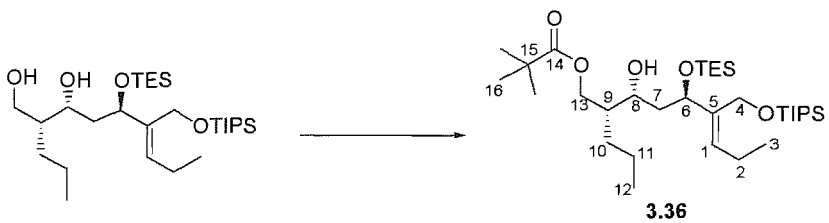
3.32

Lithium borohydride, 2.0M in THF, (877 μL, 1.75 mmol) was added dropwise to a solution of **3.28** (1.10 g, 1.59 mmol) in dry diethyl ether (22 mL) with water (32 μL, 1.75

mmol) at 0 °C. The reaction was stirred at 0 °C for 3.5 h, followed by quenching by 2N NaOH (40 mL). The reaction was warmed to room temperature when the organic phase was separated and washed with water (20 mL). The aqueous washings were extracted with CH_2Cl_2 (3×50 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Diol **3.32** (769 mg, 1.49 mmol, 94%) was isolated as a colourless oil by flash chromatography (40–60 petrol/acetone 93:7).

Mw 516.94 ($C_{28}H_{60}O_4Si_2$);
Rf 0.22 (hexane/acetone 90:10);
$[\alpha]_D$ –2.5 (c 0.24, $CHCl_3$, 23 °C);
IR (cm^{-1}) 3403 (O–H), 1461 (C=C),1240 (Si–O), 1061, 1010 (C–O);
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 ($1H_1$, t, J = 7.4 Hz), 4.74 ($1H_6$, m), 4.43 ($1H_4$, d, J = 11.8 Hz), 4.23 ($1H_{OH}$, s), 4.11 ($1H_4$, d, J = 11.8 Hz), 4.04 ($1H_8$, dd, J = 10.0, 3.0 Hz), 3.73-3.59 ($1H_9$, $1H_{OH}$, $2H_{13}$, m), 2.16-2.04 ($2H_2$, m), 1.91 ($1H_7$, m), 1.78–1.74 ($3H_{7,10}$, m), 1.41–1.16 ($2H_{11}$, m), 1.13–1.05 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, m), 1.00 ($3H_3$, t, J = 7.50 Hz), 0.96 ($9H_{TESCH3}$, t, J = 8.0 Hz), 0.89 ($3H_{12}$, t, J = 7.2 Hz), 0.61 ($6H_{TESCH2}$, q, J = 8.0 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2 (C5), 129.6 (C1), 72.9 (C6), 72.6 (C8), 64.8 (C13), 58.9 (C4), 43.8 (C9), 35.8 (C7), 29.0 (C10), 20.8 (C2), 20.7 (C11), 18.0 ($TIPSCH_3$), 14.3 (C3, 12), 11.9 (TIPSCH), 6.8 ($TESCH_3$), 4.6 ($TESCH_2$);
ES+MS m/z [%] 1056.0 [10] $(2M+Na)^+$, 539.4 [50] $(M+Na)^+$, 517.5 [40] $(M)^+$;
HRMS (ES+) for $C_{28}H_{60}O_4Si_2$ $(M+Na)^+$ calcd. 539.3922, found 539.3923.

2,2-Dimethyl-propionic acid 3*R*-hydroxy-2*R*-propyl-5*R*-(triethylsilanyl)oxy-6-(tri*iso*propylsilanyl)oxymethyl-non-6-enyl ester (3.36)



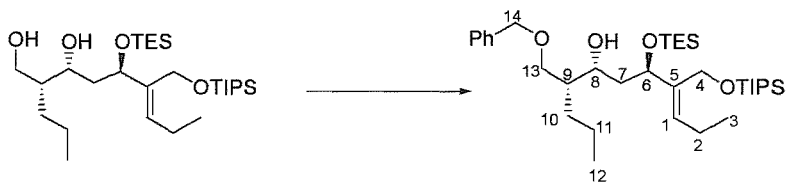
3.36

Trimethylacetyl chloride (36 μL, 0.29 mmol) was added dropwise to a solution of **3.32** (100 mg, 0.19 mmol) and 4-dimethylamino pyridine (2 mg) in CH_2Cl_2 (1.5 mL) at 0 °C. Triethylamine (54 μL, 0.39 mmol) was added dropwise, the reaction was warmed to room temperature and stirred for 2 h. The reaction was quenched by c.$NaHCO_3$ (3.0 mL) and subsequently stirred for a further 30 minutes. The aqueous phase was then extracted

with diethyl ether (3×5 mL). The combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Mono-pivaloyl protected **3.36** (72 mg, 0.12 mmol, 63%) was isolated as a colourless oil by flash chromatography (acetone/40–60 petrol 5:95)

Mw 601.06 ($C_{33}H_{68}O_5Si_2$);
Rf 0.51 (acetone/hexane 5:95);
[α]$_D$ +3.8 (c 0.5, $CHCl_3$, 22 °C);
IR (cm^{-1}) 3429 (O–H), 1463 (C=C), 1081, 1064, 1013 (C–O);
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 ($1H_1$, t, J = 7.4 Hz), 4.73 ($1H_6$, m), 4.44 ($1H_4$, d, J = 11.8 Hz), 4.17–4.08 ($1H_9$, $2H_{13}$, m), 4.08 ($1H_4$, d, J = 11.8 Hz), 3.87 ($1H_8$, m), 3.64 ($1H_{OH}$, s), 2.14-2.02 ($2H_2$, m), 1.81–1.75 ($2H_7$, m), 1.70–1.66 ($2H_{10}$, m), 1.41–1.26 ($2H_{11}$, m), 1.18 ($9H_{16}$, s), 1.10–1.04 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, m), 1.00 ($3H_3$, t, J = 7.5 Hz), 0.95 ($9H_{TESCH3}$, t, J = 8.0 Hz), 0.90 ($3H_{12}$, t, J = 5.4 Hz), 0.60 ($6H_{TESCH2}$, q, J = 8.0 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5 (C14), 137.4 (C5), 129.0 (C1), 72.6 (C6), 68.7 (C8), 64.0 (C13), 59.0 (C4), 43.2 (C9), 38.7 (C15), 37.6 (C7), 29.2 (C10), 27.1 (C16), 20.6 (C2, C11), 18.0 ($TIPSCH_3$), 14.3 (C3, C12), 11.9 (TIPSCH), 6.8 ($TESCH_3$), 4.6 ($TESCH_2$);
ES+MS m/z [%] 1224.8 [100] $(2M+Na)^+$, 623.5 [80] $(M+Na)^+$, 601.5 [100] (M^+);
HRMS (ES+) for $C_{33}H_{68}O_5Si_2$ $(M+Na)^+$ calcd. 623.4497, found 623.4506.

4*R*-Benzyloxymethyl-7*R*-(triethylsilyanyl)oxy-8-(tri*iso*propylsilanyl)oxymethyl-undec-8-en-5*R*-ol (3.38)



3.38

Silver(I) oxide (67 mg, 0.3 mmol) was added in one portion to a solution of **3.32** (100 mg, 0.2 mmol) in CH_2Cl_2 (3 mL). Benzyl bromide (25 μL, 0.2 mmol) was added dropwise to this suspension and the reaction was stirred at room temperature for 24 h. Sodium iodide (30 mg, 0.2 mmol) was added and the reaction stirred for a further 24 h. The reaction was filtered through celite before the solvent was removed under reduced pressure. The mono-benzyl protected **3.38** (40 mg, 0.07 mmol, 33%) was isolated as a colourless oil by flash chromatography (acetone/40-60 petrol 5:95).

Mw 607.07 ($C_{35}H_{66}O_4Si_2$);

Rf 0.63 (acetone/hexane 5:95);

IR (cm^{-1}) 3524 (O–H), 1454 (C=C), 1360 (Ar), 1240, 1182 (Si–O) 1085, 1070 (C–O);

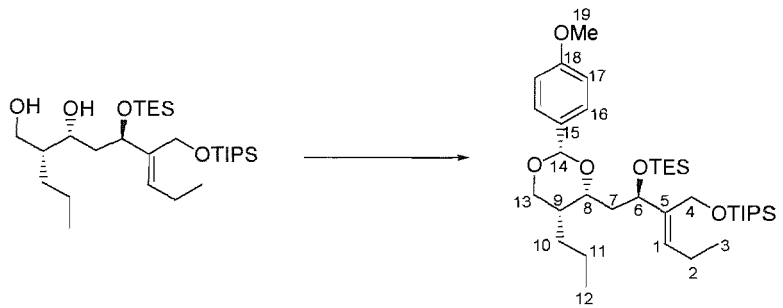
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 ($5H_{Ar}$, m), 5.61 ($1H_1$, t, J = 7.4 Hz), 4.65 ($1H_6$, t, J = 5.0 Hz), 4.51 ($1H_{14}$, d, J = 12.2 Hz), 4.47 ($1H_{14}$, d, J = 12.2 Hz), 4.38 ($1H_4$, d, J = 11.5 Hz), 4.12 ($1H_4$, d, J = 11.5 Hz), 3.94 ($1H_8$, m), 3.58-3.46 ($1H_9$, $1H_{OH}$, $2H_{13}$m), 2.15-2.05 ($2H_2$, m), 1.75–1.71 ($2H_7$, $2H_{10}$, m), 1.36–1.26 ($2H_{11}$, m), 1.14–1.03 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, m), 0.99 ($3H_3$, t, J = 7.5 Hz), 0.95 ($9H_{TESCH3}$, t, J = 8.0 Hz), 0.89 ($3H_{12}$, t, J = 7.0 Hz), 0.60 ($6H_{TESCH2}$, q, J = 8.0 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7 (C5), 138.5 (Ar), 129.4 (C1), 128.4 (Ar), 127.4 (Ar), 73.1 (C14), 72.6 (C6), 71.6 (C13), 69.6 (C8), 58.7 (C4), 43.9 (C9), 38.9 (C7), 26.4 (C10), 20.8 (C2), 20.7 (C11), 18.0 ($TIPSCH_3$), 14.4 (C3, C12), 11.9 (TIPSCH), 6.9 ($TESCH_3$), 4.7 ($TESCH_2$);

ES+MS m/z [%] 1056 [10] $(2M+Na)^+$, 539.4 [50] $(M+Na)^+$, 577.5 [40] (M^+);

HRMS (ES+) for $C_{35}H_{66}O_4Si_2$ $(M+Na)^+$ calcd. 629.4392, found 629.4403.

2*S*-(4-Methoxyphenyl)-5R-propyl-4-(2R-(triethylsilanyl)oxy-3-(tri*iso*propylsilanyl)oxymethyl-hex-3-enyl)-[1,3*R*]-dioxane (3.39)



3.39

p-Methoxybenzaldehyde (200 μL, 1.17 mmol) was added dropwise to a solution of **3.32** (102 mg, 0.20 mmol) and *p*-toluenesulfonic acid (7.0 mg, 0.36 mmol) in CH_2Cl_2 (2.0 mL). The reaction was stirred at room temperature for 4 days. The solvent was removed under reduced pressure and **3.39** (46 mg, 0.07 mmol, 36%,) was isolated as a colourless oil by flash chromatography (40-60 petrol/acetone 90:10).

Mw 634.44 ($C_{36}H_{66}O_5Si_2$);

Rf 0.77 (40-60 petrol/acetone 90:10);

$[\alpha]_D$ +38 (c 0.15, CH_3Cl_3, 22 °C);

IR (cm^{-1}) 1617, 1517, 1462 (Ar C=C), 1368 (C=C), 1247 (Si–O), 1060, 1004 (C–O);

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 ($2H_{17}$, d, J = 8.8 Hz), 6.88 ($2H_{16}$, d, J = 8.8 Hz), 5.53 ($1H_1$, t, J = 7.4 Hz), 5.46 ($1H_{14}$, s), 4.39 ($1H_6$, d, J = 10.7 Hz), 4.29 ($1H_4$, d, J = 11.0 Hz), 4.22 ($1H_4$, d, J = 11.4 Hz), 4.22–4.15 ($1H_8$, $2H_{13}$, m), 3.94 ($1H_9$, d, J = 9.4 Hz), 3.81 ($3H_{19}$, s), 2.15-2.05 ($2H_2$, m), 1.97 ($1H_7$, m), 1.81 ($1H_{10}$, m), 1.51 ($1H_7$, m), 1.40 ($1H_{10}$, m), 1.29–1.27 ($2H_{11}$, m), 1.11–1.03 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, m), 0.97 ($3H_3$, t, J = 7.5 Hz), 0.93 ($9H_{TESCH3}$, t, J = 7.7 Hz), 0.92 ($3H_{12}$, t, J = 7.0 Hz), 0.57 ($6H_{TESCH2}$, q, J = 7.5 Hz);

^{13}CNMR (75 MHz, $CDCl_3$) δ 159.7 (C18), 140.7 (C5), 131.9 (C15), 129.7 (C1), 127.4 (C17), 113.4 (C16), 101.8 (C14), 77.2 (C8), 71.2 (C6), 70.2 (C13), 58.3 (C4), 55.3 (C9), 41.7 (C7), 37.7 (C19), 26.4 (C10), 20.7 (C11, 2), 18.1 ($TIPSCH_3$), 14.2 (C12, 3), 12.0 (TIPSCH), 7.0 ($TESCH_3$), 4.8 ($TESCH_2$);

ES+MS m/z [%] 635 [10] $(M+H)^+$, 539.4 [100] (M–protecting group+Na)$^+$;

HRMS (ES+) for $C_{36}H_{66}O_5Si_2$ $(M+Na)^+$ calcd. 657.4341, found 657.4347.

4S-Benzyl-3-(2S-propyl-3*R*,5*R*-(bistriethylsilanyl)oxy-6-(tri*iso*propylsilanyl)oxymethyl-non-6-enoyl)-oxazolidin-2-one (3.42)

3.42

2,6-Lutidine (182 μL, 1.56 mmol) was added dropwise to a solution of **3.28** (432 mg, 0.62 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. Triethylsilyl trifluoromethanesulfonate (352 μL, 1.56 mmol) was then added dropwise and the reaction was stirred at 0 °C for 1.5 h, followed by quenching by pouring into 2M NH_4Cl (10 mL). The aqueous fraction was extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. **3.42** (450 mg, 0.56 mmol, 90%) was isolated as a colourless oil by flash chromatography (40–60 petrol/EtOAc 95:5).

Mw 804.37 ($C_{44}H_{81}NO_6Si_3$);

Rf 0.59 (40-60petrol/acetone 95:5);

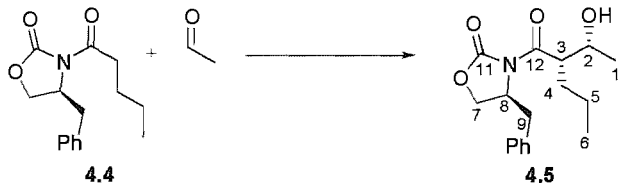
$[\alpha]_D$ +70.3 (c 1.0, $CHCl_3$, 23 °C);

IR (cm^{-1}) 1783, 1701 (C=O), 1460 (C=C), 1380, 1348 (Ar), 1237, 1206, 1194 (Si–O) 1076, 1062, 1006 (C–O);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.14 ($5H_{Ar}$, m), 5.44 ($1H_1$, t, *J* = 7.4 Hz), 4.53 ($1H_{16}$, m), 4.21–3.96 ($2H_4$, $1H_6$, $1H_8$, $1H_9$, $2H_{17}$, m), 3.25 ($1H_{15}$, dd, *J* = 13.3, 2.8 Hz), 2.64 ($1H_{15}$, dd, *J* = 13.3, 10.0 Hz), 2.10-2.03 ($2H_2$, m), 1.88 ($1H_{10}$, ddd, *J* = 14.6, 9.5, 2.0 Hz), 1.74–1.63 ($1H_7$, $1H_{10}$, m), 1.46–1.25 ($2H_{11}$, $1H_7$, m), 1.05–1.01 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, m), 0.93–0.85 ($3H_3$, $3H_{12}$, $18H_{TESCH3}$, m), 0.55 ($6H_{TESCH2}$, q, *J* = 7.8 Hz), 0.51 ($6H_{TESCH2}$, q, *J* = 8.3 Hz);
^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6 (C13), 153.2 (C14), 140.8 (C5), 135.7 (Ar), 131.0 (C1), 129.5 (Ar), 128.9 (Ar), 127.2 (Ar), 73.3 (C8), 71.6 (C6), 65.7 (C15), 58.5 (C4), 56.0 (C16), 48.6 (C9), 43.7 (C7), 37.9 (C17), 30.9 (C11), 20.9 (C2), 20.6 (C10), 18.2 ($TIPSCH_3$), 14.2 (C3, 12), 12.1 (TIPSCH), 7.0 ($TESCH_3$), 5.3 ($TESCH_2$);
ES+MS m/z [%] 826.7 [100] $(M+Na)^+$;
HRMS (ES+) for $C_{44}H_{81}NO_6Si_3$ $(M+Na)^+$ calcd. 825.5264, found 825.5263.

6.3 The β-ketoimide aldol (Chapter 4)

4S-Benzyl-3-(3*R*-hydroxy-2*S*-propyl-butyl)-oxazolidin-2-one (4.5)



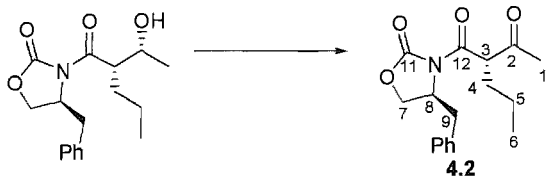
4.4 **4.5**

Dibutyl boron trifluoromethanesulfonate, 1.0M in CH_2Cl_2, (16.0 mL, 16.0 mmol) was added dropwise to a solution of **4.4** (3.6 g, 13.9 mmol) in CH_2Cl_2 (40 mL) at –78 °C. Triethylamine (2.5 mL, 18.1 mmol) was added dropwise and the reaction stirred at –78 °C for 30 minutes. The reaction was warmed to 0 °C and stirring continued for 1 h whereupon the reaction was recooled to –78 °C. Acetaldehyde (625 μL, 11.1 mmol) in CH_2Cl_2 (15 mL) was added dropwise and the reaction stirred at –78 °C for 1 h. The reaction was then warmed to 0 °C and stirred for 1 h before quenching by pH 7.2 phosphate buffer (20 mL), methanol (30 mL) and 25% aq. H_2O_2 (10 mL). The reaction was stirred for a further hour at 0 °C before warming to room temperature. The organic phase was separated and washed with water (50 mL). The aqueous washings were extracted with CH_2Cl_2 (3×100 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Evans product **4.5** (3.3 g, 10.7 mmol, 77%) was isolated as a white crystalline solid by flash chromatography (hexane/acetone 80:20). NMR analysis showed a single diastereoisomer.

Mw 304.37 ($C_{17}H_{23}NO_4$)'
m.p. 57 °C (hexane/EtOAc);
Rf 0.37 (hexane/acetone 80:20);
[α]$_D$ +77.6 (c 0.55, $CHCl_3$, 22 °C);
IR (cm^{-1}) 3534 (O–H), 1765 (C=O), 1676 (C=O), 1380 (Ar), 1350 (Ar), 1197 (C–O);
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.22 ($5H_{Ar}$, m), 4.75 ($1H_8$, m), 4.24–4.15 ($2H_7$, m), 4.14–4.06 ($2H_{2,3}$, m), 3.36 ($1H_9$, dd, J = 13.2, 3.3 Hz), 2.70 ($1H_9$, dd, J = 13.2, 10.3 Hz), 2.47 ($1H_{OH}$, d (br), J = 2.2 Hz), 1.84 ($1H_4$, m), 1.61 ($1H_4$, m), 1.38 ($2H_5$, dq, J = 14.4, 7.3 Hz), 1.24 ($3H_1$, d, J = 6.3 Hz), 0.96 ($3H_6$, t, J = 7.2 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5 (C12), 153.9 (C11), 135.2 (Ar), 129.3 (Ar), 129.0 (Ar), 127.4 (Ar), 68.9 (C2), 66.0 (C7), 55.5 (C8), 48.4 (C3), 38.0 (C9), 29.7 (C4), 20.8 (C5), 19.4 (C1), 14.3 (C6);

ES+MS m/z [%] 328.2 [100] $(M+Na)^+$;
HRMS (ES+) for $C_{17}H_{23}NO_4$ $(M+Na)^+$ calcd. 328.15247, found 328.1515.

4S-Benzyl-3-(1-oxo-2*S*-propyl-oxoethyl)-oxazolidin-2-one (4.2)

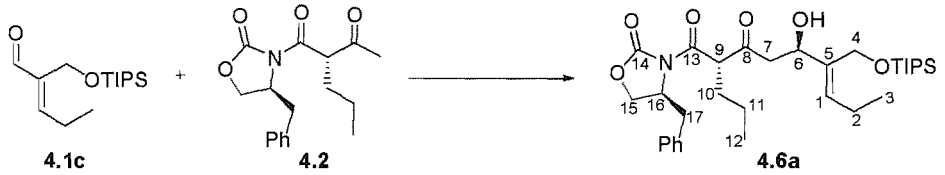


4.2

Sulfur trioxide-pyridine complex (1.4 g, 9.0 mmol) was dissolved in 1:1 CH_2Cl_2/DMSO (15 mL) and triethylamine (1.3 mL, 9.0 mmol) was added dropwise. The pale yellow solution was added dropwise to a solution of **4.5** (1.1 g, 3.6 mmol) in 1:1 CH_2Cl_2/DMSO (25 mL) at 0 °C. The reaction was stirred at 0 °C for 3 h when the reaction was warmed to room temperature. The reaction mixture was quenched by pouring into 2M NH_4Cl (50 mL) and the organic phase washed with water (50 mL). The aqueous washings were extracted with pentane (3×50 mL). The combined organic fractions were dried over $MgSO_4$ before the solvent was removed under reduced pressure. β-ketoimide reagent **4.2** (871 mg, 2.9 mmol, 81%) was isolated as white crystalline solid by flash chromatography (hexane/acetone 80:20). NMR analysis showed a single diastereoisomer

Mw 303.35 ($C_{17}H_{21}NO_4$);
m.p. 80 °C (hexane/EtOAc);
Rf 0.48 (hexane/acetone 80:20);
$[\alpha]_D$ +1.5 (c 0.95, CH_3Cl, 24 °C);
IR (cm^{-1}) 1763, 1698, 1695 (C=O), 1373, 1390, 1357 (ar C=C), 1272, 1230 (C–O).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.19 ($5H_{Ar}$, m), 4.77 ($1H_8$, m), 4.63 ($1H_3$, dd, J = 9.6, 3.7 Hz), 4.27–4.15 ($2H_7$, m), 3.30 ($1H_9$, dd, J = 13.4, 3.3 Hz), 2.79 ($1H_9$, dd, J = 13.4, 9.4 Hz), 2.30 ($3H_1$, s), 2.05($1H_4$, m), 1.77 ($1H_4$, m), 1.54–1.36 ($2H_5$, m), 0.92 ($3H_6$, t, J = 7.4 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6 (C2), 169.2 (C12), 153.8 (C11), 135.0 (Ar), 129.3 (Ar), 128.9 (Ar), 127.4 (Ar), 66.4 (C7), 58.9 (C8), 55.1 (C3), 38.0 (C9), 29.7 (C4), 28.9 (C1), 21.4 (C5), 14.0 (C6);
CIMS m/z [%] 304 [18] $(M+H)^+$, 178 [98] (Auxiliary+H)$^+$, 127 [100] (Aldehyde+H)$^+$;
HRMS (ES+) for $C_{17}H_{21}NO_4$ $(2M+Na)^+$ calcd. 629.2834, found 629.2840.

4S-Benzyl-3-(3-oxo-2*S*-propyl-5*R*-hydroxy-6-(tri*iso*propylsilanyl)oxymethyl-non-6-enoyl)-oxazolidin-2-one (4.6a)



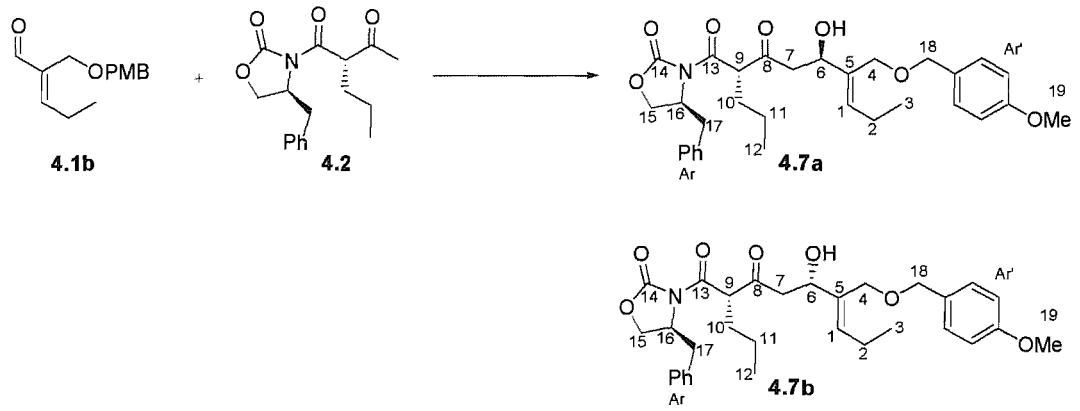
4.1c **4.2** **4.6a**

Tin(II) trifluoromethanesulfonate (673 mg, 1.61 mmol) was suspended in CH_2Cl_2 (2 mL) and triethylamine (221 μL, 1.59 mmol) was added dropwise. The reaction mixture was cooled to –20 °C whereupon **4.2** (411 mg, 1.36 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The reaction was stirred at –20 °C for 1 h when it was cooled to –78 °C. Aldehyde **4.1c** (429 mg, 1.59 mmol) in CH_2Cl_2 (2 mL) was added dropwise and the reaction was stirred at –78 °C for 20 h. The reaction was quenched by 1M $NaHSO_4$ (10 mL) before warming to room temperature. The products were extracted with CH_2Cl_2 (3×50 mL). The combined organic fractions were washed with c.$NaHCO_3$ (10 mL), dried over $MgSO_4$ before the solvent was removed under reduced pressure. **4.1c** (155 mg, 0.58 mmol, 36 %) was regained by flash chromatography (40-60 petrol/acetone 90:10). β-ketoimide reagent **4.2** (134 mg, 0.44 mmol, 33%) was regained and β-ketoimide aldol product **4.6a** (443 mg, 0.77 mmol, 59%) was isolated as a colourless oil by preparative HPLC (hexane/acetone 90:10). NMR analysis shows a 16:8:2:1 diastereomeric mixture (major isomer reported).

Mw 573.85 ($C_{32}H_{51}NO_6Si$);
Rf 0.11 (acetone/hexane 10:90);
$[\alpha]_D$ product not a single stereo isomer;
IR (cm^{-1}) 3543 (O–H), 1777, 1716 (C=O), 1462 (C=C), 1388, 1359 (ar C=C), 1211, 1053 (Si–O), 1053 (C–O);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.18 ($5H_{Ar}$, m), 5.51 ($1H_1$, t, J = 6.8 Hz), 4.68 ($1H_{16}$, m), 4.65-4.59($1H_6$, $1H_9$, m), 4.37 ($1H_4$, d, J = 11.8 Hz), 4.30 ($1H_4$, d, J = 11.8 Hz), 4.19–4.06 ($2H_{15}$, m), 3.22 ($1H_{17}$, dd, J = 13.3, 3.2 Hz), 3.15–2.83 ($2H_7$, m), 2.70 ($1H_{17}$, m), 2.01–1.67 ($2H_2$, $2H_{10}$, m), 1.40–1.26 ($2H_{11}$, m), 1.14–1.07 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, m), 1.01–0.96 ($3H_3$, $3H_{12}$, m);
^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0 (C8), 169.1 (C13), 153.7 (C14), 137.1 (C5), 135.0 (Ar), 130.5 (C1), 129.4 (Ar), 129.0 (Ar), 127.4 (Ar), 70.9 (C6), 65.9 (C15), 59.8 (C16), 58.7 (C4), 55.2 (C9), 48.4 (C7), 38.0 (C17), 29.9 (C10), 21.4 (C2), 20.7 (C11), 18.0 ($TIPSCH_3$),

14.1 (C3), 13.9 (C12), 11.9 (TIPSCH);
ES+MS m/z [%] 1170.08 [50] $(2M+Na)^+$, 596.2 [100] $(M+Na)^+$;
HRMS (ES+) for $C_{32}H_{51}NO_6Si$ $(M+Na)^+$ calcd. 657.4341, found 657.4347.

4S-Benzyl-3-(3-oxo-2*S*-propyl-5*R*-hydroxy-6-(*p*-methoxybenzyl)oxymethyl-non-6-enoyl)-oxazolidin-2-one (4.7)



4.1b **4.2** **4.7a** **4.7b**

Tin(II) trifluoromethanesulfonate (783 mg, 1.88 mmol) was suspended in CH_2Cl_2 (3.0 mL) and triethylamine (260 μL, 1.84 mmol) was added dropwise. The reaction mixture was cooled to –20 °C whereupon **4.2** (561 mg, 1.84 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise. The reaction was stirred at –20 °C for 1 h when it was cooled to –78 °C. Aldehyde **4.1b** (265 mg, 1.13 mmol) in CH_2Cl_2 (3.0 mL) was added dropwise and the reaction was stirred at –78 °C for 20 h. The reaction was quenched by 1M $NaHSO_4$ (10 mL) before warming to room temperature. The products were extracted with CH_2Cl_2 (3×50 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Aldehyde **4.1b** (73 mg, 0.31 mmol, 26 %) and β-ketoimide reagent **4.2** (182 mg, 0.59 mmol, 32%) were regained by flash chromatography (40-60 petrol/acetone 85:15). β-ketoimide aldol product **4.7** (406 mg, 0.56 mmol, 67%) was isolated as a colourless oil (which crystallised at –20 °C) by preparative HPLC (hexane/acetone 80:20). NMR analysis shows a 1.5:1 diastereomeric mixture (major isomer reported).

Mw 537.64 ($C_{31}H_{39}NO_7$);
m.p. 43-44 °C (hexane/EtOAc);
Rf 0.12 (40-60 petrol/acetone 85:15);
$[\alpha]_D$ product not a single stereo isomer;

IR (cm^{-1}) 3485 (O–H), 1775, 1715, 1699 (C=O), 1612, 1512 (C=C), 1389 (C–N), 1359 (ar C=C), 1246, 1210, 1073, 1032 (C–O);

^{1}H NMR a (400 MHz, $CDCl_3$) δ 7.29–7.18 ($5H_{Ar}$, m), 7.12-7.10 ($2H_{Ar'}$, m), 6.81-6.79 ($2H_{Ar'}$, m), 5.64 ($1H_1$, t, J = 7.5 Hz), 4.67 ($1H_{16}$, m), 4.55 ($1H_6$, m), 4.50 ($1H_9$ dd, J = 9.3, 3.5 Hz), 4.36 ($2H_{18}$, s), 4.16–3.95 ($2H_4$, $2H_7$, m), 3.72 ($3H_{19}$, s), 3.21 ($1H_{17}$, d, J = 13.3 Hz), 3.02 ($1H_{OH}$, d, J = 4.0 Hz), 2.88–2.80 ($2H_{15}$, m), 2.71 ($1H_{17}$, m), 2.04–1.86 ($2H_2$, $1H_{10}$, m), 1.68 ($1H_{10}$, m), 1.42–1.25 ($2H_{11}$, m), 0.90 ($3H_{12}$, t, J = 7.4 Hz), 0.89 ($3H_3$, t, J = 7.2 Hz);

^{1}H NMR b (400 MHz, $CDCl_3$) δ 7.29–7.18 ($5H_{Ar}$, m), 7.11-7.10 ($2H_{Ar'}$, m), 6.80-6.79 ($2H_{Ar'}$, m), 5.63 ($1H_1$, t, J = 7.5 Hz), 4.67 ($1H_{16}$, m), 4.55 ($1H_6$, m), 4.50 ($1H_9$ dd, J = 9.3, 3.5 Hz), 4.36 ($2H_{18}$, s), 4.16–3.95 ($2H_4$, $2H_7$, m), 3.72 ($3H_{19}$, s), 3.21 ($1H_{17}$, d, J = 13.3 Hz), 3.02 ($1H_{OH}$, d, J = 4.0 Hz), 2.88–2.80 ($2H_{15}$, m), 2.71 ($1H_{17}$, m), 2.04–1.86 ($2H_2$, $1H_{10}$, m), 1.68 ($1H_{10}$, m), 1.42–1.25 ($2H_{11}$, m), 0.90 ($3H_{12}$, t, J = 7.4 Hz), 0.89 ($3H_3$, t, J = 7.3 Hz);

^{13}C NMR a (100 MHz, $CDCl_3$) δ 206.6 (C8), 169.0 (C13), 159.3 (Ar'), 153.7 (C14), 135.3 (Ar'), 135.2 (Ar), 135.0 (Ar), 133.6 (C5), 130.2 (C1), 129.4 (Ar), 129.0 (Ar'), 127.4 (Ar), 113.8 (Ar'), 72.2 (C18), 71.0 (C6), 66.4 (C15), 65.3 (C16), 58.8 (C4), 55.2 (C9, C19), 47.7 (C7), 38.0 (C17), 29.4 (C10), 21.3 (C2, C11), 14.0 (C3, C12);

^{13}C NMR b (100 MHz, $CDCl_3$) δ 206.6 (C8), 169.0 (C13), 159.3 (Ar'), 153.7 (C14), 135.3 (Ar'), 135.2 (Ar), 135.0 (Ar), 133.6 (C5), 130.2 (C1), 129.4 (Ar), 129.0 (Ar'), 127.4 (Ar), 113.8 (Ar'), 72.2 (C18), 71.0 (C6), 66.4 (C15), 65.3 (C16), 58.8 (C4), 55.2 (C9, C19), 47.7 (C7), 38.0 (C17), 29.4 (C10), 21.3 (C2, C11), 14.0 (C3, C12);

ES+MS m/z [%] 560.6 [100] $(M+Na)^+$, 561.6 [40] $(M+Na+H)^+$;

HRMS (ES+) for $C_{31}H_{39}NO_7$ $(M+Na)^+$ calcd. 560.2619, found 560.2607.

4S-Benzyl-3-(3-oxo-2*S*-propyl-5*S*-hydroxy-6-(tri*iso*propylsilanyl)oxymethyl-non-6-enoyl)-oxazolidin-2-one (4.6b)

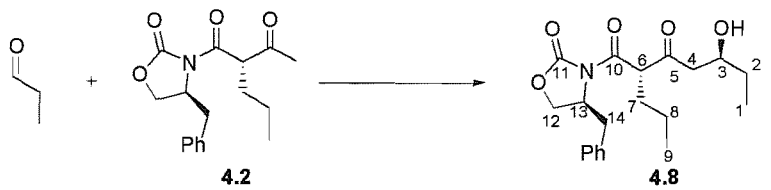
4.1c **4.2** **4.6b**

Titanium(IV) chloride, 1.0M in CH_2Cl_2 (450 μL, 0.45 mmol) was added dropwise to a solution of **4.2** (110 mg, 0.36 mmol) in CH_2Cl_2 (1 mL) at –5 °C. Di*iso*propylethylamine (76 μL, 0.43 mmol) was added and the reaction stirred at –5 °C for 1 h when it was cooled to –78 °C. Aldehyde **4.1c** (148 mg, 0.43 mmol) in CH_2Cl_2 (1 mL) was added dropwise and

the reaction was stirred at –78 °C for 20 h. The reaction was quenched by pH 7 phosphate buffer (5 mL) before warming to room temperature. The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and 2M NH_4Cl before the products were extracted with CH_2Cl_2 (3×30 mL). The combined organic fractions dried over $MgSO_4$ before the solvent was removed under reduced pressure. β-ketoimide reagent **4.2** (48 mg, 0.16 mmol, 44%) was regained and β-ketoimide aldol product **4.6b** (50 mg, 0. 09 mmol, 25%) was isolated as a colourless oil by preparative HPLC (hexane/acetone 90:10). NMR analysis shows a single diastereoisomer.

Mw 573.85 ($C_{32}H_{51}NO_6Si$);
Rf 0.11 (hexane/acetone 90:10);
[α]$_D$ +68.1 (*c* 1.2, $CHCl_3$, 22 °C);
IR (cm^{-1}) 3529 (O–H), 1777, 1716 (C=O), 1462 (C=C), 1387, 1358 (Ar), 1210 (Si–O), 1076, 1055 (C–O);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.10 ($5H_{Ar}$, m), 5.47 ($1H_1$, t, *J* = 7.3 Hz), 4.68 ($1H_{16}$, m), 4.60 ($1H_6$, m), 4.52 ($1H_9$, dd, *J* = 9.3, 3.5 Hz), 4.38 ($1H_4$, d, *J* = 12.0 Hz), 4.33 ($1H_4$, d, *J* = 12.0 Hz), 4.14 ($1H_{15}$, t, *J* = 9.0 Hz), 4.08 ($1H_{15}$, dd, *J* = 9.0, 3.0 Hz), 3.30 ($1H_{OH}$, s), 3.22 ($1H_{17}$, dd, *J* = 13.3, 3.3 Hz), 3.01 ($1H_7$, dd, *J* = 17.1, 9.0 Hz), 2.86 ($1H_7$, dd, *J* = 17.1, 3.3 Hz), 2.71 ($1H_{17}$, dd, *J* = 13.3, 9.3 Hz), 2.11–1.91 ($2H_2$, $1H_{10}$, m), 1.75 ($1H_{10}$, m), 1.46–1.28 ($2H_{11}$, m), 1.08–1.00 ($18H_{TIPSCH3}$, $3H_{TIPSCH}$, m), 0.90 ($3H_3$, $3H_{12}$, t, *J* = 7.3 Hz);
^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0 (C8), 169.1 (C13), 153.7 (C14), 136.9 (C5), 135.0 (Ar), 131.1 (C1), 129.3 (Ar), 128.9 (Ar), 127.3 (Ar), 71.5 (C6), 66.4 (C15), 59.8 (C16), 58.9 (C4), 55.2 (C9), 47.9 (C7), 38.0 (C17), 29.3 (C10), 21.5 (C2), 20.7 (C11), 18.0 ($TIPSCH_3$), 14.1 (C3), 13.9 (C12), 11.8 (TIPSCH);
ES+MS m/z [%] 596.5 [100] $(M+Na)^+$;
HRMS (ES+) for $C_{32}H_{51}NO_6Si$ $(M+Na)^+$ calcd. 596.3378, found 596.3374.

4*S*-Benzyl-3-(3-oxo-2*S*-propyl-6*S*-hydroxy-heptyl)-oxazolidin-2-one (4.8)



Tin(II) trifluoromethanesulfonate (477 mg, 1.14 mmol) was suspended in CH_2Cl_2 (3.4 mL) and triethylamine (160 μL, 1.11 mmol) was added dropwise. The reaction mixture was cooled to –20 °C whereupon **4.2** (282 mg, 0.93 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The reaction was stirred at –20 °C for 1 h when it was cooled to –78 °C. Propionaldehyde (18 μL, 1.11 mmol) was added dropwise and the reaction stirred at –78 °C for 2 h. The reaction was quenched by 1M $NaHSO_4$ (10 mL) and warmed to room temperature. The products were extracted with CH_2Cl_2 (3×20 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. β-Ketoimide aldol product **4.8** (276 mg, 0.85 mmol, 82%) was isolated as a white crystalline solid by preparative HPLC (40-60 petrol/acetone 80:20). NMR analysis shows a 3.4:1 diastereomeric mixture (major isomer reported).

Titanium(IV) chloride, 1.0M in CH_2Cl_2, (360 μL, 0.36 mmol) was added dropwise to a solution of **4.2** (92 mg, 0.30 mmol) in CH_2Cl_2 (1 mL) at –5 °C. Di*iso*propylethylamine (63 μL, 0.36 mmol) was added and the reaction stirred at –5 °C for 1 h when it was cooled to –78 °C. Propionaldehyde (30 μL, 0.36 mmol) was added dropwise and the reaction was stirred at –78 °C for 1.5 h. The reaction was quenched by pH 7 phosphate buffer (5 mL) before warming to room temperature. The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and 2M NH_4Cl the products were extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. β-Ketoimide aldol product **4.8b** (88 mg, 0.16 mmol, 81%) was isolated as a white crystalline solid by preparative HPLC (hexane/acetone 80:20). NMR analysis shows a 6.4:1 diastereomeric mixture (major isomer reported).

Mw 361.43 ($C_{20}H_{27}NO_5$);
m.p. 42 °C (hexane/EtOAc);
Rf 0.14 (hexane/acetone 80:20);
[α]$_D$ product not a single stereo isomer;
IR (cm^{-1}) 3539 (O–H), 1767, 1704 (C=O), 1397 (C–N), 1355, 1211, 1131, (C–O);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.18 ($5H_{Ar}$, m), 4.78 ($1H_{13}$, m), 4.58 ($1H_6$, dd, J = 9.3, 3.7 Hz), 4.28–4.17 ($2H_{12}$, m), 4.00 ($1H_3$, m), 3.30 ($1H_{14}$, dd, J = 13.3, 3.0 Hz), 2.87–2.64 ($2H_4$, $1H_{14}$, $1H_{OH}$, m), 2.04 ($1H_7$, m), 1.77 ($1H_7$, m), 1.58–1.35 ($2H_2$, $2H_8$, m), 0.99 ($3H_1$, t, J = 7.3 Hz), 0.96 ($3H_9$, t, J = 7.3 Hz);
^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7 (C5), 168.8 (C10), 153.9 (C11), 134.9 (Ar), 129.3 (Ar), 129.0 (Ar), 127.4 (Ar), 68.6 (C3), 66.5 (C12), 58.9 (C13), 55.1 (C6), 47.8 (C4), 37.9

(C14), 29.6 (C7), 29.2 (C2), 21.4 (C8), 13.9 (C9), 9.8 (C1);
ES+MS m/z [%] 384.4 [100] $(M+Na)^+$, 385.4 [40] $(M+Na+H)^+$;
HRMS (ES+) for $C_{20}H_{27}NO_5$ $(M+Na)^+$ calcd. 384.1781, found 384.1733.

4S-Benzyl-3-(3*R*-hydroxy-2*S*-propyl-pentyl)-oxazolidin-2-one (4.10)

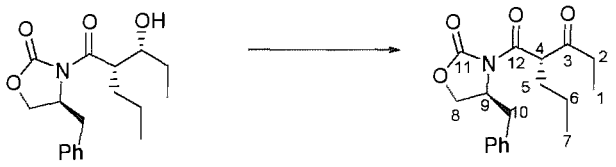
4.4 **4.10**

Dibutylboron trifluoromethanesulfonate, 1.0M in CH_2CL_2, (4.1 mL, 4.1 mmol) was added dropwise to a solution of **4.4** (1.0 g, 3.8 mmol) in CH_2Cl_2 (10 mL) at –78 °C. Triethylamine (580 μL, 4.1 mmol) was added dropwise and the reaction stirred at –78 °C for 30 minutes. The reaction was warmed to 0 °C and stirring continued for 1 h whereupon the reaction was recooled to –78 °C. Propionaldehyde (300 μL, 11.1 mmol) was added dropwise and the reaction stirred at –78 °C for 1 h. The reaction was then warmed to 0 °C and stirred for 1 h, followed by quenching by pH 7.2 phosphate buffer (5.0 mL), methanol (7.0 mL) and 25% aq. H_2O_2 (2.0 mL). The reaction was stirred for 30 minutes at 0 °C before warming to room temperature. The organic phase was separated and washed with water (25 mL). The aqueous washings were extracted with CH_2Cl_2 (3×20 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Evans product **4.10** (510 mg, 1.6 mmol, 46%) was isolated as a colourless oil by preparative HPLC (hexane/acetone 85:15). NMR analysis showed a single diastereomer.

Mw 319.20 ($C_{18}H_{25}NO_4$);
Rf 0.17 (hexane/acetone 88:12);
$[\alpha]_D$ +86.0 (c 0.55, $CHCl_3$, 22 °C);
IR (cm^{-1}) 3533 (O–H), 1776, 1695 (C=O), 1384 (C–N), 1352 (Ar), 1267, 1206 (C–O);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.15 ($5H_{Ar}$, m), 4.65 ($1H_9$, m), 4.15–4.09 ($2H_8$, m), 3.97 ($1H_4$, dt, J = 10.2, 3.8 Hz), 3.74 ($1H_3$,. dt, J = 6.8, 4.8 Hz), 3.25 ($1H_{10}$, dd, J = 13.6, 3.3 Hz), 2.69 ($1H_{10}$, dd, J = 13.6, 9.5 Hz), 1.78 ($1H_5$, m), 1.53–1.44 ($1H_{2,5}$, m), 1.28–1.17 ($2H_6$, m), 0.94 ($3H_1$, t, J = 7.4 Hz), 0.84 ($3H_7$, t, J = 7.3 Hz);
^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8 (C12), 154.1 (C11), 135.2 (Ar), 129.4 (Ar), 129.0 (Ar), 127.4 (Ar), 74.2 (C3), 66.1 (C8), 55.5 (C9), 47.5 (C4), 38.1 (C10), 28.7 (C5), 26.9 (C2),

21.0 (C6), 14.2 (C7), 10.5 (C1);
ES+MS m/z [%] 342.2 [100] $(M+Na)^+$, 661.5 [40] $(2M+Na)^+$;
HRMS (ES+) for $C_{18}H_{25}NO_4$ $(M+Na)^+$ calcd. 342.1676, found 324.1681.

4S-Benzyl-3-(1-oxo-2S-propyl-oxopropyl)-oxazolidin-2-one (4.9)

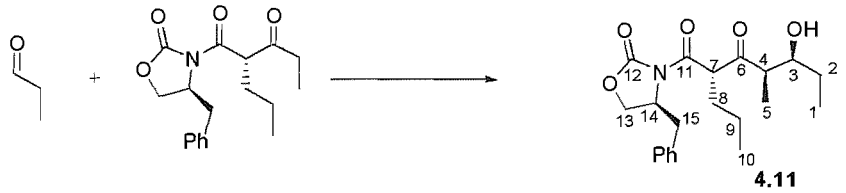


4.9

Sulfur trioxide-pyridine complex (515 mg, 3.24 mmol) was dissolved in 1:1 CH_2Cl_2 /DMSO (4 mL) and triethylamine (450 μL, 3.24 mmol) was added dropwise. The pale yellow solution was added dropwise to a solution of **4.10** (410 mg, 1.28 mmol) in 1:1 CH_2Cl_2 /DMSO (4 mL) at 0 °C. The reaction was stirred at 0 °C for 3 h before warming to room temperature and pouring into 2M NH_4Cl (20 mL). The organic phase was washed with water (20 mL) and the aqueous washings were extracted with pentane (3×50 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. β-Ketoimide reagent **4.9** (209 mg, 0.96 mmol, 52%) was isolated as a colourless oil by preparative HPLC (hexane/acetone 90:10). NMR analysis showed a single diastereoisomer.

Mw 317.16 ($C_{18}H_{23}NO_4$);
Rf 0.29 (hexane/acetone 90:10);
$[\alpha]_D$ –22.4 (*c* 1.3, $CHCl_3$, 24 °C);
IR (cm^{-1}) 1773, 1716, 1698 (C=O), 1386 (C–N), 1354, 1207 (C–O);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.16 ($5H_{Ar}$, m), 4.61 ($1H_9$, m), 4.48 ($1H_4$, dd, J = 9.5, 3.5 Hz), 4.13–4.07 ($2H_8$, m), 3.38 ($1H_{10}$, dd, J = 13.6, 3.0 Hz), 2.71–2.50 ($2H_2$, $1H_{10}$, m), 1.96 ($1H_5$, m), 1.64 ($1H_5$, m), 1.44–1.25 ($1H_6$, m), 1.03 ($3H_1$, t, J = 7.3 Hz), 0.89 ($3H_7$, t, J = 7.3 Hz);
^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2 (C3), 169.2 (C12), 153.6 (C11), 135.5 (Ar), 129.4 (Ar), 128.9 (Ar), 127.2 (Ar), 66.3 (C8), 57.9 (C9), 55.5 (C4), 37.4 (C10), 34.6 (C2), 29.8 (C5), 21.4 (C6), 14.0 (C7), 7.6 (C1);
ES+MS m/z [%] 340.0 [40] $(M+Na)^+$, 372.0 [100] $(M+Na+MeOH)^+$;
HRMS (ES+) for $C_{18}H_{23}NO_4$ $(M+Na)^+$ calcd. 340.1519, found 340.1515.

4*S*-Benzyl-3-(3-oxo-2*S*-propyl-4R-methyl-5*S*-hydroxy-heptyl)-oxazolidin-2-one (4.11)



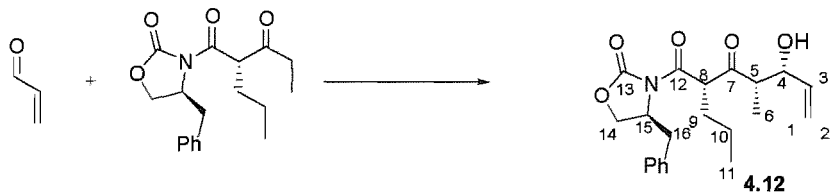
4.11

Tin(II) trifluoromethanesulfonate (148 mg, 0.35 mmol) was suspended in CH_2Cl_2 (0.7 mL) and triethylamine (48 μL, 0.35 mmol) was added dropwise. The reaction mixture was cooled to –20 °C whereupon **4.8** (89 mg, 0.28 mmol) in CH_2Cl_2 (0.8 mL) was added dropwise. The reaction was stirred at –20 °C for 1 h when it was cooled to –78 °C. Propionaldehyde (24 μL, 0.34 mmol) was added dropwise and the reaction was stirred at –78 °C for 1 h, followed by quenching by 1M $NaHSO_4$ (5 mL). The reaction was warmed to room temperature and the products extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were washed with c.$NaHCO_3$ (5 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. β-Ketoimide reagent **4.8** (50 mg, 0.16 mmol, 56 %) was regained by flash chromatography (40-60 petrol/acetone 90:10). β-ketoimide aldol product **4.11** (28 mg, 0.07 mmol, 26%) was isolated as a colourless oil by preparative HPLC (hexane/acetone 80:20). NMR analysis showed a single diastereomer.

Mw 375.20 ($C_{21}H_{29}NO_5$);
Rf 0.25 (hexane/acetone 80:20);
$[\alpha]_D$ +127.4 (*c* 1.7, $CHCl_3$, 24 °C);
IR (cm^{-1}) 3528 (O–H), 1773, 1714, 1698 (C=O), 1389 (C–N), 1359 (Ar), 1262, 1211(C–O);
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.16 ($5H_{Ar}$, m), 4.77 ($1H_7$, dd, *J* = 9.5, 3.5 Hz), 4.63 ($1H_{14}$, m), 4.14–4.12 ($2H_{13}$, m), 3.96 ($1H_3$, m), 3.38 ($1H_{15}$, dd, *J* = 13.6, 3.0 Hz), 2.82 ($1H_4$, m), 2.71 ($1H_{15}$, dd *J* = 13.3, 10.0 Hz), 1.96 ($1H_8$, m), 1.75 ($1H_8$, m), 1.52 ($1H_2$, m), 1.42–1.28 ($2H_2$, $1H_9$, m), 1.07 ($3H_5$, t, *J* = 7.0 Hz), 0.91 ($3H_1$, t, *J* = 7.3 Hz), 0.90 ($3H_{10}$, t, *J* = 7.3 Hz);
^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7 (C6), 169.12 (C11), 153.7 (C12), 135.3 (Ar), 129.4 (Ar), 129.0 (Ar), 127.3 (Ar), 72.5 (C3), 66.5 (C13), 57.2 (C14), 55.1 (C7), 49.0 (C4), 37.5 (C15), 29.9 (C8), 26.8 (C2), 21.4 (C9), 14.0 (C1), 10.7 (C10), 9.3 (C5);
ES+MS m/z [%] 733.5 [40] $(2M+Na)^+$, 398.2 [100] $(M+Na)^+$;

HRMS (ES+) for $C_{21}H_{29}NO_5$ $(M+Na)^+$ calcd. 398.1938, found 398.1940.

4*S*-Benzyl-3-(3-oxo-2*S*-propyl-4R-methyl-5*S*-hydroxy-hept-6-enyl)-oxazolidin-2-one (4.12)



4.12

Titanium(IV) chloride, 1.0M in CH_2Cl_2, (340 μL, 0.34 mmol) was added dropwise to a solution of **4.8** (89 mg, 0.28 mmol) in CH_2Cl_2 (1.5 mL) at –5 °C. Di*iso*propylethylamine (60 μL, 0.34 mmol) was added and the reaction stirred at –5 °C for 1 h when it was cooled to –78 °C. Acrolein (40 μL, 0.34 mmol) was added dropwise and the reaction was stirred at –78 °C for 30 minutes before warming to –50 °C for 30 minutes. The reaction was quenched by pH 7 phosphate buffer (5 mL) before warming to room temperature. The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and 2M NH_4Cl before the products were extracted with CH_2Cl_2 (3x10 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was removed under reduced pressure. β-Ketoimide aldol product **4.12** (66 mg, 0.18 mmol, 63%) was isolated as a colourless oil by preparative HPLC (hexane/acetone 80:20). NMR analysis showed a single diastereomer.

Mw 373.19 ($C_{21}H_{27}NO_5$);

Rf 0.21 (hexane/acetone 80:20);

[α]$_D$ –39.2 (*c* 2.3, $CHCl_3$, 24 °C);

IR (cm^{-1}) 3534 (O–H), 1771, 1712, 1691 (C=O), 1387 (C–N), 1356 (ar C=C), 1259, 1207 (C–O);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.16 ($5H_{Ar}$, m), 5.75 ($1H_3$, ddd, J = 17.1, 10.6, 5.0 Hz), 5.27 ($1H_1$, dd, J = 17.1, 1.5 Hz), 5.13 ($1H_2$, dd, J = 10.6, 1.5 Hz), 4.77 ($1H_8$, dd, J = 9.3, 3.8 Hz), 4.63 ($1H_{15}$, m), 4.59 ($1H_4$, m), 4.13–4.11 ($2H_{14}$, m), 3.35 ($1H_{16}$, dd, J = 13.6, 3.0 Hz), 2.89 ($1H_5$, qd, J = 7.0, 2.8 Hz), 2.71 ($1H_{16}$, dd, J = 13.6, 10.0 Hz), 1.95 ($1H_9$, m), 1.76 ($1H_9$, m), 1.40–1.26 ($2H_{10}$, m), 1.08 ($3H_6$, d, J = 7.0 Hz), 0.89 ($3H_{11}$, t, J = 7.0 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0 (C7), 169.0 (C12), 153.7 (C13), 137.5 (C3), 135.2 (Ar), 129.4 (Ar), 128.9 (Ar), 127.3 (Ar), 115.8 (C1), 72.0 (C4), 66.4 (C14), 57.4 (C15), 55.6 (C8), 49.7 (C5), 37.4 (C16), 29.7 (C9), 21.4 (C10), 13.9 (C11), 10.1 (C6);

ES+MS m/z [%] 396.0 [100] $(M+Na)^+$, 769.0 [50] $(2M+Na)^+$;

HRMS (ES+) for $C_{21}H_{27}NO_5$ $(M+Na)^+$ calcd. 396.1781, found 396.1777.

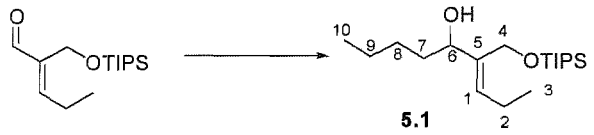
4S-Benzyl-3-(2*S*-propyl-3*R*,5*R*-dihydroxy-6-(tri*iso*propylsilanyl)oxymethyl-non-6-enoyl)-oxazolidin-2-one (4.13)

4.13

Sodium cyanoborohydride (192 mg, 0.91 mmol) was added in one portion to a solution of **4.9a** (104 mg, 0.18 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. The reaction was stirred at 0 °C for 5 h when it was quenched by the addition of water (2 mL). The reaction was partitioned between c.$NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) and the product extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were washed with water (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure giving **4.13** (102 mg, 0.18 mmol, 99%). Used crude in attempted protection reactions. Rf 0.39 (hexane/acetone 80:20).

6.4 Work towards selective epoxidation (Chapter 5)

4-(Tri*iso*propylsilanyl)oxymethyl-non-3*Z*-en-5-ol (5.1)



5.1

n-Butyl lithium, 2.5M in hexanes, (0.53 mL, 1.33 mmol) was added dropwise to a solution of **3.1c** (322 mg, 1.19 mmol) in THF (4 mL) at –78 °C. The reaction was stirred at –78 °C for 1 h, followed by quenching by 2 M NH_4Cl (4 mL) before warming to room temperature. The organic layer was washed with water (10 mL) and the combined aqueous fractions extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were dried over $MgSO_4$ before the solvent was removed reduced pressure. Alcohol **5.1** (346 mg, 1.06 mmol, 89%) was isolated as a colourless oil by flash chromatography (hexane/EtOAc 90:10).

Mw 325.37 ($C_{19}H_{40}O_2Si$);
Rf 0.46 (40-60 petrol/acetone 90:10);
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 ($1H_1$, t, J = 7.3 Hz), 4.49 ($1H_4$, d, J = 11.6 Hz), 4.40 ($1H_4$, d, J = 11.6 Hz), 4.04 ($1H_6$, t, J = 6.8 Hz), 2.14–1.98 ($2H_2$, m), 1.74–1.57 ($2H_8$, m), 2.66 ($2H_9$, m), 1.16–1.07 ($21H_{TIPS}$, $2H_7$, m), 0.99 ($3H_3$, t, J = 7.5 Hz), 0.91 ($3H_{10}$, t, J = 7.1 Hz);
^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6 (C5), 130.8 (C1), 75.2 (C6), 60.3 (C4), 35.6 (C7), 28.3 (C8), 22.6 (C9), 20.7 (C2), 18.0 ($TIPSCH_3$), 14.2 (C3), 14.0 (C10), 11.8 (TIPSCH).

2-Propylidine-heptane-1,3-diol (5.2)

5.2

Tetrabutyl ammonium fluoride, 1.0M in THF, (2.0 mL, 2.00 mmol) was added dropwise to a solution of **5.1** (454mg, 1.47 mmol) in THF (2 mL). The reaction was stirred at room temperature for 2 h. The solvent was removed reduced pressure and diol **5.2** (235 mg, 1.36 mmol, 93%) was isolated as a colourless oil by flash chromatography (hexane/acetone 90:10).

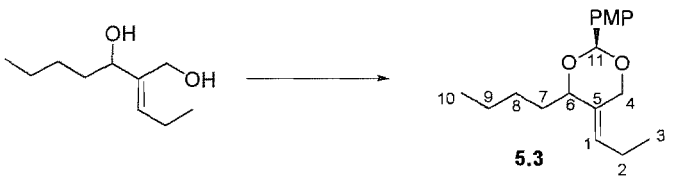
Mw 172.16 ($C_{10}H_{20}O_2$);

Rf 0.05 (hexane/acetone 90:10);

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51 ($1H_1$, t, J = 7.4 Hz), 4.32 ($1H_4$, d, J = 12.0 Hz), 4.24 ($1H_4$, d, J = 12.0 Hz), 4.14 ($1H_6$, t, J = 6.9 Hz), 2.43 ($2H_{OH}$, s, br), 2.19–2.05 ($2H_2$, m), 1.75–1.55 ($2H_7$, m), 1.41–1.18 ($4H_{8,9}$, m), 1.00 ($3H_3$, t, J = 7.5 Hz), 0.91 ($3H_{10}$, t, J = 7.1 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2 (C5), 132.9 (C1), 77.8 (C6), 58.1 (C4), 35.3 (C7), 28.2 (C8), 22.5 (C9), 20.7 (C2), 14.3 (C3), 14.0 (C10).

4-Butyl-2-(4-methoxy-phenyl)-5-propylidene-[1,3]-dioxane (5.3)



5.3

Pyridinium *p*-toluene sulfonate (10 mg, 40 μmol) and $MgSO_4$ (166 mg, 1.39 mmol) were added in one portion to a solution of **5.2** (200 mg, 1.16 mmol) in toluene (5 mL). *p*-Anisaldehyde (212 μl, 235 mg, 1.74 mmol) was added dropwise and the reaction heated to reflux for 3.5 h. The reaction was allowed to cool to room temperature before washing with c.$NaHCO_3$ (5 mL) and water (5 mL). The aqueous washings were extracted with CH_2Cl_2 (2×10 mL). The combined organic fractions were dried over $MgSO_4$ before the solvent was removed under reduced pressure. Protected diol **5.3** (191 mg, 0.65 mmol, 57%) was isolated as a 3:1 diastereomeric mixture by flash chromatography (hexane/acetone 90:10).

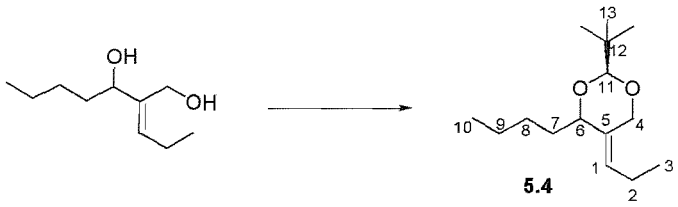
Mw 290.20 ($C_{18}H_{26}O_3$);

Rf 0.43 (40-60 petrol/acetone 90:10);

^{1}H NMR major diastereomer (300 MHz, $CDCl_3$) δ 7.44-7.41 ($2H_{Ar}$, m), 6.89 ($2H_{Ar}$, d, J = 8.8 Hz), 5.66 ($1H_{11}$, s), 5.43 ($1H_1$, t, J = 7.3 Hz), 4.86 ($1H_4$, d, J = 12.9 Hz), 4.49-4.29 ($2H_{4,6}$, m), 3.80 ($3H_{OMe}$, s), 2.18–1.96 ($2H_2$, m), 1.86–1.67 ($2H_7$, m), 1.44–1.36 ($4H_{8,9}$, m), 1.01 ($3H_3$, t, J = 7.5 Hz), 0.94 ($3H_{10}$, t, J = 7.4 Hz);

^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0 (C5), 127.8 (Ar), 127.3 (Ar), 125.9 (C1), 113.5 (Ar), 100.9 (Ar), 94.7 (C11), 78.8 (C6), 66.1 (OMe), 55.2 (C4), 30.9 (C7), 27.6 (C8), 22.7 (C9), 20.1 (C2), 14.2 (C3), 14.1 (C10).

4-Butyl-2-*t*-butyl-5-propylidene-[1,3]-dioxirane (5.4)



5.4

Pyridinium *p*-toluene sulfonate (1 mg, 3 μmol) and $MgSO_4$ (10 mg, 83 μmol) were added in one portion to a solution of **5.2** (50 mg, 0.29 mmol) in toluene (5 mL). Pivaldehyde (48 μl, 37 mg, 0.44 mmol) was added dropwise and the reaction heated to reflux for 4 h. The reaction was allowed to cool to room temperature before washing with conc.$NaHCO_3$ (5 mL) and water (5 mL). The aqueous washings were extracted with CH_2Cl_2 (3×10 mL). The combined organic fractions were dried over $MgSO_4$ before the solvent was removed reduced pressure. Protected diol **5.4** (29 mg, 0.12 mmol, 41%) was isolated as a 5:1 diastereomeric mixture by flash chromatography (hexane/acetone 90:10).

Mw 240.39 ($C_{15}H_{28}O_2$);
Rf 0.33 (40-60 petrol/acetone 90:10);
^{1}H NMR major diastereomer (300 MHz, $CDCl_3$) δ 5.31 ($1H_1$, t, J = 7.3 Hz), 4.71 ($1H_4$, d, J = 12.8 Hz), 4.26 ($1H_{11}$, s), 4.06 ($1H_4$, d, J = 12.8 Hz), 3.99 ($1H_6$, d, J = 6.3 Hz), 2.24–1.95 ($2H_2$, m), 1.80–1.40 ($2H_7$, m), 1.37–1.26 ($4H_{8,9}$, m), 0.97 ($1H_3$, t, J = 7.5 Hz), 0.92–0.89 ($12H_{10,13}$, m);
^{13}C NMR (75 MHz, $CDCl_3$) δ 132.9 (C5), 124.8 (C1), 107.4 (C11), 78.2 (C6), 65.7 (C4), 34.9 (C12), 31.0 (C7), 27.5 (C8) 24.8 (C13), 22.6 (C9), 20.0 (C2), 14.3 (C3), 14.1 (C10).

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