DEVELOPMENT OF NEW METHODS FOR THE SYNTHESIS OF DIHYDROPYRANS AND TETRAHYDROPYRANS

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Abstract

This thesis detail attempts to develop a procedure, based on the Maitland-Japp reaction, for the formation of functionalised tetrahydropyran (THP) rings. Previous work in the Clarke group has focused on the development of the Maitland-Japp reaction, but it produced mixtures of diastereomeric THPs.

The work described in this thesis details the stereocontrolled synthesis of functionalised 2,6-*cis*- and 2,6-*trans*-THP rings from dihydropyran (DHP) rings, as well as the synthesis of 3,3,6-trisubstituted THP rings. The formation of 2,6-*cis* THP rings was achieved by the addition of hydride nucleophiles to C2-substituted DHPs, and trapping with carbon electrophiles. Treatment of 2H-DHPs with carbon nucleophiles led to the formation of 2,6-*trans* THP rings. Reduction of 2H-DHPs with L-Selectride® produce the 3,6-disubstituted THP rings, while trapping of the intermediate enolate with carbon electrophiles give formation of 3,3,6-trisubstituted THP rings.

The development of a successful method for the synthesis of functionalised THP rings led to a synthesis of the A-ring of Lasonolide A and Diospongin B.

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Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is currently being submitted, in candidature for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and in the event the work of others has been used this has been fully acknowledged in the text.

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Nadiah Mad Nasir

1.0   Introduction

1.1   Natural product synthesis

Tetrahydropyran (THP) rings are common and important building blocks in natural products as they are found in many biologically active compounds.[1] There are highly functionalized tetrahydropyran rings in molecules such as lasonolide A **1** which posseses a quaternary stereocentre and displays anti-cancer activity with 50% inhibitory concentration (IC_{50}) values against the A-549 human lung carcinoma and P388 murine leukemia cell lines of 40 and 2 ng/ mL, respectively. It also inhibits cell adhesion in the EL- 4.IL-2 cell line with an IC_{50} of 19 ng/mL.[2] Multi-substituted 2,6-*cis* and 2,6-*trans* THP core units can be found in phorboxazoles A and B **2**, which show potent activity against *C. albicans* and in the National Cancer Institute's panel of 60 tumor cell line with exceptional inhibition of cell growth (GI_{50}'s < 7.9 x 10^{-10} M).[3] (-)-Mandelalide A **3** posseses potent biological activity with nanomolar cytotoxicities against both human NCI-H460 lung cancer cells respectively with IC_{50} 12 nM and mouse neuro-2A neuroblastoma cells respectively with IC_{50}, 29 nM,[4] also features 2,6-*cis* THPs ring in the structure. The 2,6-*trans* THPs ring can be observed in diospongin B **4**, which showed anti-osteoporotic properties.[5]
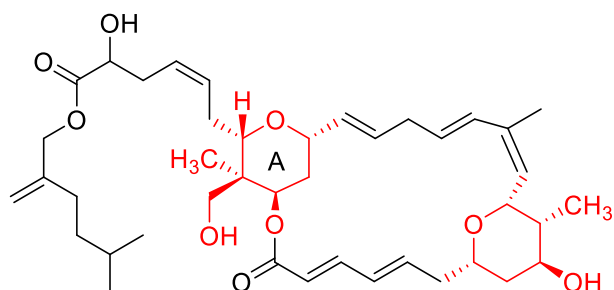
Lasonolide A **1**
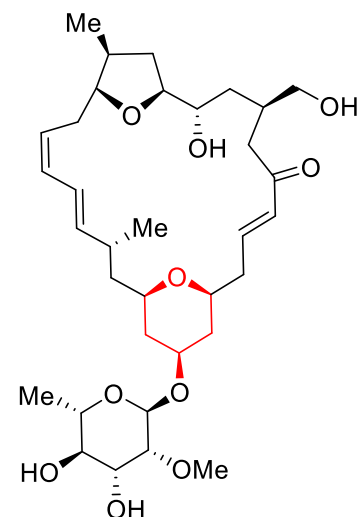
(-)-Mandelalide A **3**
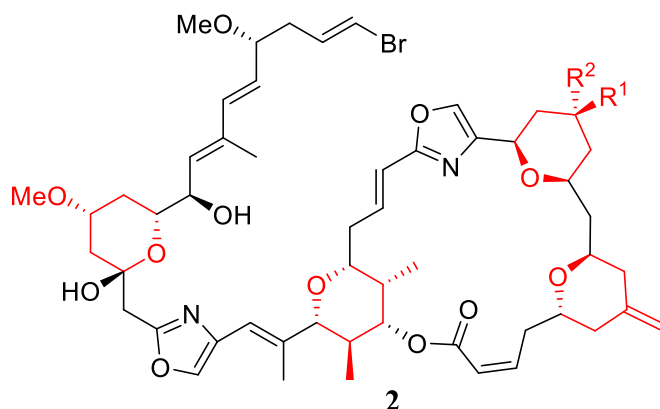
2
(+)-Phorboxazole A R1 = H, R2 = OH
(+)-Phorboxazole B R1 = OH, R2 = H
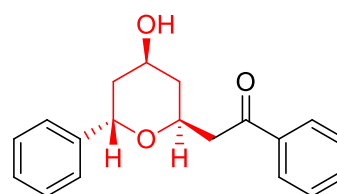
Diospongin B **4**

Our interest in the construction of tetrahydropyrans in the synthesis of natural products led us to investigate a new method to construct funtionalized THPs such as 2,6-*cis*, 2,6-*trans*, 3,6-disubstituted and 3,3,6-trisubstituted THPs ring. Several approaches have been reported.[7]

1.2 Cyclisation onto oxocarbenium ions

The Prins cyclisation is one of most utilised methods to construct the THP ring in the synthesis of natural products. The Prins reaction, first reported by Hendrik Jacobus Prins in 1919,[6] proceeds *via* acid-catalyzed electrophilic addition of olefins to aldehydes to generates carbenium ions (**A,** Scheme 1). This intermediate (**A**) can be intercepted by a nucleophile such as a second equivalent of an aldehyde to form 1,3-dioxanes **6**. Prins cyclization can occur when a homoallylic alcohol reacts with an aldehyde in the presence of a Lewis acid to form oxocarbenium intermediates (**B,** Scheme 1) which then cyclizes to give functionalized tetrahydropyrans **8**.[7]
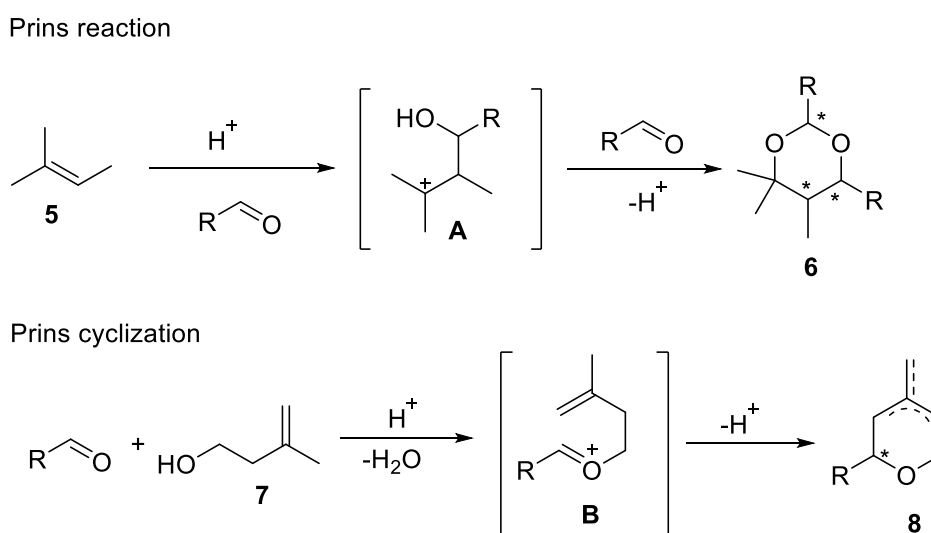
Scheme 1: Prins reaction and cyclisation.

The Aggarwal group used a three-component allylboration-Prins reaction sequence to synthesise the THP core of (-)-clavosolide A with high stereoselectivity. They applied allylic boronic ester **9a** with aldehyde **10a** followed with aldehyde **11**, but unfortunately it gave a low yield of THP **13** due to cleavage of the silyl protecting group (Scheme 2). With a simple aldehyde like acrolein **12** it gave an excellent yield of THP **14** with good diastereoselectivity (71%, 96 : 4 dr).[8]
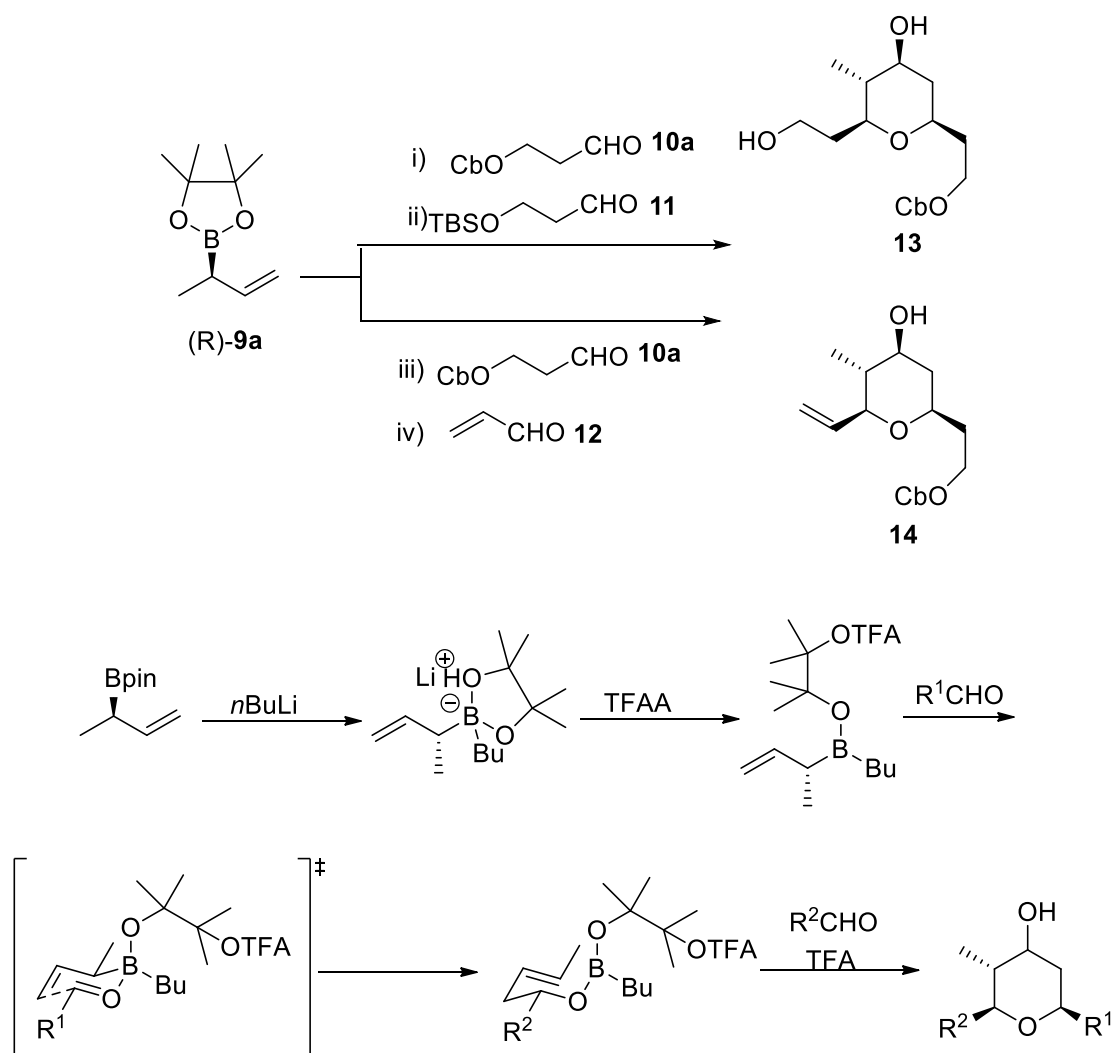
Scheme 2 Reagent & Conditions: i) nBuLi (1.1 eq), THF, −78 °C, 15 min; ii) TFAA (1.2 eq), −78 °C, 30 min; iii) **10a** (1.5 eq), −78 °C (or −100 °C), 2 hr then RT, 16 hr; iv) CH$_2$Cl$_2$, **11** (2.5 eq) or acrolein **12** (4 eq), TFA:CH$_2$Cl$_2$ (1:3), RT, 2 hr; K$_2$CO$_3$ (1.5 eq), MeOH, RT, 30 min, **13** (39%) and **14** (71%) . OCb = N, N-diisopropyl carbamate.

A novel cascade strategy has been developed by Subba Reddy group for synthesis of spirochroman derivatives using the condensation of 2-(5-hydroxy-3-methylenepentyl)phenol **15** with aromatic or aliphatic aldehyde. The reaction was successful when attempted with BF$_3$•OEt$_2$ at 0 - 25°C (Scheme 3).[9]
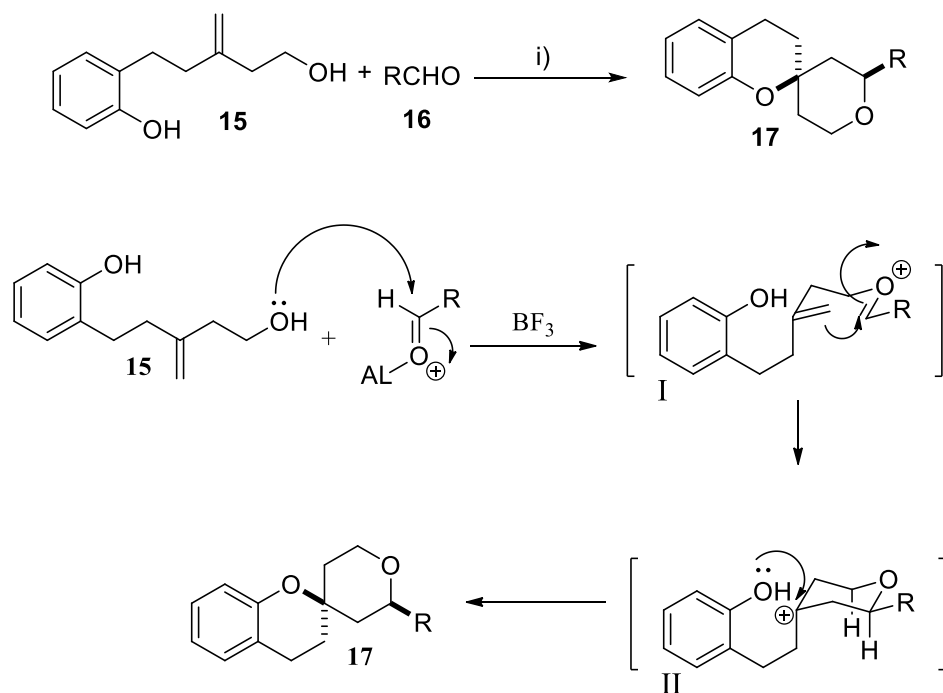
Scheme 3 Reagent & Conditions: i) BF$_3$•OEt$_2$, CH$_2$Cl$_2$, 0 – 25 °C, 1 hr, 70-95 %.

The Prins methodology was also applied successfully in the synthesis of cocosolide **18** in 8 steps. Gunasekera's group used the TMSOTf-promoted Sakurai annulation of allylsilane **19** with aldehyde **20** to construct the 2,6-*cis* THP **21** containing an exo-methylene in the 4-position. The THP **21** was formed rapidly at −78 °C (Scheme 4).[10]
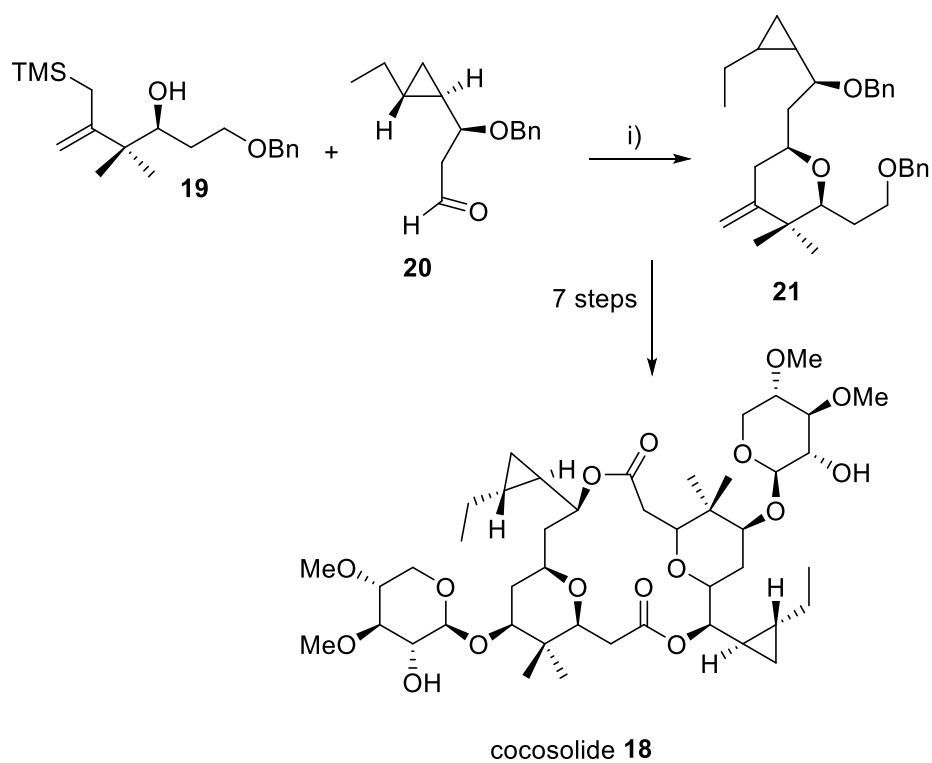
Scheme 4 Reagent & Conditions: i) TMSOTf, Et$_2$O, 4 Å MS, −78 °C, 75%.

Another example has employed a TMSOTf catalysed silyl Prins reaction by the Rychnovsky group in the total synthesis of cyanolide A **22**, where they formed the exo-olefin dimer **24** in 76% yield (Scheme 5).[11] With a further 3 steps they constructed cyanolide A **22**.
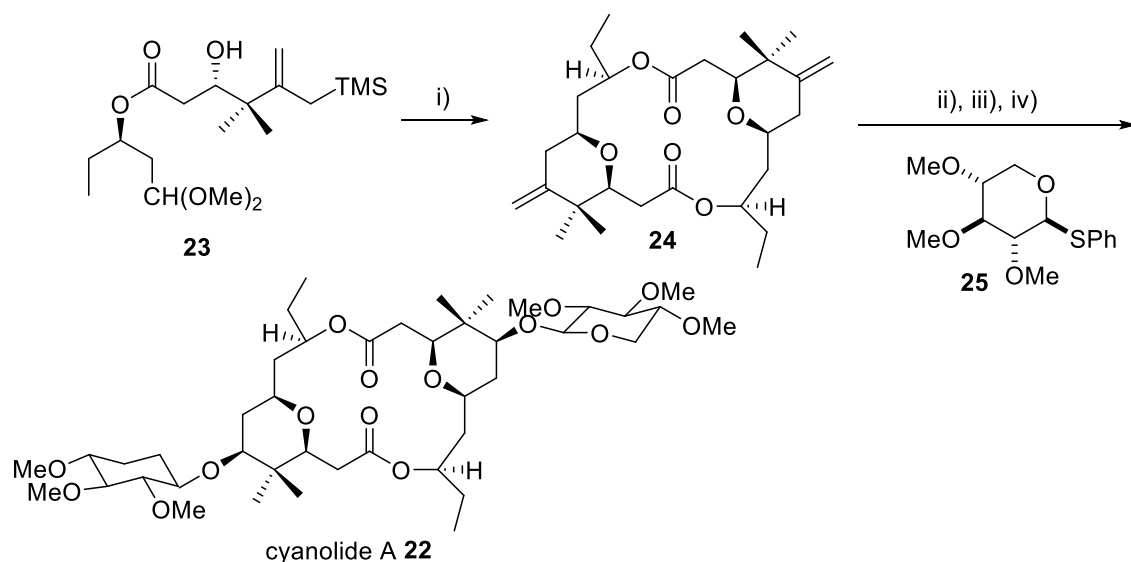
Scheme 5 Reagent & Conditions: i) TMSOTf, CH$_2$Cl$_2$, 76%, ii) OsO$_4$, NMO then NaIO$_4$, 82%, iii) NaBH$_4$, 96 %, iv) MeOTf, MS 4Å, Et$_2$O, 25 °C, 48 hr, 18%.

The Furman group also reported the use of a Prins reaction in the total synthesis of (-)-centrolobine **26**, the cyclisation of **27** with 4-tosyl-oxybenzaldehyde **28** was attempted with TMSOTf, to give dihydropyran **29** in 87% yield. Reduction of the olefin led to the formation of THP **30** in 78% yield, which was then elaborated to form (-)-centrolobine **26** in 73% over 3 steps (Scheme 6).[12]
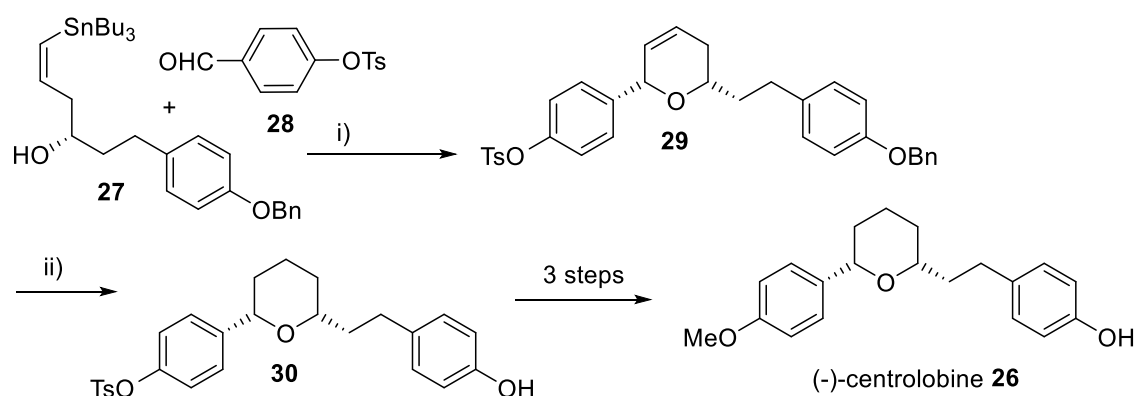
Scheme 6 Reagent & Conditions: i) TMSOTf, Et$_2$O, −78 °C, 87% ii) Pd/C, H$_2$, EtOAc, 78%.

Dobb's *et al.* reported the formation of DHP **33** using an InCl$_3$ Lewis acid mediated addition of homoallylic alcohols **32** to aldehydes **31**. The DHP **33** was produced as a

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single diastereomer and in an excellent 95% yield (Scheme 7). Hydrogenation both

reduces the olefin and removes the benzyl group and finally the alcohol was oxidised to

give the Civet secretion natural product **34** in 54 % yield.[13]
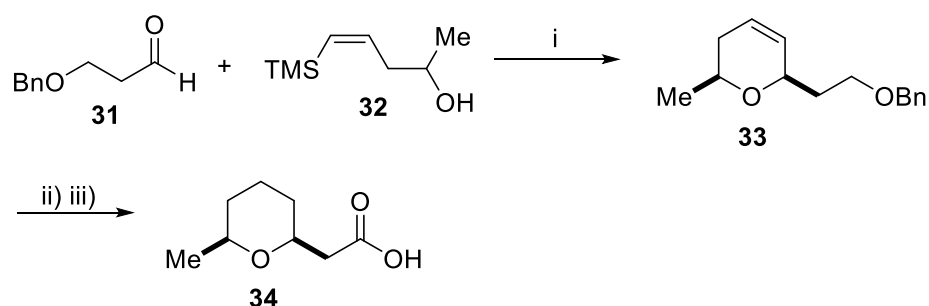
Scheme 7 Reagent & Conditions: i) $InCl_3$, CH_2Cl_2, 16 hr, RT, 95%. ii) H_2, Pd/C (10%), EtOH, iii) CrO_3,/H_2SO_4,H_2O, 54%.

The Petasis-Ferrier rearrangement is another method for cyclisation onto oxocarbenium

ions where an acid is used as a promoter for rearrangement. Cleavage of the adjacent C-

O bond **35**, results in the formation of the oxocarbenium enolate **36**, which can be cyclized

directly to form 2,6-*cis*-THP **37** (Scheme 8).[14]
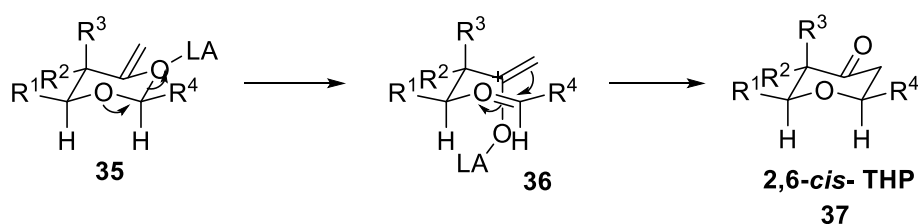
Scheme 8 The Petasis-Ferrier rearrangement.

The Smith III's group has applied this method to construct the 2,6-*cis* THP ring in total

synthesis of (-)-Enigmazole A.[15] The carbon skeleton of the THP ring was synthesined

using 'the three-stage Petasis-Ferrier union/rearrangement' where the large fragment of

38 and **39** was combined and produced the THP ring **42** with 84% yield (Scheme 9).
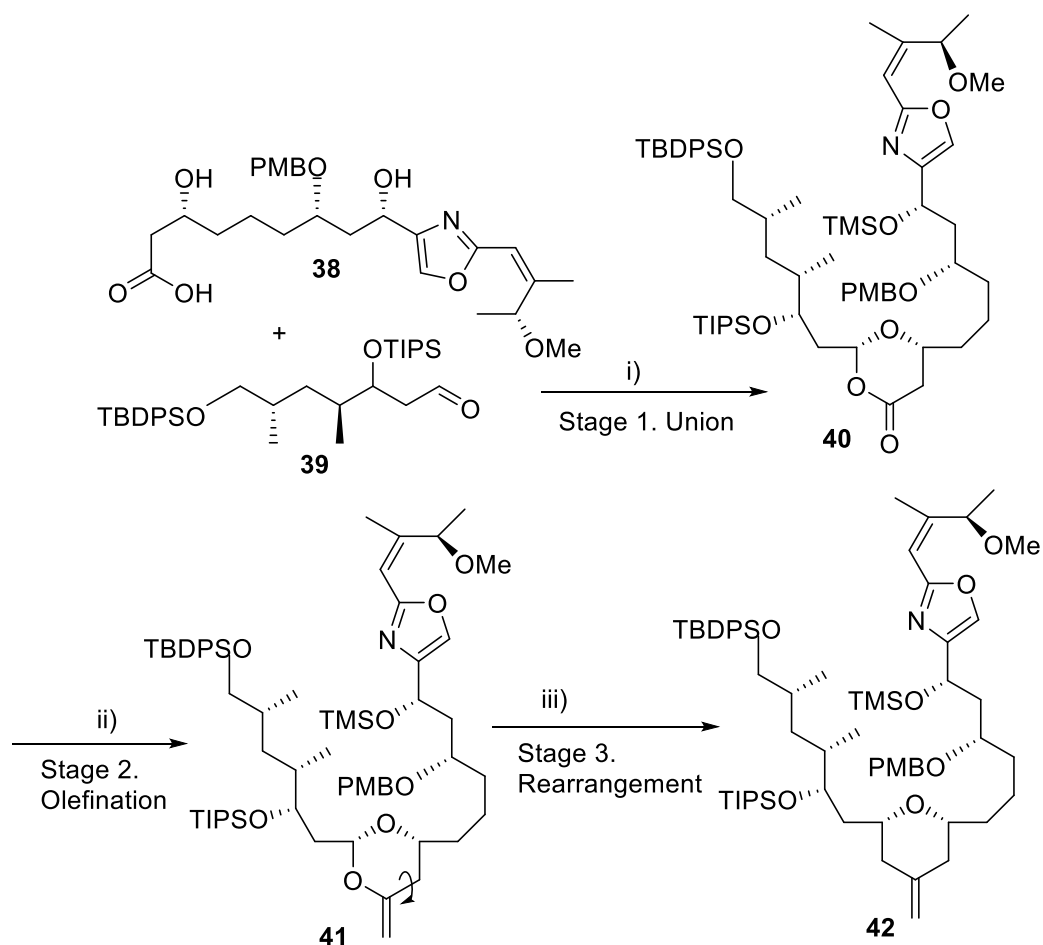
Scheme 9 Reagent & Conditions: i) **38**, HMDS, THF, **39**, TMSOTf, H_2O, CH_2Cl_2, -78 °C, 95%, ii) Cp_2TiMe_2, PhMe, THF, μ Wave 100 °C, 3 hr, 87%, iii) Me_2AlCl, CH_2Cl_2, -78 °C, 30 sec, then $Ph_3P=CH_2$, 84%.

The Petasis-Ferrier reaction has been utilised in many syntheses including in seven natural product total syntheses from the group of Amos Smith III: (+)-phorboxazole A,[16] (+)-Zampanolide,[17] (+)-Dactylolide,[16] (+)-Spongistatin 1,[18] (−)-Kendomycin,[19] (−)-Clavosolide A,[20] and (−)-Okilactomycin.[21]

The formal total synthesis of brevisamide **48** has been achieved *via* a tandem isomerization/C-O and C-C bond formation reaction. The Mohapatra group performed the cyclization by subjecting **43** and allyltrimethylsilane **44** to iodine which allowed

stereoselective allylation and produced the *trans*-DHP **45** as a single product in 96% yield.

Fragment **46** was epimerised at C-12 through a retro-oxa-Michael/oxa-Michael process

with potassium *tert*-butoxide in THF to yield the *cis*-2,6-THP **47**, the important skeleton

in brevisamide **48** (Scheme 10).[22]
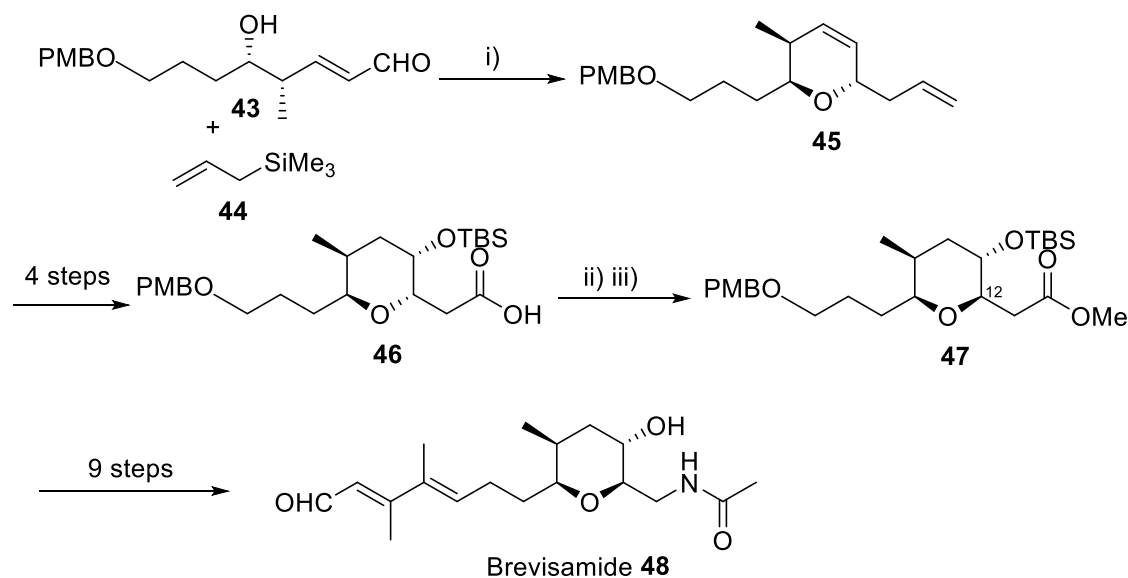
Scheme 10 Reagent & Conditions: i) THF, I_2, 45 min, 96%, ii) CH_2N_2, Et_2O, 0 °C, 15 min, 91%, iii) potassium *tert*-butoxide, THF, 0 °C, 92%.

1.3 Reduction of cyclic hemi-ketals

There are other ways to construct the THP rings in natural products, including the

reduction of cyclic hemi-ketals. This reaction proceeds *via* a cyclic oxocarbenium ion

intermediate which is trapped by the incoming nucleophile. The 2,6-*cis* or 2,6-*trans* THP

ring can be formed depending on the nucleophile, where the nucleophile addition to the

cyclic oxocarbenium ion usually occurred from a pseudoaxial orientation. The Mohapatra

group applied this method to form the THP ring of herboxidiene **52**, where the treatment

of **49** with DIBAL-H at −78 °C gave the lactol **50** in 83% yield. This was followed by

treatment with allyltrimethylsilane and catalytic AuCl₃ to give **51** in 87% yield (Scheme 11). After 9 steps, the total synthesis of herboxidiene **52** was completed.[23]
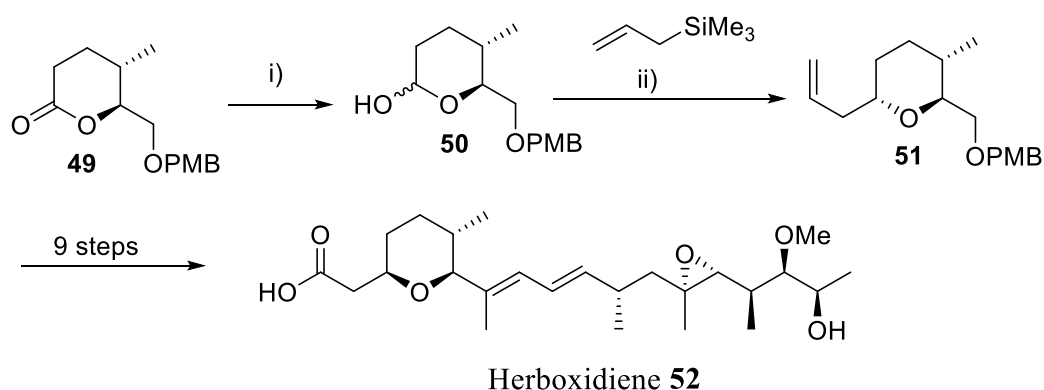
Scheme 11 Reagent & Conditions: i) DIBAL-H, CH₂Cl₂, −78 °C, 2 hr, 83%, ii) AuCl₃, RT, 3 hr, 87%.

The Cossy group also applied the same method to synthesise the *trans*-THP ring of the macrocyclic core of Leucascandrolide A **57**, where the reduction of lactone **53** by DIBAL-H followed by acylation gave **54** in 98% yield. Compound **54** was coupled with fragment **55** by using a Mukaiyama-type reaction, where an oxocarbenium intermediate was generated by treatment of **54** with ZnCl₂, then quenched with enol ether **55** to produce tetrahydropyran **56** with 89% yield (*trans: cis* = 13: 1) (Scheme 12).[24]
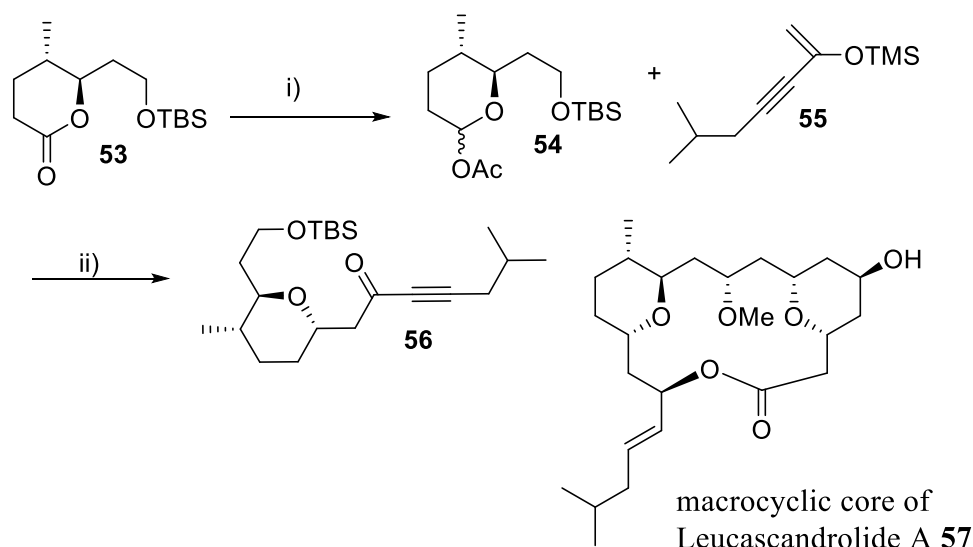
Scheme 12 Reagent & Conditions: i) DIBAL-H, CH$_2$Cl$_2$, −78 °C, then Ac$_2$O, Py, DMAP, 98%, ii) ZnCl$_2$, CH$_2$Cl$_2$, −78 °C to RT, 89%.

Smith III's group applied a similar method to synthesize the *cis*-THP ring of (+)-Spongistatin 1. A Grignard reagent was added to lactone **58** followed by reduction of lactol with Et$_3$SiH and BF$_3$•Et$_2$O to produce the desired *cis*-THP ring **59** in 89% yield (Scheme 13).[25]
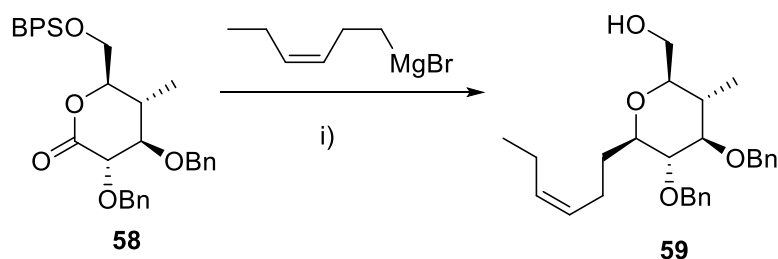
Scheme 13 Reagent & Conditions: i) Et$_3$SiH, BF$_3$•Et$_2$O, 89%.

The Zakarian group used an Achmatowicz rearrangement as a key step to produce a cyclic hemi-ketal in their synthesis of Brevisamide **48**. Furan **60** was treated with NBS and oxidative ring expansion was performed and followed by reaction with BF$_3$•Et$_2$O and Et$_3$SiH to produce intermediate **61** in 54% yield. A diastereoselective conjugate addition of Me$_2$CuLi gave lactone **62** and then the ketone was reduced by NaBH$_4$ to give *cis*-THP

ring of (+)-Brevisamide **63** as a single diastereomer in 85% yield (Scheme 14). A further 3 steps gave (+)-Brevisamide **48**.[26]
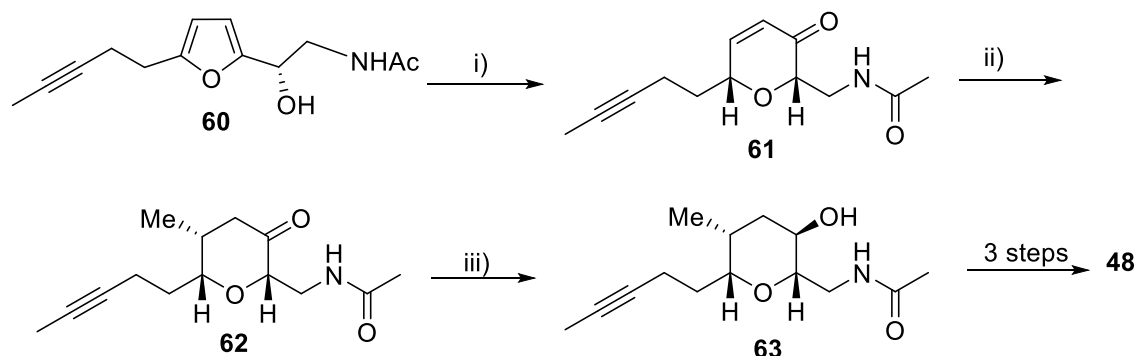
Scheme 14 Reagent & Conditions: i) NBS, NaHCO$_3$, NaOAc, THF: H$_2$O (10:1), 0 °C then Et$_3$SiH, BF$_3$•Et$_2$O, CH$_2$Cl$_2$, 0 °C, 54%, ii) Me$_2$CuLi, Et$_2$O, –60 °C, iii) NaBH$_4$, THF: H$_2$O (10:1), 85%.

1.4   Michael reactions in THP synthesis

Michael reactions are widely applied reations in organic synthesis. There are hetero-Michael reactions such as the aza-Michael, sulfa-Michael, phospha-Michael and oxa-Michael (oxo- or oxy-Michael) reactions.[27] Oxa-Michael addition, the addition of an alcohol to a conjugate acceptor, was published by Loydl as early as 1878.[28] Moreover, oxa-Michael reactions can be an efficient method to access oxygen-containing heterocycles such as tetrahydropyrans, chromenes or xanthones.[29] Fuwa has used it in the synthesis of 2,6-*cis*-tetrahydropyran *cis*-**65** and 2,6-*trans*-tetrahydropyran *trans*-**65** of Aspergillides B **66** and A **67**. The intermolecular oxa-conjugate cyclization of **64** formed *trans*-**65** as the major diastereomer (17: 1) in 96% yield when exposed to KO*t*-Bu (Scheme 15); however, when **64** was treated with DBU in toluene at 135 °C, it gave the thermodynamically favoured *cis*-**65** with diastereomer (11: 1) in 81% yield. Either *trans*-**65** or *cis*-**65** could be synthesized from **64** by switching the reaction conditions.[30]
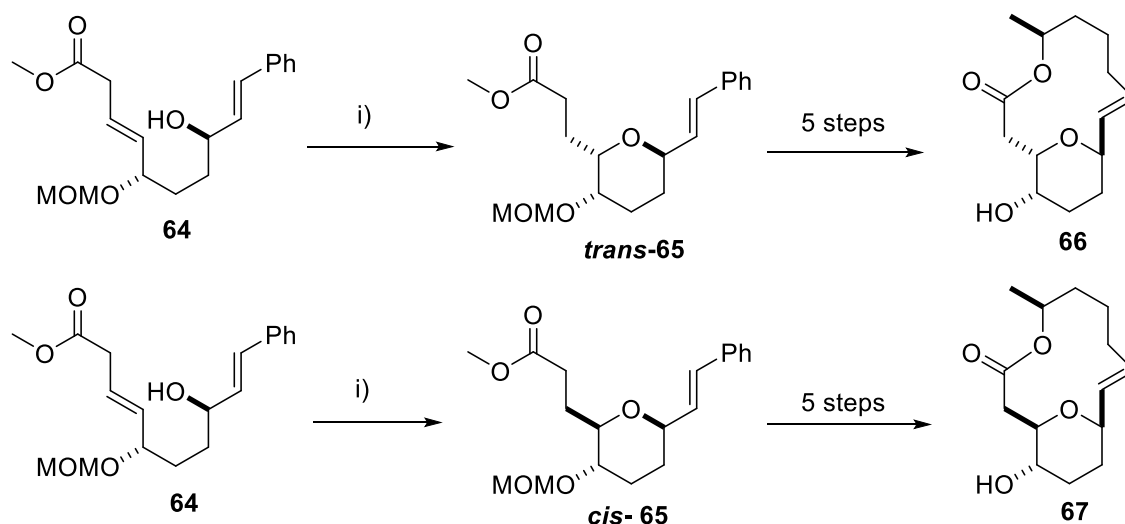
Scheme 15 Reagent & Conditions: i) KO*t*-Bu, THF, −78 °C, 0.5 hr, 96%, ii) DBU, toluene, 135 °C, 36 hr, 81%.

The Trost group also synthesized the THP ring of aspergillides B **66** but they used ruthenium-catalyzed *trans*-hydrosilylation. The hydrosilylation/protodesilylation was used to reduce the alkyne **68** chemoselectively and form an *E*-double bond, followed by deprotection/oxy-Michael reaction to form 2,6-*trans* THP **69** in 38% yield. THP **69** was then be transformed into aspergillides B **66** in 3 additional steps (Scheme 16).[31]
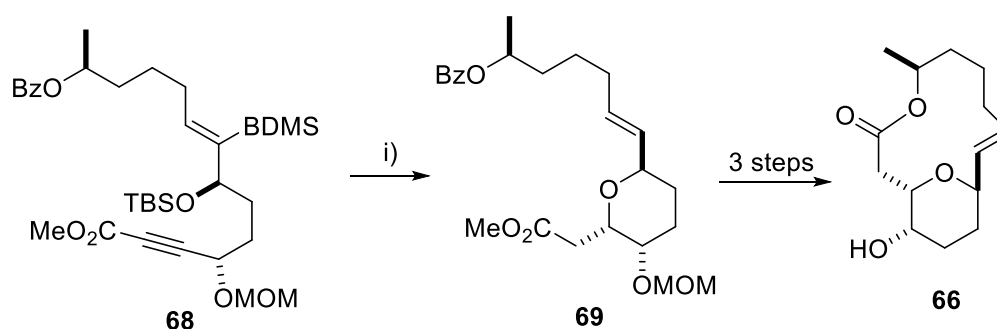
Scheme 16 Reagent & Conditions: i) Cp*Ru(CH₃CN)₃PF₆, (EtO)₃SiH, DCE 0 °C - RT, 10 hr, 38%.

Lee's group used a Michael reaction to construct *trans*-THP **73** and *cis*-THP **76** ring of leucascandrolide A macrolactone **57**. The *trans*-THP ring **71** was formed as the major

diastereomer (10: 1) from aldehyde **70** by using piperidine as the catalyst at –40 °C, but

when they used a higher temperature of 25 °C the undesired *cis*-THP was formed. This

was followed by coupling **73** and **74** as the key step for allylic oxidation/oxy-Michael

reaction (Scheme 17). The synthesis of leucascandrolide A macrolactone **57** was

completed with 5 additional steps and in 96% yield over 5 steps from **76**.[32] The Evans

group also applied a similar strategy to synthesise the THP ring of leucascandrolide A

macrolactone **57**.[33]
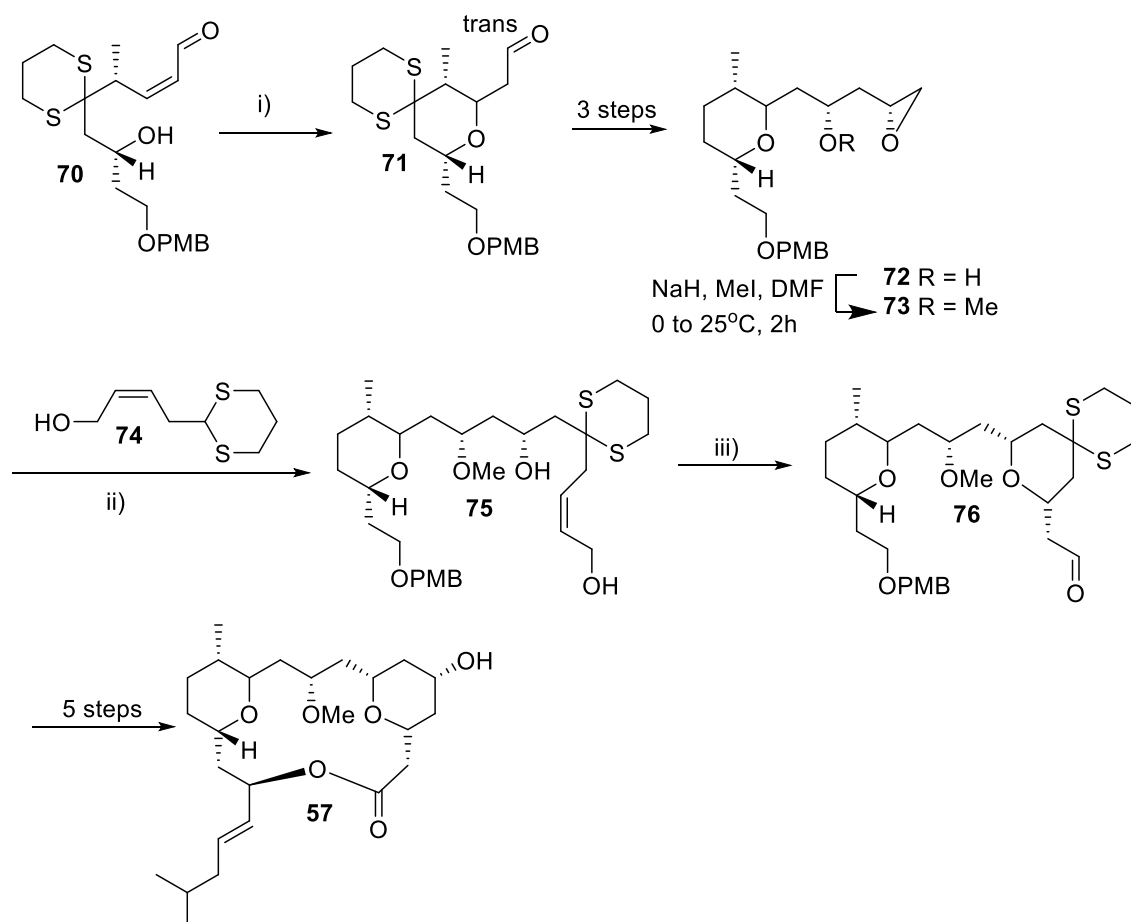
Scheme 17 Reagent & Conditions: i) piperidine, –40 °C, 24 hr, CH$_2$Cl$_2$, 96%, ii) *t*-BuLi, HMPA/THF, –78 °C, 10 min then, **74**, –78 °C, 1 hr, 92%, iii) MnO$_2$, CH$_2$Cl$_2$, 25 °C, 12 hr, 86%.

The *cis*-THP ring of cyanolide A **22** was synthesized by Hong using a Michael reaction.

The one-pot allylic oxidation/oxa-Michael/oxidation of aldehyde **78** formed 2,6 –*cis* THP

methyl ester **79** as a single diastereomer with 88% yield with no trace of 2,6 –*trans* THP methyl ester (Scheme 18). This is probably due to a highly rigid chair-like transition state induced by "double *gem*-disubstituent effect" of C4-*gem*-dimethyl and C5-1,3-dithiane groups.[34] The Reddy group also applied the same method oxa-Michael cyclization reaction to form THP ring of cyanolide A **22**.[35]
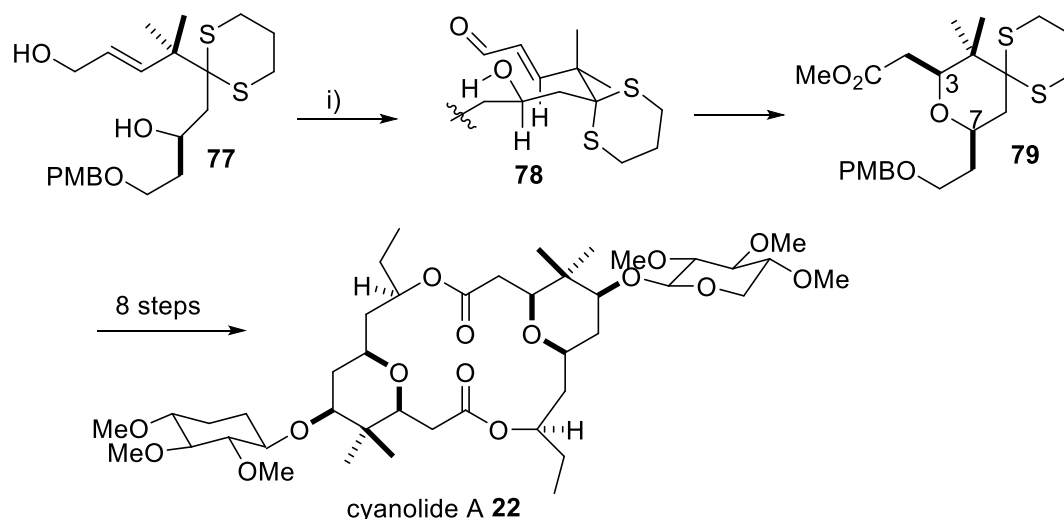
Scheme 18 Reagent & Conditions: i) MnO_2, CH_2Cl_2, 25 °C, 4 hr then dimethyl triazolium iodide, DBU, MnO_2, MeOH, MS 4 Å, 25 °C, 12 hr, 88%.

The C1-C11 fragment of madeirolide A **84** was synthesised by the Paterson group using Fuwa's acidic cyclisation conditions.[36] The condensation of aldehyde **80** with thioester phosphonate **81** under Masamune-Roush conditions[38] provided **82** in 95% yield. Removal of the acetonide and cyclisation occurred when **82** was treated with TsOH•H_2O. Deprotection of the ether PMB with DDQ gave the A ring diol **83**. With 2 further steps the C1-C11 madeirolide A fragment **84** was synthesized (Scheme 19).[38]
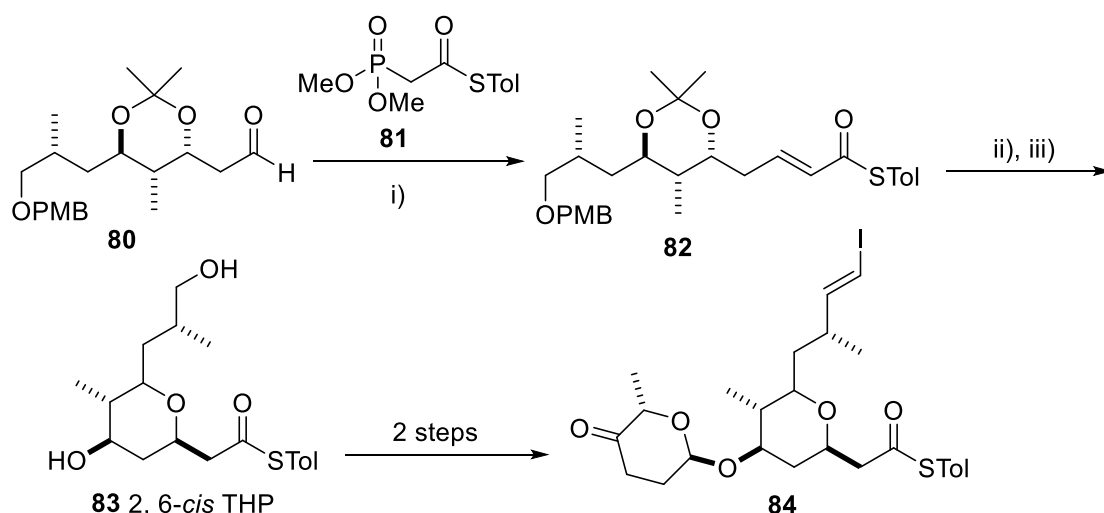
Scheme 19 Reagent & Conditions: i) LiCl, NEt$_3$, THF, −15 °C, 40 hr, 95%, ii) TsOH, CH$_2$Cl$_2$, 4.5 hr, (dr > 20:1), iii) DDQ, CH$_2$Cl$_2$, ph7 Buff, 0 °C, 1 hr, 61%.

The oxy-Michael reaction promoted by pyrrolidine catalyst **86** can create the key THP ring of (+)-dactylolide **87** as constructed by the Lee group (Scheme 20). This method gave **87** in an excellent yield of 98% as a 20: 1 diastereomeric mixture.[39]
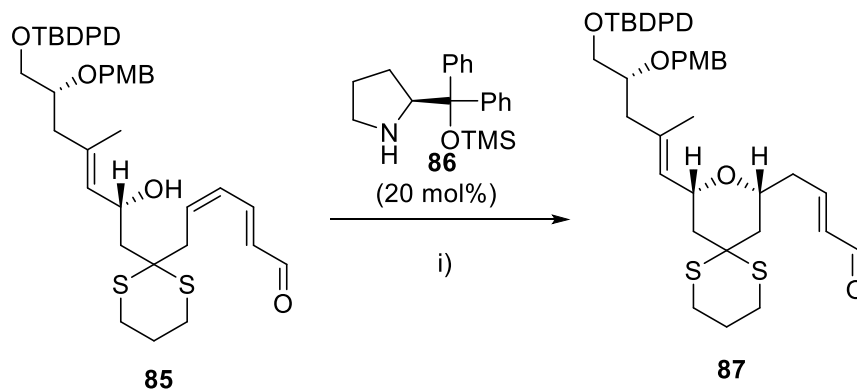
Scheme 20 Reagent & Conditions: i) BzOH (20 mol%), PhMe, 0 °C, 10 hr, 98%.

1.5   Hetero-Diels-Alder reaction

The Hetero-Diels-Alder (HDA) reaction is another method to construct THP rings in syntheses of natural products. The HDA reaction has high regioselectivity and *endo-*

stereoselectivity depending on conditions. Ghosh used the chiral tridentate Schiff base chromium (III) complex **90**, developed by Jacobsen[40] in an asymmetric HDA reaction in the key step in synthesis of B ring **92** of Lasanolide A. The reaction between diene **88** and **89**, uses TBAF/AcOH to remove the TES group and to give ketone **91** in 71% yield. Reduction of ketone with Dibal-H gave the THP of B ring in 96% yield (axial alcohol **92**: equatorial alcohol **93** = 1: 2) (Scheme 21).[41]
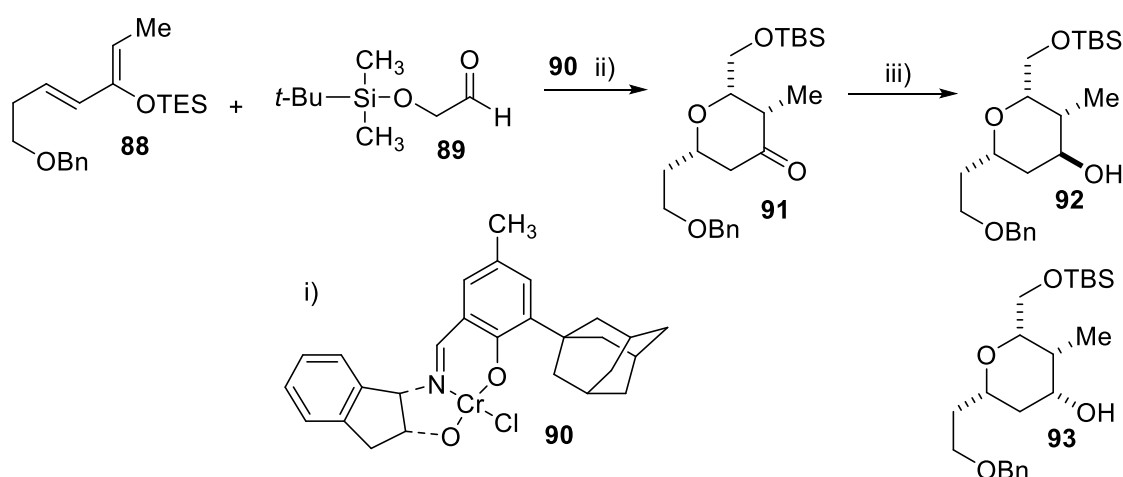
Scheme 21 Reagent & Conditions: i) **90**, ii) TBAF, AcOH, 71%, iii) Dibal-H, CH$_2$Cl$_2$, 96%.

The Raghavan group synthesised the THP ring of the macrolactone core of (+)-Neopeltolide **94**, by using the same method, a HDA reaction. The THP ring was formed between aldehyde **95** and siloxy diene **96** promoted by Jacobsen's catalyst ((S,S)-Cr(III)-salen-BF$_4$$^+$) **97**. A further 8 steps to give **94** in 60% yield (Scheme 22).[42]
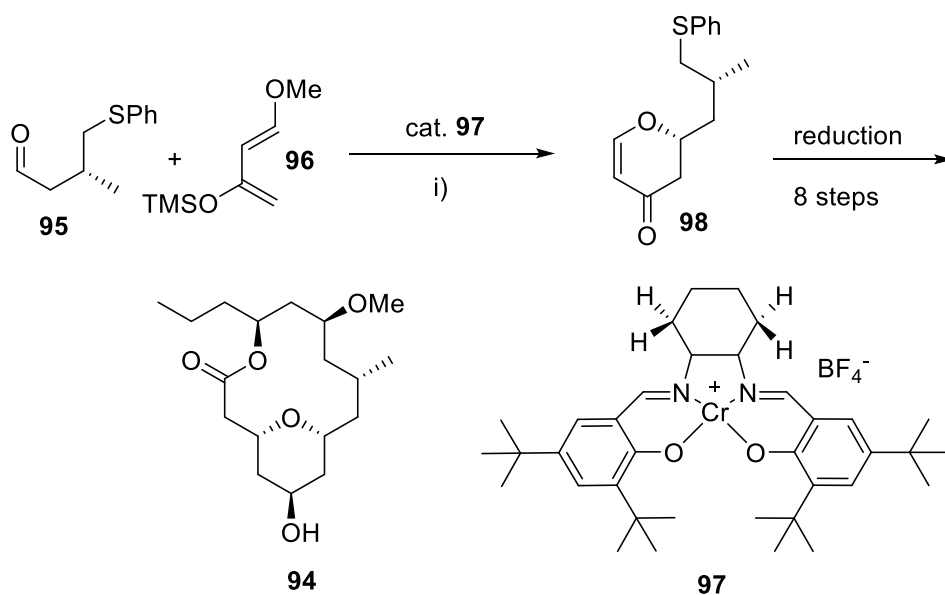
Scheme 22 Reagent & Conditions: i) TBME, –30 °C, 24 hr, then TFA, 2 hr, 75%.

An enantioselective HDA approach to the *syn*-1,3-dimethyl synthons of Azaspiracid-1 **104** was used by the Evans group. A HDA reaction took place between **99** and **100** when promoted with copper complex **101** (2 mol %). These conditions gave a mixture of *cis* and *trans* diastereomers (94: 6) of dihydropyran **102** and hydrogenation of the tetrasubstituted olefin gave THP **103** in 95% yield (Scheme 23).[43]
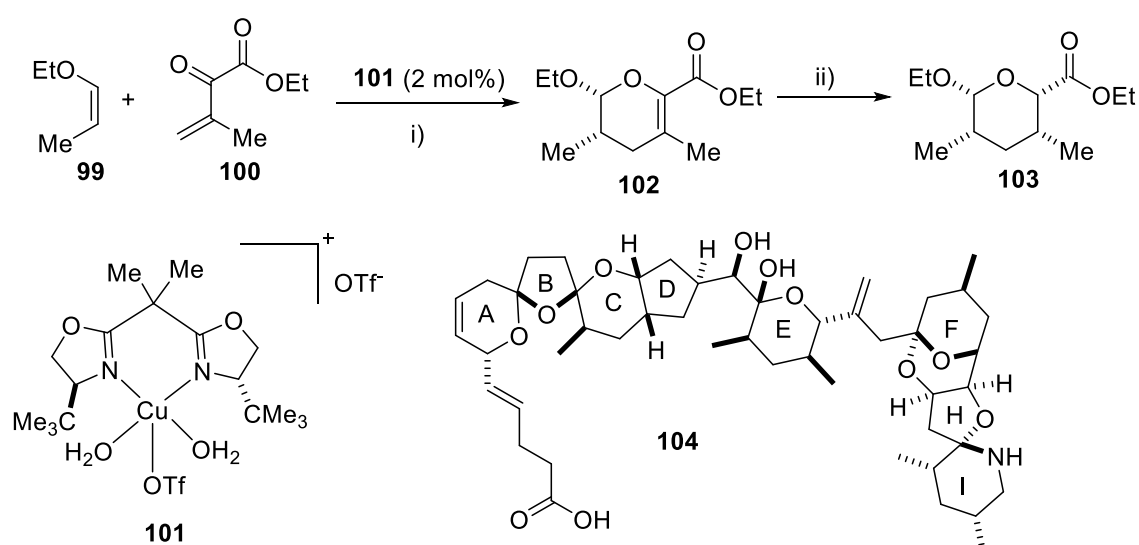
Scheme 23 Reagent & Conditions: i) 3Å MS, Et$_2$O, –40 °C, dr 94 : 6, 97% ee, 84% ii) H$_2$ (1 atm), Pd/C (5 mol%), EtOAc, 95%.

The synthesis of the THP core of pederin **110** by the Rawal group also employed a HDA reaction. Aldehyde **105** and diene **106** underwent HDA reaction in presence of Al(2,6-diphenylphenol)$_2$Me and TMSOTf to produce the pyranone **107** in 65% yield. The pyranone **107** was then treated with silyl ketene acetal **108** to produce ester **109** in excellent diastereomeric excess (dr = 20: 1). Then the reduction on the ketone with L-Selectride® gave the THP ring **110** in 92% yield (dr = 12: 1) (Scheme 24).[44]
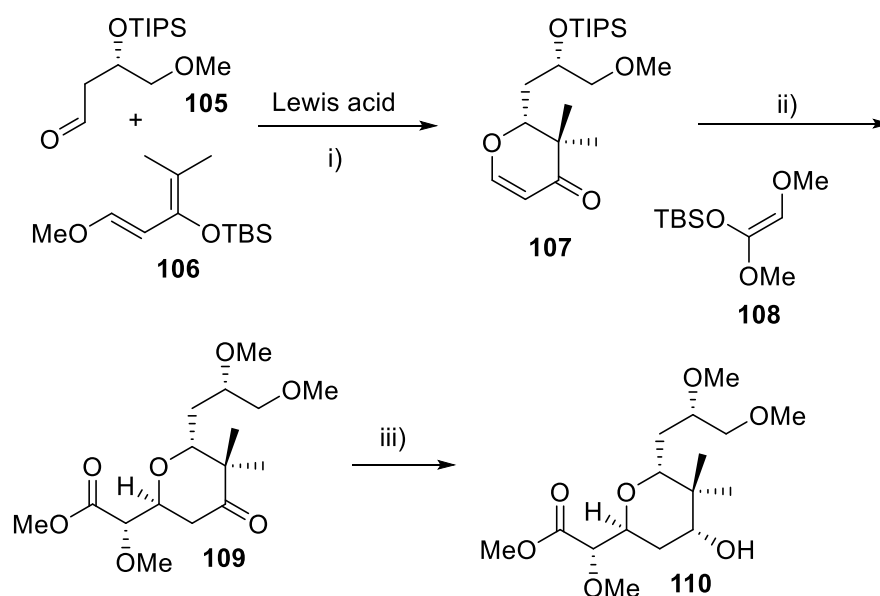
Scheme 24 Reagent & Conditions: i) Al(2, 6-diphenylphenol)$_2$Me, TMSOTf, CH$_2$Cl$_2$, 65%, ii)Sc(OTf)$_3$ (10 mol%), CH$_2$Cl$_2$, −78 °C to RT, 10% HF/MeCN, iii) L-Selectride®, THF, −78 °C, 92%.

1.6   Metal-mediated cyclisations

Metal-mediated cyclisations can be a method of constructing the THP ring in natural products. For example the Clark group applied this method to construct the THP ring of neoliacinic acid **114**. They used a copper catalyst, Cu(hfacac)$_2$ on diazo ketone **111** to form **112** which proceeded *via* a metal carbenoid oxonium ylide rearrangement. Over 2 steps **113** was formed, which was followed with methylenation of the ketone carbonyl to give the THP ring **114** in 81% yield (Scheme 25).[45]
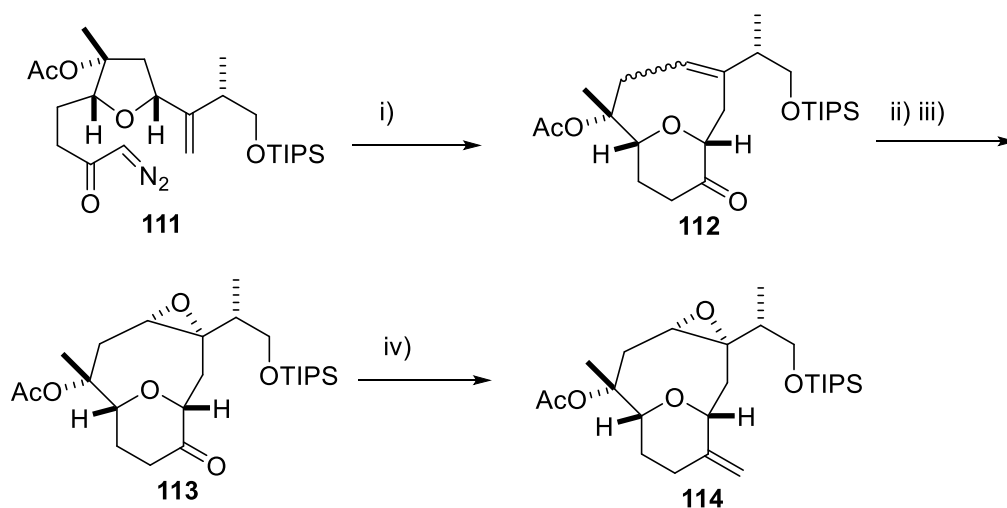
Scheme 25 Reagent & Conditions: i) Cu(hfacac)$_2$ 2 mol%, CH$_2$Cl$_2$, reflux, 69%, ii) EtSH, AIBN, C$_6$H$_6$, reflux iii) *m*-CPBA, CH$_2$Cl$_2$, reflux, 80%, iv) Cp$_2$TiMe$_2$, THF, reflux, 81%.

The Roulland group also used a metal-mediated cyclisation to synthesize the A ring of (-)-exiguolide **118**. They used three different variations of a ruthenium complex-catalysed reaction. The applied method proceeds *via* an ene-yne coupling/oxy-Michael addition with ruthenium-catalyst **117** to form THP A ring **118** in 78% yield and with a diasteromeric ratio of greater than 9 : 1 (Scheme 26).[46]
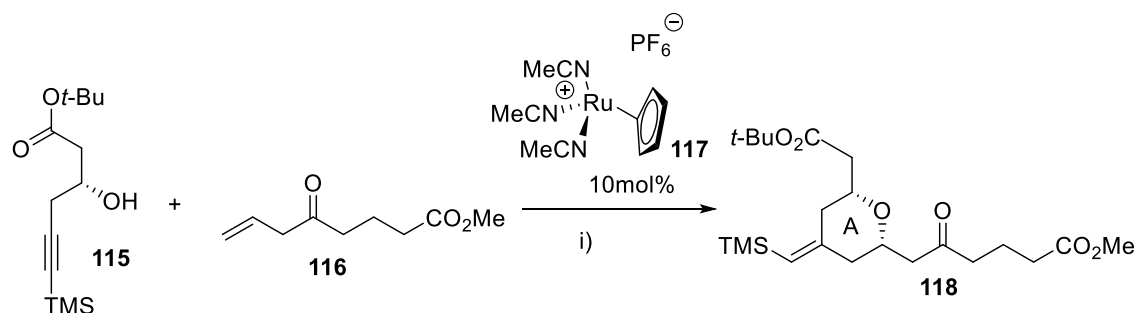
Scheme 26 Reagent & Conditions: i) acetone, AcOH (3 mol%), RT, 2 hr, 78%.

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1.7 Other methods

1.7.1 Ring-closing metathesis

Ring-closing metathesis has been used in the construction of THP rings from DHP rings in natural products. Fuwa has used the ring-closing metathesis method to construct the THP ring of (+)-neopeltolide **94**, where the ring closing metathesis was employed on diene **119** with 10 mol% of Grubbs II catalyst in toluene at 70 °C to form DHP ring **120** followed by stereoselective hydrogenation to give the *cis*-THP ring **121** in 81% yield as single stereoisomer (Scheme 27).[47] Several additional steps were needed to form (+)-neopeltolide.
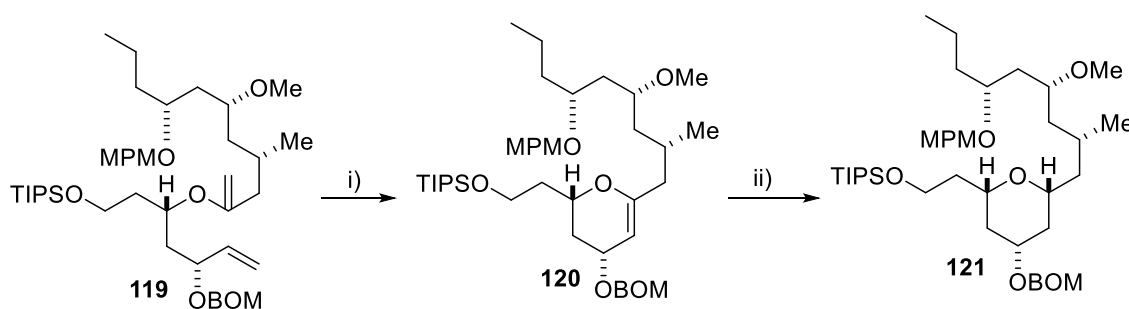
Scheme 27 Reagent & Conditions: i) Grubbs II catalyst, toluene, 70 °C, ii) H_2 (1~8 atm) 10% Pd/C, EtOAc/ MeOH (1: 1), 81%.

1.7.2 Cyclisation onto epoxides

Another method that can be used to form THP rings in natural products is cyclisation onto epoxides, but recently this method has become less prominent. Jamison's group used *endo*-selective epoxide-opening with $[Rh(CO)_2Cl]_2$ as catalyst on **122** to construct of THP of B ring synthesis of (-)-brevisin **123** with 78% yield (Scheme 28).[48]
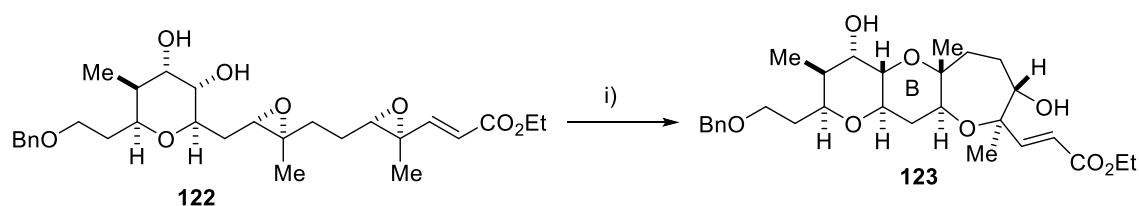
Scheme 28 Reagent & Conditions: i) [Rh(CO)$_2$Cl]$_2$ (10 mol %), THF, RT, 78%.

1.7.3 Radical cyclisations

Radical cyclisations can be useful to construct THP rings in natural products. This method was used by the Taylor group to form the *cis*-THP ring of neopeltolide **125**. The formation of *cis*-THP **125** was formed from **124** in 95% yield and with a diastereomeric ratio of 19 : 1 (Scheme 29).[49]
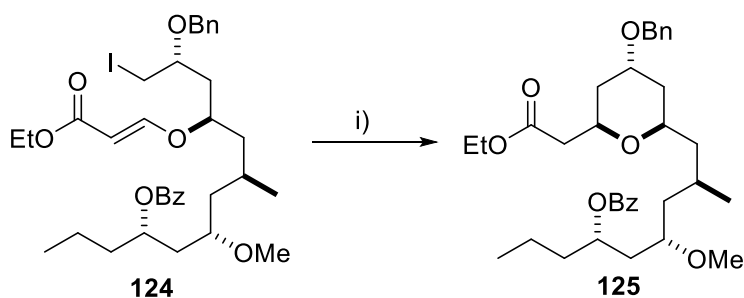
Scheme 29 Reagent & Conditions: i) Azobisisobutyronitrile (AIBN), tributyltin hydride (n-Bu$_3$SnH), 95%.

1.7.4 Carbocation cyclisations

A less common method used by the Mulzer group in formation of the THP ring of kendomycin **127** is cyclisation onto a carbocation. The reduction of ketone on **126** with NaBH$_4$ produced alcohol as mixture diastereomers. The removal of acetonide and loss of water to produce a benzylic carbocation, followed with trapping by the hydroxyl *via* a

S$_N$1 cyclisation. As a result, it formed benzofuran **127** as a *cis*-THP ring of kendomycin (Scheme 30).[50]
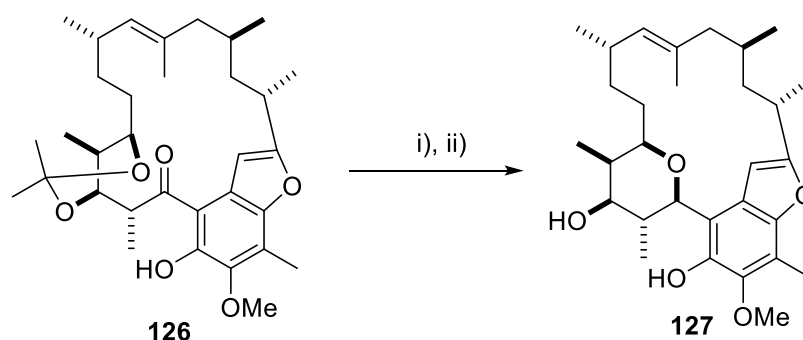
Scheme 30 Reagent & Conditions: i) NaBH$_4$, MeOH, RT, then 0.5N HCl ii) TsOH, PhMe, 60 °C, 71%.

1.8   The modified Maitland-Japp reaction and previous Clarke group work.

As has been discussed, there are different methods to construct the tetrahydropyran ring (THP) in the synthesis of natural products, such as cyclisation onto oxocarbenium ions, reduction of cyclic hemi-ketals, Michael reactions and hetero-Diels-Alder reactions. Over the last few years, the Clarke group has had particular interest in the formation of THP rings *via* the Maitland and Japp reaction. In 1904, Mailand and Japp showed that 3-butanone **129** and two molecules of benzaldehyde **128** could be condensed in a low yielding process to generate the substituted THP ring **130**.[51] In 1934, Cornubert and Robinet investigated the analogous acid promoted condensation of acetonedicarboxylic acid **131** with benzaldehyde **128**, where the cyclisation proceeded with concomitant decarboxylation to give two stereoisomers of the pyranone product in a 250: 1 ratio (**132**: **133**) (Scheme 31).[52]
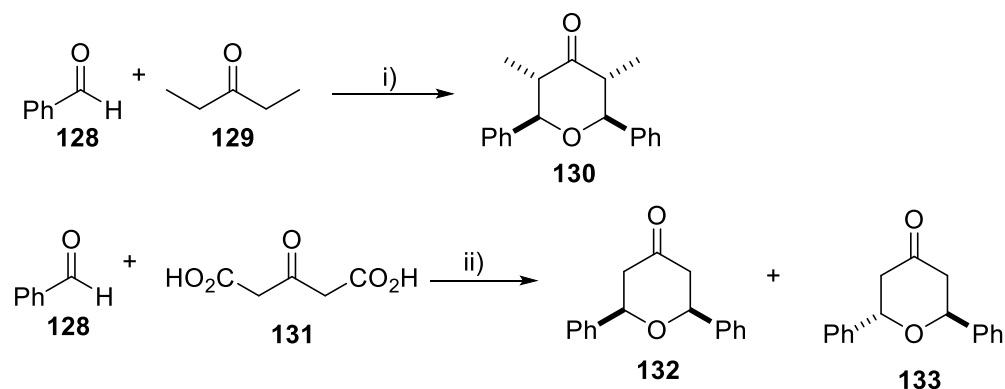
Scheme 31 Reagent & Conditions: i) KOH, EtOH, H_2O, ii) HCl, 19%.

Our group is interested in the multi-component natue of the Maitland-Japp reaction, the Clarke group proposed improving the Maitland-Japp procedure; we decided to move away from ketones as the building block for the THP ring, instead developing a β-ketoester reaction. Firstly, a regioselective aldol reaction at the γ position of a β-ketoester to give **134**, followed by a Knoevenagel condensation of a second aldehyde at the α position of the β-ketoester to give **135**, and then an intramolecular oxy- Michael reaction to give the pyran ring **136** (Scheme 32).[53]
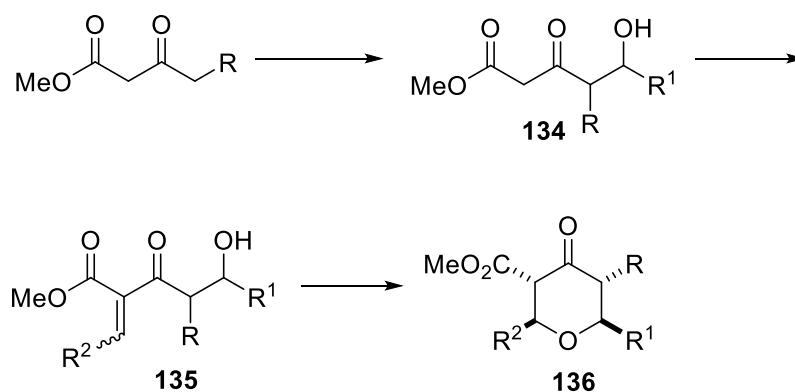
Scheme 32 Updating the Maitland-Japp reaction.

The two-pot reaction using the Weiler dianion of commercial available methyl acetoacetate **137** would give the δ-hydroxy β-ketoester **138**. To form the THP ring, Knoevenagel condensation using a Lewis acid as promoter and an intramolecular oxy-Michael steps was required. [54] Initial studies, using boron trifluoride diethyl etherate as the Lewis acid promoter, gave the pyran products as a mixture of the 2,6-*cis* ketone **139** and 2,6-*trans* enol **140** isomers that can be separated by column chromatography in good yield (Scheme 33).[55]
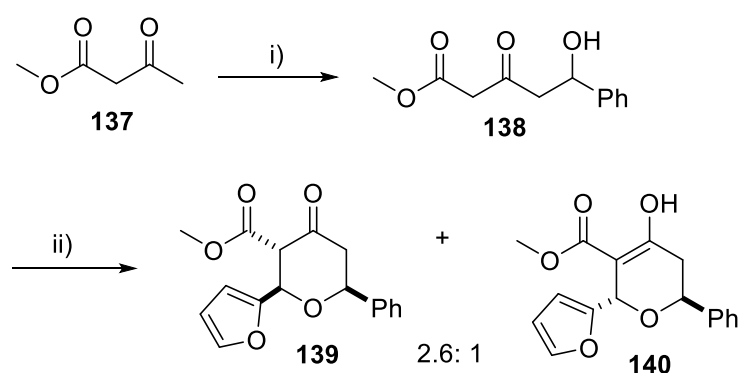
Scheme 33 Reagent & Conditions: i) NaH, THF, 0 °C, *n*BuLi, −78 °C, benzaldehyde, ii) BF₃•OEt₂, CH₂Cl₂, furaldehyde, 66% (2 steps).

The Clarke group decided to explore more variation of the reactions which would lead to a one pot reaction and a Lewis acid mediated aldol reaction by using Chan's diene[56] **141** as the nucleophile was envisaged. The Lewis acid will also mediate a Knoevenagel condensation with a second aldehyde and an intramolecular oxy-Michael ring closure to give a mixture of keto/enol products (**142/ 143**) (Scheme 34).
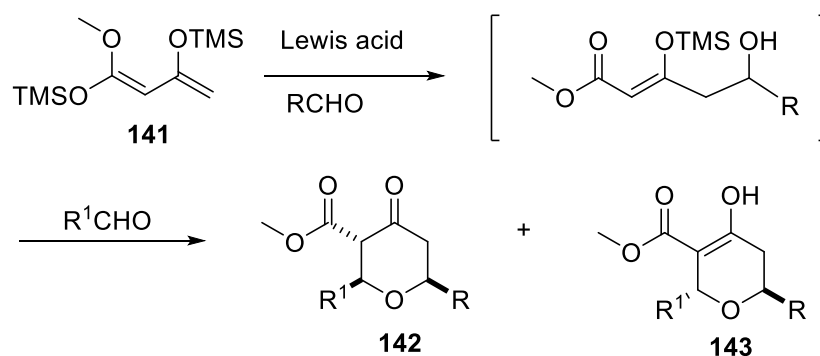
Scheme 34 The revised one-pot Maitland-Japp reaction.

In the one-pot reaction, titanium tetrachloride was used as a catalyst in both Mukiayama aldol reaction[57] and Knoevenagel condensation[58], but in order to develop a one-pot pyran reaction, the aldol product would need to be in the non-silylated form before addition of the second aldehyde. The trifluoroacetic acid (TFA) in THF was added into aldol product to deprotect the intermediate silyl ether to promote the Knoevenagel condensation followed with oxy-Michael reaction to form mixture of THP ring, the 2,6-*cis* ketone **142** and 2,6-*trans* enol **143** in excellent yield (Scheme 35, Table 1).[53]
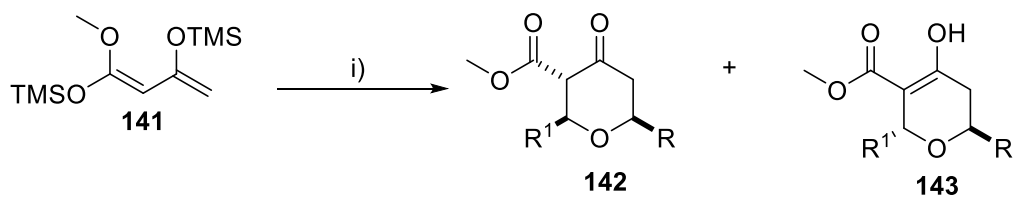
Scheme 35 Reagent & Conditions: i) TiCl$_4$ or Yb(OTf)$_3$, RCHO, −78 °C then TFA, R^{1}CHO, −78 °C to RT.

Entry	R	R^1	Lewis acid	Yield (%)^a	Ratio^b 142 : 143
a	Ph	Ph	TiCl$_4$	98	1 : 3
b	^{i}Pr	^{n}Pr	TiCl$_4$	98	1 : 1
c	^{i}Pr	Ph	TiCl$_4$	82	1 : 3
d	Ph	Ph	Yb(OTf)$_3$	98	2.5 : 1
e	^{i}Pr	^{n}Pr	Yb(OTf)$_3$	91	10 : 1
f	^{i}Pr	Ph	Yb(OTf)$_3$	80	2.5 : 1

^{a}Isolated yield after column chromatography. ^{b}Determined from the ^{1}H NMR (400 MHz) of the crude reaction mixture.

Table 1 Lewis acid promoted one-pot Maitland-Japp reaction

Due to favouring formation of 2,6-*trans* enol **143** with titanium tetrachloride, our group decided to investigate the effect of Lewis acid in formation of THP ring. Ytterbium triflate was used instead of titanium tetrachloride; interestingly 2,6-*cis* ketone **142** was formed as the major product. As titanium tetrachloride is more soluble in the reaction solvent, we propose that titanium tetrachloride could form a chelate with the 2,6-*trans* enol **143** that is more stable than the 2,6-*cis* ketone **142**. This could affect a flattening of the ring and reducing any 1,3-diaxial interactions unfavourable interaction of pseudo-axial substituent in the 2,6-*trans* enol **143**. The equatorial substituent in the 2,6-*cis* ketone **142** product

would form steric clash between the C2 and C3 substituents (Figure 1). We suggest that with absence of Lewis acid, the formation of 2,6-*cis* ketone **142** would be favoured form instead of 2,6-*trans* enol **143**. The low solubility of ytterbium triflate in the reaction solvent, so formation of chelate in itself energetically favourable would result in increased amount of the 2,6-*cis* ketone **142**.
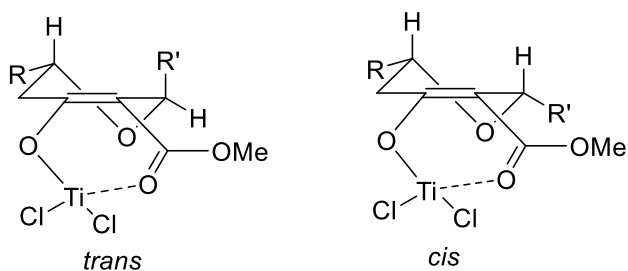
Figure 1 *cis*-Ti and *trans*-Ti chelated systems.

This method was applied to the synthesis of (±)-centrolobine **26**. Initially the group started with a two-pot reaction for the construction of tetrahydropyran-4-one, where the aldehyde **147** was prepared and reacted with Chan's diene **141** to form aldol reaction **144**, without further purification of **144**, the mixture of THP **145** and **146** was formed (diastereomer 1: 0.6) in 56% yields with boron trifluoride as promoter (Scheme 36). The one-pot reaction was applied, where it was known that ytterbium triflate favoured in the formation of the 2,6 *cis*-THP **145** over the 2,6 *trans*-THP **146** with diastereomer (2: 1) ratio with excellent yield 92%. (Scheme 37). With success in forming of **145**, decarboxylation of the THP ring using lithium hydroxide and hydrogen peroxide gave **148**, followed with removal of the ketone with dithiolane using Raney nickel giving (±)-centrolobine **26** in 50% yield (Scheme 38).[59]
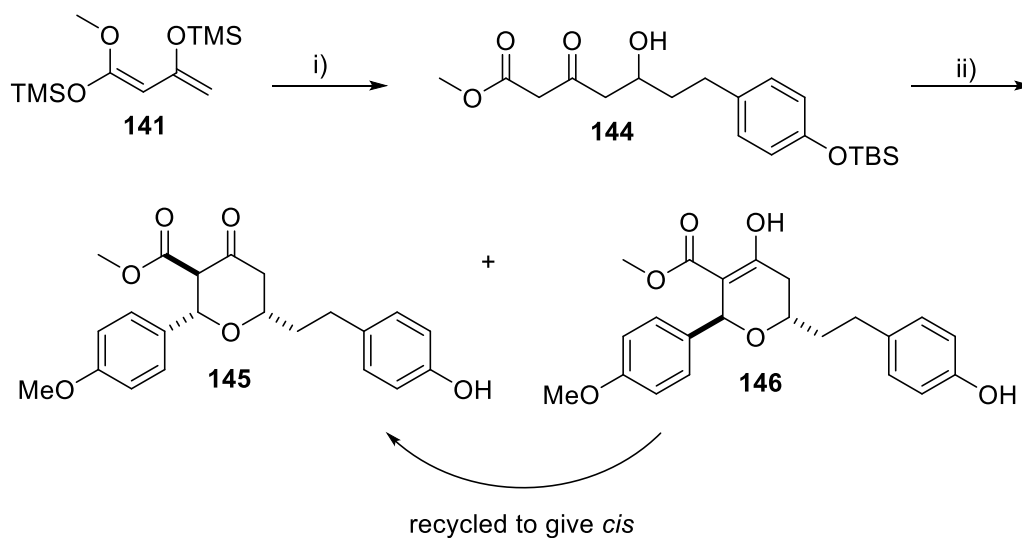
Scheme 36 Reagent & Conditions: i) TiCl$_4$, CH$_2$Cl$_2$, −78 °C, ii) anisaldehyde, BF$_3$•OEt$_2$, CH$_2$Cl$_2$, RT, 24 hr, 56% (2 steps).
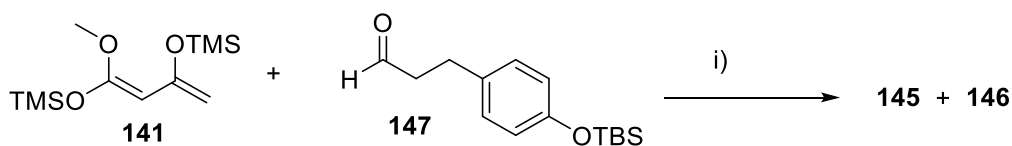
Scheme 37 Reagent & Conditions: i) Yb(OTf)$_3$, −78 °C then TFA, anisaldehyde, −78 °C to RT, 12 hr, 92%.
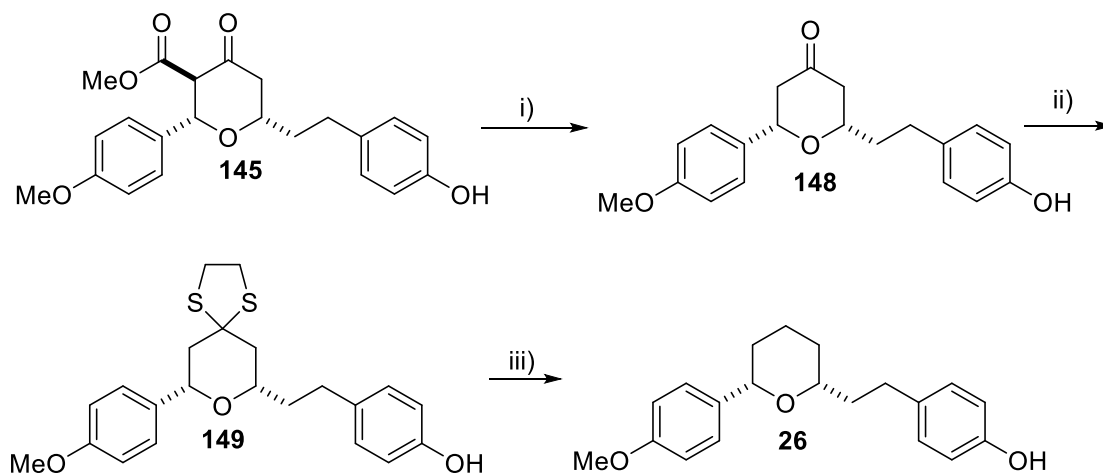
Scheme 38 Reagent & Conditions: i) H$_2$O$_2$, LiOH, THF, H$_2$O, RT, 5 hr, then 70 °C, 30 min, then RT, 12 hr, 60%, ii) HSCH$_2$CH$_2$SH, BF$_3$•OEt$_2$, CH$_2$Cl$_2$, RT, 100%, iii) Raney nickel, H$_2$, EtOH, 30 °C, 100%.

Following successful formation of the THP rings *via* a Maitland-Japp reaction, the Clarke group decided to carry out further studies on an asymmetric aldol reaction of *bis*-silylenol ether **151** with aldehyde **150**. However, the undesired *syn* diastereomer was formed as the major product in low yield **152** (13%) (Scheme 39).
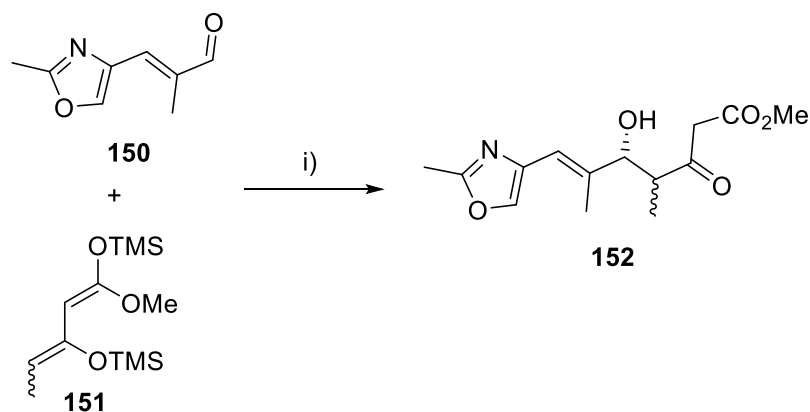
Scheme 39 Reagent & Conditions: i) Ti(O*i*-Pr)$_4$ (8 mol%), (*R*)-BINOL (8 mol %), 4 Å MS, THF, −78 °C to RT, 13%.

The group decided to change strategy by using the Masamune-Abiko auxiliary to form *anti*-aldol products asymmetrically. *β*-Keto-ester **153** could be made from aldehyde **150** in 3 steps and in a 75% combined yield. *β*-Keto-ester **153** was reacted with aldehydes under Lewis acid-catalyzed Maitland-Japp cyclisation conditions to form THP rings. Unfortunately, under all conditions attempted the reaction produced a complex mixture of 2,6-*cis/trans* diastereomers and keto/enol tautomers complicating seperation. The group changed strategy to form dihydropyran **154** by using dimethyl acetal dimethyl acetamide. The dihydropyran **154** was reduced and trapped with MeI to form THP **155** in 75% yield, which has an axial methyl group present as in the C-23 position of phoboxazoles A and B (Figure 2). The group believe the selectivity is due to pseudo-axial attack of hydride on the double bond of **154** followed by alkylation of the resultant enolate

from the pseudo-axial trajectory. After several steps, the synthesis of the C-23 epimer of the C-21 – C-32 THP core of the phoboxazoles A and B were formed. (Scheme 40).[60]
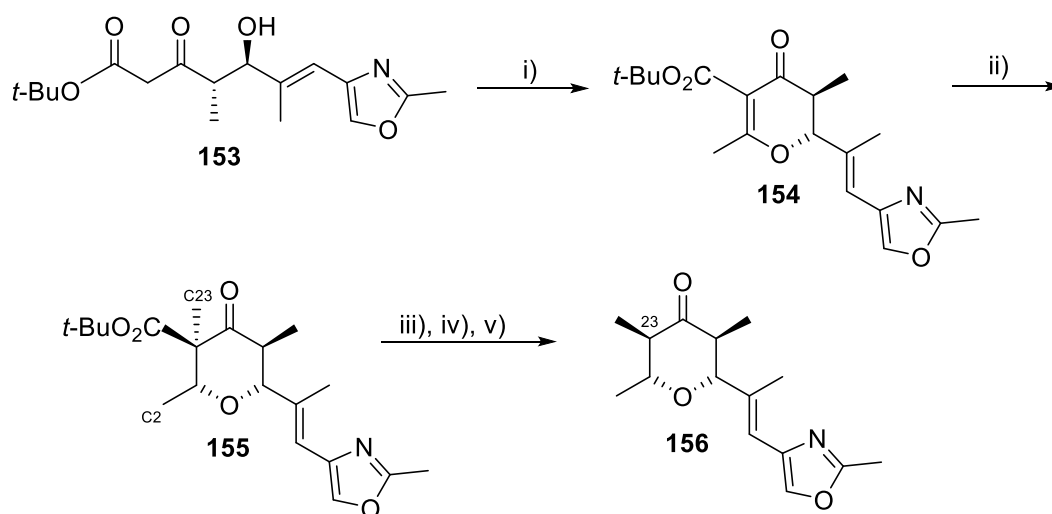
Scheme 40 Reagent & Conditions: i) $MeC(OMe)_2NMe_2$, PhMe, RT, 74%, ii) L-Selectride®, THF, −78 °C, then MeI, RT, 75%, iii) TFA, CH_2Cl_2, iv) PhH, reflux, 93% (2 steps), v) $NaBH_4$, MeOH, 0 °C, 60%.
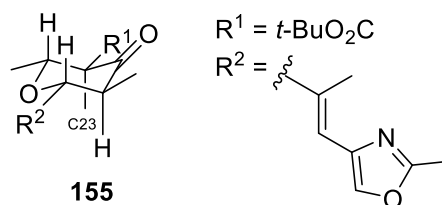
Figure 2 chair-like intermediate of 2,6-*cis* THP of **155**

Another asymmetric Maitland-Japp reaction was investigated by the Clarke group. Due to having to prepare the Chan's diene, which required two steps to synthesise, diketene **157** was used instead as it was commercially available. In the diketene Maitland-Japp reaction, the mono-γ-titanium enolate of a β-ketoester is formed by nucleophilic ring-opening of diketene *via* ligand transfer from the activating Lewis acid ($TiCl_4$ or $Ti(iOPr)_4$). The addition of methanol or isopropanol as a nucleophile would produce methyl or

isopropyl δ-hydroxy-β-ketoesters. The asymmetric Maitland-Japp reaction was developed by using Ti(*i*OPr)$_4$ as the Lewis acid with addition of a chiral Schiff's base ligand **158** to form δ-hydroxy-β-ketoester in moderate yield. Then the Knoevenagel/oxy-Michael cyclisation proceeded to give asymmetric THP ring (Scheme 41).[61]
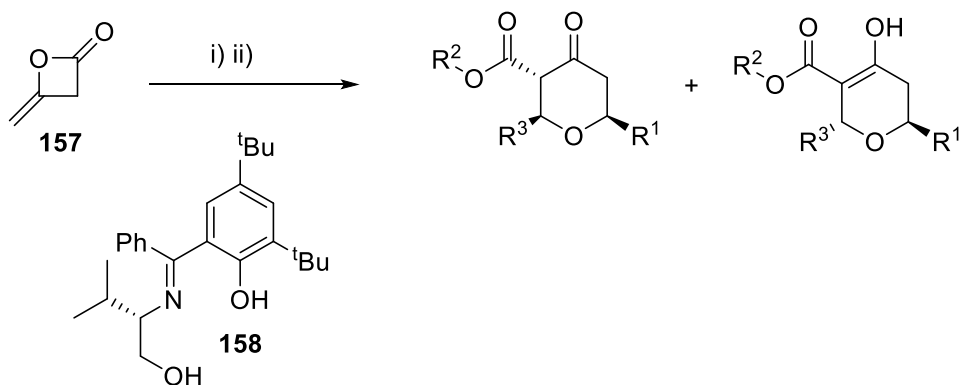
Scheme 41 Reagent & Conditions: i) Ti(*i*OPr)$_4$, **158**, R^{1}CHO, R^{2}OH, CH$_2$Cl$_2$, -20 °C, ii) TiCl$_4$, R^{3}CHO, -78 °C to RT.

Due to the successful development of an asymmetric Mailand-Japp reaction, Clarke decided to attempt this method for the synthesis of the C1-C19 *bis*-pyran unit of the phorboxazoles. The synthesis began with an asymmetric Maitland-Japp reaction between diketene **157** and aldehyde 3-benzyloxypropanal to give δ-hydroxy-β-ketoester followed with cyclisation to form a mixture of THP ring **160** and **161** with oxazole aldehyde **159** as the second aldehyde. The mixture of **160** and **161** were separable and **161** was re-equilibrated by Yb(OTf)$_3$ to form **160: 161** with diastereomeric ratio of 2:1, increasing the yield of **160** to 70% yield. The decarboxylation of THP **160** under microwave conditions was followed with reduction of ketone with NaBH$_4$ and protection of the hydroxyl group with TIPS to give **162**. Benzyl ether deprotection using H$_2$ and 10% Pd/C then Dess-Martin oxidation was performed on primary alcohol to give aldehyde **163**. A second Maitland-Japp reaction was carried out by using the Evans Cu(pybox) catalysed

reaction of Chan's diene and benzyloxy acetaldehyde to form δ-hydroxy-β-ketoester **164**, then Maitland-Japp cyclisation was applied with aldehyde **163** followed by decarboxylated to give *cis*-THP **165** in 68% yield. An additional 6 steps from *cis*-THP **165** furnished the C1-C19 *bis*-pyran unit **166** of the phorboxazoles with overall yield 10.4% (Scheme 42).[62]
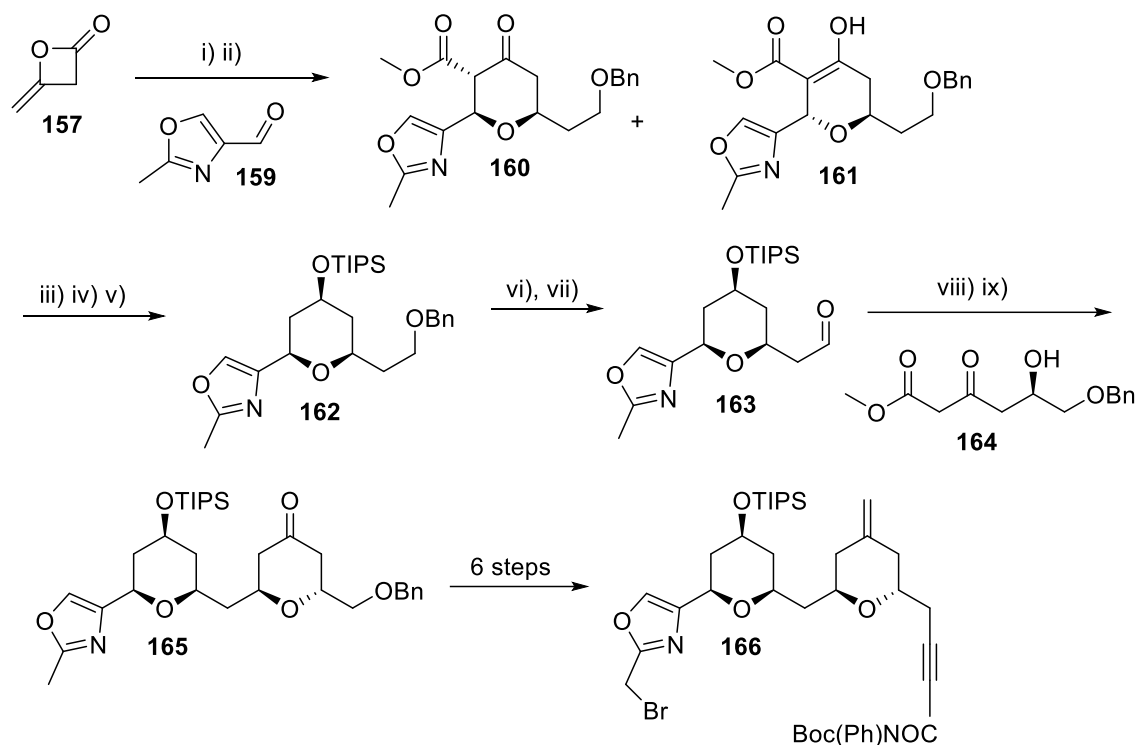
Scheme 42 Reagent & Conditions: i) Ti(iOPr)$_4$, **157**, 3-benzyloxypropanal, MeOH, CH$_2$Cl$_2$, −78 °C, ii) TiCl$_4$, **159**, −78 °C to RT iii) 300 W, μW (160 °C), 10 min,DMF/H$_2$O, 91%, iv) NaBH$_4$, MeOH, 0 °C, 100%, v) TIPSCl, imidazole, DMF, 50 °C, 86%, vi) 10% Pd/C, H$_2$, MeOH, 100%, vii) DMP, CH$_2$Cl$_2$, 100%, viii) TiCl$_4$, **164**, CH$_2$Cl$_2$, −20 °C to RT, ix) 300 W, uW (160 °C), DMF/H$_2$O, 68%.

The asymmetric diketene Maitland-Japp reaction in the synthesis of C1-C19 *bis*-pyran unit of the phorboxazoles, took a long reaction time (> 5 days) and the moderate enatioselectivities need further work.[61] Clarke decided to refocus back to the use of Chan's diene as a nucleophile to form the THP ring. The asymmetric addition of Chan's

diene was achieved by use of Ti(iOPr)$_4$/Binol/LiCl conditions to give δ-hydroxy-β-ketoester, the Knoevenagel/Michael steps to form mixture of THP **142** and **143** was promoted by TiCl$_4$ as a Lewis acid (Scheme 43). This method was applied to improve the previous route synthesis of ($\pm$)-centroboline **26**, in 55% yield and 91 % ee, and synthesis C1-C19 bis-pyran unit **166** of the phorboxazoles, 69% yield and 84 % ee.[63] The utility of this reaction provides advantages complimenting the group's previous work.
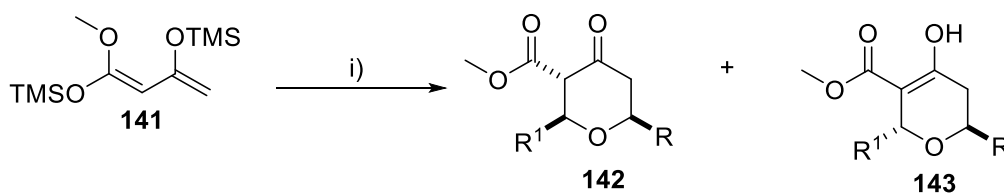
Scheme 43 Reagent & Conditions: i) Ti(iOPr)$_4$, Binol, LiCl, RCHO, THF, RT, ii) TiCl$_4$, R^{1}CHO, CH$_2$Cl$_2$

Several approaches towards developing efficient routes by Maitland-Japp reaction for the synthesis of THP ring in natural products were produced in the Clarke group. In the synthesis of phorboxazole **2**, the group pursued a strategy of breaking phorboxazole into three fragments **166**, **167** and **168** (Figure 3). The formation of C1-C19 2,6-*cis*- and 2,6-*trans*-bispyran **166** of the phorboxazoles was success by asymmetric diketene Maitland-Japp reaction[62] and then improved by asymmetric Chan's diene Maitland-Japp reaction.[62] Unfortunately, when the group tried to synthesise the C-20 – C-32 core **168** the synthesis did not give the product that they desired.[60] Thus, an alternative strategy was used to synthesis the fragment of **168**, which involved a stereodivergent oxy-Michael reaction. The formation of **171** constitutes a synthesis of C20-C32 core of phorboxazoles was achieved in seven steps with 31% overall yield (Scheme 44).[64]
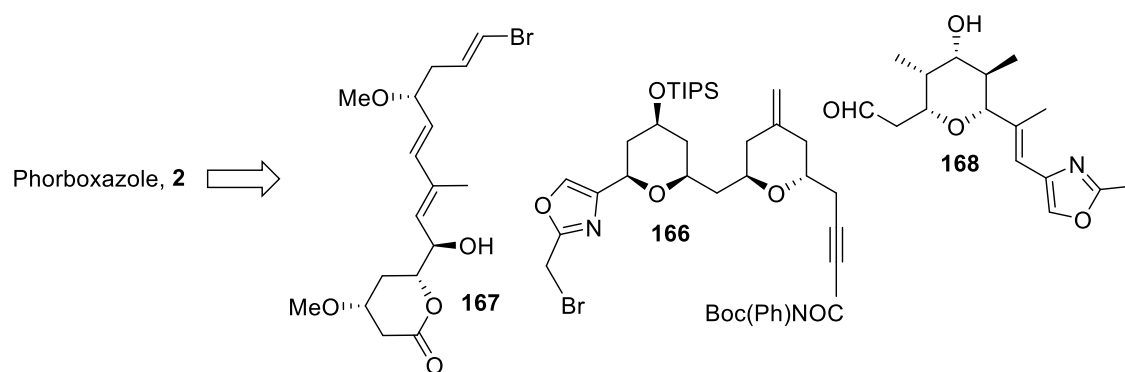
Figure 3 Retrosynthetic of Phorboxazoles.
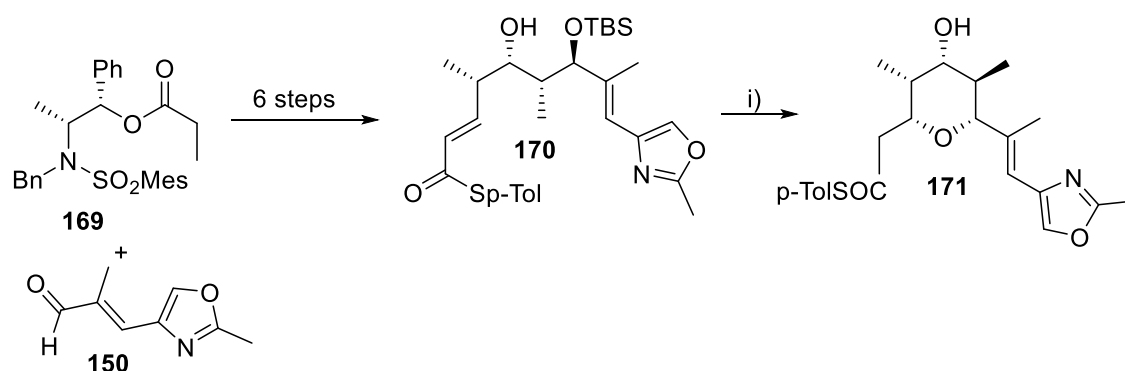
Scheme 44 Reagent & Conditions: i) TFA/CH$_2$Cl$_2$/H$_2$O, RT, 71%.

The two-pot reaction, the one-pot reaction, the asymmetric diketene Maitland-Japp reaction and the asymmetric Chan's diene Maitland-Japp reaction, all share one problem; all of these methods give mixtures of 2,6-*cis* ketone and 2,6-*trans* enol THP rings. The group decided to produce the dihydropyran (DHP) first which could then be converted selectively into either 2,6-*cis* or 2,6-*trans* THPs.

In the latest work in our group the DHP **172** underwent conjugate reduction with L-Selectride$^®$ to give a mixture of *cis/ trans* isomers (**173** : **174**) with a diasteromeric ratio of 10 : 1 (Scheme 45).
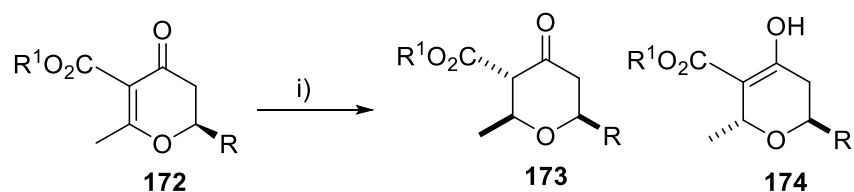
Scheme 45 Reagent & Conditions: i) L-Selectride®, THF, −78 °C.

This method was applied in synthesis of natural product civet cat secretion **34**, it began with formation of DHP by using dimethyl acetal of *N, N*-dimethyl acetamide and underwent conjugate reduction to give THP ring **175** then decarboxylated using microwave irradiation. The THP **176** was formed by the formation of dithiolane and removal of the benzyl group. Then reduction of dithiolane with Raney Ni and H_2 gave **177**, followed with oxidized with Jones' reagent to give carboxylic acid in 63% yield, finishing the total synthesis of **34** in 5 steps (Scheme 46).[65]
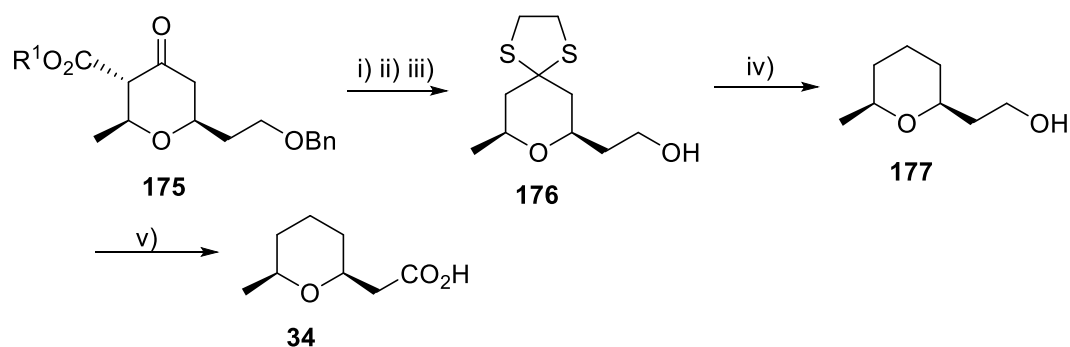
Scheme 46 Reagent & Conditions: i) μ Wave, DMF/H_2O, 10 min, 100%, ii) HSCH₂CH₂SH, BF₃•OEt₂, CH₂Cl₂, RT, 100%, iii) BCl₃•SMe₂, CH₂Cl₂, RT, 100%, iv) Raney Ni, H_2, EtOH, 50 °C, 52%, v) Jones' reagent, acetone, 63%.

1.9   Objectives.

It was our aim to improve the selectivity of the Maitland-Japp reaction to allow the controlled synthesis both 2,6-*cis* or 2,6-*trans* THP rings. It was decided to construct the DHP first and use this to form the 2,6-*cis*, 2,6-*trans*, 3,6-disubstituted and 3,3,6-trisubstituted THPS in a controlled manner. This methodology could then be used in the total synthesis of natural products.

2.0   Results and Discussion

The Clarke group's original modification of the Maitland-Japp reaction has produced a route to very highly functionalised THPs in good yield, however, there are some limitations to the methodology. The main problem is that the THPs are formed as a mixture of 2,6-*cis* and 2,6-*trans* diastereomers, so development of a selective reaction is desirable. One of the main aims of this project was to develop a route towards a selective, controlled synthesis of either 2,6-*cis* or 2,6-*trans* THPs. We were also interested in installing functionality into the THP ring, particularly incorporating substituents at the C3 positions and creating quaternary stereocentres (Figure 4).
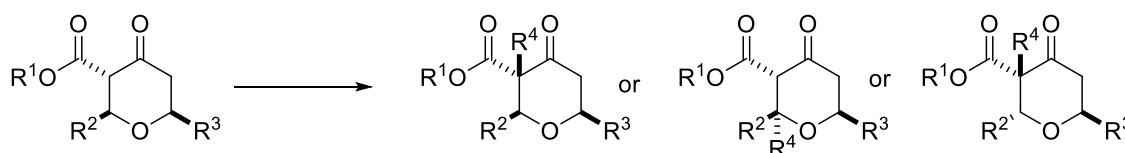
Figure 4 Functionalisation of THPs

Such a method could be applied towards the synthesis of natural products such as the A ring of Lasonolide A **1** and phorboxazoles **2**, featuring substituents at the C2, C3, and C6 positions and creating quaternary stereocentres (Figure 5 or Figure 6).
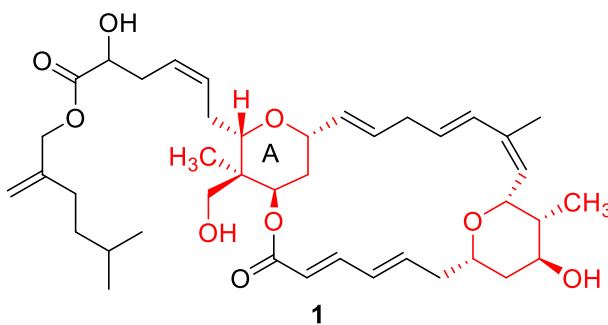
Figure 5 Lasonolide A **1**
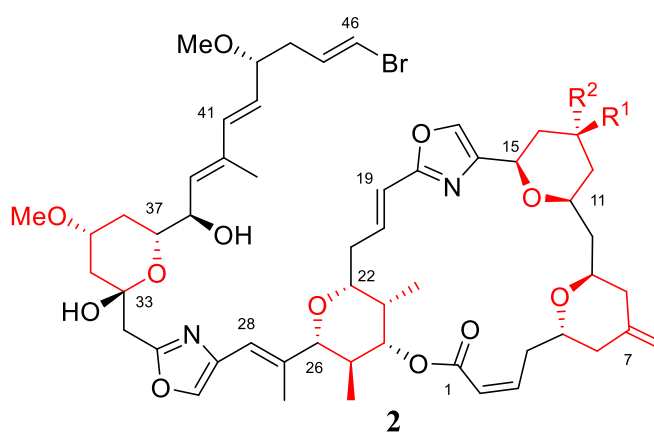
Figure 6 (+)-Phorboxazole A R^1 = H, R^2 = OH
(+)-Phorboxazole B R^1 = OH, R^2 = H

An additional C-5 substituent is required for the formation of the phorboxazoles A and B **2**. The Clarke group has synthesised the C-1 – C-19 *bis* pyran unit and C-21 – C-32 penta-substituted tetrahydropyran core of phorboxazoles A and B **2** and attempted to methylate the C5 position. They tried to methylate the β-ketoester **178** but unfortunately methylation was not observed under the conditions shown (Scheme 47). [66, 67]
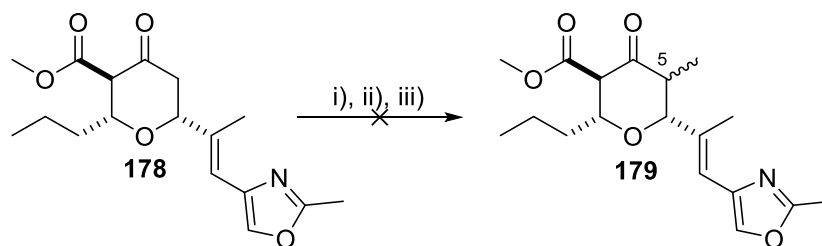
Scheme 47 Reagents & Conditions: i) NaH, THF, 0 °C, 20 min; ii) *n*BuLi, 0 °C to RT, 30 min; iii) MeI, −78 °C to RT, 4 hr, no reaction.

It was decided to modify the Maitland Japp reaction, where **153** was subjected to the Lewis acid-catalyzed Maitland-Japp cyclisation with an aldehyde to form the penta-substituted tetrahydropyran ring. Unfortunately, irrespective of which conditions were used, the reaction formed a mixture of 2,6-cis/trans diastereomers, also keto/enol tautomers **180** and **181**, greatly complicating isolation (Scheme 48).[60]
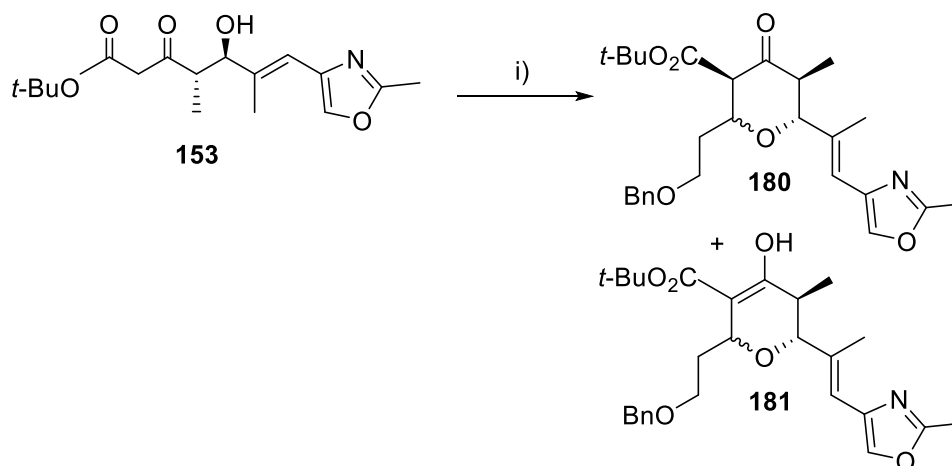
Scheme 48 Reagents & Conditions: i) Sc(OTf)$_3$, BnO(CH$_2$)$_2$CHO, CH$_2$Cl$_2$, 68%

For these reasons an alternative strategy was devised, where we decided to form the dihydropyran **154** first *via* Maitland-Japp reaction as in Scheme 49. These results showed that the products of Maitland-Japp reactions are difficult to functionalise, however, we found other strategies to construct the THP rings. The work detailed in this thesis will expand on these preliminary results to see if the DHP to THP strategy is a general one.
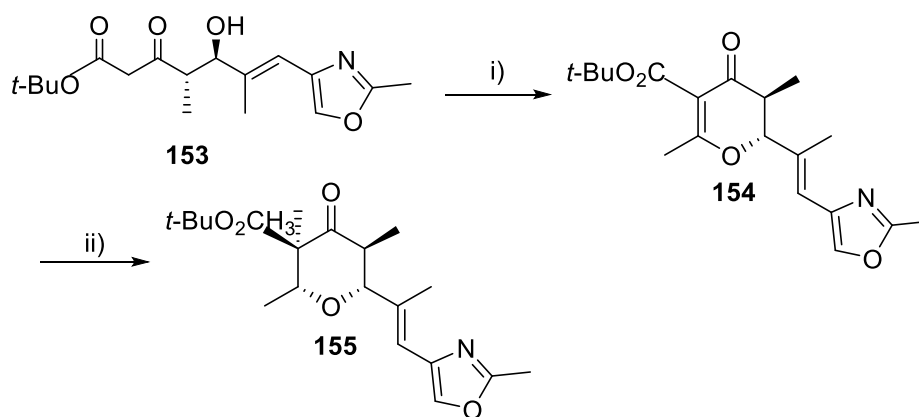
Scheme 49 Reagents & Conditions: i) MeC(OMe)$_2$NMe$_2$, PhMe, RT, 74%, ii) L-Selectride®, −78 °C in THF then MeI, 75%.

2.1   Aldol Reaction

We initially attempted to carry out the aldol reaction by a method reported by Mukaiyama[68] and later adapted by the group,[61] this involved the addition of diketene to an aldehyde promoted by a Lewis acid. In this reaction, formation of a γ-monoenolate equivalent of a β-ketoester is formed by the treatment of diketene with TiCl$_4$. This can be added to the aldehyde to produce δ-hydroxy-β-ketoesters on work up (Scheme 50). The addition of diketene **157** to an aldehyde in the presence of TiCl$_4$ as the Lewis acid formed the δ-hydroxy-β-ketoesters (entries **a** and **b,** Table 2). An alternative milder Lewis acid, Ti(O^{i}Pr)$_4$, can also be used (entries **c-i**, Table 2). In general aldol reactions with Ti(O^{i}Pr)$_4$ required longer reaction times. The δ-hydroxy-β-ketoesters produced by this diketene method gave moderate yields (23-76%)
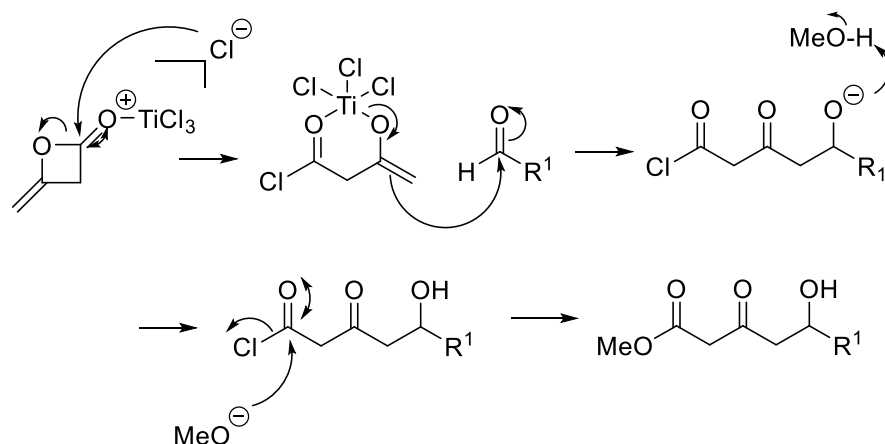
Scheme 50 Mechanism of diketene addition to aldehydes.
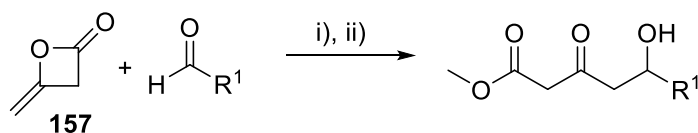
Scheme 51 Reagents & Conditions: i) Lewis acid, CH_2Cl_2, $-78\ ^{\circ}C$, ii) MeOH, -20 to $-10\ ^{\circ}C$, 40-90 min

Entry	R^1	Lewis acid	Time	Yield[a] (%)	Product
a	^iPr	$TiCl_4$	40 min	52	**182**
b	Pr	$TiCl_4$	40 min	62	**183**
c	$-CH_2OBn$	$Ti(O^iPr)_4$	90 min	23	**184**
d	Ph	$Ti(O^iPr)_4$	90 min	52	**138**
e	2-furyl	$Ti(O^iPr)_4$	90 min	62	**185**
f	2-nitro benzyl	$Ti(O^iPr)_4$	90 min	51	**186**
g	2-methyloxazole-4-carbaldehyde	$Ti(O^iPr)_4$	90 min	28	**187**
h	*E*- $CH=CHCH_3$	$Ti(O^iPr)_4$	90 min	65	**188**
i	*E*- $CH=CHPh$	$Ti(O^iPr)_4$	90 min	76	**189**

[a]Isolated yield after column chromatography.

Table 2 Synthesis of δ-hydroxy-β-ketoesters by diketene addition.

In addition to formation of the δ-hydroxy-β-ketoesters shown in Table 2, we investigated aldehydes **190**, **191** (Scheme 52) and **159** (Scheme 53), as aldehyde **159** can be used in the synthesis of natural product such as phorboxazoles **2**. Unfortunately, when we tried aldehydes **190** and **191**, the formation of δ-hydroxy-β-ketoesters were not observed It was suspected that the Lewis acid decomposed the aldehydes (Scheme 52). Gratifyingly, attempts with 2-methyloxazole-4-carbaldehyde **159**, formed the δ-hydroxy-β-ketoesters **187** in a modest 28% yield (Scheme 53).
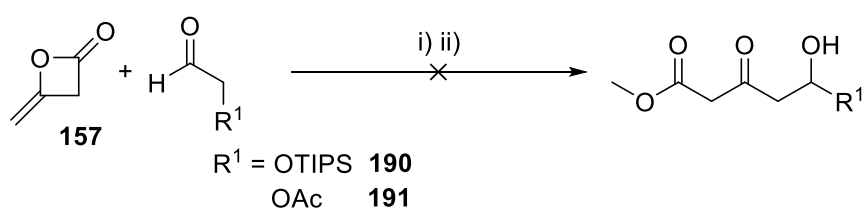
Scheme 52 Reagents & Conditions: i) Lewis acid, CH_2Cl_2, −78 °C, ii) MeOH, −20 to −10 °C, 40-90 min.
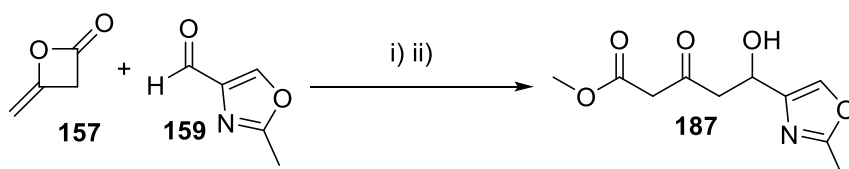
Scheme 53 Reagents & Conditions: i) $Ti(O^iPr)_4$, CH_2Cl_2, −78 °C, ii) MeOH, −20 to −10 °C, 90 min, 28%.

The addition of chan's diene to an aldehyde was also investigated. The synthesis of Chan's diene required two steps (Scheme 54).[69] Methyl acetoacetate **137** was deprotonated at the α-position then trapped with chlorotrimethylsilane to give **192**, followed by deprotonation at the γ-position with lithium diisopropylamide and trapping with chlorotrimethylsilane to give the *bis*-silyl dienolate **141**. Chan's diene should be used directly or as soon as possible after formation due to its instability. Aldol reaction between

benzyloxyacetaldehyde **193** and Chan's diene **141** generated **184** in 76% yield (Scheme 55). This can be compared with aldol formation between diketene **157** and benzyloxyacetaldehyde **193** where the highest yield was only 23%.
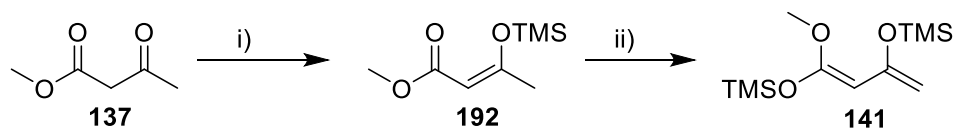
Scheme 54 Reagents & Conditions: i) Et$_3$N, TMSCl, Hexane, RT, 35% ii) LDA, THF, −78 °C, then TMSCl, 0 °C, 51%.
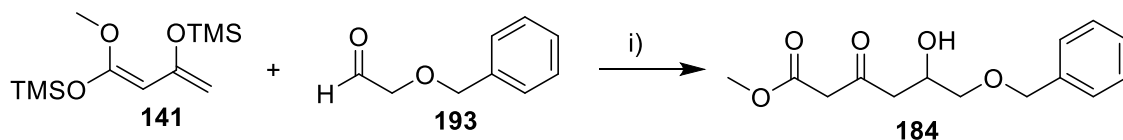
Scheme 55 Reagents & Conditions: i) TiCl$_4$, CH$_2$Cl$_2$, −78 °C, then TFA, 76%.

Due to unsuccessful or very low yields in the formation δ-hydroxy-β-ketoesters with aldehydes **190**, **191** and **159** using diketene **157** (Scheme 52 and 53), Chan's diene **141** was added to aldehydes **190**, **191** and **159** with TiCl$_4$ as Lewis acid. The formation of δ-hydroxy-β-ketoesters **187** and **194** was observed with low isolated yields but formation of δ-hydroxy-β-ketoester **195** with aldehyde **191** was not observed (Scheme 56).
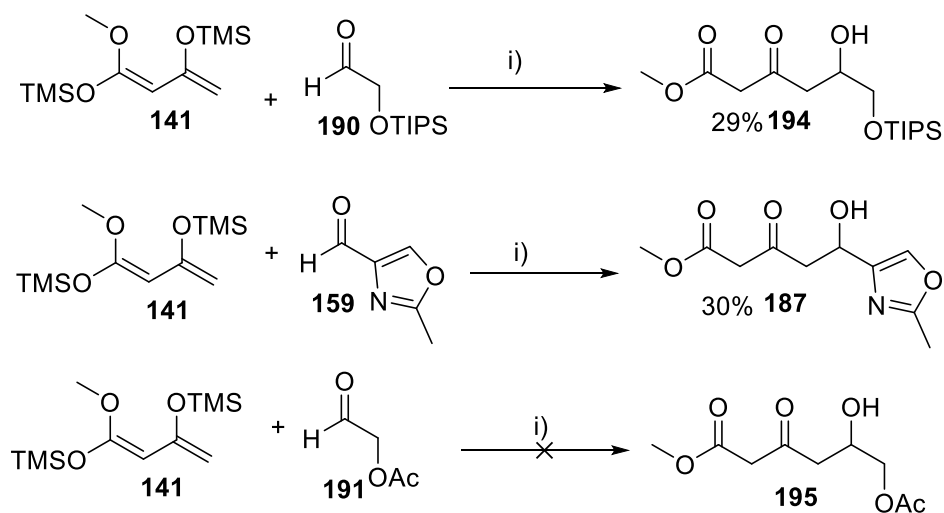
Scheme 56 Reagents & Conditions: i) TiCl$_4$, CH$_2$Cl$_2$, −78 °C, and then TFA.

As product **195** proved elusive and yields of products **187** and **194** were low, we suspected titanium tetrachloride (TiCl$_4$) may be the problem. It was suspected that it decomposed the aldehydes. We decided to investigate other methods. Thus the Weiler dianion[70] was used to form δ-hydroxy-β-ketoesters. Of the aldehydes investigated only aldehyde **190** led to product **194** in the best yield 35% (Scheme 57). Another δ-hydroxy-β-ketoester was formed by using slightly different conditions where the methylactoacetate **137** was deprotonated with lithium diisopropylamide, followed by treatment with acetaldehyde **196** to form δ-hydroxy-β-ketoester **197** in 72% yield (Scheme 58).
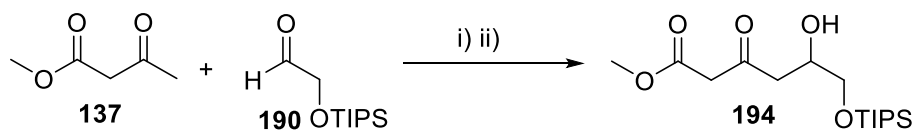
Scheme 57 Reagents & Conditions: i) NaH, THF, 0 °C, ii) *n*BuLi, −78 °C, 35%.
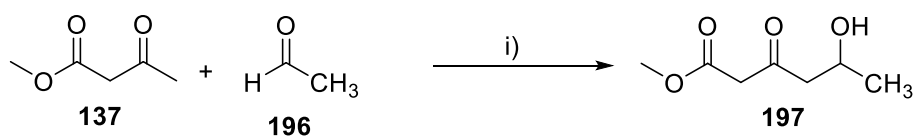
Scheme 58 Reagents & Conditions: i) 2 eq of lithium diisopropylamide, THF, −78 °C, 72%.

Lastly, we tried our asymmetric Chan's diene procedure[63] to form the δ-hydroxy-β-ketoesters with aldehydes **190**, **191** and **159**, but unfortunately, only starting material was observed (Scheme 59). It was decided not to pursue these conditions further.
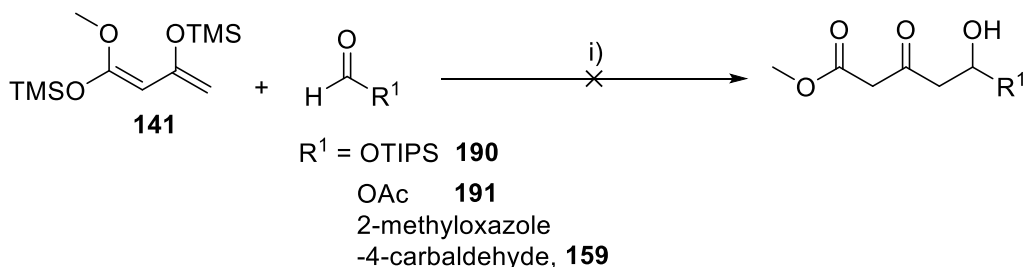
Scheme 59 Reagents & Conditions: i) Ti(O^{i}Pr)$_4$/ Binol (2 mol %), LiCl (4 mol %), THF, RT, 12 hr.
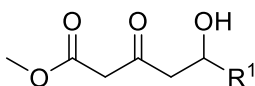
Entry	Method	R^1	Yield^a (%)	Product
a	Diketene addition	^{i}Pr	52	**182**
b	Diketene addition	Pr	62	**183**
c	Chan's diene	-CH$_2$OBn	76	**184**
d	Diketene addition	Ph	52	**138**
e	Diketene addition	2-furyl	62	**185**
f	Diketene addition	2-nitro benzyl	51	**186**
g	Chan's diene	2-methyloxazole-4-carbaldehyde	30	**187**
h	Diketene addition	E-CH=CHCH$_3$	65	**188**
i	Diketene addition	E-CH=CHPh	76	**189**
j	Weiler dianion	OTIPS	35	**194**
k	Lithium diisopropylamide condition	acetaldehyde	72	**197**

^{a}Isolated yield after column chromatography.

Table 3 Total synthesis of δ-hydroxy-β-ketoesters.

In summary, the δ-hydroxy-β-ketoesters were produced by diketene addition, Chan's diene addition, Weiler dianion and lithium diisopropylamide conditions in yields between 28-76% (Table 3). Diketene is stable and commercially available making this method particularly convienient, especially in contrast to the stability of Chan's diene.

2.2   Synthesis of Dihydropyrans

The focus of our research towards the formation of tetrahydropyrans is based on the modification of the Maitland-Japp reaction to form dihydropyrans (DHPs). Because previous Clarke group work lead to the diastereoselective formation of 2,6-*cis* ketone and its tautomeric 2,6-*trans* enol THP ring.

It was predicted that cyclisation of a δ-hydroxy-β-ketoester to form a dihydropyran would enable the diastereoselective synthesis of THPs (Figure 7). The stereocontrolled conjugate reduction of a 2,3-dihydropyranone would give 2,6-*cis* THPs (**A**, Figure 7). The electrophilic quench of the enolate intermediate should install a new substituent at C-3 position and form a new stereogenic centre (**B**, Figure 7). All of these will allow access to the THP skeletons that are found in the natural products such as lasonolide A **1** and phorboxazoles A and B **2**. The conjugate addition of a suitable nucleophile to 2,3-dihydropyranone with no substituent at C2 would give a 2,6-*trans* THP (**C**, Figure 7) providing access to the THP skeletons found in natural products such as diospongin B **4**. In a complementary approach a hydride conjugate addition on 2,3- dihydropyranone and electrophilic quench could lead to a tertiary stereogenic centre at C3 (**D**, Figure 7).
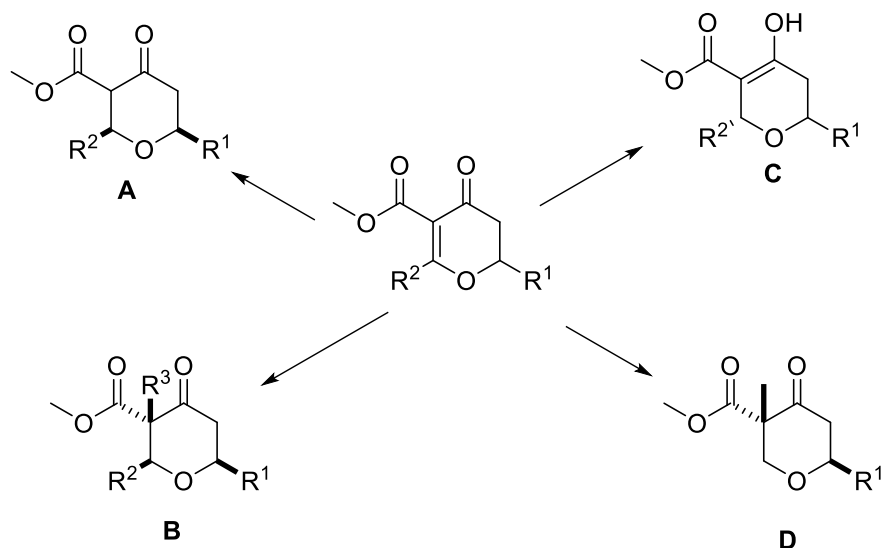
Figure 7 Proposed routes for diastereoselective THP formation.

2.3 Synthesis of Dihydropyrans: Orthoester Cyclisations

We initially attempted the cyclisation of the δ-hydroxy-β-ketoester with an orthoester. In order to form DHPs as we suspected that an orthoester could undergo a Knoevenagel-like condensation with a β-ketoester, which we anticipated this would be followed by oxy-Michael cyclisation to form the DHP (Table 4).[71-73]

In this reaction, we used microwave iradiation which has proved to be a highly effective method of heating. Different *δ*-Hydroxy-*β*-ketoesters and orthoesters were explored to produce DHP rings (Table 4).[74-76]
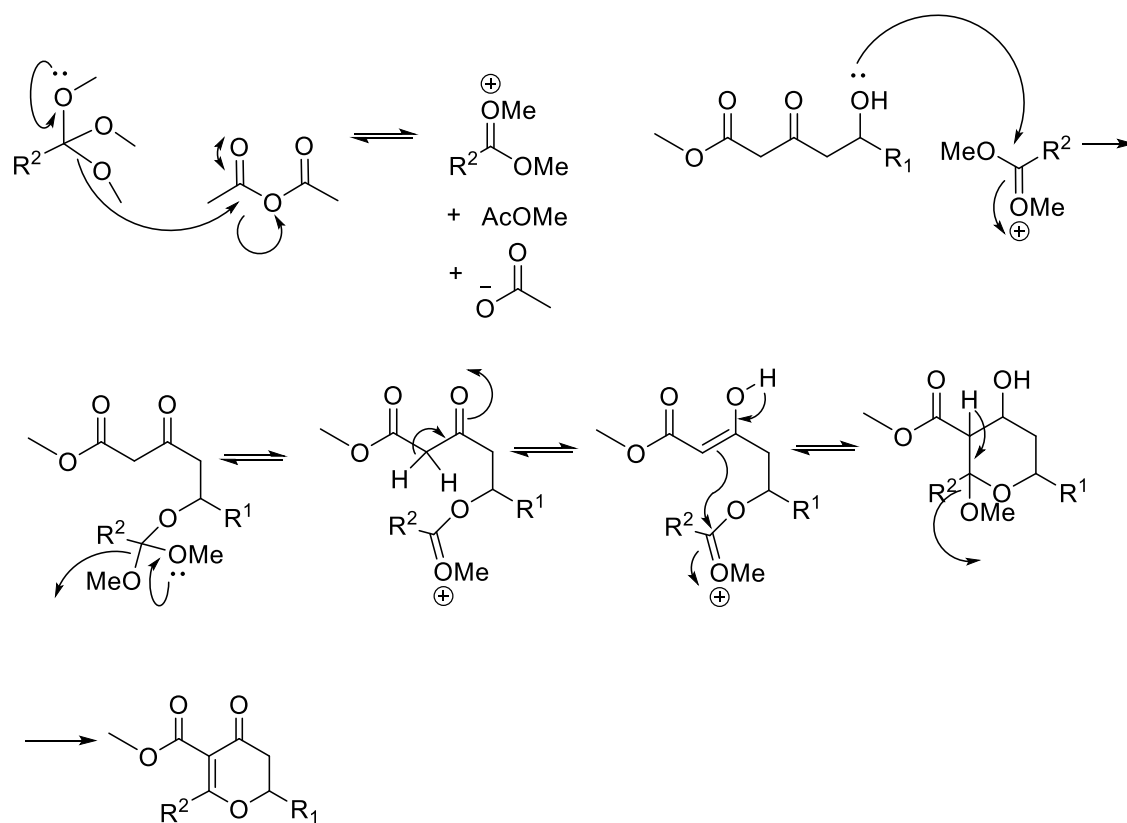
Figure 8 Proposed mechanism Knoevenagel-like condensation / oxy-Michael cyclisation.
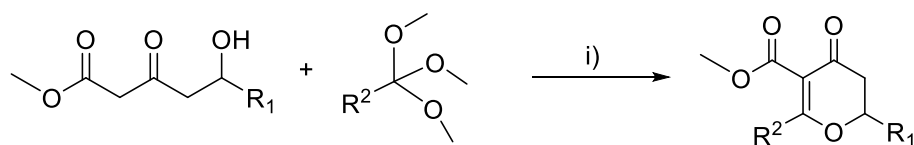
Scheme 60 Reagent & Conditions: i) Ac$_2$O, toluene, microwave (150 watt, 100 atm),15-60 min.

Entry	R^1	Starting material	Orthoester (R^2)	Time	Yield^a (%)	Product
a	Ph	**138**	^{n}Bu	15 min	90	**199**
b	-CH$_2$OBn	**184**	^{n}Bu	15 min	51	**200**
c	2-furyl	**185**	-CH$_2$Cl	60 min	-	-
d	2-nitro benzyl	**186**	-CH$_2$Cl	60 min	-	-
e	^{i}Pr	**182**	-CH$_2$Cl	60 min	-	-
f	-CH$_2$OBn	**184**	Phenyl	60 min	-	-
g	Pr	**183**	Phenyl	60 min	-	-
h	iPr	**182**	Phenyl	60 min	-	-
i	2-furyl	**185**	Me	30 min	34	**204**
j	^{i}Pr	**182**	Me	30 min	36	**205**
k	-CH$_2$OBn	**184**	Me	60 min	-	-
l	2-nitro benzyl	**186**	Me	60 min	-	-

^{a}Isolated yield after column chromatography.

Table 4 Synthesis of dihydropyrans with orthoesters.

δ-Hydroxy-β-ketoester (1 eq) was heated with trimethyl orthovalerate (2 eq) **198**, and acetic anhydride (2 eq) under microwave irradiation (150 watt, 100 atm) for 15 minutes to form the DHPs. We studied δ-hydroxy-β-ketoester **137** and trimethyl orthovalerate **198**, and it produced **199** in very good yield (Scheme 61, Table 4, entry **a**). We then

looked at a different δ-hydroxy-β-ketoester **184**, which gave 51% yield (Table 4, entry **b**).
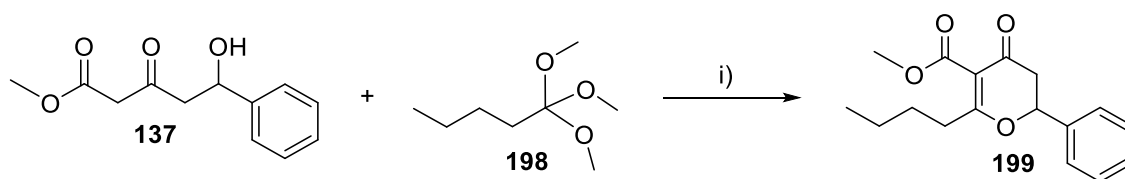
Scheme 61 Reagent & Conditions: i) Ac$_2$O, toluene, microwave (150 watt, 100 atm), 90%.

Next, we attempted the reaction with a different orthoester (2-chloro-1,1,1-trimethoxyethane **201**). Unfortunately the reaction did not produce the expected DHP (Table 4, entry **c-e**). A number of different δ-hydroxy-β-ketoesters were investigated with trimethyl orthobenzoate **202** to produce DHPs but unfortunately none of the reactions generated DHP products either (Table 4, entry **f-h**). There were numerous spots on the TLC plate, and the ^{1}H NMR showed a complex mixture of products. Extended reaction times (15-60 minute) under microwave irradiation, were also investigated but it still did not show the desired DHP.

Commercially available trimethyl orthoacetate **203** was investigated. Initially two of the reactions underwent Knoevenagel reaction and the subsequent oxy-Michael cyclisation to give the desired DHP (Table 4, entry **i-j**).

Due to promising yield of reaction between trimethyl orthoacetate **203** with δ-hydroxy-β-ketoesters **185** and **182**, we tried with δ-hydroxy-β-ketoesters **184** and **186**, frustratingly when we run reactions under these conditions no DHP was isolated. This is maybe because this reaction seems to be very substrate specific and is prone to either the

decomposition of the reagents or decomposition of the products under the reaction conditions. These disappointing results are presumably because of lack of reactivity towards the Knoevenagel step of the reaction and perhaps this is due to some problem in the formation of the intermediate oxocarbenium ion of the orthoester or it having poor susceptibility to nucleophilic attack. From these result suggest that this approach to synthesising DHPs would be problematic, due to limited success in reaction thus we decided to change to a different method to form the DHP ring.

2.4   Synthesis of dihydropyrans: amide acetal cyclisations with *N, N*-dimethylacetamide dimethyl acetal

It was apparent that the cyclisation *via* the orthoester route would not be easy. It seemed as if only a limited number of orthoesters can cyclize to construct the DHP rings. Due to this difficulty we searched for an alternative route. We found literature that utilized *N, N*-dimethylformamide dimethyl acetal or *N, N*-dimethylacetamide dimethyl acetal to react with a δ-hydroxy-β- ketoester to form a DHP.[60]

This reaction was initially tried by Dr. Jason Hargreaves within the Clarke group in a model study of the C21-C32 pentasubstituted THP core of the phorboxazoles (Scheme 62).[67, 60]
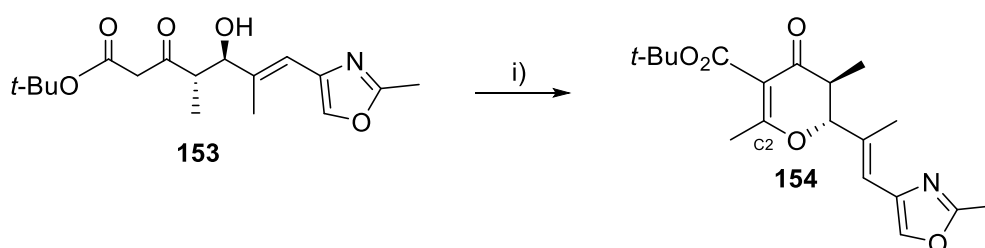
Scheme 62 Reagent & Conditions: i) MeC(OMe)$_2$NMe$_2$, toluene, RT, 74%
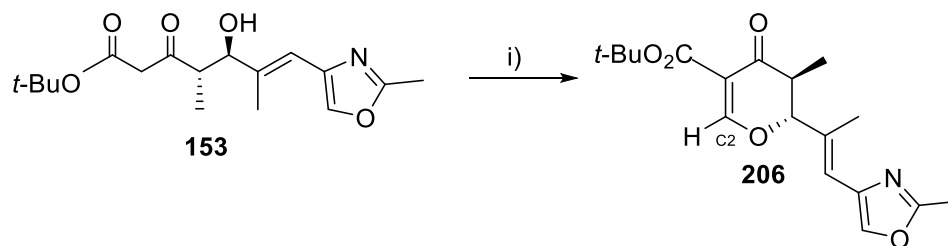
Scheme 63 Reagent & Conditions: i) HC(OMe)$_2$NMe$_2$, toluene, RT, 65%.

These excellent results led us to focus on exploring this reaction. When the reaction was run with *N, N*-dimethylacetamide dimethyl acetal and δ-hydroxy-β- ketoester, it should lead to a methyl group substituent at the C2 position of the DHP which can undergo reduction to form 2,6-*cis* THPs (Scheme 62). When *N, N*-dimethylformamide dimethyl acetal reacts with a δ-hydroxy-β- ketoester, it will install a hydrogen as the substituent at the C2 position (Scheme 63). At this point we shall focus on the cyclisation using *N, N*-dimethylacetamide dimethyl acetal and studies towards the formation of 2,6-*cis* THPs such as those in natural products such as lasanolide A **1** (Figure 4).

A multi-component one-pot reaction has been of interest to the Clarke group.[56] The combination of pot, atom and step economy (PASE) in synthesis of organic molecules which can lead to significant 'greening' of a synthetic route. Reducing the number of steps in a synthesis can increase the chemical yield of the product and reduce the amount of reagents and solvents used in work up and product isolation, including the waste that is generated from cleaning equipment and glassware.[61] Based on Sellars' work, studies were undertaken to determine whether the two steps to form the DHPs could be carried out in a single reaction (Scheme 64, **Table 5**). Mukaiyama's aldol method was used,[68] where the TiCl$_4$ was used as Lewis acid to promote the addition of diketene **157** to benzaldehyde **128**, followed with addition of *N, N*-dimethylacetamide dimethyl acetal.[78]
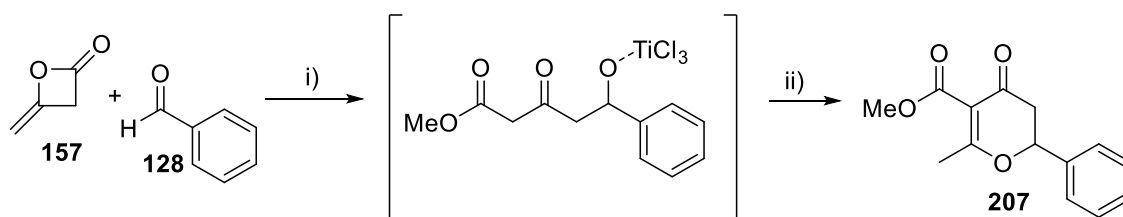
Scheme 64 Reagent & Conditions: i) TiCl$_4$, CH$_2$Cl$_2$, −78 °C then MeOH, −10 °C to −20 °C; ii) MeC(OMe)$_2$NMe$_2$.

Entry	Step 1 aqueous work-up	Step 2	Yield (%) 207
a	No	CH$_2$Cl$_2$, RT	No DHP multiple spots by TLC, β-ketoester remains
b	Yes	PhMe, RT	43
c	Yes	CH$_2$Cl$_2$, RT	33
d	Yes	MeOH, CH$_2$Cl$_2$, RT	35
e	Yes	Pyridine, CH$_2$Cl$_2$, RT	30
f	No	Pyridine, CH$_2$Cl$_2$, RT	DHP : β-ketoester ~1 : 4 (48 % mass balance)

Table 5 DHP synthesis studies

As results showed in Table 5, the one-pot procedure failed to deliver good yields, hence it was decided to use the two-pot procedure.

For our investigation, we first tried one equivalent of *N, N*-dimethylacetamide dimethyl acetal to react directly with one equivalent of δ-hydroxy-β-ketoester. The mixture was stirred for 45 minutes followed by addition of BF$_3$•OEt$_2$ as a Lewis acid. The ^{1}H NMR spectrum of the crude product clearly showed 50: 50 of starting material and product. We

decided to change the equivalents of *N, N*-dimethylacetamide dimethyl acetal and BF₃•OEt₂ from one equivalent to two equivalent which gave much better results (Table 6, Scheme 65).
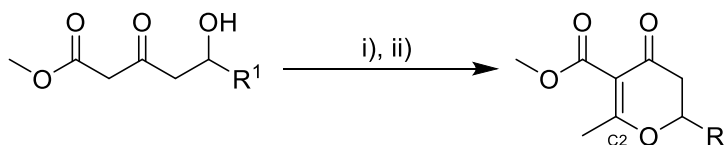
Scheme 65 Reagent & Conditions: i) MeC(OMe)₂NMe₂, CH₂Cl₂, RT, ii) BF₃•OEt₂

Entry	R^1	eq	Starting material	*N,N*-dimethylaceta mide dimethyl acetal, eq	BF₃.OEt₂, eq	Product	Yield[a] (%)
a	^{i}Pr	1	**182**	2	2	**205**	73
b	Pr	1	**183**	2	2	**208**	50
c	Phenyl	1	**138**	2	2	**207**	65
d	2-furyl	1	**185**	2	2	**204**	18
e	-CH₂OBn	1	**184**	3	3	**209**	55

[a]Isolated yield after column chromatography.

Table 6 Synthesis of dihydropyrans with *N, N*-dimethylacetamide dimethyl acetal.

The cyclisation with *N, N*-dimethylacetamide dimethyl acetal gave the desired DHPs in good yield in 1 hour at room temperature in all cases (entry **a** – **c**) except when R^1 = 2-furyl (entry **d**) and R^1 = OBn (entry **e**), where for entry **d** when we used two equivalent of *N, N*-dimethylacetamide dimethyl acetal and BF₃.OEt₂ showing trace of starting material as major product after 1 hour.

For entry **e**, we used one equivalent of *N, N*-dimethylacetamide dimethyl acetal and BF₃•OEt₂ it gave 59% recovery of product and 35 % of starting material. When we used

two equivalents of *N, N*-dimethylacetamide dimethyl acetal and BF₃•OEt₂, trace amount of starting material was observed by TLC and NMR but longer reaction times led to decomposition. We decided to increase to three equivalents of *N, N*-dimethylacetamide dimethyl acetal and BF₃•OEt₂, after 20 minutes obtained **209** in 55% yield. We suspected the BF₃•OEt₂ prefers to coordinate with the oxygen atom of furfural and oxygen of the benzyl ether, reducing reactivity towards the Knoevenagel step of the reaction.

The cyclisation to form the DHP ring by *N, N*-dimethylacetamide dimethyl acetal worked well, but in order to introduce different substituents at C2 of the DHPs, different amide acetals were required. Based on Sellars' thesis, the amide acetal was limited by commercial availability, but fortunately we found a literature procedure for the synthesis of *N, N*-dimethylbenzamide dimethyl acetal (Scheme 66).[77] The amide **211** was prepared from the corresponding acid chloride **210**. When heated in dimethyl sulfate, it will forms *N, N*-dimethylbenzamide-dimethyl sulfate complex where the oxygen is methylated and an iminium ion is formed. Then treat with sodium methoxide, the methoxide nucleophile attacks the iminium ion to form *N, N*-dimethylbenzamide dimethyl acetal **212**.
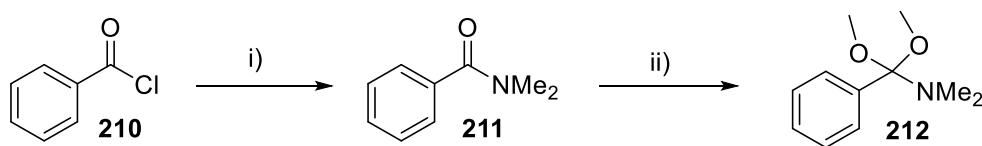
Scheme 66 Reagent & Conditions: i) Na₂CO₃, Me₂NH•HCl, CH₂Cl₂, RT, 100 %; ii) dimethyl sulfate, 90 °C then NaOMe, MeOH, RT, 40 %.

The *N, N*-dimethylbenzamide dimethyl acetal was trialled to form DHP rings, with the hopethat this would give access to the C2-phenyl DHPs. Unfortunately the synthesis of *N, N*-dimethylbenzamide dimethyl acetal is fairly low yielding.[78]

In summary we developed a method using a modification of the Maitland-Japp reaction using orthoesters and orthoamides to give a range of the DHPs in good yields. These could be used in the selective formation of either 2,6-*cis* or 2,6-*trans* THP rings.

2.5   Synthesis of 2,6-*cis* tetrahydropyran: conjugate reduction/ electrophile quench

Towards our investigation to construct the 2,6-*cis* THP rings, such as the THP of A-ring fragment of lasonolide A **1** or THP ring of phorboxazole **2**, we used L-Selectride® for the 1,4-conjugate reduction of α, β-unsaturated esters at position C2 and C3. The reactions were successfully quenched with electrophiles such as iodomethane at C3. This reaction was successful in a model system for the core fragment of the phorboxazole and gave the product of C3-alkylation in 75% yield (Scheme 49).[60]

Based on Sellars thesis, the selectivity for the 2,6-*cis* diastereomer is believed to be due to pseudo-axial attack of the hydride onto C-2 of the DHP when it is in a conformation that puts the C6 substituent in a pseudo-equatorial position (Figure 9). In order to interact correctly with the π*-orbital of C2, the hydride must approach the DHP ring from below the plane of the double bond of C2-C3 position. First, if the hydride were to approach from the bottom face it would form the chair-like intermediate **A** which has the hydrogen in a pseudo-axial position. On the other hand, if the hydride were to approach from the top face it would form the twist-boat-like intermediate **B** that could ring flip to put the hydrogen in a pseudo-equatorial position. As the twist-boat intermediate would be higher in energy, it should be disfavoured, so pseudo-axial hydride attack through intermediate **A** is favoured. Pseudo-axial quenching of enolate **A** at C3 position would be more favourable to give an all-equatorially substituted THP.
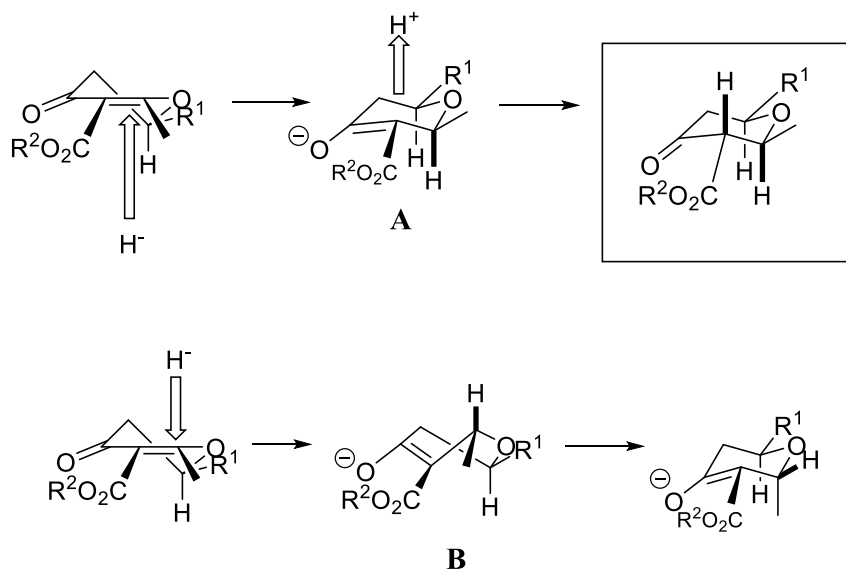
Figure 9 Hydride attack on a DHP

We proceed with our next aim which was the reduction of the DHP followed by an iodomethane quench to give a range of THPs. We initially looked at the use of a *n*-butyl substituent at the C-2 position of the DHP ring **200** with 10 equivalents of iodomethane but unfortunately the iodomethane quench did not work. However, the reduction of α, β-unsaturated esters at position C-2 and C-3 with L-Selectride® followed by a proton quench worked very well (Scheme 67). It was decided to try a different DHP ring **209**, with a methyl substituent at C-2 position with 10 equivalents of iodomethane, and from the ¹H NMR spectrum it showed a 50 : 50 ratio of reduced of unsaturated esters at position C-2 and C-3 and product of C-3 methylated. We increased the amount of MeI to 20 equivalents, and pleasingly it gave the expected product of reductive alkylation at the C-3 position in 61% yield (Scheme 68).
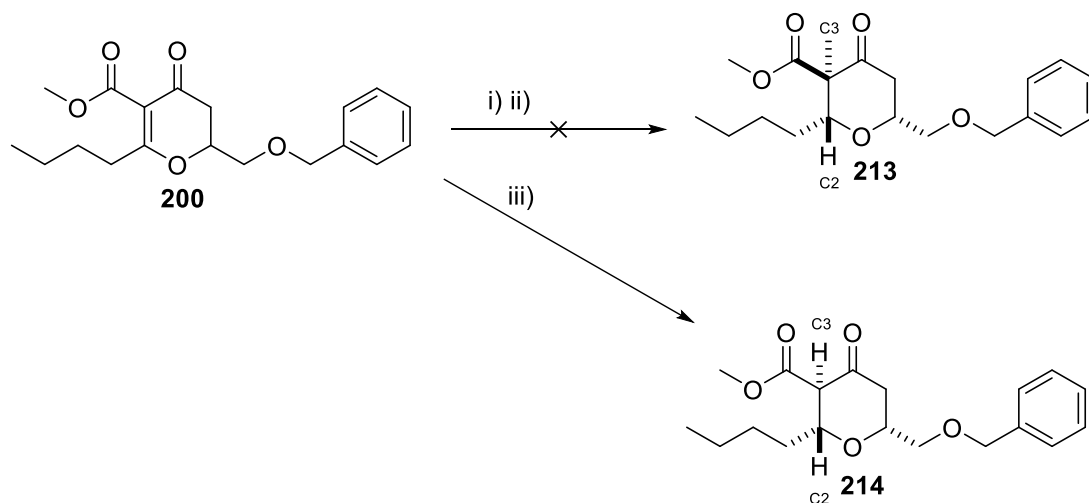
Scheme 67 Reagent & Conditions: i) L-Selectride®, THF, −78 °C, ii) MeI 10 eq, RT, iii) L-Selectride®, THF, −78 °C, 95%.
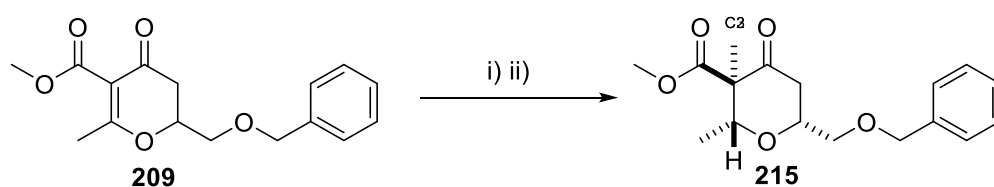
Scheme 68 Reagent & Conditions: i) L-Selectride®, THF, −78 °C, ii) MeI 20 eq, RT, 61%.

The reduction followed by an iodomethane quench was applied to a range of DHP rings (Scheme 69), Table 7. It can be seen that alkylation at C3 gave THPs diastereoselectivity, and this has proven to be a valuable diostereoselective transformation as the alkylation occurred in a diastereoselective fashion pseudo-axial quench of the enolate to form the new stereogenic centre at C3.
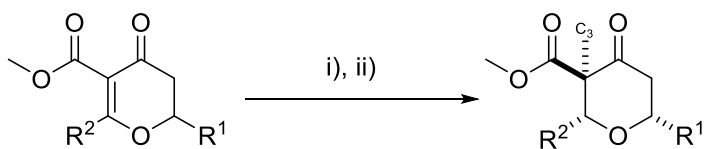
Scheme 69 Reagent & Conditions: i) L-Selectride®, −78 °C in THF, ii) MeI 20 eq, RT.

Entry	Starting material	R^1	R^2	Yield[a] (%)	Product
a	**209**	-CH$_2$OBn	Me	61	**215**
b	**205**	^{i}Pr	Me	96	**216**
c	**208**	Pr	Me	48	**217**
d	**207**	Phenyl	Me	72	**218**
e	**204**	2-furyl	Me	53	**219**
f	**200**	-CH$_2$OBn	n-Butyl	57	**213**

[a]Isolated yield after column chromatography.

Table 7 L-Selectride® reduction followed by iodomethane quench

We re-investigated the reductive alkylation of DHP **200** and interestingly, when the L-Selectride® reduction and methylation was carried out with 30 equivalents of iodomethane the alkylated product **213** was isolated.
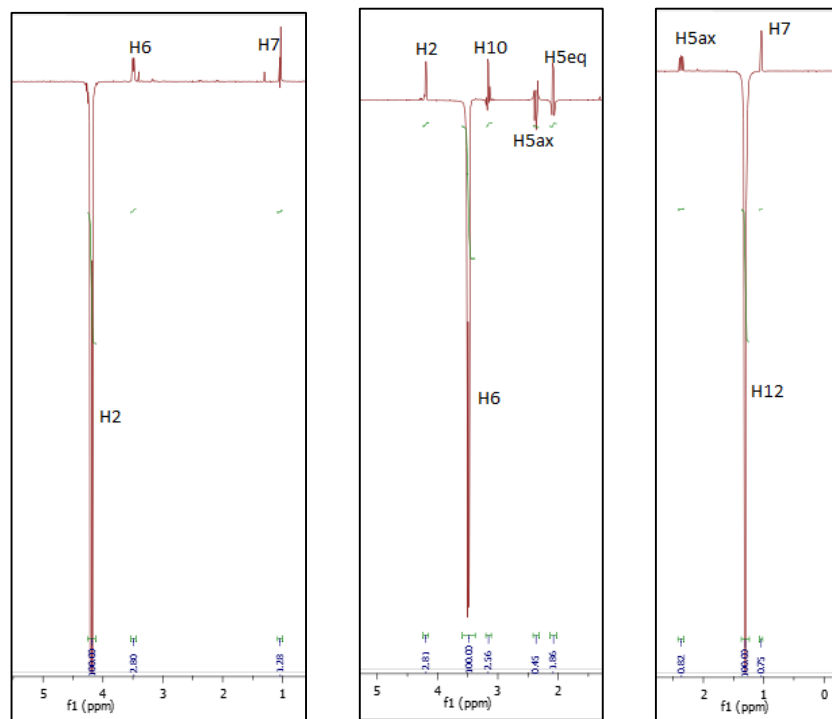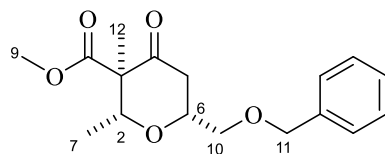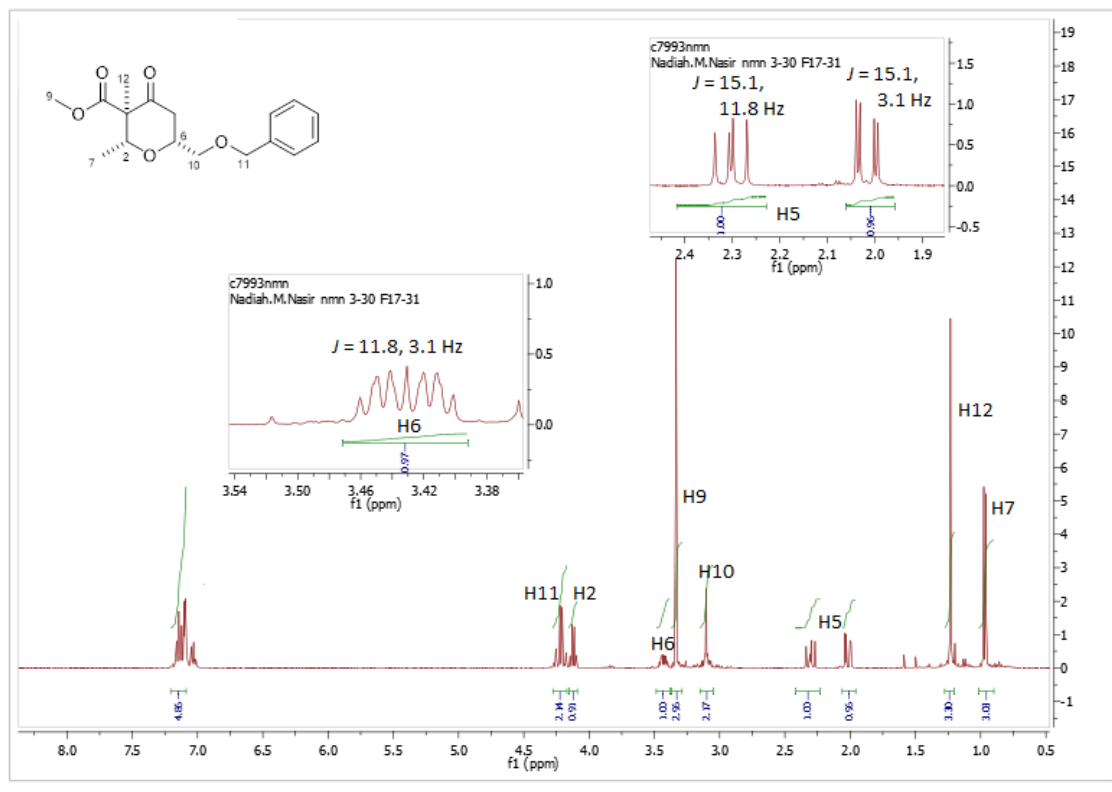
Figure 10

2.6 Synthesis of 2,6-*cis* tetrahydropyran: confirmation of stereochemistry
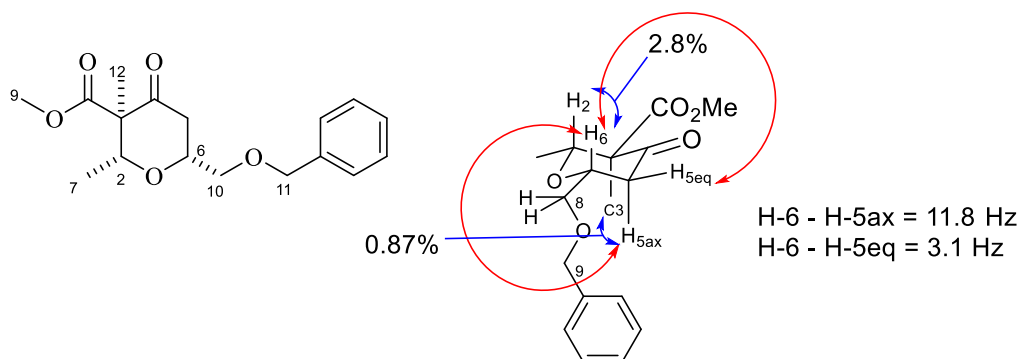
Figure 11 ^{1}H-^{1}H COSY NMR Correlation of 2,6-*cis* THP **215**

NOE Correlation of 2,6-*cis* THP **215**

The formation of 2,6-*cis* THP rings were confirmed by the ^{1}H NMR spectrum (Figure 10) of **215**. The region between 3.51-3.45 ppm was assigned as H-6 as it has *J*-value of 11.8 Hz, showed *trans*-diaxial coupling with H-5ax at peak 2.37 ppm and H-6 also has *J*-value of 3.1 Hz show axial-equatorial coupling with H-5eq at peak 2.10 ppm.

The NOE correlation between H-2 and H-6 was 2.8%. There was also a positive NOE correlation between H-5ax and the C-3 methyl substituent of 0.82% (Figure 11). From this result, it showed that the methyl quench occurred from the expected pseudo-axial trajectory, which is *anti* to the addition of a hydride.

2.7　Synthesis of THP A ring of Lasonolide A.

With the success of developing a method for the formation of 2,6-*cis* THP rings by conjugate reduction of L-Selectride[®] and electrophile quench of iodomethane on DHP ring, we decided to apply this method in the synthesis of a natural product fragment. The synthesis of the A ring of lasonolide A **1**, was chosen as its synthesis should be achievable using our method. Lasonolide A **1**, consists of a 20-membered macrolide that contains a skipped 1, 4-diene, and two highly substituted tetrahydropyran rings, it was isolated from the Caribbean marine sponge *Forcepia sp.* (**Figure 12**) by McConnell and co-workers in 1994.[2] Lasonolide A **1** is a pale orange oil whose molecular formula was deduced as $C_{41}H_{60}O_9$ and it has shown IC_{50} values of 8.6 and 89 nM against A-549 human lung carcinoma and Panc-1 human pancreatic carcinoma, respectively.[79] Furthermore, **1** inhibits cell adhesion in the EL- 4.IL-2 cell line with an IC_{50} of 19 ng/mL, however, toxicity against this cell line is greater than 25 ug/mL.[80-82]
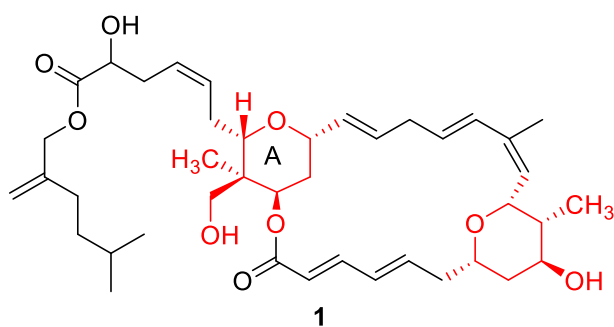
Lasonolide A　　　　　　**Figure 12:** Caribbean marine sponge *Forcepia sp.*

The total synthesis of lasonolide A **1** has been achieved by the Ghosh group. The THP ring was constructed stereoselectively by an intramolecular 1, 3-dipolar cycloaddition reaction, where the oxime **220** was treated with sodium hypochlorite which led to facile intramolecular 1, 3-dipolar cycloaddtion *via* the nitrile oxide to give isoxazoline **221** as a

single diastereomer. A further 3 steps were required to form the THP A ring (Scheme 70).[41]
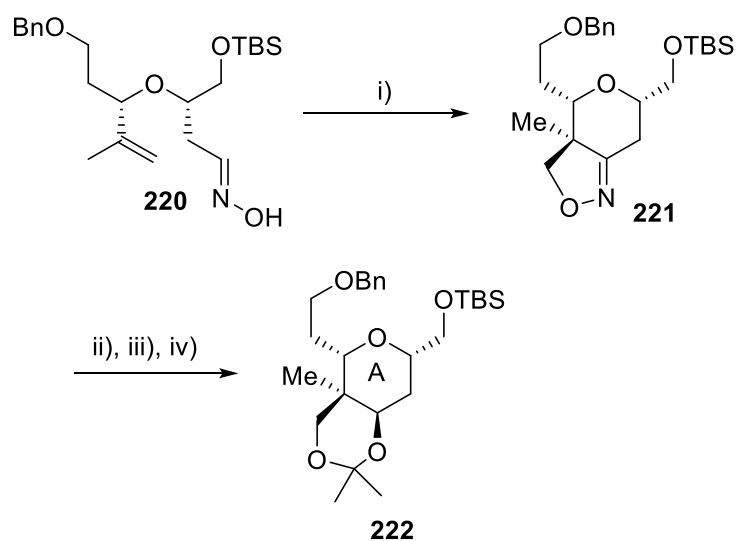
Scheme 70 Reagent & Conditions: i) aq. NaOCl, CH$_2$Cl$_2$, 74%, ii) H$_2$, Raney Ni, aq. H$_3$BO$_3$, MeOH, 89%, iii) L-Selectride$^\circledR$, iv) CSA, Me$_2$C(OMe)$_2$, 87%.

The Ghosh group also synthesised lasonolide A **1**, by using an asymmetric hetero Diels-Alder reaction to construct the THP A ring with a chiral Cr (III) catalyst **225** to give **226** (Scheme 71).[83] The DHP **226** was treated with MeLi, then the lithium enolate was react with ethyl cyanoformate to provide the β-keto ester as a mixture, the mixture went alkylation to provided the desired methylation product **227**. Then exposed **227** in L-Selectride$^\circledR$ and LiAlH$_4$ to affored THP A ring **228**.[79]
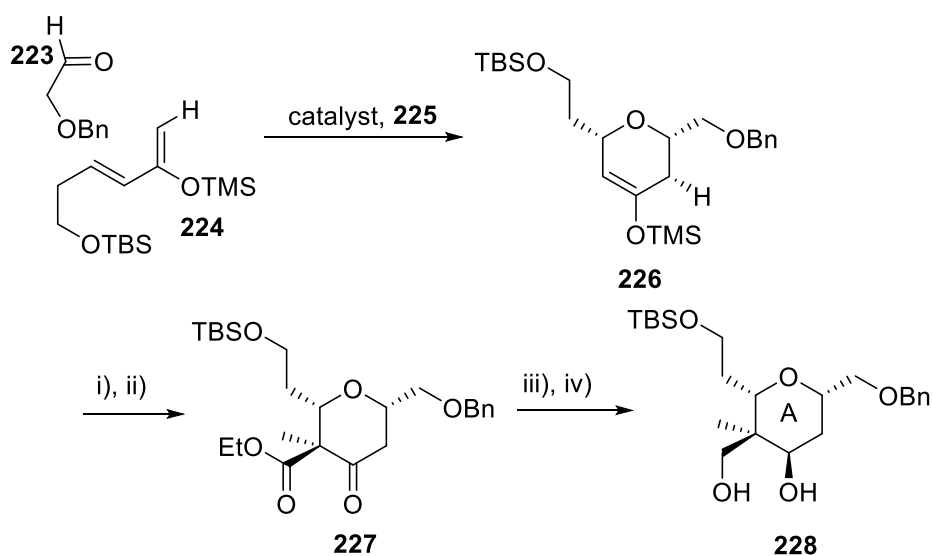
Scheme 71 Reagent & Conditions: i) MeLi, THF, NCCO$_2$Et, ii) NaH, MeI, 74%, iii) L-Selectride®, iv) LiAlH$_4$, 82%.

The SmI$_2$ Molander-Reformatsky reaction was used in the synthesis of THP A ring of lasonolide A **233** by Jennings group. Treatment the **229** with SmI$_2$ provided the Sm (III) enolate intermediate, which underwent cyclization to provide lactone **230** as a single diastereomer. Treatment with allyl magnesium bromide gave lactol **231**, which was then treated with TFA to form the oxocarbenium intermediate **232**, which was then reduced by Et$_3$SiH. The free secondary hydroxyl group was protected by TES ether under reductive conditions and to give **233** in 59% yield (Scheme 72).[84]
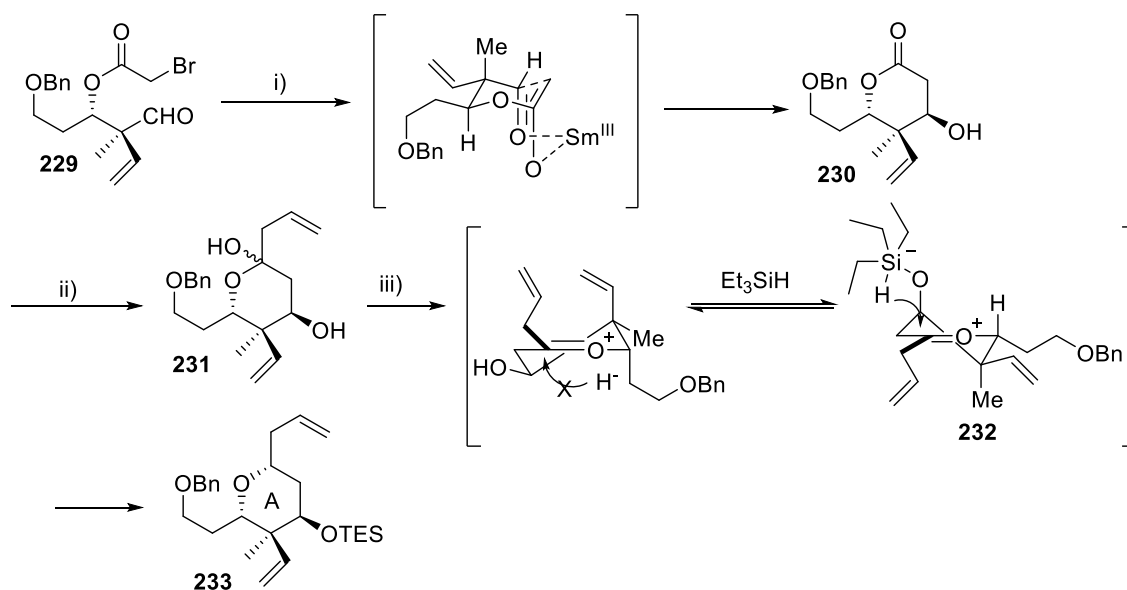
Scheme 72 Reagent & Conditions: i) SmI$_2$, THF, 0 °C, 1.5 hr, ii) allylMgBr, Et$_2$O, −78 °C, 2 hr, iii) TFA, Et$_3$SiH, CH$_2$Cl$_2$, −78 °C, 4hr, 59%.

The Trost group constructed the THP A ring of lasonolide A, by removing the silyl groups in **231** with TBAF to generate lactol **232** subsequently, the Horner-Wadsworth-Emmons olefination of **232** spontaneously formed the THP ring as a single diastereomer in 91% yield. Then 2,6-*cis* THP was formed by reversible nature of the conjugate addition, where the formation of the thermodynamic was produced **234** (Scheme 73).[85, 86]
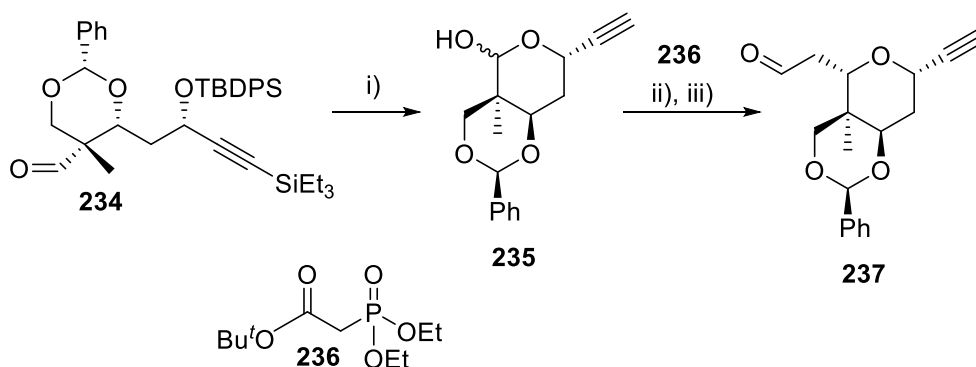
Scheme 73 Reagent & Conditions: i) TBAF, AcOH, 94%, ii) **236**, NaH, iii) DIBAL-H, 76%.

The Shishido group used methyl(trifluoromethyl)-dioxirane **239** for an epoxidation reaction of DHP **238** to give **240**, which was then was iodinated and reduced by zinc to produced **241**. Compound **241** was treated with triethyl phosphonoacetate in the presence of potassium hydride to give **242**, which was reduced with lithium aluminium hydride give the THP A ring of lasonolide A **243** (Scheme 74).[87, 88]
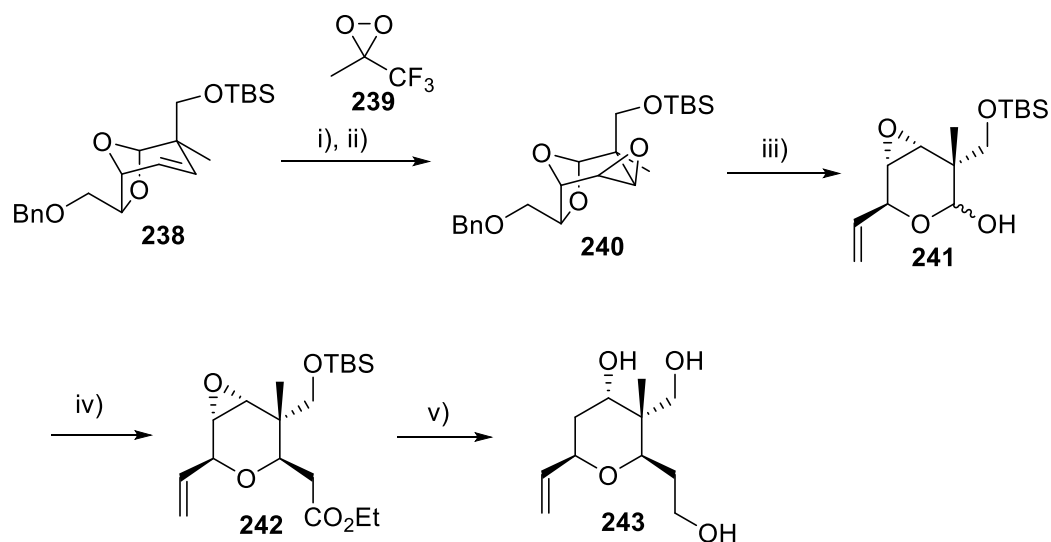
Scheme 74 Reagent & Conditions: i) **239**, NaHCO$_3$, Na$_2$EDTA, CH$_3$CN/H$_2$O, ii) Pd(OH)$_2$, cyclohexene, EtOH, 92%, iii) I$_2$, PPh$_3$, imidazole, PhH then Zn, EtOH, iv) KH, (EtO)$_2$POCH$_2$CO$_2$Et, DMF, 87%, v) LiAlH$_4$, THF.

In the Kang group, the compound **244** underwent cyclization went treated with iodine to form 2,6-*cis* THP **245**. Then the **245** went to sequence substituent, ozonolysis, a reductive workup and benzylidiene group was removed by hydrogenolysis to produce **246** (Scheme 75).[89]
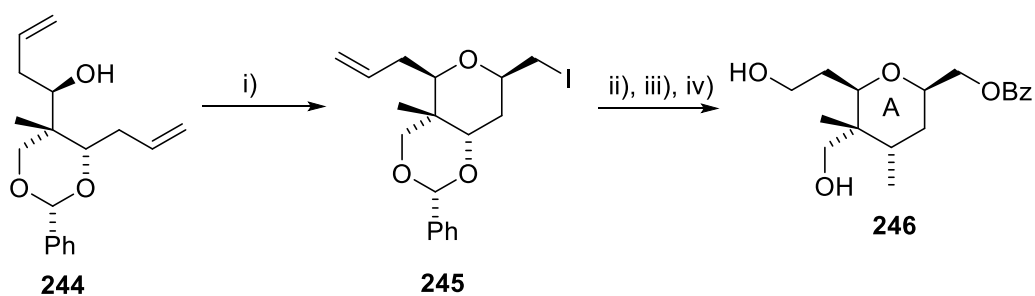
Scheme 75 Reagent & Conditions: i) I_2, K_2CO_3, MeCN, -30°C to -20°C, 95%, ii) BzONa, NMP, 100°C, 97%, iii) O_3, $NaHCO_3$, MeOH, -78°C, 96%, iv) H_2, 10% Pd/C, HOAc, MeOH, RT, 89%.

2.8 Synthesis of THP A ring of Lasonolide A – the reduction of ketone and ester by lithium aluminium hydride (LiAlH₄)

With the success of our previous reductive alkylation reaction, we proceeded toward the construction of the core model fragment of the lasonolide A **1**. We first attempted a LiAlH₄ reduction in order to reduce the ketone at position C4 and ester at position C3 to yield hydroxyl groups at C4 and C11 (Scheme 76). The reduction reaction was very rapid being completed in less than 1 hour, but unfortunately the stereochemical outcome was not what we desired. The hydroxyl on position C4 was equatorial rather than axial as in lasonolide A **1** (Figure 13).
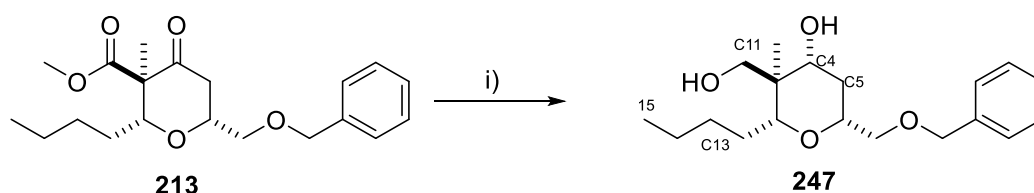
Scheme 76 Reagent & Conditions: i) LiAlH₄, 0°C, THF, 1hr, 51%.
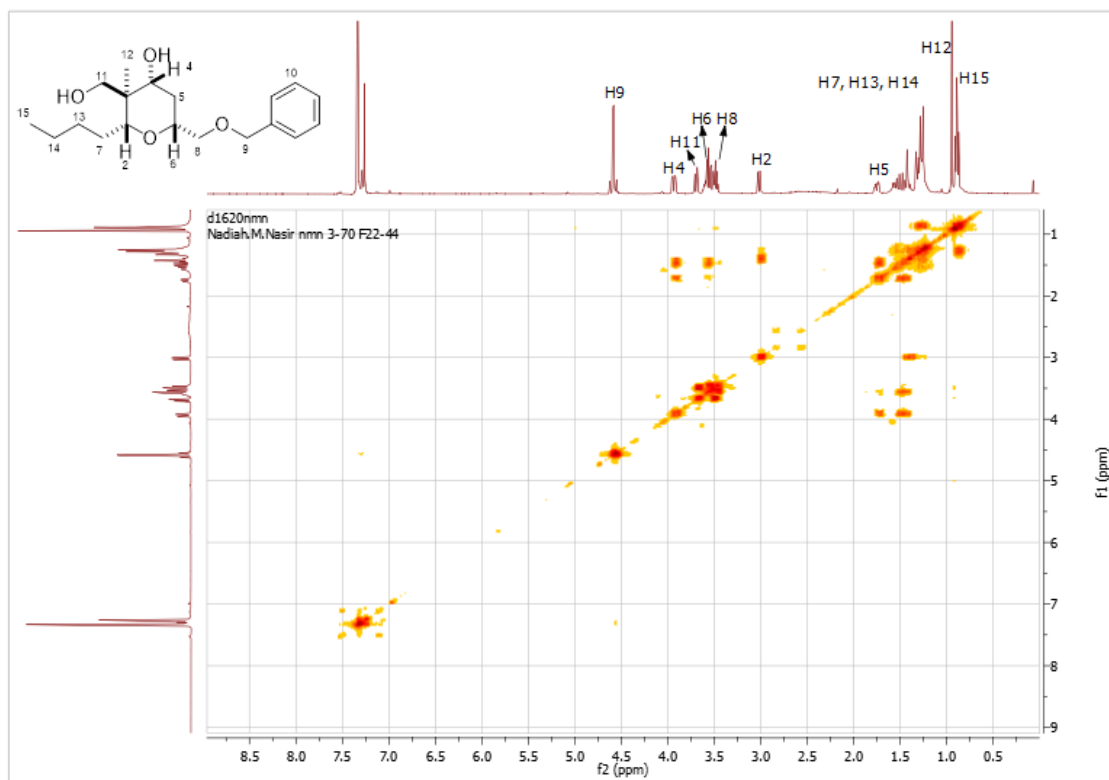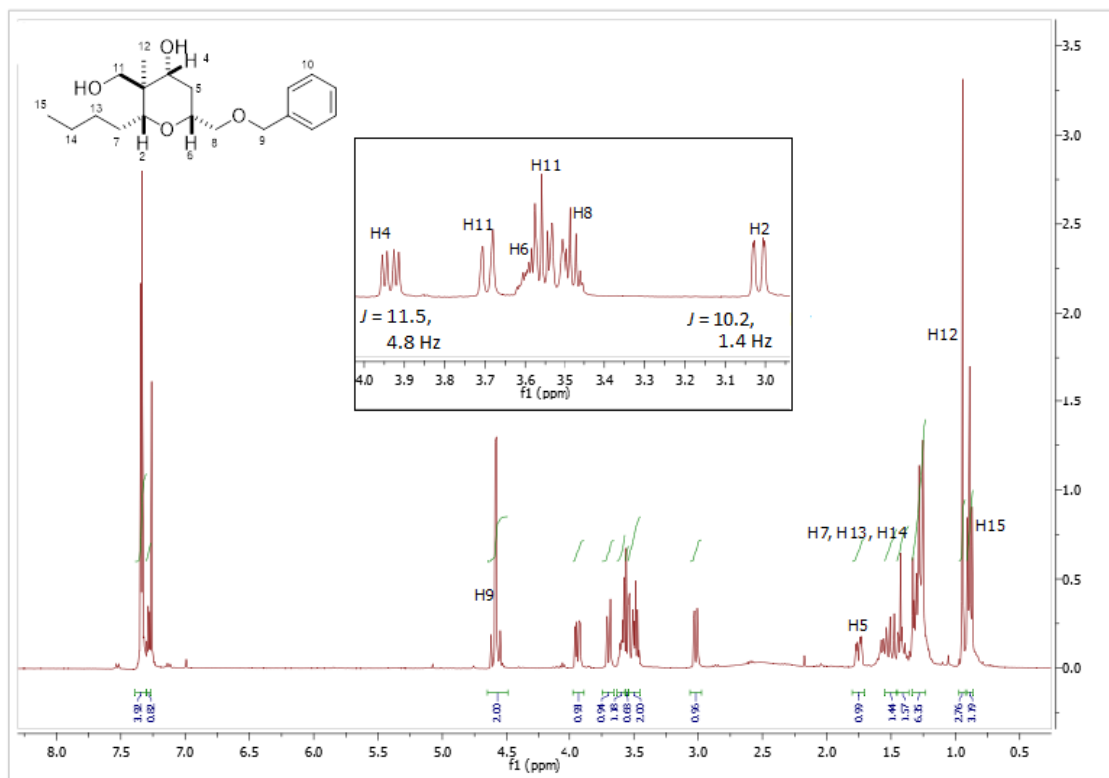
Figure 13
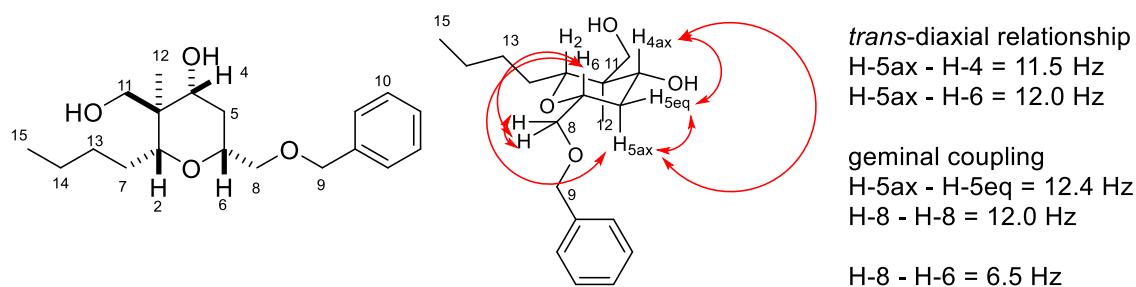
Figure 14 ¹H-¹H COSY NMR Correlation of 2, 6-*cis* THP **247**

The stereochemistry of **247** was elucidated using 1D and 2D NMR techniques with ¹H-¹H COSY spectrum (Scheme 76). The ¹H NMR spectrum (Figure 13) showed that there was a multiplet at 1.42-1.35 ppm and 1.33-1.25 ppm which were assigned as H-7, H-13 and H-14 and integrated as 6H, but since these multiplets overlapped assignment was complicated (Figure 13). There was also a 3H singlet peak at 0.94 ppm which was assigned as H-12 for methyl group, and a 3H at peak 0.89 ppm appeared as triplet and assigned as H-15.

The two double double doublets at 1.48 ppm was assigned as H-5ax and 1.75 ppm was assigned as H-5eq; H-5eq has *J*-value of 4.8 Hz showed coupled to the 3.93 ppm, which was assigned as H-4 and H-5ax has *J*-value of 11.5 Hz showed *trans*-diaxial coupled to the H-4. The H-5ax also has *J*-value of 12.0 Hz showed *trans*-diaxial coupled to the multiplet at 3.61-3.58 ppm, identifying it as H-6. The doublet of doublets at 3.55 and 3.48 ppm was assigned as H-8 and integrated as 2H has *J*-value of 6.5 Hz showed coupled to the peak at H-6.
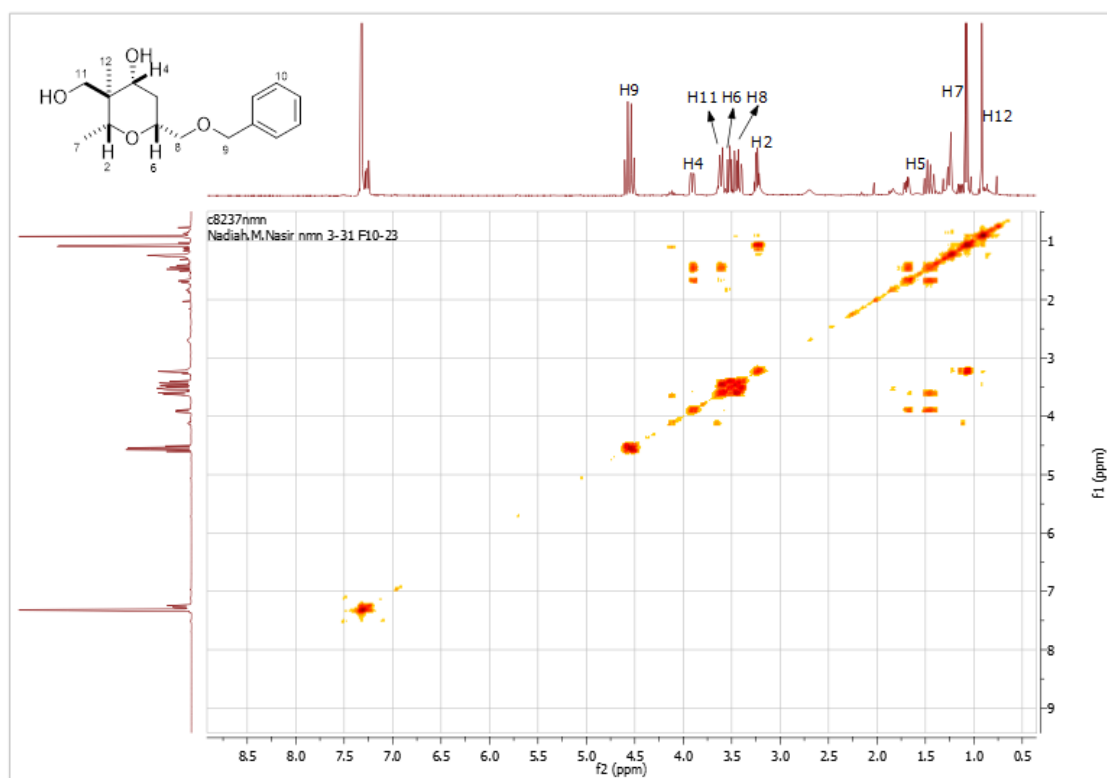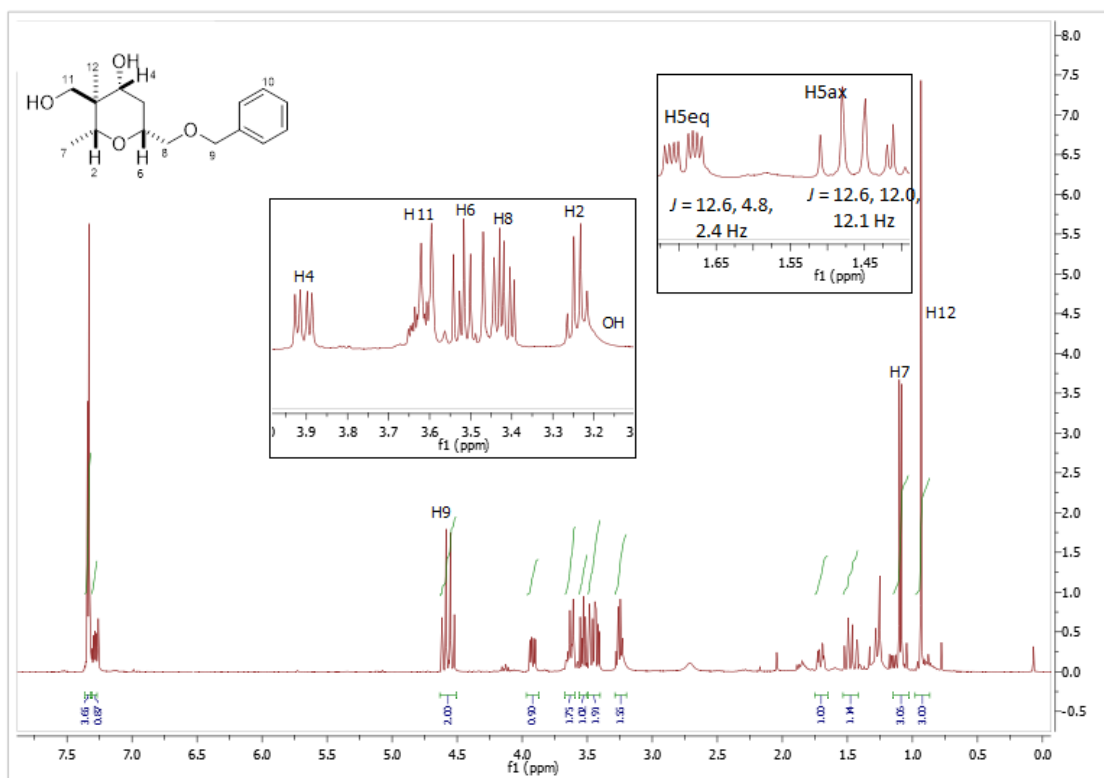
Figure 15

The most important signal in this ^{1}H-^{1}H COSY spectrum, was a doublet of doublets at 3.93 ppm which integrates for 1H, and this was assigned as H-4, as it showed *trans*-diaxial coupled to the H-5ax with *J*-value of 11.5 Hz. The OH position at C-4 is equatorial down position (Figure 14).
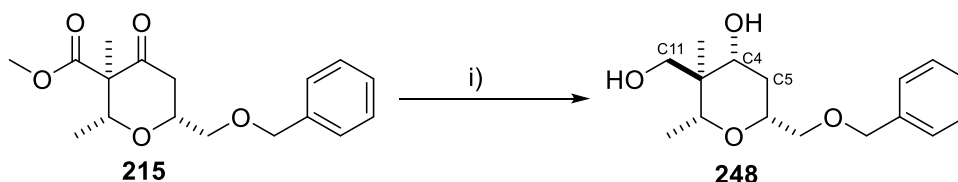
Scheme 77 Reagent & Conditions: i) LiAlH$_4$, 0 °C, THF, 1 hr, 56%.
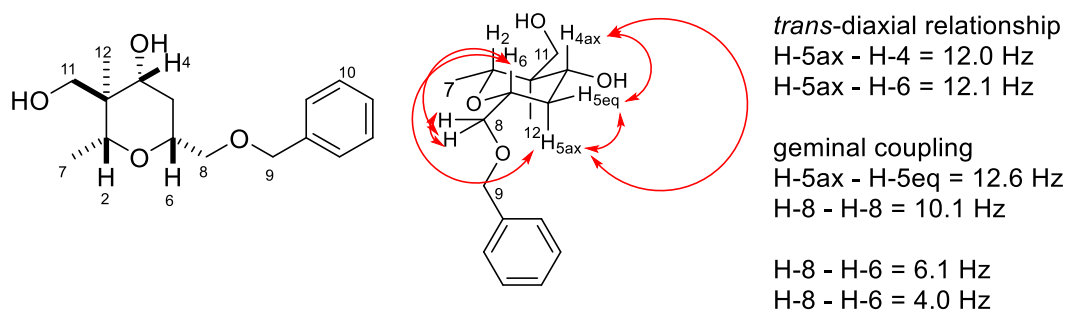
Figure 16 ^{1}H-^{1}H COSY NMR Correlation of 2, 6-*cis* THP **248**

The stereochemistry of **248** was elucidated using 1D and 2D NMR techniques with ^{1}H-^{1}H COSY spectroscopy used to determine the relative stereochemistry of the molecule (Scheme 77). There was singlet at 0.79 ppm was identified as the 3H on the C-12 methyl group. The ^{1}H–^{1}H COSY spectrum (Figure 15) confirmed the H-7 signal at peak 1.02 ppm coupled to the quartert at 3.18 ppm and was assigned as H-2 and intergrated as 1H.
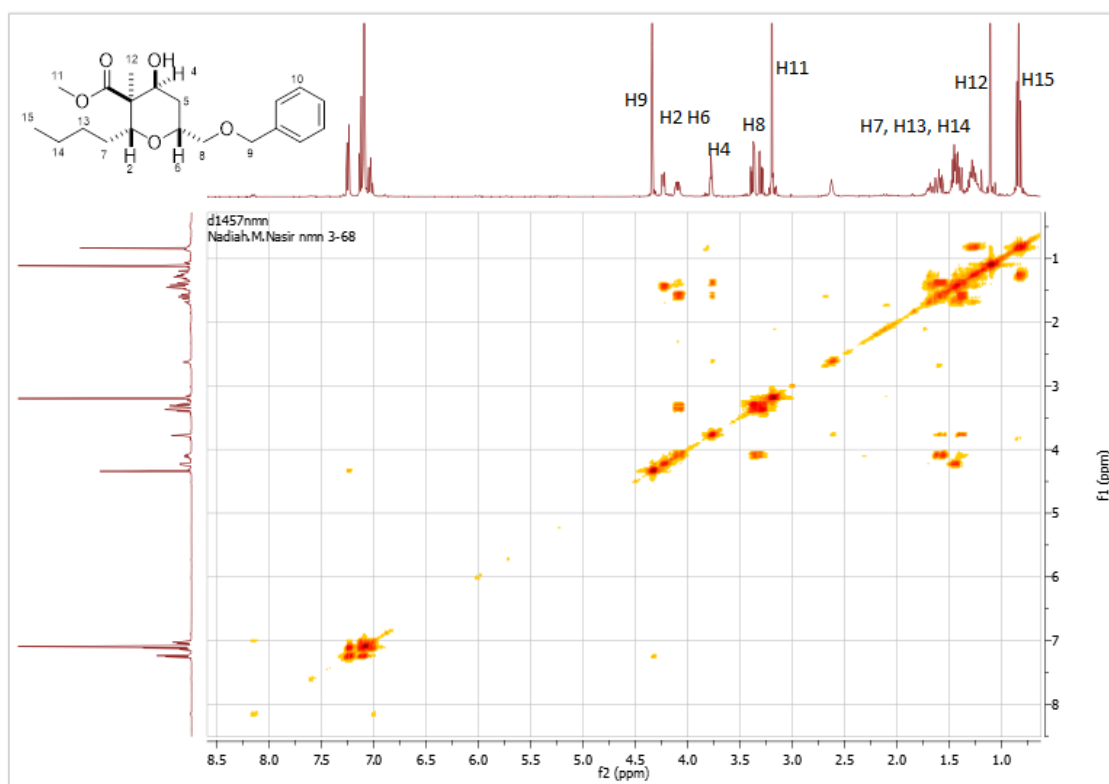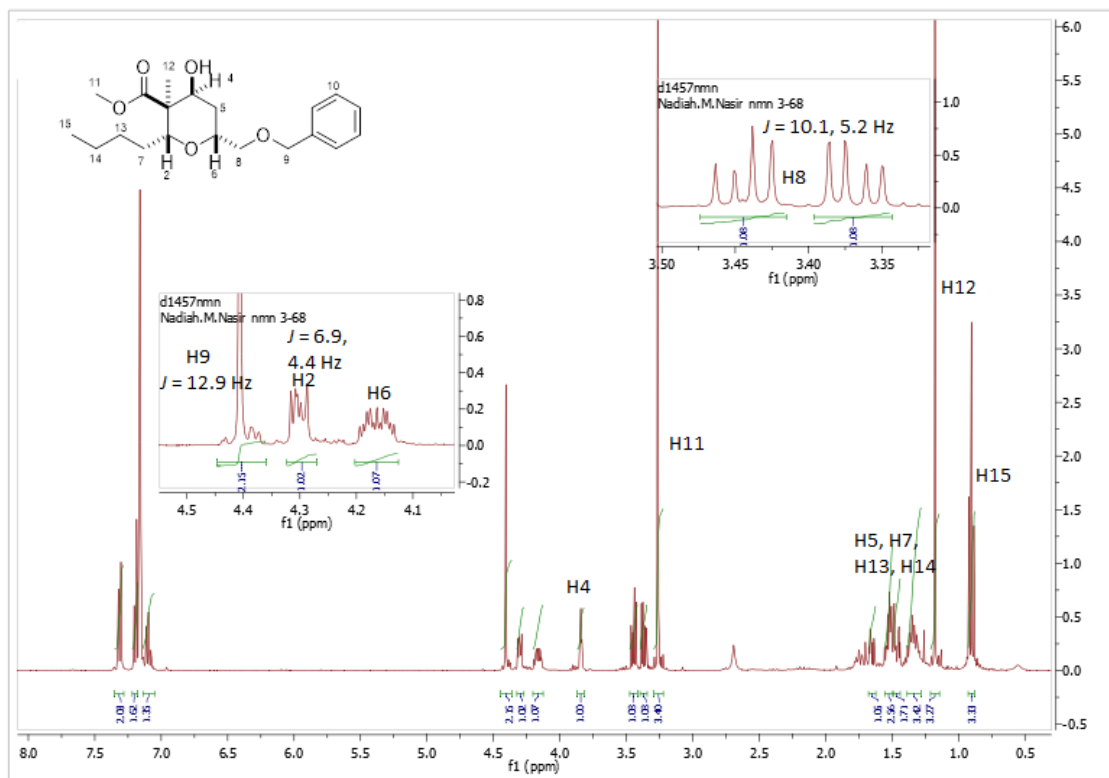
Figure 17

Next chemical shifts were very similar to those found in **247**, which suggests that there was no change in conformation (Figure 16), which is further inspection of the $^1H–^1H$ COSY spectrum showed that the H-5 proton coupled to the multiplet at 3.59–3.57 ppm, identifying it as H-6. The H-5ax and H-5eq also coupled to the double of doublet at 3.85 ppm, which was intergrated as 1H and assigned as H-4. The H-5ax has *J*-value of 12.0 Hz showed *trans*-diaxial coupling with H-4. Hence, from the ^1H NMR spectrum we concluded the OH position at C-4 is in equatorial down position (Figure 16).

2.9   Synthesis of THP A ring of Lasonolide A – The Reduction of ketone by Lithium tri-*sec*-butylborohydride solution (L-Selectride®).

Due to our unsuccesfull attempt with LiAlH$_4$ to obtained the correct stereochemistry for the C-4 OH group on the THP ringfor lasonolide A **1**, we decided to use L-Selectride® to reduce the ketone. Thankfully this reaction gave the stereochemistry we required for the synthesis of lasonolide A ring (Scheme 78).
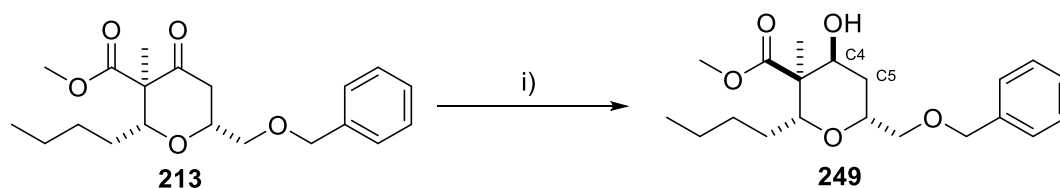
Scheme 78 Reagent & Conditions: i) L-Selectride®, –78 °C, THF, 69%.
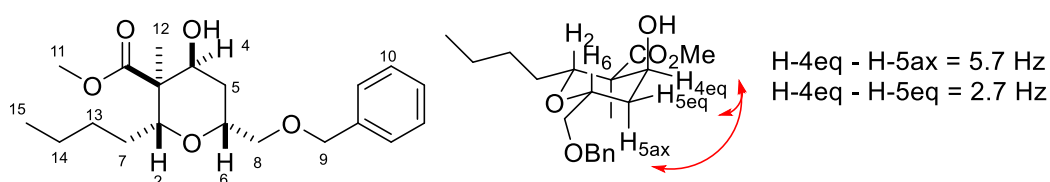
Figure 18 ^1H-^1H COSY NMR Correlation of 2, 6-*cis* THP **249**
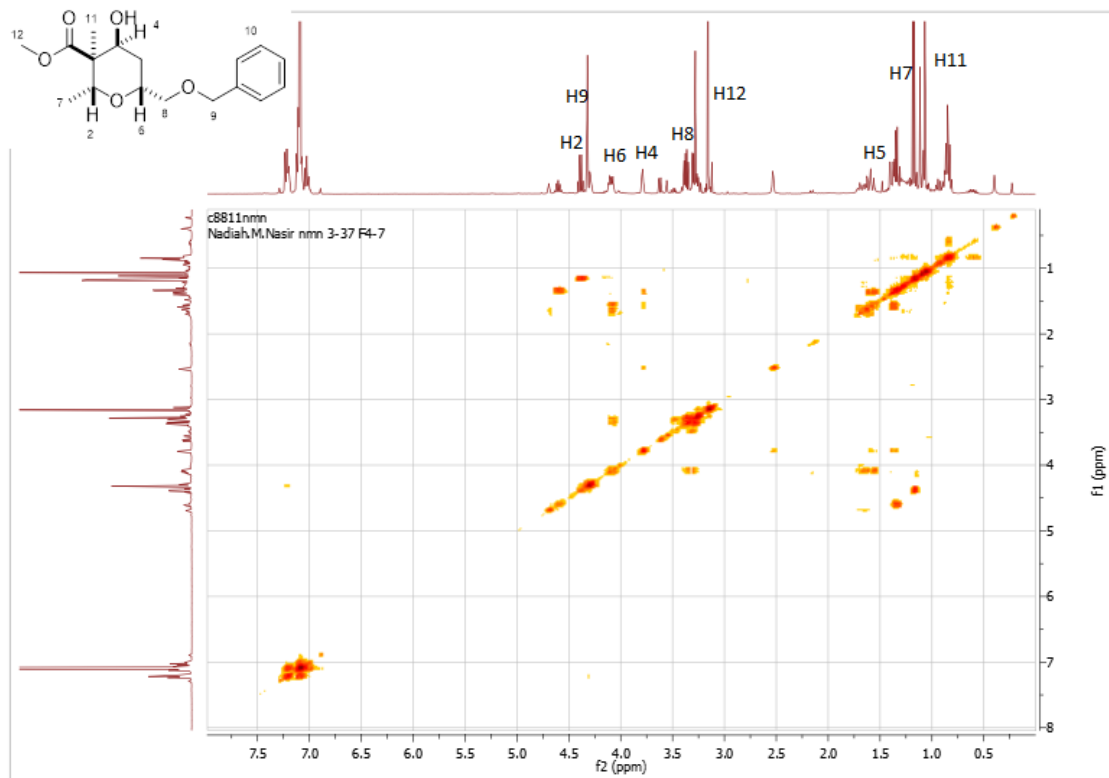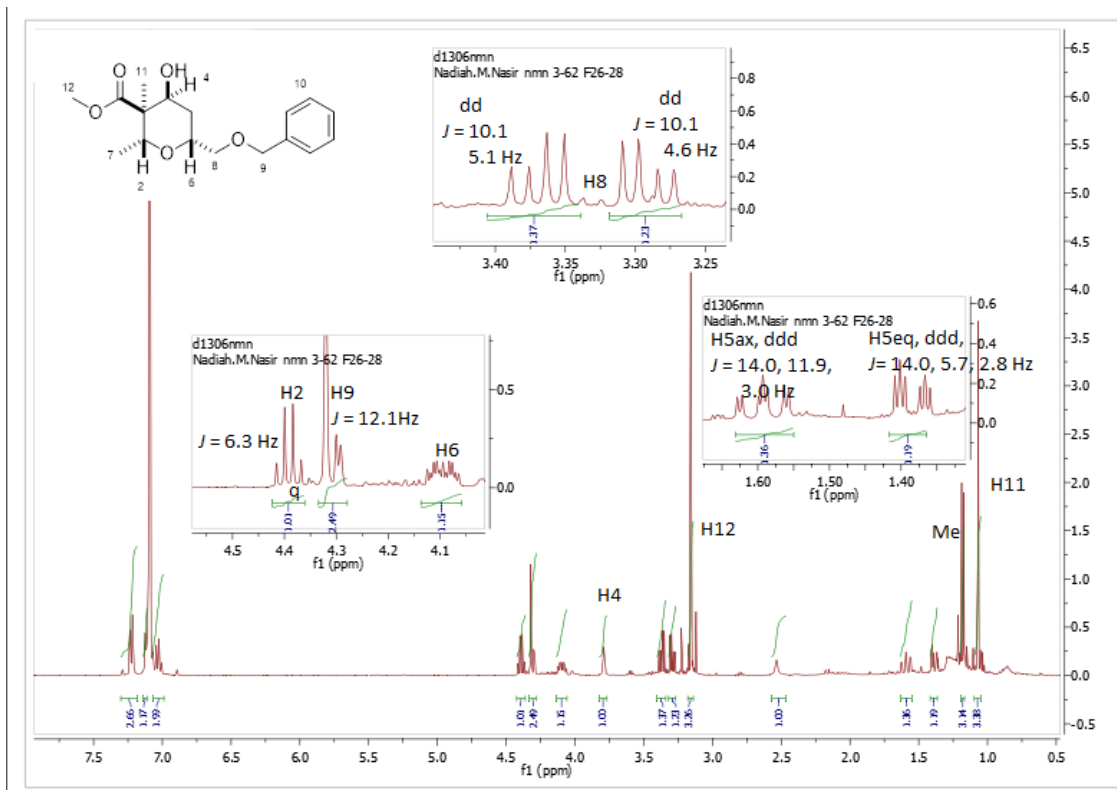
Figure 19

The stereochemistry of the THPs was determined using 1D and 2D NMR spectroscopy with ^{1}H NMR and ^{1}H- ^{1}H COSY spectra (Figure 17) - example **249** which has a CH$_2$OBn substituent at C6 and C2 was n-butyl (Scheme 78). This yielded **249** in 69% yield.

There was a peak at 3.84 ppm that integrated to 1H and this was assigned as H-4 which was a doublet of doublets, and it coupled to the H-5 protons at 1.66 ppm and 1.46 ppm, this coupling was observed in ^{1}H-^{1}H COSY. A *J*-value of 5.7 Hz showed coupling between H-4eq and H-5ax relationship and a *J*-value of 2.7 Hz showed the coupling between H-4eq and H-5eq relationship. We concluded the OH position at C-4 is in axial position and H4 at equatorial down (Figure 18).
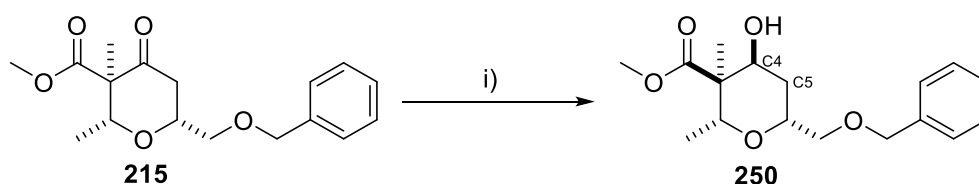
Scheme 79 Reagent & Conditions: i) L-Selectride®, –78°C, THF, 75%.

H-4eq - H-5ax = 5.7 Hz
H-4eq - H-5eq = 3.0 Hz
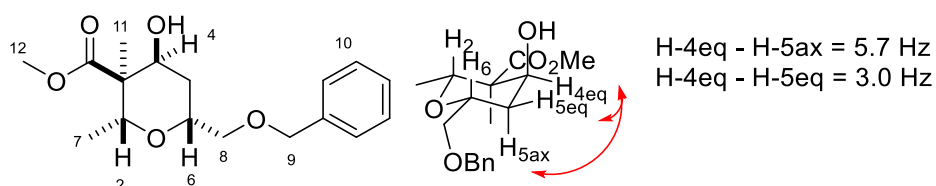
Figure 20 ^{1}H-^{1}H COSY NMR Correlation of 2, 6-*cis* THP **250**

We next investigated the reduction on compound **250**, where C2 was methyl (Scheme 79). It gave 75 % yield. In the ^{1}H NMR spectrum there is a peak at 3.87 ppm that integrates for 1H and this was assigned as H-4 which was a doublet of doublets, and it coupling to

the H-5 protons at 1.66 ppm and 1.46 ppm, this coupling was observed in ^{1}H-^{1}H COSY

(Figure 19). From the ^{1}H NMR spectrum, coupling between H-4eq – H-5ax and H-4eq –

H-5eq showed a small J value with the 5.7 and 3.0 Hz, we concluded the OH position at

C-4 is axial up and H-4 at equatorial down (Figure 20).
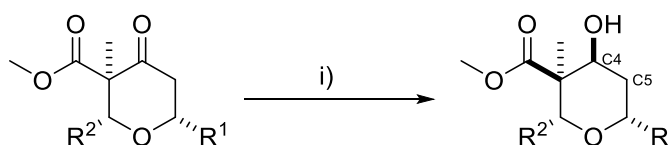
Scheme 80 Reagent & Conditions: i) L-Selectride®, −78°C, THF.

Entry	Starting material	R^1	R^2	Yield^a (%)	Cpd. No.
a	216	^{i}Pr	Me	59	251
b	218	Phenyl	Me	29	252
c	219	2-furyl	Me	79	253
d	215	-CH$_2$OBn	Me	75	250
e	213	-CH$_2$OBn	n-Butyl	69	249

^{a}Isolated yield after column chromatography.

Table 8 L-Selectride® reduction of ketone.

Then, these conditions for the reduction of the ketone were applied to a range of THPs

rings where different substituen group at position C2 and C6 (Scheme 80), Table 8. It can

be seen that all ketones on THPs can be reduce by L-Selectride® with yields in between

29-79% (entries **a – e**).

2.10 Lithium aluminium hydride (LiAlH₄) versus Lithium tri-*sec*-butylborohydride solution (L-Selectride®).

The reduction of cyclohexanones by reducing agents could give two possible products; where the hydride adds pseudo axial or pseudo equatorial depending, on the size of reducing agent. For example, on 4-*t*-butylcyclohexanone, the *t*-butyl group locks the conformation with the *t*-butyl group in the equatorial position. If the hydride attack on the same face as the *t*-butyl group, the hydrogen will be in axial and the hydroxyl group equatorial position. If the hydride attacks from the opposite face, the hydrogen will be equatorial and hydroxyl group will be axial (Figure 21).[90-92]
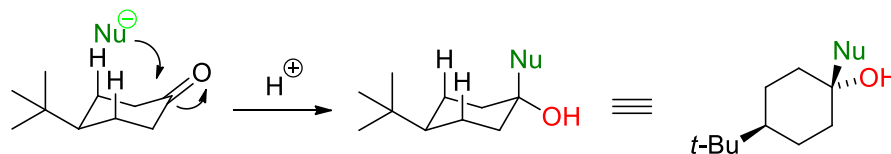
Figure 21: The axial or equatorial attack on cyclohexanone.

This observation can be applied to our THPs rings; large Nu attack equatorial and small Nu attack axially. LiAlH₄ is quite small as nucleophile and the hydride is added at the axial position and placing the hydroxyl group equatorial. This is believed, the torsional effect play as a major role in the preferences for axial approach. In the reactant conformation, the carbonyl group is almost eclipsed by the equatorial C(3) and C(5) C-H bonds. This torsional strain, is relieved by axial attack, whereas equatorial approach

increases strain because the oxygen atom must move through a fully eclipsed arrangement (Figure 22).[93, 94]
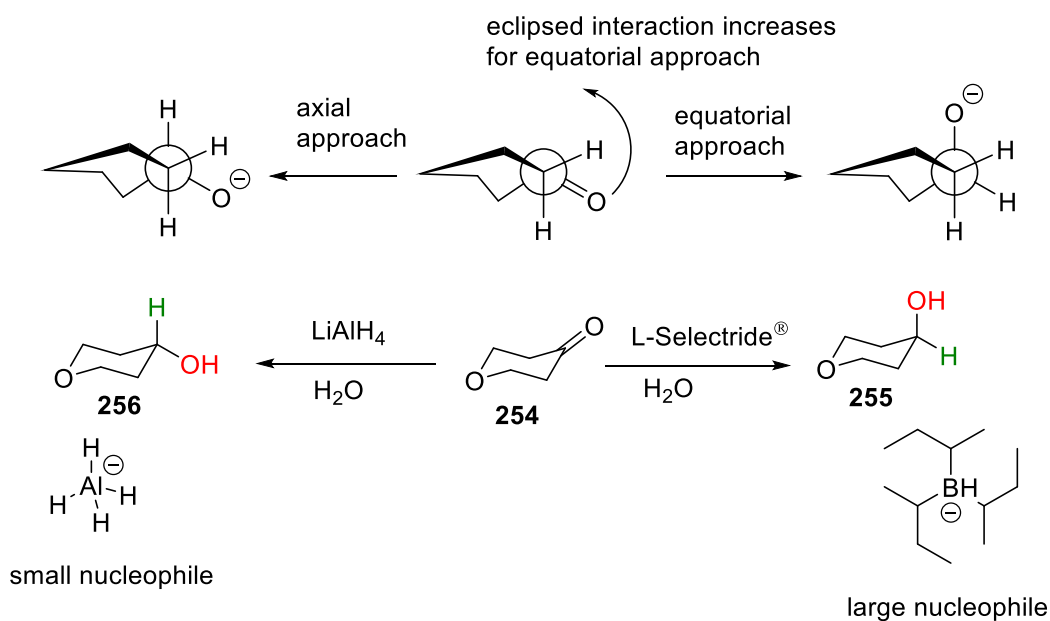
Figure 22: The L-Selectride® versus LiAlH$_4$

In constrast, L-Selectride,® as a large nucleophile (bulky reducing agent), will attack pseudo equatorially, hence the hyride will be added at equatorial position. This is because steric approach control and is the result of the van der Waals repulsion with the 2,6-axial hydrogens. The large nucleophile encounter the 2,6-axial hydrogens on the pseudo axial and therefore prefer pseudo equatorial (Figure 21 and Figure 22).[93, 94]

2.11 Synthesis of THP A ring of Lasonolide A – the reduction of ester by lithium   aluminium hydride (LiAlH$_4$).

The successful installation of the stereochemistry we desired by ketone reduction with L-Selectride®, was next followed by the reduction of the ester to a primary alcohol. To this
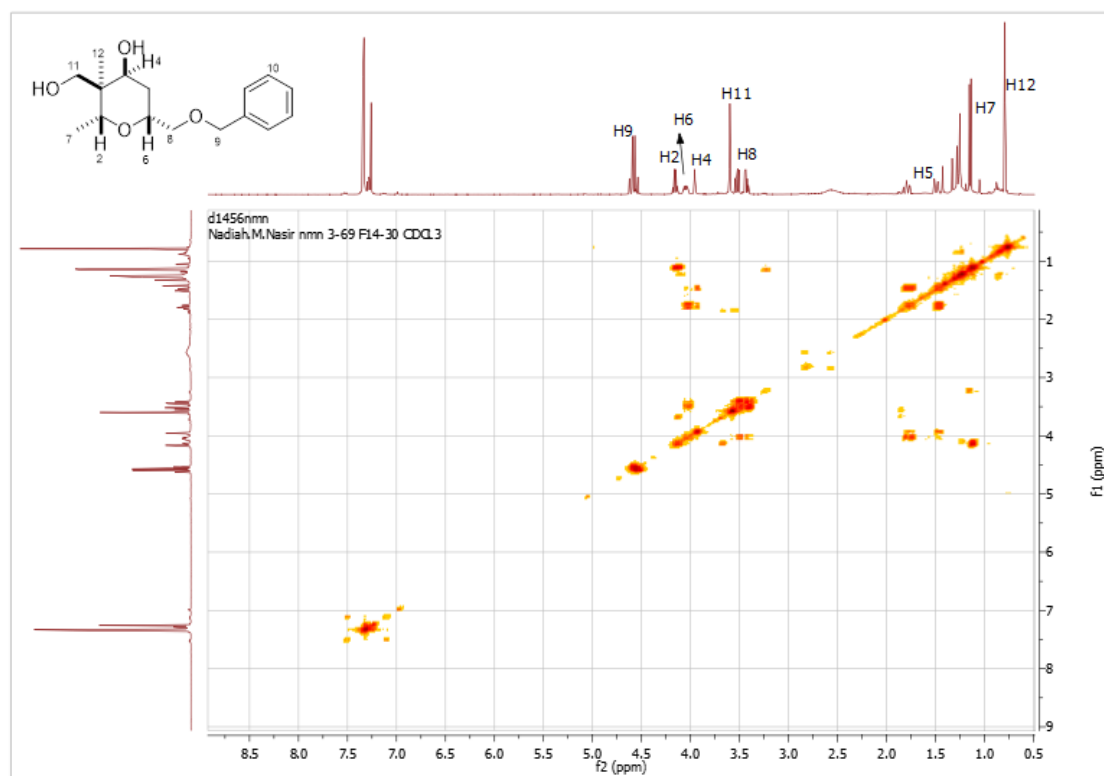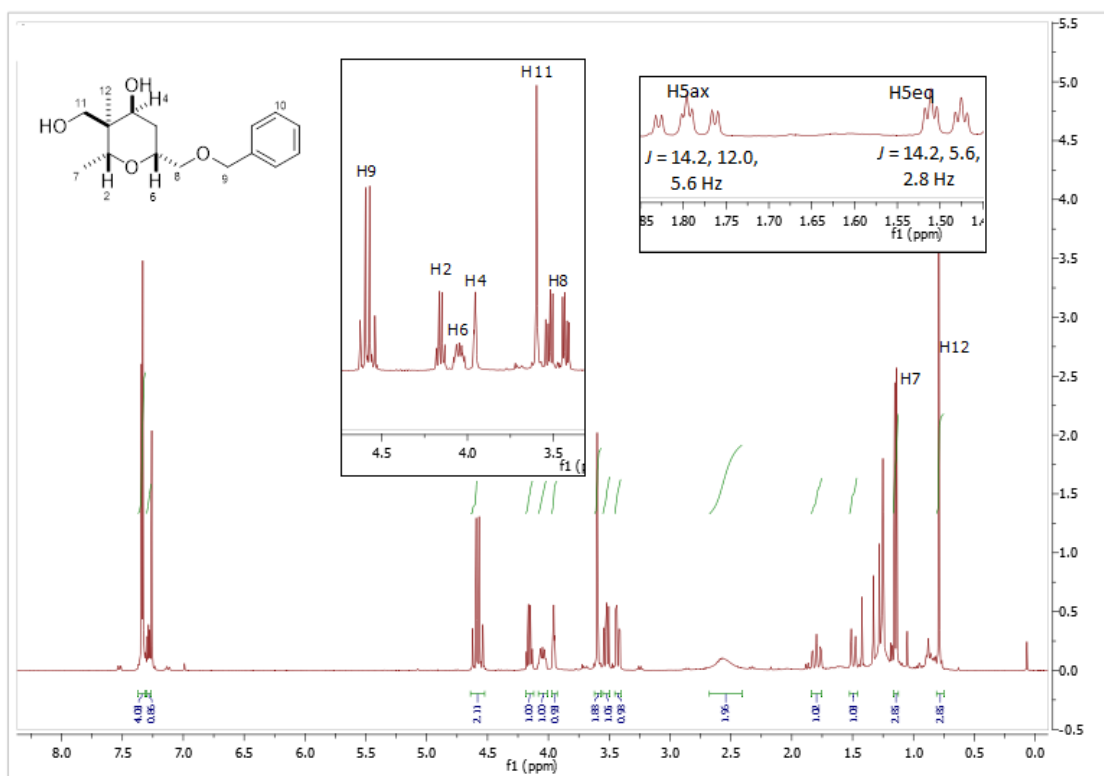
Figure 23

end, we looked at this reduction with lithium aluminium hydride (LiAlH$_4$) as a final step for the synthesis of the THP A ring of lasonolide A **1**.
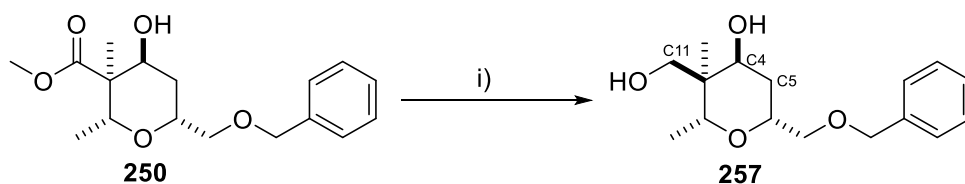
Scheme 81 Reagent & Conditions: i) LiAlH$_4$, 0 °C, THF, 1 hr, 52%.

H-4eq - H-5eq = 2.8 Hz
H-4eq - H-5ax = 5.6 Hz

H-6 - H-5eq = 5.6 Hz
H-6 - H-5ax = 12.0 Hz
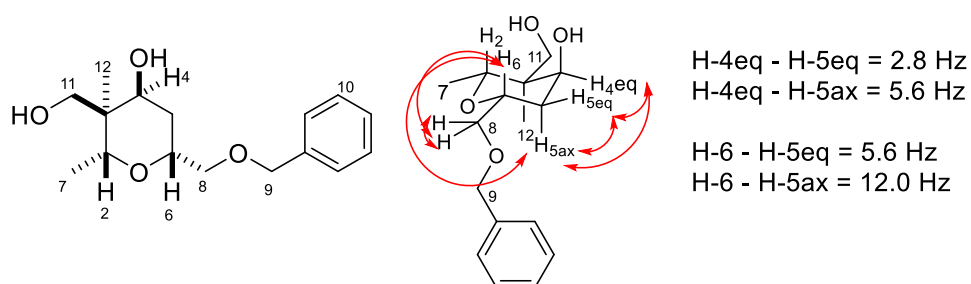
Figure 24 ^{1}H-^{1}H COSY NMR Correlation of 2, 6-*cis* THP **257**

The first attempt was with a methyl substituent at the C2 position and –CH$_2$OBn substituent at C6 position on THPs ring **250**. The reduction of the ester was a success and gave a 52% yield of **257** (Scheme 81). The compound **257** was elucidated by 1D and 2D NMR spectroscopy (Figure 23 and Figure 24).
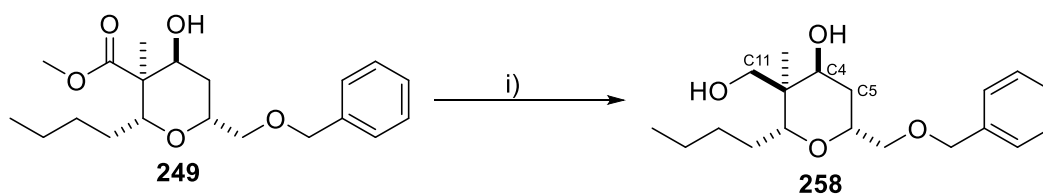
Scheme 82 Reagent & Conditions: i) LiAlH$_4$, 0 °C, THF, 1hr, 52%.
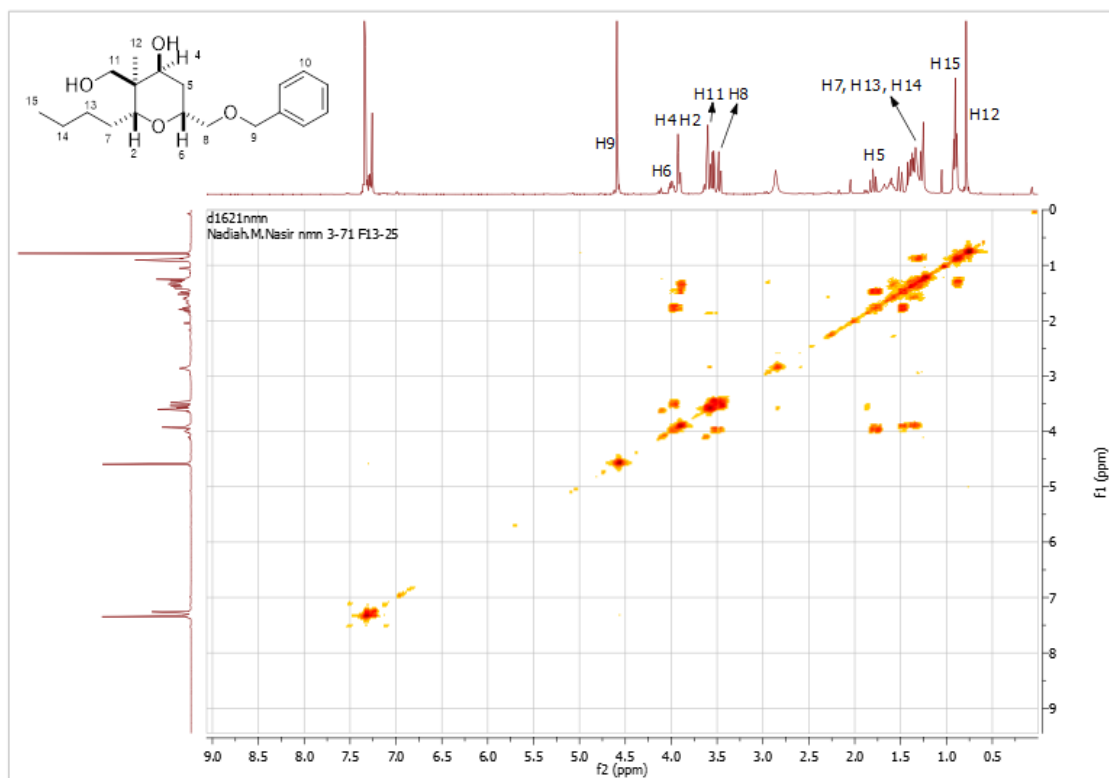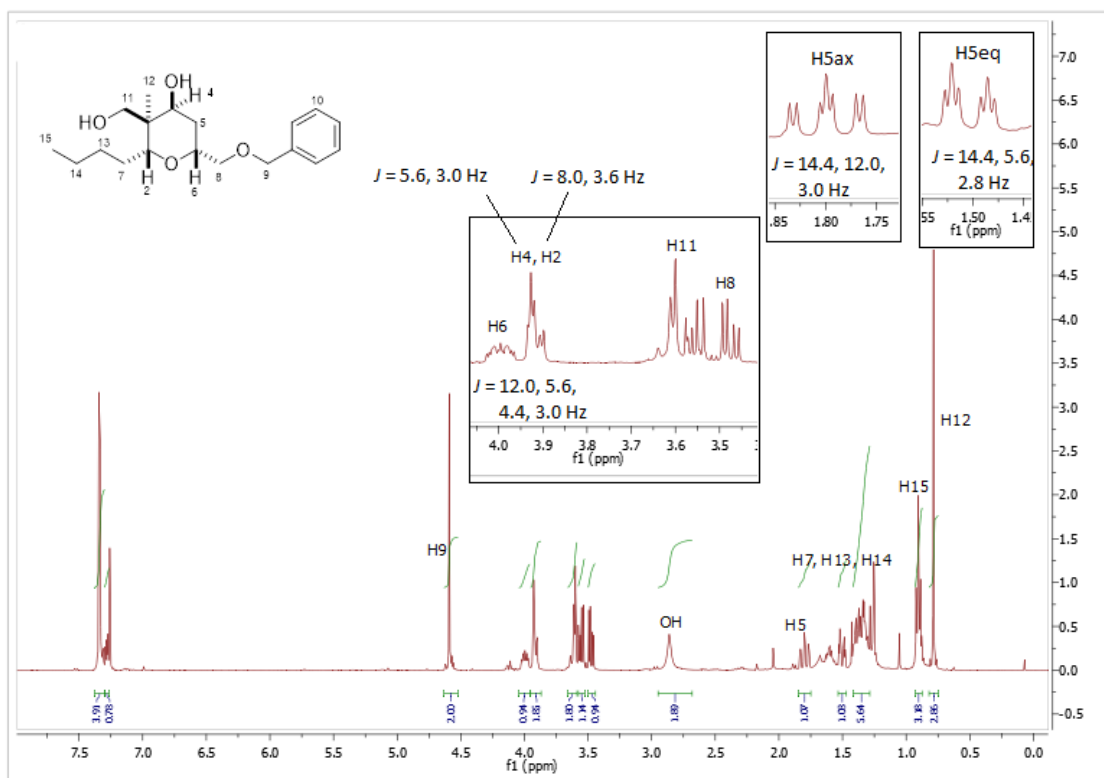
Figure 25
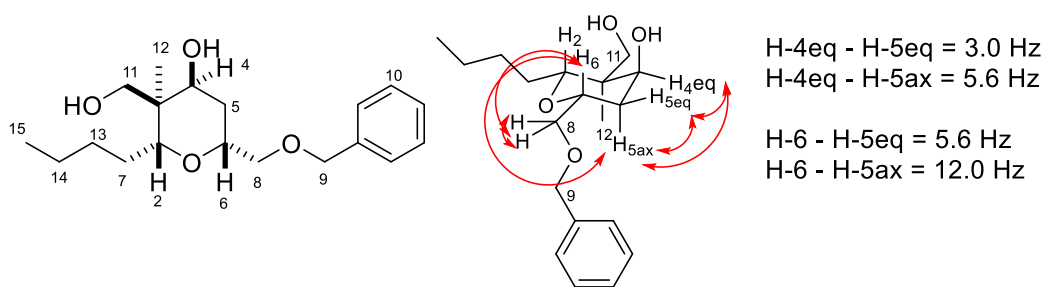
Figure 26 ^{1}H-^{1}H COSY NMR Correlation of 2, 6-*cis* THP **258**

The last step in formation of the THP A ring of lasonolides A was reduction of ester to primary alcohol, the reduction of ester was a success and gave a 52% yield (Scheme 82). The product **258** in ^{1}H NMR spectrum showed a doublet at 3.63 ppm and another doublet at 3.59 ppm, both were assigned as H-11 and integrated for 2H as it has geminal coupling with 12.6 Hz (Figure 25). Conclusion of 1D and 2D NMR spectrum, the product **258** showed the matching stereochemistry we desired to apply to the construction of THP A ring of lasonolide A **1** (Figure 26).

2.12 Synthesis of dihydropyrans: amide acetal cyclisations with *N, N*-dimethylformamide dimethyl acetal.

Having successfully formed dihydropyran rings with the orthoamide methods, it was decided to focus on exploring this reaction. When the reaction was applied to *N, N*-dimethylacetamide dimethyl acetal and a δ-hydroxy-β- ketoester, it gave a DHP with a methyl group at the C2 position. This product can undergo conjugate reduction to form 2,6-*cis* THPs. This reaction was initially tried by Dr. Jason Hargreaves within the Clarke group in a model study of the C21-C32 pentasubstituted THP core of the 22-23 phorboxazoles (Scheme 62).[60, 67]
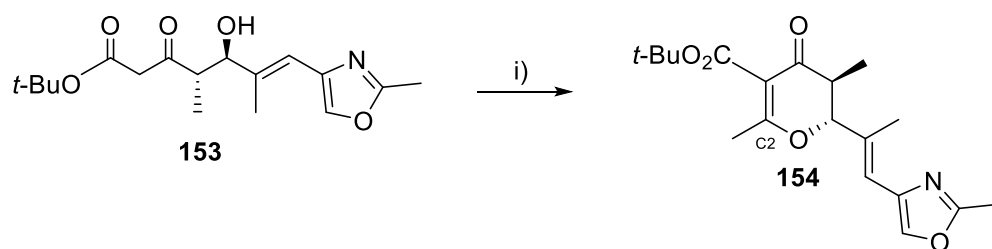
Scheme 62 Reagent & Conditions: i) MeC(OMe)$_2$NMe$_2$, toluene, RT, 74 %
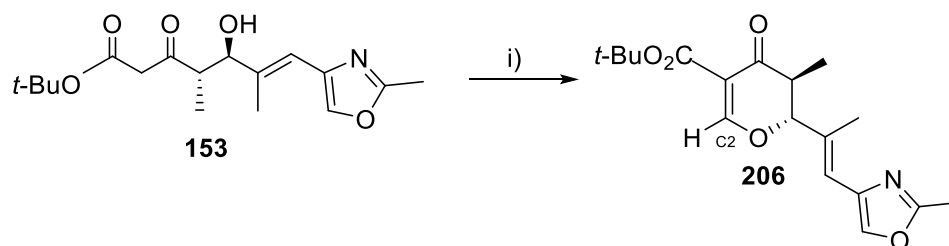
Scheme 63 Reagent & Conditions: i) HC(OMe)$_2$NMe$_2$, toluene, RT, 65 %.

We tried to utilise *N, N*-dimethylformamide dimethyl acetal with δ-hydroxy-β- ketoester to form the DHP ring as our next focus in this report. When *N, N*-dimethylformamide dimethyl acetal reacted with a δ-hydroxy-β- ketoester, the resultant dehydropyranone is unsubstituted at the C-2 position which could gave 2, 6-*trans* THPs following a Gilman cuprate conjugate addition.

Based on Sellars' thesis,[78] it started with the R1 substituent as the 2-furyl group. Unfortunately we were unable to form the 2, 6-*trans* THP. When **185** treated with *N, N*-dimethylformamide dimethyl acetal followed with Gilman cuprate conjugate addition, a product was isolated (Scheme 83), but not the desired product, instead a DHP **259** was isolated after flash chromatography.
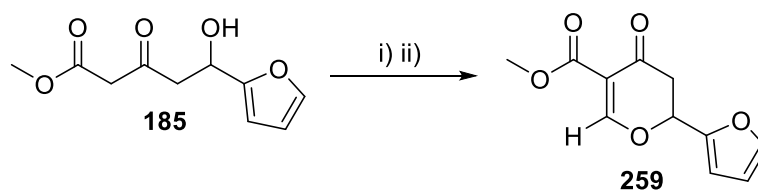
Scheme 83 Reagent & Conditions: i) HC(OMe)$_2$NMe$_2$, PhMe, rt; ii) Me$_2$CuLi, TMSCl, THF, −78 °C, 35 %.

Therefore the reaction of δ-hydroxy-β-ketoesters with *N, N*-dimethylformamide dimethyl acetal was investigated. Unfortunately, the reaction showed a mixture of products by TLC and ^{1}H NMR. After chromatography the DHP **259** was actually formed, along with a new spot that was not in the original product mixture **261** and addition to the isolation of **260** (Scheme 84).[78]
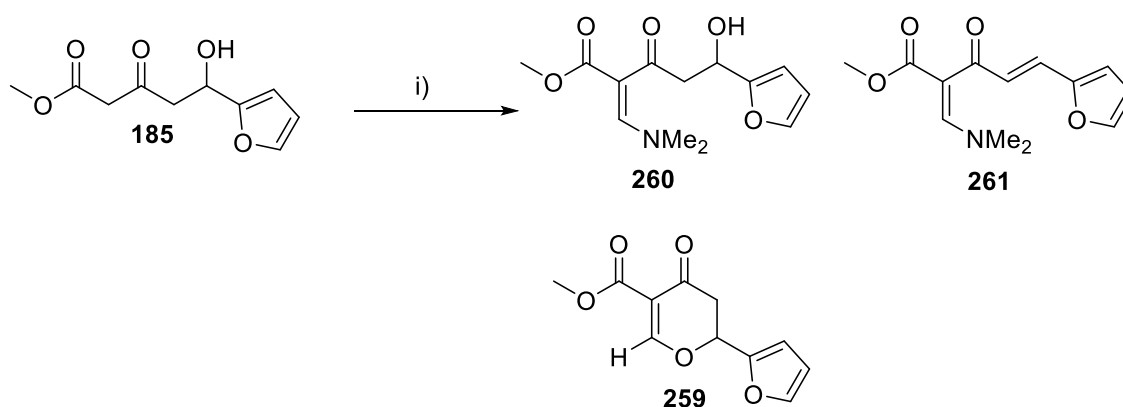
Scheme 84 Reagent & Conditions: i) HC(OMe)$_2$NMe$_2$, PhMe, RT, 15% (**260**), 26% (**259**), 18% (**261**).

It seemed that the Knoevenagel condensation had occurred, but there had been no oxy-Michael cyclisation. The product of **261** were presumably formed from the acidity of the silica that promoted the elimination of water and together activated the enaminone to allow oxy-Michael addition of the hydroxyl group to form DHP **259**. Even when the temperature was increased, this had no effect in promoting cyclisation. The Lewis acid

was added to make the enone more susceptible to nucleophilic attack from the hydroxyl group, in the presence of chlorotrimethylsilane to give 39% yield. In an attempt to improve, the chlorotrimethylsilane was replaced with $BF_3 \cdot OEt_2$ and reaction at room temperature gave 46% yield.

The yield was still a disappointing 46%, further investigation into the amount of *N, N*-dimethylformamide dimethyl acetal used was conducted varying the stoichiometry from one to ten equivalents. The solvent was changed from toluene to dicholoromethane and added slowly the $BF_3 \cdot OEt_2$ into reaction. Thankfully, these reactions gave the desired dihydropyrans in good yield and NMR purity without the need for chromatography. With this modified method, we could explore potential route towards 2, 6-*trans* THPs.[78]

Initially, it was start with one equivalent of *N, N*-dimethylformamide dimethyl acetal was used directly with one equivalent of δ-hydroxy-β- ketoester, followed by addition of $BF_3 \cdot OEt_2$ as a Lewis acid. Gratifyingly, these reactions gave the desired dihydropyrans in good yield and reasonable purity (Scheme 85).
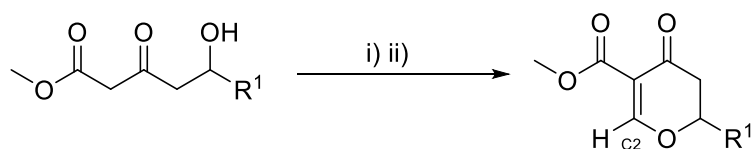
Scheme 85 Reagent & Conditions: i) HC(OMe)$_2$NMe$_2$, CH$_2$Cl$_2$, RT, ii) BF$_3$•OEt$_2$.

Entry	Starting material	R^1, eq	*N, N*-dimethylformamide dimethyl acetal, eq	BF$_3$.OEt$_2$, eq	Product	Yield (%)
a	*i*Pr	1	1	1	**262**	97
b	Pr	1	1	1	**263**	91
c	Phenyl	1	1	1	**264**	96
d	2-furyl	1	1	1	**259**	92
e	CH$_2$-OTIPS	1	1	1	**265**	87
f	2-methyloxazole	1	2	2	**266**	77
g	-CH$_2$OBn	1	2	2	**267**	-
h	*E*-CH=CHCH$_3$	1	1	1	**268**	87
i	*E*-CH=CHPh	1	2	2	**269**	97
j	CH3	1	1	1	**270**	87

Table 9 Synthesis of dihydropyrans with *N, N*-dimethylformamide dimethyl acetal

The cyclisation with *N, N*-dimethylformamide dimethyl acetal gave the desired DHPs in good yield. Disappointingly when R^1 = –CH$_2$OBn (Table 9, entry **g**), an inseparable mixture of products was obtained even after more equivalents of acetal were added.

2.13   Synthesis of 2,6-*trans* tetrahydropyran: conjugate addition.

We extended our investigation towards the formationof 2,6-*trans* THPs using the Gilman cuprates. It was previously reported that for Gilman cuprates to be an effective nucleophile in 1, 4-conjugate additions to C-2 substituent DHPs, to give THPs with 3°

centres at C2. We felt this method could be extended to the construction of 2,6-*trans* THPs.[95]

However when we attempted to add Gilman cuprates to DHPs, as expected it gave tautomeric products with enol as a major product and ketone as a minor product (Scheme 86). To solve this problem, we formed acetates in order to convert both product to a single compound (Scheme 86).[96]
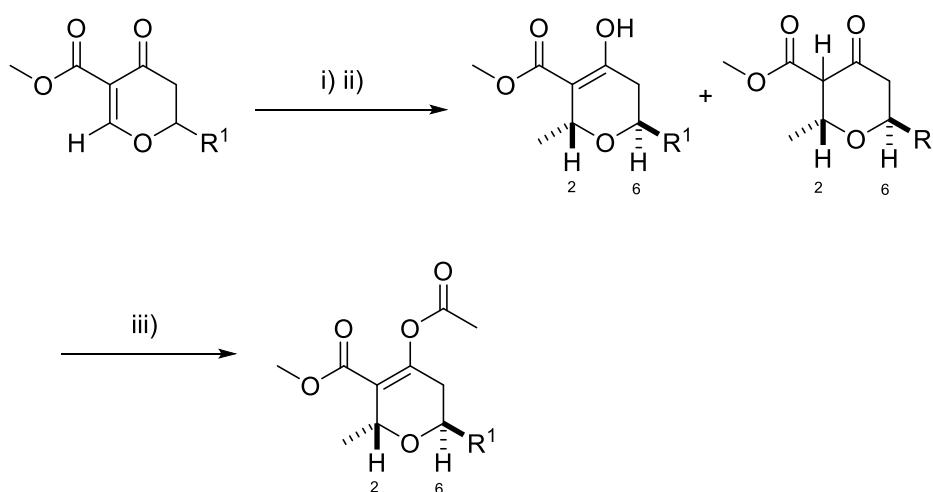
Scheme 86 Reagent & Conditions: i) Me$_2$CuLi, ii) TMSCl, −78 °C, 4.5 hr, THF, iii) Ac$_2$O, pyridine, DMAP, 40 °C, 40 min.

It was proposed that Gilman cuprate addition works *via* co-ordination of the enone to a dimeric complex of the cuprate reagent (**A**). A donation/back-donation (d-π*) interaction between the copper and the alkene can then form a cupriocyclopropane (**B**), where it subsequently rearranges to form the open-chain Cu^{III} intermediate **C**. Reductive elimination of **C** gives the enolate (silyl enol ether) product of 1,4-addition (**D**) (Figure 27).[97] It is believed that TMSCl promotes the 1,4-addition by participating in the enone-cuprate complex and also can act as a Lewis base, with the Cl donating electron density to the Li$^+$, where it can also have an effect on make the Si more Lewis acidic.[98-100]
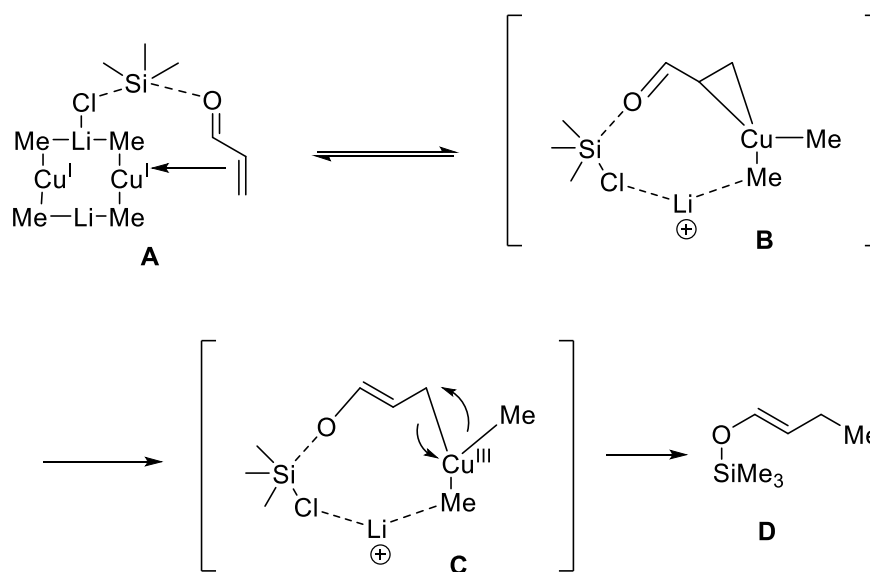
Figure 27 Mechanism for Gilman cuprate addition to enones

The 2,6-*trans* THP ring formed by conjugate addition is believed to be favoured due to pseudo-axial attack of Me$_2$CuLi at C2 of the DHP when it is in a conformation that puts the C6 substituent in a pseudo-equatorial position (Figure 28). In order to interact with the π^*-orbital of C2, the Me$_2$CuLi must approach the DHP ring from a below direction to the double bond of C2-C3 position. First, if the Me$_2$CuLi were to approach from the bottom face it would form the chair-like intermediate **A** which has the methyl in a pseudo-axial position. On the other hand, if the Me$_2$CuLi (nucleophile) were to approach from the top face it would form the twist-boat-like intermediate **B** that could ring flip to put the methyl in a pseudo-equatorial position. As the twist-boat intermediate would be higher in energy, it should be disfavoured, so pseudo-axial Me$_2$CuLi (nucleophile) attack through intermediate **A** is favoured. Pseudo-axial quenching of enolate **A** at C3 position would be more favourable to give an all-equatorially substituted THP.[101, 102]
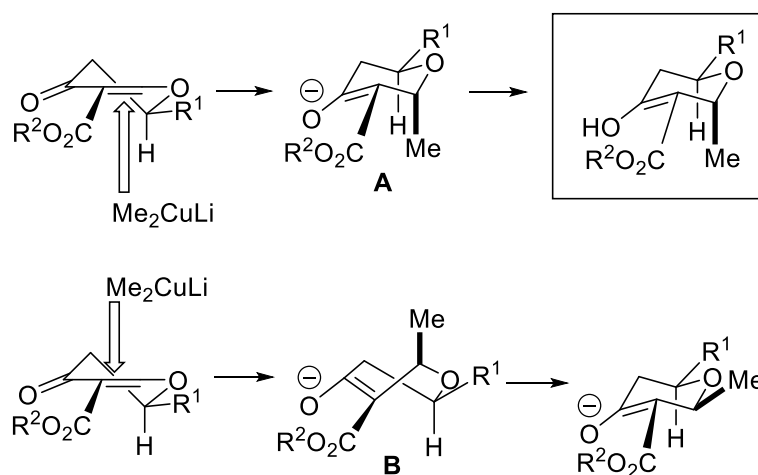
Figure 28 Me$_2$CuLi (nucleophile) attack on a DHP

Entry	Starting material	R^1	Product	Yield^a (%)
a	262	^{i}Pr	271	77
b	263	Pr	272	64
c	264	Phenyl	273	74
d	259	2-furyl	274	82
e	265	CH$_2$-OTIPS	275	81
f	268	CH=CHCH$_3$	276	56

^{a}Isolated yield after column chromatography.

Table 10 Synthesis of DHP with Me$_2$CuLi conjugate addition.

Having successfully installed a methyl group at the C2 position by Gilman cuprate addition, we investigated different substituents at C6 position, giving tautomeric mixtures. These were acetylated to simplify isolation and characterisation. The formation of 2, 6- *trans* THPs were produced in moderate yield 56-82% (Table 10, entries **a-f**).

Figure 29

H-5ax - H-6 = 9.7 Hz
H-5eq - H-6 = 4.1 Hz
H-2 - CH3 = 6.6 Hz

nOe 2.3%
H-6 and Me-2
nOe 1.86%
H-5eq and Me-2
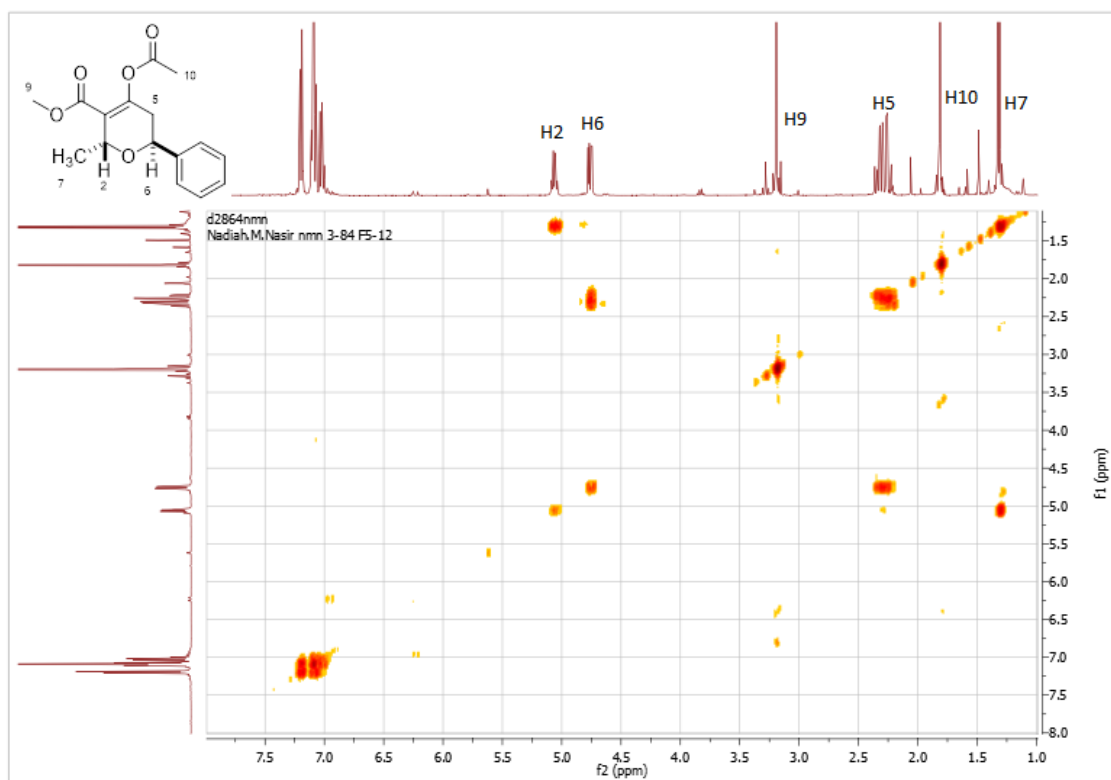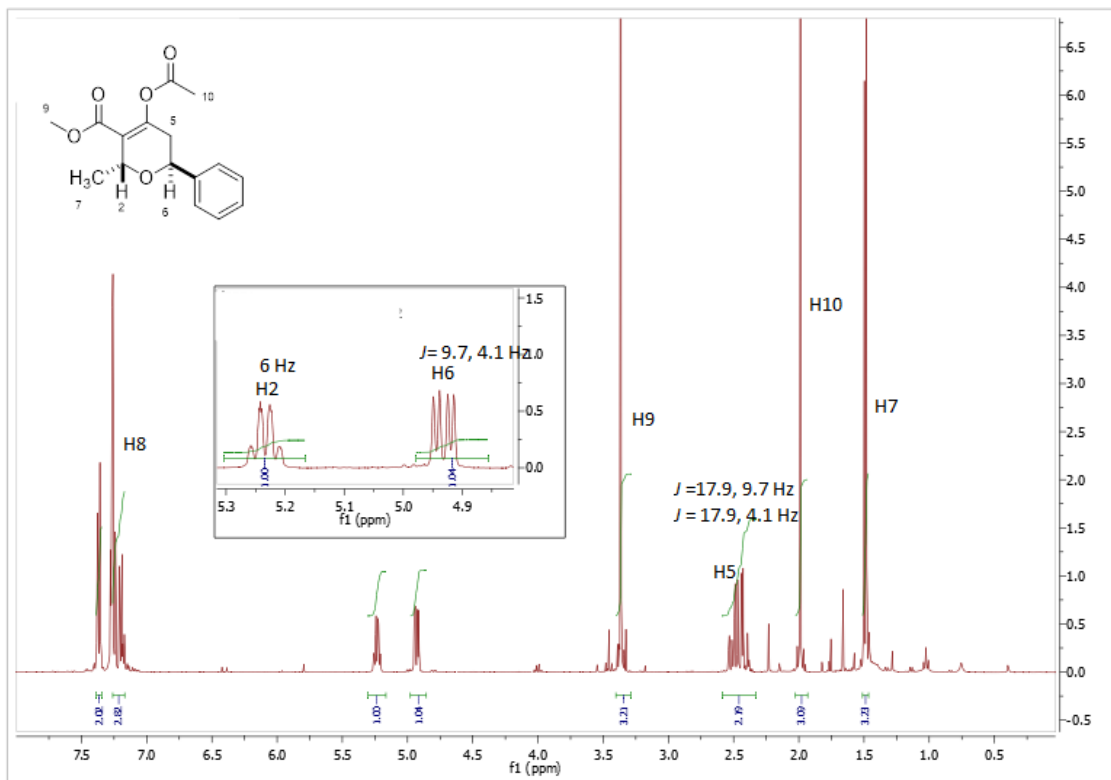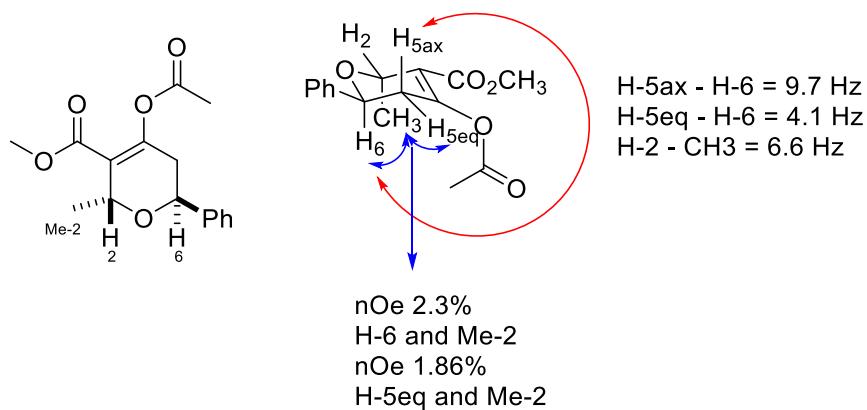
Figure 30 ^{1}H-^{1}H COSY NMR Correlation of 2,6-*trans* THP **273**

NOE Correlation of 2,6-*trans* THP **273**

For compound **273**, the ^{1}H NMR spectrum, it showed no enol peak at around 11.00-12.00 ppm that integrated for 1H as OH, but instead here appeared a singlet at 1.92 ppm which integrated as 3H implying acylation. In ^{1}H-^{1}H COSY spectrum (Figure 29), at 5.13 ppm appeared as quartet with integrated as 1H and assigned as H-2 has *J*-value of 6.6 Hz showed coupled with methyl at position C-2 at 1.39 ppm, where it was appeared as doublet and integrated as 3H.

The H-5ax at 2.40 ppm has *J*-value of 9.7 Hz showed *trans*-diaxial coupling with the double of doublets at 4.83 ppm, which was integrated as 1H and assigned as H-6. Then H-5eq at 2.31 ppm has *J*-value of 4.1 Hz and showed coupled with H-6 (Figure 30). From the *J*-value of H-5ax-H-6, showed H-6 at axial position and gave the desired 2,6- *trans* THP ring stereochemistry.

Based on NOE spectrum (Figure 30), a positive correlation of 2.3% between H-6 and Me-2 and a NOE correlation between H-5eq and Me-2 of 1.86%, confirming the

stereochemistry which is 2,6-*cis* relationship that we would expect to see after axial attack of the organocuprate onto the DHP, supporting the assignment as a 2,6-*trans* DHP.

Phenyl cuprate was added in a similar fashion and it gave good yields of the DHPs, but interestingly we could only see the enol tautomer of the conjugate addition product. It is believed that the enol tautomer is preferred due to minimisation of the unfavourable interation of having an axial phenyl substituent (Scheme 87).[103]
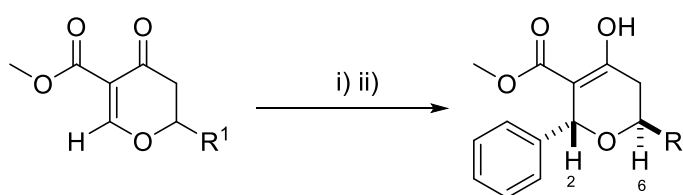
Scheme 87 Reagent & Conditions: i) Ph$_2$CuLi, ii) TMSCl, −78 ^{o}C, 30 min then 0 ^{o}C, 1.5 hr, THF.

Entry	Starting material	R^1	Product	Yield^a (%)
a	262	^{i}Pr	277	73
b	263	Pr	278	56
c	264	Phenyl	279	70
d	265	CH$_2$OTIPS	280	48
e	268	CH=CHCH$_3$	281	64
f	269	CH=CHPh	282	91

^{a}Isolated yield after column chromatography.

Table 11 Synthesis of DHP with Ph$_2$CuLi conjugate addition.

Having successfully installed a phenyl at the C-2 position by Gilman cuprate addition, we continue to investigate different substituents at C-6 position and as expected gave enol products more formed. The formation of 2,6-*trans* THPs were produced in moderate yield 56-91% (Table 11, entries **a-f**).
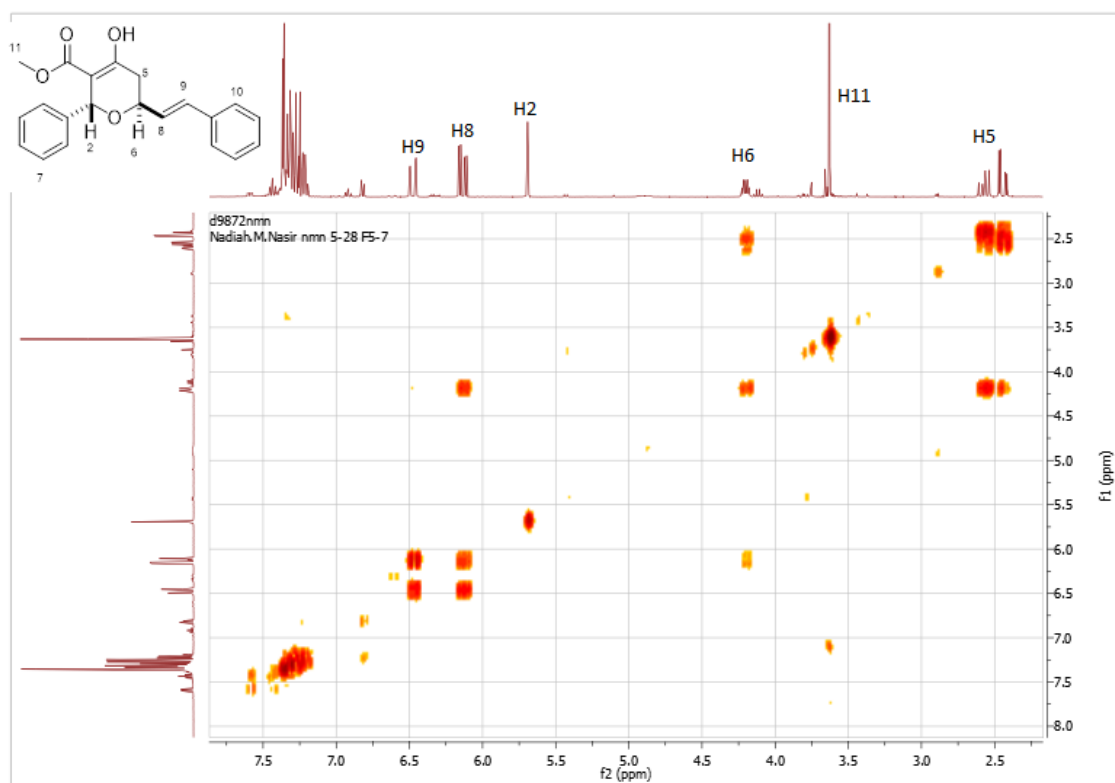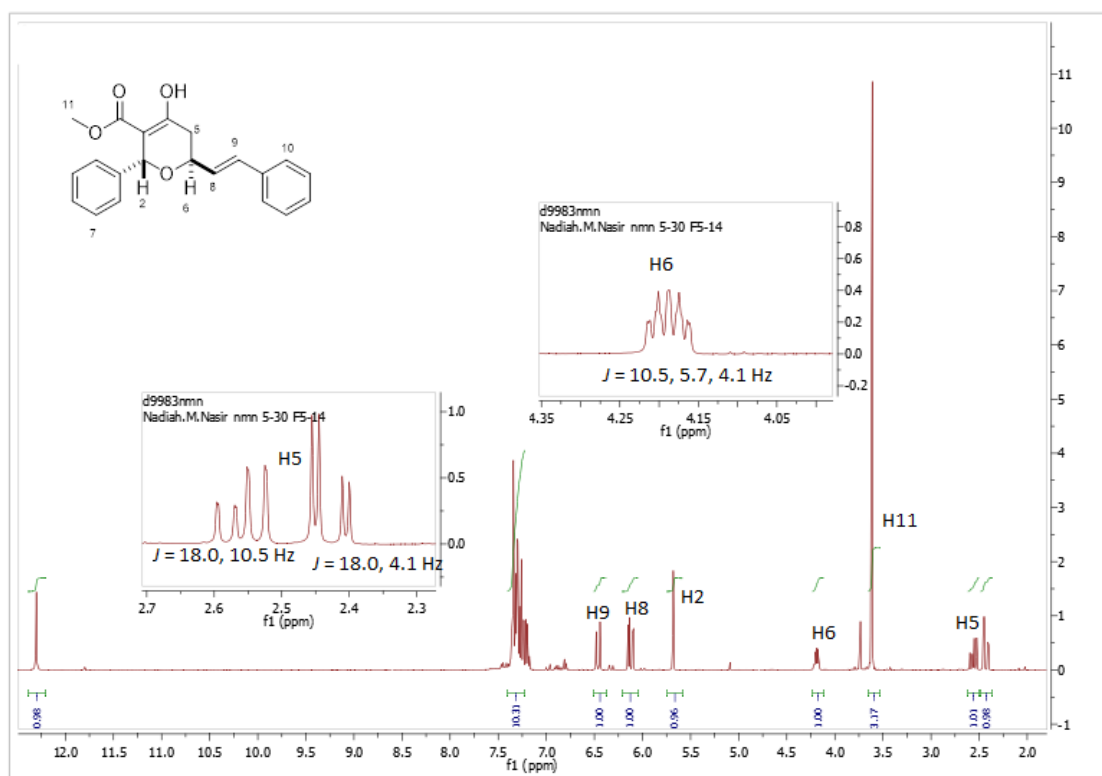
Figure 31
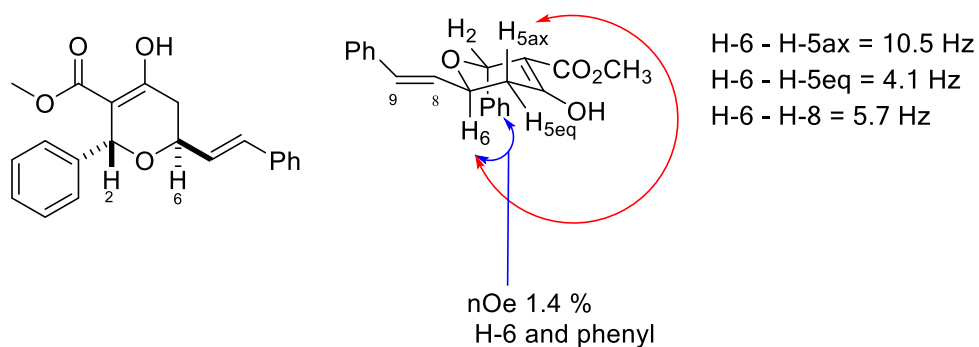
Figure 32 ^{1}H-^{1}H COSY NMR Correlation of 2,6-*trans* THP **282**

NOE Correlation of 2,6-*trans* THP **282**

The ^{1}H NMR spectrum of **282**, showed the enol with singlet at 12.3 ppm. A doublet of doublets at 6.15 ppm was assigned as H-8 and integrated as 1H with a *trans* alkene coupling of 16.1 Hz to H-9, supported by a correlation in the ^{1}H-^{1}H COSY spectrum. Proton H-8 also showed a 5.7 Hz coupling with a proton at 4.24 ppm which was assigned as H-6.

Upon further inspection, the double double doublet was assigned as H-6 and it showed matching coupling with H-8. The H-6 also has a *J*-value of 4.1 Hz and showed coupling to the H-5eq and as predicted has *trans*-diaxial relationship with H-5ax with *J*-value of 10.5 Hz. This confirmed the stereochemistry as the 2,6-*trans* THP that we desired (Figure 32).

NOE spectroscopy showed the H-6 at 4.24 ppm had a positive correlation of 1.4% between H-6 and phenyl, H-6 and H-9 of 1.35%, H-6 and H-8 1.12% and interestingly a small positive correlation between H-6 and H-2 with 0.27%. It showed this compound is 2,6-*trans* relationship between the C-2 proton and C-6 proton (Figure 32).

95

In exploring the range of Gilman cuprates used, we tried using longer chain alkyl lithium reagent. nBuLi was chosen, which also gave good yields of the 1, 4-conjugate addition products, but again a mixture of tautomers was formed. The mixture of tautomers were acylated and single enol acetate products were formed in good yields (Scheme 88).[104]
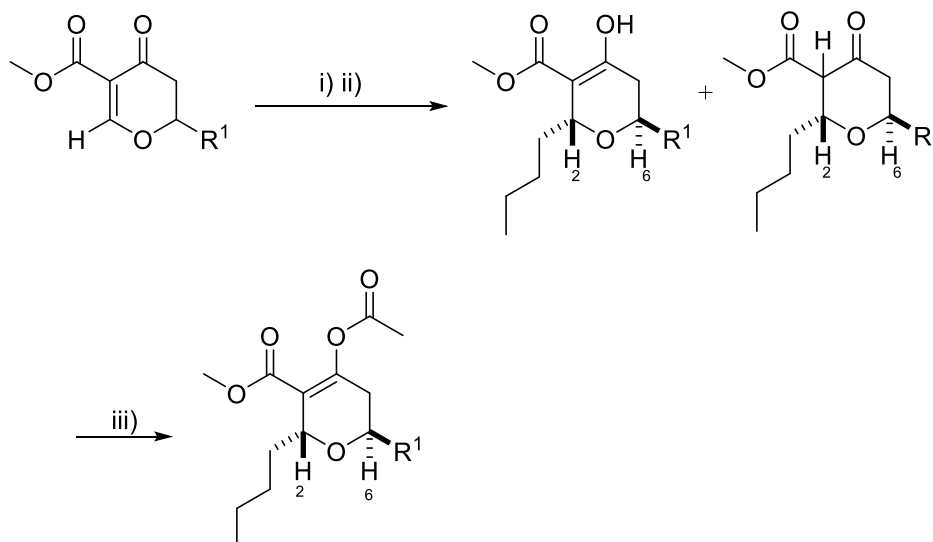
Scheme 88 Reagent & Conditions: i) nBu$_2$CuLi, ii) TMSCl, -78 °C, 4 hr, THF, iii) Ac$_2$O, pyridine, DMAP, 40 °C, 40 min.

Entry	Starting material	R^1	Product	Yield^a (%)
a	262	^{i}Pr	283	79
b	265	CH$_2$OTIPS	284	70
c	263	Pr	285	62
d	264	Phenyl	286	48

^{a}Isolated yield after column chromatography.

Table 12 Synthesis of DHP with nBu$_2$CuLi conjugate addition.

The successfully installed n-butyl group at the C2 position by Gilman cuprate addition, we investigated different substituents at C6 position, giving tautomeric mixtures. These were acetylated to simplify isolation and characterisation. The formation of 2,6- *trans* THPs were produced in moderate yield 48-79% (Table 12, entries **a-d**).
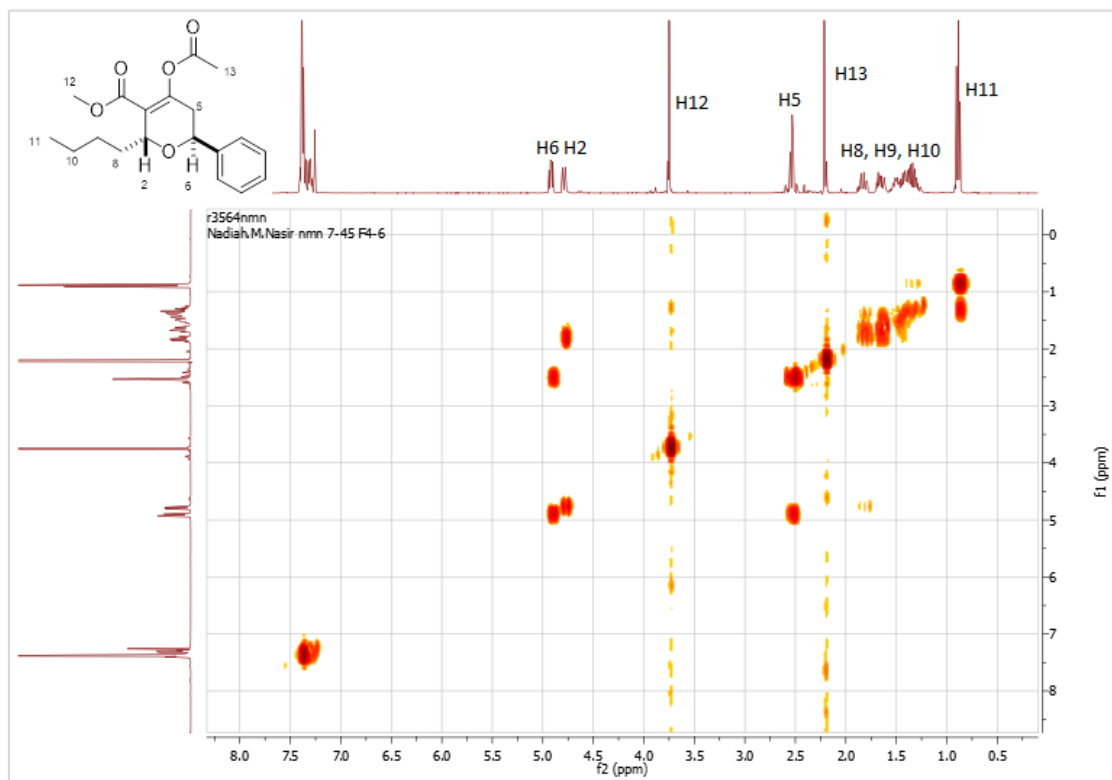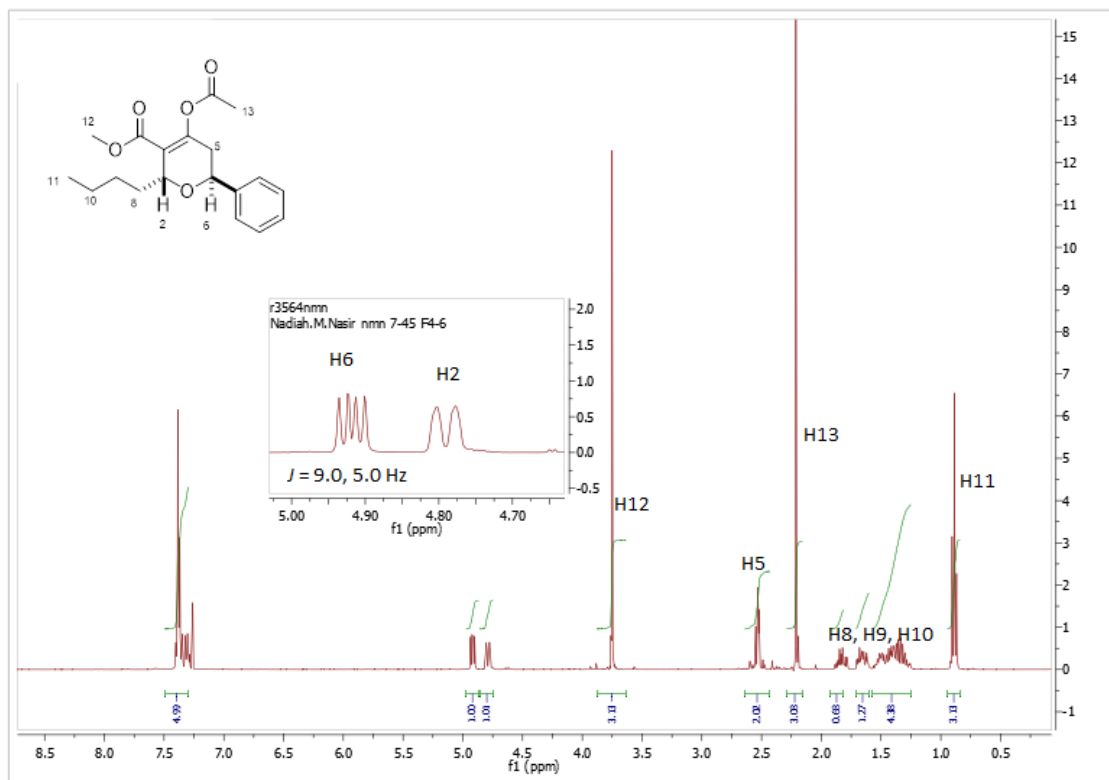
Figure 33
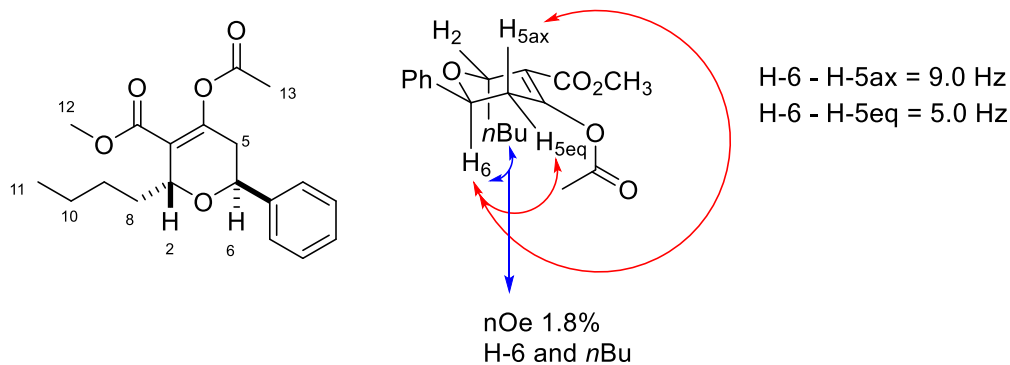
Figure 34 ^{1}H-^{1}H COSY NMR Correlation of 2,6-*trans* THP **286**

NOE Correlation of 2,6-*trans* THP **286**

Similar to the reaction of Me$_2$CuLi, the major product in the mixture was the enol tautomer, and the mixture was acylated. From the **286** ^{1}H NMR spectrum showed there are no enol peak appeared around 11-12 ppm. The peak at 1.87 ppm integrated as 3H showed that acylated was form and assigned as H-13. From the ^{1}H-^{1}H COSY spectrum (Figure 33), the doublet of doublets was assigned as H-6 with integrated as 1H has *J*-value of 9.0 Hz showed *trans*-diaxial coupling with H-5ax. The H-6 also has *J*-value of 5.0 Hz showed coupled with H-5eq. From the *J*-value in this spectrum, it showed the stereochemistry of 2,6-*trans* THP ring that we expected as in Me$_2$CuLi.

Based on NOE spectrum (Figure 34), a positive correlation of 1.8% between H-6 and *n*Butyl group, confirming a 2,6-*cis* relationship was observed between the butyl substituent C-2 and the C-6 proton, showing that the cuprate reagent had caused addition from a pseudo-axial trajectory as previously seen with methyl lithium addition.

2.14   Synthesis of Diospongin B.

The development of a synthesis of 2,6-*trans* THP ring was achieved by using conjugate addition. This encouraged us to apply this method towards the synthesis of the *trans*-THP ring of a natural product. Diospongin B **4** was choosen as the diospongin B has *trans*-THP ring as in basic skeleton. Diospongins B **4**, isolated from the rhizomes of *Dioscorea spongiosa* by S. Kadota and co-workers in 2004, comprises a novel class of cyclic 1,7-diarylheptanoid natural product (Figure 35).[6] This compound contains a trisubstituted tetrahydropyran core with different stereochemistry at the C2, C4 and C6 position. Diospongin B **4** exhibits a potent inhibitory activity on bone desorption induced by parathyroid hormone in a bone organ culture system, and is regarded as a promising lead compound for the development of antiosteoporotic drugs.[106]
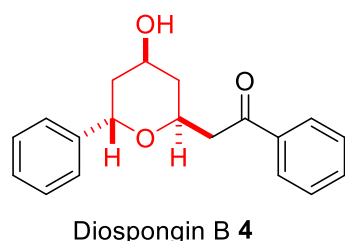
Diospongin B **4**

Figure 35 Rhizomes of *Dioscorea spongiosa*

A number of total syntheses of diospongin B **4** have been reported. The Tong group, used *trans*-2-aryl-6-alkyl THP **288** as a precursor for formation of diospongin B **4**. Reductive γ-deoxygen-pyranone **287** and Heck-Matsuda coupling proceeded smoothly to deliver the desired *trans*-2-aryl-6-alkyl THP **288**. The rhodium-catalyzed 1, 4-hydrosilylation of the enone **288** and Rubottom oxidation provided the hydroxyl ketone **289**. The deoxygenation of the carbonyl group of **289** *via* tosylhydrazone produced **290**, where PMB protection, desilylation and DMP oxidation gave the aldehyde **291**. Then with phenyl Grignard addition to **291**, DMP oxidation and DDQ deprotection of PMB group produced the total

synthesis of diospongin B **4** (Scheme 89).[106, 107] Meanwhile, the Chandrasekhar group used a base catalysed conjugate addition of an α, β-unsaturated ester and an intramolecular oxy-Michael reaction as the key steps in synthesis of Diospongin B **4**.[108]
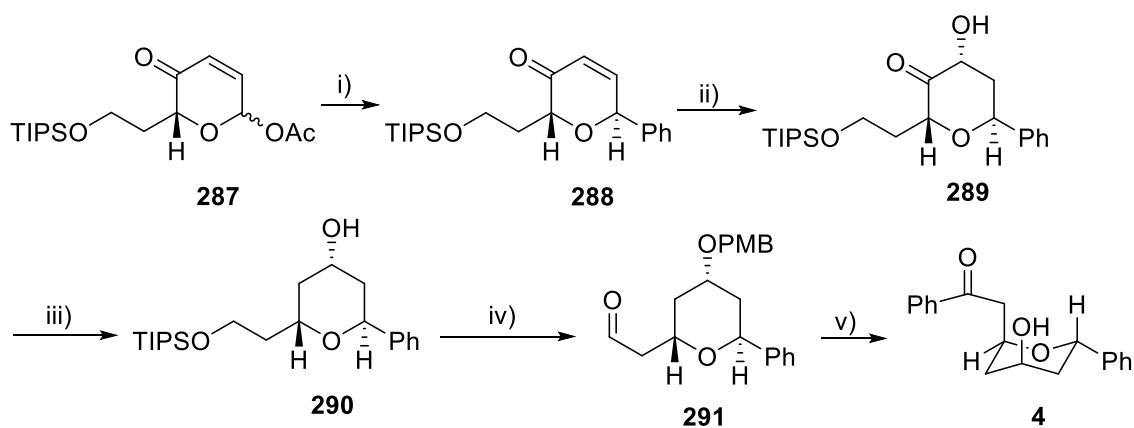
Scheme 89 Reagent & Conditions: i) Zn/AcOH, then PhN_2BF_4, Pd(0), 72% ii)$Rh_2(OAc)_4$, Et_3SiH, then *m*-CPBA, 65%, iii) $TsNHNH_2$ then $NaBH_3CN$, 68%, iv) PMBCl, TBAF, DMP, 52%, v) PhMgBr, DMP, DDQ, 62%.

The Sabitha's group synthesis of diospongin A and B, involved stereoselective reduction of a *β*-keto ester, Horner-Wadsworth-Emmons olefination and intramolecular oxy-Michael reactions. The ester **292** was cyclised by treatment with TsOH to produce *δ*-lactone **293** as an intermediate. *δ*-lactone **293** was reduced by DIBAL-H together with **294** and $Ba(OH)_2 \cdot 8H_2O$ as a base to gave diastereomer mixture of 2,6-*cis/trans* THP **295** and **4** (Scheme 90)[109]. In the Jennings group, they also used *δ*-lactone **293** as intermediate to synthesis diospongin A and B.[110]
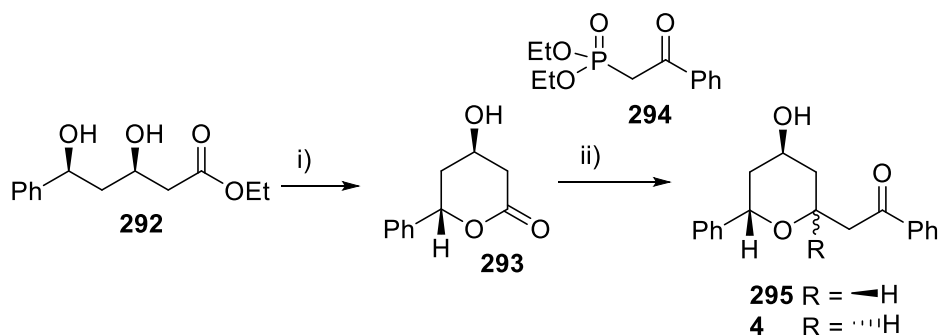
Scheme 90 Reagent & Conditions: i) TsOH, CH₂Cl₂, −78 °C, 30 min, 68%, ii) DIBAL-H, CH₂Cl₂, −78 °C, 30 min, **294**, Ba(OH)₂•8H₂O, THF/H₂O, RT, 5h, 81%.

The total synthesis of diospongin B **4** by the Hall group began by epoxidation of **296** with *m*-CPBA and gave **297**. Then the epoxide ring was treated with DIBAL-H and followed with silyl protection of the hydroxyl group using TESCl to give **299**. Mukaiyama-type addition onto the *in situ* generated oxocarbenium favoured the formation of the 2,6-*trans* THP (Scheme 91).[111]
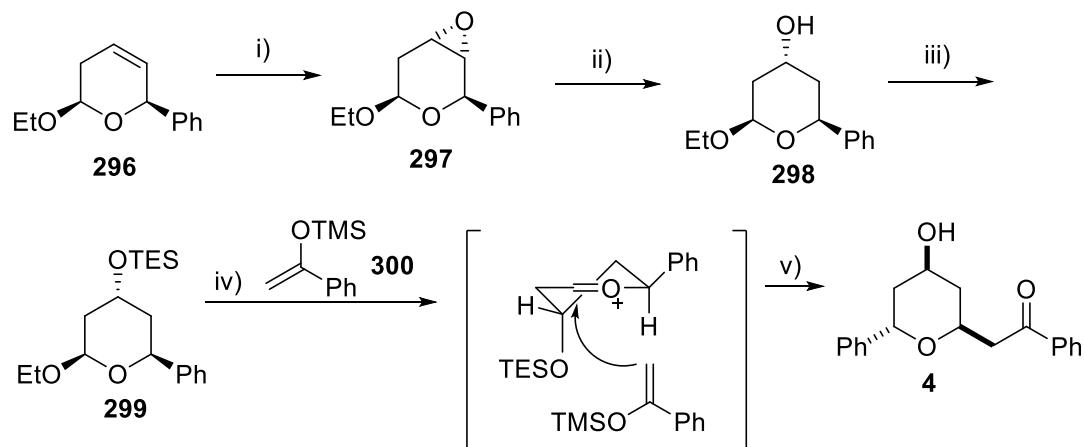
Scheme 91 Reagent & Conditions: i) *m*-CPBA, CHCl₃, 0 °C to RT, 70%, ii) DIBAL-H, THF, 0 °C to RT, 83%, iii) TESCl, 2, 6-lutidine, CH₂Cl₂, 87%, iv) SnCl₄, CH₂Cl₂, 0 °C, v) HF•py, THF, 0 °C, 66%.

In 2010, Hashimoto group, accomplished the total synthesis of diospongin B **4** by the hetero-Diels-Alder (HDA) reaction between benzaldehyde **128** and Danishefsky-type

diene **301** with 1 mol% of [Rh₂(S-BPTPI)₄] and Mukaiyama-Michael reaction on **303** as routes into *trans*-THP **304** in a one-pot sequential (Scheme 92).[105]
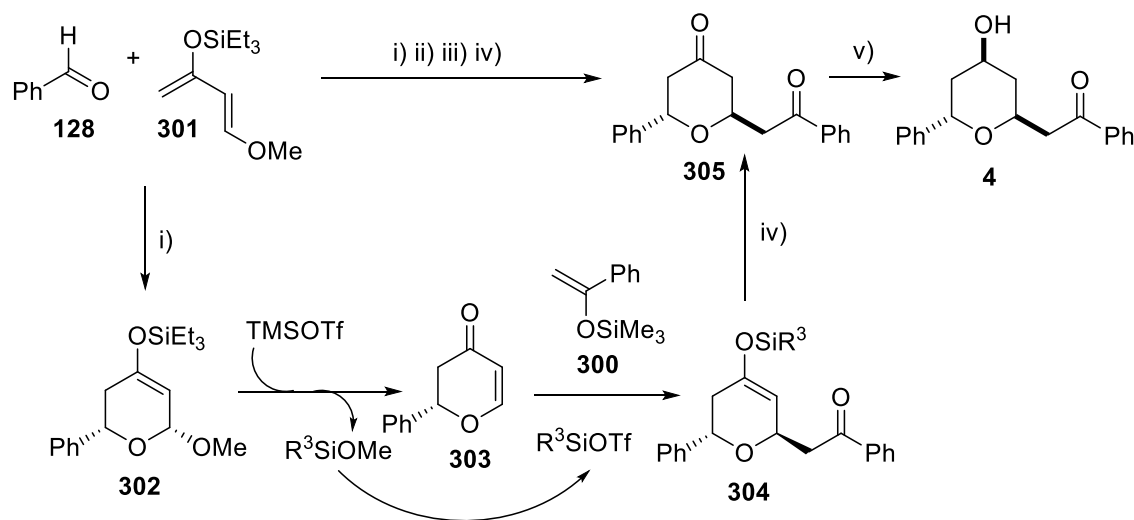
Scheme 92 Reagent & Conditions: i) Rh₂(*S*-BPTPI)₄ (1 mol%), CH₂Cl₂, 23 °C, 15 hr, ii) TMSOTf (10 mol%), −78 °C, 0.5 hr, iii) **300**, 1hr, iv) TFA, −78 °C, 1 hr, 85%, v) K-Selectride®, −78 °C, THF, 86%.

The Uenishi group completed the synthesis of diospongin B **4** by using a palladium mediated 1, 3-chirality transfer strategy. The 1, 3-chirality transfer of the starting allylic alcohol to the tetrahydropyran ring is perfectly controlled in a stereospecific *syn*-S_N2' type Pd^II-promoted 6-exo-trig cyclization. Wacker oxidation on the β-(tetrahydro-2*H*-pyran-2-yl)styrenes gives the ketone **310** (Scheme 93).[110] Interestingly, when **307** was subjected to Wacker oxidation conditions, surprisingly it gave **308** in 82%, instead of desired product of ketone. They assumed an intramolecular Wacker oxidation took place instead of intermolecular Wacker oxidation, where the nucleophilic attack of the hydroxyl group located at the *cis* position with the styryl group occurred on the Pd π-complex of **307**. The hydroxyl group was protected as the MOM-ether to undergo Wacker oxidation.[113]
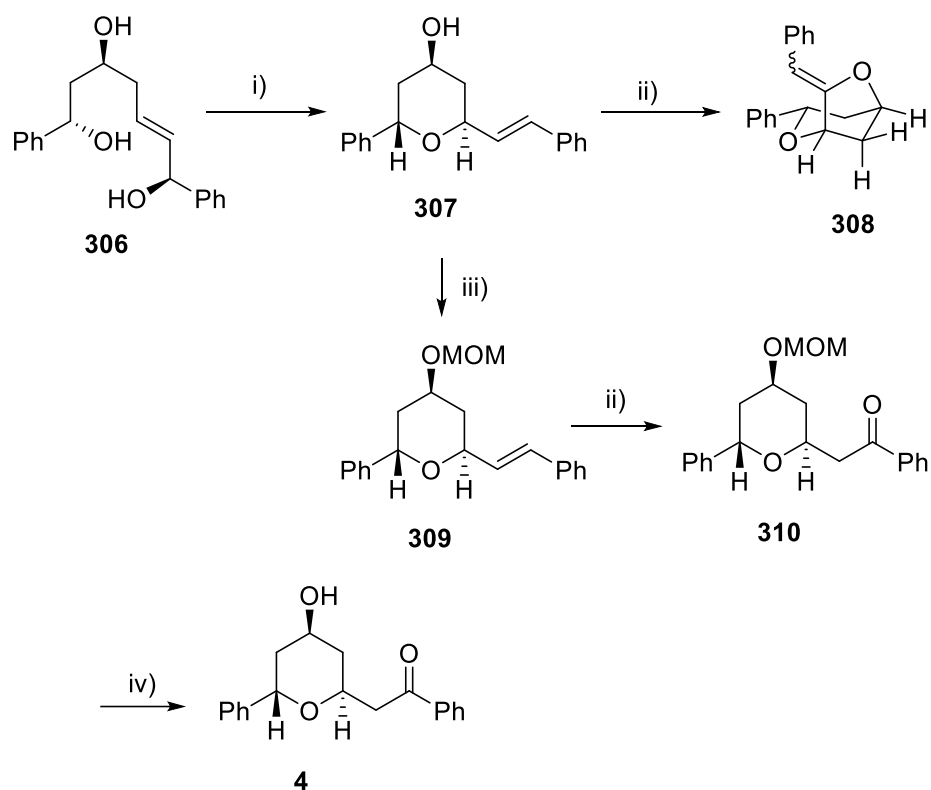
Scheme 93 Reagent & Conditions: i) PdCl$_2$(CH$_3$CN)$_2$ (10 mol%), THF, 0 °C, 20 min, 86%, ii) PdCl$_2$ (50 mol%), CuCl, O$_2$, DMF + H$_2$O, 50 °C, 55%, iii) MOMCl, ^{i}Pr$_2$NEt, NaI, THF, 55 °C, 10 hr, 86%, iv) HCl aq/ THF, RT, overnight, 91%.

Interestingly, when Chuzel and Bressy's group[114] synthesized (-)-diospongin A **312**, which contains the 2,6-*cis* THP ring, they used modified conditions described by Grubbs[115] for the Wacker oxidation reaction. Interestingly, in their synthesis of diospongin A **312** they achieve the total synthesis without the requirement of a single protecting group (Scheme 94).[113]
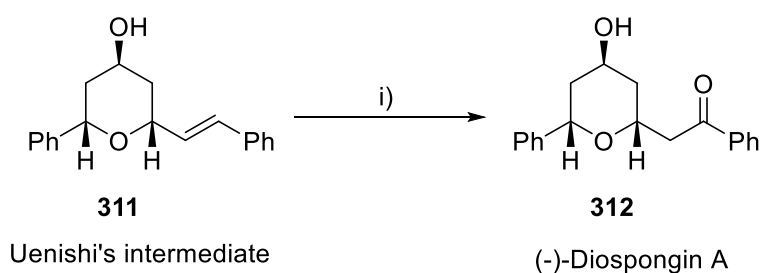
Scheme 94 Reagent & Conditions: i) Pd(OAc)$_2$ (5 mol%), HBF$_4$, BQ, DMA/MeCN/H$_2$O, RT, 46%.
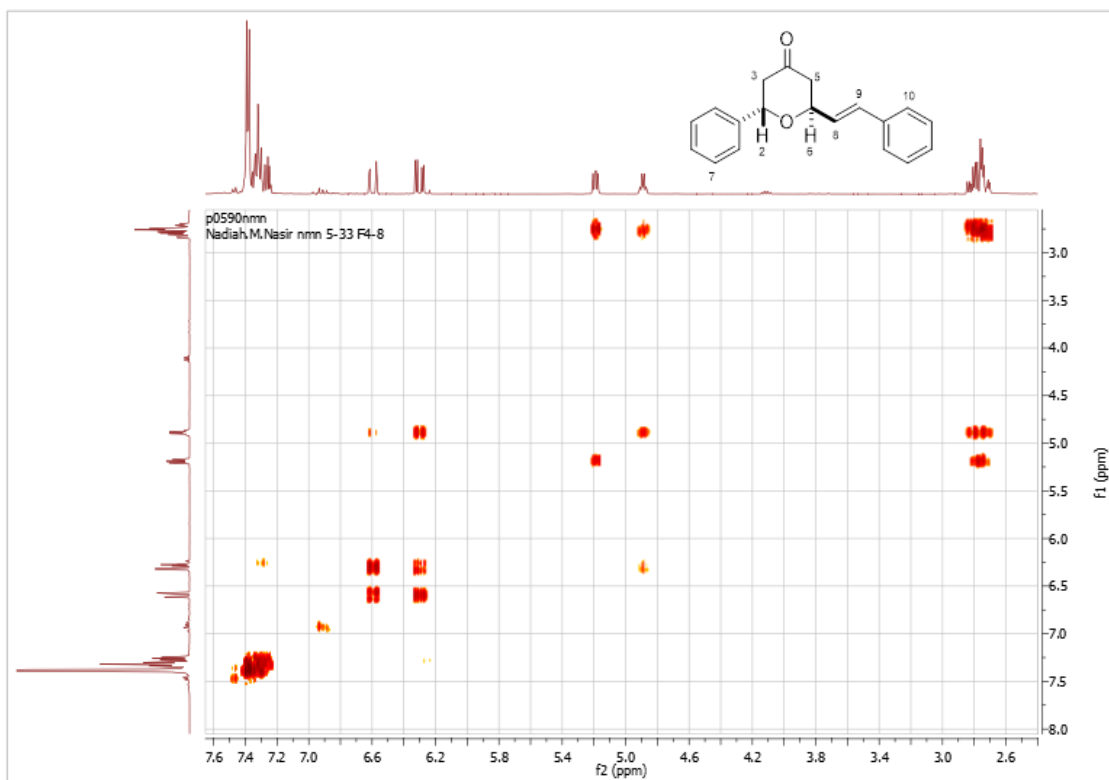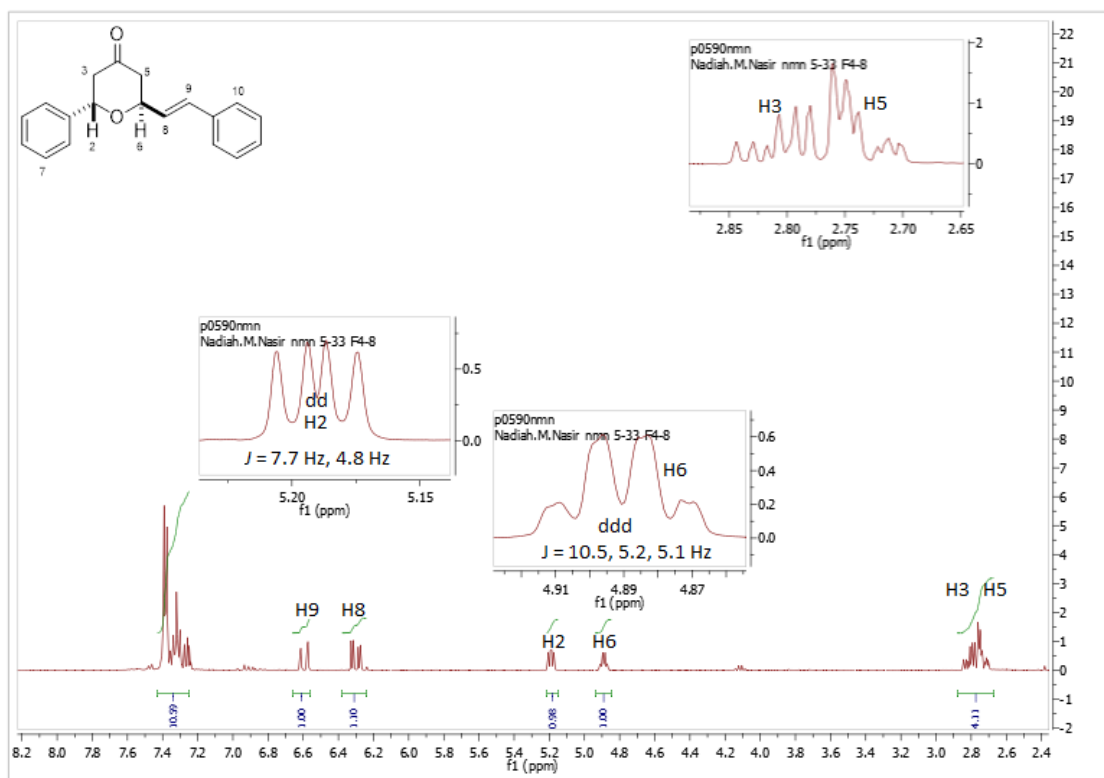
Figure 36

2.15　Toward the synthesis of Diospongin B.

Following the successful investigation towards the functionalization of 2,6-*trans* THPs using the Gilman cuprates, we decided to synthesise diospongin B **4**. The next step is decarboxylation of the ester on the THP **282** by using a microwave based method (Scheme 95). The decarboxylation reaction reaction required only 10 minutes and produced one single spot on thin layer chromatography **313**.
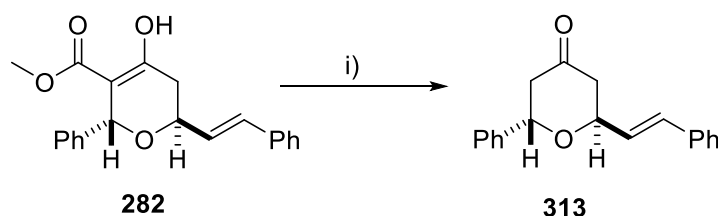
Scheme 95 Reagent & Conditions: i) DMF/H_2O, 200 Watt, µWave, 160 °C, 10 min, 91%.

H-6 - H-5ax = 10.5 Hz
H-6 - H-5eq = 5.2 Hz
H-2 - H-3ax = 7.7 Hz
H-2 - H-3eq = 4.8 Hz
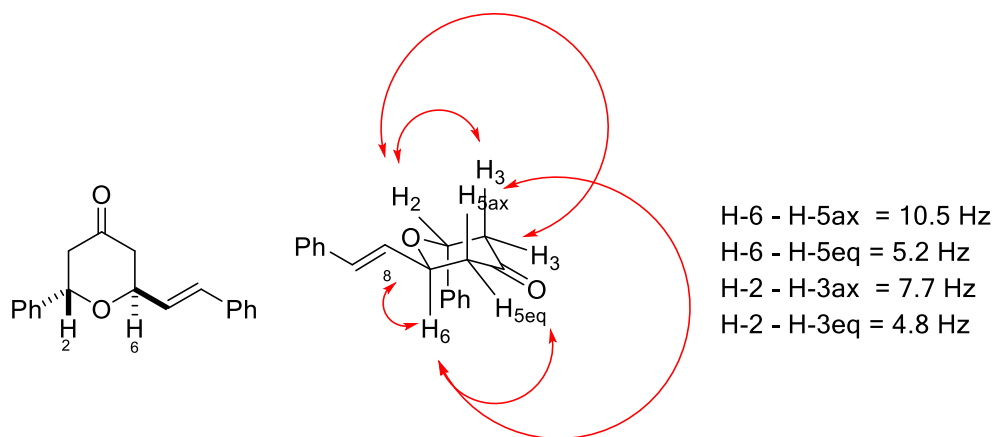
Figure 37 ^{1}H-^{1}H COSY NMR Correlation of 2,6-*trans* THP **313**

From the ^{1}H NMR spectrum of **313** (Figure 36), no methoxy (OMe) peak at 3.6 – 3.7 ppm was observed. The ^{1}H NMR spectrum showed doublet of doublet at 5.12 ppm with integrated as 1H and assigned as H-2 was coupled with H-3ax and H-3eq with *J*-value of

7.7 and 4.8 Hz indicating its equatorial position. The H-6 at 4.82 ppm has *trans*-diaxial coupling to H-5ax with *J*-value of 10.5 Hz and H-6 coupled to H-5eq with *J*-value of 5.2 Hz, indicating its axial position. From this spectrum, it showed compound **282** underwent successful decarboxylation reaction to yield **313** (Figure 37).

The next step for construction of diospongin B **4** was the reduction of the ketone with sodium borohydride. Unfortunately, this did not give the desired stereochemistry at the C-4 alcohol required for diospongin B. When **313** was treated with NaBH$_4$, a mixture of 55: 45 diastereomer ratio occurred. When L-Selectride® was used, pleasantly, it did give secondary alcohol THP **307** as the major diastereomer (9: 1) with the correct stereochemistry configuration for diospongin B **4** (Scheme 96).
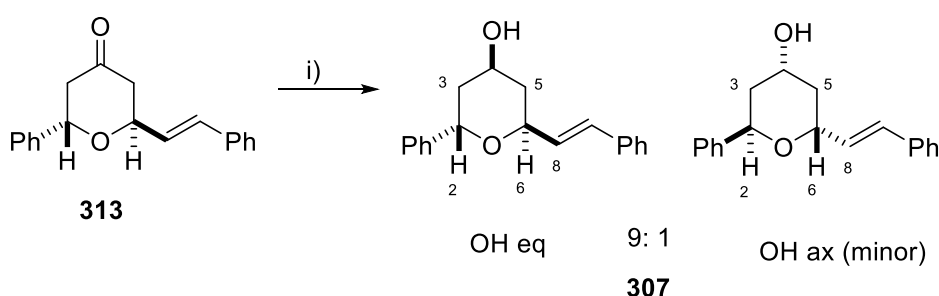
Scheme 96 Reagent & Conditions: i) L-Selectride®, THF, −78 °C, 66%.
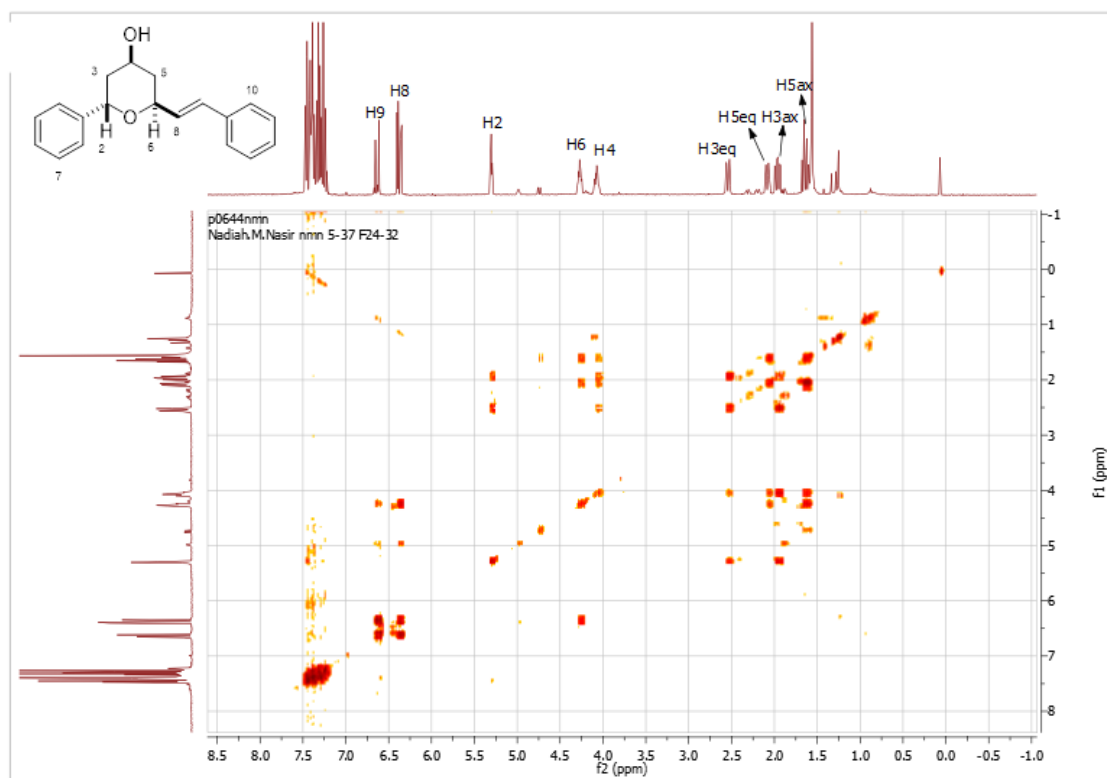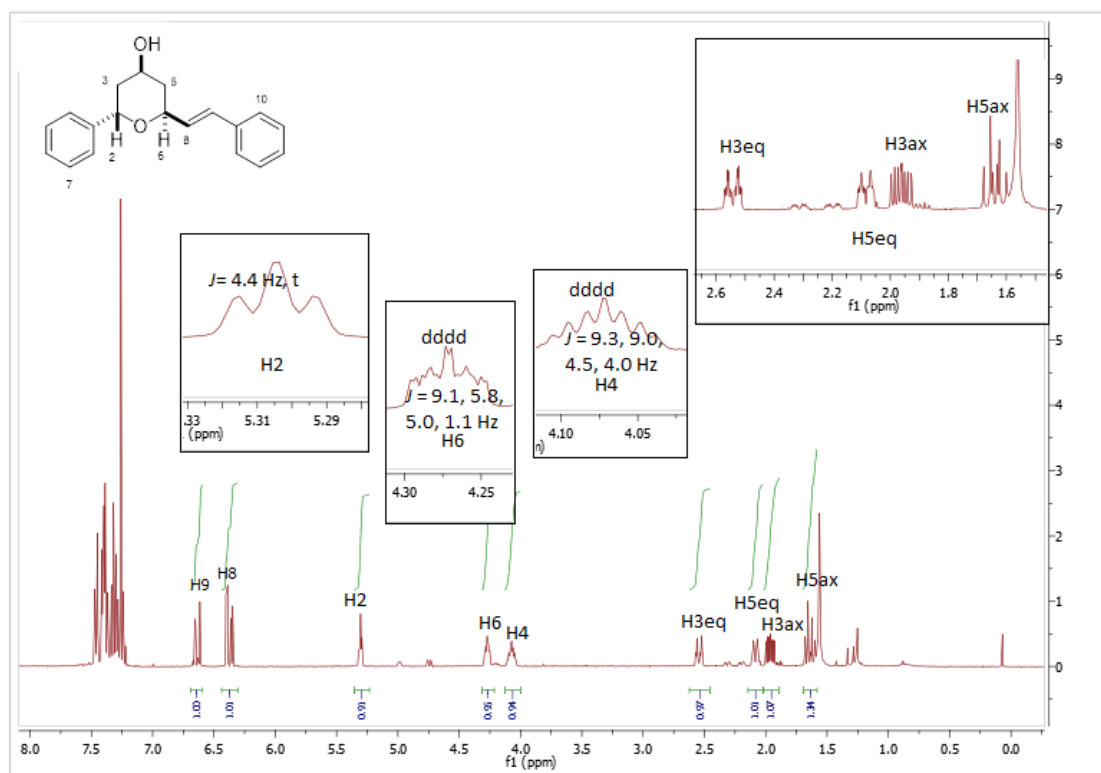
Figure 38
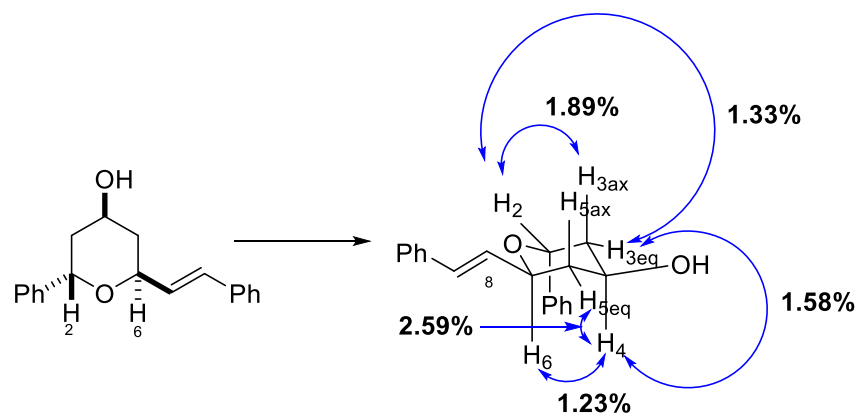
Figure 39 NOE NMR Correlation of 2,6-*trans* THP **307**

The ^{1}H NMR spectrum (Figure 38) of **307** confirmed H-4 proton at 4.07 ppm has *trans*-diaxial relationship to H-5ax with *J*-value of 9.3 Hz, and coupled to H-5eq with *J*-value of 4.5 Hz. The H-4 proton also has *trans*-diaxial coupling with H-3ax with *J*-value of 9.0 Hz and coupled to H-3eq with *J*-value of 4.0 Hz. This was confirmed by NOE correlation, where H-2 only had NOE correlation to H-3eq of 1.33% and to H-3ax of 1.89%, H-4 had NOE correlations to H-6 of 1.23% and to H-3eq of 1.58% and to H-5eq of 2.59% (Figure 39).

Based on Uenishi work,[113] if we proceeded with the Wacker oxidation on **307** without protecting the secondary alcohol group, the intramolecular Wacker oxidation reaction would take place instead of intermolecular Wacker oxidation. They describe a nucleophilic attack of the hydroxyl group located at the *cis* position to the styryl group which occurred on the Pd π-complex of **307** (Scheme 97).

The secondary alcohol group was protected with chloromethyl methyl ether (MOMCl) before undergoing Wacker oxidation. The Wacker oxidation on **309** was very slow and it
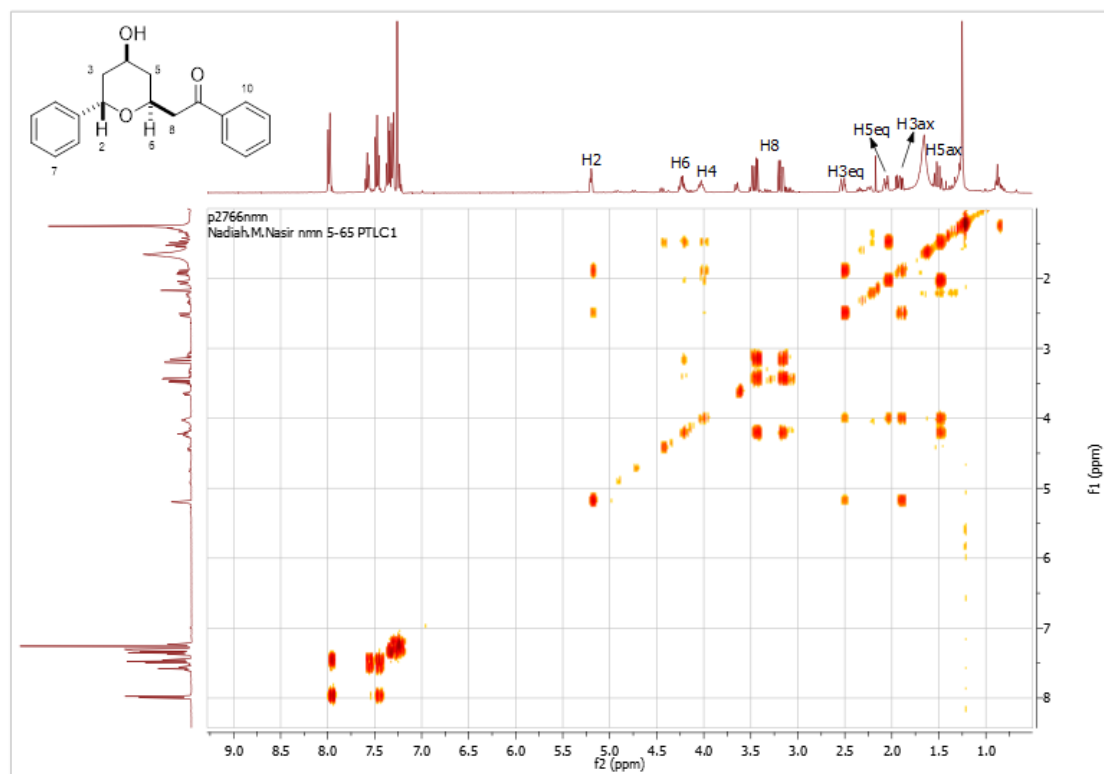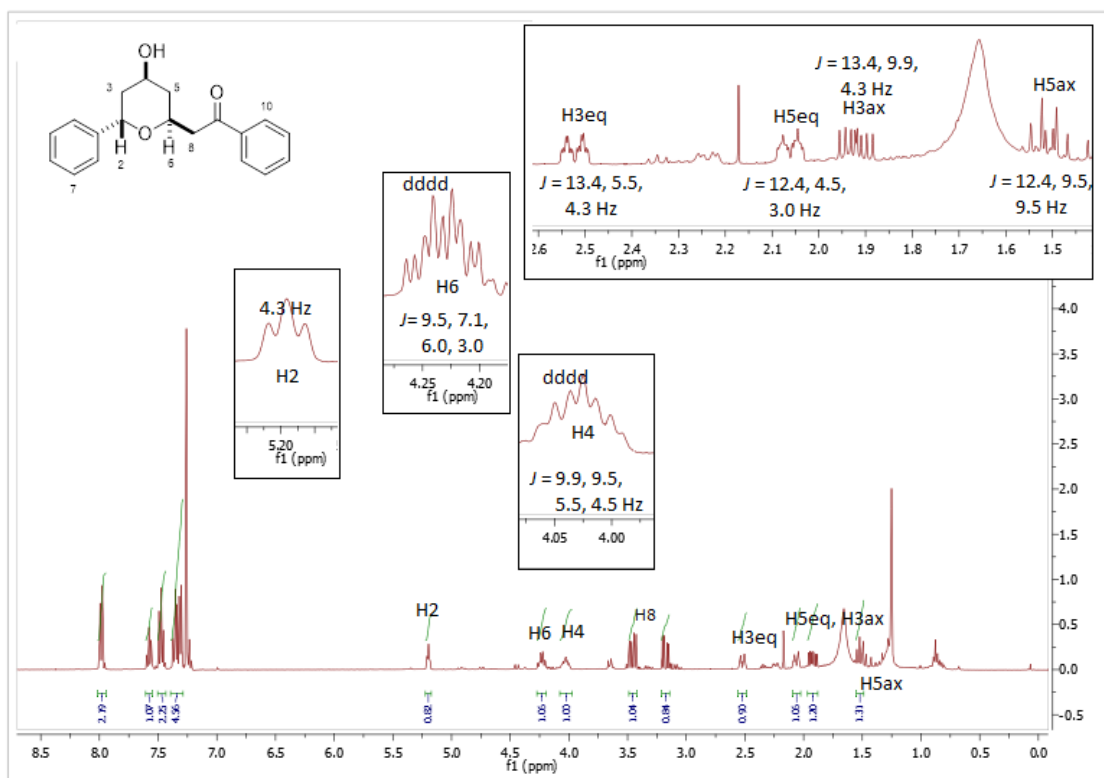
Figure 40

took 4 days and unfortunately the yield was 35%. Compound **309**, underwent Wacker oxidation in 3 days at 50°C. Pleasantly, the yield was 70% , but it is believed longer reaction times at 50 °C result in decomposition of product. Finally, the removed of MOM protected on compound **310** gave 58% yield of diospongin B **4** was produced (Scheme 97).
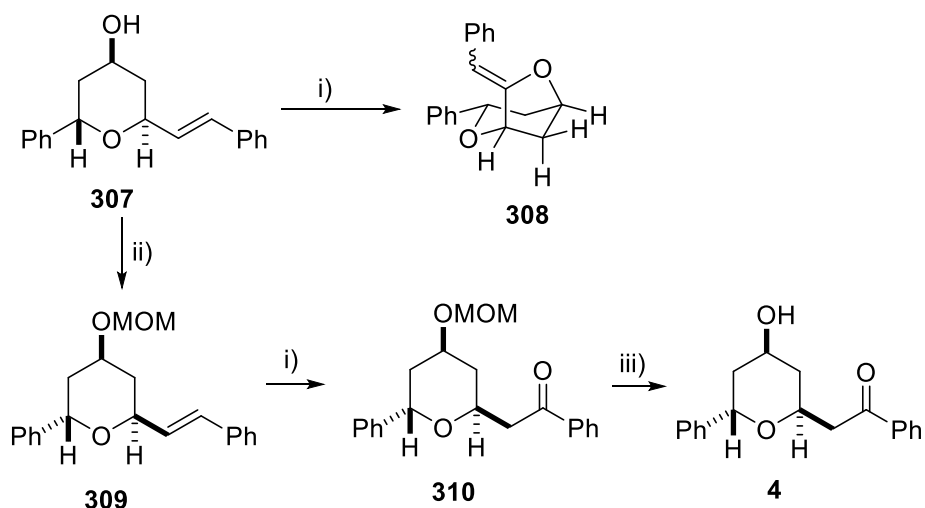
Scheme 97 Reagent & Conditions: i) PdCl$_2$ (50 mol%), CuCl, O$_2$, DMF + H$_2$O, 50 °C, 70% ii) MOMCl, ^{i}Pr$_2$NEt, NaI, THF, 55 °C, 10 hr, 60% iii) HCl aq/ THF, RT, 2 hr, 58%.

H2 - H3$_{eq}$ = 4.3 Hz	H6 - H8 = 7.1 Hz	H4 - H3$_{eq}$ = 5.5 Hz
H2 - H3$_{ax}$ = 4.3 Hz	H6 - H8 = 6.0 Hz	H4 - H3$_{ax}$ = 9.9 Hz
	H6 - H5$_{eq}$ = 3.0 Hz	H4 - H5$_{eq}$ = 4.5 Hz
	H6 - H5$_{ax}$ = 9.5 Hz	H4 - H5$_{ax}$ = 9.5 Hz
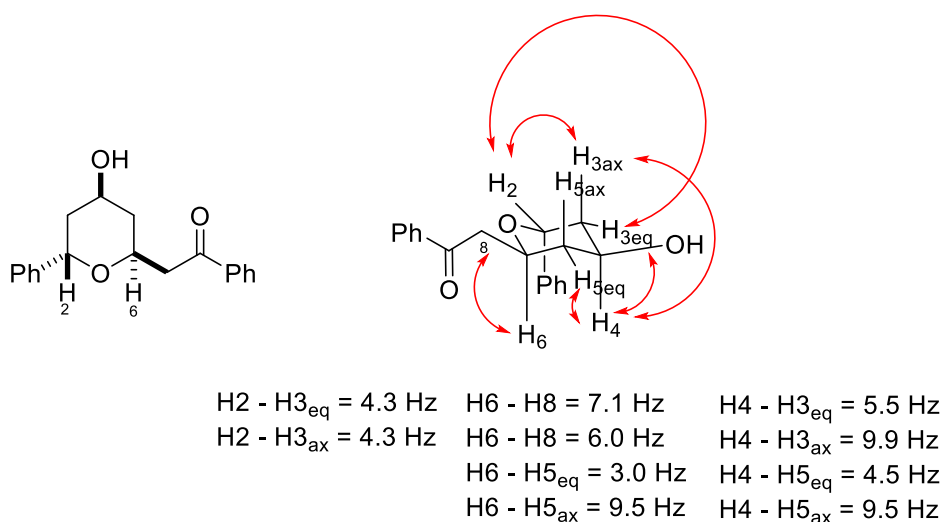
Figure 41 ^{1}H-^{1}H COSY NMR Correlation of diospongin B **4**

The ^{1}H-^{1}H COSY spectrum of diospongin B **4** (Figure 40), shows a double triplet at 1.51 ppm which was integrated as 1H and assigned as H-5ax. This proton shows geminal coupling to H-5eq with a *J*-value of 12.4 Hz. The H-5ax also shows a *trans*-diaxial coupling with H-4 and H-6 both with *J*-value of 9.5 Hz.

The two double double doublets at 2.52 and 1.92 ppm was assigned as H-3eq and H-3ax, showing *trans*-diaxial coupling between H-3ax and H-4 with *J*-value of 9.9 Hz. The H-3ax has a *J*-value of 4.3 Hz and showed coupling to H-2, and a geminal coupling to H-3 with a *J*-value of 13.4 Hz. Two doublet of doublets at 3.46 and 3.18 ppm were assigned as H-8 and showed matching coupling with H-6 with *J*-value of 7.1 and 6.0 Hz and geminal coupling with *J*-value of 15.8 Hz.

There was a double double double doublet at 4.03 ppm which was assigned as H-4 and integrated for 1H, it showed matching coupling with both H-3, H-4 and H-5. Another double double double doublet at 4.23 ppm that integrated for 1H and this was assigned as H-6, it showed matching coupling to the both H-5, and coupled to both H-8.

There was a peak at 5.19 ppm was assigned as H-2 and integrated as 1H, which coupled to both H-3eq and H-3ax. Lastly, the aromatic protons peak in between 7.98 -7.3 ppm that integrated for 10H. It showed the ^{1}H NMR spectrum of diospongin B **4** were identical to those reported in the literature (Figure 41).[113]

2.16 The synthesis of 3,6-disubstituted tetrahydropyran.

With a successful strategy developed for the synthesis of 2,6-*cis* THP rings and 2,6-*trans*-THPs rings, we turned our intention to expand our conversions of DHPs into THPs ring with other substitution patterns.

It was decided to explore the synthesis of 3,6-disubstituted THPs, where the THP can be formed by the conjugate reduction of the C2-C3 double bond. When DHPs were treated with L-Selectride® at −78 °C and quenched, the enol tautomer was formed as a major product and also a minor keto-tautomer was formed. Again, in order to characterize the product mixture, it was converted into the enol acetate by treatment with Ac$_2$O, pyridine and DMAP (Scheme 98).
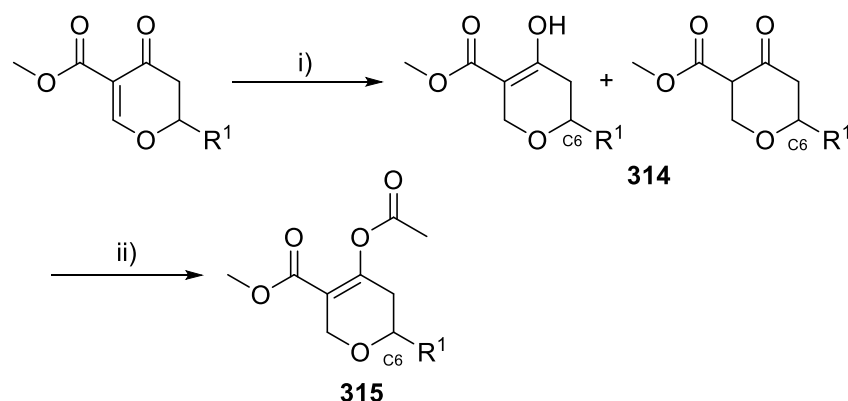
Scheme 98 Reagent & Conditions: i) L-Selectride®, THF, −78 °C, ii) Ac$_2$O, pyridine, DMAP, 45 °C.

Entry	Starting material	R^1	Yield (%) 314	Ratio^{a,b} enol: keto	Yield (%) 315	Product
a	259	2-Furyl	44	1: 0.4	58	316
b	264	Phenyl	74	1: 0.2	68	317
c	263	Pr	89	1: 0.2	51	318
d	265	CH2-OTIPS	65	1: 0.2	65	319
e	269	CH=CHPh	51	1: 0.4	56	320

^{a}After flash column chromatography. ^{b}Determined by integration of the ^{1}H NMR.

Table 13 Synthesis of 3,6-disubstituted THPs.
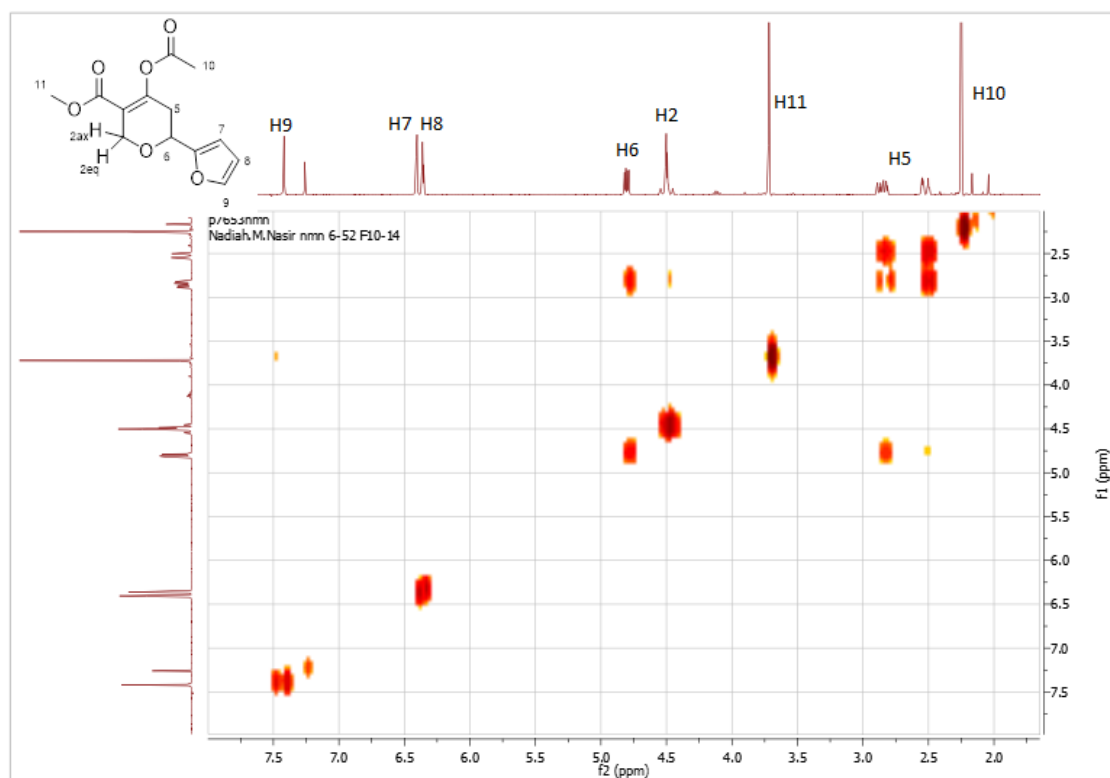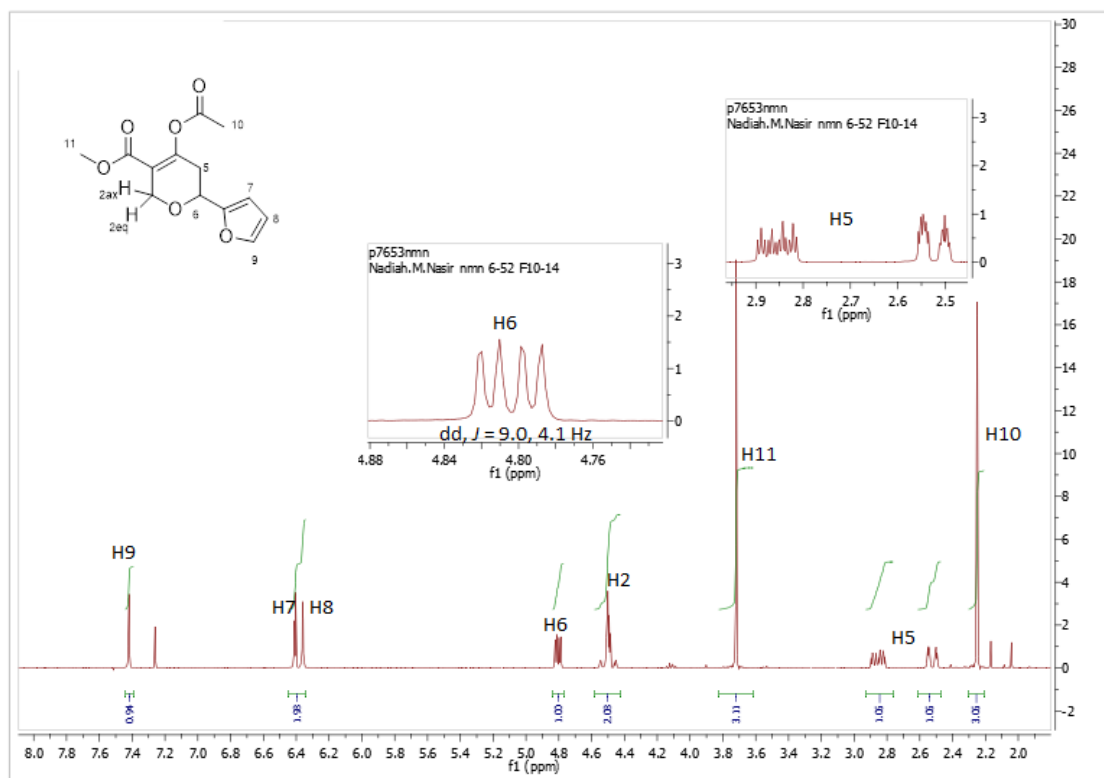
Figure 42

Then we tried with different substituent at position C6, and the reaction worked well with moderate yields 51-68%. From the ^{1}H NMR spectrum. We did not detect any reduction of the ester or ketone in any of the examples shown (Table 13, entries **a-e**).
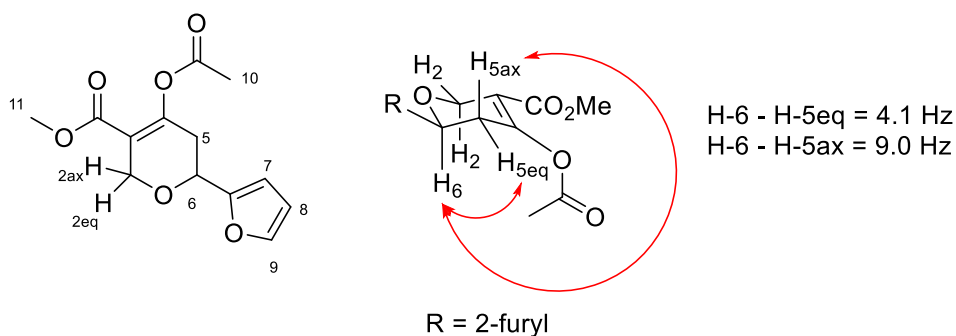
Figure 43 ^{1}H-^{1}H COSY correlation of 3,6-disubstituted THPs **316**

The major product in the mixture was the enol tautomer, the mixture was then acylated. From the ^{1}H NMR spectrum of **316** (Figure 42), there are no enol peak signals around 11-12 ppm, meaning acylation went to completion. The peak at 2.52 ppm integrated as 3H which showed that the acetyl ester was formed and assigned as H-10. From the ^{1}H-^{1}H COSY spectrum, the doublet of doublet peak was assigned as H-6 and integrated as 1H has *J*-value of 9.0 Hz showed *trans*-diaxial coupling with H-5ax at 2.89 ppm and H-6 also has *J*-value of 4.1 showed coupled with H-5eq (Figure 43). The ^{1}H-^{1}H COSY spectrum also showed multiplet peak at 4.51 ppm was assigned as H-2 has geminal coupling between H-2 only. From this spectrum, the *J*-value showed the stereochemistry of 3,6-disubstituted THP ring.

2.17   The synthesis of 3,3,6-trisubstituted tetrahydropyran.

The successful reduction of DHPs with L-Selectride® generated an enolate to construct the 3,6-disubstituted THP ring **314**. We were interested to discover whether these reactions can work when we intercept the enolate with a carbon electrophile to construct the 3,3,6-trisubstituted THP ring. The stereochemistry could be determined when the hydride would attacked from the pseudo-axial trajectory and the electrophilic quenching would occur from the opposite face of the THP ring (Figure 44). Hence, the electrophile would gave THP products with a quaternary stereocenter at C3. Initially, this was studied with iodomethane (Scheme 99).
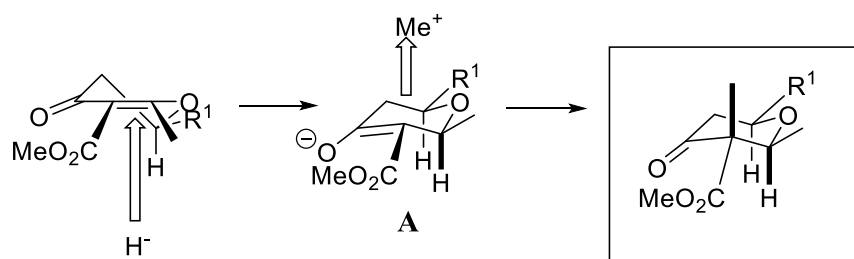
Figure 44 Hydride (nucleophile) attack on a DHP, followed quenched with MeI.
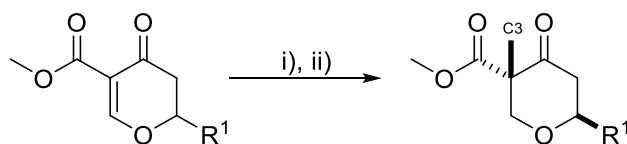
Scheme 99 Reagent & Conditions: i) L-Selectride®, THF, −78 °C, ii) MeI, −78 °C to RT.

Entry	Starting material	R^1	Yield^a (%)	Product
a	264	Phenyl	59	321
b	263	Pr	58	322
c	265	CH2-OTIPS	57	323
d	269	CH=CHPh	53	324
e	259	2-furyl	57^b	325

^{a}Isolated yield after column chromatography. ^{b}Total yield of diastereomer.

Table 14 Synthesis of 3, 3, 6-trisubstituted THPs with iodomethane.

The reduction of the DHP ring with L-Selectride® followed with an electrophilic quench in all examples (Table 14, entries **a-d**) gave a single product in yields between 53-59%, except for entry **e** (Table 14), where it formed a mixture of inseperable diastereomers (dr 1 : 0.2 based on integration of the signals ^{1}H NMR).

Having successfully installed a methyl group at the C3 position using iodomethane as the electrophile, we expanded our interest to other alkyl halides; allyl bromide and benzyl bromide as the electrophile with hydrogen at C2 position. Pleasingly, in all cases a moderate yield of the desired product was obtained. From the ^{1}H NMR spectrum of the reaction mixture, no other diastereomers was detected for entries **a** to **d** (Scheme 100, Table 15 and Scheme 101, Table 16), but for the entry **e** (Table 15 and Table 16), two

diastereomers were formed (dr 1 : 0.2) when we used allylbromide and benzyl bromide as the electrophile.
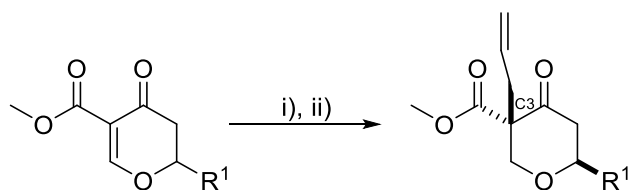
Scheme 100 Reagent & Conditions: i) L-Selectride®, THF, −78 °C, ii) Allylbromide, −78 °C to RT.

Entry	Starting material	R^1	Yield^a (%)	Product
a	264	Phenyl	52	326
b	263	Pr	52	327
c	265	CH$_2$-OTIPS	57	328
d	269	E-CH=CHPh	83	329
e	259	2-furyl	47^b	330

^{a}Isolated yield after column chromatography. ^{b}Total yield of diastereomer.

Table 15 Synthesis of 3,3,6-trisubstituted THPs with allylbromide.
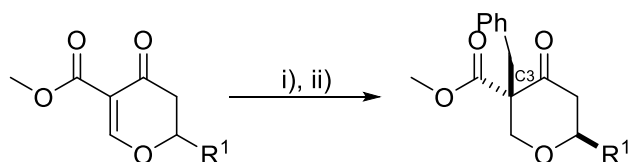
Scheme 101 Reagent & Conditions: i) L-Selectride®, THF, −78 °C, ii) Benzyl bromide, −78 °C to RT.

Entry	Starting material	R^1	Yield^a (%)	Product
a	264	Phenyl	65	331
b	263	Pr	62	332
c	265	CH$_2$-OTIPS	62	333
d	269	E-CH=CHPh	51	334
e	259	2-furyl	40^b	335

^{a}Isolated yield after column chromatography. ^{b}Total yield of diastereomer.

Table 16 Synthesis of 3,3,6-trisubstituted THPs with benzyl bromide.

This reaction gave the desired functionalised products when alkyl halide electrophiles were used. However, when we tried to intercept the enolate with an aldehyde or an epoxide, we were unable generate any product, which could be due to stability of the β-keto-ester's enolate anion. The reduction with L-Selectride® does occour but when it was quenched with those electrophiles, only the reduction product was observed even it was stirred at room temperature for more than 5 days.
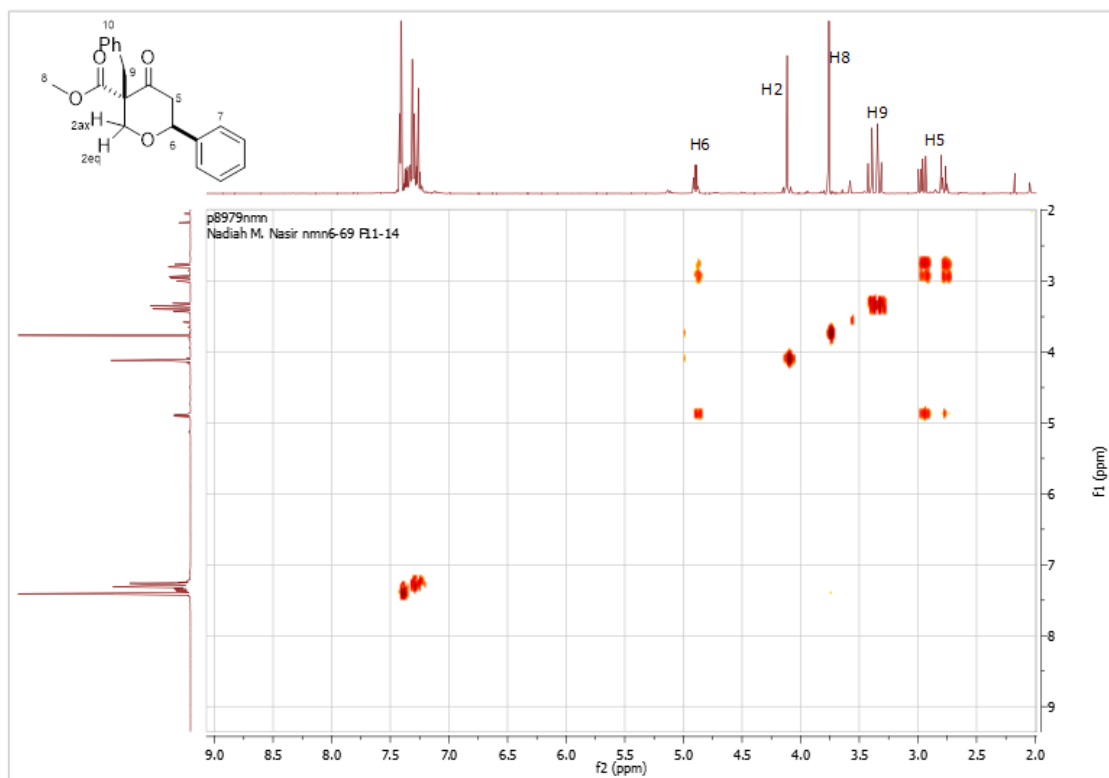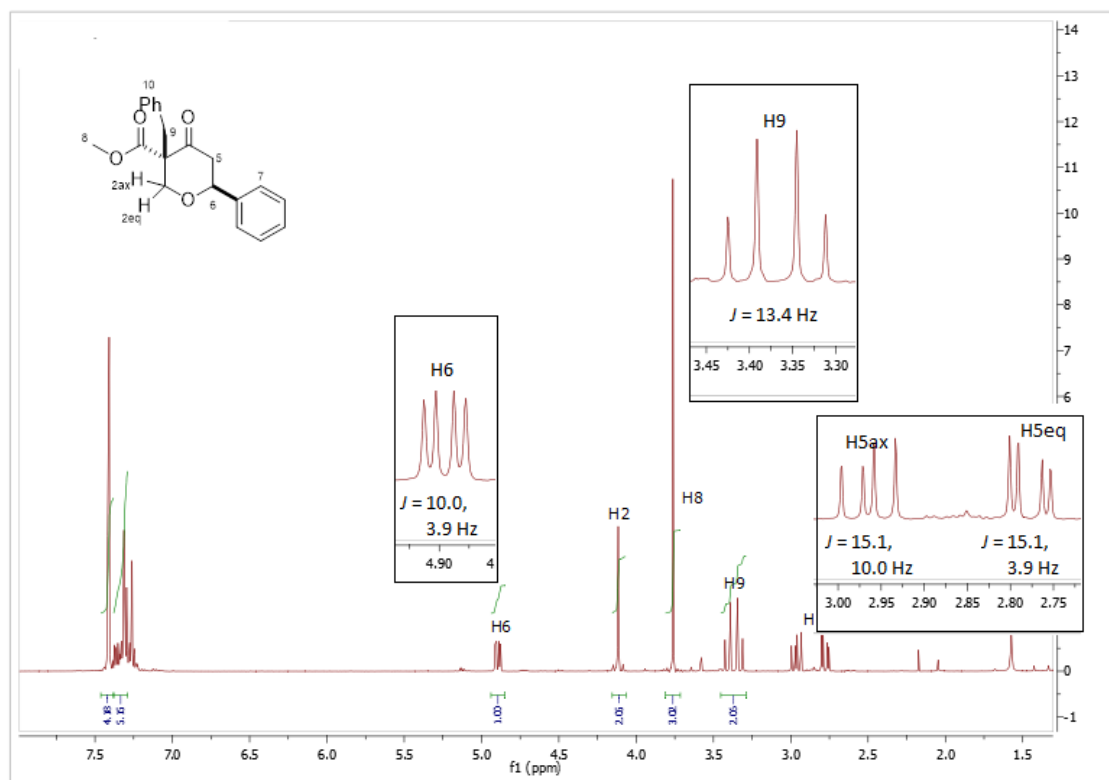
Figure 45
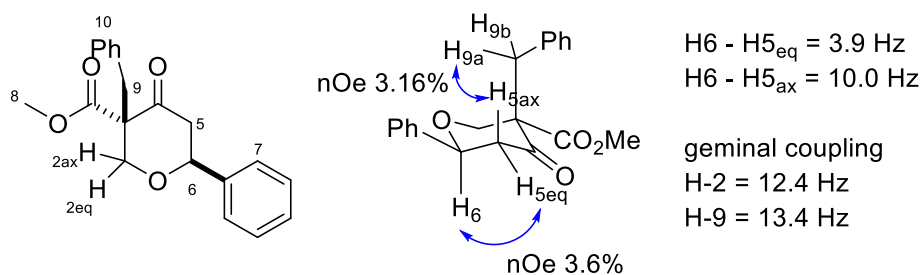
Figure 46 NOE Correlation of 3,3,6-trisubstituted THP **331**

The ^{1}H-^{1}H COSY spectrum of **331** (Figure 45) showed there were two doublet of doublets at 2.96 and 2.78 ppm which were assigned as H-5 and coupled with peak at 4.89 ppm which was assigned as H-6. The H-5ax has J-value of 10.0 Hz showed *trans*-diaxial coupling with H-6, while the H-5eq has J-value of 3.9 Hz showed coupling with H-6.

Then H-9a at 3.40 ppm has J-value of 13.4 Hz showing geminal coupling with H-9b at 3.33 ppm. Another geminal coupling between H-2 as doublet at 4.13 and 4.10 ppm with J-value of 12.4 Hz.

The NOE correlation confirmed, there was NOE correlation between H-6 and H-5eq with 3.6% when H-6 was irradiated. When H-5eq was irradiated a NOE to H-6 of 2.26% was seen. Another NOE between H-5ax and the benzyl CH_2 group of 3.16% which indicating that these were both axial (Figure 46).

From this, the 3,3,6-trisubstituted THP was characterised and the stereochemical configuration confirmed by ^{1}H NMR and NOE correlations. This provide some

encouragement that this avenue of research could provide a useful route towards 3,3,6-trisubstituted THPs to apply in synthesis of natural product.

2.18 Conclusions and Further Work.

Conclusions.

We have successfully developed a method to construct 2,6-*cis* and 2,6-*trans* substituted tetrahydropyrans from dihydropyrans. Initially we attempted the cyclisation of the δ-hydroxy-β-ketoester with an orthoester for the formation of DHPs. Unfortunately the scope is limited to commercially available orthoesters.

Dihydropyrans could be prepared using *N*, *N* -dimethylacetamide dimethyl acetal or *N*, *N* -dimethylformamide dimethyl acetal with δ-hydroxy-β-ketoesters to produce dihydropyrans. Pleaseingly the products were produced with modest to good yields with varying substitutions.

Functionalisation of DHPs was achieved by reduction of DHPs using L-Selectride®. Quenching with iodomethane gave access to 2,6-*cis* THPs in good yields. With the successful construction of the 2,6-*cis* THP ring, we applied this method to the construction of A ring of lasonolide A **1**.

DHPs without substitution at C-2 were prepared enabling the synthesis of 2,6-*trans* substituted THPS *via* conjugate addition. The total synthesis of diospongin B was completed using this approach.

Our work in forming 3,6-disubstituted tetrahydropyrans by the conjugate reduction of the C-2 – C-3 double bond, by treatment with L-Selectride® followed by treatment with an alkyl halide has been successfully used to form 3,3,6-trisubstituted THPS.

Future Work.

Our work in the formation of 2,6- *cis* THPs, 2,6-*trans* THPs, 3,6-disubstituted THPs and 3,3,6-trisubstituted THPs has been successful. Thus the next step in our research would be to expand the scope of these methods in the synthesis of natural products. For example, the 2,6- *cis* THP ring method could be applied in the synthesis of cyanolide A **22**, which exhibits significant molluscicidal activity against *Biomphalaria glabrata*.[12]

The 2,6-*trans* THP ring method could be applied in the synthesis of dihydroisocoumarin derivatives **336**, which has anti-inflammatory effects in lipopolysaccharide-induced BV2 microglia. [116]

The 3,3,6-trisubstituted THP method could be applied in the synthesis of (-)-Bissetone **337**, which display potent anti-microbial activity.[117]

cyanolide A **22**

Dihydroisocoumarin
derivatives
336

(-)-Bissetone **337**
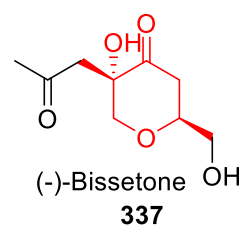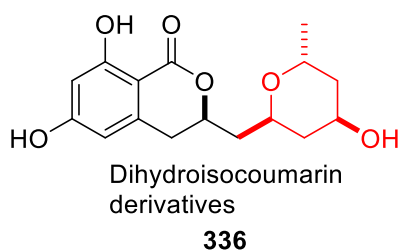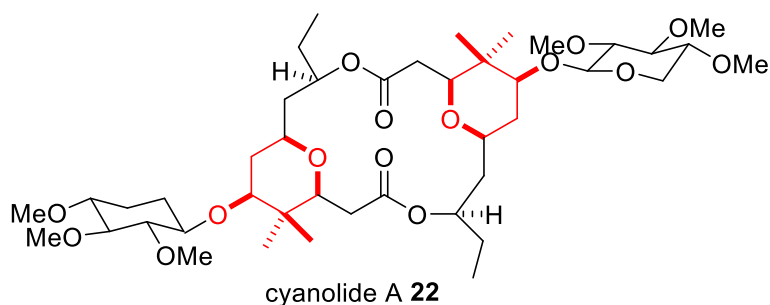
3.0　Experimental

3.1　General experimental

Infra-red absorbances were recorded on a ThermoNicolet Avatar 370 FT-IR spectrometer using NaCl plates. Nuclear magnetic resonance spectra were recorded on a Jeol ECX-400, Jeol ECS-400 or Bruker DRX 500 spectrometer at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: chloroform-*d* 7.26 ppm for ^{1}H NMR; chloroform-*d* 77.0 ppm for ^{13}C NMR. Coupling constants (*J*) are quoted in Hertz. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI) technique. Thin layer chromatography was performed on glass-backed plates coated with Merck Silica gel 60 F_{254}. The plates were developed using ultraviolet light, basic aqueous potassium permanganate or ethanolic anisaldehyde. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Fluorochem or silica gel Merck TLC grade 11695 supplied by Sigma-Aldrich. Dry solvents were acquired from a PureSolv PS-MD-7 solvent tower or distilled as follows: CH_2Cl_2 was distilled from calcium hydride; THF was distilled from sodium–benzophenone ketyl; Et_2O was distilled from $LiAlH_4$; toluene and triethylamine were distilled from calcium hydride and methanol from $CaSO_4$ or Mg/I_2. All other solvents and reagents were used as received from commercial suppliers. All numbering on the structures below is for the benefit of characterisation and does not conform to IUPAC rules.

3.2 Experimental procedures

Aldol reaction

Method A: Weiler dianion

To a slurry of sodium hydride (414 mg, 10.34 mmol) in THF (20 ml) at 0 °C was added methyl acetoacetate (100 mg, 8.62 mmol) slowly over 5 minutes during which time gas evolution was observed. The colourless solution was stirred for 10 min at 0 ºC and then n-butylithium (3.79 mL, 9.48 mmol, 2.5 M in hexanes) was added. The light yellow solution was stirred at room temperature for 20 min and was then cooled in an acetone dry ice bath. Once the temperature had reached −78 ºC the aldehyde (9.48 mmol) was added over a 5 min period. The solution was kept at −78 ºC for 5 min and was then warmed to room temperature over 30 min. The light yellow solution was stirred for 30 min and then H_2O (10 mL) was added. The mixture was extracted with EtOAc (50 mL) and washed with 5% $NaHCO_3$ (3 x 30 mL) and brine (2 x 30 mL), dried with $MgSO_4$, and concentrated *in vacuo* to give the crude product which was further purified by flash silica gel column chromatography (hexane – ethyl acetate) to give the product.

Method B: Alternative Weiler dianion Procedure

A 2.5 M n-butylithium (36.00 mL, 90 mmol) in hexanes was added to diisopropylamine (12.60 mL, 90 mmol) in THF at −78 ºC, the mixture was stirred for 15 minutes at −78 ºC then warm-up to room temperature for 5 minutes then the mixture was cool to −78 ºC. Lithium diisopropylamide (90 mmol) was stirred in dry THF (156 mL) at −78 °C under a nitrogen atmosphere. A solution of methyl acetoacetate (4.90 mL, 45 mmol) in dry THF (31 mL) was added slowly over 10 minutes and the reaction mixture were stirred for 30 minutes. Aldehyde (0.84 mL, 15 mmol) in dry THF (31 mL) was added to the reaction mixture at −50 ºC and stirred for 30 min. Acetic acid (10 M in THF) (23 mL) was added

at −50 °C, and the crude reaction was extracted with EtOAc (2x50 mL) and the combined organic phases were washed with H_2O (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$. After concentration in *vacuo*, the crude product was purified by column chromatography on silica gel (hexane – ethyl acetate).

Method C: Diketene addition

A 3.0 M solution of titanium tetrachloride in CH_2Cl_2 (0.50 mL, 1.50 mmol) was added to a stirred solution of aldehyde (1.30 mmol) and diketene (0.19 mL, 2.50 mmol) in CH_2Cl_2 (6.50 mL) at −78 °C. After 5 minutes methanol (2 mL) was added, and the mixture stirred at −20 to −10 °C for 40 minutes. The mixture was poured onto ice-cooled K_2CO_3 solution (0.44 M aqueous solution, 10.00 mL, 4.4 mmol). The pale yellow precipitate formed was filtered, and the precipitate extracted with Et_2O (2 x 20.00 mL). The organic extracts were combined and washed with sat. aq. $NaHCO_3$ (2 x 20.0 mL) and brine (20.0 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification via flash column chromatography (hexane – ethyl acetate) afforded the product.

Method D: Alternative Diketene Procedure

Titanium tetraisopropoxide (2.86 mL, 9.70 mmol) was added to a stirred solution of aldehyde (9.70 mmol) and diketene (1.34 mL, 17.40 mmol) in CH_2Cl_2 (26.00 mL) at −78 °C. After 5 minutes methanol (1.56 mL, 38.60 mmol) was added, and the mixture stirred at −20 to −10 °C for 1.5 hours. The reaction mixture was diluted with Et_2O (20.00 mL), and washed with (20 % w/v) citric acid solution (30.00 mL). The aqueous layer was extracted with Et_2O (2 x 20.00 mL), and the combined organic extracts washed with brine (2 x 20.00 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (hexane – ethyl acetate) gave the product.

Method E: Chan's Diene Addition

Titanium tetrachloride (0.63 mL, 5.70 mmol) was added to a stirred solution of aldehyde (5.70 mmol) in CH_2Cl_2 (55.00 mL) at −78 °C. After 5 minutes Chan's diene in neat (2.97 g, 11.40 mmol) was added dropwise over one minute, and the mixture stirred at −78 °C for 20 minutes before being quenched with TFA (1.69 mL, 22.80 mmol). The mixture was diluted with EtOAc (150 mL) then washed with sat. aq. $NaHCO_3$ (2 x 60.00 mL) and brine (60.00 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (hexane – ethyl acetate) gave the product.

Methyl 5-hydroxy-6-methyl-3-oxoheptanoate (182)
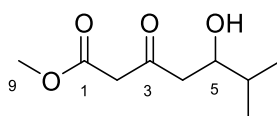
Method C, isobutyraldehyde (0.12 mL, 1.30 mmol), diketene (0.19 mL, 2.50 mmol), 3.0 M solution of $TiCl_4$ in CH_2Cl_2 (0.50 mL, 1.50 mmol), MeOH (2.00 mL, 49.40 mmol), CH_2Cl_2 (6.50 mL); purification (hexane – ethyl acetate = 3: 2), percentage yield 0.127 g, 52 % light yellow oil. υ max/cm^{-1} (film) 3474 (OH) , 2959 (C-H), 2931 (C-H), 1741(C=O), 1710 (C=O), 1437 (CH_3), 1320 (CH_3), 1259 (C-O), 1151 (C-O); δ_H (400 MHz, CDCl$_3$): δ 3.85–3.80 (1H, m, H-5), 3.72 (3H, s, H-9), 3.51 (1H, d, J = 12.3 Hz, H-2), 3.48 (1H, d, J = 12.3 Hz, H-2), 2.75 (1H, br s, OH), 2.71 (1H, dd, J = 16.0, 4.0 Hz, H-4), 2.62 (1H, dd, J = 16.0, 8.0 Hz, H-4), 1.71–1.63 (1H, m, H-6), 0.91 (3H, d, J = 8.0 Hz, H-7) and 0.89 (3H, d, J = 8.0 Hz, H-8); δ_C (100 MHz, CDCl$_3$): 203.9 (C=O), 167.3 (C=O), 72.3 (C-5), 52.5 (C-9), 49.8 (C-2), 46.9 (C-4), 33.2 (C-6), 18.4 (C-7) and 17.8 (C-8); *m/z* (ESI+) 211 (M + Na)$^+$. (Found 211.0948 (M + Na)$^+$. $C_9H_{16}NaO_4$ requires 211.0946). NMR data were in agreement with the literature.[53]

Methyl 5-hydroxy-3-oxooctanoate (183)
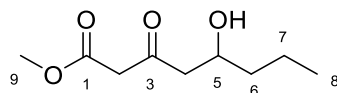
Method C, butyraldehyde (0.24 mL, 2.60 mmol), diketene (0.38 mL, 5.00 mmol), 3.0 M solution of $TiCl_4$ in CH_2Cl_2 (1.00 mL, 3.00 mmol), MeOH (4.00 mL, 98.80 mmol), CH_2Cl_2 (13.00 mL); purification (hexane – ethyl acetate = 3: 2), percentage yield 0.303 g, 62 % light yellow oil. υ max/cm^{-1} (film) 3395 (OH), 2914 (C-H), 2889 (C-H), 1719 (C=O), 1687 (C=O), 1386 (CH$_3$), 1250 (C-O), 1136 (C-O); δ_H (400 MHz, CDCl$_3$): δ 4.07–4.01 (1H, br m, H-5), 3.70 (3H, s, H-9), 3.44 (1H, d, J = 14.5 Hz, H-2), 3.41 (1H, d, J = 14.5 Hz, H-2), 2.70 (1H, br s, OH), 2.67 (1H, dd, J = 17.3, 3.3 Hz, H-4), 2.61 (1H, dd, J = 17.3, 8.6 Hz, H-4), 1.50–1.28 (4H, m, H-6, H-7) and 0.90–0.87 (3H, t, J = 8.0 Hz, H-8); δ_C (100 MHz, CDCl$_3$): 203.7 (C=O), 167.5 (C=O), 67.3 (C-5), 52.5 (C-9), 49.8 (C-2), 49.7 (C-4), 38.7 (C-6), 18.7 (C-7) and 13.9 (C-8); m/z (ESI+) 211 (M + Na)$^+$. (Found 211.0944 (M + Na)$^+$. C$_9$H$_{16}$NaO$_4$ requires 211.0946). NMR data were in agreement with the literature.[53]

Methyl 6-(benzyloxy)-5-hydroxy-3-oxohexanoate (184)
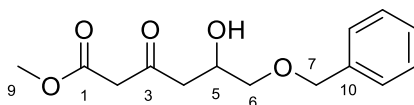
Method D, Benzyloxyacetaldehyde (1.36 mL, 9.70 mmol), diketene (1.34 mL, 17.40 mmol), Ti(O^{i}Pr)$_4$ (2.86 mL, 9.70 mmol), MeOH (1.56 mL, 38.60 mmol), CH_2Cl_2 (26.00 mL): purification (hexane – ethyl acetate = 3: 2), percentage yield 0.593 g, 23 % oil. Method E, Benzyloxyacetaldehyde (0.80 mL, 5.7 mmol), Chan's diene (2.97 g, 11.4 mmol), $TiCl_4$ (0.63 mL, 5.7 mmol), TFA (1.69 mL, 22.8 mmol), CH_2Cl_2 (55.0 mL): purification (hexane – ethyl acetate = 3: 2), percentage yield 1.152 g, 76 % light yellow

oil. υ max/cm^{-1} (film) 3452 (OH), 2861 (C-H), 1741 (C=O), 1712 (C=O), 1252 (C-O), 1203 (C-O), 1096 (C-O), 738 (Ar), 698 (Ar), 481 (Ar); δ_H (400 MHz, CDCl$_3$): δ 7.38–7.27 (5H, m, Ar), 4.58 (1H, d, J = 12.1 Hz, H-7), 4.52 (1H, d, J = 12.1 Hz, H-7), 4.32–4.24 (1H, m, H-5), 3.73 (3H, s, H-9), 3.11 (1H, d, J = 12.1 Hz, H-2), 3.08 (1H, d, J = 12.1 Hz, H-2), 3.49 (1H, dd, J = 9.6, 4.6 Hz, H-4), 3.44 (1H, dd, J = 9.6, 6.12 Hz, H-4), 2.78 (1H, dd, J = 17.1, 6.5 Hz, H-6) and 2.73 (1H, dd, J = 17.1, 3.9 Hz, H-6);δ_C (100 MHz, CDCl$_3$): 202.7 (C=O), 167.8 (C=O), 138.1 (C-10), 128.6 (Ar), 127.9 (Ar), 127.8 (Ar), 73.5 (C-4), 73.1 (C-7), 66.8 (C-5), 52.5 (C-9), 49.9 (C-2), 46.5 (C-6); m/z (ESI+) 289 (M + Na)$^+$. (Found 289.1058 (M + Na)$^+$. C$_{14}$H$_{18}$NaO$_5$ requires 289.1052). NMR data were in agreement with the literature.[53]

Methyl 5-hydroxy-3-oxo-5-phenylpentanoate (138)
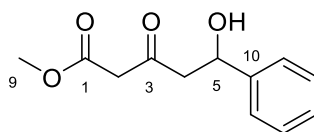
Method D, Benzaldehyde (1.97 mL, 19.40 mmol), diketene (5.36 mL, 34.80 mmol), Ti(O^{i}Pr)$_4$ (5.74 mL, 19.40 mmol), MeOH (3.12 mL, 77.20 mmol), CH$_2$Cl$_2$ (52.00 mL); purification (hexane – ethyl acetate = 3: 2), percentage yield 2.239 g, 52 % light yellowoil. υ max/cm^{-1} (film) 3452 (OH), 2953 (C-H), 1739 (C=O), 1710 (C=O), 1475 (Ar), 1264 (C-O), 1196 (C-O), 750 (Ar), 700 (Ar), 538 (Ar); δ_H (400 MHz, CDCl$_3$): δ 7.32–7.24 (5H, m, Ar), 5.14 (1H, dd, J = 8.0, 4.0 Hz, H-5), 3.69 (3H, s, H-9), 3.46 (2H, s, H-2), 3.36 (1H, br s, OH), 2.96 (1H, dd, J = 16.0, 10.0 Hz, H-4), 2.84 (1H, dd, J = 16.0, 4.0 Hz, H-4); δ_C (100 MHz, CDCl$_3$): 202.7 (C=O), 167.6 (C=O), 142.7 (C-10), 128.7 (Ar), 127.9 (Ar), 125.7 (Ar), 69.9 (C-5), 52.6 (C-9), 51.7 (C-2) and 49.7 (C-4); m/z (ESI+) 245 (M + Na)$^+$. (Found 245.0784 (M + Na)$^+$. C$_{12}$H$_{14}$NaO$_4$ requires 245.0790). NMR data were in agreement with the literature.[53]

Methyl 5-(furan-2-yl)-5-hydroxy-3-oxopentanoate (185)
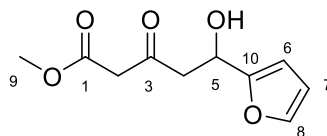
Method D, Furfural (0.80 mL, 9.70 mmol), diketene (1.34 mL, 17.40 mmol), Ti (O^{i}Pr)$_4$ (2.86 mL, 9.70 mmol), MeOH (1.56 mL, 38.60 mmol), CH$_2$Cl$_2$ (26.00 mL); purification (hexane – ethyl acetate = 3: 2), percentage yield 1.275 g, 62 % light yellow oil. υ max/cm^{-1} (film) 3407 (OH), 1704 (C=O), 1711 (C=O), 1618 (C=C), 1208 (C-O), 1248 (C-O), 1148 (C-O), 1011 (C-O); δ_H (400 MHz, CDCl$_3$): δ 7.37 (1H, dd, J = 1.8, 0.8 Hz, H-8), 6.33 (1H, dd, J = 3.2, 1.8 Hz, H-7), 6.28 (1H, dd, J = 3.2, 0.7 Hz, H-6), 5.20 (1H, dd, J = 8.8, 3.4 Hz, H-5), 3.75 (3H, s, H-9), 3.55 (1H, d, J = 12.2 Hz, H-2), 3.51 (1H, d, J = 12.2 Hz, H-2), 3.17 (1H, dd, J = 17.6, 8.8 Hz, H-4), 3.04 (1H, dd, J = 17.6, 3.4 Hz, H-4); δ_C (100 MHz, CDCl$_3$): 202.2 (C=O), 167.5 (C=O), 154.7 (C-10), 142.7 (C-7), 110.5 (C-8), 106.4 (C-6), 63.7 (C-5), 52.3 (C-9), 49.9 (C-2), and 48.1 (C-4); m/z (ESI$^+$) 235 (M + Na)$^+$. (Found 235.0577 (M + Na)$^+$. C$_{10}$H$_{12}$NaO$_5$ requires 235.0582). NMR data were in agreement with the literature.[119]

Methyl 5-hydroxy-5-(2-nitrophenyl)-3-oxopentanoate (186)
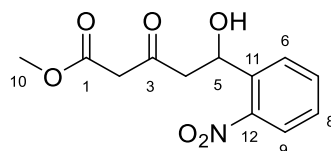
Method D, 2-nitrobenzaldehyde (1.47g, 9.70 mmol), diketene (1.34 mL, 17.40 mmol), Ti(O^{i}Pr)$_4$ (2.86 mL, 9.70 mmol), MeOH (1.56 mL, 38.60 mmol), CH$_2$Cl$_2$ (26.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 1.321 g, 51 % yellow solid. υ max/cm^{-1} (film) 3496 (OH), 2942 (C-H), 1734 (C=O), 1695 (C=O), 1524 (C=C), 1350

(N=O), 1299 (C-N), 1128 (C-O), 1078 (C-O), 788 (Ar), 737 (Ar), 689 (Ar); δ_H (400 MHz, CDCl$_3$): δ 7.87 (1H, dd, J = 8.4, 1.2 Hz, H-6), 7.82 (1H, dd, J = 7.7, 1.2 Hz, H-9), 7.60 (1H, ddd, J = 7.7, 7.0, 1.2 Hz, H-8), 7.38 (1H, ddd, J = 8.4, 7.0, 1.4 Hz, H-7), 5.63 (1H, dd, J = 9.3, 2.1 Hz, H-5), 3.75 (1H, OH) 3.66 (3H, s, H-10), 3.52 (1H, d, J = 14.6 Hz, H-2), 3.49 (1H, d, J = 14.6 Hz, H-2), 3.09 (1H, dd, J = 17.4, 2.3 Hz, H-4) and 2.83 (1H, dd, J = 17.4, 9.3 Hz, H-4); δ_C (100 MHz, CDCl$_3$): 202.2 (C=O), 167.5 (C=O), 147.0 (C-12), 138.5 (C-11), 133.9 (Ar), 128.5 (Ar), 128.2 (Ar), 124.5 (Ar), 65.5 (C-5), 52.6 (C-10), 50.9 (C-4) and 49.3 (C-2); m/z (ESI$^+$) 290 (M + Na)$^+$. (Found 290.0635 (M + Na)$^+$. C$_{12}$H$_{13}$NaO$_6$ requires 290.0641). NMR data were in agreement with the literature.[120]

Methyl 5-hydroxy-3-oxo-6-((triisopropylsilyl)oxy)hexanoate (194)
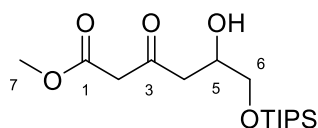
Method A, 2-((triisopropylsilyl)oxy) acetaldehyde (1.06 g, 4.90 mmol), methylacetoacetate (5.40 mmol), NaH (0.26 g, 6.40 mmol), 1.8 M n-BuLi in hexanes (3.27 mL) in THF (10 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.569 g, 35 % light yellow oil. υ max/cm^{-1} (film) 3453 (OH) , 2943 (C-H), 2866 (C-H), 1746 (C=O), 1715 (C=O), 1462 (CH$_3$), 1237 (C-O), 1114 (C-O), 1064 (C-O); δ_H (400 MHz, CDCl$_3$): δ 4.12–4.05 (1H, dddd, J = 7.5, 6.0, 4.9, 4.8 Hz, H-5), 3.54 (1H, dd, J = 9.8, 4.9 Hz, H-6), 3.48 (1H, dd, J = 9.8, 6.0 Hz, H-6), 3.26 (3H, s, H-7), 3.09 (2H, s, H-2), 2.67 (1H, br s, OH), 2.48 (1H, dd, J = 16.6, 7.5 Hz, H-4), 2.42 (1H, dd, J = 16.6, 4.8 Hz, H-4) and 1.03 (21H, m, OTIPS); δ_C (100 MHz, CDCl$_3$): 204.4 (C=O), 167.0 (C=O), 68.3 (C-5), 66.6 (C-6), 51.4 (C-7), 49.4 (C-2), 45.8 (C-4), 17.8 (C-OTIPS) and 11.9 (C-OTIPS); m/z (ESI+) 355 (M + Na)$^+$. (Found 355.1905 (M + Na)$^+$. C$_{16}$H$_{32}$NaO$_5$Si requires 355.1917). NMR data were in agreement with the literature.[121]

Methyl 5-hydroxy-5-(2-methyloxazol-4-yl)-3-oxopentanoate (187)
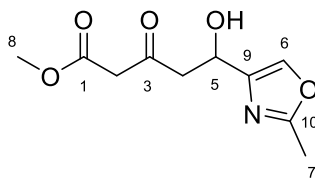
Method E, 2-methyloxazole-4-carbaldehyde (0.25 g, 2.30 mmol), Chan's diene (1.20 g, 4.50 mmol), 3.0 M solution of $TiCl_4$ in CH_2Cl_2 (0.25 mL, 2.30 mmol), TFA (0.70 mL, 9.00 mmol) in dicholoromethane (22.00 mL); purification (hexane – ethyl acetate = 1: 4), percentage yield 0.151 g, 30 % light yellow oil. υ max/cm^{-1} (film) 3337 (OH), 2955 (C-H), 2920 (C-H), 1741 (C=O), 1713 (C=O), 1600 (C=C), 1267 (C-N), 1092 (C-O), 865 (C=C), 657 (C=C); δ_H (400 MHz, CDCl$_3$): δ 7.47 (1H, s, H-6), 5.13–5.10 (1H, m, H-5), 3.73 (3H, s, H-8), 3.52 (2H, s, H-2), 3.08–3.06 (2H, m, H-4) and 2.42 (3H, s, H-7); δ_C (100 MHz, CDCl$_3$): 202.6 (C=O), 167.5 (C=O), 161.6 (C-9), 142.1 (C-10), 134.9 (C-6), 63.4 (C-5), 52.6 (C-8), 49.7 (C-2), 48.6 (C-4) and 13.9 (C-7); m/z (ESI+) 250 (M + Na)$^+$. (Found 250.0682 (M + Na)$^+$. $C_{10}H_{13}NaO_5$ requires 250.0691).

Methyl 5-hydroxy-3-oxooct-6-enoate (188)
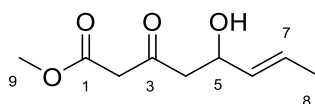
Method D, crotonaldehyde (1.61 g, 19.40 mmol), diketene (2.68 mL, 34.80 mmol), Ti(O^{i}Pr)$_4$ (5.70 mL, 19.40 mmol), MeOH (3.12 mL), CH$_2$Cl$_2$ (52.00 mL); purification (hexane – ethyl acetate = 3: 2), percentage yield 2.346 g, 65 % light yellow oil. υ max/cm^{-1} (film) 3424 (OH) , 2955 (C-H), 2920 (C-H), 1741 (C=O), 1710 (C=O), 1450 (CH$_3$), 1262 (C-O), 1151 (C-O), 967 (C=C); δ_H (400 MHz, CDCl$_3$): δ 5.52 (1H, m, H-7), 5.33 (1H, m, H-6), 4.40 (1H, m, H-5), 3.28 (3H, s, H-7), 3.10 (1H, d, J = 15.7 Hz, H-2), 3.06 (1H, d, J = 15.7 Hz, H-2), 2.41 (1H, dd, J = 16.5, 8.5 Hz, H-4), 2.26 (1H, dd, J = 16.5,

3.7 Hz, H-4) and 1.49 (3H, d, J = 6.5 Hz, H-8); δ_C (100 MHz, CDCl$_3$): 201.8 (C=O), 167.0 (C=O), 133.0 (C-6), 125.7 (C-7), 69.3 (C-5), 52.4 (C-9), 51.4 (C-4), 49.6 (C-2), 17.4 (C-8); m/z (ESI+) 209 (M + Na)$^+$. (Found 209.0784 (M + Na)$^+$. C$_9$H$_{14}$NaO$_4$ requires 209.0784).

(*E*)-Methyl 5-hydroxy-3-oxo-7-phenylhept-6-enoate (189)
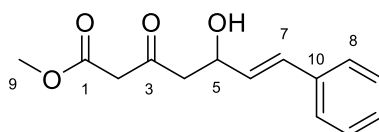
Method D, cinnamaldehyde (5.00 g, 38.80 mmol), diketene (5.37 mL, 69.60 mmol), Ti(O^{i}Pr)$_4$ (11.50 mL, 38.80 mmol), MeOH (6.24 mL), CH$_2$Cl$_2$ (104.00 mL); purification (hexane – ethyl acetate = 3: 2), percentage yield 7.313 g, 76 % light yellow oil. υ max/cm$^-$^{1} (film) 3423 (OH) , 3050 (Ar), 2953 (C-H), 1740 (C=O), 1710 (C=O), 1266 (C-O), 1149 (C-O), 967 (Ar), 747 (Ar), 694 (Ar); δ_H (400 MHz, CDCl$_3$): δ 7.28–7.05 (5H, m, H-8), 6.57 (1H, d, J = 16.0 Hz, H-7), (1H, dd, J = 16.0, 5.4 Hz, H-6), 4.62 (1H, m, H-5), 3.30 (3H, s, H-9), 3.20 (1H, d, J = 16.0 Hz, H-2), 3.16 (1H, d, J = 16.0 Hz, H-2), 2.49 (1H, dd, J = 16.8, 8.9 Hz, H-4), 2.31 (1H, dd, J = 16.8, 3.6 Hz, H-4); δ_C (100 MHz, CDCl$_3$): 201.8 (C=O), 167.0 (C=O), 136.9 (C-10), 130.8 (C-7), 129.9 (C-6), 128.6 (Ar), 127.8 (Ar), 126.6 (Ar), 68.3 (C-5), 51.5 (C-9), 50.5 (C-2), 49.2 (C-4); m/z (ESI+) 271 (M + Na)$^+$. (Found 271.0937 (M + Na)$^+$. C$_{14}$H$_{16}$NaO$_4$ requires 271.0941).

Methyl 5-hydroxy-3-oxohexanoate (197)
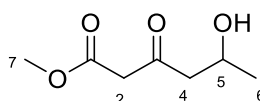
Method B, methyl acetoacetate (4.90 mL, 45 mmol), acetaldehyde (0.84 mL, 15 mmol), 2.5 M *n*-BuLi (36.00 mL, 90 mmol), diisopropylamine (12.60 mL, 90 mmol), THF (216

mL); purification (hexane – ethyl acetate = 3: 2), percentage yield 1.728 g, 72 % orange oil. υ max/cm^{-1} (film) 3417 (OH), 2970 (C-H), 1738 (C=O), 1709 (C=O), 1375 (CH$_3$), 1263 (C-O), 1139 (C-O); δ_H (400 MHz, CDCl$_3$): δ 4.25 (1H, m, H-5), 3.72 (3H, s, H-7), 3.47 (2H, s, H-2), 2.89 (1H, bs, OH), 2.70 (1H, dd, J = 17.6, 3.6 Hz, H-4), 2.64 (1H, dd, J = 17.6, 8.4 Hz, H-4) and 1.18 (1H, d, J = 6.4 Hz, H-6); δ_C (100 MHz, CDCl$_3$): 203.4 (C=O), 167.4 (C=O), 63.7 (C-5), 52.4 (C-7), 51.0 (C-4), 49.5 (C-2), 22.4 (C-6); m/z (ESI$^+$) 183 (M + Na)$^+$. (Found 183.0620 (M + Na)$^+$. C$_7$H$_{12}$NaO$_4$ requires 183.0628). NMR data were in agreement with the literature.[68]

3-Trimethylsilanyloxy-but-2-enoic acid methyl ester (192)
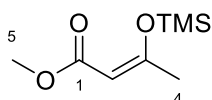
To a solution of methyl acetoacetate (5.00 mL, 0.046 mol) in hexane (200 mL) stirring at room temperature under a N$_2$ atmosphere was added triethylamine (5.70 g, 0.056 mol) and the reaction was stirred for 30 minutes. The reaction was treated with chlorotrimethylsilane (7.00 g, 0.064 mol) and stirred for 17 hours. The mixture was filtered through a pad of celite with hexane (200 mL) and the filtrate was concentrated in *vacuo* to give a pale yellow oil. Purification by Kugelrhor distillation (RT - 50 °C, 10^{-1} mbar) gave a colourless oil (3.00 g, 35 %). The ^{1}H NMR data were found to be in agreement with the literature. δ_H (400 MHz, CDCl$_3$): δ 5.05 (1H, s, H-2), 3.58 (3H, s, H-5), 2.25 (3H, s, H-4) and 0.20 (9H, s, H-6). ^{1}H NMR data were in agreement with the literature.[122]

1- Methoxy-1,3-bis-trimethylsilanyloxy-buta-1,3-diene (141)
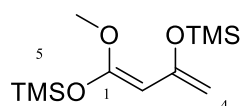
To a solution of diisopropylamine (1.90 g, 19 mmol) in THF (30 mL) stirring under a N_2 atmosphere at −78 °C was added a 2.5 M solution of *n*-BuLi in hexanes (7.00 mL, 17 mmol). After 5 minutes the mixture was warmed to room temperature and stirred for 15 minutes then cooled to −78 °C. The reaction was treated with a solution of **189** (3.00 g, 16 mmol) in THF (20 mL) over a 10 minutes period and was stirred for a further 20 minutes. The reaction was treated with chlorotrimethylsilane (2.30 g, 21 mmol) and was warmed to 0 °C and left to stir for 1 hour. The resulting yellow solution was concentrated *in vacuo*. The salts were removed by filtration through a pad of celite and washed with hexane (100 mL). The filtrate was concentrated *in vacuo* to give a crude yellow oil which was purified by Kugelrhor distillation (RT - 50 °C, 10^{-1} mbar) to give a colourless oil (51%). The ^{1}H NMR data were found to be in agreement with the literature. δ_H (400 MHz, CDCl$_3$): δ 4.47 (1H, s, H-2), 4.14 (1H, s, H-4), 3.93 (1H, s, H-4), 3.55 (3H, s, H-5), 0.27 (9H, s, H-6/H-7), 0.25 (9H, s, H-6/H-7). ^{1}H NMR data were in agreement with the literature.[122]

General procedure for orthoester cyclisations:

A mixture of δ-hydroxy-β-ketoester (0.30 mmol), trimethyl orthoester (0.05 mL, 0.30 mmol) and acetic anhydride (0.05 mL, 0.50 mmol) in toluene (2.00 mL) was run under microwave for 15 minute. The mixture was then cooled and the solvent removed *in vacuo*. Flash column chromatography (petroleum ether – ethyl acetate) gave the product.

Methyl 6-phenyl-2-butyl-4-oxo-5,6-dihydro-2H-pyran-3-carboxylate (199)
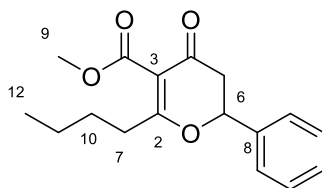
δ-Hydroxy-β-ketoester **138** (0.035 g, 0.15 mmol), trimethyl orthovalerate (0.05 mL, 0.30 mmol), Ac$_2$O (0.05 mL, 0.50 mmol), PhMe (1.00 mL); purification (petroleum ether – ethyl acetate = 4:1), percentage yield 0.039 g, 90 %, light yellow oil. υ max/cm^{-1} (film) 2961(C-H), 2924 (C-H), 2863 (C-H), 1722 (C=O), 1592 (C=C), 1260 (C-O), 1219 (C-O), 1158 (C-O), 756, (Ar), 698 (Ar); δ$_H$ (400MHz, CDCl$_3$) 7.44–7.34 (5H, m, Ar), 5.41 (1H, dd, *J* = 16.0, 4.0 Hz, H-6), 3.84 (3H, s, H-9), 2.88 (1H, dd, *J* = 16.0, 12.0 Hz, H-5ax), 2.71 (1H, dd, *J* = 16.0, 4.0 Hz, H-5eq), 2.55 (2H, t, *J* = 8.0 Hz, H-7), 1.68- 1.60 (2H, m, H-10), 1.42–1.33 (2H, m, H-11) and 0.91 (3H, t, *J* = 8.0 Hz, H-12); δ$_C$ (100 MHz, CDCl$_3$) 188.4 (C=O), 180.6 (C=O), 166.7 (C-2), 137.4 (C-8), 128.7 (Ar), 127.6 (Ar), 126.8 (Ar), 111.1 (C-3), 80.0 (C-6), 52.4 (C-9), 42.4 (C-5), 33.6 (C-7), 29.7 (C-10), 17.6 (C-11) and 13.8 (C-12); *m/z* (ESI$^+$) 311 (M + Na)$^+$, 289 (M + H)$^+$. (Found 311.1256 (M + Na)$^+$. C$_{17}$H$_{20}$NaO$_4$ requires 311.13).

Methyl 6-(benzyloxymethyl)-2-butyl-4-oxo-5,6-dihydro-2H-pyran-3-carboxylate (200)
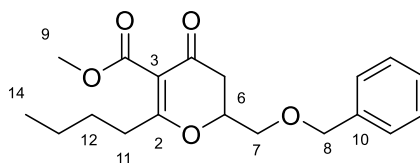
δ-Hydroxy-β-ketoester **184** (0.045 g, 0.15 mmol), trimethyl orthovalerate (0.05 mL, 0.30 mmol), Ac$_2$O (0.05 mL, 0.50 mmol), PhMe (1.00 mL); purification (petroleum ether – ethyl acetate = 4:1), percentage yield 0.025 g, 51 %, light yellow oil. υ max/cm^{-1} (film)

2955 (C-H), 2926 (C-H), 2869 (C-H), 1718 (C=O),1680 (C=C), 1375 (CH$_3$), 1341 (C-O), 1208 (C-O), 1066 (C-O), 804 (Ar), 737 (Ar), 698 (Ar); δ_H (400MHz, CDCl$_3$) 7.31–7.24 (5H, m, Ar), 4.62 (1H, d, J = 12.12 Hz, H-8), 4.58 (1H, d, J = 12.12 Hz, H-8), 4.57–4.53 (1H, m, H-6), 3.80 (3H, s, H-10), 3.73 (1H, dd, J = 10.9, 3.7 Hz, H-7), 3.68 (1H, dd, J = 10.9, 5.0 Hz, H-7), 2.72 (1H, dd, J = 16.7, 13.6 Hz, H-5ax), 2.51 (1H, dd, J = 16.7, 3.5 Hz, H-5eq), 2.49 (2H, d, J = 7.6 Hz, H-11), 1.65–1.57 (2H, m, H-12), 1.42- 1.32 (2H, m, H-13) and 0.92 (3H, t, J = 8.0 Hz, H-14); δ_C (100 MHz, CDCl$_3$) 188.4 (C=O), 179.8 (C=O), 166.7 (C-2), 137.4 (C-10), 128.5 (Ar), 127.8 (Ar), 127.1 (Ar), 112.3 (C-3), 78.1 (C-6), 73.5 (C-8), 70.4 (C-7), 52.2 (C-10), 37.5 (C-5), 33.4 (C-11), 29.1 (C-12), 22.50 (C-13) and 13.8 (C-14); m/z (ESI$^+$) 355 (M + Na)$^+$, 333 (M + H)$^+$. (Found 355.1515 (M + Na)$^+$. C$_{19}$H$_{24}$NaO$_5$ requires 355.1521).

Methyl 2-isopropyl-6-methyl-4-oxo-3,4-dihydro-2H-pyran-5-carboxylate (205)
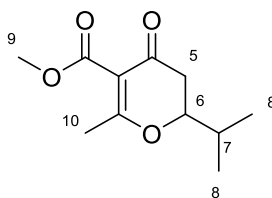
δ-Hydroxy-β-ketoester **182** (0.031 g, 0.15 mmol), trimethyl orthoacetate (0.04 mL, 0.30 mmol), Ac$_2$O (0.05 mL, 0.50 mmol), PhMe (1.00 mL); purification (petroleum ether – ethyl acetate = 4:1), percentage yield 0.010 g, 32 %, light yellow oil. υ max/cm^{-1} (film) 2955 (C-H), 2926 (C-H), 2869 (C-H), 1718 (C=O), 1672 (C=C), 1375 (CH$_3$), 1208 (C-O), 1066 (C-O), 804 (C=C), 737 (C=C); δ_H (400MHz, CDCl$_3$) 3.66 (3H, s, H-9), 3.46 (1H, m, H-6), 2.07 (1H, dd, J = 9.24, 7.12 Hz, H-5ax), 2.04 (1H, dd, J = 9.24, 1.88 Hz, H-5eq), 1.93 (3H, s, H-10), 1.43 (1H, m, H-7), 0.68 (3H, d, J = 6.8 Hz, H-8) and 0.68 (3H, d, J = 6.8 Hz, H-8); δ_C (100 MHz, CDCl$_3$) 188.8 (C=O), 175.2 (C=O), 166.3 (C-2), 111.9 (C-3), 83.9 (C-6), 52.20 (C-9), 38.1 (C-5), 31.7 (C-7), 20.67 (C-10), 17.6 (C-8) and

16.9 (C-8); m/z (ESI+) 235 (M + Na)$^+$, 213 (M + H)$^+$. (Found 235.0952 (M + Na)$^+$.
$C_{11}H_{16}NaO_4$ requires 235.09).

Methyl 2-(furan-2-yl)-6-methyl-4-oxo-3,4-dihydro-2H-pyran-5-carboxylate (204)
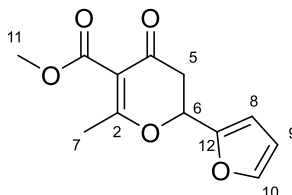
δ-Hydroxy-β-ketoester **185** (0.032 g, 0.15 mmol), trimethyl orthoacetate (0.04 mL, 0.30 mmol), Ac_2O (0.05 mL, 0.50 mmol), PhMe (1.00 mL); purification (petroleum ether – ethyl acetate = 4:1), percentage yield 0.012 g, 34 %, light yellow oil. υ max/cm^{-1} (film) 2950 (C-H), 2925 (C-H), 1705 (C=O), 1667 (C=C), 1381 (CH$_3$), 1039 (C-O); δ_H (400MHz, C_6D_6) 6.86 (1H, dd, J = 1.8, 0.8 Hz, H-13), 5.86 (1H, d, J = 3.3 Hz, H-11), 5.84 (1H, dd, J = 3.3, 1.8 Hz, H-12), 4.56 (1H, dd, J = 12.5, 3.9 Hz, H-6), 3.48 (3H, s, H-9), 2.51 (1H, dd, J = 16.6, 12.5 Hz, H5ax), 2.13 (1H, dd, J = 16.6, 3.9 Hz, H-5eq) and 1.78 (3H, s, H-7); δ_C (100 MHz, C_6D_6) 185.6 (C=O), 174.4 (C=O), 165.9 (C-2), 150.0 (C-12), 143.2 (C-8), 113.3 (C-3), 110.3 (C-10), 109.5 (C-9), 72.8 (C-6), 51.4 (C-11), 38.4 (C-5) and 19.3 (C-7); m/z (ESI+) 259 (M + Na)+, 237 (M + H)+, 205 (M - CH$_3$OH)+. (Found 259.0577 (M + Na)+. $C_{12}H_{12}NaO_5$ requires 259.0577).

Synthesis of dihydropyrans: amide acetal cyclisations

General procedure for the synthesis of 2-methyl dihydropyrans:

N,N-Dimethylacetamide dimethyl acetal (0.06 mL, 0.40 mmol) was added to a stirred solution of δ-hydroxy- β-ketoester (0.20 mmol) in dry CH_2Cl_2 (2.00 mL) at room temperature. After the mixture was stirred for 45 minute, then BF$_3$.OEt$_2$ (0.05 mL, 0.40 mmol) was added into mixture. The solution was stirred at room temperature and

monitored by TLC. Upon completion of the reaction, the mixture was diluted with EtOAc (40.0 mL) and washed with sat. aq. $NaHCO_3$ (10.0 mL). The aqueous layer was extracted with EtOAc (15.0 mL) and the combined organic extracts were washed with brine (10.0 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the DHP. Flash column chromatography (hexane – ethyl acetate) gave the product.

Methyl 6-isopropyl-2-methyl-4-oxo-5,6-dihydro-2H-pyran-3-carboxylate (205)
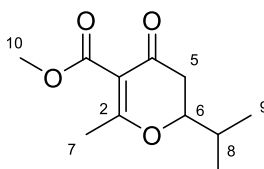
δ-Hydroxy-β-ketoester **182** (0.086 g, 0.46 mmol), *N,N*-dimethylacetamide dimethyl acetal (0.13 mL, 0.92 mmol), $BF_3.OEt_2$ (0.11 mL, 0.92 mmol), CH_2Cl_2 (4.00 mL), purification (hexane – ethyl acetate = 4:1): percentage yield 0.071 g, 73%, light yellow oil. υ max/cm^{-1} 2964 (C-H), 2882 (C-H), 1715 (C=O), 1673 (C=C), 1396 (CH_3), 1217 (C-O), 1082 (C-O), 1053 (C-O), 800 (C=C), 597 (C=C); δ$_H$ (400MHz, C_6D_6) 3.52 (3H, s, H-10), 3.30 (1H, m, H-6), 1.92 (1H, dd, *J* = 9.24, 7.12 Hz, H-5ax), 1.92 (1H, dd, *J* = 9.24, 1.88 Hz, H-5eq) 1.84 (3H, s, H-7), 1.30 (1H, m, H-8), 0.53 (3H, d, *J* = 6.8 Hz, H-9) and 0.47 (3H, d, *J* = 6.8 Hz, H-9); δ$_C$ (100 MHz, C_6D_6) 187.0 (C=O), 175.1 (C=O), 166.3 (C-2), 113.0 (C-3), 83.1 (C-6), 51.4 (C-10), 37.8 (C-5), 31.2 (C-8), 19.3 (C-7), 17.2 (C-9) and 16.9 (C-9); *m/z* (ESI$^+$) 235 (M + Na)$^+$, 213 (M + H)$^+$, (Found 235.0945 (M + Na)$^+$. $C_{11}H_{16}NaO_4$ requires; 235.0941.

Methyl 6-(furan-2-yl)-2-methyl-4-oxo-5,6-dihydro-2H-pyran-3-carboxylate (204)
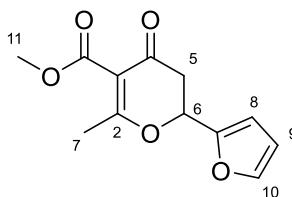
δ-Hydroxy-β-ketoester **185** (0.14 g, 0.65 mmol), *N,N*-dimethylacetamide dimethyl acetal (0.19 mL, 1.30 mmol), $BF_3.OEt_2$ (0.16 mL, 1.30 mmol), CH_2Cl_2 (4.00 mL), purification (hexane – ethyl acetate = 4:1): percentage yield 0.027 g, 18%, light orange oil . υ max/cm$^-$^{1} 2951 (C-H), 2920 (C-H), 1714 (C=O), 1663 (C=C), 1337 (CH_3), 1204 (C-O), 777 (C=C), 700 (C=C); δ_H (400MHz, C_6D_6) 6.86 (1H, dd, *J* = 1.8, 0.8 Hz, H-8), 5.86 (1H, d, *J* = 3.3 Hz, H-9), 5.84 (1H, dd, *J* = 3.3, 1.8 Hz, H-10), 4.56 (1H, dd, *J* = 12.5, 3.9 Hz, H-6), 3.48 (3H, s, H-11), 2.51 (1H, dd, *J* = 16.6, 12.5 Hz, H-5ax), 2.13 (1H, dd, *J* = 16.6, 3.9 Hz, H-5eq) and 1.78 (3H, s, H-7); δ_C (100 MHz, C_6D_6) 185.6 (C=O), 174.4 (C=O), 165.9 (C-2), 150.0 (C-12), 143.2 (C-8), 113.3 (C-3), 110.3 (C-10), 109.5 (C-9), 72.8 (C-6), 51.4 (C-11), 38.4 (C-5), and 19.3 (C-7); *m/z* (ESI$^+$) 259 (M + Na)$^+$, 237 (M + H)$^+$, (Found 259.0577 (M + Na)$^+$. $C_{12}H_{12}NaO_5$ requires; 259.0577.

Methyl 2-methyl-4-oxo-6-propyl-5,6-dihydro-2H-pyran-3-carboxylate (208)
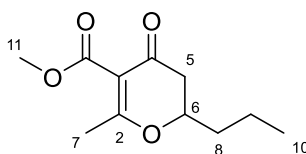
δ-Hydroxy-β-ketoester **183** (0.13 g, 0.70 mmol), *N,N*-dimethylacetamide dimethyl acetal (0.20 mL, 1.40 mmol), $BF_3.OEt_2$ (0.16 mL, 1.40 mmol), CH_2Cl_2 (5.00 mL), purification (hexane – ethyl acetate = 4:1): percentage yield 0.074 g, 50%, light yellow oil. υ max/cm$^-$^{1} 2957 (C-H), 2849 (C-H), 1715 (C=O), 1675 (C=C), 1397 (CH_3), 1205 (C-O), 1081 (C-O), 1043 (C-O), 802 (C=C), 579 (C=C); δ_H (400MHz, C_6D_6) 3.50 (1H, m, H-6), 3.47 (3H,

s, H-11), 1.88 (1H, dd, $J = 16.5$, 3.7 Hz, H-5ax), 1.80 (3H, s, H-7), 1.79 (1H, dd, $J = 16.5$, 13.1 Hz, H-5eq), 1.14–0.77 (4H, m, H-8, H-9) and 0.54 (3H, t, $J = 7.3$ Hz, H-10); δ_C (100 MHz, C_6D_6) 187.0 (C=O), 175.2 (C=O), 166.5 (C-2), 113.3 (C-3), 78.8 (C-6), 51.6 (C-11), 40.9 (C-5), 36.1 (C-8), 19.6 (C-7), 18.0 (C-9) and 13.7 (C-10); m/z (ESI$^+$) 235 (M + Na)$^+$, 213 (M + H)$^+$, (Found 235.0937 (M + Na)$^+$. $C_{11}H_{16}NaO_4$ requires; 235.0941.

2-Methyl-4-oxo-6-phenyl-5,6-dihydro-4H-pyran-3-carboxylic acid methyl ester (207)
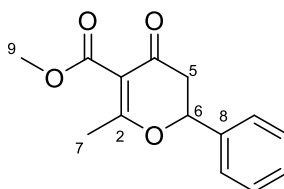
δ-Hydroxy-β-ketoester **138** (0.13 g, 0.52 mmol), *N,N*-dimethylacetamide dimethyl acetal (0.16 mL, 1.00 mmol), BF$_3$.OEt$_2$ (0.12 mL, 1.00 mmol), CH$_2$Cl$_2$ (4.00 mL), purification (hexane – ethyl acetate = 4:1): percentage yield 0.083 g, 65%, light yellow solid. υ max/cm^{-1} 2951 (C-H), 2920 (C-H), 1714 (C=O), 1663 (C=C), 1394 (CH$_3$), 1204 (C-O), 777 (C=C), 700 (C=C); δ_H (400MHz, C_6D_6) 7.44–7.34 (5H, m, Ar), 5.41 (1H, dd, $J = 14.3$, 3.3 Hz, H-6), 3.82 (3H, s, H-9), 2.88 (1H, dd, $J = 16.6$, 14.3 Hz, H-5ax), 2.67 (1H, dd, $J = 16.6$, 3.3 Hz, H-5eq), 2.28 (3H, s, H-7); δ_C (100 MHz, C_6D_6) 186.1 (C=O), 176.9 (C=O), 166.0 (C-2), 137.9 (C-8), 128.6 (Ar), 128.4 (Ar), 125.8 (Ar), 113.6 (C-3), 80.2 (C-6), 51.4 (C-9), 42.1 (C-5), and 19.3 (C-7); m/z (ESI$^+$) 269 (M + Na)$^+$, 247 (M + H)$^+$, (Found 269.0772 (M + Na)$^+$. $C_{14}H_{14}NaO_4$ requires; 269.0784.

**Methyl 6-(benzyloxymethyl)-2-methyl-4-oxo-5,6-dihydro-2H-pyran-3-carboxylate (209)**
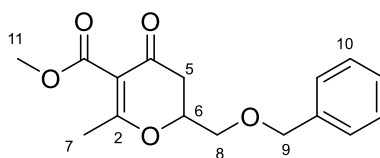
δ-Hydroxy-β-ketoester **184** (0.40 g, 1.52 mmol), *N,N*-dimethylacetamide dimethyl acetal (0.67 mL, 4.60 mmol), $BF_3.OEt_2$ (0.67 mL, 4.60 mmol), CH_2Cl_2 (15.00 mL), purification (hexane – ethyl acetate = 4:1): percentage yield 0.242 g, 55%, light yellow oil. υ max/cm^{-1} 2952 (C-H), 2865 (C-H), 1715 (C=O), 1672 (C=C), 1396 (CH_3), 1208 (C-O), 1078 (C-O), 1055 (C-O), 738 (C=C), 698 (C=C); $δ_H$ (400MHz, C_6D_6) 7.36–7.06 (5H, m, Ar), 4.16 (1H, d, *J* = 12.0 Hz, H-9), 4.11 (1H, d, *J* = 12.0 Hz, H-9), 3.79 (1H, dddd, *J* = 13.5, 5.0, 3.5, 3.5 Hz, H-6), 3.54 (3H, s, H-11), 3.03 (1H, dd, *J* = 10.5, 3.5 Hz, H-8), 2.97 (1H, dd, *J* = 10.5, 5.0 Hz, H-8), 2.26 (1H, dd, *J* = 16.5, 13.5 Hz, H-5ax), 1.99 (1H, dd, *J* = 16.5, 3.5 Hz, H-5eq), 1.87 (3H, s, H-7); $δ_C$ (100 MHz, C_6D_6) 186.6 (C=O), 175.1 (C=O), 166.4 (C-2), 138.2 (C-12), 128.6 (Ar), 128.1 (Ar), 127.9 (Ar), 113.3 (C-3), 78.0 (C-6), 73.2 (C-9), 70.4 (C-8), 51.7 (C-11), 37.4 (C-5), and 19.6 (C-7); *m/z* (ESI$^+$) 313 (M + Na)$^+$, 291 (M + H)$^+$, (Found 313.1038 (M + Na)$^+$. $C_{16}H_{18}NaO_5$ requires; 313.1046.

General procedure for the synthesis of 2-*H* dihydropyrans:

N,N-Dimethylformamide dimethyl acetal (0.03 mL, 0.20 mmol) was added to a stirred solution of δ-hydroxy-β-ketoester (0.20 mmol) in dry CH_2Cl_2 (2.00 mL) at room temperature. After the mixture was stirred for 45 minute, then $BF_3.OEt_2$ (0.03 mL, 0.20 mmol) was added into mixture. The solution was stirred at room temperature and monitored by TLC (hexane – ethyl acetate = 4: 1). Upon completion of the reaction, the mixture was diluted with EtOAc (40.0 mL) and washed with sat. aq. $NaHCO_3$ (10.0 mL).

The aqueous layer was extracted with EtOAc (15.0 mL) and the combined organic extracts were washed with brine (10.0 mL), dried over MgSO$_4$ and concentrated *in vacuo* to give the DHP. No further purification was carried out on the product.

Methyl 2-isopropyl-4-oxo-3,4-dihydro-2H-pyran-5-carboxylate (262)
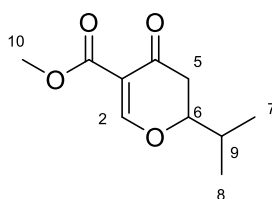
δ-Hydroxy-β-ketoester **182** (0.06 g, 0.30 mmol), *N,N*-dimethylformamide dimethyl acetal (0.04 mL, 0.30 mmol), BF$_3$.OEt$_2$ (0.04 mL, 0.30 mmol), CH$_2$Cl$_2$ (3.00 mL), yielded 0.057 g, 97%, light yellow oil. υ max/cm^{-1} 2962 (C-H), 1741 (C=O), 1699 (C=O), 1633 (C=C), 1435 (CH$_3$), 1383 (CH$_3$), 1295 (C-O), 1122 (C-O), 1047 (C-O), 771 (C=C), 593 (C=C); δ$_H$ (400MHz, CDCl$_3$) 8.33 (1H, s, H-2), 4.28–4.22 (1H, m, H-6), 3.76 (3H, s, H-10), 2.55 (1H, dd, *J* = 16.3, 13.6 Hz, H-5ax), 2.46 (1H, dd, *J* = 16.3, 3.8 Hz, H-5eq), 2.05–1.97 (1H, m, H-9), 0.97 (3H, d, *J* = 6.8 Hz, H-7) and 0.99 (3H, d, *J* = 6.8 Hz, H-8); δ$_C$ (100 MHz, CDCl$_3$) 187.8 (C=O), 171.8 (C-2), 164.2 (C=O), 110.6 (C-3), 85.7 (C-6), 51.9(C-10), 39.0 (C-5), 31.7 (C-9), 17.8 (C-7) and 17.6 (C-8); *m/z* (ESI$^+$) 221 (M + Na)$^+$, 199 (M + H)$^+$, (Found 221.0786 (M + Na)$^+$. C$_{10}$H$_{14}$NaO$_4$ requires; 221.0790).

Methyl 4-oxo-2-propyl-3,4-dihydro-2H-pyran-5-carboxylate (263)
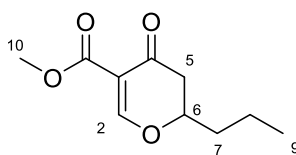
δ-Hydroxy-β-ketoester **183** (0.05 g, 0.27 mmol), *N,N*-dimethylformamide dimethyl acetal (0.04 mL, 0.27 mmol), $BF_3.OEt_2$ (0.04 mL, 0.27 mmol), CH_2Cl_2 (3.00 mL), yielded 0.049 g, 91%, light yellow oil. υ max/cm^{-1} 2958 (C-H), 2874 (C-H), 1741 (C=O), 1700 (C=O), 1589 (C=C), 1435 (CH_3), 1380 (CH_3), 1300 (C-O), 1147 (C-O), 1074 (C-O), 799 (C=C), 506 (C=C); δ_H (400MHz, C_6D_6) 7.97 (1H, s, H-2), 3.71–3.64 (1H, m, H-6), 3.52 (3H, s, H-10), 1.97 (1H, dd, *J* = 16.2, 4.1 Hz, H-5eq), 1.89 (1H, dd, *J* = 16.2, 12.4 Hz, H-5ax), 1.24–0.98 (2H, m, H-7), 0.98–0.86 (2H, m, H-8) and 0.64 (3H, t, *J* = 7.2 Hz, H-9); δ_C (100 MHz, C_6D_6) 187.6 (C=O), 171.5 (C-2), 164.5 (C=O), 116.9 (C-3), 81.3 (C-6), 51.9 (C-10), 41.6 (C-5), 36.0 (C-7), 17.9 (C-8) and 13.7 (C-9); *m/z* (ESI$^+$) 221 (M + Na)$^+$, 199 (M + H)$^+$, (Found 221.0782 (M + Na)$^+$. $C_{10}H_{14}NaO_4$ requires; 221.0790).

Methyl 4-oxo-2-phenyl-3,4-dihydro-2H-pyran-5-carboxylate (264)
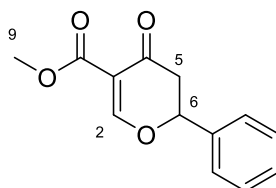
δ-Hydroxy-β-ketoester **138** (0.05 g, 0.20 mmol), *N,N*-dimethylformamide dimethyl acetal (0.03 mL, 0.20 mmol), $BF_3.OEt_2$ (0.03 mL, 0.20 mmol), CH_2Cl_2 (2.00 mL), yielded 0.045 g, 96 %, orange solid. υ max/cm^{-1} 2955 (C-H), 1738 (C=O), 1572 (C=C), 1472 (Ar), 1290 (C-O), 1244 (C-O), 1146 (C-O), 845 (Ar), 761 (Ar), 698 (C=C); δ_H (400MHz, CDCl$_3$) 8.43 (1H, s, H-2), 7.43–7.36 (5H, m, Ar), 5.54 (1H, dd, *J* = 12.0, 4.0 Hz, H-6), 3.81 (3H, s, H-9), 2.96 (1H, dd, *J* = 16.0, 4.0 Hz, H-5ax) and 2.76 (1H,d, *J* = 16.0, 4.0 Hz, H-5eq); δ_C (100 MHz, CDCl$_3$) 186.8 (C=O), 171.3 (C-2), 164.2 (C=O), 136.9 (Ar), 129.4 (Ar), 129.0 (Ar), 126.2 (Ar), 111.2 (C-3), 82.3 (C-6), 52.1 (C-9) and 43.1 (C- 5); *m/z* (ESI$^+$) 255 (M + Na)$^+$, 233 (M + H)$^+$, (Found 255.0631 (M + Na)$^+$. $C_{13}H_{12}NaO_4$ requires; 255.0633.

Methyl 2-(furan-2-yl)-4-oxo-3,4-dihydro-2H-pyran-5-carboxylate (259)
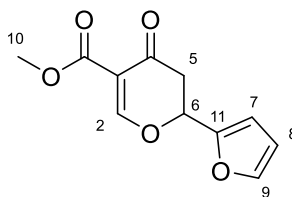
δ-Hydroxy-β-ketoester **185** (0.69 g, 3.29 mmol), *N,N*-dimethylformamide dimethyl acetal (0.44 mL, 3.30 mmol), BF$_3$.OEt$_2$ (0.44 mL, 3.30 mmol), CH$_2$Cl$_2$ (33.00 mL), yielded 0.674 g, 92 %, light yellow oil . υ max/cm^{-1} 2953 (C-H), 1738 (C=O), 1704 (C=O), 1579 (C=C), 1296 (C-O), 1133 (C-O), 1013 (C-O), 816 (C=C), 732 (C=C); δ$_H$ (400MHz, CDCl$_3$) 8.27 (1H, s, H-2), 7.44 (1H, dd, *J* = 1.8, 0.6 Hz, H-7), 6.45 (1H, d, *J* = 3.3 Hz, H-8), 6.36 (1H, dd, *J* = 3.3, 1.8 Hz, H-9), 5.58 (1H, dd, *J* = 11.5, 4.3 Hz, H-6), 3.74 (3H, s, H-10), 3.07 (1H, dd, *J* = 16.6, 11.5 Hz, H-5ax) and 2.79 (1H, dd, *J* = 16.6, 4.3 Hz, H-5eq); δ$_C$ (100 MHz, CDCl$_3$) 186.8 (C=O), 170.5 (C-2), 170.4 (C=O), 163.8 (C-11), 148.7 (C-8), 143.9 (C-7), 110.8 (C-3), 110.6 (C-9), 74.7 (C-6), 51.9 (C-10) and 39.3 (C-5); *m/z* (ESI$^+$) 245 (M + Na)$^+$, 223 (M + H)$^+$, (Found 245.0423 (M + Na)$^+$. C$_{11}$H$_{10}$NaO$_5$ requires; 245.0426).

Methyl 4-oxo-2-((((triisopropylsilyl)oxy)methyl)-3,4-dihydro-2H-pyran-5-carboxylate (265)
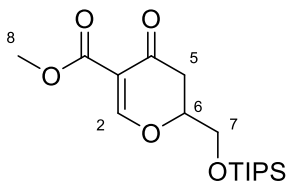
δ-Hydroxy-β-ketoester **194** (0.03 g, 0.09 mmol), *N,N*-dimethylformamide dimethyl acetal (0.02 mL, 0.09 mmol), BF$_3$.OEt$_2$ (0.02 mL, 0.09 mmol), CH$_2$Cl$_2$ (1.00 mL), yielded 0.029 g, 88%, light orange oil . υ max/cm^{-1} 2953 (C-H), 1738 (C=O), 1704 (C=O), 1579 (C=C), 1465 (CH$_2$), 1296 (C-O), 1133 (C-O), 1013 (C-O), 816 (C=C), 732 (C=C); δ$_H$ (400MHz,

C_6D_6) 7.99 (1H, s, H-2), 3.81–3.75 (1H, m, H-6), 3.49 (3H, s, H-8), 3.29–3.25 (1H, m, H-7), 2.42 (1H, dd, J = 16.2, 13.0 Hz, H-5ax), 2.07 (1H, dd, J = 16.2, 3.8 Hz, H-5eq) and 1.10–9.94 (21H, m, OTIPS); δ_C (100 MHz, C_6D_6) 187.4 (C=O), 171.4 (C-2), 164.3 (C=O), 110.6 (C-3), 81.5 (C-6), 64.2 (C-7), 52.0 (C-8), 38.2 (C-5), 17.9 (C-OTIPS) and 11.9 (C-OTIPS); m/z (ESI$^+$) 365 (M + Na)$^+$ (Found 365.1741 (M + Na)$^+$. $C_{17}H_{30}NaO_5Si$ requires; 365.1760).

Methyl 2-(2-methyloxazol-4-yl)-4-oxo-3,4-dihydro-2H-pyran-5-carboxylate (266)
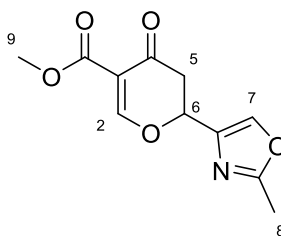
δ-Hydroxy-β-ketoester **187** (0.08 g, 0.34 mmol), *N,N*-dimethylformamide dimethyl acetal (0.04 mL, 0.34 mmol), BF$_3$.OEt$_2$ (0.04 mL, 0.34 mmol), CH$_2$Cl$_2$ (2.00 mL), yielded 0.062 g, 77%, light yellow oil . υ max/cm^{-1} 2953 (C-H), 1738 (C=O), 1704 (C=O), 1579 (C=C), 1465 (CH$_2$), 1383 (CH$_3$), 1296 (C-N), 1133 (C-O), 1013 (C-O), 816 (C=C), 732 (C=C); δ_H (400MHz, CDCl$_3$) 8.34 (1H, s, H-2), 7.61 (1H, s, H-7), 5.55 (1H, dd, J = 12.0, 4.0 Hz, H-6), 3.80 (3H, s, H-9), 3.10 (1H, dd, J = 16.7, 12.0 Hz, H-5ax), 2.81 (1H, dd, J = 16.7, 4.0 Hz, H-5eq) and 2.48 (3H, s, H-8); δ_C (100 MHz, CDCl$_3$) 198.7 (C=O), 167.7 (C-2), 160.1 (C=O), 137.2 (C-3), 63.0 (C-10), 52.6 (C-6), 49.6 (C-9), 45.5 (C-5), 31.5 (C-11), 30.1 (C-7) and 14.2 (C-8); m/z (ESI$^+$) 260 (M + Na)$^+$ (Found 260.0523 (M + Na)$^+$. $C_{11}H_{11}NNaO_5$ requires; 260.0535).

Methyl 4-oxo-2-(prop-1-en-1-yl)-3,4-dihydro-2H-pyran-5-carboxylate (268)
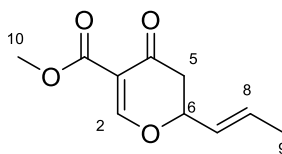
δ-Hydroxy-β-ketoester **188** (0.30 g, 1.61 mmol), *N,N*-dimethylformamide dimethyl acetal (0.21 mL, 1.61 mmol), BF$_3$.OEt$_2$ (0.21 mL, 1.61 mmol), CH$_2$Cl$_2$ (16.10 mL), yielded 0.274 g, 87%, light orange oil. υ max/cm^{-1} 2952 (C-H), 2919 (C-H), 1740 (C=O), 1701 (C=O), 1579 (C=C), 1435 (CH$_2$), 1380 (CH$_3$), 1297 (C-O), 1135 (C-O), 1053 (C-O), 965 (C=C); δ$_H$ (400MHz, CDCl$_3$) 8.01 (1H, s, H-2), 5.28 (1H, m, H-7), 5.08 (1H, m, H-8), 4.20 (1H, ddd, *J* = 8.6, 7.0, 7.0 Hz, H-6), 3.51 (3H, s, H-10), 2.08 (2H, m, H-5) and 1.31 (3H, d, *J* = 6.5, H-9); δ$_C$ (100 MHz, CDCl$_3$) 181.2 (C=O), 169.9 (C-2), 164.3 (C=O), 131.5 (C-7), 127.0 (C-8), 111.5 (C-3), 80.9 (C-6), 51.3 (C-10), 41.8 (C-5) and 17.5 (C-9); *m/z* (ESI$^+$) 219 (M + Na)$^+$ (Found 219.0629 (M + Na)$^+$. C$_{10}$H$_{12}$NaO$_4$ requires; 219.0628).

Methyl 4-oxo-2-styryl-3,4-dihydro-2H-pyran-5-carboxylate (269)
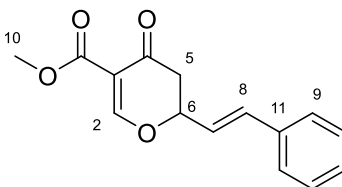
δ-Hydroxy-β-ketoester **189** (0.11 g, 0.43 mmol), *N,N*-dimethylformamide dimethyl acetal (0.11 mL, 0.85 mmol), BF$_3$.OEt$_2$ (0.11 mL, 0.85 mmol), CH$_2$Cl$_2$ (4.00 mL), yielded 0.107 g, 97%, orange solid. υ max/cm^{-1} 2951 (C-H), 1693 (C=O), 1569 (C=C), 1436 (CH$_2$), 1260 (C-O), 1295 (C-O), 1060 (C-O), 966 (C=C), 747 (Ar), 692 (Ar); δ$_H$ (400MHz, CDCl$_3$) 8.04 (1H, s, H-2), 7.10–7.03 (5H, m, Ar), 6.19 (1H, dd, *J* = 16.0, 1.1 Hz, H-8), 5.73 (1H, dd, *J* = 16.0, 6.8 Hz, H-7), 4.26 (1H, ddd, *J* = 9.1, 6.9, 6.8 Hz, H-6), 3.53 (3H,

s, H-10) and 2.12 (2H, m, H-5); δ_C (100 MHz, CDCl$_3$) 193.2 (C=O), 184.9 (C=O), 169.9 (C-2), 164.9 (C-11)), 135.6 (C-Ar), 134.3 (C-8), 128.9 (Ar), 127.1 (Ar), 124.2 (C-7), 111.8 (C-3), 81.0 (C-6), 51.5 (C-10) and 42.0 (C-5); m/z (ESI$^+$) 281 (M + Na)$^+$ (Found 281.0781 (M + Na)$^+$. C$_{15}$H$_{14}$NaO$_4$ requires; 281.0784).

Methyl 2-methyl-4-oxo-3,4-dihydro-2H-pyran-5-carboxylate (270)
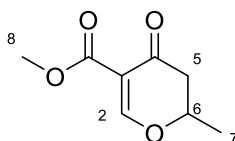
δ-Hydroxy-β-ketoester **197** (0.08 g, 0.51 mmol), *N,N*-dimethylformamide dimethyl acetal (0.07 mL, 0.51 mmol), BF$_3$.OEt$_2$ (0.07 mL, 0.51 mmol), CH$_2$Cl$_2$ (5.00 mL), yield 0.061 g, 70 %, light yellow oil. υ max/cm^{-1} 2962 (C-H), 1741 (C=O), 1699 (C=O), 1637 (C=C), 1430 (CH$_3$), 1383 (CH$_3$), 1296 (C-O), 1122 (C-O), 1047 (C-O), 771 (C=C), 593 (C=C); δ_H (400MHz, C$_6$D$_6$) 7.81 (1H, s, H-2), 3.55 (1H, ddd, J = 12.5, 6.4, 3.8 Hz, H-6), 3.36 (3H, s, H-8), 1.74 (1H, dd, J = 16.2, 3.8 Hz, H-5eq), 1.64 (1H, dd, J = 16.2, 12.5 Hz, H-5ax), and 0.56 (3H, d, J = 6.4 Hz, H-7); δ_C (100 MHz, C$_6$D$_6$) 186.2 (C=O), 169.7 (C-2), 164.2 (C=O), 110.9 (C-3), 76.9 (C-6), 51.3 (C-8), 42.3 (C-5) and 19.1 (C-7); m/z (ESI$^+$) 193 (M + Na)$^+$, 171 (M + H)$^+$, (Found 193.0476 (M + Na)$^+$, (Found 171.0651 (M + H)$^+$. C$_8$H$_{10}$NaO$_4$ requires; 193.0471). C$_8$H$_{11}$O$_4$ requires; 171.0652).

General Procedure for L-Selectride® reduction of dihydropyrans:

A 1.0 M solution of L-Selectride® in THF (0.04 mL, 0.19 mmol) was added to a stirred solution of DHP (0.04 mmol) in THF (1.00 mL) at −78 °C. The mixture was stirred for 1 hour and monitor by TLC until completion, when it was partitioned between Et$_2$O (10.0 mL) and sat. aq. NHCl$_4$ (10.0 mL). The aqueous layer was washed with Et$_2$O (10.0 mL) and the combined organic extracts were washed with brine (20.0 mL), dried over MgSO$_4$

and concentrated in vacuo. Purification by flash column chromatography (hexane – ethyl acetate) afforded the product.

(2R*,3R*,6R*)-Methyl 6-((benzyloxy)methyl)-2-butyl-4-oxotetrahydro-2H-pyran-3-carboxylate (214)
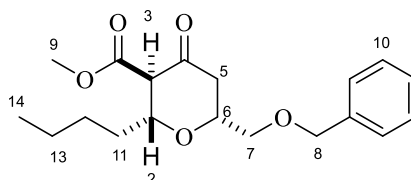
Dihydropyran **200** (0.04 g, 0.12 mmol), L-Selectride® solution 1.0M in THF (0.12 mL, 0.56 mmol), THF (3.00 mL), purification (hexane – ethyl acetate = 4:1): percentage yield 0.038 g, 95 %, light yellow oil. υ max/cm^{-1} (film) 2955 (C-H), 2928 (C-H), 2861 (C-H), 1744 (C=O), 1716 (C=O), 1600 (Ar), 1375 (CH$_3$), 1263 (C-O), 1112 (C-O), 1029 (C-O), 831 (Ar), 736 (Ar); δ_H (400MHz, C$_6$D$_6$) 7.27–7.17 (4H, m, Ar), 7.11–7.06 (1H, m, Ar), 4.27 (1H, d, J = 12.7 Hz, H-8), 4.24 (1H, d, J = 12.7 Hz, H-8), 3.94 (1H, m, H-6), 3.43 (3H, s, H-9), 3.40 (1H, m, H-2), 3.14 (1H, s, H-3), 3.15 (1H, dd, J = 15.4, 3.8 Hz, H-7), 3.12 (1H, dd, J = 15.4, 7.7 Hz, H-7), 2.18 (1H, dd, J = 14.2, 2.7 Hz, H-5eq), 2.04 (1H, dd, J = 14.2, 11.5 Hz, H-5ax), 1.58–1.50 (2H, m, H-13), 1.44–1.29 (2H, m, H-12), 1.27–1.15 (2H, m, H-11) and 0.83 (3H, t, J = 7.32 Hz, H-14); δ_C (100 MHz, C$_6$D$_6$) 193.3 (C=O), 168.5 (C=O), 138.5 (Ar), 128.3 (Ar), 127.6 (Ar), 127.4 (Ar), 78.5 (C-6), 76.2 (C-2), 72.9 (C-8), 71.9 (C-7), 62.9 (C-3), 51.1 (C-9), 43.3 (C-5), 34.7 (C-13), 27.4 (C-12), 22.6 (C-11) and 13.9 (C-14); m/z (ESI$^+$) 357 (M + Na)$^+$, 335 (M + H)$^+$. (Found 357.1659 (M + Na)$^+$. C$_{19}$H$_{26}$NaO$_5$ requires 357.1672).

General Procedure for L-Selectride reduction of dihydropyrans with electrophile quench:

A 1.0 M solution of L-Selectride® in THF (0.04 mL, 0.19 mmol) was added to a stirred solution of DHP (0.04 mmol) in THF (1.00 mL) at -78 °C. The mixture was stirred for 1 hour, after which time the electrophile (0.40 mmol) was added. The reaction mixture was stirred at room temperature until complete, when it was partitioned between Et_2O (10.0 mL) and sat. aq. $NHCl_4$ (10.0 mL). The aqueous layer was washed with Et_2O (10.0 mL) and the combined organic extracts were washed with brine (20.0 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexane – ethyl acetate or cyclohexane – ethyl acetate) afforded the product.

(2R*,3R*,6R*)-Methyl 6-isopropyl-2,3-dimethyl-4-oxotetrahydro-2H-pyran-3 carboxylate (216)
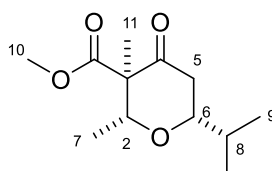
Dihydropyran **205** (0.07 g, 0.34 mmol), L-Selectride® solution 1.0M in THF (0.34 mL, 1.59 mmol), MeI (0.42 mL, 6.73 mmol), THF (9.00 mL); purification (hexane – ethyl acetate = 7: 3); Percentage yield 0.074 g, 96%, light yellow oil; υ max/cm^{-1} 2960 (C-H), 2878 (C-H), 1740 (C=O), 1712 (C=O), 1267 (C-O), 1096 (C-O); δ_H (400MHz, C_6D_6) 4.15 (1H, q, J = 6.3 Hz, H-2), 3.43 (3H, s, H-10), 2.99–2.94 (1H, m, H-6), 2.03 (1H, dd, J = 14.8, 9.6 Hz, H-5ax), 1.98 (1H, dd, J = 14.8, 4.4 Hz, H-5eq), 1.48–1.40 (1H, m, H-8), 1.28 (3H, s, H-11), 1.03 (3H, d, J = 6.3 Hz, H-7), 0.77 (3H, d, J = 6.8 Hz, H-9) and 0.65 (3H, d, J = 6.8 Hz, H-9); δ_C (100 MHz, C_6D_6) 205.6 (C=O), 193.2 (C=O), 171.1 (C-3), 81.3 (C-6), 75.9 (C-2), 51.6 (C-10), 39.8 (C-5), 32.8 (C-8), 17.6 (C-9), 17.4 (C-9), 15.7

(C-7) and 13.5 (C-11) ppm; m/z (ESI$^+$) 251 (M + Na)$^+$, 229 (M + H)$^+$, (Found 251.1260

(M + Na)$^+$. $C_{12}H_{20}NaO_4$ requires; 251.1254).

(2R*,3R*,6S*)-Methyl 2,3-dimethyl-4-oxo-6-propyltetrahydro-2H-pyran-3-carboxylate (217)
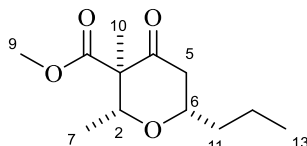
Dihydropyran **208** (0.09 g, 0.47 mmol), L-Selectride$^®$ solution 1.0M in THF (0.46 mL,

2.20 mmol), MeI (0.57 mL, 9.30 mmol), THF (12.00 mL); purification (hexane – ethyl

acetate = 7: 3); Percentage yield 0.051 g, 48%, light yellow oil; υ max/cm^{-1} 2957 (C-H),

2874 (C-H), 1739 (C=O), 1712 (C=O), 1263 (C-O), 1095 (C-O); δ_H (400MHz, C_6D_6)

4.16 (1H, q, J = 6.2 Hz, H-2), 3.42 (3H, s, H-9), 3.28–3.18 (1H, m, H-6), 1.99 (1H, dd, J

= 14.8, 4.5 Hz, H-5), 1.94 (1H, dd, J = 14.8, 2.6 Hz, H-5), 1.29 (3H, s, H-10), 1.83–1.26

(2H, m, H-11), 1.19–1.05 (1H, m, H12), 1.03 (3H, d, J = 6.2 Hz, H-7) and 0.75 (3H, t, J

= 7.2 Hz, H- 13); δ_C (100 MHz, C_6D_6) 198.3 (C=O), 171.1 (C=O), 76.4 (C-6), 76.0 (C-

2), 62.3 (C-3), 51.5 (C-9), 43.0 (C-5), 38.1 (C-11), 18.2 (C12), 15.8 (C-7), 13.7 (C-13)

and 13.5 (C-10); m/z (ESI$^+$) 251 (M + Na)$^+$, 229 (M + H)$^+$, (Found 251.1255 (M + Na)$^+$.

$C_{12}H_{20}NaO_4$ requires; 251.1254).

(2R*,3R*,6R*)-Methyl 2,3-dimethyl-4-oxo-6-phenyltetrahydro-2H-pyran-3-carboxylate (218)
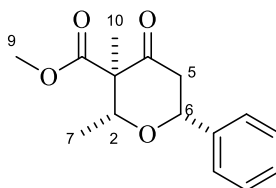
Dihydropyran **207** (0.13 g, 0.54 mmol), L-Selectride® solution 1.0M in THF (0.53 mL, 2.50 mmol), MeI (0.67 mL, 10.80 mmol), THF (14.00 mL); purification (hexane – ethyl acetate = 7: 3); Percentage yield 0.102 g, 72%, light yellow solid; υ max/cm^{-1} 2985 (C-H), 2951 (C-H), 1737 (C=O), 1710 (C=O), 1245 (C-O), 1266 (C-O), 1094 (C-O), 761 (Ar), 698 (Ar), 563 (Ar); δ_H (400MHz, C_6D_6) 7.19–7.17 (3H, m, Ar), 7.14–7.13 (2H, m, Ar), 4.35 (1H, q, J = 6.2 Hz, H-2), 4.32–4.28 (1H, m, H-6), 3.48 (3H, s, H-9), 2.34 (1H, dd, J = 15.0, 9.2 Hz, H-5ax), 2.30 (1H, dd, J = 15.0, 3.3 Hz, H-5eq), 1.37 (3H, s, H-10) and 1.12 (3H, d, J = 6.2 Hz, H-7); δ_C (100 MHz, C_6D_6) 193.2 (C=O), 170.9 (C=O), 141.0 (Ar), 128.4 (Ar), 127.6 (Ar), 125.6 (Ar), 78.3 (C-2), 76.3 (C-6), 62.3 (C-3), 51.6 (C-9), 44.9 (C-5), 15.8 (C-7) and 13.6 (C-10); m/z (ESI$^+$) 285 (M + Na)$^+$, 262 (M + H)$^+$, (Found 285.1095 (M + Na)$^+$. $C_{15}H_{18}NaO_4$ requires; 285.1097).

(2R*,3R*,6R*)-Methyl 6-(furan-2-yl)-2,3-dimethyl-4-oxotetrahydro-2H-pyran-3-carboxylate (219)
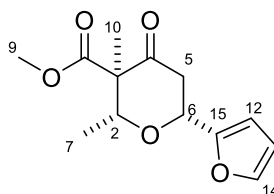
Dihydropyran **204** (0.04 g, 0.19 mmol), L-Selectride® solution 1.0M in THF (0.19 mL, 0.89 mmol), MeI (0.23 mL, 3.71 mmol), THF (5.00 mL); purification (hexane – ethyl acetate = 7: 3); Percentage yield 0.025 g, 53%, light yellow oil; υ max/cm^{-1} 2985 (C-H), 2952 (C-H), 1737 (C=O), 1713 (C=O), 1271 (C-O), 1260 (C-O), 1088 (C-O), 743 (C=C), 558 (C=C); δ_H (400MHz, C_6D_6) 7.01–6.99 (1H, m, H-14), 5.99 (1H, m, H-13), 5.96 (1H, m, H-12), 4.30 (1H, dd, J = 12.1, 3.1 Hz, H-6), 4.25 (1H, q, J = 6.3 Hz, H-2), 3.39 (3H, s, H-9), 2.71 (1H, dd, J = 15.1, 12.1 Hz, H-5ax), 2.23 (1H, dd, J = 15.1, 3.1 Hz, H-5eq), 1.32 (3H, s, H-10) and 1.02 (3H, d, J = 6.3 Hz, H-7); δ_C (100 MHz, C_6D_6) 204.0 (C=O),

170.1 (C=O), 152.1 (C-15), 142.6 (C-14), 109.8 (C-13), 107.7 (C-12), 75.9 (C-2), 71.2 (C-6), 62.5 (C-3), 51.9 (C-9), 40.3 (C-5), 15.9 (C-7) and 13.2 (C-10); m/z (ESI$^+$) 275 (M + Na)$^+$, 253 (M + H)$^+$, (Found 275.0891 (M + Na)$^+$. $C_{13}H_{16}NaO_5$ requires; 275.0890).

(2R*,3R*,6R*)-Methyl 6-((benzyloxy)methyl)-2,3-dimethyl-4-oxotetrahydro-2H-pyran-3-carboxylate (215)
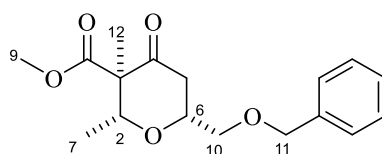
Dihydropyran **209** (0.15 g, 0.51 mmol), L-Selectride$^®$ solution 1.0M in THF (0.51 mL, 2.39 mmol), MeI (0.31 mL, 5.12 mmol), THF (13.00 mL); purification (hexane – ethyl acetate = 7:3), Percentage yield 0.095 g, 61%, light yellow oil; υ max/cm^{-1} (film) 2955 (C-H), 2913 (C-H), 2849 (C-H), 1738 (C=O), 1712 (C=O), 1454 (CH$_3$), 1260 (C-O), 1089 (C-O), 1016 (C-O), 795 (Ar), 736 (Ar), 697 (Ar); δ_H (400MHz, C$_6$D$_6$) 7.24–7.17 (2H, m, Ar), 7.15–7.06 (3H, m, Ar), 4.29 (1H, d, J = 12.2 Hz, H-11), 4.25 (1H, d, J = 12.2 Hz, H-11), 4.18 (1H, q, J = 6.3 Hz, H- 2), 3.51–3.46 (1H, m, H-6), 3.39 (3H, s, H-9), 3.19–3.12 (2H, m, H-10), 2.36 (1H, dd, J = 15.1, 11.8 Hz, H-5ax), 2.07 (1H, dd, J = 15.1, 3.1 Hz, H-5eq), 1.28 (3H, s, H-12) and 1.02 (3H, d, J = 6.3 Hz, H-7); NOE H6 – H2 2.84%, H6 – H8 2.60% and H6 – H5 1.12%, H2 – H6 2.83%, Me-2 – H5ax 0.82%; δ_C (100 MHz, C$_6$D$_6$) 204.0 (C=O), 170.9 (C=O), 138.4 (Ar), 128.3 (Ar), 127.9 (Ar), 127.1 (Ar), 76.2 (C-2), 75.9 (C-6), 73.1 (C-11), 71.9 (C-10), 62.6 (C-3), 51.5 (C-9), 39.4 (C-5), 15.8 (C-7) and 13.4 (C-12); m/z (ESI$^+$) 329 (M + Na)$^+$. (Found 329.1361 (M + Na)$^+$. $C_{17}H_{22}$ NaO$_5$ requires 329.1359).

(2R*,3R*,6R*)-Methyl 6-((benzyloxy)methyl)-2-butyl-3-methyl-4 oxotetrahydro-2H-pyran-3-carboxylate (213)
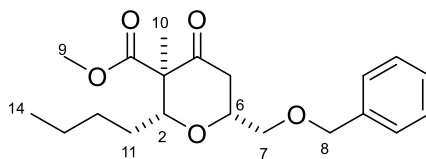
Dihydropyran **200** (0.05 g, 0.17 mmol), L-Selectride® solution 1.0M in THF (0.16 mL, 0.79 mmol), MeI (0.20 mL, 3.30 mmol), THF (4.00 mL); purification (hexane – ethyl acetate = 7:3), Percentage yield 0.033 g, 57%, light yellow oil; υ max/cm^{-1} (film) 2913 (C-H), 2849 (C-H), 1738 (C=O), 1712 (C=O), 1454 (CH$_3$), 1260 (C-O), 1089 (C-O), 1016 (C-O), 795 (Ar), 736 (Ar), 697 (Ar); δ_H (400MHz, C$_6$D$_6$) 7.27–7.17 (4H, m, Ar), 7.14–7.08 (1H, m, Ar), 4.31 (1H, d, J = 12.3 Hz, H-8), 4.27 (1H, d, J = 12.3 Hz, H-8), 4.08 (1H, dd, J = 9.5, 2.2 Hz, H-2), 3.51–3.45 (1H, m, H-6), 3.43 (3H, s, H-9), 3.17 (2H, m, H-7), 2.37 (1H, dd, J = 15.1, 11.8 Hz, H-5ax), 2.10 (1H, dd, J = 15.1, 3.1 Hz, H-5eq), 1.63–1.50 (2H, m, H-11), 1.34 (3H, s, H-10), 1.27–1.15 (4H, m, H-12, H-13) and 0.84 (3H, t, J = 8.3 Hz, H-14); δ_C (100 MHz, C$_6$D$_6$) 204.9 (C=O), 171.0 (C=O), 138.6 (Ar), 128.3 (Ar), 127.8 (Ar), 126.5 (Ar), 80.2 (C-2), 76.2 (C-6), 72.7 (C-8), 71.9 (C-7), 62.2 (C-3), 51.3 (C-9), 39.9 (C-5), 30.6 (C-11), 28.5 (C-12), 22.6 (C-13), 14.05 (C-14) and 13.8 (C-10); m/z (ESI$^+$) 371 (M + Na)$^+$. (Found 371.1828 (M + Na)$^+$. C$_{20}$H$_{28}$ NaO$_5$ requires 371.1829).

General Procedure for L-Selectride reduction of ketone on tetrahydropyrans:

A 1.0 M solution of L-Selectride® in THF (0.36 mL, 1.68 mmol) was added to a stirred solution of THP (0.14 mmol) in THF (2.00 mL) at −78 °C. The mixture was stirred for 1 hour at −78 °C and followed with stirring at room temperature until completion. The

reaction mixture was stirred at room temperature until completion. Then it was partitioned between Et$_2$O (10.0 mL) and sat. aq. NHCl$_4$ (10.0 mL). The aqueous layer was washed with Et$_2$O (10.0 mL) and the combined organic extracts were washed with brine (20.0 mL), dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography (toluene – methanol) afforded the product.

(2R*,3S*,4S*,6R*)-M-ethyl4-hydroxy-6-isopropyl-2,3-dimethyl-tetrahydro-2H-pyran-3-carboxylate (251)
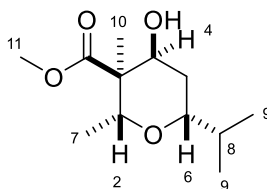
Tetrahydropyrans **216** (0.07 g, 0.33 mmol), L-Selectride® solution 1.0M in THF (0.85 mL, 4.00 mmol), THF (4.00 mL); purification (toluene – methanol = 49 : 1), Yield 0.044 g, 59%, light yellow oil; υ max/cm^{-1} (film) 3376 (OH), 2953 (C-H), 2931 (C-H), 2877 (C-H), 1735 (C=O), 1465 (CH$_2$), 1379 (CH$_3$), 1246 (C-O), 1090 (C-O), 1028 (C-O); δ$_H$ (400MHz, C$_6$D$_6$) 4.39 (1H, q , J = 6.3 Hz, H-2), 3.87 (1H, dd, J = 6.0, 3.0 Hz, H- 4), 3.61 (1H, ddd, J = 9.5, 6.2, 3.3 Hz, H-6), 3.24 (3H, s, H-11), 2.74 (1H, br s, OH), 1.66–1.58 (1H, m, H-8), 1.42 (1H, ddd, J = 16.0, 9.5, 3.0 Hz, H-5ax), 1.37 (1H, ddd, J = 16.0, 6.0, 3.3 Hz, H-5eq), 1.23 (3H, d, J = 6.3 Hz, H-7), 1.13 (3H, s, H-10), 0.98 (3H, d, J = 6.8 Hz, H-9) and 0.87 (3H, d, J = 6.8 Hz, H-9); δ$_C$ (100 MHz, C$_6$D$_6$) 193.1 (C=O), 76.2 (C-6), 71.7 (C-4), 70.7 (C-2), 50.1 (C-11), 41.9 (C-3), 32.7 (C-8), 30.6 (C-5), 18.2 (C-9), 18.0 (C-9), 16.9 (C-7) and 14.0 (C-10); *m/z* (ESI$^+$) 253 (M + Na)$^+$. (Found 253.1408 (M + Na)$^+$. C$_{12}$H$_{22}$ NaO$_4$ requires 253.1410).

(2*R**,3*S**,4*S**,6*R**)-Methyl4-hydroxy-2,3-dimethyl-6-phenyl-tetrahydro-2H-pyran-3-carboxylate (252).
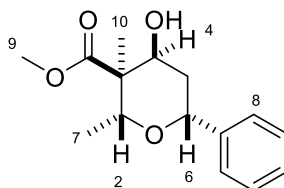
Tetrahydropyrans **218** (0.10 g, 0.39 mmol), L-Selectride® solution 1.0M in THF (0.98 mL, 4.63 mmol), THF (8.00 mL); purification (toluene – methanol = 49 : 1), Percentage yield 0.029 g, 29%, light yellow oil; υ max/cm^{-1} (film) 3462 (OH), 2923 (C-H), 2856 (C-H), 1733 (C=O), 1453 (CH$_3$), 1262 (C-O), 1091 (C-O), 1082 (C-O), 735 (Ar), 697 (Ar); δ_H (400MHz, C$_6$D$_6$) 7.41–7.34 (3H, m, Ar), 7.12–7.08 (2H, m, Ar), 4.99 (1H, dd, J = 11.1, 3.4 Hz, H-6), 4.58 (1H, q, J = 6.3 Hz, H-2), 3.84 (1H, dd, J = 6.4, 3.0 Hz, H- 4), 3.25 (3H, s, H-9), 2.82 (1H, br s, OH), 1.71 (1H, ddd, J = 14.0, 11.1, 3.0 Hz, H-5ax), 1.64 (1H, ddd, J = 14.0, 6.4, 3.4 Hz, H-5eq), 1.29 (3H, d, J = 6.3 Hz, H-7) and 1.18 (3H, s, H-10); δ_C (100 MHz, C$_6$D$_6$) 193.0 (C=O), 143.3 (Ar), 128.2 (Ar), 127.1 (Ar), 125.9 (Ar), 73.8 (C-6), 71.7 (C-4), 71.1 (C-2), 51.1 (C-9), 49.1 (C-3), 36.6 (C-5), 17.0 (C-7), and 14.1 (C-10); m/z (ESI$^+$) 287 (M + Na)$^+$. (Found 287.1247 (M + Na)$^+$. C$_{15}$H$_{20}$NaO$_4$ requires 287.1254).

(2*R**,3*S**,4*S**,6*R**)-Methyl   6-(furan-2-yl)-4-hydroxy-2,3-dimethyl-tetrahydro-2H-pyran-3-carboxylate (253).
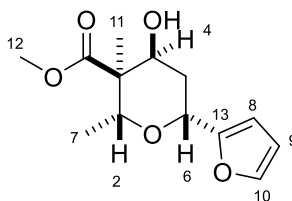
Tetrahydropyrans **219** (0.03 g, 0.10 mmol), L-Selectride® solution 1.0M in THF (0.25 mL, 1.20 mmol), THF (3.00 mL); purification (toluene – methanol = 49 : 1), Percentage

yield 0.020 g, 79%, light yellow oil; υ max/cm⁻¹ (film) 3463 (OH), 2976 (C-H), 2952 (C-H), 1723 (C=O), 1251 (C-O), 1144 (C-O), 1066 (C-O), 1033 (C-O), 961 (C=C), 738 (C=C); δ_H (400MHz, C_6D_6) 7.08 (1H, dd, J = 1.8, 0.8 Hz, H-10), 6.14 (1H, d, J = 3.2 Hz, H-8), 6.06 (1H, dd, J = 3.2, 1.8 Hz, H-9), 5.07 (1H, dd, J = 12.0, 3.0 Hz, H-6), 4.56 (1H, q , J = 6.3 Hz, H-2), 3.86 (1H, dd, J = 5.5, 2.1 Hz, H- 4), 3.22 (3H, s, H-12), 2.74 (1H, br s, OH), 2.09 (1H, ddd, J = 14.0, 12.0, 2.6, Hz, H-5ax), 1.63 (1H, ddd, J = 14.0, 5.6, 3.0 Hz, H-5eq), 1.23 (3H, d, J = 6.3 Hz, H-7) and 1.17 (3H, s, H-11); δ_C (100 MHz, C_6D_6) 179.0 (C=O), 155.3 (C-13), 141.7 (C-10), 110.0 (C-8), 106.6 (C-9), 71.3 (C-2), 71.1(C-4), 67.5 (C-6), 51.1 (C-12), 49.1 (C-3), 32.3 (C-5), 16.9 (C-7) and 14.0 (C-11); *m/z* (ESI⁺) 277 (M + Na)⁺. (Found 277.1038 (M + Na)⁺. $C_{13}H_{18}$ NaO₅ requires 277.10465).

(2R*,3S*,4S*,6R*)-Methyl 6-(benzyloxymethyl)-4-hydroxy-2,3-dimethyl-tetrahydro-2H-pyran-3-carboxylate (250)
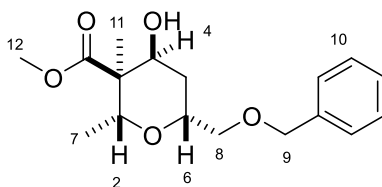
Tetrahydropyrans **215** (0.04 g, 0.14 mmol), L-Selectride® solution 1.0M in THF (0.35 mL, 1.68 mmol), THF (2.00 mL); purification (toluene – methanol = 49 : 1), Percentage yield 0.032 g, 75%, light orange oil; υ max/cm⁻¹ (film) 3462 (OH), 2923 (C-H), 2856 (C-H), 1733 (C=O), 1453 (CH₃), 1262 (C-O), 1091 (C-O), 1082 (C-O), 735 (Ar), 697 (Ar); δ_H (400MHz, C_6D_6) 7.36–7.28 (3H, m, Ar), 7.19–7.05 (2H, m, Ar), 4.46 (1H, q, J = 6.3 Hz, H-2), 4.40 (1H, d, J = 12.1 Hz, H-9), 4.37 (1H, d, J = 12.1 Hz, H-9), 4.19–4.13 (1H, m, H-6), 3.87 (1H, dd, J = 5.7, 3.0 Hz, H- 4), 3.44 (1H, dd, J = 10.1, 5.1 Hz, H-8), 3.36 (1H, dd, J = 10.1, 4.6 Hz, H-8), 3.23 (3H, s, H-12), 2.64 (1H, br s, OH), 1.66 (1H, ddd, J = 14.0, 11.9, 3.0 Hz, H-5ax), 1.46 (1H, ddd, J = 14.0, 5.7, 2.8 Hz, H-5eq), 1.25 (3H, d, J

= 6.4 Hz, H-7) and 1.14 (3H, s, H-11); δ_C (100 MHz, C$_6$D$_6$) 193.1 (C=O), 138.0 (Ar),
128.2 (Ar), 127.8 (Ar), 127.3 (Ar), 73.3 (C-9), 73.1 (C-8), 71.4 (C-2), 71.2 (C-4), 70.7
(C-6), 50.9 (C-12), 41.2 (C-3), 30.1 (C-5), 16.9 (C-7), and 14.1 (C-11); m/z (ESI$^+$) 331
(M + Na)$^+$. (Found 331.1502 (M + Na)$^+$. C$_{17}$H$_{24}$ NaO$_5$ requires 331.1516).

(2R*,3S*,4S*,6R*)-Methyl 6-(benzyloxymethyl)-2-butyl-4-hydroxy-3-methyl-tetrahydro-2H-pyran-3-carboxylate (249)
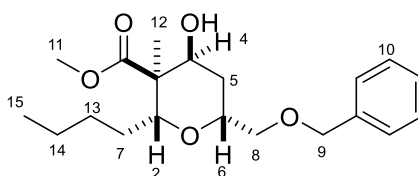
Tetrahydropyrans **213** (0.06 g, 0.18 mmol), L-Selectride$^®$ solution 1.0M in THF (0.46
mL, 2.19 mmol), THF (9.00 mL); purification (toluene – methanol = 49 : 1), Percentage
yield 0.044 g, 69%, light yellow oil; υ max/cm^{-1} (film) 3462 (OH), 2953 (C-H), 2926 (C-
H), 2856 (C-H), 1731 (C=O), 1454 (CH$_3$), 1264 (C-O), 1101 (C-O), 1042 (C-O), 734
(Ar), 697 (Ar) ; δ_H (400MHz, C$_6$D$_6$) 7.32–7.30 (2H, m, Ar), 7.20–7.18 (2H, m, Ar), 7.11–
7.07 (1H, m, Ar), 4.42 (1H, d, J = 12.9 Hz, H-9), 4.39 (1H, d, J = 12.9 Hz, H-9), 4.30
(1H, dd, J = 6.9, 4.4 Hz, H-2), 4.19–4.13 (1H, m, H-6), 3.84 (1H, dd, J = 5.7, 2.7 Hz, H-
4), 3.44 (1H, dd, J = 10.1, 5.2 Hz, H-8), 3.37 (1H, dd, J = 10.1, 4.5 Hz, H-8), 3.26 (3H,
s, H-11), 2.69 (1H, br s, OH), 1.79–1.72 (1H, m, H-7), 1.48–44 (1H, m, H-7), 1.66 (1H,
ddd, J = 14.0, 12.0, 2.7 Hz, H-5ax), 1.46 (1H, ddd, J = 14.0, 5.7, 2.4 Hz, H-5eq), 1.55–
1.50 (2H, m, H-13), 1.38–1.29 (2H, m, H-14), 1.17 (3H, s, H-12) and 0.90 (3H, t, J = 7.3
Hz, H-15); δ_C (100 MHz, C$_6$D$_6$) 195.0 (C=O), 139.1 (Ar), 128.2 (Ar), 127.3 (Ar), 127.0
(Ar), 75.2 (C-2), 73.4 (C-9), 73.1 (C-8), 71.6 (C-6), 71.4 (C-4), 51.1 (C-11), 49.5 (C-3),

31.2 (C-7), 31.0 (C-5), 29.1 (C-13), 22.8 (C-14), 14.6 (C-12) and 14.0 (C-15); m/z (ESI$^+$)

373 (M + Na)$^+$. (Found 373.1980 (M + Na)$^+$. $C_{20}H_{30}NaO_5$ requires 373.1985).

General Procedure for lithium aluminium hydride reduction of ketone and ester on tetrahydropyran:

All apparatus are oven dried and flushed with N_2 gas. A round bottom flasked was charged with N_2 gas and LiAlH$_4$ (0.01 g, 0.33 mmol). Dried THF (3.00 mL) was added slowly so that the LiAlH$_4$ was a grey suspension. The reaction was cooled to 0°C and the tetrahydropyran (0.05 g, 0.17 mmol) in dried THF (3.00 mL) was added drop wise. The reaction was stirred at 0°C and monitored by TLC until it was shown to be complete. The reaction mixture was quenched by the drop wise addition of 5 mL of H$_2$O, 15 mL of 15% of NaOH solution followed with 3 x 5 mL of H$_2$O. It was then dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexane – ethyl acetate) afforded the product.

(2*R*,3S*,4R*,6R**)-6-((Benzyloxy)methyl)-3-(hydroxymethyl)-2,3-dimethyltetrahydro-2H-pyran-4-ol (248)
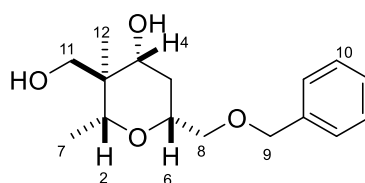
Tetrahydropyrans **215** (0.05 g, 0.17 mmol), LiAlH$_4$ (0.01 g, 0.33 mmol), THF (2.00 mL); purification (hexane – ethyl acetate = 1:1), Percentage yield 0.026 g, 56%, light yellow oil; υ max/cm^{-1} (film) 3379 (OH), 2925 (C-H), 2860 (C-H), 1465 (CH$_2$), 1453 (CH$_3$), 1375 (CH$_3$), 1255 (C-O), 1091 (C-O), 1027 (C-O), 735 (Ar), 697 (Ar), 654 (Ar); δ$_H$ (400MHz, CDCl$_3$) 7.29-7.27 (2H, m, Ar), 7.23–7.18 (3H, m, Ar), 4.53 (1H, d, J = 12.2

Hz, H-9), 4.47 (1H, d, J = 12.2 Hz, H-9), 3.85 (1H, dd, J = 12.0, 4.8 Hz, H- 4), 3.55 (1H, d, J = 10.0 Hz, H-11), 3.39 (1H, d, J = 10.0 Hz, H-11), 3.59–3.57 (1H, m, H-6), 3.46 (1H, dd, J = 10.1, 6.1 Hz, H-8), 3.35 (1H, dd, J = 10.1, 4.0 Hz, H-8), 3.18 (1H, q, J = 6.4 Hz, H-2), 2.64 (1H, br s, OH), 1.64 (1H, ddd, J = 12.6, 4.8, 2.4 Hz, H-5eq), 1.40 (1H, dd, J = 12.6, 12.0, 12.1 Hz, H-5ax), 1.02 (3H, d, J = 6.4 Hz, H-7) and 0.86 (3H, s, H-12); δ_C (100 MHz, CDCl$_3$) 138.5 (Ar), 128.5 (Ar), 127.8 (Ar), 127.7 (Ar), 75.6 (C-2), 75.3 (C-6), 74.0 (C-4), 73.5 (C-9), 73.2 (C-8), 69.8 (C-11), 42.9 (C-3), 33.2 (C-5), 15.1 (C-7), and 8.55 (C-12); m/z (ESI$^+$) 303 (M + Na)$^+$. (Found 303.1564 (M + Na)$^+$. C$_{16}$H$_{24}$ NaO$_4$ requires 303.1567).

(2R*,3S*,4R*,6R*)-6-(Benzyloxymethyl)-2-butyl-3-(hydroxymethyl)-3-methyl-tetrahydro-2H-pyran-4-ol (247)
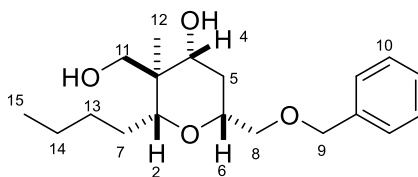
Tetrahydropyrans **213** (0.03 g, 0.09 mmol), LiAlH$_4$ (0.01 g, 0.24 mmol), THF (3.00 mL); purification (hexane – ethyl acetate = 1:1), Percentage yield 0.015 g, 51%, colourless oil; υ max/cm^{-1} (film) 3369 (OH), 2927 (C-H), 2857 (C-H), 1453 (CH$_3$), 1375 (CH$_3$), 1113 (C-O), 1086 (C-O), 1025 (C-O), 733 (Ar), 696 (Ar), 665 (Ar); δ_H (400MHz, CDCl$_3$) 7.34–7.22 (4H, m, Ar), 7.31–7.27 (1H, m, Ar), 4.60 (1H, d, J = 12.0 Hz, H-9), 4.56 (1H, d, J = 12.0 Hz, H-9), 3.93 (1H, dd, J = 11.5, 4.8 Hz, H- 4), 3.69 (1H, d, J = 10.4 Hz, H-11), 3.52 (1H, d, J = 10.4 Hz, H-11), 3.61–3.58 (1H, m, H-6), 3.55 (1H, dd, J = 12.0, 6.5 Hz, H-8), 3.48 (1H, dd, J = 12.0, 6.5 Hz, H-8), 3.02 (1H, dd, J = 10.2, 1.4 Hz, H-2), 2.41 (1H, br s, OH), 1.75 (1H, ddd, J = 12.4, 4.8, 2.0 Hz, H-5eq), 1.48 (1H, dd, J = 12.4, 12.0, 11.5 Hz, H-5ax), 1.42–1.35 (2H, m, H-7), 1.33–1.25 (2H, m, H-14), 0.94 (3H, s, H-12) and 0.89

(3H, t, J = 7.1 Hz, H-15); δ_C (100 MHz, CDCl$_3$) 138.5 (Ar), 128.4 (Ar), 127.7 (Ar), 127.4 (Ar), 80.3 (C-2), 75.6 (C-6), 74.3 (C-4), 73.4 (C-9), 73.2 (C-8), 69.8 (C-11), 42.8 (C-3), 33.3 (C-5), 29.8 (C-13), 22.8 (C-14), 20.9 (C-7) 14.2 (C-15) and 9.1 (C-12); (m/z (ESI$^+$) 345 (M + Na)$^+$. (Found 345.2042 (M + Na)$^+$. C$_{19}$H$_{30}$NaO$_4$ requires 345.2036).

(2R*,3S*,4S*,6R*)-6-(Benzyloxymethyl)-3-(hydroxymethyl)-2,3-dimethyl-tetrahydro-2H-pyran-4-ol (257)
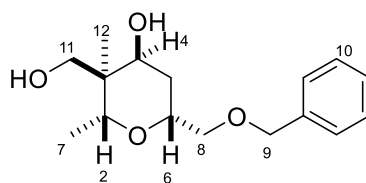
Tetrahydropyrans **250** (0.02 g, 0.08 mmol), LiAlH$_4$ (0.006 g, 0.16 mmol), THF (2.00 mL); purification (hexane – ethyl acetate = 1:1), Percentage yield 0.011 g, 52%, light yellow oil; υ max/cm^{-1} (film) 3368 (OH), 2923 (C-H), 2856 (C-H), 1452 (CH$_3$), 1375 (CH$_3$), 1088 (C-O), 1029 (C-O), 736 (Ar), 697 (Ar), 597 (Ar); δ_H (400MHz, CDCl$_3$) 7.34–7.33 (4H, m, Ar), 7.29–7.27 (1H, m, Ar), 4.61 (1H, d, J = 12.2 Hz, H-9), 4.55 (1H, d, J = 12.2 Hz, H-9), 4.16 (1H, q, J = 6.6 Hz, H-2), 4.05 (1H, dddd, J = 12.0, 6.0, 4.2, 5.6 Hz, H-6), 3.96 (1H, dd, J = 5.6, 2.8 Hz, H- 4), 3.61 (1H, d, J = 10.0 Hz, H-11), 3.58 (1H, d, J = 10.0 Hz, H-11), 3.63 (1H, dd, J = 10.2, 6.0 Hz, H-8), 3.43 (1H, dd, J = 10.2, 4.2 Hz, H-8), 2.83 (1H, br s, OH), 1.80 (1H, ddd, J = 14.2, 12.0, 5.6 Hz, H-5ax), 1.49 (1H, ddd, J = 14.2, 5.6, 2.8 Hz, H-5eq), 1.15 (3H, d, J = 6.6 Hz, H-7) and 0.79 (3H, s, H-12); δ_C (100 MHz, CDCl$_3$) 138.4 (Ar), 128.4 (Ar), 127.8 (Ar), 127.7 (Ar), 74.8 (C-4), 73.4 (C-9), 73.3 (C-8), 71.4 (C-6), 70.6 (C-2), 70.2 (C-11), 40.5 (C-3), 33.4 (C-5), 15.1 (C-7), and 15.0 (C-12); m/z (ESI$^+$) 303 (M + Na)$^+$. (Found 303.1570 (M + Na)$^+$. C$_{16}$H$_{24}$ NaO$_4$ requires 303.1567).

(2R*,3S*,4S*,6R*)-6-(Benzyloxymethyl)-2-butyl-3-(hydroxymethyl)-3-methyl-tetrahydro-2H-pyran-4-ol (258)
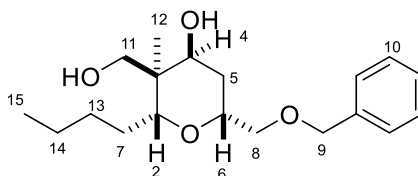
Tetrahydropyrans **249** (0.027 g, 0.08 mmol), LiAlH$_4$ (0.006 g, 0.15 mmol), THF (6.00 mL); purification (hexane – ethyl acetate = 1:1), Percentage yield 0.011 g, 52%, colorless oil; υ max/cm^{-1} (film) 3351 (OH), 2924 (C-H), 2857 (C-H), 1453 (CH$_3$), 1377 (CH$_3$), 1092 (C-O), 1028 (C-O), 732 (Ar), 697 (Ar), 613 (Ar); δ$_H$ (400MHz, CDCl$_3$) 7.34–7.33 (4H, m, Ar), 7.31–7.27 (1H, m, Ar), 4.61 (1H, d, J = 12.4 Hz, H-9), 4.58 (1H, d, J = 12.4 Hz, H-9), 3.99 (1H, dddd, J = 12.0, 5.6, 4.4, 3.0 Hz, H-6), 3.93 (1H, dd, J = 5.6, 3.0 Hz, H- 4), 3.91 (1H, dd, J = 8.0, 3.6 Hz, H-2), 3.63 (1H, d, J = 12.6 Hz, H-11), 3.59 (1H, d, J = 12.6 Hz, H-11), 3.56 (1H, dd, J = 10.4, 5.6 Hz, H-8), 3.48 (1H, dd, J = 10.4, 4.4 Hz, H-8), 2.86 (2H, br s, OH), 1.80 (1H, ddd, J = 14.4, 12.0, 3.0 Hz, H-5ax), 1.50 (1H, ddd, J = 14.4, 5.6, 2.8 Hz, H-5eq), 1.63–1.58 (2H, m, H-14), 1.43–1.25 (4H, m, H-7, H-13), 0.90 (3H, t, J = 7.0 Hz, H-15) and 0.78 (3H, s, H-12); δ$_C$ (100 MHz, CDCl$_3$) 138.6 (Ar), 128.4 (Ar), 127.7 (Ar), 127.6 (Ar), 75.3 (C-2), 75.1 (C-4), 73.4 (C-9), 73.3 (C-8), 71.6 (C-6), 70.1 (C-11), 40.5 (C-3), 33.5 (C-5), 29.0 (C-13), 28.7 (C-14), 22.9 (C-7), 15.7 (C-12) and 14.3 (C-15); (*m/z* (ESI$^+$) 345 (M + Na)$^+$. (Found 345.2044 (M + Na)$^+$. C$_{19}$H$_{30}$ NaO$_4$ requires 345.2036).

General Procedure for the Synthesis 2,6-*trans*-tetrahydropyran-4-ones from dihydropyrans by conjugate addition

Addition of Ph$_2$CuLi:

Phenyl lithium 1.9M in dibutyl ether solution (0.58 mL, 0.90 mmol) was added to a suspension of copper iodide (86.30 mg, 0.45 mmol) in THF (3.00 mL) at 0 °C. The mixture was stirred at this temperature for 20 minutes then cooled to −78 °C. Addition of chlorotrimethylsilane (0.18 mL, 1.40 mmol) was followed by addition of DHP (0.28 mmol) in THF (2.00 mL) at −78 °C. The reaction mixture was stirred at this temperature for 30 minutes then at 0 °C for 1.5 hours. The reaction was quenched with sat. aq. NH$_4$Cl (2.50 mL) and allowed to warm to rt with vigorous stirring. The mixture was diluted with sat. aq. NH$_4$Cl (10.0 mL) and extracted with EtOAc (5 x 15.0 mL). The combined organic extracts were washed with H$_2$O (15.0 mL) and brine (15.0 mL), then dried over MgSO$_4$ and concentrated *in vacuo*. Flash column chromatography (hexane – ethyl acetate) afforded the product.

(2R*,6S*)-Methyl 4-hydroxy-2,6-diphenyl-5,6-dihydro-2H-pyran-3-carboxylate (279)
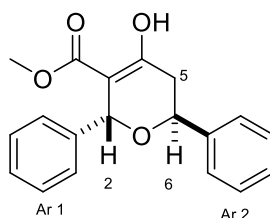
Dihydropyran **264** (0.08 g, 0.37 mmol), phenyl lithium 1.9 M in dibutyl ether (0.79 ml, 1.22 mmol), copper iodide (0.11 g, 0.61 mmol), cholorotrimethylsilane (0.24 ml, 1.90 mmol), THF (6.80 ml); purification (hexane – ethyl acetate = 4: 1), Percentage yield 0.082 g, 70%, light brown oil. υ max/cm^{-1} (film) 2955 (C-H), 2931 (C-H), 2872 (C-H), 1768 (C=O), 1465 (CH$_2$), 1177 (C-O), 1149 (C-O), 1055 (C-O), 875 (Ar), 480 (Ar); δ$_H$ (400 MHz, CDCl$_3$) 12.4 (1H, s, OH), 7.41–7.24 (10H, m, Ar1, Ar2), 5.80 (1H, s, H-2), 4.56 (1H, dd, *J* =10.8, 4.0 Hz, H-6), 3.66 (3H, s, H-9), 2.73 (1H, dd, *J* = 18.1, 10.8 Hz, H-5ax), 2.59 (1H, dd, *J* = 18.1, 4.0 Hz, H-5eq); δ$_C$ (100 MHz, CDCl$_3$) 193.0 (C=O), 171.2 (C-3),

140.7 (C-4), 128.6 (Ar), 128.3 (Ar), 128.0 (Ar), 127.9 (Ar), 126.0 (Ar), 125.8 (Ar), 98.6 (Ar), 73.3 (C-2), 68.4 (C-6), 51.8 (C-9), 41.1 (C-11), and 35.6 (C-5); m/z (ESI$^+$) 333 (M + Na)$^+$ (Found 333.1108 (M + Na)$^+$. $C_{19}H_{18}NaO_4$ requires; 333.1103).

(2R*,6S*)-Methyl 4-hydroxy-6-isopropyl-2-phenyl-5,6-dihydro-2H-pyran-3-carboxylate (277)
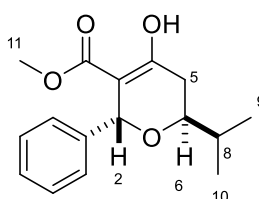
Dihydropyran **262** (0.06 g, 0.30 mmol), phenyl lithium 1.9M in dibutyl ether (0.49 ml, 0.72 mmol), copper iodide (0.06, 0.36 mmol), cholorotrimethylsilane (0.06 ml, 0.54 mmol), THF (5 ml); purification (hexane – ethyl acetate = 4: 1), Percentage yield 0.060 g, 73%, light yellow oil. υ max/cm^{-1} (film) 2924 (C-H), 2852 (C-H), 1739 (C=O), 1661 (Ar), 1365 (CH$_3$), 1268 (C-O), 1222 (C-O), 1060 (C-O), 841 (Ar); δ_H (400 MHz, CDCl$_3$) 12.30 (1H, s, OH), 7.37–7.27 (5H, m, Ar), 5.62 (1H, s, H-2), 3.63 (3H, s, H-11), 3.10 (1H, dd, J =10.8, 3.9 Hz, H-6), 2.36 (1H, dd, J = 18.0, 10.8 Hz, H-5ax), 2.23 (1H, dd, J = 18.0, 3.9 Hz, H-5eq), 1.64–1.56 (1H, m, H-8), 0.80 (3H, d, J = 6.8 Hz, H-9) and 0.77 (3H, d, J = 6.8 Hz, H-10); δ_C (100 MHz, CDCl$_3$) 193.2 (C=O), 171.5 (C-3), 141.5 (C-4), 128.6 (Ar), 128.0 (Ar), 127.7 (Ar), 98.5 (Ar), 72.6 (C-2), 71.6 (C-6), 51.2 (C-11), 32.8 (C-5), 32.3 (C-7), 18.4 (C-9) and 17.8 (C-10); m/z (ESI$^+$) 299 (M + Na)$^+$ (Found 299.1245 (M + Na)$^+$. $C_{16}H_{20}NaO_4$ requires; 299.1254).

(2R*,6S*)-Methyl 4-hydroxy-2-phenyl-6-(((triisopropylsilyl)oxy)methyl)-5,6-dihydro-2H-pyran-3-carboxylate (280)
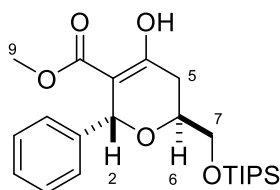
Dihydropyran **265** (0.07 g, 0.21 mmol), phenyl lithium 1.9M in dibutyl ether (0.40 ml, 0.70 mmol), copper iodide (0.08 g, 0.44 mmol), cholorotrimethylsilane (0.13 ml, 1.10 mmol), THF (2.00 ml); purification (hexane – ethyl acetate = 4: 1), Percentage yield 0.043 g, 48%, light yellow oil. υ max/cm^{-1} (film) 2941 (C-H), 2861 (C-H), 1660 (C=C), 1600 (Ar), 1465 (CH$_2$), 1280 (C-O), 1264 (C-O), 1215 (C-O), 1095 (C-O), 880 (Ar), 681 (Ar); δ_H (400 MHz, C$_6$D$_6$) 12.90 (1H, s, OH), 7.38–7.36 (2H, m, Ar), 7.18–7.08 (3H, m, Ar) 5.79 (1H, s, H-2), 3.65–3.60 (1H, m, H-6), 3.55–3.46 (2H, m, H-7), 3.05 (3H, s, H-9), 2.59 (1H, dd, J = 18.1, 10.8 Hz, H-5ax), 2.18 (1H, dd, J = 18.1, 2.8 Hz, H-5eq) and 1.01 (21H, m, OTIPS); δ_C (100 MHz, C$_6$D$_6$) 172.3 (C=O), 170.5 (C-3), 141.5 (C-4), 128.9 (Ar), 128.4 (Ar), 127.9 (Ar), 99.0 (Ar), 73.1 (C-2), 67.9 (C-6), 66.3 (C-7), 51.0 (C-9), 31.4 (C-5), 18.1 (C-OTIPS) and 12.2 (C-OTIPS); m/z (ESI$^+$) 443 (M + Na)$^+$ (Found 443.2209 (M + Na)$^+$. C$_{23}$H$_{36}$NaO$_5$Si requires; 443.2224).

(2R*,6R*)-Methyl 4-hydroxy-2-phenyl-6-propyl-5,6-dihydro-2H-pyran-3-carboxylate (278)
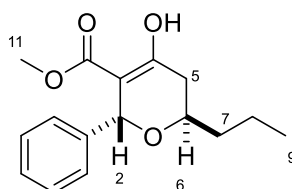
Dihydropyran **263** (0.04g, 0.22 mmol), phenyl lithium 1.9M in dibutyl ether (0.40 ml, 0.74 mmol), copper iodide (0.07 g, 0.37 mmol), cholorotrimethylsilane (0.14 ml, 1.15

mmol), THF (2.00 ml); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.035

g, 56%, light yellow oil. υ max/cm^{-1} (film) 2955 (C-H), 2927 (C-H), 2875 (C-H), 1658

(C=O), 1621 (Ar), 1441 (CH$_3$), 1262 (C-O), 1216 (C-O), 1043 (C-O), 775 (Ar), 698 (Ar);

δ_H (400 MHz, CDCl$_3$) 12.29 (1H, s, OH), 7.37–7.27 (5H, m, Ar), 5.59 (1H, s, H-2), 3.63

(3H, s, H-11), 3.47–3.41 (1H, m, H-6), 2.32 (1H, dd, J = 18.0, 10.0 Hz, H-5ax), 2.23 (1H,

dd, J = 18.0, 4.2 Hz, H-5eq), 1.05–1.43 (2H, m, H-7), 1.37–1.28 (2H, m, H-8) and 0.72

(3H, t, J = 7.2 Hz, H-9); δ_C (100 MHz, CDCl$_3$) 171.7 (C=O), 171.2 (C-3), 141.1 (C-4),

128.5 (Ar), 128.1 (Ar), 127.8 (Ar), 98.6, 72.2 (C-2), 66.3 (C-6), 51.7 (C-11), 37.8 (C-7),

35.0 (C-5), 18.3 (C-8) and 13.8 (C-9); m/z (ESI$^+$) 299 (M + Na)$^+$ (Found 299.1255 (M +

Na)$^+$. C$_{16}$H$_{20}$NaO$_4$ requires; 299.1254).

(2R*,6S*)-Methyl 4-hydroxy-2-phenyl-6-((E)-prop-1-en-1-yl)-5,6-dihydro-2H-

pyran-3-carboxylate (281)
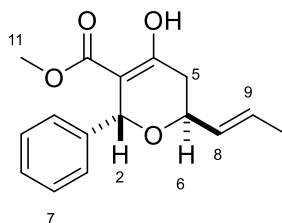
Dihydropyran **268** (0.05 g, 0.28 mmol), phenyl lithium 1.9M in dibutyl ether (0.58 ml,

0.90 mmol), copper iodide (0.08 mg, 0.45 mmol), cholorotrimethylsilane (0.17 ml, 1.40

mmol), THF (5.00 ml); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.049

g, 64%, light yellow oil. υ max/cm^{-1} (film) 2952 (C-H), 2896 (C-H), 1618 (C=C), 1437

(CH$_3$), 1325 (CH$_3$), 1243 (C-O), 1205 (C-O), 1181 (C-O), 1051 (C-O), 958 (Ar), 740

(Ar), 690 (Ar); δ_H (400 MHz, CDCl$_3$) 12.30 (1H, s, OH), 7.40-7.27 (5H, m, Ar), 5.62 (1H,

s, H-2), 5.56 (1H, d, J = 16.0, 4.0 Hz, H-8), 5.44 (1H, dd, J = 16.0, 4.0 Hz, H-9), 3.97

(1H, ddd, J = 12.0, 4.0, 4.0 Hz, H-6) , 3.62 (3H, s, H-11), 2.47 (1H, dd, J = 16.0, 12.0 Hz,

H-5ax), 2.32 (1H, dd, J = 16.0, 4.0 Hz, H-5eq) and 1.65 (1H, d, J = 4.0 Hz, H-10); δ_C

(100 MHz, CDCl$_3$) 171.1 (C=O), 168.5 (C-3), 140.9 (C-4), 130.4 (C-9), 128.5 (C-8), 128.2 (Ar), 127.9 (Ar), 127.1 (Ar), 98.6 (Ar), 73.0 (C-2), 67.1 (C-6), 51.6 (C-11), 34.4 (C-5), and 17.9 (C-10); m/z (ESI$^+$) 297 (M + Na)$^+$ (Found 297.1091 (M + Na)$^+$. C$_{16}$H$_{18}$NaO$_4$ requires; 297.1097).

(2*R**,6*S**)-Methyl 4-hydroxy-2-phenyl-6-((E)-styryl)-5,6-dihydro-2H-pyran-3-carboxylate (282)
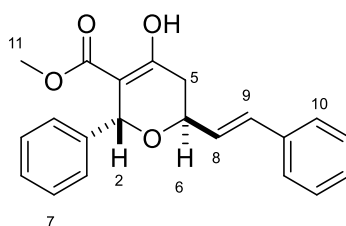
Dihydropyran **269** (0.98 g, 3.82 mmol), phenyl lithium 1.9M in dibutyl ether (8.12 ml, 12.60 mmol), copper iodide (1.16 g, 6.10 mmol), cholorotrimethylsilane (2.41 ml, 19.00 mmol), THF (68.00 ml); purification (hexane – ethyl acetate = 4: 1), percentage yield 1.170 g, 91 %, light yellow oil. υ max/cm^{-1} (film) 2952 (C-H), 2896 (C-H), 1662 (C=C), 1618 (C=C), 1437 (CH$_2$), 1205 (C-O), 1181 (C-O), 1051 (C-O), 958 (Ar), 740 (Ar), 690 (Ar); δ_H (400 MHz, CDCl$_3$) 12.32 (1H, s, OH), 7.46–7.20 (10H, m, Ar), 6.49 (1H, d, $J =$ 16.1 Hz, H-9), 6.15 (1H, dd, $J =$ 16.1, 5.7 Hz, H-8), 5.70 (1H, s, H-2), 4.24 (1H, ddd, $J =$ 10.5, 5.7, 4.1 Hz, H-6) , 3.64 (3H, s, H-11), 2.58 (1H, dd, $J =$ 18.0, 10.5 Hz, H-5ax) and 2.46 (1H, dd, $J =$ 18.0, 4.1 Hz, H-5eq); NOE C2 (Phenyl) – H6 1.4%, H6 – H9 1.35% and H6 – H8 1.12%; δ_C (100 MHz, CDCl$_3$) 171.1 (C=O), 170.9 (C-3), 140.8 (C-4), 136.4 (Ar), 131.4 (C-9), 128.6 (Ar), 128.5 (Ar), 128.3 (C-8), 128.0 (Ar), 127.9 (Ar), 126.6 (Ar), 115.4 (Ar), 98.3 (Ar), 73.0 (C-2), 67.4 (C-6), 51.8 (C-11), 34.5 (C-5); m/z (ESI$^+$) 359 (M + Na)$^+$ (Found 359.1249 (M + Na)$^+$. C$_{21}$H$_{20}$NaO$_4$ requires; 359.1254).

Addition of Me₂CuLi:

Methyl lithium 1.6M in Et₂O (0.56 ml, 0.72 mmol) was added to a suspension of copper iodide (0.069g, 0.36 mmol) in THF (2.00 mL) at 0 °C. The mixture was stirred at this temperature for 20 minutes after which chlorotrimethylsilane (0.14 ml, 0.54 mmol) then DHP (0.10 mmol) in THF (2.00 mL) were added at −78 °C. The reaction mixture was stirred at this temperature for 4.5 hours then sat. aq. NH₄Cl (1.70 mL) was added to the mixture, which was stirred rapidly for 30 minutes at rt. The mixture was diluted with H₂O (10.0 mL) extracted with Et₂O (2 x 20.0 mL) and washed with H₂O (20.0 mL) and brine (20.0 mL). The organic layer was dried over MgSO₄ and concentrated *in vacuo*. Flash column chromatography (hexane:ethyl acetate 7:1 to 3:1) afforded the products as an inseparable mixture of enol and ketone tautomers which were then subjected to acylation. The THP mixture (0.03 mmol), acetic anhydride (0.10 mL, 0.10 mmol) and DMAP (2 mg) were stirred in pyridine (0.47 mL) at 40 °C for 40 minutes. The mixture was cooled to rt, concentrated in vacuo, then partitioned between Et₂O (30.00 mL) and H₂O (10.00 mL). The organic layer was washed with H₂O (10.00 mL) and brine (10.00 mL), then dried over MgSO₄ and concentrated in vacuo. Flash column chromatography (hexane-ethyl acetate) gave the product.

(2R*,6S*)-Methyl 4-acetoxy-2-methyl-6-phenyl-5,6-dihydro-2H-pyran-3-carboxylate (273)
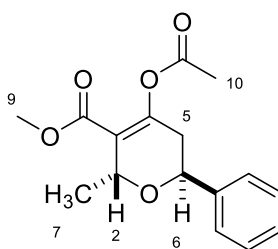
Dihydropyran **264** (0.25 g, 1.09 mmol), methyl lithium 1.6M in Et$_2$O (0.47 ml, 0.61 mmol), copper iodide (0.05g, 0.31 mmol), cholorotrimethylsilane (0.11 ml, 0.92 mmol), THF (1.70 ml). Then, THP (0.10 g, 0.40 mmol), Ac$_2$O (1.33 mL, 1.33 mmol), DMAP (2 mol %), pyridine (6.70 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.149 g, (47 % after 2 steps), light yellow oil. υ max/cm^{-1} (film) 2945 (C-H), 2931 (C-H), 1766 (C=O), 1720 (C=O), 1664 (C=C), 1365 (CH$_3$), 1247 (C-O), 1174 (C-O), 1053 (C-O), 758 (Ar), 698 (Ar); δ_H (400 MHz, C$_6$D$_6$) 7.30–7.23 (2H, m, Ar), 7.17–7.16 (1H, m,Ar), 7.14–7.05 (2H, m, Ar), 5.13 (1H, q, J = 6.6 Hz, H-2), 4.83 (1H, dd, J = 9.7, 4.1 Hz, H-6), 3.26 (3H, s, H-9), 2.40 (1H, dd, J =17.9, 9.7 Hz, H-5ax), 2.31 (1H, dd, J = 17.9, 4.1 Hz, H-5eq), 1.88 (3H, s, H-10) and 1.39 (3H, d, J = 6.6 Hz, H-7); NOE C2(Me) – H6 2.3% and C2(Me) – H5eq 1.86%; δ_C (100 MHz, C$_6$D$_6$) 193.5 (C=O), 167.8 (C=O), 163.9 (C-3), 154.1 (C-4), 141.0 (Ar), 128.6 (Ar), 126.7 (Ar), 121.7 (Ar), 69.5 (C-2), 68.8 (C-6), 51.1 (C-9), 36.9 (C-5), 20.5 (C-10) and 19.5 (C-7); m/z (ESI$^+$) 313 (M + Na)$^+$ (Found 313.1040 (M + Na)$^+$. C$_{16}$H$_{18}$NaO$_5$ requires; 313.1052).

(2R*,6S*)-Methyl 4-acetoxy-2-methyl-6-((((triisopropylsilyl)oxy)methyl)-5,6-dihydro-2H-pyran-3-carboxylate (275)
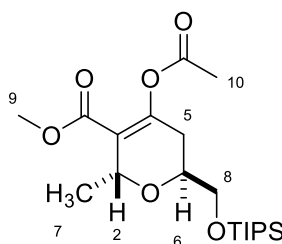
Dihydropyran **265** (0.05 g, 0.16 mmol), methyl lithium 1.6M in Et$_2$O (0.47 ml, 0.61 mmol), copper iodide (0.06 g, 0.31 mmol), cholorotrimethylsilane (0.11 ml, 0.92 mmol), THF (1.70 ml). Then, THP (0.03 g, 0.09 mmol), Ac$_2$O (0.30 mL, 0.30 mmol), DMAP (2 mol%), pyridine (1.41 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield

0.040 g, (61 % after 2 steps), light yellow oil. υ max/cm^{-1} (film) 2941 (C-H), 2866 (C-H), 1771 (C=O), 1725 (C=O), 1365 (CH$_3$), 1246 (C-O), 1177 (C-O), 1149 (C-O), 1055 (C-O); δ_H (400 MHz, C$_6$D$_6$) 5.04 (1H, q, J = 6.5 Hz, H-2), 4.03–3.97 (1H, m, H-6), 3.76 (1H, dd, J =10.2, 5.1 Hz, H-8), 3.63 (1H, dd, J =10.2, 5.2 Hz, H-8), 3.23 (3H, s, H-9), 2.44 (1H, dd, J =17.8, 10.0 Hz, H-5ax), 2.25 (1H, dd, J = 17.8, 3.8 Hz, H-5eq), 1.87 (3H, s, H-10), 1.39 (3H, d, J =6.5 Hz, H-7) and 1.09 (21H, m, OTIPS); δ_C (100 MHz, C$_6$D$_6$) 168.0 (C=O), 163.8 (C=O), 154.4 (C-3), 121.8 (C-4), 69.1 (C-2), 68.1 (C-6), 66.4 (C-8), 51.1 (C-9), 32.0 (C-5), 20.6 (C-10) 19.4 (C-7), 18.3 (C-OTIPS) and 12.2 (C-OTIPS); m/z (ESI$^+$) 423 (M + Na)$^+$ (Found 423.2160 (M + Na)$^+$. C$_{20}$H$_{36}$NaO$_6$Si requires; 423.2179).

(2R*,6S*)-Methyl4-acetoxy-6-(furan-2-yl)-2-methyl-5,6-dihydro-2H-pyran-3-carboxylate (274)
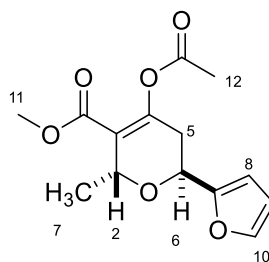
Dihydropyran **259** (0.03 g, 0.12 mmol), methyl lithium 1.6M in Et$_2$O (0.40 ml, 0.36 mmol), copper iodide (0.04 g, 0.23 mmol), cholorotrimethylsilane (0.08 ml, 0.70 mmol), THF (3.00 ml). Then, THP (0.02 g, 0.06 mmol), Ac$_2$O (0.21 mL, 0.21 mmol), DMAP (2 mol%), pyridine (1.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.015 g, (42 % after 2 steps), light yellow oil. υ max/cm^{-1} (film) 2955 (C-H), 2924 (C-H), 2854 (C-H), 1766 (C=O), 1720 (C=O), 1435 (CH$_3$), 1364 (CH$_3$), 1253 (C-O), 1176 (C-O), 1144 (C-O), 1052 (C-O); δ_H (400 MHz, CDCl$_3$) 7.41 (1H, s, H-10), 6.37-6.35 (2H, m, H-8, H-9), 5.04 (1H, dd, J = 9.2, 4.2 Hz, H-6), 4.85 (1H, q, J = 6.5 Hz, H-2), 3.74 (3H, s, H-11), 2.79 (1H, dd, J =17.9, 9.2 Hz, H-5ax), 2.53 (1H, dd, J = 17.9, 4.2 Hz, H-5eq),

2.22 (3H, s, H-12) and 1.48 (3H, d, J = 6.5 Hz, H-7); δ_C (100 MHz, CDCl$_3$) 168.5 (C=O), 164.0 (C=O), 157.5 (C-3), 152.6 (C-4), 142.9 (C-10), 121.6 (C-13), 110.4 (C-8), 108.0 (C-9), 69.0 (C-2), 63.4 (C-6), 51.9 (C-11), 32.6 (C-5), 21.1 (C-12) and 19.3 (C-7) ppm; m/z (ESI$^+$) 303 (M + Na)$^+$ (Found 303.0827 (M + Na)$^+$. C$_{14}$H$_{16}$NaO$_6$ requires; 303.0845).

(2R*,6S*)-Methyl 4-acetoxy-6-isopropyl-2-methyl-5,6-dihydro-2H-pyran-3-carboxylate (271)
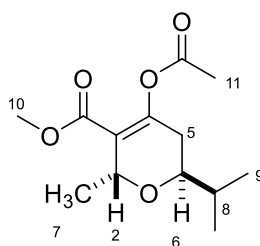
Dihydropyran **262** (0.04 g, 0.20 mmol), methyl lithium 1.6M in Et$_2$O (0.28 ml, 0.36 mmol), copper iodide (0.03 g, 0.18 mmol), cholorotrimethylsilane (0.06 ml, 0.54 mmol), THF (2.00 ml). Then, THP (0.01 g, 0.06 mmol), Ac$_2$O (0.21 mL, 0.21 mmol), DMAP (2 mol%), pyridine (1.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.019 g, (37 % after 2 steps), light yellow oil. υ max/cm^{-1} (film) 2959 (C-H), 2927 (C-H), 2875 (C-H), 1768 (C=O), 1723 (C=O), 1435 (CH$_3$), 1367 (CH$_3$), 1249 (C-O), 1177 (C-O), 1142 (C-O), 1058 (C-O); δ_H (400 MHz, C$_6$D$_6$) 5.00 (1H, q, J = 6.5 Hz, H-2), 3.45–3.40 (1H, m, H-6), 3.24 (3H, s, H-10), 2.17 (1H, dd, J =17.7, 10.1 Hz, H-5ax), 2.02 (1H, dd, J = 17.7, 3.4 Hz, H-5eq), 1.92 (3H, s, H-11), 1.60–1.53 (1H, m, H-8), 1.34 (3H, d, J = 6.5 Hz, H-7), 0.93 (3H, d, J =6.5 Hz, H-9) and 0.73 (3H, d, J = 6.5 Hz, H-9); δ_C (100 MHz, C$_6$D$_6$) 193.5 (C=O), 168.3 (C=O), 164.1 (C-3), 155.0 (C-4), 121.8 (C-8), 71.4 (C-6), 69.0 (C-2), 50.8 (C-10), 33.0 (C-5), 20.6 (C-11), 19.3 (C-7), 18.4 (C-9) and 18.0 (C-9); m/z (ESI$^+$) 279 (M + Na)$^+$ (Found 279.1199 (M + Na)$^+$. C$_{13}$H$_{20}$NaO$_5$ requires; 279.1208).

(2R*,6R*)-Methyl 4-acetoxy-2-methyl-6-propyl-5,6-dihydro-2H-pyran-3-carboxylate (272)
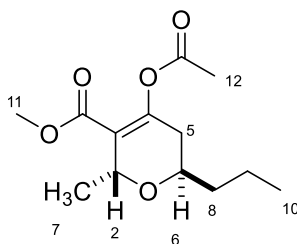
Dihydropyran **263** (0.03 g, 0.15 mmol), methyl lithium 1.6M in Et$_2$O (0.28 ml, 0.36 mmol), copper iodide (0.034 g, 0.18 mmol), cholorotrimethylsilane (0.06 ml, 0.54 mmol), THF (2.00 ml). Then, THP (0.02 g, 0.10 mmol), Ac$_2$O (0.33 mL, 0.33 mmol), DMAP (2 mol%), pyridine (1.60 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.015 g, (40 % after 2 steps), light yellow oil. υ max/cm^{-1} (film) 2955 (C-H), 2931 (C-H), 2872 (C-H), 1768 (C=O), 1723 (C=O), 1435 (CH$_3$), 1363 (CH$_3$), 1254 (C-O), 1177 (C-O), 1149 (C-O), 1055 (C-O); δ_H (400 MHz, C$_6$D$_6$) 5.02 (1H, q, J = 6.5 Hz, H-2), 3.73–3.67 (1H, m, H-6), 3.25 (3H, s, H-11), 2.09–2.02 (2H, m, H-5), 1.90 (3H, s, H-12), 1.50-1.39 (2H, m, H-8), 1.35 (3H, d, J =6.5 Hz, H-7), 1.31-1.12 (2H, m, H-9) and 0.82 (3H, t, J = 7.2 Hz, H-10); δ_C (100 MHz, C$_6$D$_6$) 193.8 (C=O), 168.0 (C=O), 163.9 (C-3), 154.4 (C-4), 68.9 (C-2), 66.4 (C-6), 51.0 (C-11), 37.6 (C-8), 35.4 (C-5), 20.7 (C-12), 19.0 (C-9), 18.8 (C-7) and 14.0 (C-10); m/z (ESI$^+$) 279 (M + Na)$^+$ (Found 279.1202 (M + Na)$^+$. C$_{13}$H$_{20}$NaO$_5$ requires; 279.1208).

(2R*,6S*)-Methyl 4-acetoxy-2-methyl-6-((E)-prop-1-en-1-yl)-5,6-dihydro-2H-pyran-3-carboxylate (276)
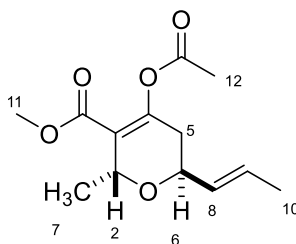
Dihydropyran **268** (0.05 g, 0.25 mmol), methyl lithium 1.6M in Et$_2$O (0.72 ml, 0.92 mmol), copper iodide (0.089 g, 0.47 mmol), cholorotrimethylsilane (0.17 ml, 1.40 mmol), THF (5.20 ml). Then, THP (0.03 g, 0.14 mmol), Ac$_2$O (0.46 mL, 0.46 mmol), DMAP (2 mol%), pyridine (2.20 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.019 g, (29 % after 2 steps), light yellow oil. υ max/cm^{-1} (film) 2952 (C-H), 2930 (C-H), 1767 (C=O), 1721 (C=O), 1664 (C=C), 1436 (CH$_3$), 1366 (CH$_3$), 1245 (C-O), 1212 (C-O), 1176 (C-O), 1046 (C-O), 1050 (C-O); δ_H (400 MHz, CDCl$_3$) 5.78 (1H, dd, J = 16.0, 4.0 Hz, H-8), 5.52 (1H, dq, J = 16.0, 4.0 Hz, H-9), 4.85 (1H, q, J = 8.0 Hz, H-2), 4.37 (1H, ddd, J = 8.0, 4.0, 4.0 Hz, H-6), 3.72 (3H, s, H-11), 2.30 (2H, m, H-5), 2.20 (3H, s, H-12), 1.71 (2H, d, J = 4.0 Hz , H-10) and 1.42 (3H, d, J = 8.0 Hz, H-7); δ_C (100 MHz, CDCl$_3$) 168.7 (C=O), 164.1 (C=O), 153.3 (C-3), 130.2 (C-4), 129.2 (C-8), 121.3 (C-9), 68.8 (C-2), 67.9 (C-6), 51.9 (C-11), 34.8 (C-5), 21.0 (C-12), 19.6 (C-7) and 17.9 (C-10); m/z (ESI$^+$) 277 (M + Na)$^+$ (Found 277.1047 (M + Na)$^+$. C$_{13}$H$_{18}$NaO$_5$ requires; 277.1046).

General method for n-Bu$_2$CuLi:

nButyl lithium 2.5M in hexane solution (0.26 mL, 0.60 mmol) was added to a suspension of copper iodide (57.20 mg, 0.30 mmol) in THF (1.70 mL) at 0 °C. The mixture was stirred at this temperature for 20 minutes. After this time the mixture was cooled to −78 °C and chlorotrimethylsilane (0.12 mL, 0.90 mmol) was added followed by addition of

DHP (0.20 mmol) in THF (1.80 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 4 hours, then quenched with sat. aq. NH$_4$Cl (1.50 mL) and allowed to warm to rt with vigorous stirring. The mixture was diluted further with sat. aq. NH$_4$Cl (10.0 mL) and extracted with EtOAc (5 x 15.0 mL). The combined organic extracts were washed with H$_2$O (15.0 mL) and brine (15.0 mL), then dried over MgSO$_4$ and concentrated *in vacuo*. Flash column chromatography (hexane – ethyl acetate) afforded the products as an inseparable mixture of enol and ketone tautomers, which were then subjected to acylation. The THP mixture (0.03 mmol), acetic anhydride (0.10 mL, 0.10 mmol) and DMAP (2 mol%) were stirred in pyridine (0.47 mL) at 40 °C for 40 minutes. The mixture was cooled to rt, concentrated *in vacuo*, then partitioned between Et$_2$O (30.00 mL) and H$_2$O (10.00 mL). The organic layer was washed with H$_2$O (10.00 mL) and brine (10.00 mL), then dried over MgSO$_4$ and concentrated *in vacuo*. Flash column chromatography (hexane-ethyl acetate) gave products.

(2R*,6S*)-Methyl 4-acetoxy-2-butyl-6-isopropyl-5,6-dihydro-2H-pyran-3-carboxylate (283)
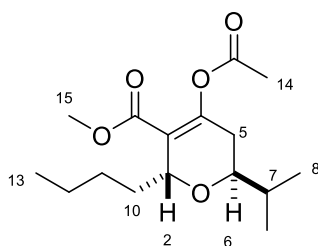
Dihydropyran **262** (0.04 g, 0.18 mmol), *n*-butyl lithium 2.5M in hexane (0.26 ml, 0.60 mmol), copper iodide (0.05 g, 0.30 mmol), cholorotrimethylsilane (0.11 ml, 0.90 mmol), THF (1.82 ml). Then, THP (0.02 g, 0.10 mmol), Ac$_2$O (0.33 mL, 0.33 mmol), DMAP (2 mol%), pyridine (1.60 mL); purification (Hex: EA = 4.0: 1.0), percentage yield 0.020 g, (37 % after 2 steps), light yellow oil. υ max/cm^{-1} (film) 2955 (C-H), 2929 (C-H), 1767

(C=O), 1724 (C=O), 1435 (CH₃), 1365 (CH₃), 1249 (C-O), 1202 (C-O), 1177 (C-O), 1056 (C-O); δ_H (400 MHz, C$_6$D$_6$) 4.89 (1H, d, J = 10.0 Hz, H-2), 3.43–3.38 (1H, m, H-6), 3.28 (3H, s, H-15), 2.15 (1H, dd, J = 17.7, 9.6 Hz, H-5ax), 2.07 (1H, dd, J = 17.7, 4.3 Hz, H-5eq), 1.92 (3H, s, H-14), 1.74–1.53 (2H, m, H-10), 1.48–1.39 (1H, m, H-7), 1.37–1.24 (4H, m, H-11, H-12), 0.96 (3H, d, J = 6.7 Hz, H-9), 0.88 (3H, t, J = 7.3 Hz, H-13) and 0.74 (3H, d, J = 6.8 Hz, H-8); δ_C (100 MHz, C$_6$D$_6$) 167.9 (C=O), 164.0 (C=O), 154.4 (C-3), 121.4 (C-4), 72.8 (C-2), 71.4 (C-6), 51.0 (C-15), 32.9 (C-10), 32.2 (C-5), 28.7 (C-7), 22.6 (C-14), 20.6 (C-12, C-11), 18.6 (C-9), 18.3 (C-8) and 14.2 (C-13); m/z (ESI⁺) 321 (M + Na)⁺ (Found 321.1669 (M + Na)⁺. C$_{16}$H$_{26}$NaO$_5$ requires; 321.1672).

(2R*,6S*)-Methyl 4-acetoxy-2-butyl-6-((((triisopropylsilyl)oxy)methyl)-5,6-dihydro-2H-pyran-3-carboxylate (284)
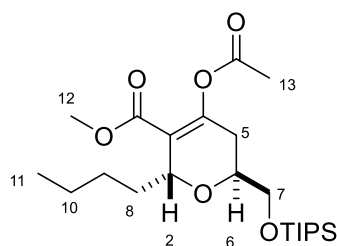
Dihydropyran **265** (0.05 g, 0.16 mmol), n-butyl lithium 2.5M in hexane (0.28 ml, 0.51 mmol), copper iodide (0.049g, 0.26 mmol), cholorotrimethylsilane (0.10 ml, 0.80 mmol), THF (3.00 ml). Then, THP (0.03 g, 0.08 mmol), Ac₂O (0.26 mL, 0.26 mmol), DMAP (2 mol%), pyridine (1.25 mL); purification (Hex: EA = 4.0: 1.0), percentage yield 0.012 g, (70 % after 2 steps), light yellow oil. υ max/cm⁻¹ (film) 2941 (C-H), 2865 (C-H), 1770 (C=O), 1725 (C=O), 1364 (CH₃), 1247 (C-O), 1192 (C-O), 1177 (C-O), 1146 (C-O), 1094 (C-O); δ_H (400 MHz, C$_6$D$_6$) 4.89 (1H, d, J = 9.6 Hz, H-2), 3.99–3.93 (1H, m, H-6), 3.75 (1H, dd, J = 10.3, 5.6 Hz, H-7), 3.61 (1H, dd, J = 10.3, 4.8 Hz, H-7), 3.27 (3H, s, H-12), 2.35 (1H, dd, J = 17.9, 10.0 Hz, H-5ax), 2.21 (1H, dd, J = 17.9, 3.9 Hz, H-5eq), 1.87 (3H,

s, H-13), 1.73–1.59 (2H, m, H-8), 1.49–1.39 (2H, m, H-9), 1.38–1.23 (2H, m, H-10), 1.10 (21H, m, OTIPS) and 0.89 (3H, t, J = 7.3 Hz, H-11); δ_C (100 MHz, C_6D_6) 167.9 (C=O), 163.9 (C=O), 154.0 (C-3), 121.5 (C-4), 72.8 (C-2), 67.9 (C-6), 66.5 (C-7), 51.0 (C-12), 32.4 (C-8), 31.8 (C-5), 28.5 (C-9), 22.6 (C-10), 20.6 (C-13), 18.2 (OTIPS), 14.2 (C-11) and 12.2 (OTIPS); m/z (ESI$^+$) 465 (M + Na)$^+$ (Found 465.2625 (M + Na)$^+$. $C_{23}H_{42}NaO_6Si$ requires; 465.2643).

(2R*,6S*)-Methyl 4-acetoxy-2-butyl-6-phenyl-5,6-dihydro-2H-pyran-3-carboxylate (286)

(prepared by Alejandra M. Peter)
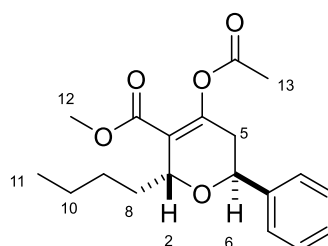
Dihydropyran **264** (0.10 g, 0.43 mmol), *n*-butyl lithium 2.5M in hexane (0.60 ml, 1.29 mmol), copper iodide (0.12 g, 0.65 mmol), cholorotrimethylsilane (0.25 ml, 1.94 mmol), THF (8.00 ml). Then, THP (0.10 g, 0.36 mmol), Ac$_2$O (1.20 mL, 1.20 mmol), DMAP (2 mol%), pyridine (5.64 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.056 g, (39 % after 2 steps), light yellow oil. υ max/cm^{-1} (film) 2953 (C-H), 2860 (C-H), 1764 (C=O), 1721 (C=O), 1248 (C-O), 1174 (C-O), 1055 (C-O); δ_H (400 MHz, CDCl$_3$) 7.40–7.29 (5H, m, Ar), 4.92 (1H, dd, J = 9.0, 5.0 Hz, H-6), 4.79 (1H, d, J = 10.1 Hz, H-2), 3.75 (3H, s, H-12), 2.69–2.47 (2H, m, H-5), 2.21 (3H, s, H-13), 1.88–1.24 (6H, m, H-8, H-9, H-10), and 0.89 (3H, t, J = 7.3 Hz, H-11); δ_C (100 MHz, CDCl$_3$) 168.9 (C=O), 164.1 (C=O), 153.2 (C-3), 141.0 (C-4), 128.6 (Ar), 128.0 (Ar), 126.0 (Ar), 121.2 (Ar),

73.2 (C-2), 68.4 (C-6), 51.8 (C-12), 36.0 (C-5), 32.2 (C-8), 28.3 (C-9), 22.4 (C-13), 21.0 (C-10) and 14.0 (C-11); m/z (ESI$^+$) 355 (M + Na)$^+$ (Found 355.1509 (M + Na)$^+$. $C_{19}H_{24}NaO_5$ requires; 355.1516).

(2R*,6R*)-Methyl 4-acetoxy-2-butyl-6-propyl-5,6-dihydro-2H-pyran-3-carboxylate (285)

(prepared by Alejandra M. Peter)
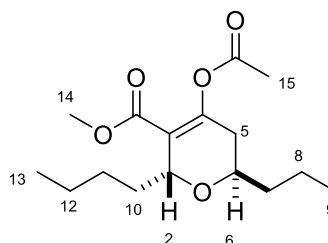
Dihydropyran **263** (0.070g, 0.35 mmol), n-butyl lithium 2.5M in hexane (0.48 ml, 1.10 mmol), copper iodide (0.10 g, 0.54 mmol), cholorotrimethylsilane (0.20 ml, 1.62 mmol), THF (6.00 ml). Then, THP (0.06 g, 0.24 mmol), Ac$_2$O (0.80 mL, 0.80 mmol), DMAP (2 mol%), pyridine (4.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.037 g, (35 % after 2 steps), light yellow oil. υ max/cm^{-1} (film) 2956 (C-H), 2932 (C-H), 2872 (C-H), 1767 (C=O), 1722 (C=O), 1241 (C-O), 1177 (C-O), 1053 (C-O); δ_H (400 MHz, CDCl$_3$) 4.61 (1H, d, J = 10.3 Hz, H-2), 2.84 (1H, m, H-6), 3.71 (3H, s, H-14), 2.22–2.16 (2H, m, H-5), 2.18 (3H, s, H-15), 1.74–1.25 (10H, m, H-7, H-8, H-10, H-11, H-12), and 0.95–0.88 (6H, m, H-9, H-13); δ_C (100 MHz, CDCl$_3$) 168.6 (C=O), 164.3 (C=O), 153.9 (C-3), 121.1 (C-4), 77.3 (C-2), 66.2 (C-6), 51.8 (C-14), 37.7 (C-7), 35.0 (C-5), 32.0 (C-8), 28.2 (C-10), 22.3 (C-11), 21.0 (C-15), 18.8 (C-12) and 14.1 (C-9, C-13); m/z (ESI$^+$) 321 (M + Na)$^+$ (Found 321.1681 (M + Na)$^+$. $C_{16}H_{26}NaO_5$ requires; 321.1672).

(2S*,6S*)-2-Phenyl-6-((E)-styryl)dihydro-2H-pyran-4(3H)-one (313)
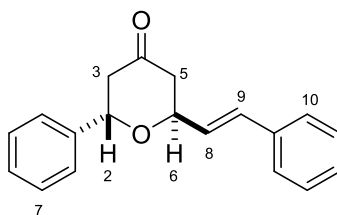
A solution of THP **282** (0.06 g, 0.17 mmol) in DMF (0.92 mL) and H_2O (0.02 mL) was submitted to 200 W microwave radiation in a sealed tube at 160 °C for 10 minutes. The solution was cooled to rt and taken up in EtOAc (30.0 mL). The mixture was washed with H_2O (2 x 20.0 mL). The aqueous layer was extracted with EtOAc (30.0 mL) and the combined organic extracts were washed with brine (20.0 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give (0.044 g, 91 %) as a pale yellow solid. υ max/cm^{-1} (film) 2978 (C-H), 2881 (C-H), 1721 (C=O), 1230 (C-O), 1047 (C-O), 966 (Ar), 753 (Ar), 737 (Ar), 695 (Ar); δ_H (400 MHz, CDCl$_3$) 7.34–7.17 (10H, m, Ar), 6.53 (1H, dd, J = 16.3, 1.3 Hz, H-9), 6.23 (1H, dd, J = 16.3, 5.1 Hz, H-8), 5.12 (1H, dd, J = 7.7, 4.8 Hz, H-2), 4.82 (1H, ddd, J = 10.5, 5.2, 5.1 Hz, H-6),and 2.78–2.68 (4H, m H-3, H-5); δ_C (100 MHz, CDCl$_3$) 205.9 (C=O), 140.5 (Ar), 135.7 (Ar), 133.5 (C-9), 128.8 (Ar), 128.7 (Ar), 128.3 (Ar), 128.2 (Ar), 127.9 (Ar), 126.7 (C-8), 126.5 (Ar), 73.6 (C-2), 72.9 (C-6), 47.8 (C-3), 45.4 (C-5); *m/z* (ESI$^+$) 301 (M + Na)$^+$. (Found 301.1196 (M + Na)$^+$. $C_{19}H_{18}NaO_2$ requires 301.1199).

(2S*,4S*,6S*)-2-Phenyl-6-((E)-styryl)tetrahydro-2H-pyran-4-ol (307)
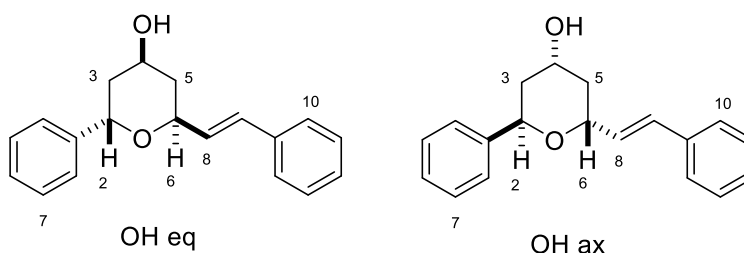
55: 45

The NaBH$_4$ (0.009g, 0.26 mmol) was added to a stirred solution of crude decarboxylated product **313** (0.03 g, 0.13 mmol) in MeOH (2.00 mL) at 0 °C. The mixture was stirred at this temperature for 30 minutes and warm to room temperature for 1 hour, the reaction mixture was stirred at this this temperature until completion. The mixture was diluted with Et$_2$O (20 mL) and washed with sat. aq. NH$_4$Cl (20 mL). The aqueous layer was washed with Et$_2$O (20 mL) and the combined organic extracts were washed with brine (20 mL), dried MgSO$_4$ and concentrated *in vacuo* to give **301** 0.024g (69%), light yellow oil. Diastereomers (55: 45, OH eq: OH ax). υ max/cm^{-1} (film) 3374 (OH), 2925 (C-H), 1448 (C=C), 1052 (C-O), 695 (Ar); δ$_H$ (400 MHz, CDCl$_3$) **OH eq** 7.47–7.22 (10H, m, Ar), 6.64 (1H, dd, J = 16.0, 1.9 Hz, H-9), 6.37 (1H, dd, J = 16.0, 5.2 Hz, H-8), 5.30 (1H, t, J = 4.4 Hz, H-2), 4.98 (1H, t, J = 5.64 Hz, H-6), 4.20 (1H, m, H-4), 2.51 (1H, m, H-3eq), 2.04 (1H, m, H-5eq), 1.97 (1H, m, H-3ax), 1.67 (1H, m, H-5ax), and 1.64 (1H, bs, OH eq); δ$_H$ (400 MHz, CDCl$_3$) **OH ax** 7.47-7.22 (10H, m, Ar), 6.64 (1H, dd, J = 16.0, 1.9 Hz, H-9), 6.37 (1H, dd, J = 16.0, 5.2 Hz, H-8), 4.74 (1H, J = 11.3, 2.1 Hz, H-2), 4.27 (1H, m, H-6), 4.06 (1H, m, H-4), 2.30 (1H, m, H-3eq), 2.17 (1H, m, H-5eq), 1.92 (1H, m, H-3ax), 1.59 (1H, m, H-5ax), and 1.64 (1H, bs, OH ax); δ$_C$ (100 MHz, CDCl$_3$) 140.6 (Ar), 136.9 (Ar), 130.6 (C-9), 129.9 (C-8), 128.7 (Ar), 128.6 (Ar), 127.7 (Ar), 127.3 (Ar), 126.6 (Ar), 126.4 (Ar), 72.3 (C-2), 70.5 (C-6), 64.8 (C-4), 40.6 (C-5) and 36.9 (C-3); *m/z* (ESI$^+$) 303 (M + Na)$^+$. (Found 303.1349 (M + Na)$^+$. C$_{19}$H$_{20}$NaO$_2$ requires 303.1356).

(2S*,4S*,6S*)-2-Phenyl-6-((E)-styryl)tetrahydro-2H-pyran-4-ol (307)

OH eq   OH ax (minor)
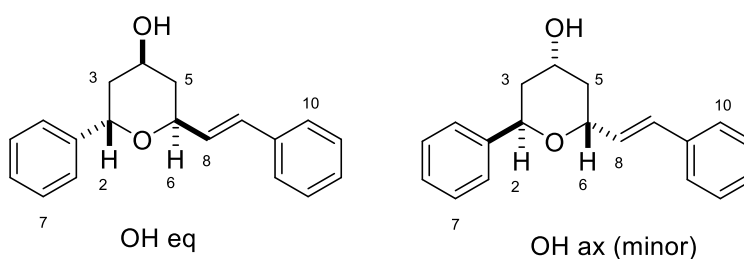
9: 1

The 1.0 M solution of L-Selectride® in THF (0.73 mL) was added to a stirred solution of crude decarboxylated product **313** (0.079g, 0.28 mmol) in THF (3.50 mL) at –78 °C. The mixture was stirred at this temperature for 15 minutes and warm to room temperature for 1 hour, the reaction mixture was stirred at this this temperature until completion. The mixture was diluted with Et_2O (20 mL) and washed with sat. aq. NH_4Cl (20 mL). The aqueous layer was washed with Et_2O (20 mL) and the combined organic extracts were washed with brine (20 mL), dried $MgSO_4$ and concentrated *in vacuo* to give **307** 0.052g (66%), light yellow oil. Diastereomers (9: 1, OH eq: OH ax (minor)). υ max/cm^{-1} (film) 3374 (OH), 2925 (C-H), 1448 (C=C), 1052 (C-O), 695 (Ar); δ_H (400 MHz, CDCl$_3$) 7.47–7.22 (10H, m, Ar), 6.64 (1H, dd, *J* = 16.1, 1.1 Hz, H-9), 6.37 (1H, dd, *J* = 16.1, 5.8 Hz, H-8), 5.31 (1H, t, *J* = 4.4 Hz, H-2), 4.98 (1H, m, H-6 minor), 4.74 (1H, m, H-2 minor), 4.27 (1H, dddd, *J* = 9.1, 5.8, 5.0, 1.1 Hz, H-6), 4.19 (1H, m, H-4 minor), 4.07 (1H, dddd, *J* = 9.3, 9.0, 4.5, 4.0 Hz, H-4), 2.54 (1H, ddd, *J* = 13.5, 4.4, 4.0 Hz, H-3eq), 2.31 (1H, m, H-3 minor), 2.19 (1H, m, H-5 minor), 2.08 (1H, ddd, *J* = 12.6, 5.0, 4.5 Hz, H-5eq), 1.96 (1H, ddd, *J* = 13.5, 9.0, 4.4 Hz, H-3ax), 1.89 (1H, m, H-5 minor), 1.64 (1H, ddd, *J* = 12.6, 9.3, 9.1 Hz, H-5ax) and 1.64 (1H, bs, OH); δ_C (100 MHz, CDCl$_3$) 140.7 (Ar), 136.8 (Ar), 130.6 (C-9), 129.9 (C-8), 128.8 (Ar), 128.7 (Ar), 127.8 (Ar), 127.3 (Ar), 126.6 (Ar), 126.4 (Ar), 72.2 (C-2), 70.6 (C-6), 64.7 (C-4), 40.5 (C-5) and 37.0 (C-3); *m/z* (ESI$^+$) 303 (M + Na)$^+$. (Found 303.1361 (M + Na)$^+$. C$_{19}$H$_{20}$NaO$_2$ requires 303.1356). NMR data were in agreement with the literature.[113]

(2S*,4S*,6S*)-4-(Methoxymethoxy)-2-phenyl-6-((E)-styryl)tetrahydro-2H-pyran (309)
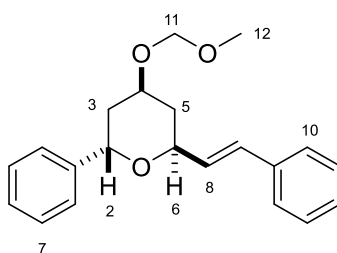
To the stirred solution of THP **307** (0.08 g, 0.28 mmol) in THF (5.00 mL) was added N,N-diisopropylethylamine (0.60 mL, 3.36 mmol), MOMCl (0.34 mL, 4.48 mmol), and sodium iodide (0.10 g, 0.67 mmol) at room temperature. The mixture was heated at 50 °C for 10 hours. After the solvent was removed under vacuum, the reaction mixture was diluted with H_2O (20 mL x 7) and extracted with EtOAc (20 mL). The extract was washed with brine and dried over $MgSO_4$ and concentrated *in vacuo* to give the product **309** 0.054 g (60 %) as a light yellow oil. υ max/cm^{-1} (film) 2923 (C-H), 2854 (C-H), 1145 (C-O), 1033 (C-O), 695 (Ar); δ_H (400 MHz, CDCl$_3$) 7.47–7.22 (10H, m), 6.62 (1H, d, *J* = 16.0 Hz), 6.38 (1H, dd, *J* = 16.0, 6.0 Hz), 5.29 (1H, t, *J* = 4.4 Hz), 4.74, (2H, s), 4.26 (1H, dddd, *J* = 9.2, 6.0, 4.6 Hz), 3.96 (1H, dddd, *J* = 9.4, 9.2, 5.0, 4.0 Hz), 3.41, (3H, s), 2.54 (1H, dddd, *J* = 13.4, 4.4, 4.0, 1.5 Hz), 2.09 (1H, ddd, *J* = 12.8, 5.0, 4.6, 1.5 Hz), 2.03 (1H, ddd, *J* = 13.4, 9.4, 4.4 Hz), and 1.67 (1H, dt, *J* = 12.8, 9.2, 9.2 Hz); δ_C (100 MHz, CDCl$_3$) 140.6 (Ar), 136.9 (Ar), 130.5 (C-9), 129.9 (C-8), 128.7 (Ar), 128.6 (Ar), 127.7 (Ar), 127.3 (Ar), 126.6 (Ar), 126.4 (Ar), 94.9 (C-11), 72.3 (C-2), 70.8 (C-6), 69.8 (C-4), 55.4 (C-12), 37.9 (C-5) and 34.6 (C-3); *m/z* (ESI$^+$) 347 (M + Na)$^+$. (Found 347.1618 (M + Na)$^+$. $C_{21}H_{24}NaO_3$ requires 347.1618). NMR data were in agreement with the literature.[113]

2-((2S*,4S*,6S*)-4-(Methoxymethoxy)-6-phenyltetrahydro-2H-pyran-2-yl)-1-phenylethanone (310)
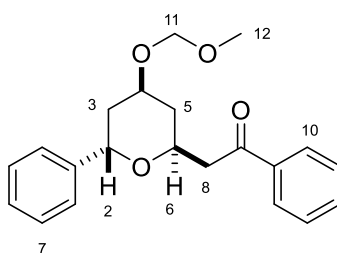
To the stirred solution of THP MOM-protected alcohol **309** (0.014g, 0.04 mmol) in DMF (0.50 mL) and H_2O (0.50 mL) was added $PdCl_2$ (0.004g, 0.02 mmol), Copper chloride (0.006g, 0.06 mmol) at room temperature. The mixture was heated at 50 °C for 3 days under oxygen atmosphere. After the solvent was removed under vacuum to give **310** 0.010 g (70 %) as a light yellow oil. υ max/cm^{-1} (film) 2921 (C-H), 1682 (C=O), 1445 (C=C), 1036 (C-O), 690 (Ar); δ_H (400 MHz, CDCl$_3$) 7.97 (2H, dd, J = 7.0, 1.0 Hz), 7.57 (1H, tt, J = 7.4, 1.2 Hz), 7.47 (2H, t, J = 7.3 Hz), 7.35-7.29 (5H, m), 5.16 (1H, t, J = 4.3 Hz), 4.70 (2H, s), 4.24 (1H, dddd, J = 9.3, 7.0, 5.9, 3.0 Hz), 3.91 (1H, dddd, J = 9.8, 9.3, 4.2, 4.1 Hz), 3.42 (1H, dd, J = 15.9, 7.0 Hz), 3.38, (3H, s), 3.18 (1H, dd, J = 15.9, 5.9 Hz), 2.52 (1H, ddd, J = 13.5, 4.3, 4.1 Hz), 2.08 (1H, ddd, J = 12.6, 4.2, 3.0 Hz), 1.98 (1H, ddd, J = 13.5, 9.8, 4.3 Hz), and 1.67 (1H, dt, J = 12.6, 9.3, 9.3 Hz); δ_C (100 MHz, CDCl$_3$) 198.1 (C-O), 140.4 (Ar), 137.2 (Ar), 133.2 (Ar), 128.7 (Ar), 128.3 (Ar), 127.2 (Ar), 126.4 (Ar), 98.6 (Ar), 95.2 (C-11), 72.4 (C-2), 69.5 (C-6), 67.5 (C-4), 55.4 (C-12), 44.4 (C-O), 38.1 (C-5), and 34.7 (C-3); m/z (ESI$^+$) 363 (M + Na)$^+$. (Found 363.1559 (M + Na)$^+$. C$_{21}$H$_{24}$NaO$_4$ requires 363.1567). NMR data were in agreement with the literature.[113]

Diospongin B

2-((2*S**,4*S**,6*S**)-4-Hydroxy-6-phenyltetrahydro-2H-pyran-2-yl)-1-phenylethanone (4)
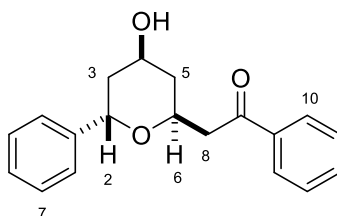
A solution of THP **310** (0.013 mg, 0.04 mmol) and 30% HCl (0.68 mL) was stirred in THF (2.10 mL) at room temperature for 2 hours. Then, water was added to the mixture and the reaction mixture was neutralized with $NaHCO_3$ and extracted with EtOAc (30.0 mL) and the organic extracts were washed with H_2O (20.0 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give **diospongin B**, 0.006 g (58%) as a light yellow oil. υ max/cm^{-1} (film) 3375 (OH), 2916 (C-H), 2846 (C-H), 1702 (C=O), 1411 (C-O), 1129 (C-O); δ_H (400 MHz, CDCl$_3$) 7.98 (2H, dd, J = 8.0, 1.7 Hz, Ar), 7.58 (1H, tt, J = 7.1, 1.3 Hz, Ar), 7.47 (2H, td, J = 7.6, 2.2 Hz, Ar), 7.37-7.3 (5H, m, Ar), 5.19 (1H, t, J = 4.3 Hz, H-2), 4.23 (1H, dddd, J = 9.5, 7.1, 6.0, 3.0 Hz, H-6), 4.03 (1H, dddd, J = 9.9, 9.5, 5.5, 4.5 Hz, H-4), 3.46 (1H, dd, J = 15.8, 7.1 Hz, H-8), 3.18 (1H, dd, J = 15.8, 6.0 Hz, H-8), 2.52 (1H, ddd, J = 13.4, 5.5, 4.3 Hz, H-3eq), 2.06 (1H, ddd, J = 12.4, 4.5, 3.0 Hz, H-5eq), 1.92 (1H, ddd, J = 13.4, 9.9, 4.3 Hz, H-3ax), and 1.51 (1H, dt, J = 12.4, 9.5, 9.5 Hz, H-5ax); δ_C (100 MHz, CDCl$_3$) 198.5 (C=O), 140.4 (Ar), 137.2 (Ar), 133.3 (Ar), 128.7 (Ar), 128.6 (Ar), 128.4 (Ar), 127.2 (Ar), 126.4 (Ar), 72.5 (C-2), 67.0 (C-6), 64.3 (C-4), 44.7 (C-O), 40.3 (C-5) and 36.8 (C-3); *m/z* (ESI$^+$) 319 (M + Na)$^+$. (Found 319.1300 (M + Na)$^+$. C$_{19}$H$_{20}$NaO$_3$ requires 319.1305). NMR data were in agreement with the literature.[113]

General Procedure for the Synthesis of 3,6-disubstituted-tetrahydropyran-4-ones.

A 1.0 M solution of L-Selectride® in THF (0.04 mL, 0.04 mmol) was added to a stirred solution of DHP (0.04 mmol) in THF (1.00 mL) at −78 °C. The mixture was stirred for 1 hour at −78 °C until completion. Then it was diluted with Et$_2$O (10.0 mL) and quench with sat. aq. NHCl$_4$ (10.0 mL). The aqueous layer was washed with Et$_2$O (10.0 mL) and the combined organic extracts were washed with brine (20.0 mL), dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexane − ethyl: acetate with 4:1) afforded the tautomer product.

Methyl 6-(furan-2-yl)-4-hydroxy-5,6-dihydro-2H-pyran-3-carboxylate (338)
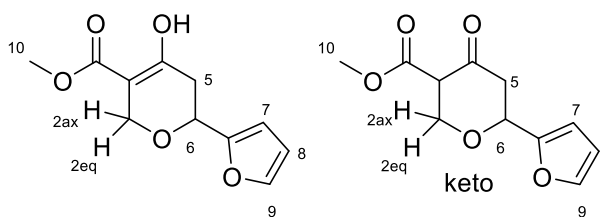
Dihydropyran **259** (0.09 g, 0.43 mmol), L-Selectride® (0.44 mL, 0.44 mmol), THF (11 mL); purification (hexane − ethyl acetate = 4: 1), percentage yielded 0.043 g, 44 %, light yellow oil. υ max/cm^{-1} (film) 2954 (C-H), 2927 (C-H), 2868 (C-H), 1737 (C=O), 1667 (C=O), 1627 (C=O), 1442 (C=C), 1275 (C-O), 1066 (C-O), 1011 (C-O), 739 (C=C), 598 (C=C); δ$_H$ (400 MHz, CDCl$_3$): δ 11.81 (OH, s), 7.42 (1H, m, H-7), 7.38 (1H, m, *keto* H-7) 6.37–6.33 (2H, m, H-8, H-9), 6.28–6.27 (2H, m, *keto* H-8, H-9), 5.08 (1H, dd, J = 11.6, 2.9 Hz, *keto* H-6), 4.88 (1H, dd, J = 10.0, 3.6 Hz, *keto* H-3), 4.73 (1H, dd, J = 9.9, 3.9 Hz, H-6), 4.50 (2H, m, H-2), 4.44 (1H, d, J = 14.0, H-2ax), 4.37 (1H, d, J = 14.0 Hz, H-2eq), 3.77 (3H, s, H-10), 3.70 (3H, s, *keto* H-10), 2.86 (1H, dd, J = 17.8, 9.9 Hz, H-5), 2.80 (1H, m, *keto* H-5), 2.53 (1H, dd, J = 17.8, 3.8 Hz, H-5), and 2.08 (1H, m, *keto* H-5); δ$_C$

(100 MHz, CDCl$_3$): 170.4 (C=O), 168.2 (C=O), 152.7 (C-3), 143.0 (C-7), 110.4 (C-8), 107.9 (C-9), 106.2 (*keto*), 97.1 (C-4), 72.9 (*keto* C-3), 68.9 (C-6), 67.7 (*keto* C-6), 62.9 (C-2), 51.6 (C-10, *keto* C-10), 31.9 (C-5), 26.1 (*keto* C-5); *m/z* (ESI$^+$) 247 (M + Na)$^+$. (Found 247.0575 (M + Na)$^+$. C$_{11}$H$_{12}$NaO$_5$ requires 247.0577).

Methyl 4-hydroxy-6-phenyl-5,6-dihydro-2H-pyran-3-carboxylate (339)
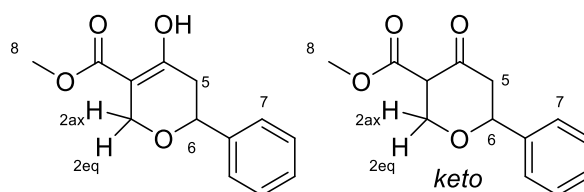
Dihydropyran **264** (0.10 g, 0.42 mmol), L-Selectride$^®$ (0.43 mL, 0.43 mmol), THF (11 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield, 0.074 g, 74 %, light yellow oil. υ max/cm^{-1} (film) 2952 (C-H), 2922 (C-H), 2852 (C-H), 1664 (C=O), 1622 (C=O), 1445 (C=C), 1269 (C-O), 1209 (C-O), 1066 (C-O), 1027 (C-O), 699 (Ar); δ$_H$ (400 MHz, CDCl$_3$): δ 11.29 (OH, s), 7.43–7.29 (5H, m, H-7), 4.70 (1H, m, *keto* H-6), 4.67 (1H, dd, *J* = 10.48, 3.71 Hz, H-6), 4.59 (1H, m, *keto* H-3), 4.55-4.36 (2H, m, *keto* H-2), 4.44 (1H, d, *J* = 14.0, H-2ax), 4.39 (1H, d, *J* = 14.0 Hz, H-2eq), 3.81 (3H, s, H-8), 3.80 (3H, s, *keto* H-8), 3.02-2.68 (2H, m, *keto* H-5) and 2.67-2.49 (2H, m, H-5); δ$_C$ (100 MHz, CDCl$_3$): 170.4 (C=O), 168.7 (C=O), 167.8 (*keto*), 140.7 (C-3), 139.8 (*keto*), 128.9 (*keto* Ar), 128.6 (*keto* Ar), 128.2 (Ar), 128.0 (Ar), 125.8 (Ar), 125.5 (*keto* Ar), 97.1 (Ar), 80.3 (*keto*), 75.5 (C-6), 68.2 (*keto* C-6), 63.4 (C-2), 57.2 (*keto* C-2), 52.3 (*keto* C-8), 51.4 (C-8), 49.4 (*keto*), 48.6 (*keto*), and 35.7 (C-5); *m/z* (ESI$^+$) 257 (M + Na)$^+$. (Found 257.0782 (M + Na)$^+$. C$_{13}$H$_{14}$NaO$_4$ requires 257.0784).

(*E*)-Methyl 4-hydroxy-6-styryl-5,6-dihydro-2H-pyran-3-carboxylate (340)
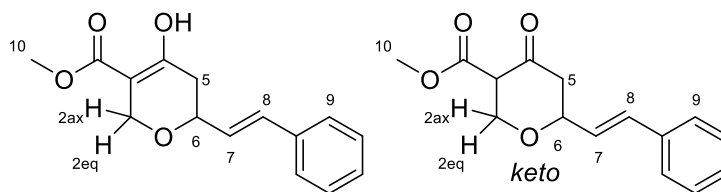
Dihydropyran **269** (0.10 g, 0.38 mmol), L-Selectride® (0.17 mL, 0.17 mmol), THF (5 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.051 g, 51 %, light yellow oil. υ max/cm^{-1} (film) 2953 (C-H), 2839 (C-H), 1665 (C=O), 1626 (C=O), 1441 (C=C), 1263 (C-O), 1211 (C-O), 1059 (C-O), 965 (Ar), 795 (Ar), 746 (C=C), 692 (C=C);

δ_H (400 MHz, CDCl₃): δ 11.78 (OH, s), 7.41–7.23 (5H, m, H-9), 6.65 (1H, d, *J* = 16.0 Hz, H-8), 6.58 (1H, m, *keto* H-8), 6.23 (1H, dd, *J* = 16.0, 6.0 Hz, H-7), 6.19 (1H, m, *keto* H-7), 4.48 (1H, d, *J* = 13.9, H-2ax), 4.47 (1H, m, *keto* H-2ax), 4.32 (1H, d, *J* = 13.9 Hz, H-2eq), 4.28 (1H, m, H-6), 4.26 (1H, m, *keto* H-2eq), 3.79 (3H, s, *keto* H-10), 3.77 (3H, s, H-10), 2.84 (1H, m, *keto* H-5), 2.67 (1H, m, *keto* H-5) and 2.69–2.38 (2H, m, H-5); δ_C (100 MHz, CDCl₃): 170.5 (C=O), 168.5 (C=O), 136.4 (C-3), 136.0 (Ar), 132.3 (*keto* C-8), 131.8 (C-8), 128.8 (*keto* Ar), 128.7 (Ar), 128.4 (*keto*) 128.1 (C-7), 128.1 (Ar), 127.3 (*keto* C-7), 126.8 (*keto* Ar), 126.7 (Ar), 97.2 (C-4), 78.8 (*keto*), 74.0 (C-6), 68.0 (*keto*), 62.9 (C-2), 52.4 (*keto*), 51.6 (C-10), 47.7 (*keto*) and 34.3 (C-5); *m/z* (ESI⁺) 283 (M + Na)⁺. (Found 283.0934 (M + Na)⁺. C₁₅H₁₆NaO₄ requires 283.0941).

Methyl 4-hydroxy-6-((((triisopropylsilyl)oxy)methyl)-5,6-dihydro-2H-pyran-3-carboxylate (341)
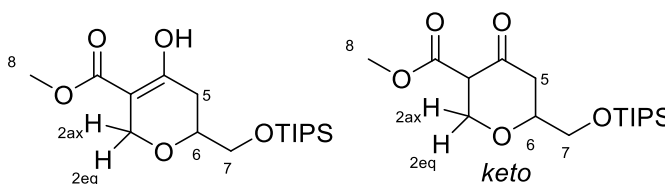
Dihydropyran **265** (0.09 g, 0.27 mmol), L-Selectride® (0.30 mL, 0.30 mmol), THF (8 mL); purification (hexane – ethyl acetate = 4: 1), percentage yielded 0.062 g, 65 %, light yellow oil. υ max/cm^{-1} (film) 2924 (C-H), 2865 (C-H), 1774 (C=O), 1729 (C=O), 1709 (C=O), 1148 (C-O), 1057 (C-O), 881 (C=C); δ_H (400 MHz, CDCl$_3$): δ 11.78 (OH, s), 4.69–4.66 (2H, m, *keto* H-2), 4.43 (1H, d, J = 13.9, H-2ax), 4.22 (1H, d, J = 13.9 Hz, H-2eq), 3.93 (1H, m, *keto* H-6), 3.88 (1H, m, H-6), 3.83-3.79 (2H, m, H-7), 3.76 (3H, s, *keto* H-8), 3.75 (3H, s, H-8), 3.62–3.59 (2H, m, *keto* H-7), 2.82 (1H, m, *keto* H-5), 2.61–2.28 (2H, m, H-5), 2.31 (1H, m, *keto* H-5) and 1.06-1.05 (21H, m, OTIPS); δ_C (100 MHz, CDCl$_3$): 170.4 (C=O), 169.2 (C=O), 97.1 (C-4), 79.1 (*keto* C-6), 74.4 (C-6), 66.0 (C-7), 63.1 (C-2), 52.2 (C-8), 51.3 (*keto*), 44.1 (*keto*), 31.1 (C-5), 17.9 (OTIPS) and 11.8 (OTIPS); m/z (ESI$^+$) 367 (M + Na)$^+$. (Found 367.1905 (M + Na)$^+$. C$_{17}$H$_{32}$NaO$_5$Si requires 367.1911).

Methyl 4-hydroxy-6-propyl-5,6-dihydro-2H-pyran-3-carboxylate (342)
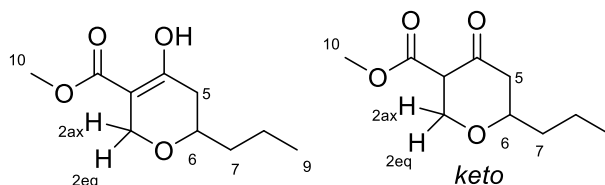
Dihydropyran **263** (0.10 g, 0.50 mmol), L-Selectride® (0.50 mL, 0.50 mmol), THF (13 mL); purification (hexane – ethyl acetate = 4: 1), percentage yielded 0.089 g, 89 %, light yellow oil. υ max/cm^{-1} (film) 2957 (C-H), 2871 (C-H), 1666 (C=O), 1441 (C=C), 1213 (C-O), 1074 (C-O), 807 (C=C); δ_H (400 MHz, C$_6$D$_6$): δ 12.09 (OH, s), 4.50 (1H, d, J = 13.7, H-2ax), 4.40 (1H, m, *keto* H-2ax), 4.11 (1H, d, J = 13.7 Hz, H-2eq), 4.05 (1H, m, *keto* H-2eq), 3.22 (3H, s, H-10), 3.21 (3H, s, *keto* H-10), 3.20 (1H, m, H-6), 3.05 (1H, m, *keto* H-6), 2.12 (2H, m, *keto* H-5), 2.08 (1H, m, H-5), 1.94 (1H, m, H-5), 1.47–0.96 (4H, m, H-7, H-8) and 0.79 (3H, t, J = 7.2 Hz, H-9); δ_C (100 MHz, C$_6$D$_6$): 170.5 (C=O), 169.7

(C=O), 97.3 (C-4), 73.2, 70.0 (*keto* C-2), 62.9 (C-2), 54.0 (*keto* C-6), 52.0 (*keto* C-10), 50.5 (C-6, C-10), 37.7, 34.5 (C-5), 18.3 (C-7,C-8) and 13.9 (C-9); *m/z* (ESI$^+$) 223 (M + Na)$^+$. (Found 223.0938 (M + Na)$^+$. $C_{10}H_{16}NaO_4$ requires 223.0941).

General procedure for the acylation of 3, 6-disubstituted-tetrahydropyran-4-ones. Formation of enol acetates.

The THP mixture (0.03 mmol), acetic anhydride (0.10 mL, 0.10 mmol) and DMAP (2 mol%) were stirred in pyridine (0.47 mL) at 40 °C for 40 minutes. The mixture was cooled to room temperature and concentrated *in vacuo*. Then partitioned between Et_2O (30.0 mL) and H_2O (10.0 mL). The organic layer was washed with H_2O (10.0 mL) and brine (10.0 mL), then dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography (hexane – ethyl acetate = 4:1) gave the product.

Methyl 4-acetoxy-6-(furan-2-yl)-5,6-dihydro-2H-pyran-3-carboxylate (316)
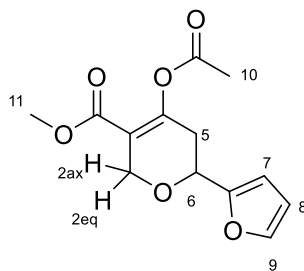
Tetrahydropyran **338** (0.04 g, 0.19 mmol), acetic anhydride (0.60 mL, 0.60 mmol), DMAP (2 mol%), pyridine (3.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.031 g, 71 % colorless oil. υ max/cm^{-1} (film) 2953 (C-H), 2847 (C-H), 1760 (C=O), 1723 (C=O), 1671 (C=C), 1365 (CH$_3$), 1253 (C-O), 1173 (C-O), 1132 (C-O), 1059 (C-O), 743 (C=C); δ$_H$ (400 MHz, CDCl$_3$): δ 7.41 (1H, s, H-7), 6.41 (1H, m, H-8), 6.35 (1H, m, H-9), 4.80 (1H, dd, *J* = 9.0, 4.1 Hz, H-6), 4.51–4.48 (2H, m, H-2ax, H-

2eq), 3.72 (3H, s, H-11) 2.89 (1H, m, H-5), 2.55 (1H, m, Hz, H-5) and 2.52 (3H, s, H-10); δ_C (100 MHz, CDCl$_3$): 168.4 (C=O), 163.1 (C=O), 153.3 (C-3), 152.2 (C-12), 143.0 (C-7), 116.5 (C-4), 110.4 (C-8), 108.3 (C-9), 68.7 (C-6), 64.0 (C-2), 51.8 (C-11), 32.4 (C-5) and 21.0 (C-10); m/z (ESI$^+$) 289 (M + Na)$^+$. (Found 289.0692 (M + Na)$^+$. C$_{13}$H$_{14}$NaO$_6$ requires 289.0683).

(*E*)-Methyl 4-acetoxy-6-styryl-5,6-dihydro-2H-pyran-3-carboxylate (320)
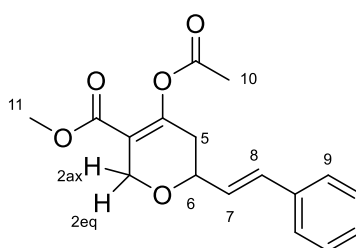
Tetrahydropyran **340** (0.015 g, 0.05 mmol), acetic anhydride (0.19 mL, 0.19 mmol), DMAP (2 mol%), pyridine (0.94 mL); purification (hexane – ethyl acetate = 4: 1), percentage yielded 0.01 g, 56 % light yellow oil. υ max/cm^{-1} (film) 2951 (C-H), 2844 (C-H), 1761 (C=O), 1723 (C=O), 1248 (C-O), 1172 (C-O), 1142 (C-O), 1051 (C-O), 748 (Ar), 693 (Ar); δ_H (400 MHz, CDCl$_3$): δ 7.40–7.23 (5H, m, H-9), 6.68 (1H, d, J = 16.0 Hz, H-8), 6.23 (1H, dd, J = 16.0, 6.1 4.1 Hz, H-7), 4.63 (1H, d, J = 15.0 Hz, H-2ax), 4.43 (1H, d, J = 15.0 Hz, H-2eq), 4.33 (1H, m, H-6), 3.72 (3H, s, H-11), 2.52 (1H, m, H-5), 2.37 (1H, m, H-5) and 2.24 (3H, s, H-10); δ_C (100 MHz, CDCl$_3$): 168.4 (C=O), 163.3 (C=O), 153.8 (C-3), 136.3 (Ar), 132.1 (C-7), 128.7 (Ar), 128.1 (Ar), 127.6 (C-8), 126.7 (Ar), 116.5 (C-4), 73.9 (C-6), 64.3 (C-2), 51.8 (C-11), 34.9 (C-5) and 21.0 (C-10); m/z (ESI$^+$) 325 (M + Na)$^+$. (Found 325.1053 (M + Na)$^+$. C$_{17}$H$_{18}$NaO$_5$ requires 325.1046).

Methyl 4-acetoxy-6-phenyl-5,6-dihydro-2H-pyran-3-carboxylate (317)
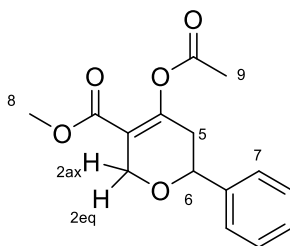
Tetrahydropyran **339** (0.07 g, 0.31 mmol), acetic anhydride (1.04 mL, 1.04 mmol), DMAP (2 mol%, pyridine (5.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yielded 0.059 g, 68 % solid white. υ max/cm^{-1} (film) 2949 (C-H), 2842 (C-H), 1765 (C=O), 1718 (C=O), 1664 (Ar), 1166 (C-O), 1131 (C-O), 1060 (C-O), 743 (Ar), 700 (Ar); δ_H (400 MHz, CDCl$_3$): δ 7.38–7.28 (5H, m, H-7), 6.69 (1H, d, J = 16.0 Hz, H-2ax), 4.67 (1H, m, H-6), 4.49 (1H, d, J = 16.0, 4.0 Hz, H-2eq), 3.74 (3H, s, H-8), 2.63 (1H, m, H-5), 2.47 (1H, m, H-5) and 2.24 (3H, s, H-9); δ_C (100 MHz, CDCl$_3$): 168.4 (C=O), 163.3 (C=O), 154.1 (C-3), 140.1 (Ar), 128.7 (Ar), 128.2 (Ar), 125.9 (Ar), 116.5 (C-4), 75.5 (C-6), 64.9 (C-2), 51.7 (C-8), 36.5 (C-5) and 21.0 (C-9); m/z (ESI$^+$) 299 (M + Na)$^+$. (Found 299.0894 (M + Na)$^+$. C$_{15}$H$_{16}$NaO$_5$ requires 299.0890).

Methyl 4-acetoxy-6-((((triisopropylsilyl)oxy)methyl)-5,6-dihydro-2H-pyran-3-carboxylate (319)
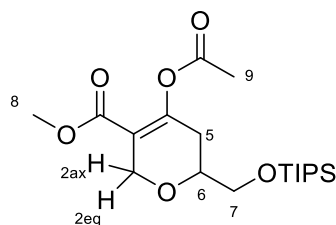
Method acylation of THP, THP **341** (0.04 g, 0.11 mmol), acetic anhydride (0.38 mL, 0.38 mmol), DMAP (2 mol%), pyridine (0.63 mL); purification (hexane – ethyl acetate = 4: 1), isolated yielded 0.029 g, 65 % light yellow oil. υ max/cm^{-1} (film) 2924 (C-H), 2865

(C-H), 1774 (C=O), 1729 (C=O), 1148 (C-O), 1057 (C-O); δ_H (400 MHz, C_6D_6): 4.70 (1H, dd, J = 15.5, 2.0 Hz, H-2ax), 4.33 (1H, dd, J = 15.5, 3.4 Hz, H-2eq), 3.82 (1H, dd, J = 10.0, 5.0 Hz, H-7), 3.70 (1H, dd, J = 10.0, 5.0 Hz, H-7), 3.65 (1H, m, H-6), 3.30 (3H, s, H-8), 2.59 (1H, m, H-5), 2.27 (1H, m, H-5), 2.02 (3H, s, H-9) and 1.18-1.17 (21H, m, OTIPS); δ_C (100 MHz, C_6D_6): 167.7 (C=O), 163.0 (C=O), 154.9 (C-3), 116.7 (C-4), 74.7 (C-6), 66.1 (C-7), 64.8 (C-2), 50.8 (C-8), 32.0 (C-5), 20.6 (C-9), 18.1 (OTIPS) and 12.2 (OTIPS); m/z (ESI$^+$) 409 (M + Na)$^+$. (Found 409.2022 (M + Na)$^+$. $C_{19}H_{34}NaO_6Si$ requires 409.2017).

Methyl 4-acetoxy-6-propyl-5,6-dihydro-2H-pyran-3-carboxylate (318)
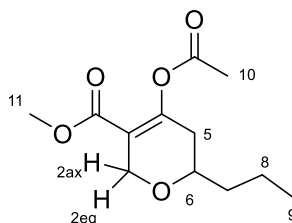
Tetrahydropyran **342** (0.09 g, 0.45 mmol), acetic anhydride (1.49 mL, 1.49 mmol), DMAP (2 mol%), pyridine (1.41 mL); purification (hexane – ethyl acetate = 4: 1), isolated yielded 0.056 g, 51 % light yellow oil. υ max/cm^{-1} (film) 2957 (C-H), 2872 (C-H), 1768 (C=O), 1726 (C=O), 1250 (C-O), 1212 (C-O), 1177 (C-O); δ_H (400 MHz, CDCl$_3$): 4.53 (1H, dd, J = 15.0 Hz, H-2ax), 4.31 (1H, dd, J = 15.0 Hz, H-2eq), 3.70 (3H, s, H-11), 3.60 (1H, m, H-6), 2.30–2.14 (2H, m, H-5), 2.23 (3H, s, H-10) 1.64–1.50 (5H, m, H-7, H-8) and 0.93 (3H, t, J = 7.2 Hz, H-9); δ_C (100 MHz, CDCl$_3$): 168.4 (C=O), 163.5 (C=O), 154.7 (C-3), 116.3 (C-4), 73.5 (C-6), 64.6 (C-2), 51.7 (C-11), 37.4 (C-7), 35.0 (C-5), 21.0 (C-10), 18.5 (C-8) and 14.1 (C-9); m/z (ESI$^+$) 265 (M + Na)$^+$. (Found 265.1052 (M + Na)$^+$. $C_{12}H_{18}NaO_5$ requires 265.1046).

General procedure for L-Selectride reduction of dihydropyrans with electrophile quench:

A 1.0 M solution of L-Selectride® in THF (0.04 mL, 0.04 mmol) was added to a stirred solution of DHP (0.04 mmol) in THF (1.00 mL) at −78 °C. The mixture was stirred for 1 hour at −78 °C, then the electrophile (0.40 mmol) was added. Then, the reaction mixture was stirred at room temperature until completion, followed with mixture were diluted with Et$_2$O (10.0 mL) and quench with sat. aq. NHCl$_4$ (10.0 mL). The aqueous layer was washed with Et$_2$O (10.0 mL) and the combined organic extracts were washed with brine (20.0 mL), dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography (hexane – ethyl acetate with 4 : 1) to afforded the product.

(3S*,6S*)-Methyl 6-(furan-2-yl)-3-methyl-4-oxotetrahydro-2H-pyran-3-carboxylate (325)
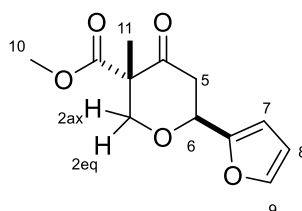
Dihydropyran **259** (0.10 g, 0.45 mmol), L-Selectride® (0.45 mL, 0.45 mmol), MeI (0.56 mL, 9.00 mmol), THF (11 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.062 g, 57 % light yellow oil. Diastereomers (1: 0.3). υ max/cm^{-1} (film) 2957 (C-H), 2872 (C-H), 1768 (C=O), 1726 (C=O), 1249 (C-O), 1212 (C-O), 1175 (C-O), 1148 (C-O), 1055 (C-O), 797 (C=C), 771 (C=C); δ$_H$ (400 MHz, CDCl$_3$): δ 7.42 (1H, m, H-7), 6.39–6.31 (2H, m, H-8, H-9), 5.19 (1H, dd, J = 6.3, 5.0 Hz, H-6), 4.17 (1H, dd, J = 12.0, 2.8 Hz, H-6 minor), 4.63 (1H, d, J = 11.6 Hz, H-2ax minor), 4.28 (1H, d, J = 12.0 Hz, H-2ax), 3.78 (3H, s, H-10), 3.53 (1H, d, J = 12.0 Hz, H-2eq), 3.48 (1H, d, J = 11.6 Hz, H-

2eq minor), 3.21 (1H, dd, J = 14.4, 12.0 Hz, H-5 minor), 3.03 (1H, dd, J = 15.0, 6.3 Hz, H-5), 2.91 (1H, dd, J = 15.0, 5.0 Hz, H-5), 2.72 (1H, dd, J = 14.4, 2.8 Hz, H-5 minor), 1.32 (3H, s, H-11) and 1.26 (3H, s, H-11 minor); δ_C (100 MHz, CDCl$_3$): 203.4 (C=O), 171.4 (C=O), 151.4 (C-12), 143.3 (C-9), 110.3 (C-7), 109.9 (C-8), 74.5 (C-6 minor), 73.9 (C-2 minor), 71.7 (C-6), 70.6 (C-2), 58.3 (C-3), 52.8 (C-10), 44.2 (C-5 minor), 41.9 (C-5), 16.9 (C-11) and 15.4 (C-11 minor); m/z (ESI$^+$) 261 (M + Na)$^+$. (Found 261.0743 (M + Na)$^+$. C$_{12}$H$_{14}$NaO$_5$ requires 261.0733).

(3S*,6S*)-Methyl 3-methyl-4-oxo-6-phenyltetrahydro-2H-pyran-3-carboxylate (321)

(prepared by James Burroughs)

Dihydropyran **264** (0.10 g, 0.43 mmol), L-Selectride® (0.43 mL, 0.43 mmol), MeI (0.53 mL, 8.62 mmol), THF (11.00 mL); purification (hexane – ethyl acetate = 4: 1), isolated yielded 0.063 g (59 %) light yellow oil. υ max/cm^{-1} (film) 3032 (Ar), 2953 (C-H), 2877 (C-H), 1736 (C=O), 1710 (C=O), 1268 (C-O), 1233 (C-O), 1095 (C-O), 1075 (C-O), 699 (Ar), 762 (Ar); δ_H (400 MHz, CDCl$_3$): δ 7.41–7.31 (5H, m, H-9), 4.89 (1H, dd, J = 9.5, 4.1 Hz, H-6), 4.29 (1H, d, J = 11.7 Hz, H-2ax), 3.94 (1H, d, J = 11.7 Hz, H-2eq), 3.79 (3H, s, H-8), 2.86 (1H, dd, J = 15.2, 9.5 Hz, H-5ax), 2.75 (1H, dd, J = 15.2, 4.1 Hz, H-5eq) and 1.54 (3H, s, H-9); δ_C (100 MHz, CDCl$_3$): 204.9 (C=O), 171.3 (C=O), 139.8 (Ar), 128.8 (Ar), 128.4 (Ar), 126.0 (Ar), 79.5 (C-6), 72.5 (C-2), 58.6 (C-3), 52.6 (C-8), 45.1 (C-5) and 18.6 (C-9); m/z (ESI$^+$) 271 (M + Na)$^+$. (Found 271.0936 (M + Na)$^+$. C$_{14}$H$_{16}$NaO$_4$ requires 271.0941).

(3S*,6S*)-Methyl 3-methyl-4-oxo-6-((E)-styryl)tetrahydro-2H-pyran-3-carboxylate (324)
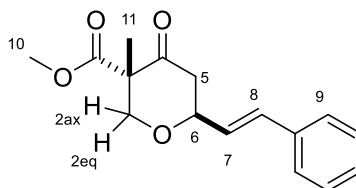
Dihydropyran **269** (0.12 g, 0.46 mmol), L-Selectride® (0.47 mL, 0.47 mmol), MeI (0.57 mL, 9.30 mmol), THF (12.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.063 g, 53 % light yellow oil. υ max/cm^{-1} (film) 3026 (Ar), 2952 (C-H), 2875 (C-H), 1733 (C=O), 1713 (C=O), 1232 (C-O), 1264 (C-O), 1114 (C-O), 1088 (C-O), 967 (Ar), 748 (Ar), 693 (Ar); δ_H (400 MHz, C$_6$D$_6$): δ 7.18–7.02 (5H, m, H-9), 6.44 (1H, d, J = 16.0 Hz, H-8), 5.94 (1H, dd, J = 16.0, 5.3 Hz, H-7), 4.19 (1H, d, J = 11.6 Hz, H-2ax), 4.06 (1H, ddd, J = 9.0, 5.3, 4.4 Hz, H-6), 3.66 (1H, d, J = 11.6 Hz, H-2eq), 3.36 (3H, s, H-10), 2.41 (1H, dd, J = 15.0, 4.4 Hz, H-5eq), 2.29 (1H, dd, J = 15.0, 9.0 Hz, H-5ax) and 1.31 (3H, s, H-11); δ_C (100 MHz, C$_6$D$_6$): 203.2 (C=O), 171.9 (C=O), 136.6 (Ar), 132.2 (C-7), 128.9 (Ar), 128.1 (Ar), 127.9 (Ar), 126.9 (C-8), 77.7 (C-6), 72.1 (C-2), 58.7 (C-3), 52.0 (C-10), 43.9 (C-5) and 18.1 (C-11); m/z (ESI$^+$) 297 (M + Na)$^+$. (Found 297.1095 (M + Na)$^+$. C$_{16}$H$_{18}$NaO$_4$ requires 297.1097).

(3S*,6S*)-Methyl 3-methyl-4-oxo-6-((((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-3-carboxylate (323)
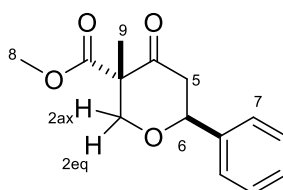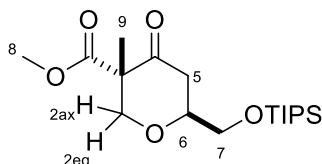

Dihydropyran **265** (0.09 g, 0.28 mmol), L-Selectride® (0.30 mL, 0.30 mmol), MeI (0.34 mL, 5.60 mmol), THF (8.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage

yield 0.057 g, 57 % light yellow oil. υ max/cm^{-1} (film) 2942 (C-H), 2866 (C-H), 1738 (C=O), 1715 (C=O), 1105 (C-O); δ$_H$ (400 MHz, C$_6$D$_6$): 4.13 (1H, d, J = 11.4 Hz, H-2ax), 3.73 (1H, d, J = 11.4 Hz, H-2eq), 3.58 (1H, dddd, J = 10.0, 3.5, 3.8, 3.8, Hz H-6), 3.45 (1H, dd, J = 8.0, 3.8 Hz, H-7), 3.40 (1H, dd, J = 8.0, 3.8 Hz, H-7), 3.36 (3H, s, H-8), 2.59 (1H, dd, J = 15.1, 10.0 Hz, H-5ax), 2.25 (1H, dd, J = 15.1, 3.5 Hz, H-5eq), 1.43 (3H, s, H-9) and 1.05–1.04 (21H, m, OTIPS); δ$_C$ (100 MHz, C$_6$D$_6$): 205.0 (C=O), 171.1 (C=O), 78.6 (C-6), 73.0 (C-2), 65.9 (C-7), 58.8 (C-3), 51.9 (C-8), 40.2, 18.6 (C-9), 18.1 (OTIPS) and 12.2 (OTIPS); m/z (ESI$^+$) 381 (M + Na)$^+$. (Found 381.2065 (M + Na)$^+$. C$_{18}$H$_{34}$NaO$_5$Si requires 381.2068).

(3S*,6R*)-Methyl   3-methyl-4-oxo-6-propyltetrahydro-2H-pyran-3-carboxylate (322)
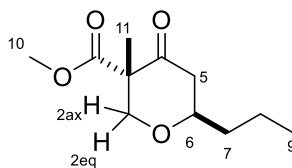
Dihydropyran **263** (0.10 g, 0.50 mmol), L-Selectride$^®$ (0.50 mL, 0.50 mmol), MeI (0.62 mL, 10.10 mmol), THF (13.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yielded 0.063 g, 58 % colorless oil. υ max/cm^{-1} (film) 2956 (C-H), 2929 (C-H), 2872 (C-H), 1738 (C=O), 1714 (C=O), 1263 (C-O), 1100 (C-O); δ$_H$ (400 MHz, C$_6$D$_6$): δ 4.08 (1H, d, J = 11.5 Hz, H-2ax), 3.62 (1H, d, J = 11.5 Hz, H-2eq), 3.38 (3H, s, H-10), 3.24 (1H, m, H-6), 2.12 (1H, dd, J = 15.0, 3.6 Hz, H-5eq), 1.99 (1H, dd, J = 15.0, 10.2 Hz, H-5ax), 1.35 (3H, s, H-11), 1.32–0.93 (4H, m, H-7, H-8) and 0.74 (3H, t, J = 7.3 Hz, H-9); δ$_C$ (100 MHz, C$_6$D$_6$): 204.3 (C=O), 171.9 (C=O), 77.8 (C-6), 72.2 (C-2), 58.8 (C-3), 51.8 (C-10), 44.2 (C-5), 37.7 (C-8), 18.7 (C-11), 18.5 (C-7) and 14.0 (C-9); m/z (ESI$^+$) 237 (M + Na)$^+$. (Found 237.1100 (M + Na)$^+$. C$_{11}$H$_{18}$NaO$_4$ requires 237.1097).

(3S*,6S*)-Methyl 3-allyl-6-(furan-2-yl)-4-oxotetrahydro-2H-pyran-3-carboxylate (330)
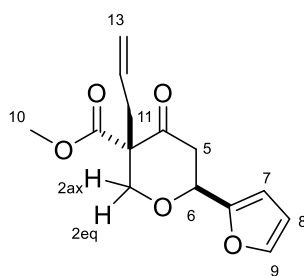
Dihydropyran **259** (0.10 g, 0.45 mmol), L-Selectride® (0.45 mL, 0.45 mmol), Allyl Bromide (0.77 mL, 9.00 mmol), THF (11.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.047 g, 47 % light yellow oil. υ max/cm^{-1} (film) 2954 (C-H), 1716 (C=O), 1227 (C-O), 1145 (C-O), 1075 (C-O), 1013 (C-O), 988 (C=C), 745 (C=C); δ_H (400 MHz, CDCl$_3$): δ 7.13 (1H, m, H-7), 6.36–6.32 (2H, m, H-8, H-9), 5.83 (1H, m, H-12 minor), 5.77 (1H, m, H-12), 5.13 (1H, m, H-13), 5.07 (1H, dd, J = 7.6, 6.9 Hz, H-6), 4.69 (1H, dd, J = 12.0, 2.8 Hz, H-6 minor), 4.62 (1H, d, J = 12.0 Hz, H-2 minor), 4.25 (1H, d, J = 12.0 Hz, H-2ax), 3.77 (3H, s, H-10), 3.70 (1H, d, J = 12.0 Hz, H-2eq), 3.57 (1H, d, J = 12.0 Hz, H-2 minor), 3.16 (1H, dd, J = 14.4, 11.6 Hz, H-11 minor), 2.97 (1H, dd, J = 15.2, 6.1 Hz, H-11), 2.89 (1H, dd, J = 15.2, 5.6 Hz, H-11), 2.73 (1H, dd, J = 14.4, 2.8 Hz, H-5 minor), 2.63 (1H, dd, J = 14.0, 6.9 Hz, H-5), 2.48 (1H, dd, J = 14.0, 7.6 Hz, H-5) and 2.35 (1H, dd, J = 14.4, 12.0 Hz, H-5 minor); δ_C (100 MHz, CDCl$_3$): 202.6 (C=O), 170.3 (C=O), 151.3 (C-14), 143.3 (C-7), 132.1 (C-12), 119.2 (C-13), 110.4 (C-8), 109.8 (C-9), 73.9 (C-6 minor), 73.2 (C-2 minor), 71.8 (C-6), 68.7 (C-2), 62.1 (C-3), 52.6 (C-10), 44.8 (C-11 minor), 42.5 (C-11) and 35.4 (C-5); *m/z* (ESI$^+$) 287 (M + Na)$^+$. (Found 287.0886 (M + Na)$^+$. C$_{14}$H$_{16}$NaO$_5$ requires 287.0890).

(3S*,6S*)-Methyl 3-allyl-4-oxo-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-3-carboxylate (328)
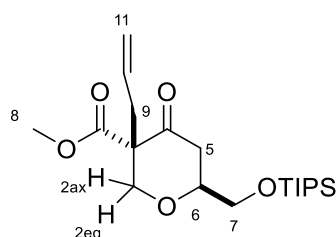
Dihydropyran **265** (0.09 g, 0.28 mmol), L-Selectride® (0.30 mL, 0.30 mmol), Allyl Bromide (0.48 mL, 5.60 mmol), THF (8.00 mL); purification (hexane – ethyl acetate = 4: 1), isolated yielded 0.061 g, 57 % light yellow oil. υ max/cm^{-1} (film) 2943 (C-H), 2866 (C-H), 1739 (C=O), 1715 (C=O), 1231 (C-O), 1124 (C-O), 1083 (C-O), 881 (C=C), 680 (C=C); δ_H (400 MHz, C$_6$D$_6$): δ 6.05 (1H, dddd, J = 16.8, 9.9, 7.1, 7.0 Hz, H-10), 5.29 (1H, dd, J = 16.8, 1.8 Hz Hz, H-11*trans*), 5.14 (1H, dd, J = 9.9, 1.8 Hz, H-11*cis*), 4.17 (1H, d, J = 11.6 Hz, H-2ax), 4.14 (1H, d, J = 11.6 Hz, H-2eq), 3.70 (1H, m, H-6), 3.50 (2H, m, H-7), 3.47 (3H, s, H-8), 2.90 (1H, dd, J = 13.6, 7.0 Hz, H-9), 2.79 (1H, dd, J = 13.6, 7.1 Hz, H-9), 2.73 (1H, dd, J = 15.0, 8.0 Hz, H-5ax) and 2.33 (1H, dd, J = 15.0, 3.2 Hz, H-5eq) and 1.16–1.14 (21H, m, OTIPS); δ_C (100 MHz, C$_6$D$_6$): 203.6 (C=O), 170.1 (C=O), 133.2 (C-10), 119.4 (C-11), 78.7 (C-6), 70.3 (C-2), 65.8 (C-7), 62.7 (C-3), 51.8 (C-8), 41.0 (C-5), 36.0 (C-9), 18.1 (OTIPS) and 12.2 (OTIPS); *m/z* (ESI$^+$) 407 (M + Na)$^+$. (Found 407.2211 (M + Na)$^+$. C$_{20}$H$_{36}$NaO$_5$Si requires 407.2224).

(3S*,6S*)-Methyl 3-allyl-4-oxo-6-((E)-styryl)tetrahydro-2H-pyran-3-carboxylate (329)
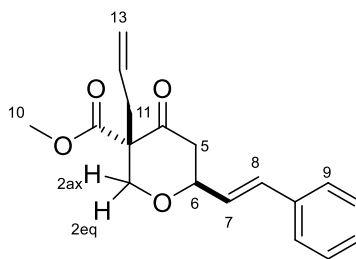
Dihydropyran **269** (0.10 g, 0.38 mmol), L-Selectride® (0.09 mL, 0.40 mmol), allyl Bromide (0.66 mL, 7.74 mmol), THF (10.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yielded 0.097 g, 83 % light yellow oil. υ max/cm^{-1} (film) 2952 (C-H), 1736 (C=O), 1712 (C=O), 1226 (C-O), 1073 (C-O), 1031 (C-O), 966 (C=C), 748 (C=C); δ$_H$ (400 MHz, C$_6$D$_6$): δ 7.19–7.02 (5H, m, H-9), 6.45 (1H, dd, J = 16.0, 1.2 Hz, H-8), 5.95 (1H, dd, J = 16.0, 5.4 Hz, H-7), 5.88 (1H, dddd, J = 17.1, 10.1, 7.5, 7.0 Hz, H-12), 5.05 (1H, dd, J = 17.1, 4.4 Hz, H-13*trans*), 4.99 (1H, dd, J = 10.1, 4.4 Hz, H-13*cis*), 4.16(1H, d, J = 11.8 Hz, H-2ax), 4.03 (1H, dddd, J = 9.0, 5.4, 4.2, 1.2 Hz, H-6), 3.98 (1H, d, J = 11.8 Hz, H-2eq), 3.36 (3H, s, H-10), 2.69 (1H, dd, J = 13.8, 7.0 Hz, H-11), 2.52 (1H, dd, J = 13.8, 7.5 Hz, H-11), 2.41 (1H, dd, J = 14.7, 4.2 Hz, H-5eq) and 2.31 (1H, dd, J = 14.7, 9.0 Hz, H-5ax); δ$_C$ (100 MHz, C$_6$D$_6$): 202.6 (C=O), 170.6 (C=O), 136.6 (C-8), 133.0 (C-12), 132.1 (Ar), 128.9 (Ar), 126.9 (Ar), 119.4 (C-13), 77.8 (C-6), 69.8 (C-2), 62.7 (C-3), 51.9 (C-10), 44.8 (C-5), and 35.9 (C-11); m/z (ESI$^+$) 323 (M + Na)$^+$. (Found 323.1242 (M + Na)$^+$. C$_{16}$H$_{21}$NaO$_4$ requires 323.1230).

(3*S**,6*S**)-Methyl 3-allyl-4-oxo-6-phenyltetrahydro-2H-pyran-3-carboxylate (326)

(prepared by James Burroughs)

Dihydropyran **264** (0.10 g, 0.43 mmol), L-Selectride® (0.43 mL, 0.43 mmol), allyl Bromide (0.74 mL, 8.62 mmol), THF (11.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yielded 0.061 g, 52 % light yellow oil. υ max/cm⁻¹ (film) 2952 (C-H), 2875 (C-H), 1736 (C=O), 1711 (C=O), 1227 (C-O), 1076 (C-O), 763 (Ar), 699 (C=C); δ_H (400 MHz, CDCl$_3$): δ 7.42–7.32 (5H, m, H-7), 5.80 (1H, m, H-10), 5.20 (1H, dd, *J* = 17.2, 4.4 Hz, H-11*trans*), 5.15 (1H, dd, *J* = 10.1, 4.4 Hz, H-11*cis*), 4.86 (1H, dd, *J* = 9.3, 4.6 Hz, H-6), 4.21 (1H, d, *J* = 11.8 Hz, H-2ax), 4.12 (1H, d, *J* = 11.8 Hz, H-2eq), 3.79 (3H, s, H-8) and 2.82–2.71 (4H, m, H-5, H-9); δ_C (100 MHz, CDCl$_3$): 203.8 (C=O), 170.2 (C=O), 139.9 (C-10), 132.1 (Ar), 128.8 (Ar), 128.4 (Ar), 126.0 (Ar), 119.9 (C-11), 79.6 (C-6), 70.1 (C-2), 62.5 (C-3), 52.5 (C-8), 46.2 (C-5) and 36.1 (C-9); *m/z* (ESI⁺) 297 (M + Na)⁺. (Found 297.1101 (M + Na)⁺. C$_{16}$H$_{18}$NaO$_4$ requires 297.1097).

(3*S**,6*R**)-Methyl 3-allyl-4-oxo-6-propyltetrahydro-2H-pyran-3-carboxylate (327)
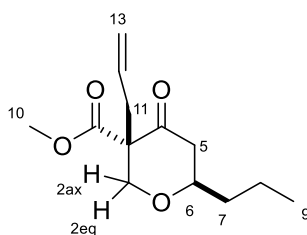
Dihydropyran **263** (0.10 g, 0.50 mmol), L-Selectride® (0.50 mL, 0.50 mmol), allyl Bromide (0.87 mL, 10.10 mmol), THF (13.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yielded 0.063 g, 52 % light yellow oil. υ max/cm^{-1} (film) 2958 (C-H), 2873 (C-H), 1737 (C=O), 1712 (C=O), 1229 (C-O), 1081 (C-O), 922 (C=C); δ_H (400 MHz, CDCl$_3$): δ 5.76 (1H, dddd, J = 17.4, 10.2, 7.3, 7.2 Hz, H-12), 5.18 (1H, dd, J = 17.4, 1.4 Hz, H-11*trans*), 5.10 (1H, dd, J = 10.2, 1.4 Hz, H-11*cis*), 4.05 (1H, d, J = 11.8 Hz, H-2ax), 4.01 (1H, d, J = 11.8 Hz, H-2eq), 3.74 (3H, s, H-10), 3.74 (1H, m, H-6), 2.69 (1H, dd, J = 13.8, 7.3 Hz, H-11a), 2.64 (1H, dd, J = 13.8, 7.2 Hz, H-11b), 2.45 (1H, dd, J = 14.8, 3.6 Hz, H-5), 2.36 (1H, J = 14.8, 10.0 Hz, H-5), 1.51–1.34 (4H, m, H-7, H-8) and 0.93 (1H, t, J = 7.0 Hz, H-9); δ_C (100 MHz, CDCl$_3$): 204.6 (C=O), 170.3 (C=O), 132.3 (C-12), 119.7 (C-13), 78.1 (C-6), 70.1 (C-2), 62.5 (C-3), 52.4 (C-10), 45.2 (C-5), 37.7 (C-7), 36.0 (C-11), 18.4 (C-8) and 13.9 (C-9); m/z (ESI$^+$) 263 (M + Na)$^+$. (Found 263.1264 (M + Na)$^+$. C$_{13}$H$_{20}$NaO$_4$ requires 263.1254).

(3*S**,6*S**)-Methyl 3-benzyl-4-oxo-6-(((triisopropylsilyl)oxy)methyl)tetrahydro-2H-pyran-3-carboxylate (333)
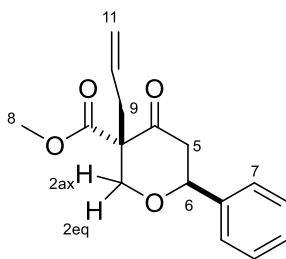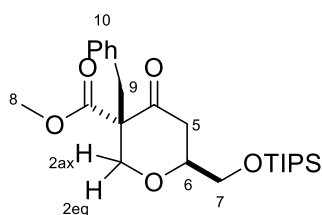

Dihydropyran **265** (0.10 g, 0.29 mmol), L-Selectride® (0.29 mL, 0.29 mmol), benzyl bromide (0.69 mL, 5.84 mmol), THF (7.30 mL); purification (hexane – ethyl acetate = 4: 1), percentage yielded 0.078 g, 62 % colorless oil. υ max/cm^{-1} (film) 2942 (C-H), 2865 (C-H), 1736 (C=O), 1713 (C=O), 1121 (C-O), 1074 (C-O), 881 (Ar), 682 (Ar); δ_H (400 MHz, C$_6$D$_6$): δ 7.48–7.02 (5H, m, H-10), 4.15 (1H, d, J = 12.0 Hz, H-2ax), 3.97 (1H, d, J = 12.0 Hz, H-2eq), 3.64 (1H, m, H-6), 3.43 (2H, m, H-7), 3.34 (3H, s, H-8), 3.42 (1H,

d, J = 13.0 Hz, H-9), 3.27 (1H, d, J = 13.0 Hz, H-9), 2.79 (1H, dd, J = 15.0, 10.6 Hz, H-5ax), 2.22 (1H, dd, J = 15.0, 3.4 Hz, H-5eq) and 1.08–1.00 (21H, m, OTIPS); δ_C (100 MHz, C_6D_6): 203.7 (C=O), 169.6 (C=O), 131.2 (Ar), 128.6 (Ar), 128.1 (Ar), 127.9 (Ar), 79.0 (C-6), 69.2 (C-2), 65.8 (C-3), 64.2 (C-7), 51.7 (C-8), 40.5 (C-5), 36.6 (C-9), 18.1 (OTIPS) and 12.2 (OTIPS); m/z (ESI$^+$) 457 (M + Na)$^+$. (Found 457.2388 (M + Na)$^+$. $C_{24}H_{38}NaO_5Si$ requires 457.2381).

(3S*,6S*)-Methyl 3-benzyl-4-oxo-6-((E)-styryl)tetrahydro-2H-pyran-3-carboxylate (334)
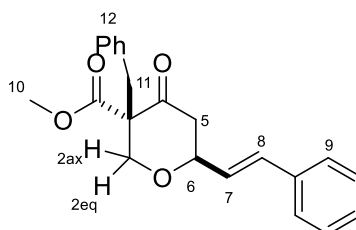
Dihydropyran **269** (0.09 g, 0.37 mmol), L-Selectride® (0.37 mL, 0.37 mmol), benzyl bromide (0.88 mL, 7.44 mmol), THF (9.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yielded 0.066 g, 51 % light yellow oil. υ max/cm^{-1} (film) 2958 (C-H), 2860 (C-H), 1734 (C=O), 1712 (C=O), 1209 (C-O), 1070 (C-O), 742 (Ar), 703 (Ar); δ_H (400 MHz, CDCl$_3$): δ 7.42–7.19 (10H, m, H-9, H-12), 6.67 (1H, dd, J = 16.1, 1.0 Hz, H-8), 6.26 (1H, dd, J = 16.1, 5.7 Hz, H-7), 4.59 (1H, dddd, J = 8.6, 5.7, 4.5, 1.0 Hz, H-6), 4.11 (1H, d, J = 12.2 Hz, H-2ax), 4.05 (1H, d, J = 12.2 Hz, H-2eq), 3.73 (3H, s, H-10), 3.34 (1H, d, J = 13.5 Hz, H-11), 3.20 (1H, d, J = 13.5 Hz, H-11), 2.83 (1H, dd, J = 14.8, 8.6 Hz, H-5) and 2.73 (1H, dd, J = 14.8, 4.5 Hz, H-5); δ_C (100 MHz, CDCl$_3$): 204.0 (C=O), 169.8 (C=O), 136.0 (Ar), 135.1 (Ar), 132.9 (C-8), 130.7 (Ar), 128.8 (Ar), 128.5 (Ar), 128.4 (Ar), 127.4 (Ar), 127.3 (Ar), 126.8 (C-7), 78.1 (C-6), 68.7 (C-2), 63.8 (C-3), 52.5 (C-10), 44.6 (C-5), and 36.7 (C-11); m/z (ESI$^+$) 373 (M + Na)$^+$. (Found 373.1401 (M + Na)$^+$. $C_{22}H_{22}NaO_4$ requires 373.1410).

**(3S*,6S*)-Methyl   3-benzyl-4-oxo-6-phenyltetrahydro-2H-pyran-3-carboxylate (331)**
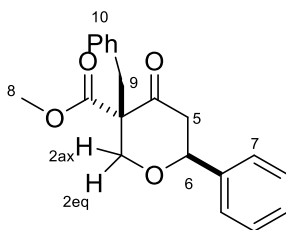
Dihydropyran **264** (0.05 g, 0.21 mmol), L-Selectride® (0.22 mL, 0.22 mmol), benzyl bromide (0.51 mL, 4.30 mmol), THF (6.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yielded 0.045 g, 65 % light yellow oil. υ max/cm^{-1} (film) 2948 (C-H), 2920 (C-H), 1710 (C=O), 1207 (C-O), 1073 (C-O), 767 (Ar), 702 (Ar), 597 (Ar); δ_H (400 MHz, CDCl$_3$): δ 7.41–7.24 (10H, m, H-10, H-7), 4.89 (1H, dd, J = 10.0, 3.9 Hz, H-6), 4.13 (1H, d, J = 12.4 Hz, H-2ax), 4.10 (1H, d, J = 12.4 Hz, H-2eq), 3.76 (3H, s, H-8), 3.40 (1H, d, J = 13.4 Hz, H-9), 3.33 (1H, d, J = 13.4 Hz, H-9), 2.96 (1H, dd, J = 15.1, 10.0 Hz, H-5) and 2.78 (1H, dd, J = 15.1, 3.9 Hz, H-5); δ_C (100 MHz, CDCl$_3$): 203.9 (C=O), 169.7 (C=O), 140.1 (Ar), 135.0 (Ar), 130.8 (Ar), 128.9 (Ar), 128.6 (Ar), 128.5 (Ar), 127.3 (Ar), 126.0 (Ar), 80.0 (C-6), 69.1 (C-2), 63.9 (C-3), 52.4 (C-8), 46.0 (C-5) and 37.0 (C-9); *m/z* (ESI$^+$) 347 (M + Na)$^+$. (Found 347.1252 (M + Na)$^+$. C$_{20}$H$_{20}$NaO$_4$ requires 347.1254).

(3S*,6R*)-Methyl   3-benzyl-4-oxo-6-propyltetrahydro-2H-pyran-3-carboxylate (334)
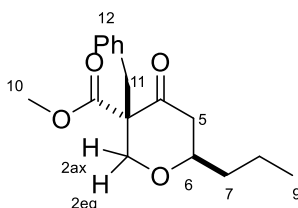
Dihydropyran **263** (0.05 g, 0.25 mmol), L-Selectride® (0.25 mL, 0.25 mmol), benzyl bromide (0.59 mL, 5.04 mmol), THF (5.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yielded 0.045 g, 62 % light yellow oil. υ max/cm^{-1} (film) 2956 (C-H), 2932 (C-H), 2872 (C-H), 1734 (C=O), 1711 (C=O), 1262 (C-O), 1206 (C-O), 1077 (C-O), 1016 (C-O), 702 (Ar); δ_H (400 MHz, CDCl$_3$): δ 7.27–7.20 (5H, m, H-12), 3.99 (1H, d, J = 12.2 Hz, H-2ax), 3.94 (1H, d, J = 12.2 Hz, H-2eq), 3.81 (1H, m, H-6), 3.70 (3H, s, H-10), 3.31 (1H, d, J = 13.4 Hz, H-11), 3.21 (1H, d, J = 13.4 Hz, H-11), 2.56 (1H, dd, J = 15.0, 9.8 Hz, H-5), 2.48 (1H, dd, J = 15.0, 3.8 Hz, H-5), 1.58–1.37 (4H, m, H-7, H-8) and 0.95 (3H, t, J = 7.16 Hz, H-9); δ_C (100 MHz, CDCl$_3$): 204.7 (C=O), 169.8 (C=O), 135.2 (Ar), 130.7 (Ar), 128.5 (Ar), 127.7 (Ar), 78.4 (C-6), 69.0 (C-2), 63.9 (C-3), 52.3 (C-10), 44.9 (C-5), 37.7 (C-7), 36.8 (C-11), 18.3 (C-8) and 14.0 (C-9); m/z (ESI$^+$) 313 (M + Na)$^+$. (Found 313.1416 (M + Na)$^+$. C$_{17}$H$_{22}$NaO$_4$ requires 313.1410).

**(3S*,6S*)-mMthyl 3-benzyl-6-(furan-2-yl)-4-oxotetrahydro-2H-pyran-3-carboxylate (335)**
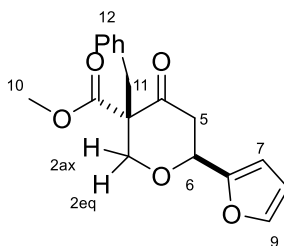
Dihydropyran **259** (0.10 g, 0.45 mmol), L-Selectride® (0.45 mL, 0.45 mmol), benzyl bromide (1.07 mL, 9.00 mmol), THF (11.00 mL); purification (hexane – ethyl acetate = 4: 1), percentage yield 0.060 g, 40 % light yellow oil. υ max/cm^{-1} (film) 2951 (C-H), 2920 (C-H), 2845 (C-H), 1714 (C=O), 1227 (C-O), 1207 (C-O), 1069 (C-O), 741 (Ar), 701 (C=C); δ_H (400 MHz, CDCl$_3$): δ 7.40 (1H, m, H-7), 7.28–7.16 (5H, m, H-12), 6.32 (2H, m, H-8, H-9), 5.13 (1H, dd, J = 11.8, 5.7 Hz, H-6), 4.68 (1H, dd, J = 11.8, 2.8 Hz, H-6

minor), 4.63 (1H, d, J = 12.0 Hz, H-2ax minor), 4.15 (1H, d, J = 12.0 Hz, H-2ax), 3.71 (1H, d, J = 12.0 Hz, H-2eq), 3.70 (3H, s, H-10), 3.57 (1H, d, J = 12.0 Hz, H-2eq minor), 3.31 (1H, d, J = 13.0 Hz, H-11), 3.07 (1H, d, J = 13.0 Hz, H-11), 3.11 (1H, dd, J = 15.0, 11.8 Hz, H-5), 2.99 (1H, dd, J = 15.0, 5.7 Hz, H-5) and 2.76 (1H, dd, J = 14.4, 2.8 Hz, H-5 minor); δ_C (100 MHz, CDCl$_3$): 202.9 (C=O), 169.4 (C=O), 151.6 (C-13), 143.5 (C-7), 135.3 (Ar), 130.4 (Ar), 128.7 (Ar), 127.2 (Ar), 110.4 (C-8), 109.7 (C-9), 74.1 (C-6 minor), 73.0 (C-2 minor), 71.9 (C-6), 68.3 (C-2), 63.6 (C-3), 52.4 (C-10), 44.9 (C-5 minor), 42.4 (C-5) and 36.6 (C-11); m/z (ESI$^+$) 337 (M + Na)$^+$. (Found 337.1045 (M + Na)$^+$. C$_{18}$H$_{18}$NaO$_5$ requires 337.1046).

Abbreviations

Å	Ångstrom
a.u.	atomic units
acac	acetylacetonate
BHT	butylated hydroxy toluene (2,6-di-t-butyl-4-methylphenol)
BINOL	1,1'-bi-2-naphthol
Boc	*t*-butyloxycarbonyl
brsm	based on recovered starting material
Bz	benzoyl
cdk4	cycline-dependent kinase 4
CSA	camphorsulfonic acid
Cy	cyclohexyl
Cp	cyclopentadienyl
d	day
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DET	diethyl tartrate

DFT	density functional theory
DHA	docosahexaenoic acid
DHP	dihydropyran
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethyl ether
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethysulfoxide
DNA	deoxyribonucleic acid
ESI	electrospray ionization
eV	electronvolt
FDA	US Food and Drug Administration
hr	hour
HG II	Hoveyda-Grubbs 2nd generation catalyst
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide

HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
Hz	hertz
Ipc	isopinocampheyl
i-**Pr**	isopropyl
IR	infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant (Hz)
kg	kilogram
kJ	kilojoule
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	molar
m-CPBA	meta-chloroperoxybenzoic acid
Mes	mesityl (2,4,6-trimethylphenyl)
Ms	mesyl (methanesulfonyl)
MHz	megahertz
MMFF94	Merck Molecular Force Field '94

MOM	methoxymethyl
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NCI	National Cancer Institute
nM	nanomolar
NMO	*N*-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance spectroscopy
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
Piv	pivaloyl
PMB	p-methoxybenzyl
py	pyridine
RNA	ribonucleic acid
RT	room temperature
TBAF	tetra-n-butylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBHP	*t*-butylhydroperoxide
TBS	*t*-butyldimethylsilyl

*t*Bu	*tert*-butyl
TES	triethylsilyl
Tf	Tf triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TPS	triphenylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	tetramethylsilyl
Tol	*p*-tolyl
TPS	triphenylsilyl
Ts	tosyl
TS	transition state
ν	vibration frequency (cm-1)

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