SYNTHESIS OF PYRAN AND RELATED NATURAL PRODUCTS

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Abstract

This study was aimed at preparing dihydropyrans (DHPs) for the synthesis of 2,6-disubstituted tetrahydropyrans (THPs) in a diastereoselective manner.

In an attempt to develop a novel methodology for the synthesis of DHPs from δ-hydroxy-β-ketoester and thioamide in the presence of Lewis acid, unexpected dihydrothiopyran (DHT) formed as the sole product in the reaction instead of the expected DHP. A thorough investigation of the DHT forming-reaction showed that it is a promising method to synthesize 2,6-disubstituted DHT compounds. Various substituents at C2 and C6 positions were incorporated into the DHT by using different δ-hydroxy-β-ketoesters and thioamides.

This methodology was applied to the first total synthesis of citreothiopyrane A in 4% yield over three steps. The synthesis of a number of citreothiopyrane A analogs with different substituents at C6 position was also achieved.

N-heterocyclic carbene and quinuclidine were tested to promote the formation of δ-hydroxy-β-ketoesters form diketene, but the only product identified was the methyl acetoacetonate and stable quinuclidine-enolate respectively.

In the investigation of (-)-apicularen A synthesis, it was proposed that the THP core could be accessed by the asymmetric Maitland-Japp reaction, using Chan’s diene and two synthesized aldehydes. However, it was found that the aldehyde with ketal protecting group is too unstable under Lewis acid condition. Further improvements are needed, such as using a more acid-stable protecting group, or by replacement of the aldehyde functionality.

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Finally, I wish to thank all of people, especially my mother, who provided me all the supports besides financial help, otherwise I could not travel from Hong Kong to study here and have so many wonderful experience.

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.

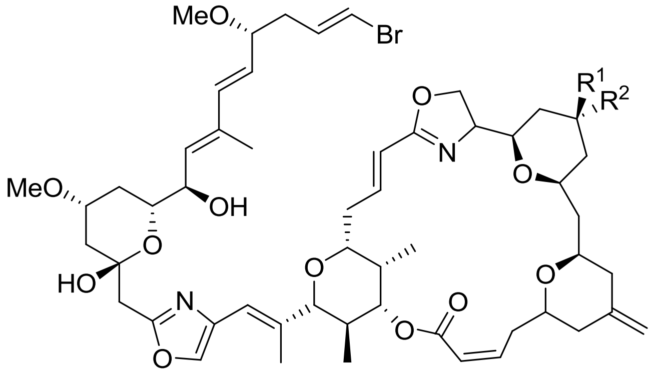
I also declare that the work embodied in this thesis is the result of my own investigations and where the work of others has been used this has been fully acknowledged in the text.

Bun Yeung

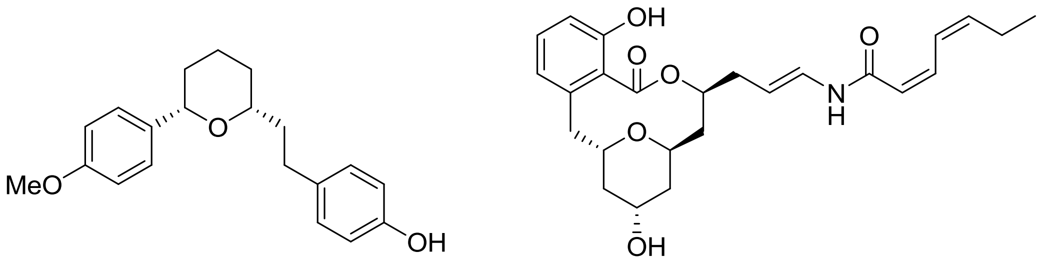
1. Introduction

1.1 Natural products with tetrahydropyran building blocks

The tetrahydropyran is a common feature in many natural products, such as phorboxazole A **1** and B **2**, centrolobine **3** and apicularen A **4** (**Figure 1**) which are shown to have useful biological properties.[1-3] Therefore, the development of methodologies toward the synthesis of tetrahydropyrans (THP) has been the subject of much attention from many research groups.



(+)-Phorboxazole A, **1**- R^1 = H, R^2 = OH
(+)-Phorboxazole B, **2**- R^1 = OH, R^2 = H



(-)-Centrolobine, **3**

(-)-Apicularen A, **4**

Figure 1: Tetrahydropyran containing natural products.

Phorboxazoles isolated from an Indian Ocean sponge (genus *Phorbas* sp.), show an impressive cytostatic property. It can inhibit the growth of tumour cells at nanomolar concentrations, such as colon tumour cells HCT-116 (GI_{50} 4.36 x 10^{-10} M) and HT29 (3.31 x 10^{-10} M), leukemia CCRF-CBM (2.45 x 10^{-10} M), prostate cancer PC-3 (3.54 x 10^{-10} M), and breast cancer MCF7 cell lines (5.62 x 10^{-10} M).[1b] Besides the anticancer activity, the phorboxazoles also have a great in vitro antifungal activity aginst *Candida albicans* and *Saccharomyces carlsbergensis* at 0.1 μg/disk in the agar disk diffusion assay.[1b]

Centrolobine is a naturally occurring antibiotic, isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinum potabile* in the amazon forest.[2a] It is proved to be an anti-leishmania agent against *Leishmania amazonensis promastigotes*, a parasite associated with leishmaniasis.[2b]

Apicularen A is isolated from various strains of the myxobacterial genus *Chondromyces*, shows antiproliferative properties against a variety of cancer cells lines including drug-resistant line, such as ovarian, prostate, lung, kidney, cervix, leukemia, and histiocytic cells with IC_{50} values in the range of 0.23-6.79 nM.[3a] It has also proven to be a potential medicine for antiangiogenesis.[3b]

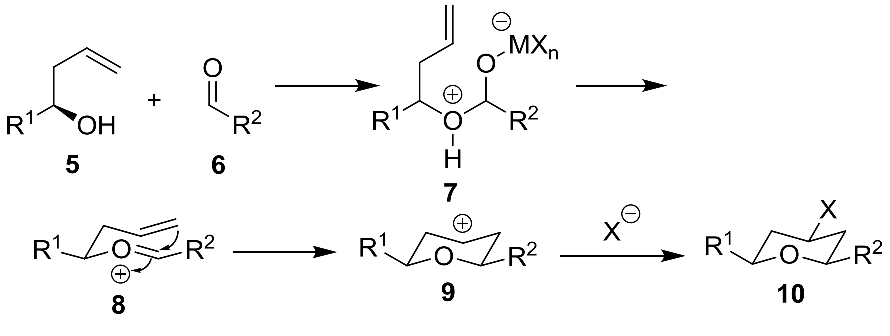
Besides the synthetic challenge for the natural product synthesis, the important biological activities of these natural products make the development of the methodologies for the total synthesis more and more attractive. As a key fragment of these natural products, the synthesis of THP becomes an important research topic.

1.2. Methodologies toward THP ring synthesis

THP rings can be prepared in a number of methods, such as Prins cyclization, hetero-Diels-Alder reaction, Petasis-Ferrier rearrangement, intramolecular oxy-Michael addition and Maitland-Japp reaction. These are introduced below in more detail.

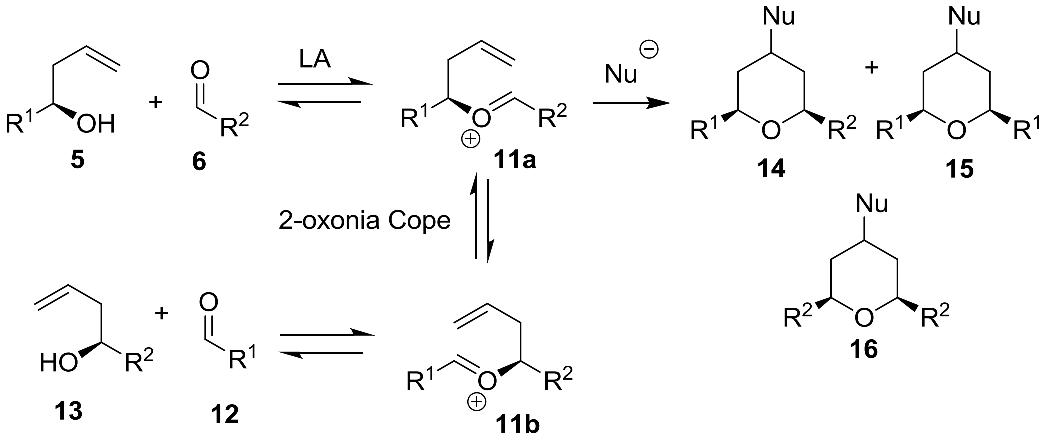
1.2.1 Prins cyclization

The Prins cyclization has demonstrated a great potential for the synthesis of THP rings.[4] The synthesis of THP using the Prins cyclization is achieved by a mixture of homoallylic alcohol **5** and aldehyde **6** in the presence of a Lewis acid. The reaction proceeds *via* an oxycarbenium intermediate **8** produced from a Lewis acid chelated hemiacetal **7** and followed by a 6-ene cyclization to give a THP cation **9** that is trapped by a nucelophilic anion to form the THP product **10**. In general the two substituents in the C2 and C6 positions are equatorially positioned and formed in a *cis*-configuration (**Scheme 1**).[5, 6]



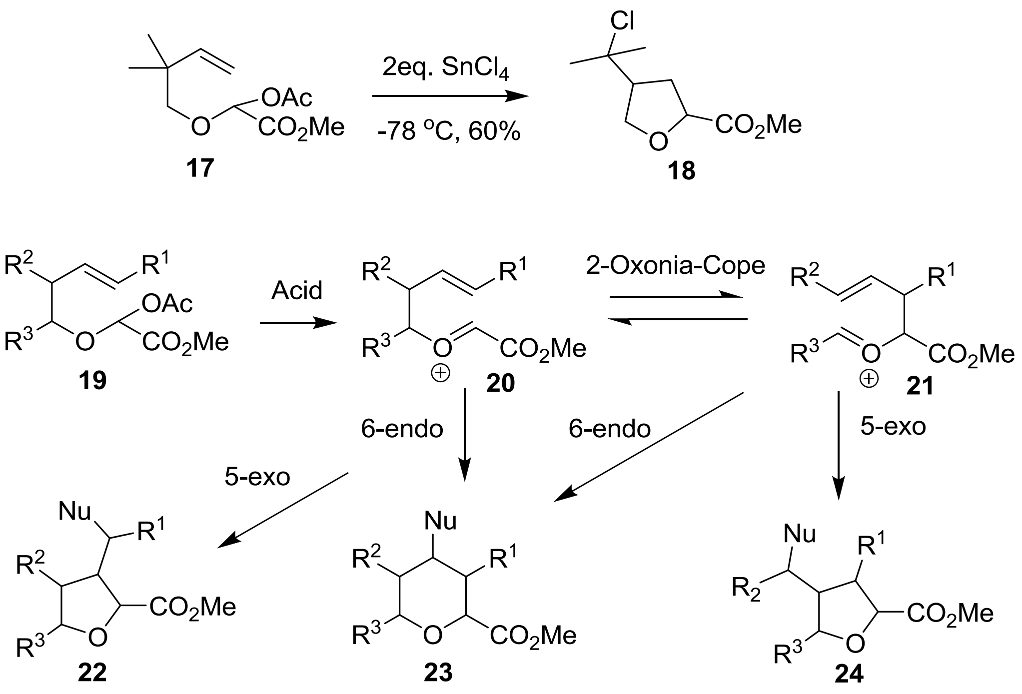
Scheme 1: Prins cyclization.

However, two problems were identified with the Prins cyclization that is side chain exchange and racemization both due to a 2-oxonia Cope rearrangement. This can result in a mixture of products and loss of enantiomeric excess (**Scheme 2**).



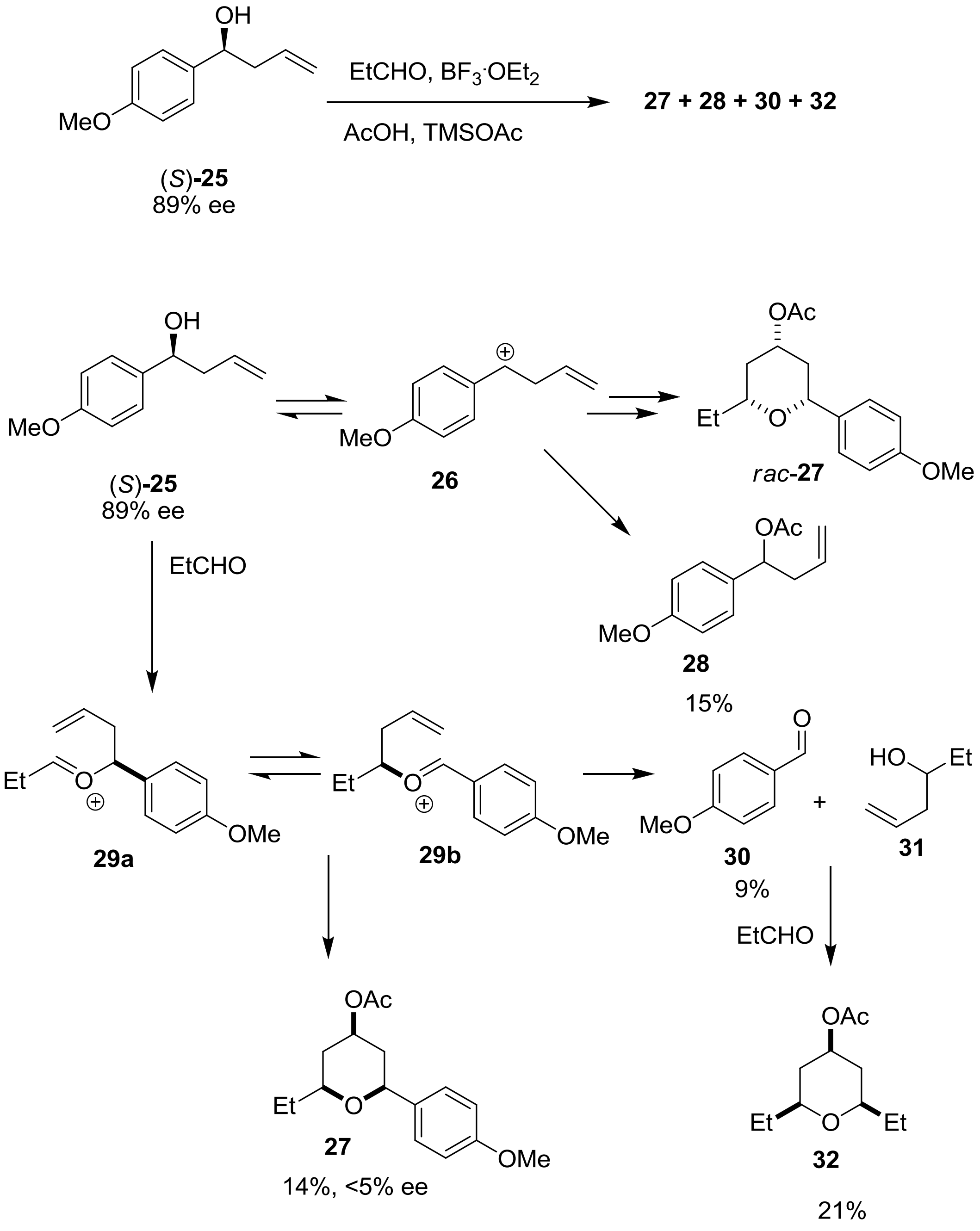
Scheme 2: Side chain exchange and racemization *via* 2-oxonia Cope rearrangement in Prins cyclization

Speckamp first showed the 2-oxonia Cope rearrangement product in the reaction of π-cyclizations of α-methoxycarbonyl oxycarbenium ions (**Scheme 3**).[7] In the reaction, the α-acetoxyester **17** was reacted with $SnCl_4$ to undergo a cyclisation reaction. Theoretically, both of 5-membered and 6-membered heterocycles were expected to form as the product of the reaction via *5-exo* and *6-endo* mode of cyclization. However, there was only one 5-membered heterocycle **18** formed exclusively, and its formation can only be explained by a 2-oxonia Cope rearrangement of the oxycarbenium intermediate from **20** to **21**.



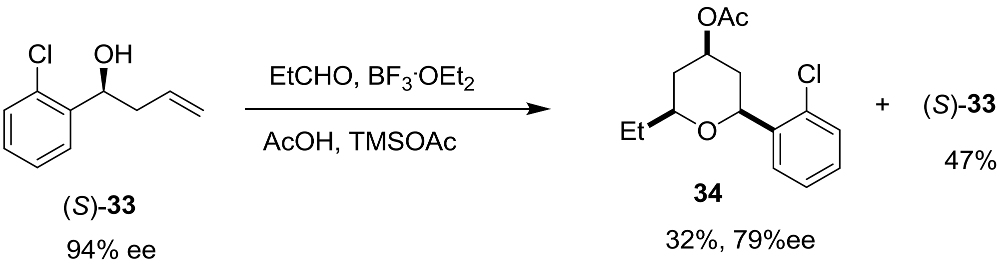
Scheme 3: π-cyclizations of α -methoxycarbonyl oxycarbenium ions.

As the ratio of the Prins cyclised product and 2-oxonia Cope rearranged product is dependent on the rate of Prins cyclization and 2-oxonia Cope rearrangement, it is anticipated that the faster rate of 2-oxonia Cope rearrangement would favour the formation of side products. Willis and co-workers showed that Prins cyclization using homoallylic alcohol with an electron rich aromatic substituent favoured 2-oxonia Cope rearrangement (**Scheme 4**).[8] In the experiment, an enantioenriched homoallylic alcohol **(S)-25** (89% ee) was treated with propanal, $BF_3 \cdot OEt_2$, AcOH and TMSOAc. The yield and enantiomeric excess of the target THP **27** was very low (14% yield, <5% ee), and the major product of the reaction was a symmetrical THP **32** formed *via* a side chain exchange process.[8] The reason for the loss of optical purity was rationalized by the formation of racemic THP *rac*-**27** from the benzylic cation **26**, which is stabilized by the electron rich aromatic substituent, formed by sovolysis of the homoallylic alcohol or oxocarbenium intermediate,[9] and its presence in the reaction was proved by the formation of the acetate **28**. The symmetrical THP **32** was generated as the major product, which indicated side group exchange occurred.



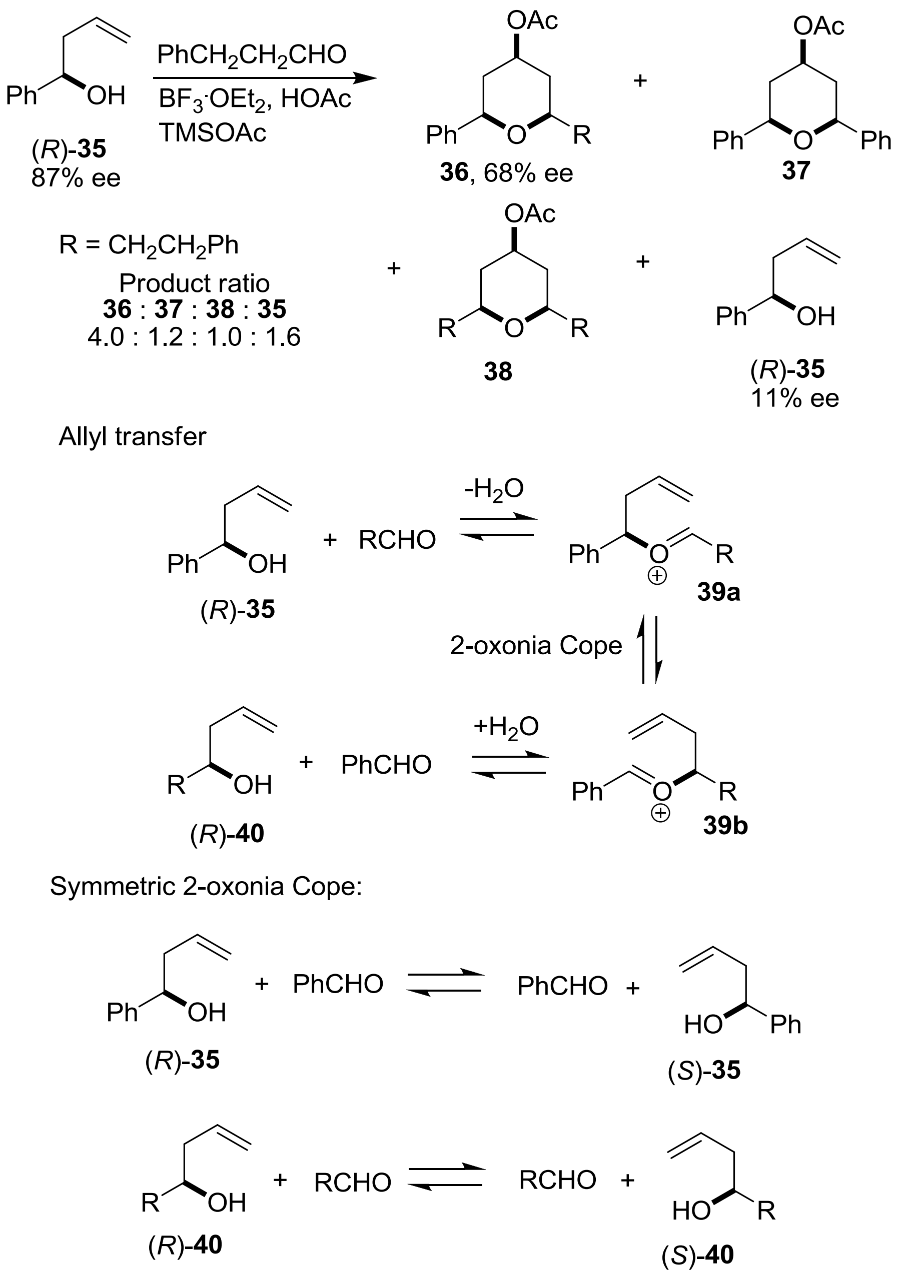
Scheme 4: Cyclization of electron-rich enantioenriched alcohol.[8]

Willis also demonstrated the influence of substituents on the outcome of Prins cyclization with the opposite electronic effect. Another enantioenriched homoallylic alcohol with an electron-deficient substituent **33** was investigated (**Scheme 5**). It was found that no symmetrical THP was generated in the reaction, and the target THP **34** was formed as the only product with a good enantiomeric excess (79%). This result proved that both of 2-oxonia Cope rearrangement and solvolysis are less favourable with an electron-deficient substituent.



Scheme 5: Cyclization of electron-deficient enantioenriched Alcohol.[8]

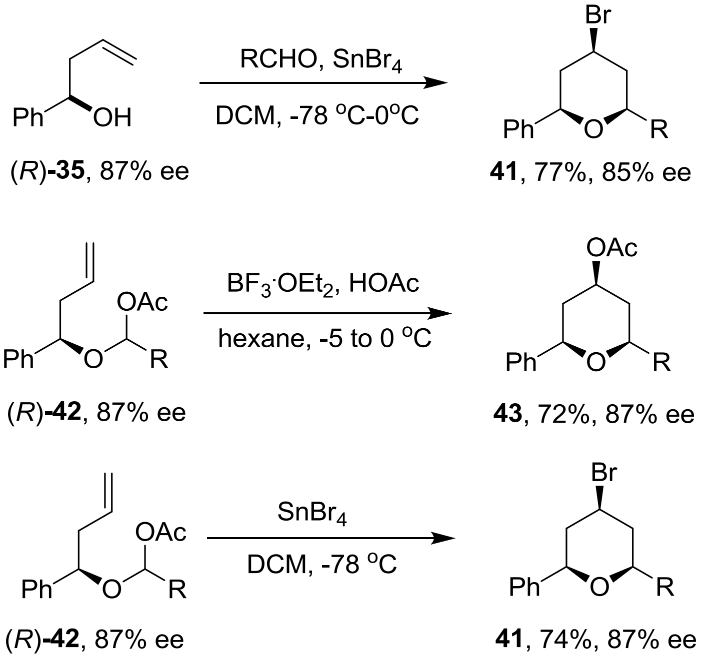
Besides the influence of electron rich substituents, Rychnovsky and co-workers also found that racemisation in the Prins cyclization occurred without the electronic effect, and proposed a racemization mechanism due to allyl transfer and 2-oxonia Cope rearrangement (**Scheme 6**).[9,10] In their reaction, an optically active homoallylic alcohol (*R*)**-35** **(**87% ee**)** was reacted with hydrocinnamaldehyde in the presence of BF$_3$·OEt$_2$ and acetic acid. Besides the expected THP **36**, isolated with a deteriorated enantiomeric excess (68% ee), two symmetrical THP products **37** and **38** were detected, and the remaining alcohol (*R*)**-35** was found with decreased optical activity. The result was accounted for by an allyl transfer occurring during 2-oxonia Cope rearrangement.[10] The water molecule generated by condensation of the alcohol and aldehyde attacks the oxocarbenium intermediate resulting in a new fragmented alcohol (*R*)**-40** and benzaldehyde. Then the initial alcohol (*R*)**-35** condensed with the benzaldehyde and fragmented to the epimeric alcohol (*S*)**-35** *via* a symmetric 2-oxonia Cope rearrangement.[9] Also, the epimeric alcohol (*S*)**-40** was generated in the same process. Therefore, the Prins cyclised THP resulted in lower enantiomeric excess and symmetrical THP obtained.



Scheme 6: Racemization of Prins cyclization by allyl transfer and 2-oxonia Cope rearrangement.[9, 10]

Rychnovsky found that cyclization promoted by $SnBr_4$ instead of $BF_3{\cdot}Et_2O$ can effectively suppress racemization because the fast cyclization step outpaced the rearrangement process. Also, they improved the cyclization by a segment-coupling procedure using α-acetoxy ethers as the cyclization substrate (**Scheme**

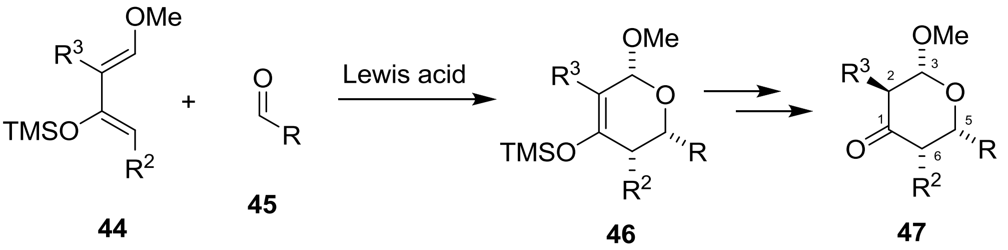
7), which are prepared by reductive acetylation of homoallylic esters.[11] This replaced the direct alcohol-aldehyde cyclization, and no loss of optical purity in the product was detected using $BF_3{\cdot}Et_2O$ or $SnBr_4$ as a Lewis acid. Presumably because there is no water molecule formed in α-acetoxy ethers cyclization. [10]



Scheme 7: Improved Prins cyclization.[10]

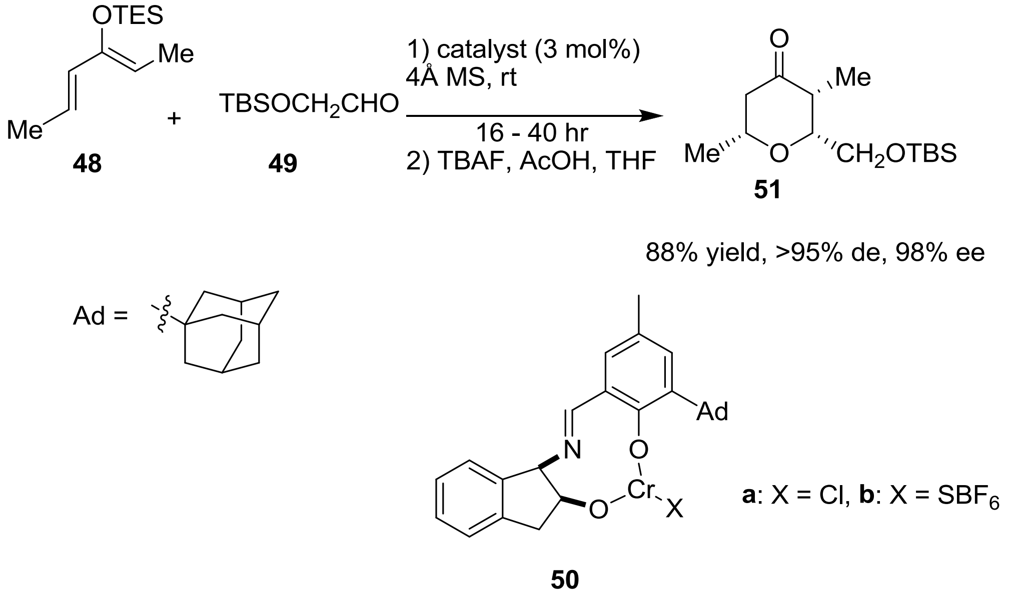
1.2.2 Hetero-Diels-Alder reaction

Hetero-Diels-Alder (HDA) reaction is a powerful method for functionalized THP synthesis. Usually, the HDA reaction involves an electron rich diene, for instance the 1-methoxy-3-(trimethylsilyloxy)butadiene also called Danishefsky's diene, and electron poor dienophile, such as a carbonyl compound. Danishefsky and coworkers published the HDA reaction using the Danishefsky's diene **44** and a range of aliphatic and aromatic aldehydes **45** in the presence of lanthanide Lewis acids, tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) europium (Eu(fod)$_3$) or tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato) ytterbium (Yb(fod)$_3$), to achieve the six-membered tetrahydropyran products **47**.[12, 13] In their reaction, three stereogenic centres were formed through the suprafacial *endo*-cycloaddition process, the forth stereocentre at C2 position was controlled by the axial protonation of the silyl enol ether **46** (**Scheme 8**).



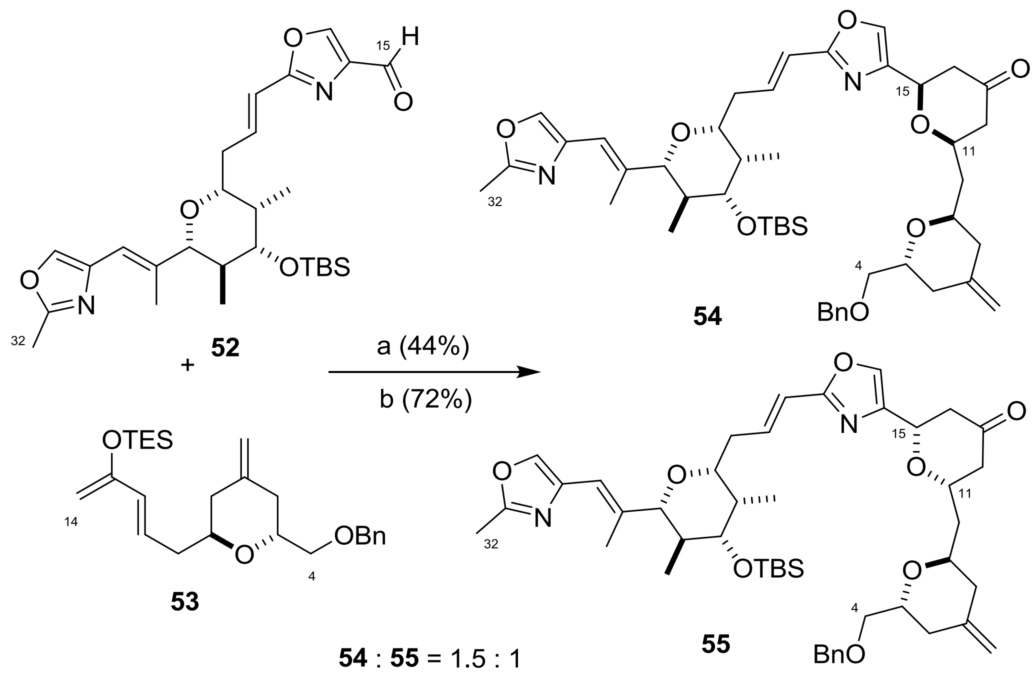
Scheme 8: HDA reaction with Danishefsky’s diene and aldehyde.

In addition to the Danishefsky’s diene, Jacobsen and co-workers successfully employed tridentate Schiff base chromium(III) complexes to catalyze diastereoselective HDA reaction between a less electron rich diene **48** and aldehydes, giving the THP in high diastereomeric and enantiomeric excess.[14] They found that the adamantyl-substituted chromium(III) Schiff base complex **50** (Jacobsen’s catalyst) demonstrated an increase in enantioselectivity in HDA reactions, such as the reaction between the diene **48** and an aliphatic aldehyde **49**, giving the THP **51** in 88% yield, >95% de and 98% ee (**Scheme 9**).



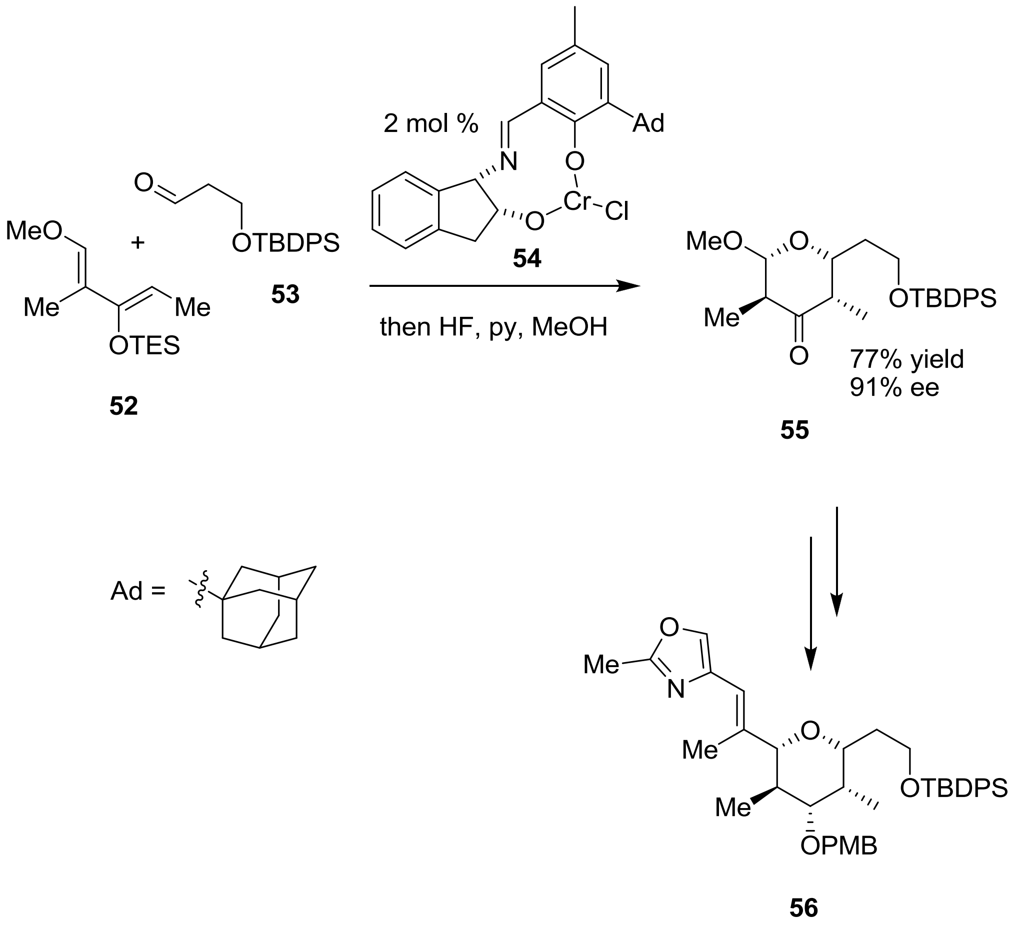
Scheme 9: Diastereoselective hetero Diels-Alder reaction catalyzed by chromium(III) Schiff base complex.[14]

Paterson applied the Jacobsen HDA reaction in the synthesis of a more complex cycloaddition product, the pentacyclic C4 – C32 segment of phorboxazole **54** from the C5 – C9 *trans*–tetrahydropyran ring of the phorboxazoles **53** and full C15 – C32 sequence of the phorboxazoles **52** (**Scheme 10**).[15] However, the result was not very successful, both the yield and selectivity of the products are lower than the HDA reaction with simple reaction substrate, only 44% yield of a mixture of cycoaddition products **54** and **55** were formed in 1.5:1 ratio.



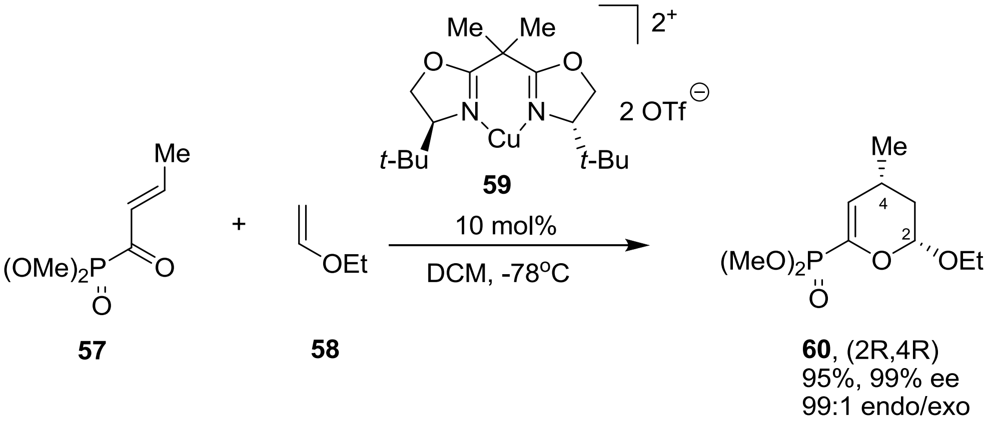
Scheme 10: *Reagents and conditions:* a) Jacobsen's catalyst **50b** (17%), 4 Å mol. sieves, **52**, Me_2CO, 3 hr, then **53**, 38 hr; b) AcOH (2 eq), TBAF (1.5 eq), THF, 20 °C, 1.5 hr.[15]

Burke also demostrated the asymmetric HDA reaction catalyzed by Jacobsen's catalyst in the synthesis of the THP core of the C20 – C32 segment of the phorboxazole **56**.[16] In the presence of Jacobsen's Cr(III) amino indanol Schiff base catalyst **54**, an aldehyde **53** reacted with diene **52** to give a five-substituted THP core **55** in 77% yield and 91% *ee* (**Scheme 11**).



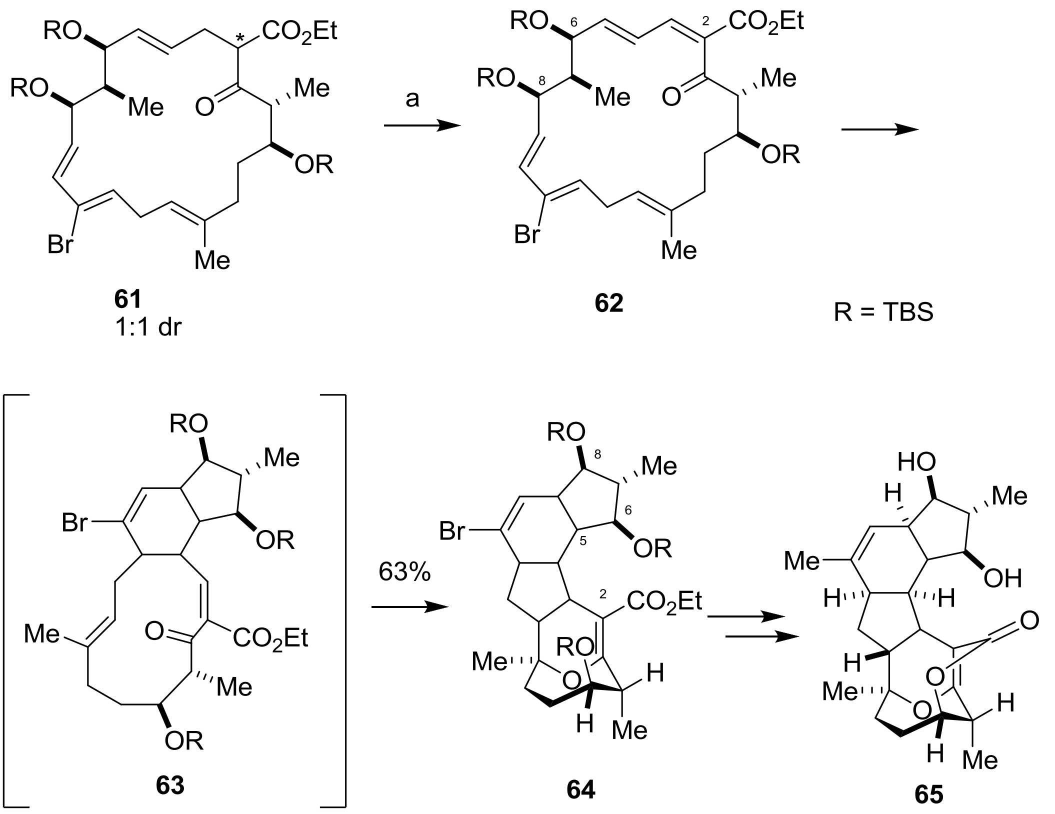
Scheme 11: Synthesis of five-substituted THP by HDA reaction.[16]

Besides the HDA reaction with electron rich dienes and electron poor dienophiles, the inverse electron – demand HDA reaction also revealed its importance as a synthetic methodology in THP and related natural product synthesis. Evans's group developed a simple asymmetric synthesis of dihydropyrans with C_2-symmetric bis(oxazoline) Cu(II) complex **59** as catalyst to promote the reaction between α, β-unsaturated carbonyl compounds (electron poor diene) and electron rich alkenes in good to excellent yield and enantioselectivity.[17] In the reaction, α,β-unsaturated acyl phosphonates **57** reacted with an electron rich olefin **58** to give a dihydropyran **60** in 95% yield, 99:1 endo/exo ratio and 99% *ee* (**Scheme 12**).



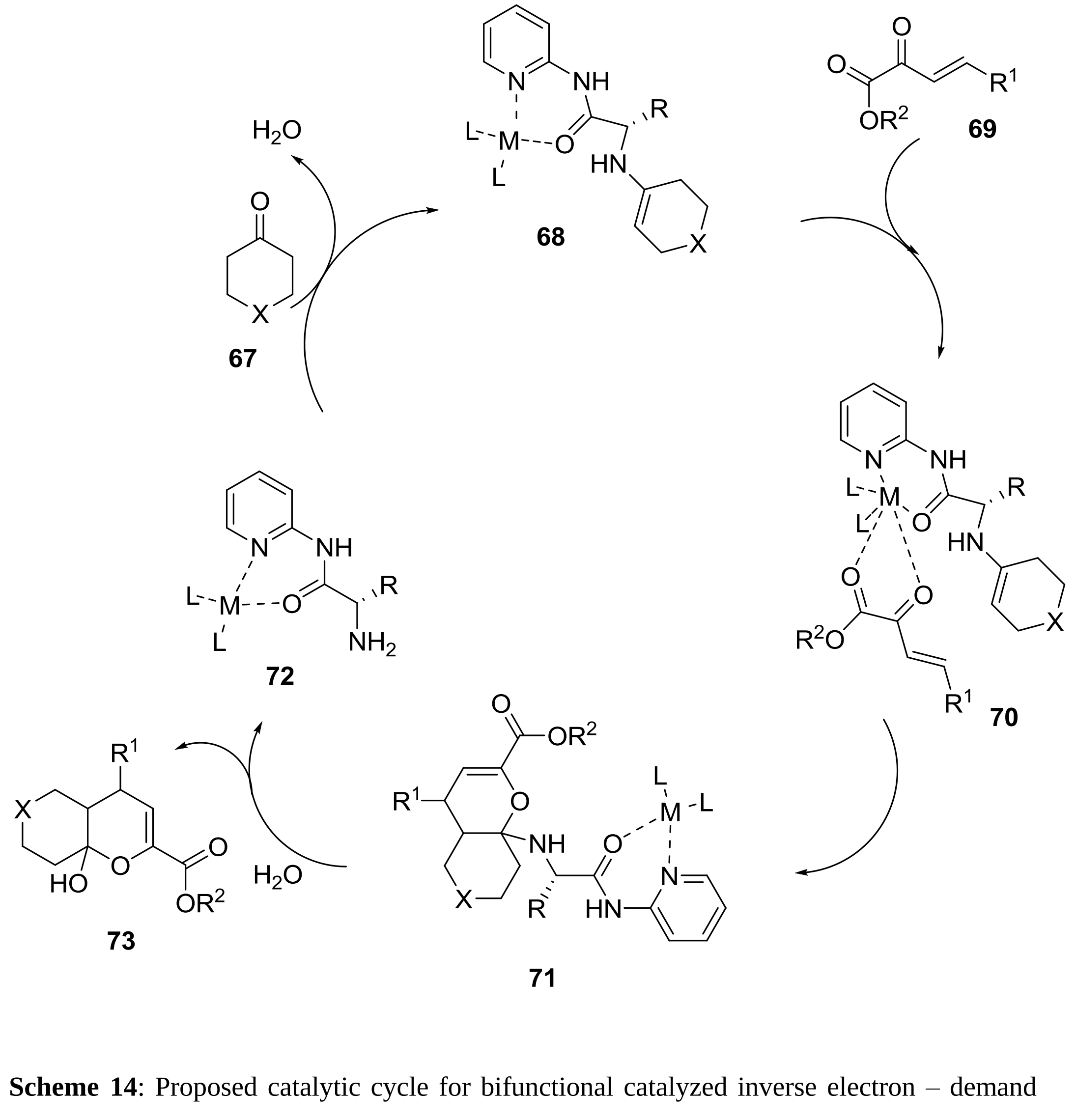
Scheme 12: Asymmetric synthesis of DHP by inverse electron – HDA reaction.[17]

Evans and co-workers also made use of the inverse electron – demand HDA reaction in the synthesis of cytotoxic natural product (-)-FR182877 **65**.[18] The cycloaddition reaction was triggered by a selenium based oxidation of C2 – C3 bond of macrocycle **61** ($Ph_2Se_2O_3$, SO_3-pyr, TEA, THF, room temperature then 50 °C) to macrocycle **62**, then a normal electron – demand Diels – Alder reaction occurred spontaneously to give a tricyclic compound **63** followed by an inverse electron – demand HDA reaction to form the pentacyclic compound **64** as a single diastereomer as the only isolable product in 63% yield (**Scheme 13**).



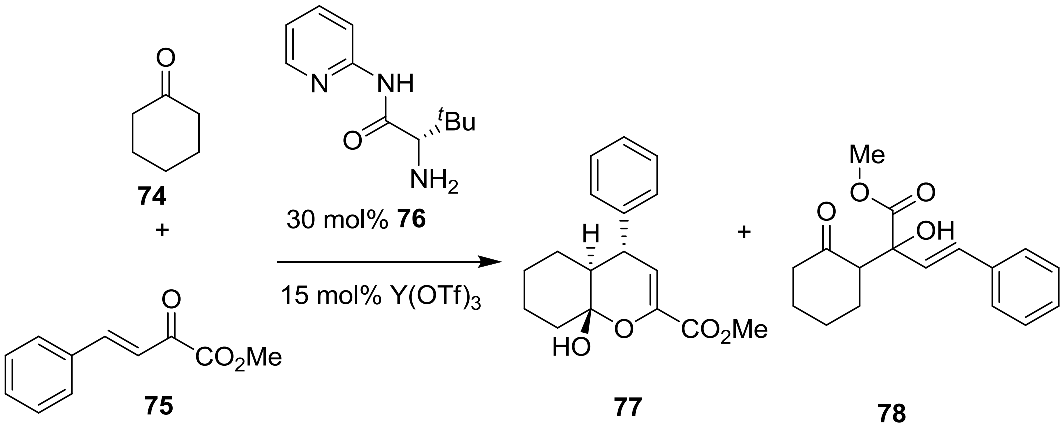
Scheme 13: *Reagents and conditions:* a) $Ph_2Se_2O_3$, SO_3-Pyr, TEA, THF, 23 °C then hexanes, 50 °C, 63%.[18]

In 2011, Wang and co-workers published a novel asymmetric inverse electron – demand HDA reaction promoted by a bifunctional enamine/ metal Lewis acid catalyst.[19] There is a great advantage of combining the organocatalysis and metal catalysis in organic synthesis, as the acidity of the Lewis acid can be modified simply by changing different metals, and the bifunctional catalysts can also convert the intermolecular reaction to a potentially more efficient and selective intramolecular reaction. In their study, Wang tried to activate a ketone (which is usually less reactive toward HDA reaction due to steric reasons) by the organocatalyst to form an enamine. The organocatalyst also acted as a metal ligand to chelate the metal Lewis acid and brought it closer to catalyze a reaction. It was believed that the ketone **67** would reacted with the primary amine to give an enamine **68** *in situ*, and the enone **69** was caught and activated by the metal Lewis acid, therefore the ketone and enone could react intramolecularly forming the targeted cycloaddition product **73**, and the bifunctional catalyst **72** was regenerated (**Scheme 14**).



Scheme 14: Proposed catalytic cycle for bifunctional catalyzed inverse electron – demand HDA reaction.[19]

In the reaction, besides the desired dihydropyran **77**, an aldol product **78** was identified. In addition to the properties of bifunctional catalysts, the yield, chemo and stereoselectivity of the reaction was dependent on temperature and solvent. With the primary amine **76** and Y(OTf)$_3$, the best result was achieved with THF as solvent and doing the reaction in 4 ^{o}C giving the desired product **77** almost exclusively in 81% yield, 9:1 *dr* and more than 99% *ee* (**Table 1**, **Entry c**).



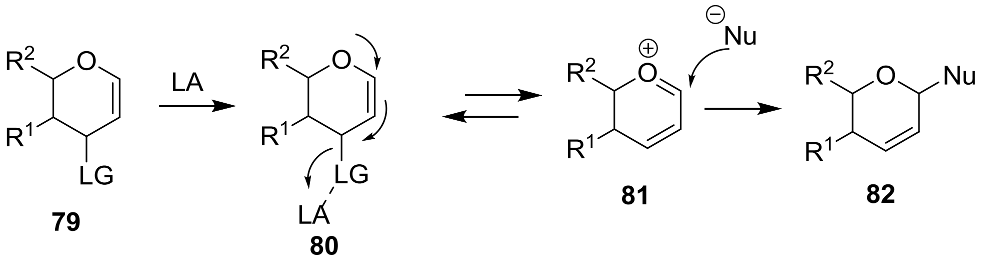
Scheme 15: Bifunctional-catalyzed inverse electron – demand HDA reaction.[19]

Table 1: Reaction screening of HDA reaction.[19]

Entry	Temp. (^{o}C)	Sovent	Time (hr)	Yield (%)	d.r.	77 : 78	ee (%)
a	rt	CH_3CN	36	91	3 : 1	98 : 2	92
b	4	CH_3CN	72	86	2.5 : 1	>99 : 1	>99
c	4	THF	84	81	9 : 1	>99 : 1	>99

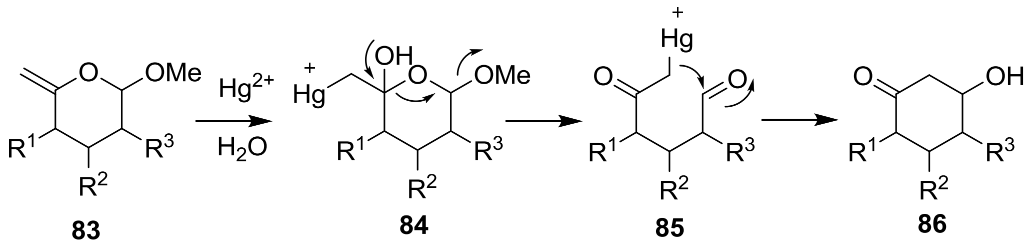
1.2.3 Petasis-Ferrier Rearrangement

Petasis-Ferrier rearrangement is a powerful reaction that allows construction of 2,6-*cis*-subsitituted THP motif in complex natural product.[20] In 1962, Ferrier, the pioneer of this type of rearrangement reaction, reported the construction of 2,3-unsaturated glycosides **82** *via* Lewis acid catalyzed rearrangement of 1,2–glycols **79** with *O*-, *S*-, *N*- linked unclueophiles, and it is called the Ferrier I type rearrangement (**Scheme 16**).[21] Firstly, the Lewis acid coordinated to the leaving group and triggered the formation of oxycarbenium intermediate **81** which in turns reacted with a nucleophile to give **82**.

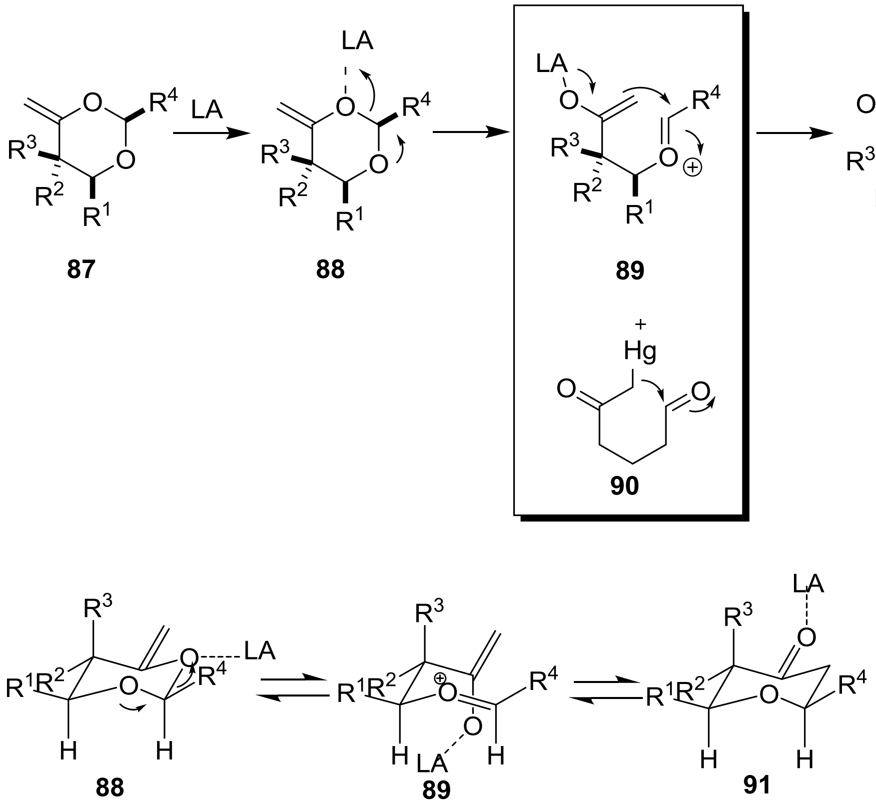


Scheme 16: Ferrier I type rearrangement, LA = $BF_3.OEt_2$, $SnCl_4$, Nu = OR, SR_2, NR_2.[21]

The rearrangement was extended to the formation of β-hydroxy cyclohexanones **86** from exocyclic enol ether **83** in the presence of mercury(II) ions, which is called the Ferrier II type rearrangement (**Scheme 17**).[22] In the process, the mercury(II) ions coordinated to the *exo*-olefin of **83** to generate a reactive oxycarbenium intermediate which was immediately trapped by water molecule to give hemiacetal **84** and initiated the fragmentation to **85** followed by an intramolecular aldol reaction to **86**.

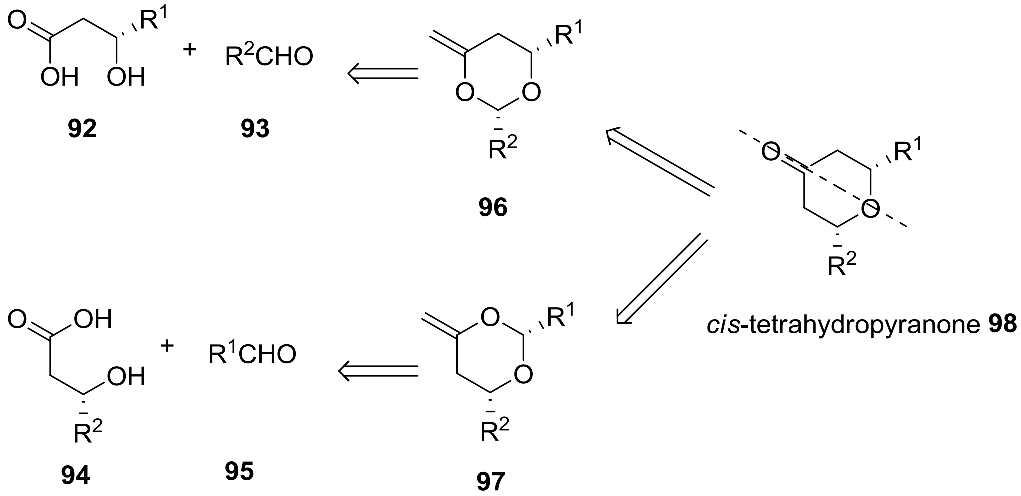


Scheme 17: Ferrier II type rearrangement.[22]



Scheme 18: Petasis rearrangement.

Based on the Ferrier type rearrangement, Petasis and co-workers developed a similar rearrangement reaction for the synthesis of THPs utilizing Al(^{i}Bu)$_3$ as a Lewis acid catalyst (**Scheme 18**).[23] The Petasis rearrangement moves the oxygen atom into the ring instead of coming from the water. And, similarly, fragmentation is triggered by the Lewis acid to give an oxycarbenium intermediate **89** followed by an *endo* cyclization to give the THP **91**. This process is closely related to the Ferrier II type rearrangement. The configuration of enol acetal **87** is retained or enhanced during the rearrangement.

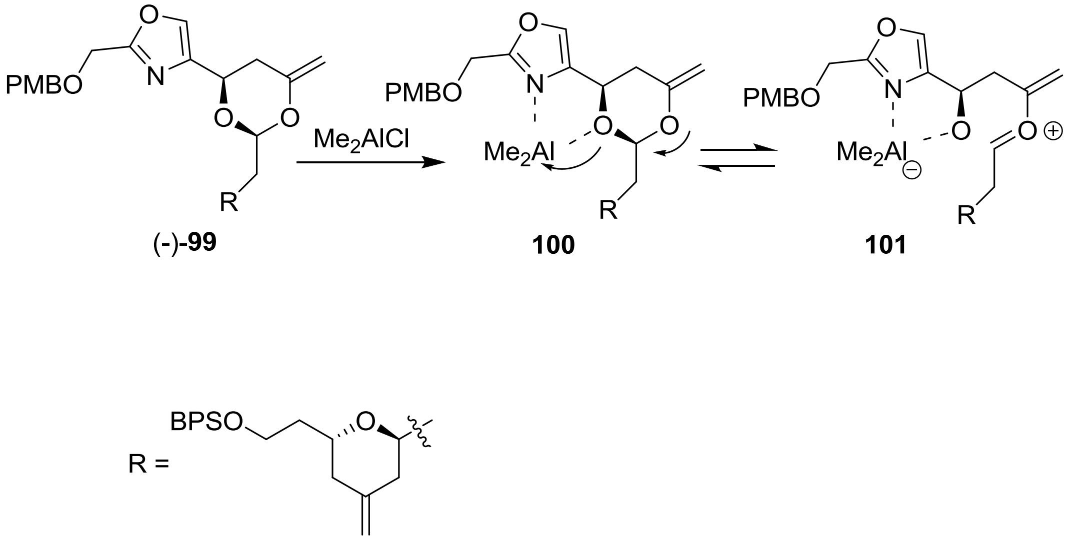


Scheme 19: Petasis-Ferrier rearrangement for *cis*-tetrahydropyranone synthesis.

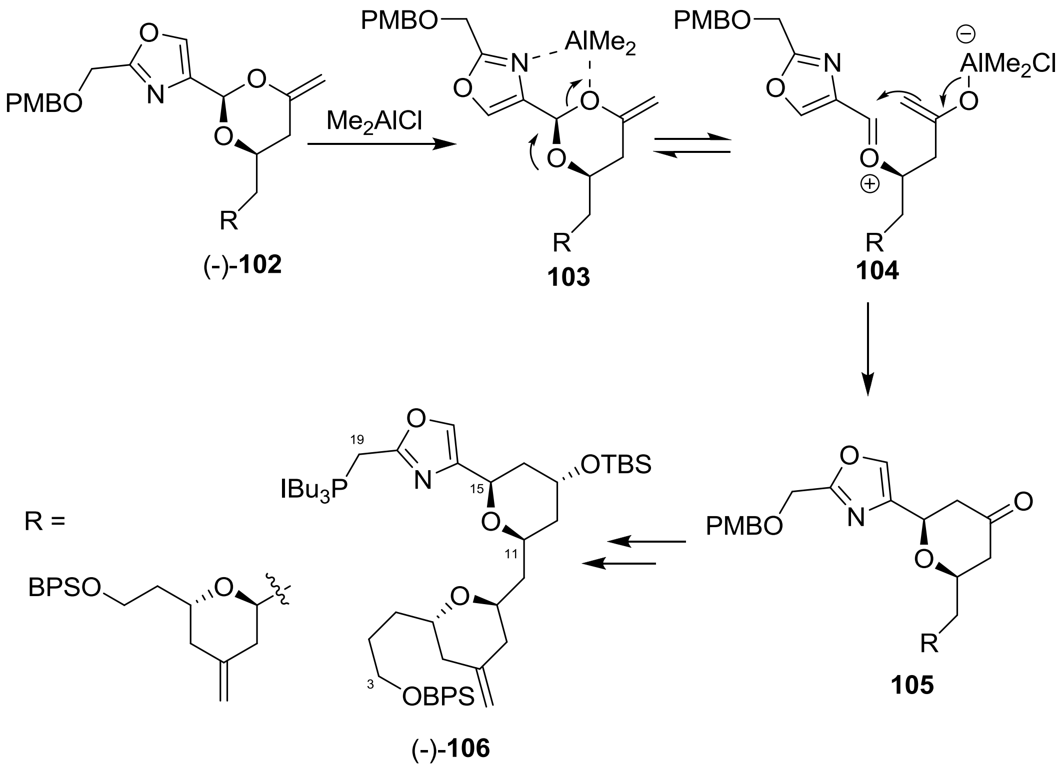
Another advantage of this rearrangement is the latent element of symmetry inherent in the *cis*-tetrahydropyranones (**Scheme 19**). It allows the access of *cis*-tetrahydropyranone **98** from both of enol acetals **96** or **97**, which can be generated from different set of starting materials, therefore increase the flexibility of this reaction.

Petasis-Ferrier rearrangement was applied on the synthesis of phorboxazoles by Smith's group.[24-26] In 2001, Smith and co-workers demonstrated the construction of both the C3 – C19 and C22 – C26 THP motifs in (+)-phorbozaxole A macrocycle by Petasis-Ferrier rearrangement.[25]

In the synthesis of C3 – C19 THP motif (-)-**106**, it was found that the enol ether **99** could not carry out a desired rearrangement reaction to form the tetahydropyranone required. And, this was explained by the unproductive coordination of AlMe$_2$Cl catalyst to the wrong enol ether oxygen in (-)-**99** because of the the neighboring oxazole nitrogen which excerted a directing effect for the incoming Lewis acid catalyst (**Scheme 20**).[25a]

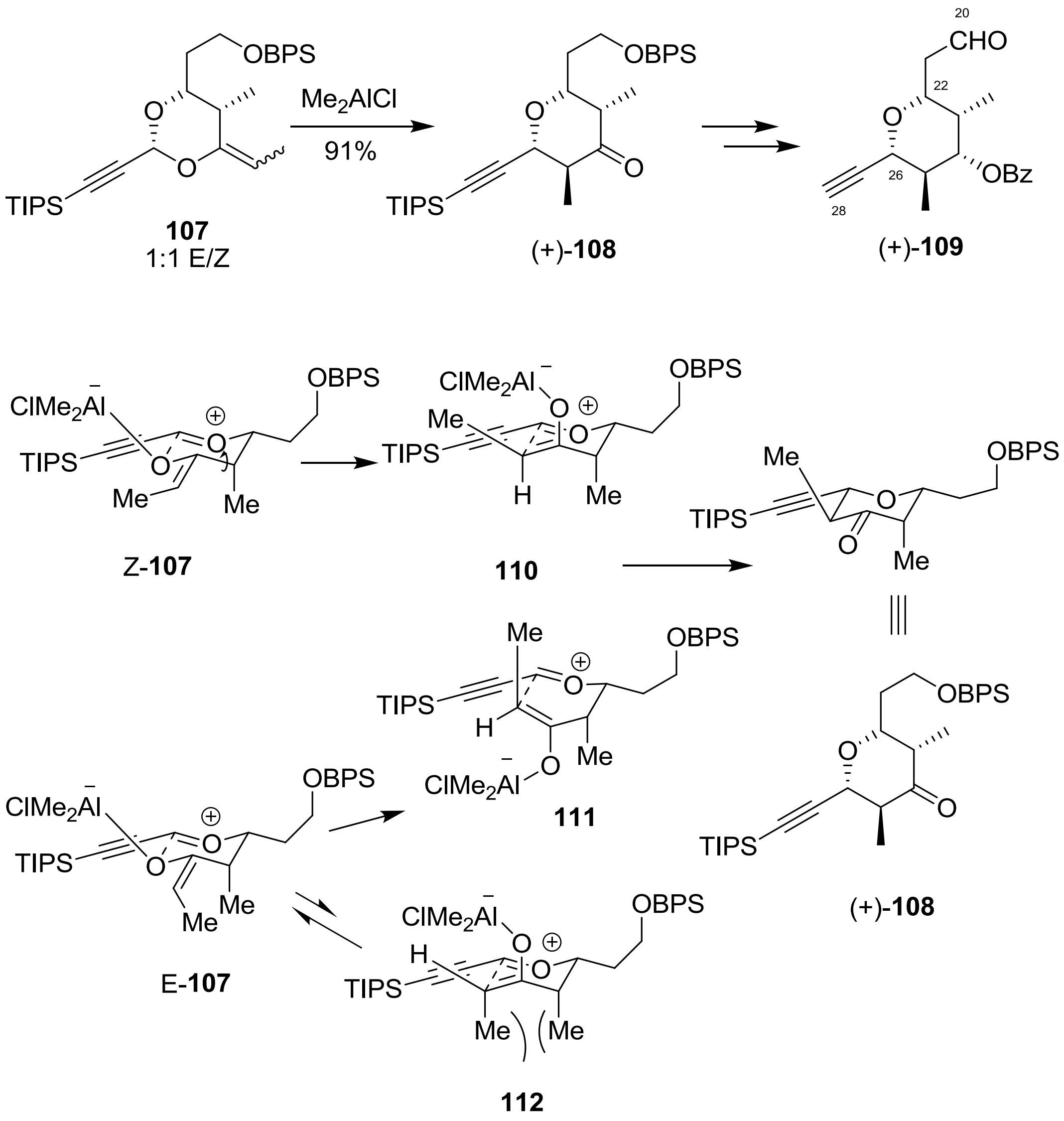


Scheme 20: Unproductive coordination of an aluminium Lewis acid leading to fail rearrangement.[25a]



Scheme 21: Productive coordination of an aluminium Lewis acid giving to suceessful rearrangement.[25a]

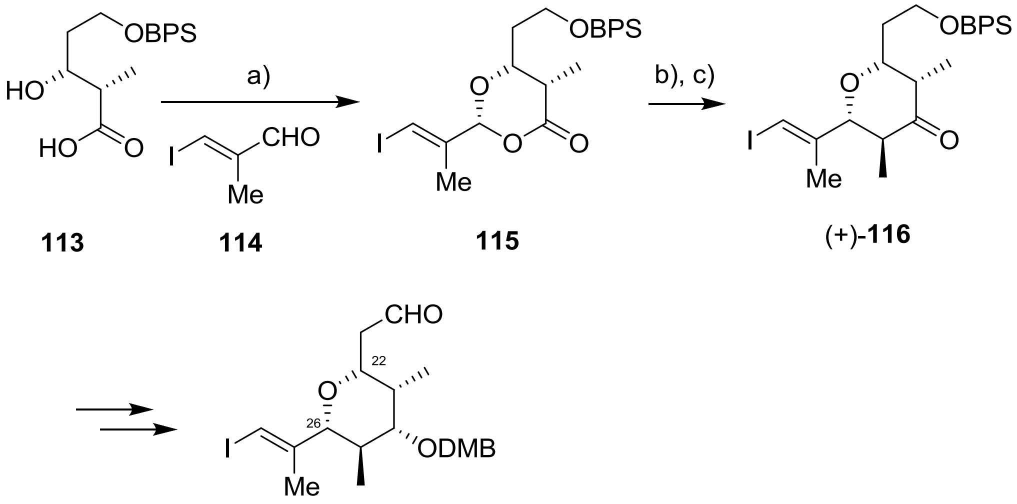
In this case, the symmetry inherent in *cis*-tetrahydropyranone synthesis played an important role to solve this problem. Another enol ether (-)-**102**, in which the oxygen atom moved to a different position, was prepared for the Petasis-Ferrier rearrangement. Again, the oxazole nitrogen acted as a directing group for the $AlMe_2Cl$ Lewis acid, but this time the Lewis acid coordinated to the correct oxygen atom in **103** and allowed the Petasis rearrangement to occur (**Scheme 21**).



Scheme 22: Construction of C20 – C28 THP motif by Petasis-Ferrier rearrangement.[25a]

In the synthesis of THP core of C20 – C28 fragment of phorboxazoles, Smith *et al.* adopted the enol ether **107** as a mixture of geometric isomers in 1:1 ratio in the Petasis-Ferrier rearrangement (**Scheme 22**). It was noticeable that only a single diastereomer (+)-**108** was formed, which was the desired tetrahydropyranone. It was expected that the *Z*-isomer *Z*-**107** may rearranged to the target product *via* a chair comformation **110**. On the other hand, it was possible for the *E*-isomer *E*-**107** to adopt a chair comformation **112** giving the opposite diastereomer, but it was not the most favourable comformation due to the 1,3–diaxial interaction between the methyl groups. Instead, it may favour a boat-like configuration **111** giving the required diastereomer.

A second generation total synthesis of (+)-phorbozaxole A reported by the Smith's group showed a more convergent approach to shorten the number of steps, from 27 to 24 steps, and increased the overall yield from 3% to 4.6%.[25, 26] In this approach a more functionalized THP (C22 – C26) unit (+)-**117** was used as a precursor for Stille coupling from the rearranged product (+)-**116**. Petasis-Ferrier rearrangement afforded (+)-**116** from the dioxane **115** which was formed by a condensation reaction between **113** and **114** (**Scheme 23**).[26]



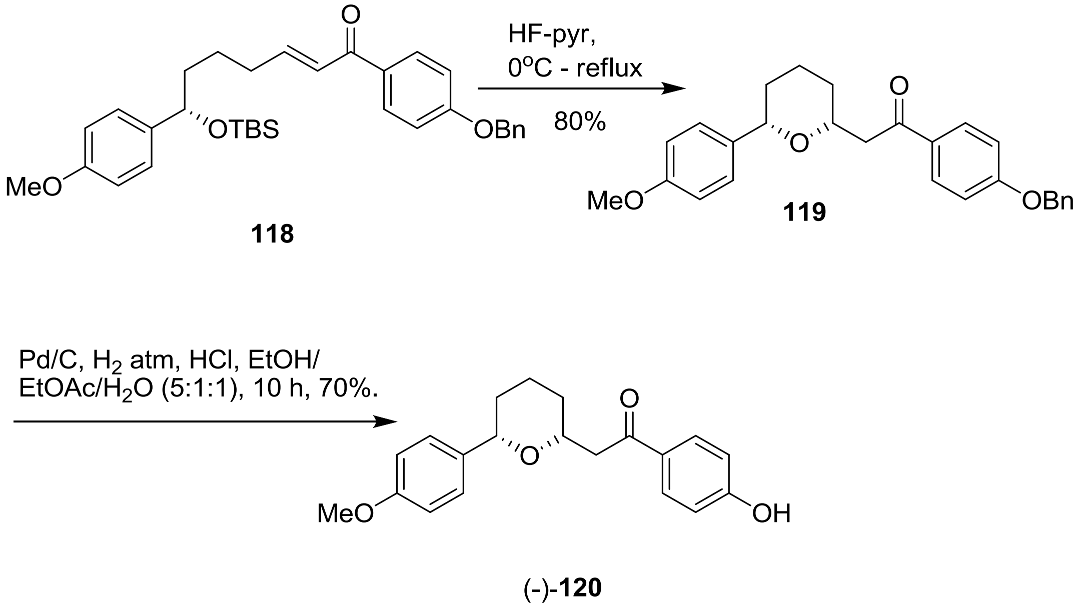
113 **114** **115** (+)-**116**

(+)-**117**

Scheme 23: ***Reagents and conditions***: a) i. HMDS, DCM, ii. TMSOTf, TfOH, 2,6-DTBMP, 93%, 20:1 *dr*; b) Cp_2TiMe_2, THF, 55 ^{o}C, 79%; c) Me_2AlCl, DCM, -78 ^{o}C, 99%.[26]

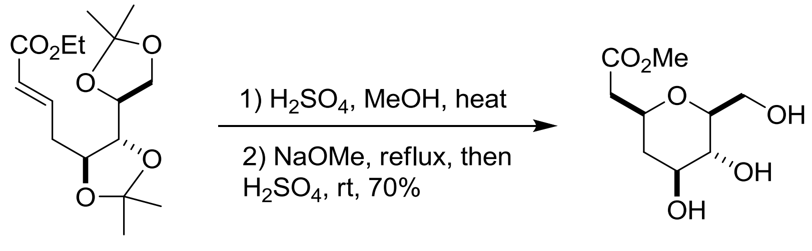
1.2.4 Intramolecular oxy-Michael addition

Tetrahydropyran rings can be constructed by an intramolecular oxy-Michael addition reaction between an alcohol functional group and an α,β-unsaturated carbonyl functional group. One of the examples of using this strategy for synthesis of THP rings is the total synthesis of (-)-centrolobine **120**, report by Chandrasekhar and co-workers.[27] In their synthesis, a *cis*-2,6-disubstituted THP skeleton **119** was generated stereoselectively as a key step in the natural product construction. The silyl protecting group of compound **118** was removed by HF-pyridine and initiated the intramolecular oxy-Michael addition giving **119** in 80% yield (**Scheme 24**).



Scheme 24: Construction of *cis*-2,6-disubstituted THP skeleton by oxy-Michael addition.[27]

Apart from (-)-centrolobine, this method was also applied to the synthesis of the A ring of (+)-ambruticin S, which was obtained from the corresponding α,β-unsaturated compound **6.121**. A global deprotection of the acetal groups with acid resulted in free hydroxyl groups. The formation of the most thermodynamically stable pyran **122** was favoured under reflux in the presence of excess amount of NaOMe for 24 hours (**Scheme 25**).[28]

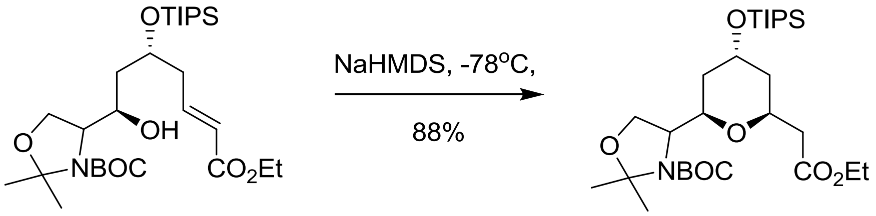


121

122

Scheme 25: Construction of A ring of (+)-ambruticin by oxy-Michael addition.[28]

Pattenden's group exploited the intramolecular oxy-Michael addition reaction to synthesis the THP core in C3 – C19 fragment of phorboxazoles.[29] The hydroxy unsaturated ester **123** was treated with NaHMDS at -78 ^{o}C producing the *cis*-THP selectively in 88% yield.

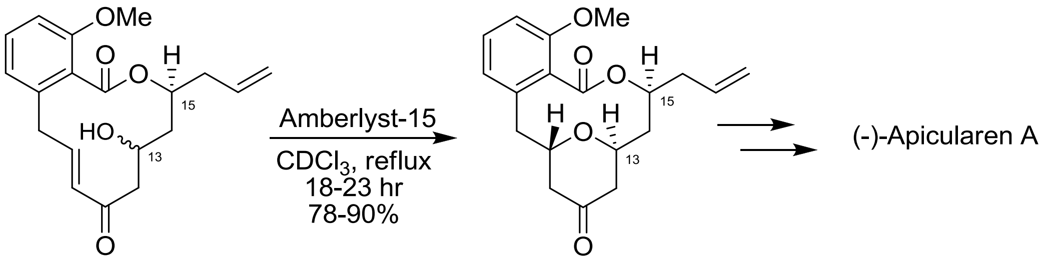


123

124

Scheme 26: Construction of THP core of C3 – C19 fragment of phorboxazoles.[29]

Rizzacasa's group also employed this methodology in the synthesis of THP core of (-)-apicularen A.[30] In their study, Amberlyst-15, an acidic ion exchange resin, was used to promote the addition of hydroxyl group to the α, β-unsaturated carbonyl group in macrolactone **125** under reflux in $CDCl_3$ resulted in the formation of *trans*-**126** as major product (>10:1 selectivity) in 90% yield (**Scheme 27**). It was proved that both isomers of **125a** and **125b** favoured the formation of *trans*-**126** which is the thermodynamically favourable product, and the *cis*-diastereomer can be formed at room temperature as a kinetic product.[30]



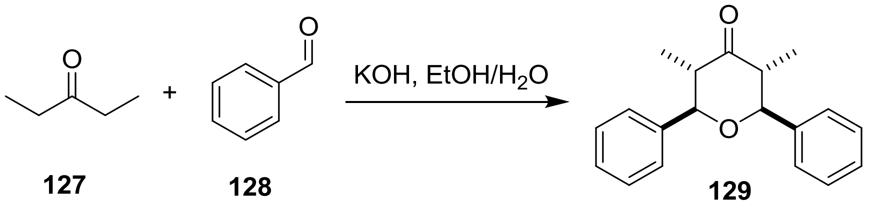
125a (13 *S*)
or
125b (13 *R*)

126

Scheme 27: Construction of THP core of apicularen A.[30]

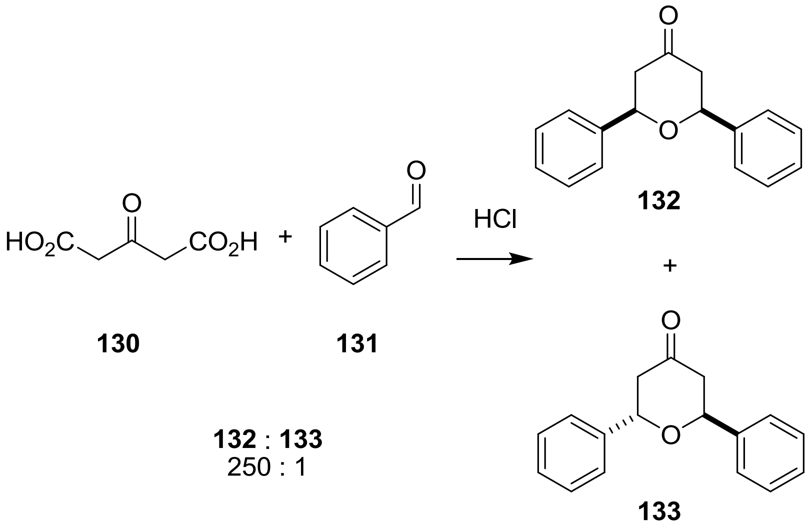
1.2.5 Maitland-Japp reaction

The original Maitland-Japp reaction, published in 1904, is a condensation reaction between one equivalent of pentan-3-one **127** and two equivalents of benzaldehyde **128** to generate a symmetric biphenyl substituted tetrahydropyran-4-one **129** as a product (**Scheme 28**).[31]



Scheme 28: Original Maitland-Japp reaction.[31]

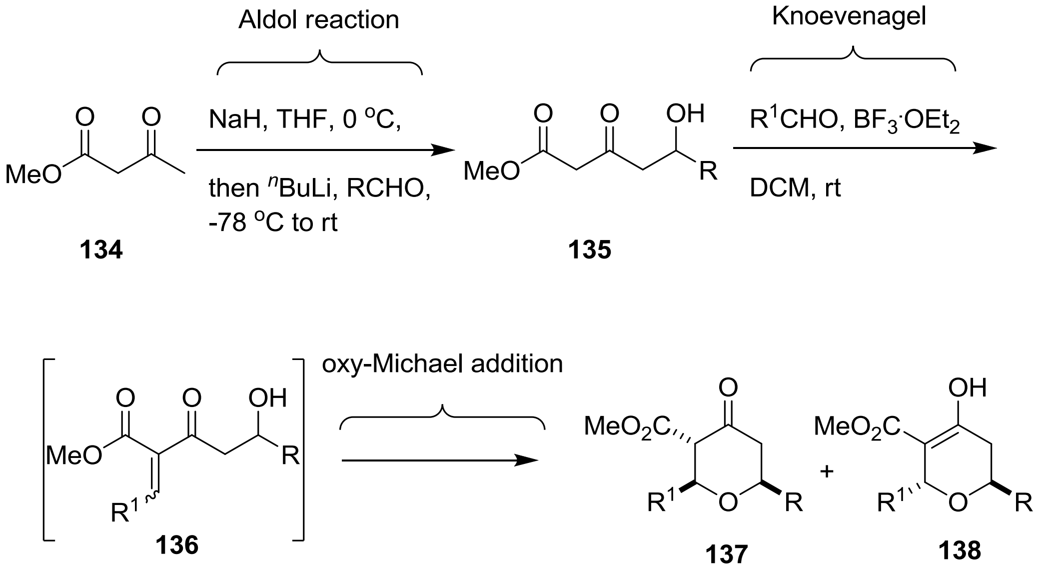
After 30 years, Cornubert and Robinet reported an acid-promoted condensation of acetonedicarboxylic acid **130** and benzaldehyde **131** *via* a decarboxylation to give two diastereomers, *cis*-**132** and *trans*-**133** in a ratio of 250:1 (**Scheme 29**).[32]



Scheme 29: Acid-promoted Maitland-Japp reaction.[32]

In past few years, Clarke's group developed a series of modern versions of the Maitland-Japp reaction which gave promising results for fuctionalized THP ring synthesis and a wide scope of flexibility to change the substituents in C2 and C6 positions of the ring.

In an attempt to synthesize non-symmetrical THP rings, initially, in a two pot Maitland-Japp reaction (**Scheme 30**), β-ketoester derivatives, such as methyl acetoacetate **134**, were chosen to replace the symmetric ketone as starting materials. The δ-hydroxy-β-ketoester **135** was formed by aldol reaction with an aldehyde. And then, the δ-hydroxy-β-ketoester **135** was reacted with a second aldehyde in the presence of a Lewis acid to give the THP **137** and **138** *via* Knoevenagel condensation and intramolecular oxy-Michael addition reaction of **136**, the ratio of *cis*- and *trans*-diastereomers varied considerably and depended on the substituents at C2 and C6 positions (**Table 2**).[33]

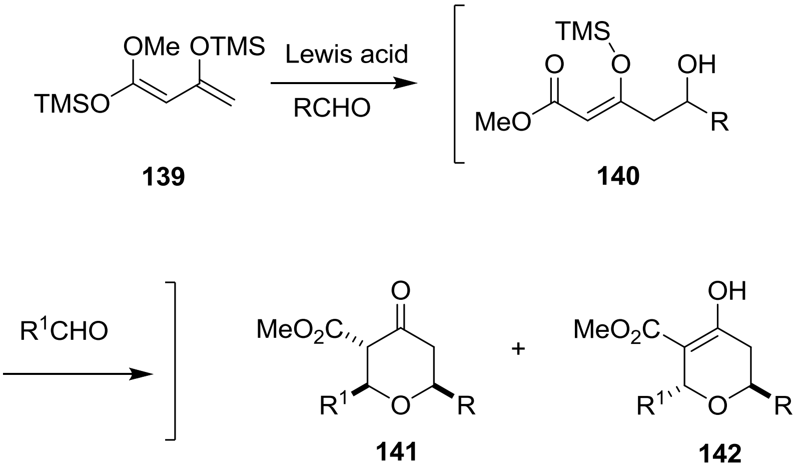


Scheme 30: The revisited two-pot Maitland-Japp reaction.[33]

Table 2: Two-pot Maitland-Japp reaction.[33]

Entry	R	R^1	Yield(%)	Ratio 137 : 138
a	Heptyl	Ph	80	6.4 : 1
b	Hexyl	^{n}Pr	80	12.3 : 1
c	^{i}Pr	^{n}Pr	55	1 : 1
d	^{i}Pr	Hexyl	55	1 : 1.4

In addition, a Lewis acid mediated one-pot Maitland-Japp reaction was also developed with another β-ketoester derivative the *bis*-trimethylsilyl enol ether of methyl acetoacetate (Chan's diene). In the reaction (**Scheme 31**), $TiCl_4$ was chosen as a catalyst because of its catalytic activity toward Mukiayama aldol reaction[34] and Knoevenagel condensation.[35] Chan's diene **139** acted as a nucleophile reacted with the aldehyde to give an aldol intermediate **140**, then *via* Knoevenagel condensation and oxy-Michael addition to give the THP **141** and **142**, and the distribution of THP products varied remarkably as in the previous case, and affected by the kind of Lewis acids employed in the reaction (**Table 3**).[33, 36]



Scheme 31: The revisited one-pot Maitland-Japp reaction.[33, 36]

Table 3: One-pot Maitland-Japp reaction.[36]

			$TiCl_4$	**$TiCl_4$**	**$Yb(OTf)_3$**	**$Yb(OTf)_3$**
Entry	**R**	**R^1**	**Yield(%)**	**141 : 142**	**Yield(%)**	**141 : 142**
a	^{i}Pr	Pr	98	1 : 1	91	10 : 1
b	Ph	Ph	98	1 : 3	98	2.5 : 1
c	Ph	^{i}Pr	80	1 : 0	75	1 : 0
d	^{i}Pr	Ph	82	1 : 3	80	2.5 : 1

It was also found that the formation of THP was reversible and tended to equilibrate to give the same *cis* and *trans* ratio as before when a pure *cis*- or *trans*-diastereomer was submitted to the THP-forming condition. The 2,6-*cis* isomer was formed with the substituents in C2 and C6 position pointing to the equatorial position, on the other hand the 2,6-*trans* isomer existed as enol form with the substitents to pseudo-equatorial position. The 2,6-*trans*-enol isomer was stabilized by the hydrogen bonding between the enol proton and the ester carbonyl group, and the chemical shift of the proton was around 12 ppm.[33, 36]

It was a surprise that the Lewis acid promoted Maitland-Japp reaction generated a mixture of two diastereomers, as the original Maitland-Japp reaction only produced a single *cis*-substituted diastereomer. Obviously, the addition of Lewis acid exerts an influence to the distribution of *cis*- and *trans*-diastereomers formation. The reaction catalyzed by $TiCl_4$ tended to favour the formation of *trans*-enol isomer **142b** and **142d** in 1:3 ratio (**Table 2, Entry b, d**), whereas the same reactions promoted by $Yb(OTf)_3$ tended to be more favourable the *cis*-keto isomer **141b** and **141d** in 2.5:1 ratio (**Table 2, Entry b, d**). Therefore the diastereoselectivity may relate to the interaction between the *trans*-enol isomer and the Lewis acids. The $Yb(OTf)_3$ is much less soluble in DCM which was adopted as solvent than $TiCl_4$, the $TiCl_4$ can interact and stabilize the 2,6-*trans* diastereomer in the enol form so as to have the substituent (R^1) pointing to the pseudo-equatorial position (**Figure 2**).

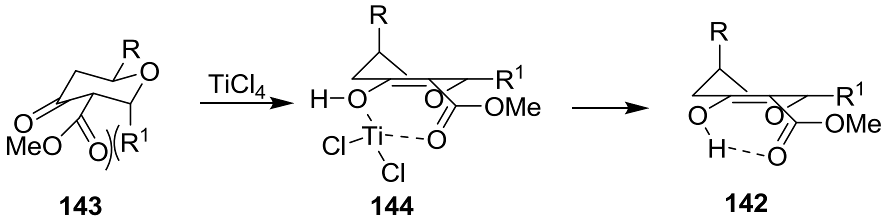
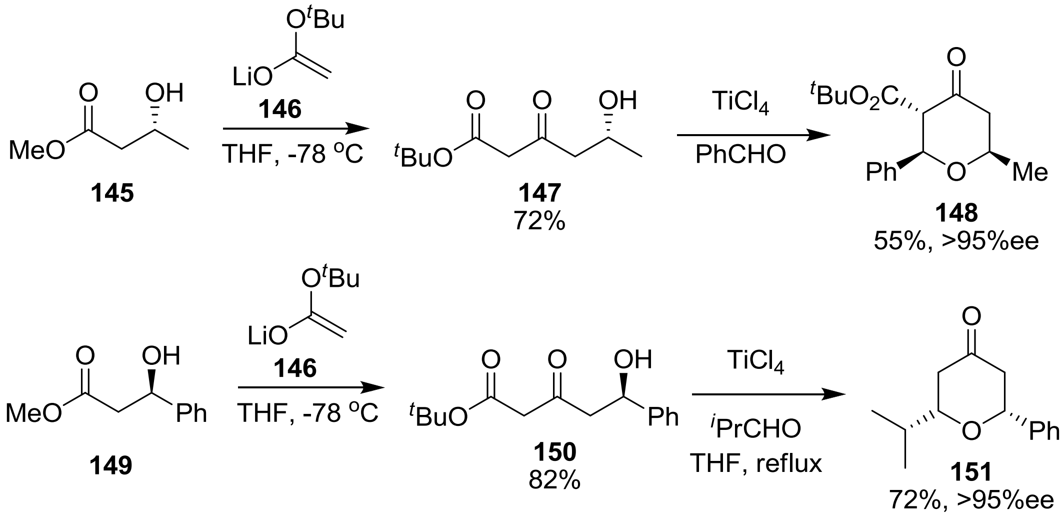


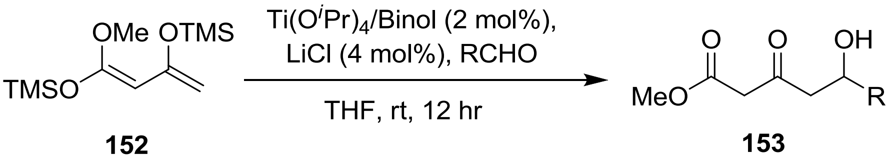
Figure 2: Stabilizing 2,6-*trans* enol isomer by $TiCl_4$.

The chiral information in δ-hydroxy-β-ketoester was found to be retained in the THP product in the Maitland-Japp reaction, which allowed the development of asymmetric version of Maitland-Japp reaction (**Scheme 32**).[33, 36] Hence, the development of an effective asymmetric aldol reaction for producing enantiomerically enriched δ-hydroxy-β-ketoester was essential.



Scheme 32: Formation of single enantiomers of **148**, **151**.[33, 36]

In 2011, an asymmetric version of the Maitland-Japp reaction (**Scheme 33**) was developed with Soriente's procedure for asymmetric aldol reaction.[37, 38] In the procedure, Keck reagent ($Ti(Binol)_2$) was used to catalyze asymmetric aldol reaction by the addition of Chan's diene **152** to different aldehydes, and the enantiomerically enriched δ-hydroxy-β-ketoester **153** was formed in good yield and excellent *ee* (**Table 4**).[38] There was only 2 mol% of Ti/Binol catalyst required to promote the reaction at room temperature, giving the **153a** in 89% yield, 97% *ee* and **153b** in 83% yield, 99% *ee*. However, at the beginning of the study, the result of the asymmetric aldol reaction was not repeatable until LiCl was added as an additive, which was absent in Soriente's procedure. It was believed that the Li metal ions may be a major contaminant in Chan's diene, and are essential to make the reaction work, but it was removed during the purification of Chan's diene by distillation.

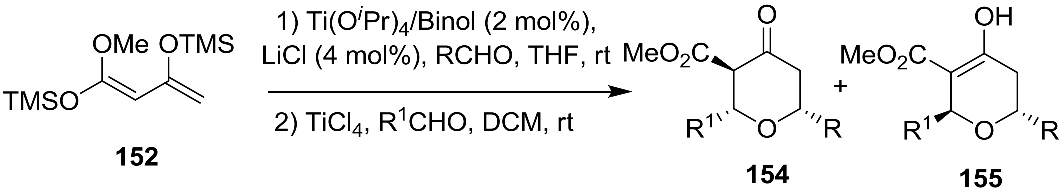


Scheme 33: Asymmetric addition of Chan's diene to aldehydes.[38]

Table 4: Asymmetric addition of Chan's diene to aldehydes.[38]

Entry	**R**	**Catalyst**	**Yield(%)**	**%ee**	$[\alpha]_D$
a	Ph	(*R*)-Binol	89	97 (*R*)	27.3
b	Pr	(*S*)-Binol	83	99 (*R*)	-16.5

In the asymmetric Maitland-Japp reaction (**Scheme 34**), the crude product of enantiomerically-enriched δ-hydroxy-β-ketoester was submitted to Lewis acid catalyzed cyclization reaction condition, and formed the enantiomerically enriched THP **154** and **155** in moderate to good yield (36 – 90%) and excellent *ee* (>95%) (**Table 5**).[38]



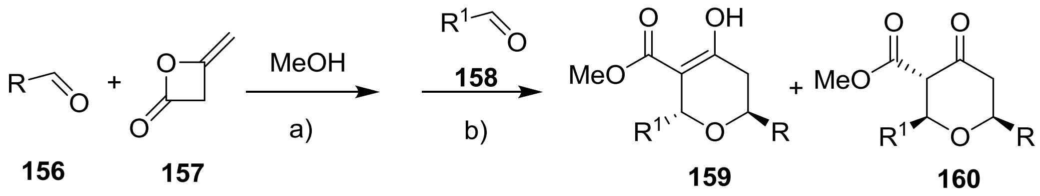
Scheme 34: Asymmetric Maitland-Japp reaction.[38]

Table 5: Asymmetric Maitland-Japp reaction.[38]

Entry	**R**	**R^1**	**Yield(%)**	**Ratio of 154 : 155**	**%ee**
a^a	^{i}Pr	Ph	90	1 : 2.8	99
b^b	Ph	^{i}Pr	69	10 : 1	97
c^b	Cy	Ph	70	1 : 1.5	99
d^b	Ph	2-furyl	36	10 : 1	97

a : (*S*)-Binol used; absolute stereochemistry of C6 centre is (*S*).
b : (*R*)-Binol used; absolute stereochemistry of C6 centre is (*R*).

Apart from Chan’s diene, commercially available diketene **157** was studied as starting material for one pot Mailtland-Japp reaction (**Scheme 35**). In the reaction, δ-hydroxy-β-ketoester was formed by $TiCl_4$ promoted diketene addition reaction on an aldehyde *via* an aldol reaction.[39] Then it underwent a Knoevenagel condensation with a second aldehyde and intramolecular oxy-Micheal addition to give the THP **159** and **160** in moderate to good yield (28 – 87%) (**Table 6**).[40]

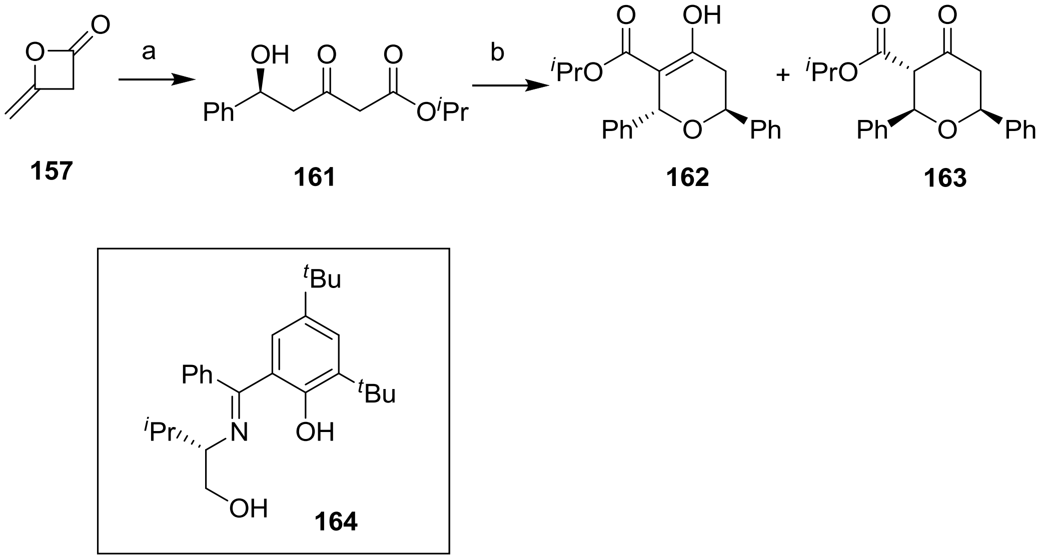


Scheme 35: *Reagents and conditions:* a) $TiCl_4$ (1.0 eq), DCM, -78 °C, 5 min, then MeOH (4.0 eq), -78 °C to -20 °C, 30 min; b) 2nd aldehyde (1.2 eq), -78 °C to -20 °C, overnight.[40]

Table 6: One-pot preparation of tetrahydropyrans by diketene addition.[40]

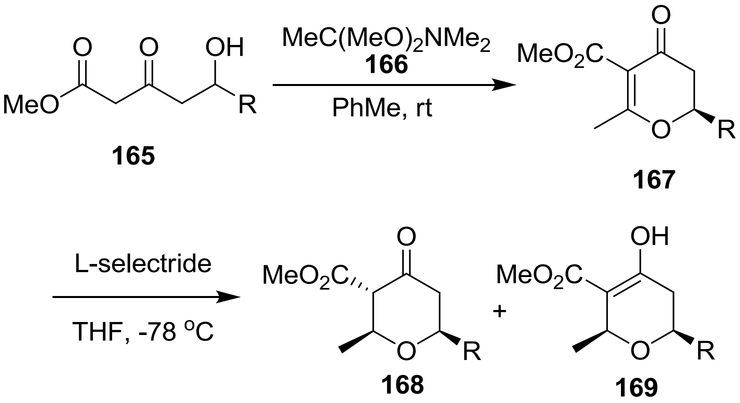
Entry	R^1	R	Yield(%)	Ratio 159 : 160
a	^{i}Pr	Ph	87	1 : 1.5
b	Ph	^{i}Pr	69	1 : 0.6
c	CH_2OBn	Pr	58	1 : 4.2
d	2-furyl	Ph	28	1 : 0.4

An enantiomerically-enriched δ-hydroxy-β-ketoester can also be acquired from the reaction between diketene and aldehydes. A Schiff base ligand **164** was adopted in order to achieve the asymmetric aldol reaction. In which, the Schiff base chelated with the Ti metal centre, so as to catalyze the enantioselective addition of diketene to the aldehydes, and then the formation of THP rings. The reaction gave good *ee* (>90%), but a diminished yield (43%) and two diastereomers were formed as product **162** and **163** in 2:1 ratio (**Scheme 36**).[40]



Scheme 36: *Reagents and conditions:* a) 1.0 eq Ti(O^{i}Pr)$_4$, 1.1 eq **164**, DCM, rt, 1 hr, then 1.0 eq PhCHO, 1.8 eq diketene **157**, 3.0 eq ^{i}PrOH, -20 ^{o}C, 5 d; b) 1.1 eq TiCl$_4$, -78 ^{o}C to -20 ^{o}C, 16 h, 43% (from diketene), 2:1 *trans*- **162**/*cis*-**163** ratio by ^{1}H NMR of crude reaction mixture.[40]

Although the revisited Maitland-Japp and asymmetric Maitland-Japp reaction proved a promising strategy for THP synthesis, the formation of two difficult to separate *cis*- and *trans*-diastereomers is a limitation of this reaction. In order to solve this problem, a modified Maitland-Japp reaction was developed to deliver the the 2,6-disubstituted 2,3-dihydropyran-4-one, which was reduced selectively to formed the desired tetrahydropyran-4-one (**Scheme 37**).[41]



Scheme 37: Formation of 2-methyltetrahydropyran-4-ones.[41]

Table 7: Formation of 2-methyltetrahydropyran-4-ones.[41]

Entry	R	Yield of 165 (%)	168 : 169[b]	Yield[a](%)
a	Ph	60	1 : 0.34	69
b	Pr	70	1 : 0.13	61
c	^{i}Pr	70	1 : 0.13	67
d	2-Furyl	40	1 : 0.2	84
e	BnOCH$_2$	61	1 : 0.15	62
f	BnOCH$_2$CH$_2$	72	1 : 0.19	67

a: The overall yield of **166** and **167**.
b: Ratio of **166**:**167** determined from the ^{1}H NMR spectra of crude reaction.

During the study of 2-methyltetrahydropyran-4-ones formation, δ-hydroxy-β-ketoester **165** with a series of alkyl and aryl substituents were reacted with the dimethyl acetal of *N*,*N*-dimethyl acetamide **166**, giving the dihydropyran-4-one **167**, which in turns reduced stereoselectively by L-selectride to form the 2-methyltetrahydropyran-4-ones in moderate to good yield. The THP product existed in both *cis*-keto and *cis*-enol tautomers in a ratio predominated by the *cis*-keto tautomer (**Table 7**).

1.3 Aims and Objectives

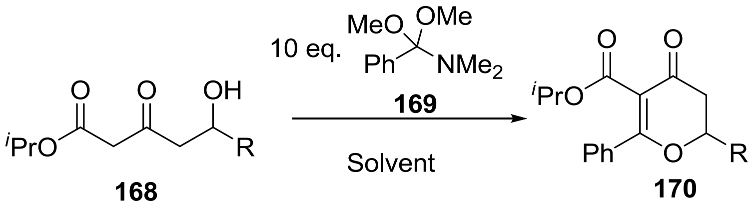
In order to improve the formation of THP diastereoselectively, a study of synthesis of DHP and utilizing 1,4 – addition reaction for the synthesis of 2,6-*trans*-disubstituted THP was performed. For that, a DHP with no substituent at C2 position was synthesized and achieved the conjugated addition of methyl group at C2 position with organocuprate reagent. Further study of using organocatalyst to promote the synthesis of δ-hydroxy-β-ketoester from diketene was conducted toward the synthesis of (-)-apicularen A. An investigation of novel methodology for the formation of 2,6-disubstituted DHT from δ-hydroxy-β-ketoester and thioamide was conducted, and prove the scope of the methodology towards a more efficient construction of natural product. In order to optimize the reaction, different Lewis acids, solvent and temperature were tested, and incorporation of different δ-hydroxy-β-ketoesters and thioamides.

2. Results and discussion

2.1. Synthesis of Dihydropyrans

The two step synthesis of 2-methyltetrahydropyran-4-ones from the corresponding dihydropyrans (DHPs) showed an encouraging result to replace the Maitland-Japp reaction for delivery of a single diastereomer of the target THP. Therefore, it was worth to investigate the scope of DHP formation by changing the methyl substituent at C2 position to other groups, in this study a phenyl group at C2 position was introduced to the DHP by use of the dimethyl acetal of *N*,*N*-dimethyl benzamide. A number of dihydropyrans were synthesized *via* the reaction of δ-hydroxy-β-ketoester with dimethyl acetal of *N*,*N*-dimethyl benzamide and different substituents at C6 position were tested by use of δ-hydroxy-β-ketoesters with different substituents.

Firstly, the isopropyl ester of δ-hydroxy-β-ketoester **168** was used to synthesize the DHP, however, only the DHP **170a** with an isopropyl group at C6 position was obtained successfully. The synthesis of the DHP with 2-furyl and methyleneoxybenzyl groups by this method was not successful (**Table 8, Entry b to c**). The TLC showed that δ-hydroxy-β-ketoester was consumed but no desired product could be isolated. The major limitation of this reaction is that the rate of the reaction was very slow, even though the DHP **170a** was formed in 53% yield, two weeks was needed for the reaction to go to completion (**Table 8, Entry a**). When a higher temperature was then employed, only a 19% yield was obtained (**Table 8, Entry b**), which was lower than the yield of reaction run at room temperature. As 10 equivalents of dimethyl acetal of *N*,*N*-dimethyl benzamide **169** was added to the reaction, it was also possible to use this as a solvent in the reaction. However this too failed to yield any product. The slow rate of product formation could be due to the repulsion between the isopropyl group (R^1) and the phenyl ring at C2 position.



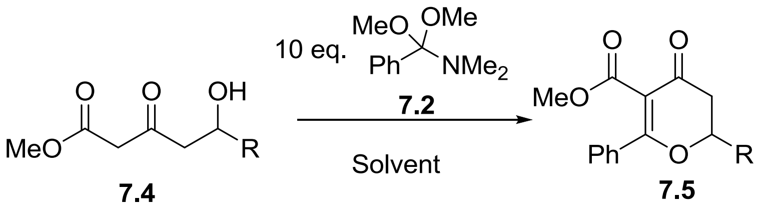
Scheme 38: Reaction between δ-hydroxy-β-ketoester and benzamide acetal.

Table 8: Synthesis of dihydropyran.

Entry	R	Solvent	Temp.(°C)	Time	%Yield
a	^{i}Pr	Toluene	rt	2 weeks	53
b	^{i}Pr	Toluene	40	1 week	19
c	2-furyl	Toluene	rt	16 hr	N/D
d	2-furyl	neat	rt	16 hr	N/D
e	CH_2OBn	neat	rt	16 hr	N/D
f	CH_2OBn	neat	50	16 hr	N/D

N/D : No DHP was detected.

Hence, the less bulky methyl ester of δ-hydroxy-β-ketoester **171** was investigated (**Scheme 39**), and some extent of improvement for several reactions was identified. The DHP **172a** with the methyleneoxybenzyl group was obtained in 11% yield (**Table 9, Entry a, b**), but the DHP **172c** with 2-furyl and **172d** with the phenyl groups were not formed (**Table 9, Entry c, d**). The DHP **172e** with a more extended ethyleneoxybenzyl group was obtained in 33% yield and the DHP **172f** with cyclohexyl group was formed in 41 % yield (**Table 9, Entry e, f**).



Scheme 39: Reaction between δ-hydroxy-β-ketoester and benzamide acetal.

Table 9: Synthesis of dihydropyran at room temperature in toluene.

Entry	R	Time (hr)	%Yield
a	CH_2OBn	16	11
b	CH_2OBn	5	11
c	2-furyl	16	N/D
d	Ph	16	N/D
e	CH_2CH_2OBn	16	41
f	Cy	16	33

N/D : No DHP was detected from the 1H NMR of crude reaction.

These results demonstrated that the yield of DHP formation using the dimethyl acetal of *N*,*N*-dimethyl benzamide was always lower than that of dimethyl acetal of *N*,*N*-dimethyl acetamide. The reason may be because of the lower reactivity of benzamide and the stronger repulsive effect of phenyl ring as a barrier to the reaction.

According to the previous study, it was known that the 1,4-reduction of DHP by L-selectride, in which the hydride prefers to attack the DHP at C2 from a pseudo-axial direction, generated the corresponding THP stereoselectively as a *cis*-isomer in a more favourable chair comformation.[41] This eliminates the disadvantage of forming two diastereomers in the Maitland-Japp reaction. Theoretically, a *trans*-isomer could also be synthesized in the same manner but replacing the hydride with carbanions (**Figure 3**).

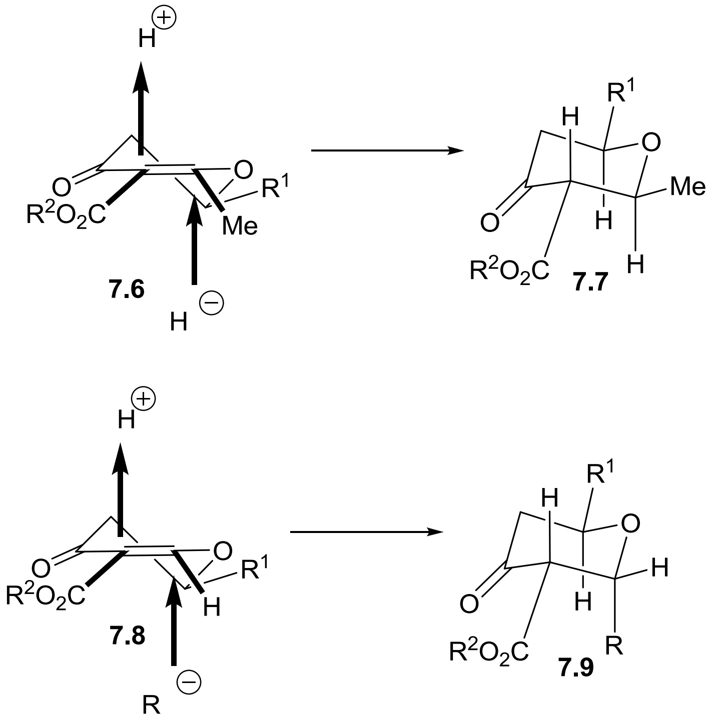
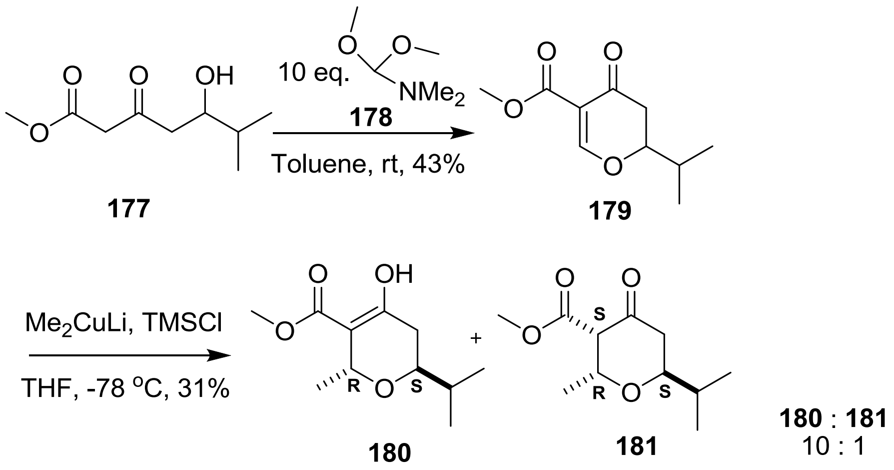


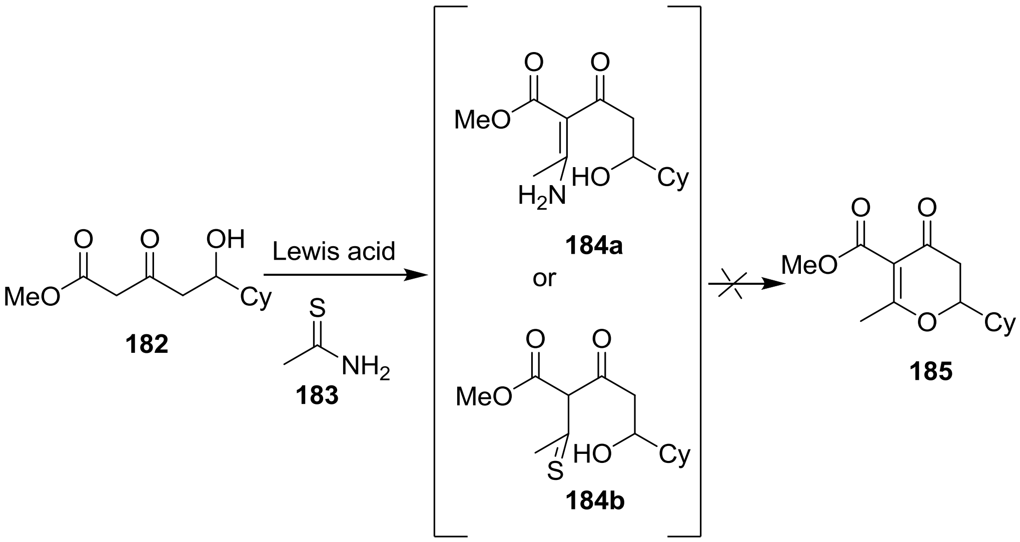
Figure 3: An explanation for the stereoselective formation of THP.

In an attempt to test this hypothesis, a DHP **179** with a proton at the C2 position was prepared by utilizing the dimethyl acetal of *N*,*N*-dimethyl formamide **178**, the isolated yield of the DHP **179** was 43%. This was followed by a 1,4-addition reaction with Gilman cuprate reagent, resulting in a THP as a *trans*-isomer with enol **180** and keto **181** tautomers in 31% yield, and the ratio of enol tautomer to keto tautomer is 10:1 identified by ^{1}H NMR spectrum of the crude raction mixture (**Scheme 40**).



Scheme 40: Stereoselective 1,4-addition to DHP.

Owing to the noticeable result of forming a single diastereomeric THP from the corresponding DHP by 1,4-addition, it was tried to develop a new method for DHP synthesis. In the new method, a thioacetamide **183** was chosen to replace the dimethyl acetal of amides to react with δ-hydroxy-β-ketoester **182**. It was anticipated that the similar Knoevenagel product **184a** or **184b** would be formed with a suitable Lewis acid and then condensed to give the DHP **185** (**Scheme 41**).

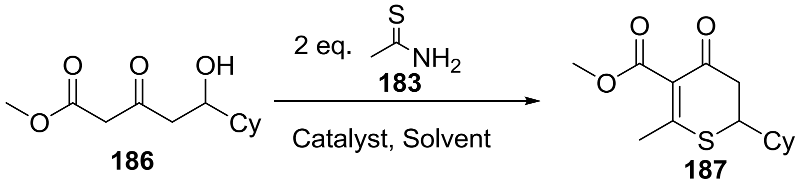


Scheme 41: Proposed methodology for DHP synthesis.

However, at the end of the reaction no DHP was found. The ^{1}H NMR spectrum was quite similar as the spectrum expected for DHP but the proton signal of at C6 was slightly upfield shifted by about 0.1 ppm, also the MS data showed the product with a molecular mass 16 unit greater than expected, plus the product had a noticeable odour. All of these indicated the product formed was not a pyran but a thiopyran which had the oxygen atom replaced by a sulfur atom. The product was identified as a dihydrothiopyran-4-one (DHT) as the major product, thus it was decided to investigate this reaction further.

2.2. Synthesis of dihydrothiopyrans

During the investigation of DHT reaction, different Lewis acids (no reaction occurred without a suitable Lewis acid) (**Table 10, Entry d)**, solvents and temperatures were tested (**Table 10 – 12**). In the reaction, δ-hydroxy-β-ketoester **186** was reacted with two equivalent of thioacetamide **183** (**Scheme 42)**.



Scheme 42: Reaction between δ-hydroxy-β-ketoester and thioamide.

Initially, the Lewis acids, including Hg(II), Zn(II) and Au(I) metal ions, with strong affinity to the sulfur atom was exploited to facilitate the elimination of sulfur atom and promoted the DHP **185** formation from the δ-hydroxy-β-ketoester **182** and thioacetamide **183** (**Scheme 41**). However, precipitates were formed immediately when mercury(II) acetate acid [$Hg(OAc)_2$] and gold(I) chloride [$AuCl{\cdot}Me_2S$] were mixed with the reaction mixture (**Table 9, Entry a, b**). This suggested the Lewis acids coordinated with the thioacetamide **183** directly and formed insoluble precipitates instead of catalyzing a reaction. The zinc(II) triflate [$Zn(OTf)_2$] only returned the starting materials (**Tablet 9, Entry b**).

Table 10: Synthesis of DHT with Lewis acids have strong affinity to sulphur atom.

Entry	Catalyst	Solvent	Temp. (^oC)	Time	%Yield
a	$Hg(OAc)_2$	DCM	rt	< 1 min	black ppt.
b	$AuCl.Me_2S$	1,4-Dioxane	101	<1 min	grey ppt.
c	$Zn(OTf)_2$	DCM	rt	16 hr	SM.
d	No	THF	35	16 hr	SM.

Next, we exammed the more conventional Lewis acids (**Table 11**). It was found that $Ti(O^iPr)_4$ was not a suitable catalyst for the reaction and no DHT was formed (**Table 11, Entry a-c**). However, the more Lewis acidic $TiCl_4$ was a better catalyst for this reaction. The reaction occured slowly at room temperature when only 10 mol% of $TiCl_4$ was added, so more $TiCl_4$ was added gradually to one equivalent and the reaction was warmed to 35 ^oC, the DHT **187** was acquired in 44% yield in THF over three days (**Table 11, Entry d**). When we started with one equivalent of $TiCl_4$ in THF at 35 ^oC, 33% yield of the DHT **187** was formed after 16 hours. The yield of DHT **187** became lower (10%) when the amount of $TiCl_4$ was reduced to 10 mol%, or lower the temperature (26% yield) (**Table 11, Entry f, g**). It was also found that the yield of the reaction was more or less the same in DCM or $CHCl_3$, which gave 37% yield of DHT **187** (**Table 11, Entry l**). Although $TiCl_4$ catalyzed DHT formation, several problems were observed. It was proved that higher reaction temperature increased the rate of the reaction, but the $TiCl_4$ worked poorly when the reaction was heated under reflux in DCM or chloroform and gave a black precipitate at the end of the reaction (**Table 11, Entry m, n**). Also, some undefined side product was formed in the reaction when using $TiCl_4$ as Lewis acid, which was difficult to separate from the DHT by flash column chromatography on silica gel.

Table 11: Synthesis of dihydrothiopyran catalyzed by Ti Lewis catalysts.

Entry	Catalyst	Solvent	Temp.(^{o}C)	Time (hr)	%Yield
a	0.1 eqTi(O^{i}Pr)$_4$	Toluene	rt	16	SM.
b	0.1-1 eq Ti(O^{i}Pr)$_4$	THF	rt	16	SM.
c	0.1 eq Ti(O^{i}Pr)$_4$	THF	35	16	SM.
d	0.1-1 eq TiCl$_4$	THF	rt - 35	72	44
e	TiCl$_4$	THF	35	16	33
f	0.1 eq TiCl$_4$	THF	35	16	10
g	TiCl$_4$	THF	rt	16	26
h	0.1eq TiCl$_4$	DCM	rt	16	3
i	0.1eq TiCl$_4$	DCM	35	16	18
j	TiCl$_4$	DCM	rt	16	17
k	TiCl$_4$	CHCl$_3$	rt	16	3
l	TiCl$_4$	DCM	35	16	37
m	TiCl$_4$	DCM	40	16	decomp.
n	TiCl$_4$	CHCl$_3$	62	16	decomp.

One equivalent of Lewis acid was added if not specified.
decomp.: decomposition of δ-hydroxy-β-ketoester observed, no DHT was detected in the reaction.

In addition to Ti Lewis acids, Yb(OTf)$_3$ was tested (**Table 12**). It was found that Yb(OTf)$_3$ was a less reactive catalyst in the reaction at room temperature or 35 ^{o}C compared to TiCl$_4$, only 3 – 15% yield of DHT **187** was formed regardless of the solvent used (**Table 12, Entry a, b, d**), but gave better performance at high temperatures in refluxing THF and CHCl$_3$, 16 – 31% yield (**Table 12, Entry c, e**). The best result was obtained when the reaction was carried out in refluxing 1,4-dioxane, which has a boiling point at 101 ^{o}C, giving DHT **187** in 27 – 42% yield, and shorten the reaction time effectively to one hour (**Table 12, Entry h**). More importantly, there was no side product contamination in the reaction catalyzed by Yb(OTf)$_3$.

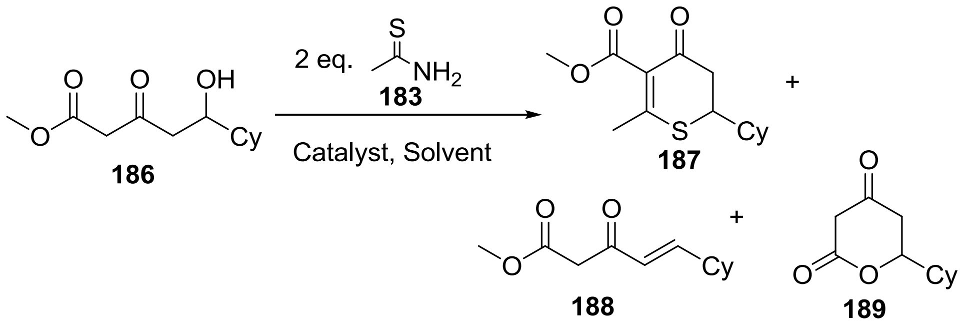
Table 12: Synthesis of dihydrothiopyran catalyzed by Yb Lewis catalyst.

Entry	Catalyst	Solvent	Temp.(^{o}C)	Time (hr)	%Yield
a	Yb(OTf)$_3$	THF	rt	16	3
b	Yb(OTf)$_3$	THF	35	16	15
c	Yb(OTf)$_3$	THF	66	16	16
d	Yb(OTf)$_3$	CHCl$_3$	rt	16	SM.
e	Yb(OTf)$_3$	CHCl$_3$	62	16	31
f	Yb(OTf)$_3$	MeOH	64	16	N/D
g	Yb(OTf)$_3$	MeCN	82	16	15
h	Yb(OTf)$_3$	1,4-Dioxane	101	1	27-42
i	Yb(OTf)$_3$	CPME	106	1	22

N/D: reaction gave complicated crude ^{1}H NMR spectrum, not DHT was detected in the reaction.

Different solvents, including DCM, CHCl$_3$, THF, MeOH, MeCN, 1,4-dioxane, cyclopentyl methyl ether, were screened, but no noticeable influence to the yield of reaction was observed.

Besides TiCl$_4$ and Yb(OTf)$_3$, other Lewis acids were investigated (**Table 13**), unfortunately, no better result was observed. Only the Sc(OTf)$_3$ gave 7% yield of DHT **187**, other Lewis acids gave enone **188** or self-cyclized lactone **189** as product according to the crude ^{1}H NMR (**Scheme 43**).



Scheme 43: Enone and lactone formation from DHT reaction.

Table 13: Synthesis of DHT catalyzed by other catalysts at refluxing 1,4-dioxane.

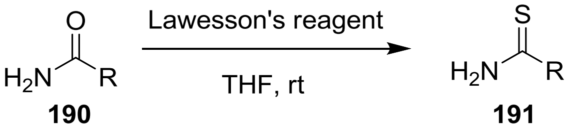
Entry	Catalyst	Time	Product
a	$Sc(OTf)_3$	3hr	DHT (7%)
b	$FeCl_3$	3hr	enone
c	$CeCl_3$	3hr	enone
d	$InCl_3$	3hr	N/D
e	$BF_3 \cdot OEt_2$	1hr	enone
f	TMSOTf	3hr	N/D
g	PPTS	3hr	lactone
h	CSA	3hr	lactone

N/D: reaction gave complicated crude ^{1}H NMR spectra, DHT, enone and lactone were not detected.

It was found that a mass loss occurred in the reaction, which may explain the low yield of the reaction. 50 mg of δ-hydroxy-β-ketoester was used in the reaction, but only 30 mg of crude product was obtained after work-up. The DHT was re-submitted to the reaction conditions after 16 hours reaction and work-up, there was no decomposition of product and more than 95 % of product was recovered after usual work-up procedure and flash column chromatography.

After the optimal reaction conditions were confirmed, we tried to expand the scope of this reaction and enable the installation of different substituents of the DHT at C2 and C6 positions. In this study, a series of δ-hydroxy-β-ketoesters with different substituents (R^1), including cyclohexyl, isopropyl, phenyl, methyleneoxybenzyl and methyl groups, were adopted to react with the thioacetamide. Different thioamides with substituents (R^2) including methyl, phenyl, methyleneoxybenzyl and hexyl groups, were examined (**Scheme 45**).

The required thioamides **191** were synthesized by thiolation of the corresponding amides **190** with Lawesson's reagent[42] in yields ranging from 55 – 84% (**Scheme 44**, **Table 14**).

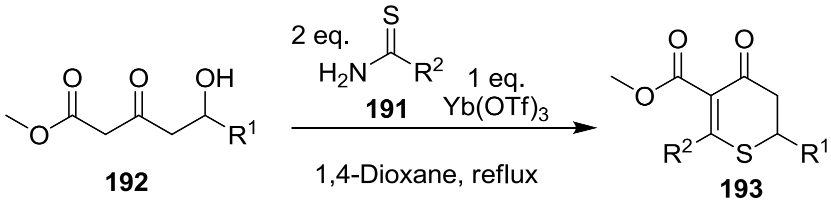


Scheme 44: Synthesis of thioamides from the amides and Lawesson's reagents.

Table 14: Synthesis of thioamides from the amides and Lawesson's reagents.

Entry	R	Yield (%)
a	Ph	56
b	CH_2OBn	84
c	^{n}hexyl	77

The results showed that δ-hydroxy-β-ketoesters **192** with different R^1 groups reacted with the thioacetamide (**Table 15, Entry e-h**), giving the corresponding DHT in comparable yields ranged from 8% to 23%. However, only the thioamide with aliphatic substituents, such as methyl and ^{n}hexyl groups can give the desired DHTs **193a** and **193d** (**Table 15, Entry a, d**), the thioamide with functionalities, like phenyl and methyleneoxybenzyl groups, produced complicated ^{1}H NMR spectra, and no DHT was indentified (**Table 15, Entry b, c**).



Scheme 45: Synthesis of DHT with different substituents as C2 and C6 positions.

Table 15: Synthesis of DHT with different substituents as C2 and C6 positions.

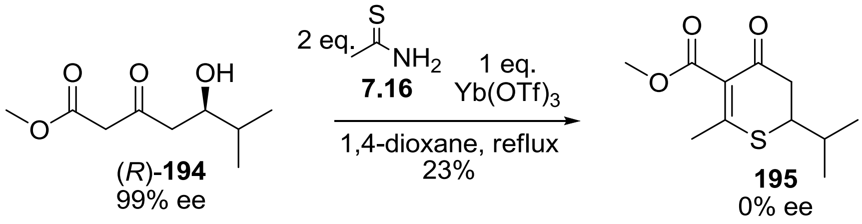
Entry	R^1	R^2	Yield (%)
a	Cy	Me	42
b	Cy	Ph	N/D
c	Cy	CH_2OBn	N/D
d	Cy	hexyl	23
e	^{i}Pr	Me	23
f	Ph	Me	8
g	CH_2OBn	Me	19
h	Me	Me	13

N/D: reaction gave complicated crude ^{1}H NMR spectra, no DHT was formed in the reaction.

2.3. Study of mechanism and formation of dihydrothiopyran

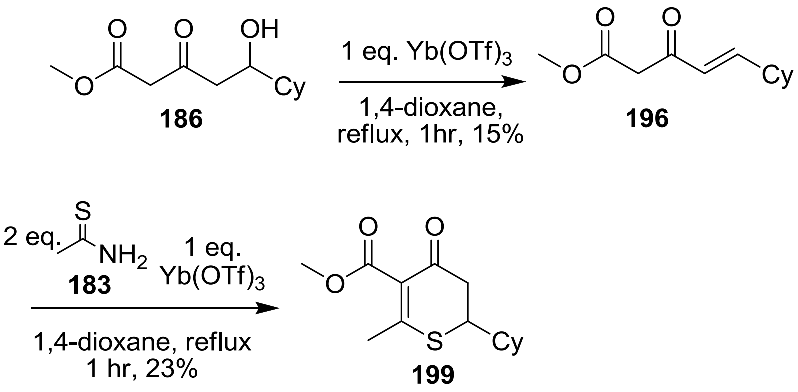
In the formation of DHT, it is possible to follow one of two possible mechanisms for cycloaddition. One possibility is an intramolecular S_N2 mechanism, and an inversion of stereogenic centre should be expected when the sulphur atom as a nucleophile attacked the carbon atom and expelled the Lewis acid chelated hydroxyl group. Another possibility is an elimination/ conjugated addition mechanism, the hydroxyl group of the δ-hydroxy-β-ketoesters would be eliminated, which was facilitated by the participation of Lewis acid and elevated temperature, then the sulfide would undergo a conjugated addition to give the DHT.

An enantiomerically-enriched δ-hydroxy-β-ketoester (*R*)-**194** was synthesized in order to prove whether the reaction followed an intramolecular S_N2 mechanism or not (**Scheme 46**). However, the resulting DHT **195** formed was a racemic mixture determined by HPLC. Thus, the possibility of the reaction taking place *via* an intramolecular S_N2 mechanism was ruled out. In other words, this also proved that the reaction may follow the elimination/ conjugated addition mechanism.



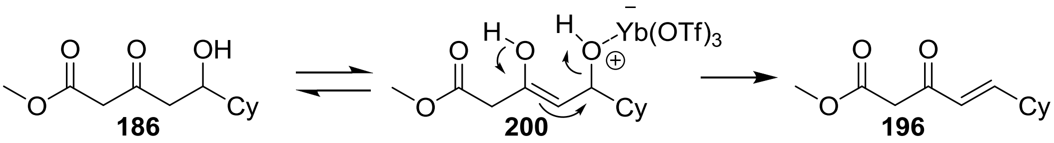
Scheme 46: Formation of DHT from enantiomerically-enriched δ-hydroxy-β-ketoester.

In order to prove the elimination/ conjugated addition mechanism, firstly, the enone **196** was prepared from the corresponding δ-hydroxy-β-ketoester **186** and $Yb(OTf)_3$, the reaction condition was the same as the reaction condition in the formation of DHT (**Scheme 47**). Then, the enone **196** was reacted with the thioacetamide **183**, the DHT **199** was formed as the product. Therefore, the elimination/ conjugated addition mechanism was highly possible to account for the formation of DHT.



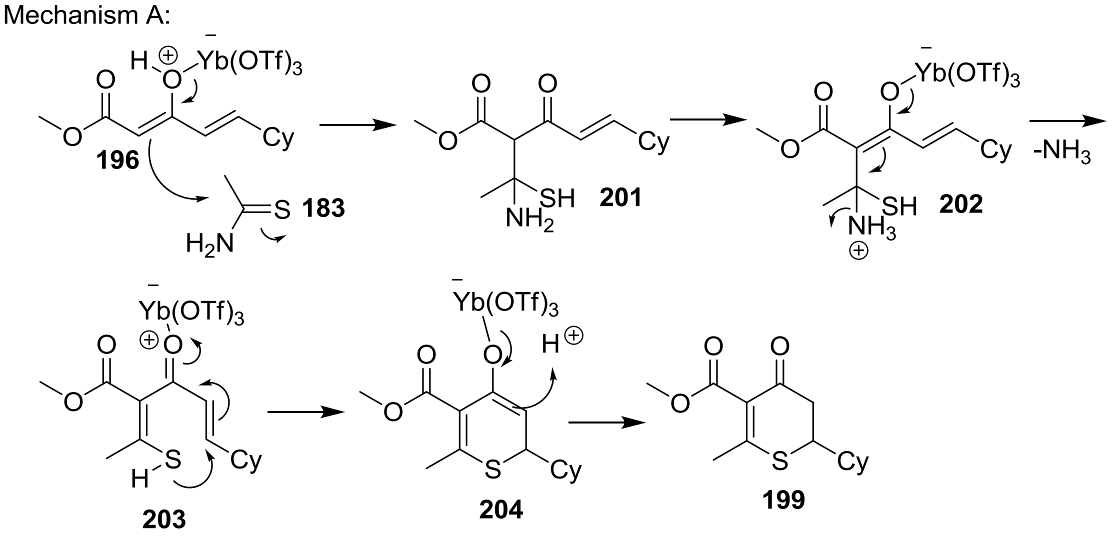
Scheme 47: DHT formation from the corresponding enone.

The loss of hydroxyl group from **186** may follow an $E1_{cb}$ mechanism in the presence of Lewis acids and a high temperature in order to achieve a reasonable rate of reaction.



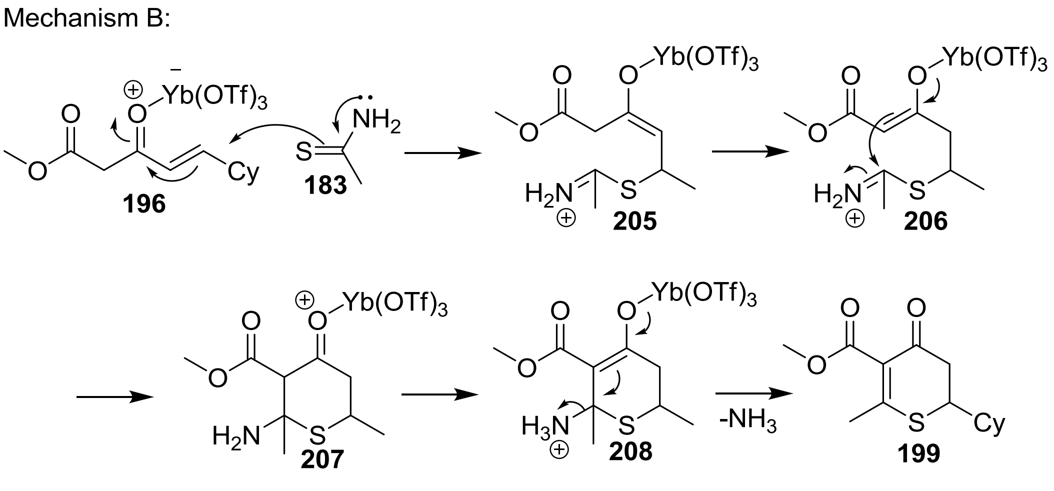
Scheme 48: Proposed mechanism for the formation of enone.

In the next step, the enone **196** may act as a nuclueophile to attack the thioacetamide **183** to give an intermediate **201**, and then the DHT **199** was formed after elimination of ammonia from **202**, conjugated addition of sulphur to the α,β-unsaturated double bond in **203** and protonation of **204**.



Scheme 49: Mechanism A for the formation of DHT.

It could be also possible for the thioacetamide **183** to act as a nucleophile to attack the α,β-unsaturated double bond of the enone **196** first, and then form the DHT after nucleophilic attack of imine bond in **206** and elimination of ammonia of **208**.



Scheme 50: Mechanism B for the formation of DHT.

It was also noticed that the yield of DHT formation from the enone was similar to that formed directly from the δ-hydroxy-β-ketoester. This may suggest that the course of low yielding of this reaction could be due to the nucleophilic addition step of the sulfur to the conjugated double bond. The Lewis acidic reaction medium may lower the nucleophilicity of the sulphur atom. Therefore, the addition step may not be fast enough to eliminate any other side reactions that gave no DHT.

2.4. Synthesis of citreothiopyrane A

In the course of investigation of the DHT reaction, a DHT containing natural product called citreothiopyrane A **209** (**Figure 4**) was found. Citreothiopyrane A is a metabolite isolated from the mycelia of hybrid strains KO 0201 and 0211 derived from penicillium *citreo-viride B. IFO 6200* and *4692.*[43] The bioassay of citreothiopyran A **209** indicated that is a plant growth inhibitor can slow down the germination of lettuce seed.[43] Its structure provided by the literature[43] was very similar to the DHT product **211** which was formed from δ-hydroxy-β-ketoester **210** and thioacetamide **183**, the DHT reaction was applied to the synthesis of citreothiopyran A **209**.

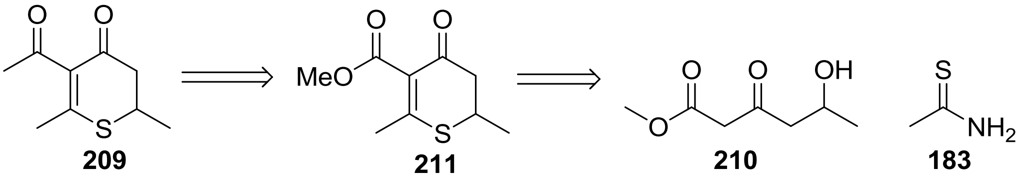
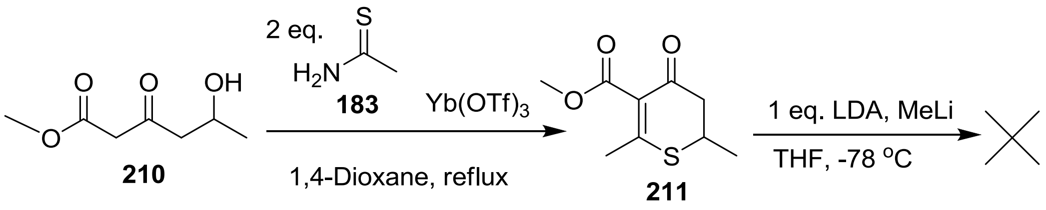


Figure 4: First retroanalysis of citreothiopyrane A.

Firstly, our proposed synthetic scheme was to convert the ester functional group of the dihydrothiopyran **211** to a ketone functional group by methyl lithium reagent (**Scheme 51**). Ideally, the dihydrothiopyran would undergo a deprotonation at the C5 position by the LDA and generate an enolate which would protect the carbonyl group from being attacked by methyl lithium reagent, and the ester group could react with one equivalent of methyl lithium reagent to give the target product **211**. However, the reaction only returned the starting material and little amount of undefined product. Because, it was very difficult to convert the ester group to a ketone group, another retroanalysis of citreothiopyran A was proposed (**Figure 5**). The idea is to employ an aldol product **212**, which has already possessed a ketone functional group, and can be prepared from acetyl acetone **213** and acetaldehyde **214**.



Scheme 51: First proposed synthetic scheme for citreothiopyran A.

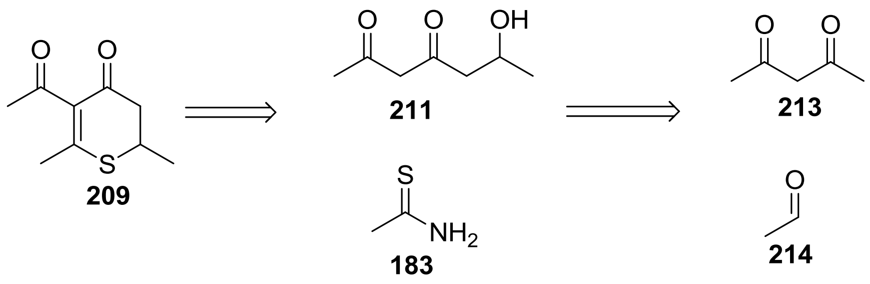
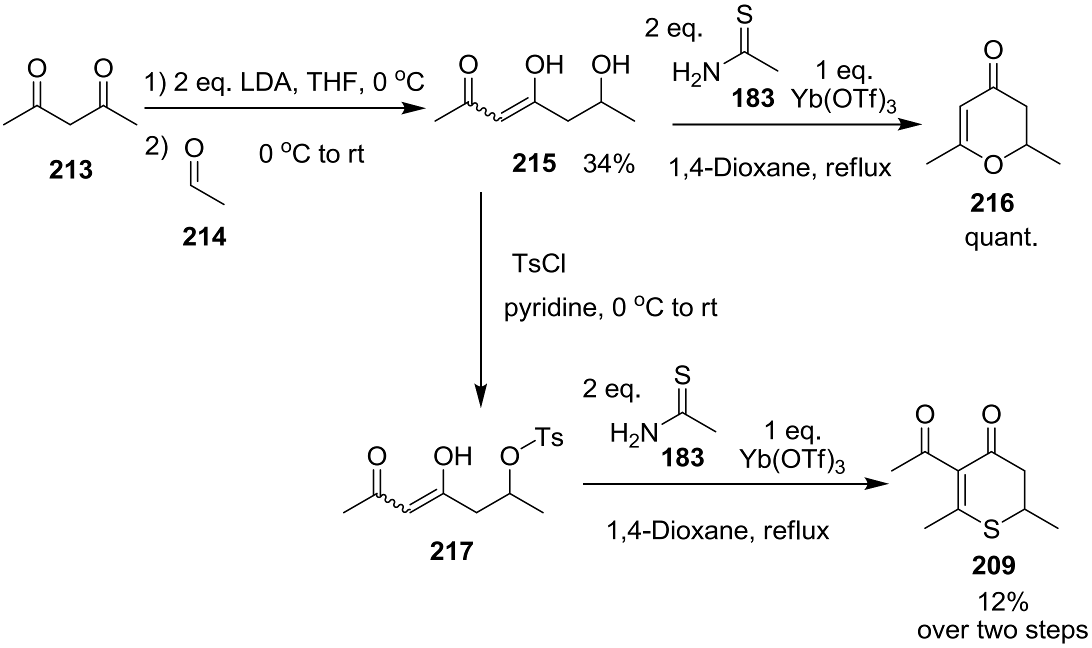


Figure 5: Retroanalysis of citreothiopyrane A.

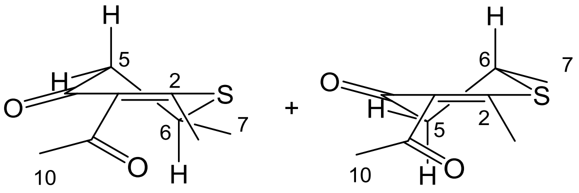
In the second synthetic pathway (**Scheme 52**), the aldol product **215**, which existed as the enol tautomer of **212**, was formed by the reaction between the acetyl acetone **213** and two equivalents of LDA and then one equivalent of acetaldehyde **214** in 34% yield, the product was dominated in the enol tautomer named 4,6-dihydroxyhept-3-en-2-one **215**. As an analogue of δ-hydroxy-β-ketoester, we expected it can carry out the same DHT reaction with thioacetamide and $Yb(OTf)_3$. However, in the next step, when the 4,6-dihydroxyhept-3-en-2-one **215** was treated with thioacetamide and $Yb(OTf)_3$, the product obtained was a self-cyclized dihydropyran **216** in quantitative yield. The self-cyclization was much more favourable over the the DHT reaction, which even took place at room temperature with 10 mol% of Lewis acid. A similar reaction was published for this dihyropyran synthesis.[44]



Scheme 52: Second proposed synthetic scheme to citreothiopyran A.

In order to prevent the compound **215** from self-cyclization, it was necessary to protect the hydroxyl group, however, as it was known that the elimination of hydroxyl group was also an essential step for the DHT formation. Thus, the compound **215** was converted to a tosylate **217**, and this offered two advantages, one was to block the self-cyclization, and another was to activate the elimination of the hydroxyl group. When the tosylate **217** was treated with thioacetamide and $Yb(OTf)_3$ under reflux in 1,4-dioxane, the desired natural product, citreothiopyran A **209**, was formed in 4% yield over three steps. The spectroscopic data (NMR, MS and IR) of citreothiopyran A obtained from the compound synthesized by our procedure do match to the spectroscopic data reported in the literature.[43]

Owing to the simplicity of the structure of citreothiopyran A, the assignment of 1 D NMR spectrum can show the structure of DHT **209** match to that of citreothiopyran A. The ^1H NMR of DHT **209** displayed a mutiplet at 3.56 ppm which was assigned as the H_6. Theoretically, the multiplicity of H_6 should give a doublet of doublet of quartet, however the signal was not clearly resolved in this case. The doublet of doublet at 2.78 ppm (J = 15.9, 3.4 Hz) was assigned to H_5 pointing to the pseudo-equatorial position, and another doublet of doublet at 2.58 ppm (J = 15.9, 11.9 Hz) was assigned to H_5 pointing to the pseudo-axial position. These two doublet of doublets are one of the characteristic peaks of a DHT ring. The DHT ring adopts a half-chair conformation with the methyl substituent at C6 pointing to the pseudo-equatorial position, and the proton pointing to the pseudo-axial position (**Figure 6**). Therefore, the two ^1H NMR signals for H_5 displayed very different coupling constant with H_6 due to the dihedral angel difference. The two singlets with integration of three at 2.36 and 2.16 ppm were assigned to the methyl group protons at C10 and C8 repectively. The remaining doublet at 1.39 ppm with integration of three was assigned to the methyl group proton at C7, which coupled to the H_6 with a coupling constant of 7.0 Hz.



209a **209b**

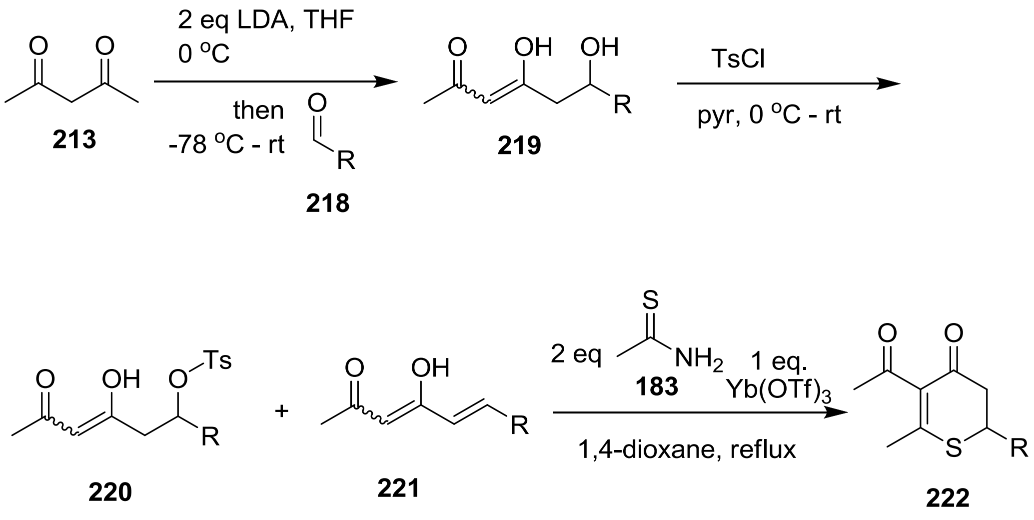
Figure 6: Half-chair conformation of racemic citreothiopyrane A.

Also, the IR spectrum as an indication of functional groups displayed absorption bands at 1668, 1629, 1527, 1400 cm^{-1}, these showed the presence of two different carbonyl groups and carbon – carbon double bond in the compound.

Lastly, the mass spectrum (ESI) showed the molecular weight of the compound matched to that of citreothiopyran A.

2.5. Synthesis of citreothiopyrane A analogs

As the citreothiopyrane A **209** was successfully constructed with the newly developed methodology, it was decided to examme the scope of this reaction (**Scheme 53**). A modification of the substituents in the C6 position of citreothiopyrane A was achieved by using different aldehydes **218** to form the aldol products with different substituents **219**, which was converted to the corresponding tosylate **220a** with *p*-tolenesulfonyl chloride (TsCl), and then the tosylate was reacted with thioacetamide **183** and catalysted by $Yb(OTf)_3$ to give the citreothiopyran A analogs **222**.



Scheme 53: Synthesis of citreothiopyran A analogs.

Table 16: Synthesis of citreothiopyran A analogs.

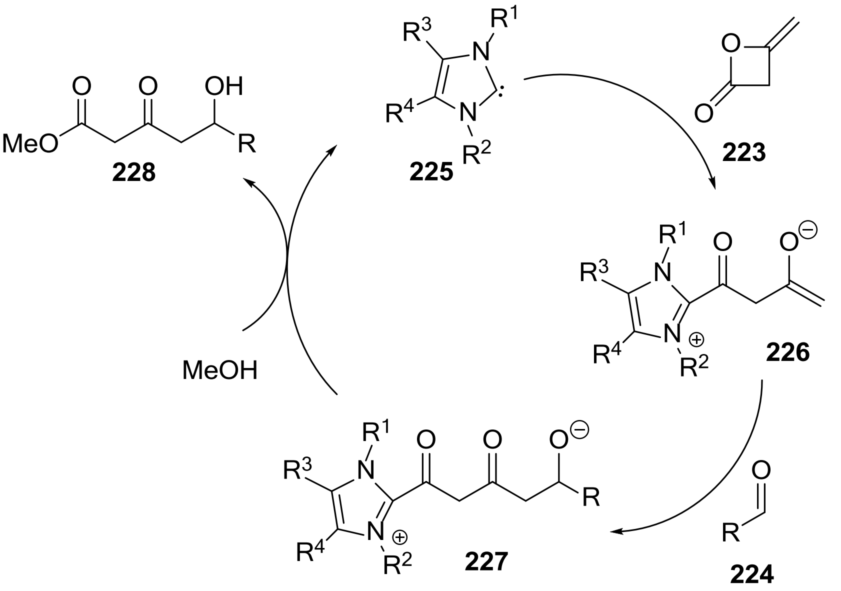
Entry	R	%Yield of 219	220 : 221[b]	%Yield of 222[a]
a	Pr	59	1.3 : 1	19
b	^{i}Pr	42.3	2.0 : 1	15
c	Ph	38.2	0 : 1	4
d	Cy	34	1.75 : 1	10
e	2-furyl	57	0 : 1	5
f	CH_2OBn	37	1 : 0	15

a: yield obtained over 2 steps from **7.43**.
b: Ratio of **7.44** and **7.45** was determined by ^1H NMR spectrum of crude reaction.

During the study, the compound **219** with different substituents (R) were synthesed by the typical dianionic aldol reaction and formed in 34% to 59% yield (**Table 16**), which was not optimized. When the compounds **219** were treated with TsCl, besides the expected tosylates **220**, the dehydrated compounds **221** were also obtained, and the aldol products with a phenyl and 2-furyl substituents, **219c** and **219e** gave the dehydrated compound as the only product. This could be explained by the formation of more favourable conjugated unsaturated system. The yield of the citreothiopyran A analogs ranged from about 4% to 19% over 2 steps (**Table 16**). This result was found comparable to those DHT compound with an ester group. The yield of reaction was especially lower for the compounds with an aromatic substituent, 4% and 5% for **222c** and **222e** respectively (**Table 16**, **Entry c and e**). The low yield of these reactions may be due to the less favourable attack of the nucleophilic sulphur atom to the less electrophilic conjugated unsaturated double bond.

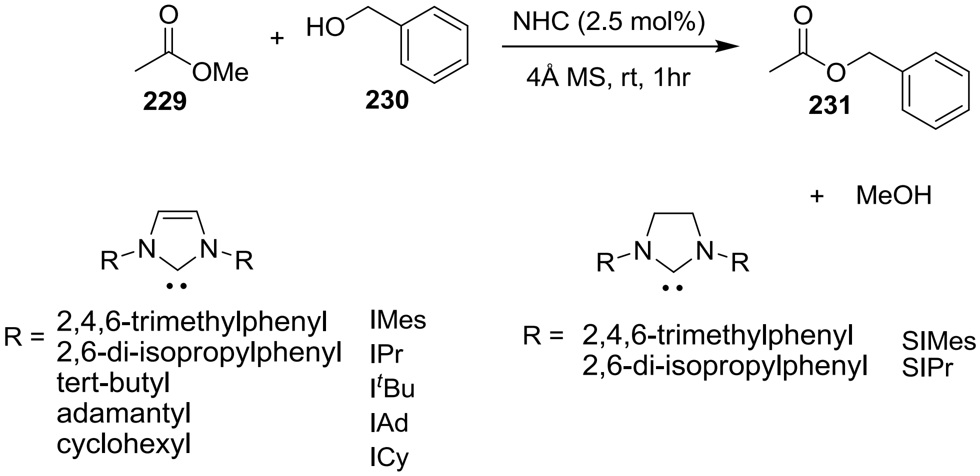
2.6. Investigation of using *N*-heterocyclic carbene as an organic catalyst for the diketene addition reaction

The diketene addition reaction with various aldehydes catalyzed by $TiCl_4$ has proved to be an effective methodology for the synthesis of δ-hydroxy-β-ketoester and THP (**Scheme 35**).[40] However, this methodology involved the using of one equivalent of $TiCl_4$ in order to achieve a completed reaction. In an attempt to replace the Ti Lewis acid and promote the diketene addition reaction, a well-known nucleophilic organocatalyst, *N*-heterocyclic carbene (NHC) **225**,[45, 46] was chosen to be a potential catalyst for the diketene addition reaction. In our proposed catalytic cycle (**Scheme 54**), the NHC **225** may attack the diketene **223** to give an NHC – enolate adduct **226** which in turn may attack an aldehyde **224** to form the δ-hydroxy-β-ketoester **228** after quenching with methanol.



Scheme 54: Proposed diketene addition reaction initiated by NHC.

In essence, the NHC catalyzed diketene addition reaction may follow a transesterfication mechanism to generate the δ-hydroxy-β-ketoester, and indeed, NHC was adopted as nucleophilic organocatalyst in transesterfication reactions (**Scheme 55**).[47] The transesterfication reactions between methyl acetate **229** and benzyl alcohol **230** were catalized by NHC catalysts giving the new ester **231** and methanol in moderate to excellent yield dependent on the type of NHC used.

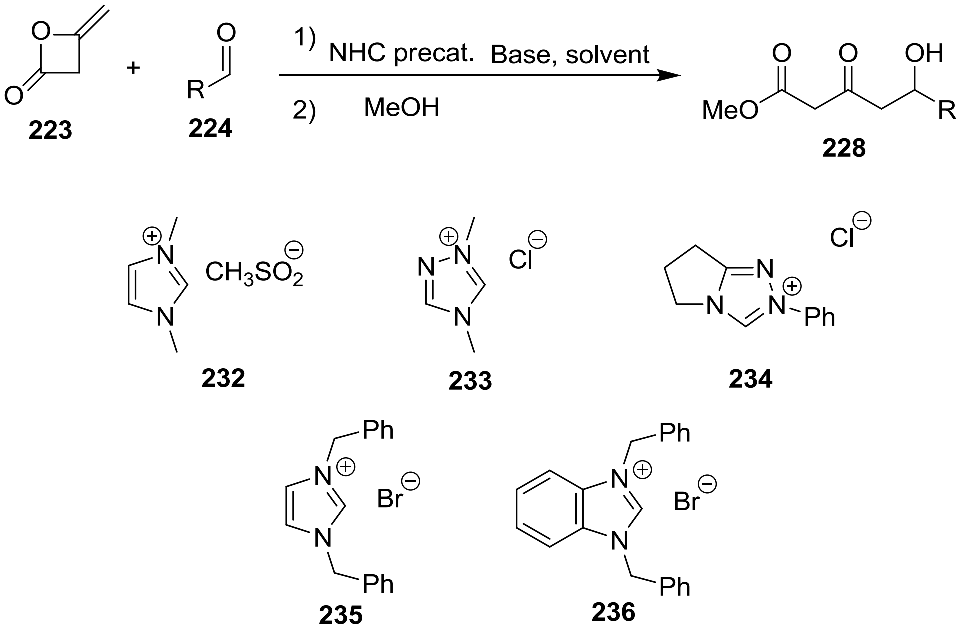


Scheme 55: Transesterfication reaction catalyzed by NHC.

Table 17: Transesterfication reaction catalyzed by NHC.

Entry	Catalyst	Yield (%)
a	Imes	93
b	IPr	45
c	Icy	100
d	Iad	100
e	$I^{t}Bu$	100
f	SIMes	21
g	SIPr	21

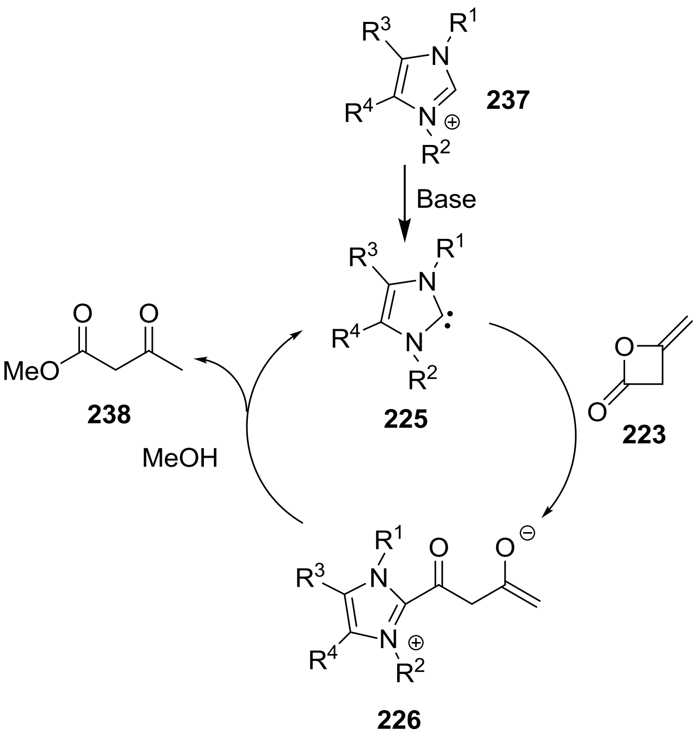
Theoretically, in our reaction (**Scheme 56**), one equivalent of diketene **223** and aldehyde **224** were added to NHC which was generated *in situ* between the imidazolium or triazolium salt **232** – **236** and base, and then freshly distilled methanol was added to quench the reaction after the consumption of aldehyde. The diketene disappeared after adding it to NHC, however, there was no reaction with the aldehyde which remained according to TLC analysis, and no reaction intermediate could be isolated.



Scheme 56: NHC diketene addition reaction.

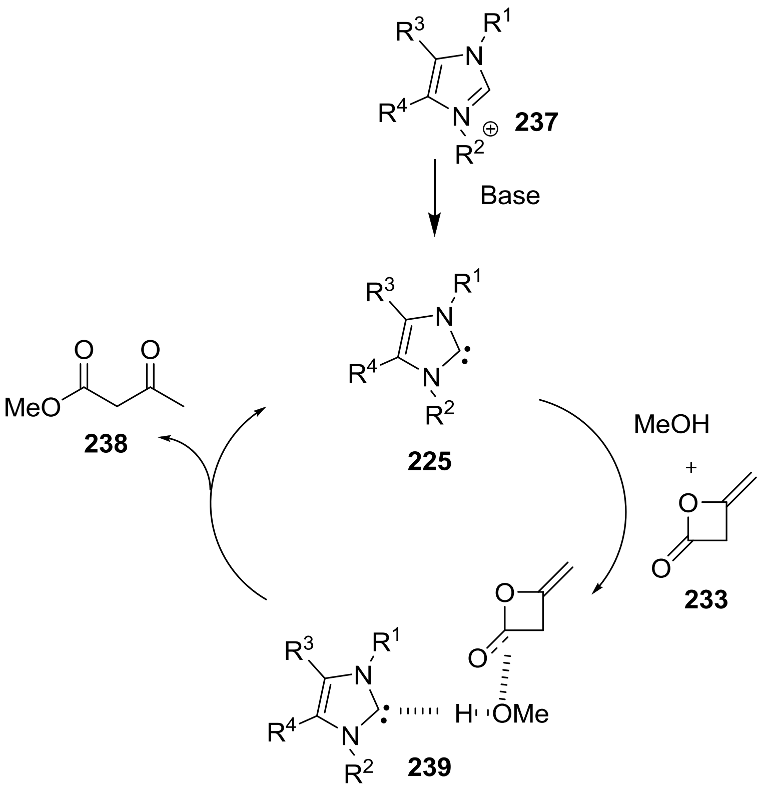
Different aldehydes (isobutraldehyde and benzaldehyde), bases (NaH, NaHMDS, KtOBu, NaOAc and ^{n}BuLi), solvents (THF, acetonitrile, DCM and toluene) and temperatures (-78 ^{o}C to reflux in THF) were tested, but no δ-hydroxy-β-ketoester was formed. It was known that the NHC may trigger a polymerization reaction, and it could potentially react with the diketene and form polymeric compound,[48] but such a polymer was not detected in the mass spectrum. Next, adding all of the reactants together were investigated, however, the only product identified was methyl acetoacetonate **238**. The formation of methyl acetoacetonate **238** from the diketene and methanol can be explained by a transesterfication reaction, and there were two possible mechanisms.[48]

The first possible transesterfication mechanism is the typical nucleophilic attack of the NHC on ester and replaced by an incoming alcohol. In our case, the ester was replaced by a diketene. So, the NHC **225** may attack the diketene **223** in the reaction (**Scheme 57**), this would give a NHC-enolate adduct **226**, and the NHC **225** was replaced by a methanol to give the methyl acetoacetonate **238**. However, this mechanism may not be able to apply to our reaction, because, the methyl acetoacetonate **238** was only formed when the methanol was added shortly after addition of diketene. When the methanol was added to the reaction about one hour after adding the diketene and aldehyde, no methyl acetoacetonate **238** was found. Also, there was no envidence of NHC-enolate adduct **226** formation. It was thought to investigate this by React IR experiment but the highly basic reaction medium may damage the React IR probe.



Scheme 57: Proposed nucleophilic mechanism of methyl acetoacetonate formation.

Another possible transesterfication mechanism is the activation of methanol by the NHC (**Scheme 58**). The NHC **225** may interact with the methanol and made it a better nucleophile to attack the diketene **233** and generated the methyl acetoacetonate **238**. This mechanism was proposed by Movassaghi's group in their study of NHC carbene catalyzed amidation of unactivated esters with amino alcohols, and it was supported by the first X-ray structure of a hydrogen-bonded carbene – alcohol complexes.[49] This mechanism explains the observation of the reaction for the methyl acetoacetonate formation.



Scheme 58: Proposed alcohol-activated mechanism of methyl acetoacetonate formation.

As the NHC cannot promote the diketene addition reaction as anticipated, one possible reason could be the lack of reactivity of the aldehyde, because the aldehyde was also activated by the Lewis acid catalyst in the Lewis acid catalyzed aldol reaction. Thus, we tried to adopt a NHC – Brønsted acid and NHC – Lewis acid cooperative catalytic reaction condition.[50, 51]

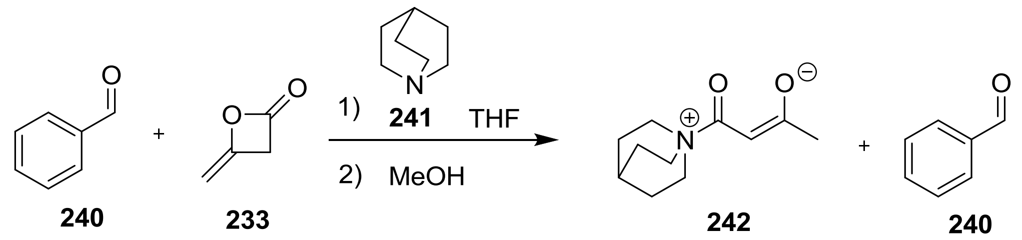
In the NHC – Brønsted acid cooperative catalytic reaction,[50] a weak base (sodium acetate) was adopted to generate the NHC from the precatalyst **233**. The hypothesis is that, a Brønsted acid base equilibrium could be achieved between the weak acid and NHC precatalyst, the conjugated base of the NHC precatalyst may attack the diketene and the acetic acid could activate the aldehyde to allow the reaction to occur. Unfortunately, this did not work in this case, and the result was the same with other bases.

In the NHC – Lewis acid cooperative catalytic reaction,[51] it was proposed that weak Lewis acids, such as early metal with alkoxide ligands ($Ti(O^iPr)_4$) can promote some reactions which could not be promoted by NHC along, as the Lewis acid can activate the starting material. It was proved that the $Ti(O^iPr)_4$ can initiate the diketene addition reaction, but the reaction take three days to have an acceptable conversion.[40] However, in our reaction the result was more or less the same with the reaction without $Ti(O^iPr)_4$, and not δ-hydroxy-β-ketoester was observed.

Ideally, it was managed to use the NHC to replace Ti Lewis acid in diketene addition reaction, and to induce an asymmetric synthesis of δ-hydroxy-β-ketoester by adopting a chiral NHC. However, the result of the reaction showed that no δ-hydroxy-β-ketoester was formed in the reaction.

2.7. Investigation of using tertiary amine to catalyze the diketene addition reaction

Along with the study of NHC-catalyzed diketene addition reaction, the tertiary amine was also studied, such as quinuclidine **241** as a nucleophilic catalyst (**Scheme 59**). In theory, the quinuclidine **241** is a good nucelophile but not so hindered because the substituents are bound in the heterocyclic system.



Scheme 59: Diketene addition reaction initiated by quinuclidine

However, the result was similar to that of NHC reactions, no δ-hydroxy-β-ketoester was obtained. According to TLC analysis, the diketene **233** vanished after addition of quinuclidine **241**, but the aldehyde **240** did not reduce. In order to analyze the reason, a reaction was done in an NMR tube, in which the quinuclidine **241** was added to diketene **233** in $CDCl_3$, and a NMR experiment was run. In the ^{1}H NMR spectrum, all of diketene **233** was consumed and a quinuclidine-opened diketene adduct **242** (**Figure 7**) was identified. Then one equivalent of freshly distilled methanol was added to the NMR tuble reaction, and a NMR experiment was run with the same sample. The ^{1}H NMR spectrum of this sample was more or less the same as the previous one, but the presence of a methanol signal (**Figure 8**). It was surprising that the methanol did not replace the quinuclidine.

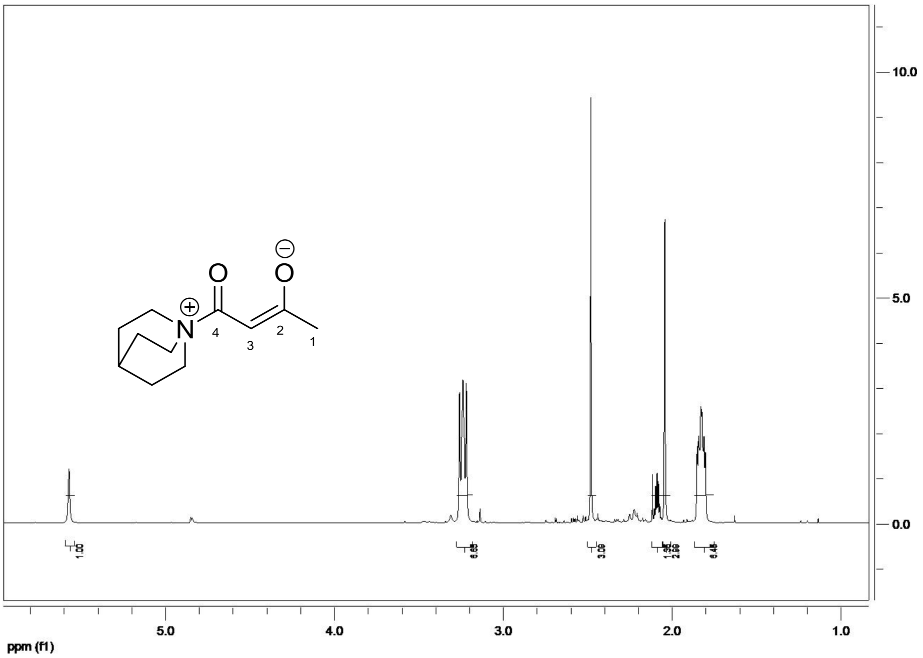


Figure 7: ^{1}H NMR ($CDCl_3$) spectrum of the reaction of diketene addition initiated by quinuclidine without MeOH.

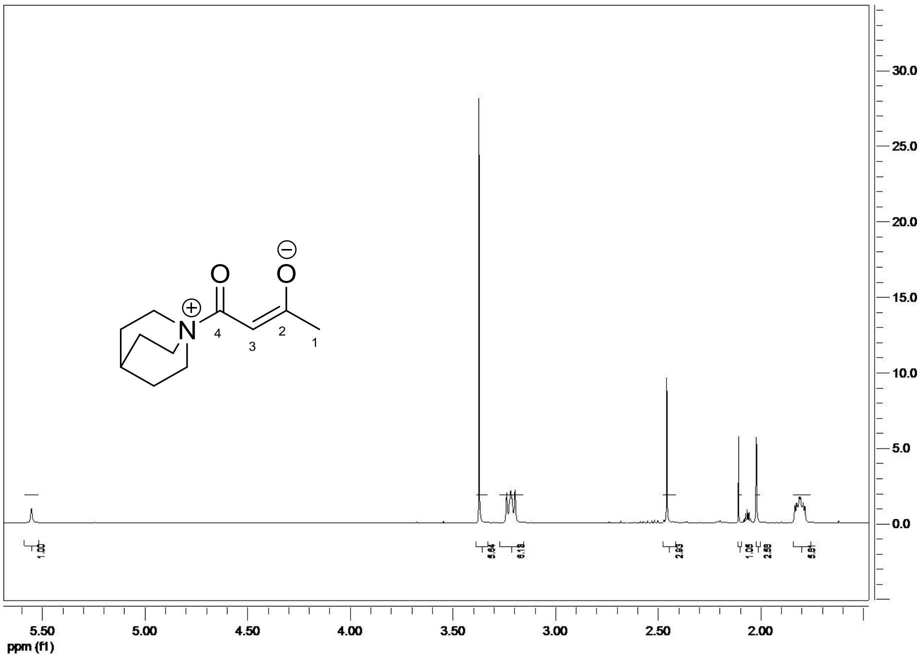
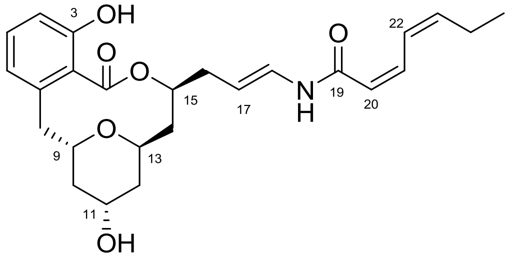


Figure 8: ^{1}H NMR ($CDCl_3$) spectrum of the reaction of diketene addition reaction initiated by quinuclidine with MeOH.

These ^{1}H NMR experiments showed that there may be a quinuclidine – diketene adduct formed in the reaction, but the expected aldol reaction with an aldehyde did not occurr. This could be due to the lack of activity of aldehyde or the adduct was too stable.

2.8. Investigation toward the synthesis of THP fragment (C1 – C15) of (-)-apicularen A

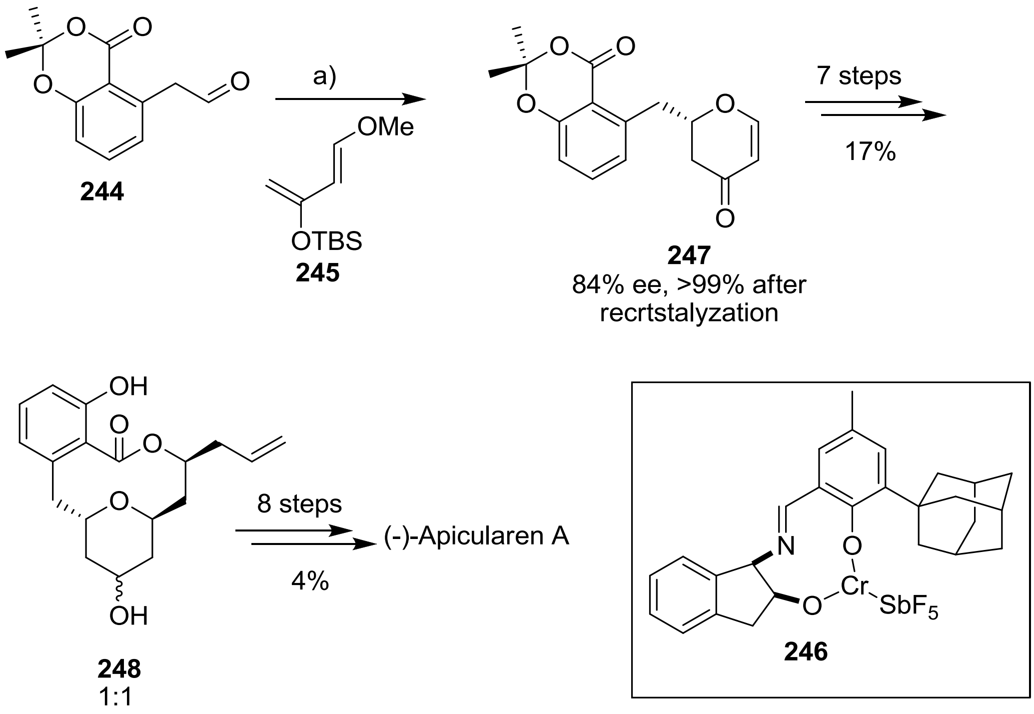
(-)-Apicularen A has demostrated potent anticancer properties to many cancer cell lines (**Section 1.1, page 2**).[3] The main C1 – C15 fragment of apicularen A **243** is a 12 menbered macrolactone consisting of a 2,6-*trans*-disubstituted THP unit. Besides these, there are two stereogenic centres at the C11 and C15 positions. As the fascinating molecular architecture and potent biological activity of this natural product, it is one of the synthetic targets to organic chemists.



(-)-Apicularen A
243

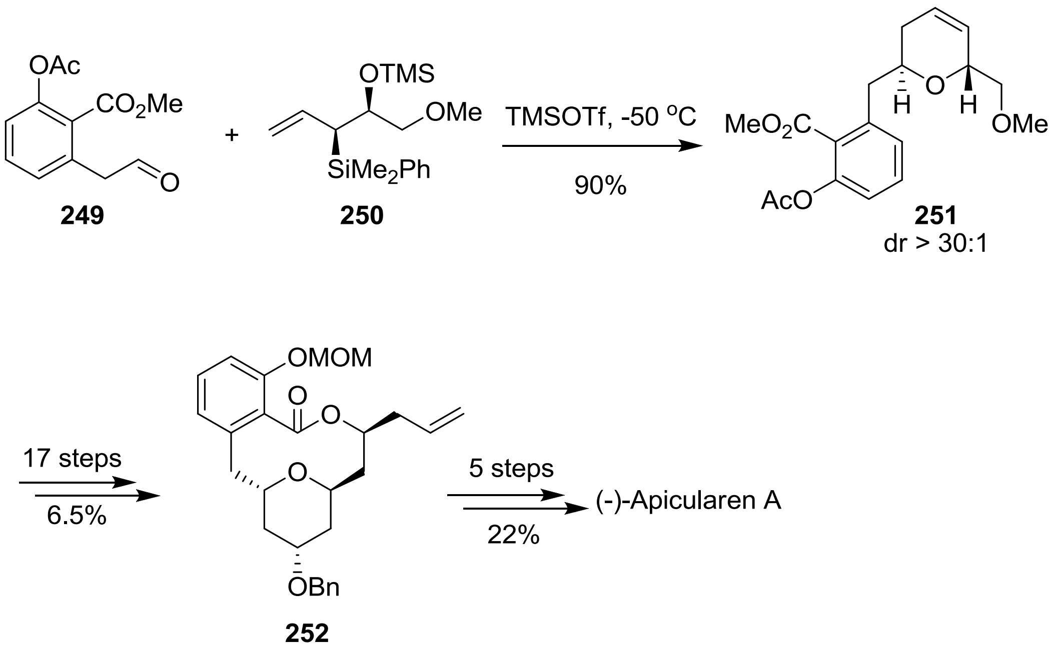
Figure 9: Structure of (-)-apicularen A.

A number of strategies toward (-)-apicularen A have been published. The first total synthesis was achieved by De Brabander *et. al.* (**Scheme 60**).[52] The pyran unit **247** was constructed *via* HDA reaction between the aldehyde **244** and diene **245** in 60% yield and 99% ee after recrystalization. The macrolactone **248** was formed in 17% yield after 7 steps as a mixture of epimers (1:1). The installation of the allyl substituent completed the natural product in 4% yield over 8 steps.



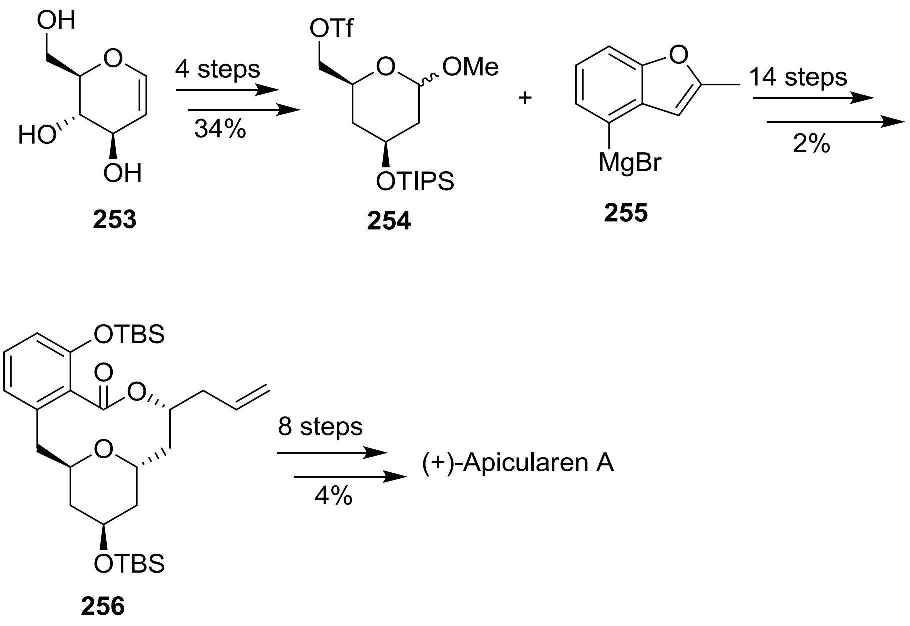
Scheme 60: *Reagents and conditions:* a) cat. **246**, 4Å MS, acetone, rt, 24 hr, then CF_3CO_2H, DCM, 0 ^{o}C, 1 hr, 60%.

Panek and co-workers reported anther total synthesis of (-)-apicularen A *via* a highly diastereo- and enantioselective [4+2] annulation of the functionalized pyran core **251** from aldehyde **249** and silane **250** (90% yield, *dr* > 30:1).[53] The pyran core **251** was converted to the macrolactone **252** in 6.5% yield after 17 steps, and the alkyl chain was installed in 22% yield by **252** after 5 steps (**Scheme 61**).



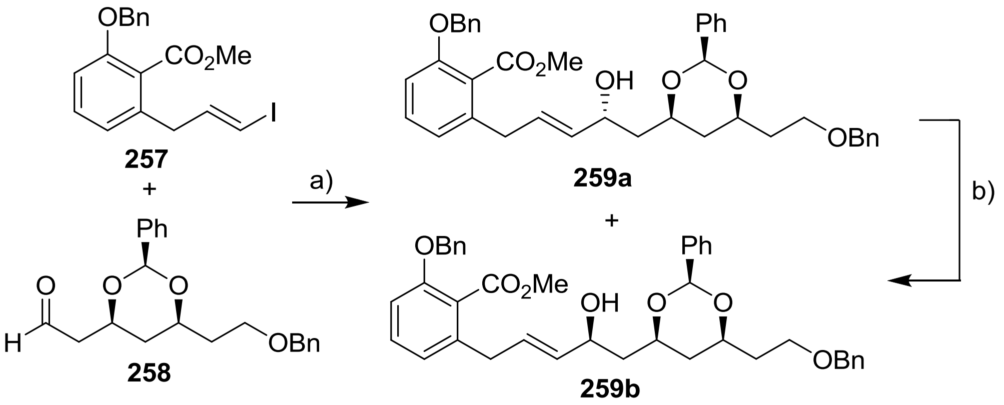
Scheme 61: [4 + 2] annulations for the assembly of THP core **252**.

Taylor and co-workers also demonstrated a total synthesis of (+)-apicularen A by utilizing a commercially available starting material called D-glucal **253** (**Scheme 62**).[54] The D-glucal **253** was converted to the THP core **254** in 34% yield over 4 steps, and the macrolactone **256** was fabricated from the THP core **254** with a Grignard reagent **255** in 2% yield over 14 steps. Side chain elaboration (8% yield over 8 steps) then completed the synthesis of (+)-apicularen A.



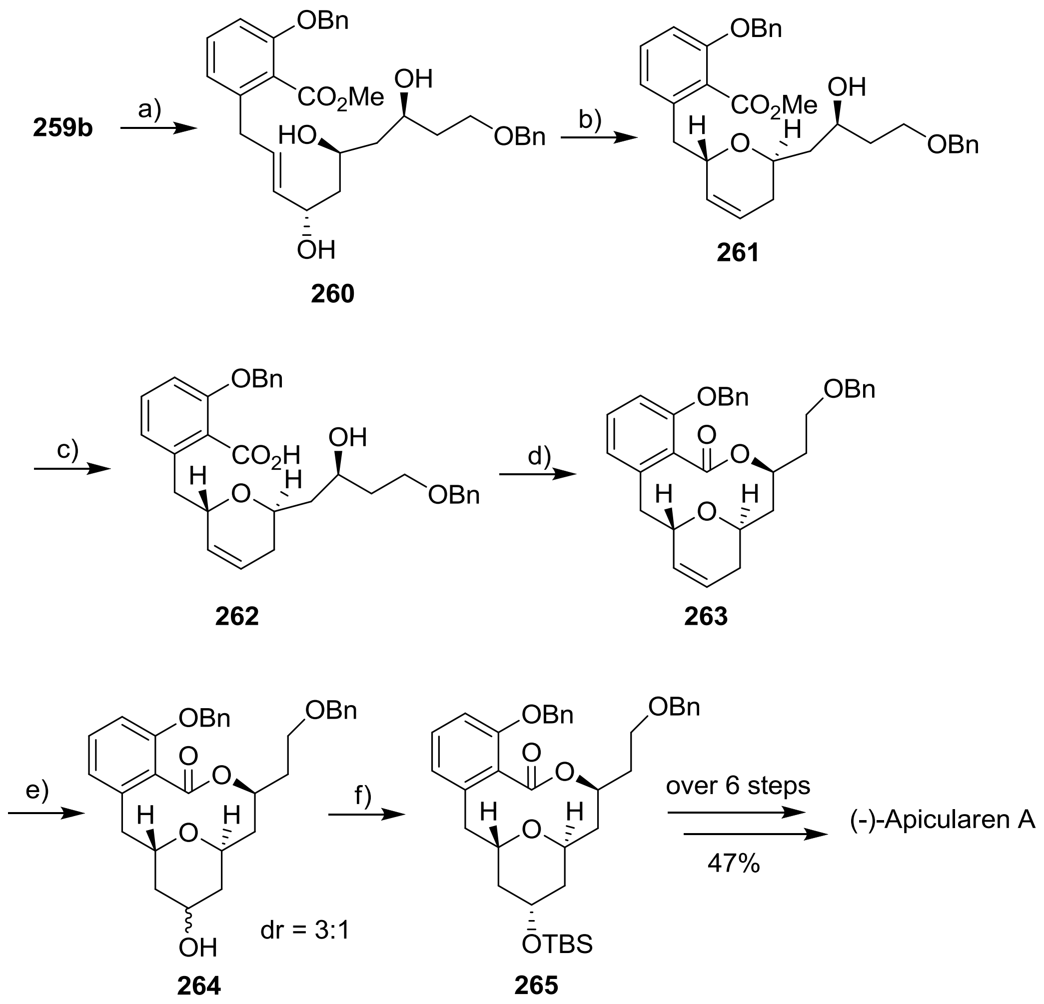
Scheme 62: Synthesis of (+)-apicularen A from D-glucal.

Uenishi and co-workers reported a total synthesis of (-)-apicularen A with a more convergent synthetic pathway to achieve the C1 – C15 fragment of (-)-apicularen A including all of required stereogenic centres.[55] The C1 – C15 fragment was prepared in 7 steps from an iodoalkene **257** and an aldehyde **258**. The fragments **257** and **258** were assembled by Nozaki-Hiyama-Kishi (NHK) coupling[56] to give a mixture of diastereomeric allylic alcohols **259a** and **259b** in 32 and 43% yield repectively. The allylic alcohol **259a** was converted to the desired allylic alcohol **259b** *via* Dess-Martin oxidation[57] and diastereofacially selective reduction of the resulting ketone using (*R*)-CBS reagent[58] in 72% yield over two steps (**Scheme 63**).



Scheme 63: *Reagents and conditions:* a) 0.1% $NiCl_2$ in $CrCl_2$, DMSO, 75% (dr = 1:1.3), b) DMP, 90%, c) (*R*)-CBS, BH_3, THF, rt to -40 ^{o}C, 88% (*dr* = 10:1).

Then the deprotection of benzylidene group of **259b** in a mild acidic medium gave the triol **260** in 77% yield, and this was then submitted to Pd(II)-catalyzed cyclization to yield the 2,6-*trans*-dihydropyran **261** in 72% yield as a single diastereomer. The ester group of **261** was hydrolyzed with LiOH to give acid **262** in 95% yield, which in turn underwent a Yamaguchi macrolactonization[59] to form the macrolactone **263** in 80% yield. The hydroxyl group at C11 position was installed from the α-face of the dihydropyran **263** by an oxymercuration and successive reductive demercuration. The α-hydroxyl product **264** was formed as a mixture with the β-hydroxyl isomer in a 3:1 ratio. Isolation of the desired diastereomer was achieved after silylation with TBSOTf in 69% yield of **265**. At the end, the (-)-apicularen A was synthesized from the C1 – C15 fragment in 47% yield over six steps (**Scheme 64**).



Scheme 64: *Reagents and conditions:* a) 70% AcOH, 60 °C, 77%, b) 20 mol% $PdCl_2(CH_3CN)_2$, THF, rt, 72%, c) LiOH, dioxane/H_2O, 80 °C, 95%, d) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, DMAP, THF/Toluene, 80%, e) $Hg(OCOCF_3)_2$, THF/H_2O, then NaOH(aq), $NaBH_4$, 80%, *dr* = 3:1, f) TBSOTf, 2,6-lutidine, 69%.

The advantage of Uenishi's total synthesis of (-)-apicularen A was to inherit most of the required stereogenic centres from the aldehyde **258**, and the formation of chiral centre at C9 position was easily achieved due to the existing chiral centre at C13 position. Therefore, a new strategy for the synthesis of (-)-apicularen A with a more convergent and efficient way to generate the stereogenic centres is presented.

In a proposed retrosyntetic plan of (-)-apicularen A (**Figure 10**), the natural product **243** could be formed by a Wittig reaction[60] from the side chain **266** and macrolactone **267**. The macrolactone **267**, in turns, could be generated from the *trans*-2,6-disubstituted THP unit **268** by esterification. Then the key step of the natural product synthesis was to achieve the THP core **268** by the asymmetric Maitland-Japp reaction[39] with the Chan's diene **269** as a nucleophile and the required aldehydes **270** and (*S*)-**271**.

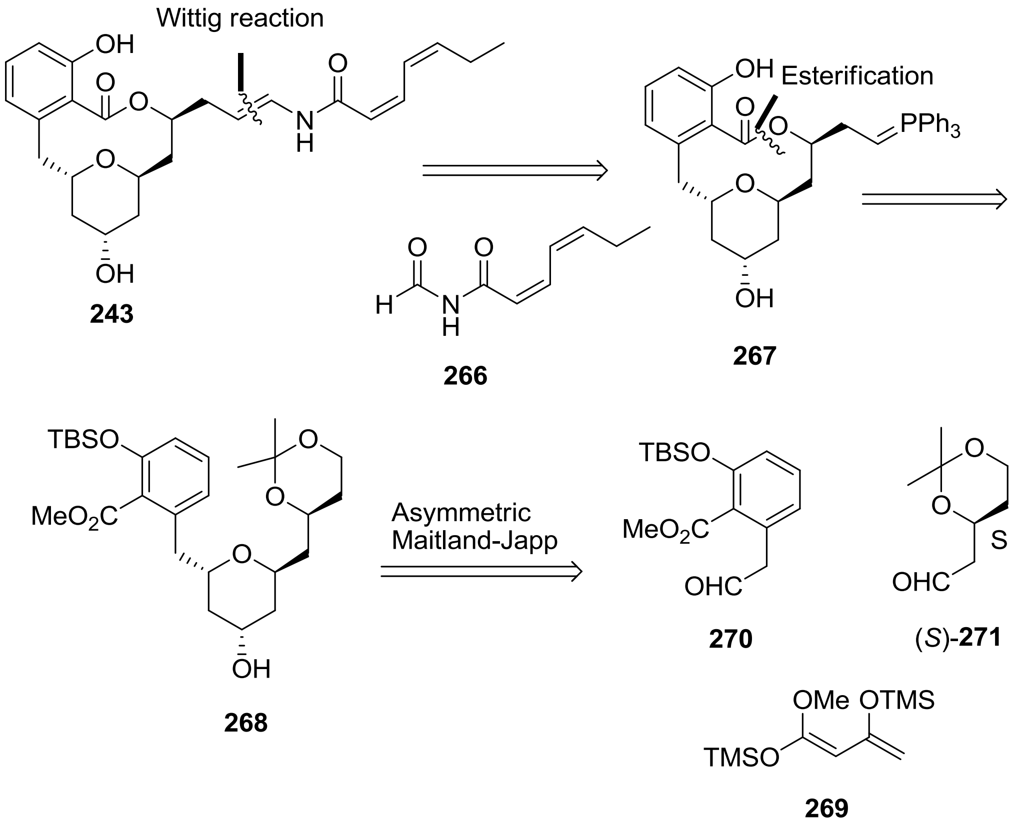
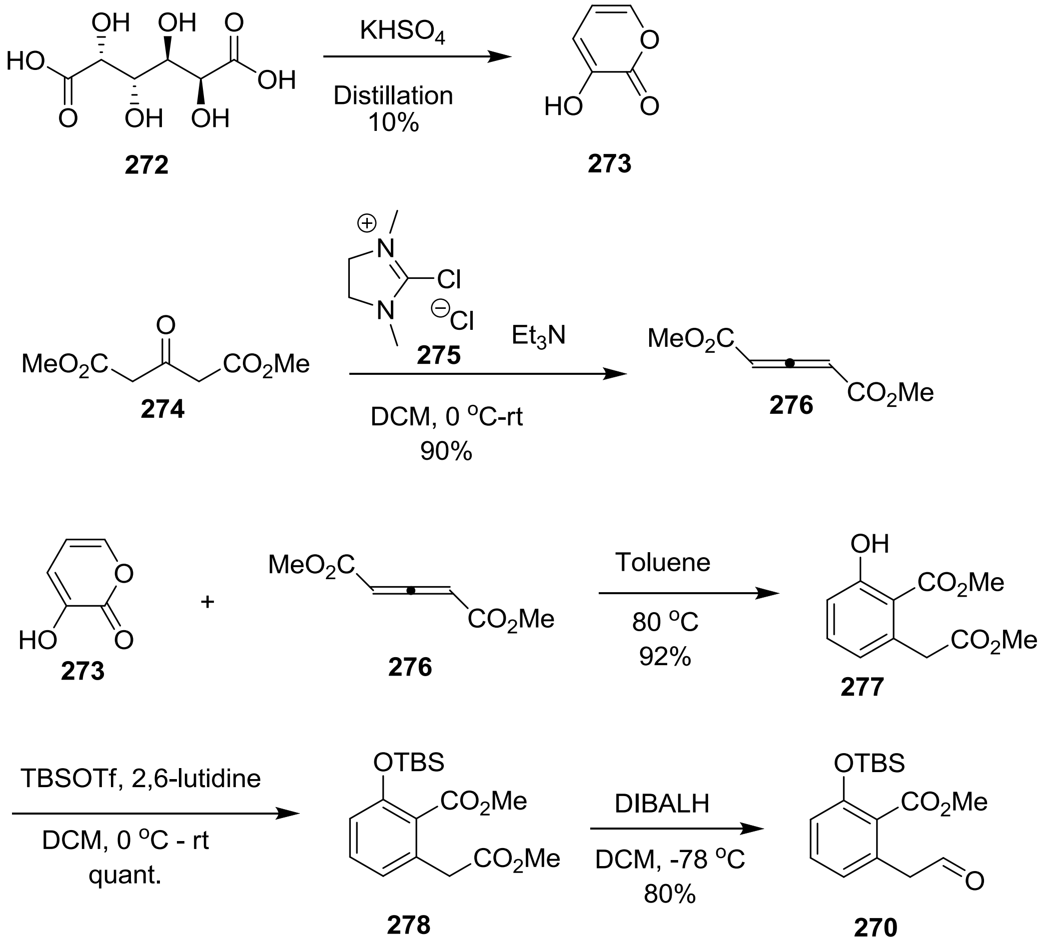


Figure 10: Retroanalysis of (-)-apicularen A.

Although the development of δ-hydroxy-β-ketoester formation *via* NHC triggered diketene addition failed, therefore the existing asymmetric Maitland-Japp reaction[39] was applied to the synthesis of THP containing natural product. Our target was to synthesize the 2,6-*trans*-disubstituted THP unit **268** *via* asymmetric Maitland-Japp reaction.

Before the Maitland-Japp reaction was tested, two aldehydes **270** and (*S*)-**271** needed to be synthesized. The aldehyde **270** was synthesized according to the literature procedure (**Scheme 65**).[61]

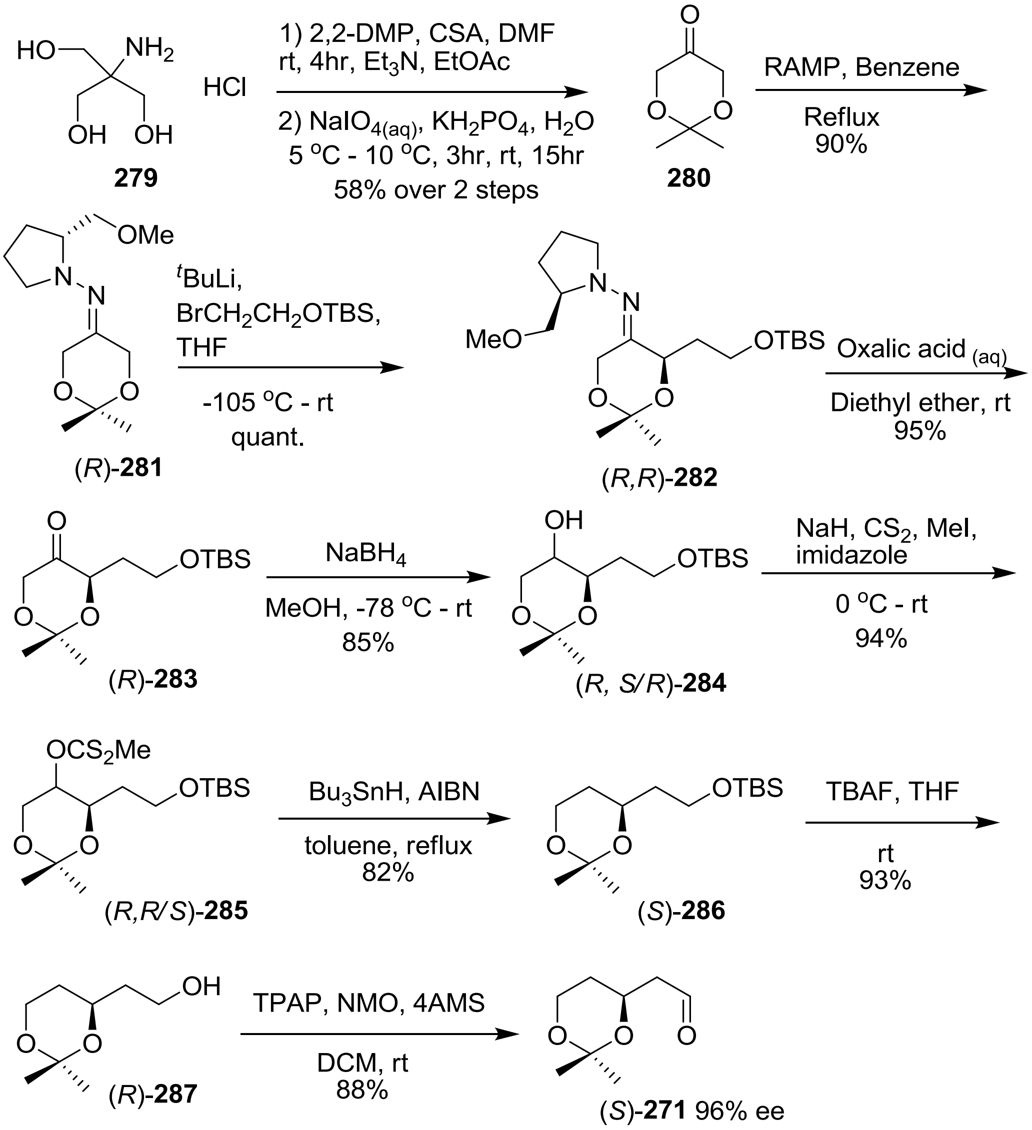


Scheme 65: Synthesis of aldehyde **270**.

The greatest challenge faced by aldehyde **270** formation was the synthesis of 3-hydroxy-2-pyrone **273**. The 3-hydroxy-2-pyrone **273** was formed *via* distillation of a mixture of mucic acid **272** and $KHSO_4$ in only about 10% yield similar to the literature[61b] reported by Wiley and co-workers. As the reagents were mixed in solid state, it was difficult to ensure that all of the mucic acid molecules were surrounded by the $KHSO_4$ or vice versa, so the yield of the reaction was low. The allene **276** was formed from dimethyl 1,3-acetonedicarboxylate **274** in the presence of triethyl amine and 2-chloro-1,3-dimethylimidazolium chloride **275** in 90% yield. Then, a Diels-Alder reaction between 3-hydroxy-2-pyrone **273** and allene **276** was carried out to give the diester **278** in 92% yield. In the literature,[61a] the diester **277** underwent a reduction without the TBS protecting group. However, a silyl ether protected aldehyde would be more suitable for our synthesis. Thus, the TBS group diester **278** was prepared by treating the diester **277** with TBSOTf and 2,6-lutidine before the reduction by DIBALH to give the desired aldehyde **270** in 80% yield.

The aldehyde (*S*)-**271** was synthesized according to literature procedure in 25% yield (**Scheme 7.26**).[62] Firstly, the 1,3-dioxanone **280** was synthesized from the triol **279** with 2,2-dimethyl propane and $NaIO_4$ oxidative cleavage in 58% yield over 2 steps. Then, the RAMP, acted as a chiral auxiliary, was installed to the 1,3-dioxanone **280** by imine formation in 90% yield. The chiral centre in (*S*)-**271** was preliminary created in compound **282** *via* stereoselective alkylation with the RAMP-hydrazone (*R*)-**281** giving the alkylated product (*R*,*R*)-**282** in quantitative yield. The RAMP was easily removed by stirring in saturated aqueous oxalic acid solution (95% yield), and the resulting(*R*)-**283** was reduced by $NaBH_4$ to a mixture of diastereomeric alcohol (*R*,*S/R*)-**284** in 85% yield. The alcohol (*R*,*S/R*)-

284 was treated with NaH, CS_2 and MeI to form the (*R,S/R*)-**285** (94% yield), and then underwent a Bu_3SnH reduction to give the TBS protected alcohol (*S*)-**286** in 82% yield. Then the TBS group was removed with TBAF and the resulting alcohol (*S*)-**287** (93% yield) carried out a TPAP oxidation to give the aldehyde (*S*)-**271** in 88% yield.

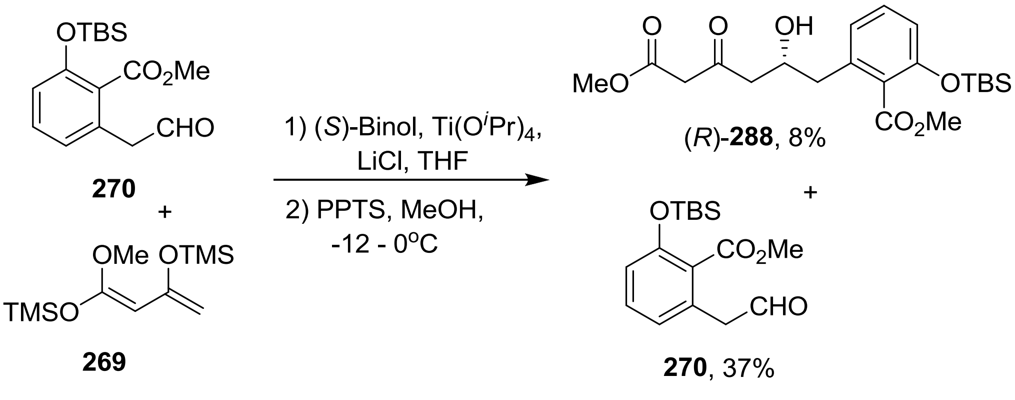


Scheme 66: Synthesis toward (*S*)-**271**.

The enantiomeric excess of aldehyde (*S*)-**271** was not determined, before the Maitland-Japp reaction was successful. However, the optical analysis (**[α]$_D$**) of (*S*)-**271** measured by us was +13.6, this value was similar to that provided by literature[62a] (**[α]$_D$** = +11.9), so the aldehyde (*S*)-**271** should be formed with about 96% *ee*.

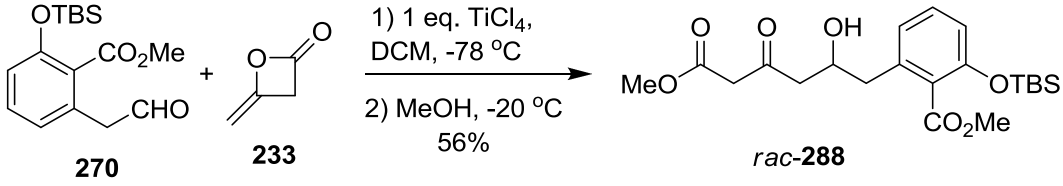
With the two required aldehydes **270** and (*S*)-**271**, the asymmetric aldol reaction toward the synthesis of enantiomerically enriched δ-hydroxy-β-ketoester was attempted.

When the aldehyde **270** was treated with two equivalent of Chan's diene **269** and (*S*)-Binol/Ti(^{i}OPr)$_4$ catalyst in THF with LiCl, the desired δ-hydroxy-β-ketoester (*R*)-**288** was formed successfully though the yield of the reaction was remarkably low, only 8% was isolated (**Scheme 67**). It was found that the aldehyde **270** was not comsumed completely in the reaction even adding more Chan's diene **269** and longer reaction time, there was about 37% of the aldehyde **270** was recovered. The incomplete consumption of aldehyde **270** may explain the low reaction yield.



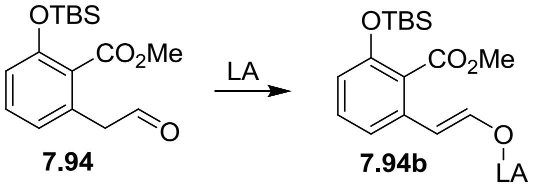
Scheme 67: Synthesis of δ-hydroxy-β-ketoester (*R*)-**288**.

However, it was found that the formation of δ-hydroxy-β-ketoester *rac*-**288** by $TiCl_4$-promoted diketene addition resulted in a much higher yield (56%) (**Scheme 68**).



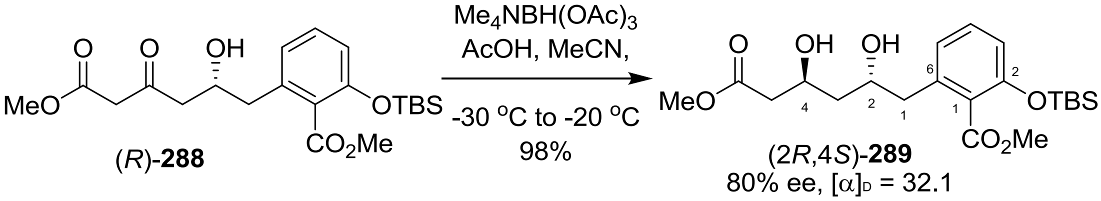
Scheme 68: Synthesis of δ-hydroxy-β-ketoester *rac*-**288**.

One of the possible reasons for the incomplete comsuption of aldehyde **270** may be because of enolization of aldehyde **270** in the presence of Lewis acid (**Scheme 69**) Besides the influence of Lewis acid, the enolized aldehyde **270b** could be stabilized due to the more conjugated double bond with the aromatic ring. Therefore the enolized aldehyde **270b** could no longer react with Chan's diene.



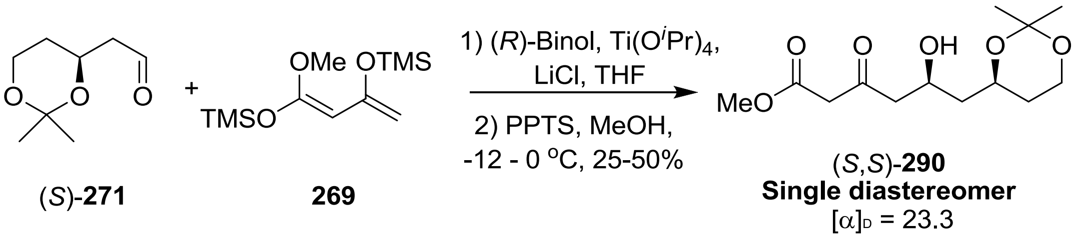
Scheme 69: Enolization of aldehyde **270**.

The measurement of enantiomeric excess from δ-hydroxy-β-ketoester (*R*)-**288** by either HPLC or chiral shift reagent was unsuccessful, thus the compound (*R*)-**288** was converted to the corresponding diol (2*R*,4*S*)-**289** *via* anti-reduction by tetramethylammonium triacetoxyborohydride in 98% yield (**Scheme 70**), in which the chiral information of (*R*)-**288** should not be eroded according to preliminary work.[40] HPLC showed the diol (2*R*,4*S*)-**289** obtained by anti-reduction resulted in 80% *ee*.



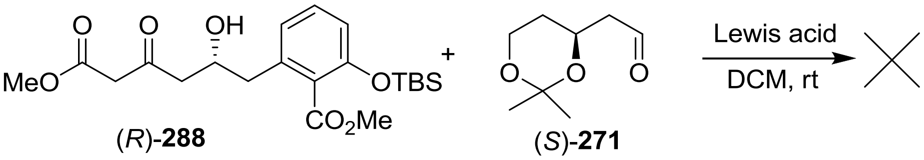
Scheme 70: Synthesis of diol (2*R*,4*S*)-**289**.

Before we submitted the second aldehyde (S)-**271** to the asymmetric aldol reaction, it was thought that the ketal protecting group of (*S*)-**271** may fall off in acidic medium. The asymmetric aldol reaction gave the desired δ-hydroxy-β-ketoester (*S,S*)-**290** in 25% to 50% yield, and only a single diastereomer was isolated by flash column chromatography (**Scheme 71**). The variable yield may be due to the deprotection of the ketal protecting group of the aldehyde or the product in the reaction. Also, it was found that the δ-hydroxy-β-ketoester (*S,S*)-**290** decomposed quickly in $CDCl_3$ during NMR experiment, therefore benzene d_6 was employed as the NMR solvent.



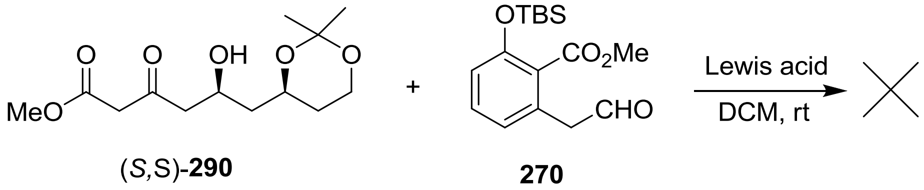
Scheme 71: Synthesis of δ-hydroxy-β-ketoester (*S*,*S*)-**290**.

Although the formation of the δ-hydroxy-β-ketoester (*R*)-**288** was not very efficient, still a series of Maitland-Japp reactions with different Lewis acids including $TiCl_4$, $Yb(OTf)_3$ and $Sc(OTf)_3$, were tested with this ester and the enentiomerically-enriched aldehyde (*S*)-**271** (**Scheme 72**). However, only disappointing results were achieved. Aldehyde (*S*)-**271** decomposed easily in the presence of Lewis acid, and no pyran product was identified.



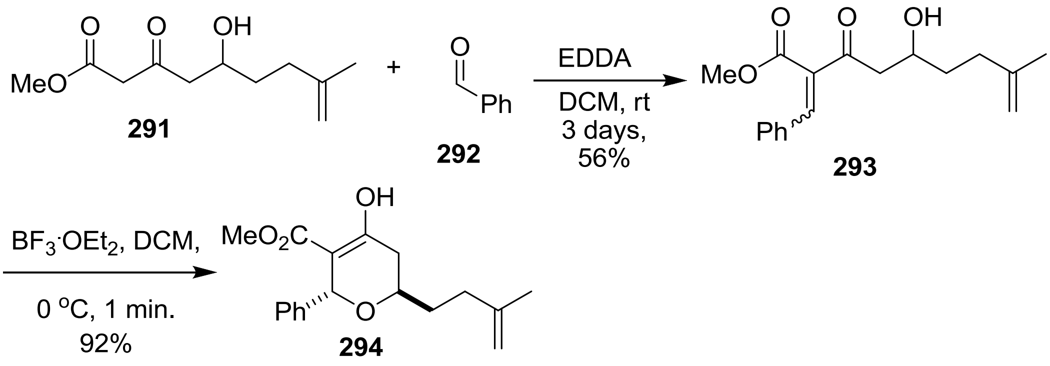
Scheme 72: Trial of Maitland-Japp reaction with (*R*)-**288** and (*S*)-**271**; Lewis acids tested include $TiCl_4$, $Yb(OTf)_3$ and $Sc(OTf)_3$.

Therefore, another combination of δ-hydroxy-β-ketoester (*S*,*S*)-**290** and aldehyde **270** was examed for the Maitland-Japp reaction (**Scheme 73**). Firstly, $TiCl_4$ was chosen as the Lewis acid to promote the reaction, but black precipitate was formed, which was a signal of δ-hydroxy-β-ketoester decomposition. So the Lewis acid was replaced by $Yb(OTf)_3$, and the reaction gave some undefined products providing complicated NMR spectra, in which no ketal methyl groups (two singlets at around 1.48 and 1.37 ppm) or any feature signals of THP was identified.



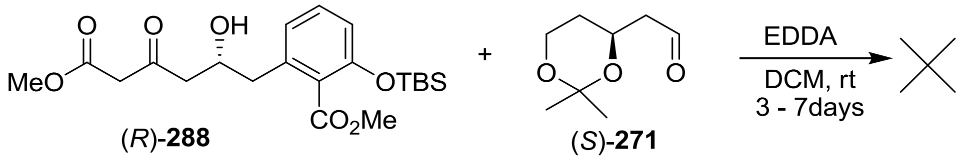
Scheme 73: Trial of Maitland-Japp reaction with (*S*,*S*)-**290** and **270**, Lewis acids tested include $TiCl_4$ and $Yb(OTf)_3$.

From the above experiments (**Schem 72** and **73**), the conclusion was obtained that both of the aldehyde (*S*)-**271** and δ-hydroxy-β-ketoester (*S*,*S*)-**290** were too unstable toward Lewis acid condition due to the vulnerable ketal protecting group. Therefore, it may be worth to test a less Lewis acidic reaction condition and short reaction time, such as 1 minute, to prevent the decomposition of ketal protecting group in the Maitland-Japp reaction. Before those metal Lewis acids ($TiCl_4$, $Yb(OTf)_3$ or $Sc(OTf)_3$) were adopted to catalyze the Maitland-Japp reaction, it was studied to form a Knoevenagel product **293** by treating δ-hydroxy-β-ketoester **291** and benzaldehyde **292** with ethylene diamine diacetate (EDDA) at room temperature, which in turn was treated with trifloroborane ($BF_3 \cdot OEt_2$), then quenched by water after one minute to deliver the THP **294** (**Scheme 74**).[33]



Scheme 74: Formation of THP *via* Knoevenagel product.

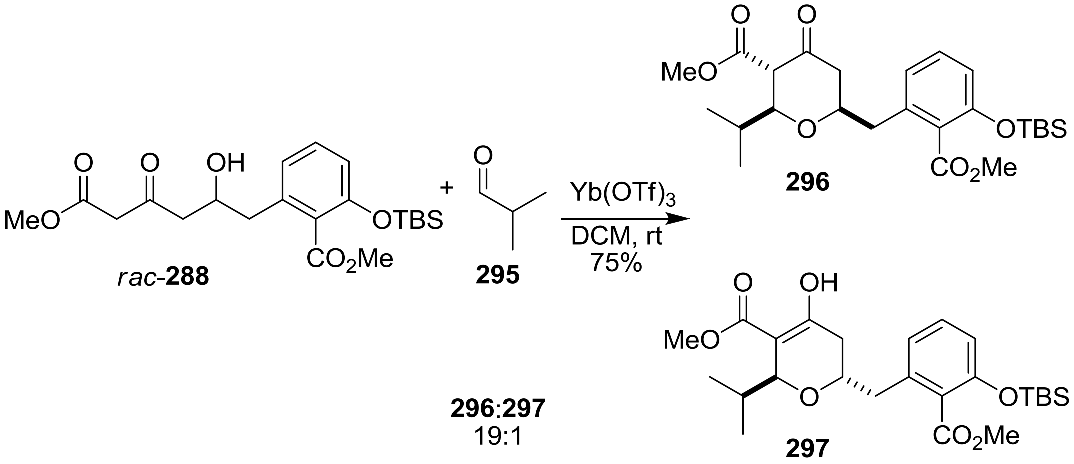
When 6 mol% of EDDA was added to the mixture of δ-hydroxy-β-ketoester (*R*)-**288** and aldehyde (*S*)-**271** in DCM, no new spot was found when the reaction was monitored by the TLC even after three days. Thus, the amount of EDDA was made up to one equivalent, still no sign of a new product formed in the reaction but decomposition of aldehyde (*S*)-**271** in one week. From the ^{1}H NMR of the crude reaction, no Knoevenagel product was identified.



Scheme 75: Reaction between (*R*)-**288** and (*S*)-**271** with EDDA.

As the unstable ketal protecting group of the aldehyde (*S*)-**271** and δ-hydroxy-β-ketoester (*S*,*S*)-**290** was thought to be the reason for the failure of the synthesis of the THP core **268** of apicularen A synthesis *via* the Lewis acid promoted Maitland-Japp reaction. It was decided to see if the lack of success related with

(*S*)-**271** by attempting a Maitland-Japp reaction between δ-hydroxy-β-ketoester (*R*)-**288** and isobutaraldehyde. When a mixture of isobutaraldehyde and δ-hydroxy-β-ketoester *rac*-**288** was treated with Yb(OTf)$_3$ in DCM (**Scheme 76)** giving the *cis*-keto isomer **296** and *trans*-enol isomer **297** in 75% yield and 19:1 ratio determined by the ^{1}H NMR spectrum of the crude reaction.



Scheme 76: Maitland-Japp reaction between (*R*)-**288** and isobutaraldehyde.

Thus, the success of the Maitland-Japp reaction (**Scheme 76**) proved that the aldehyde (*S*)-**271** and the ketal protecting group should be the problem-leading to the failure of the Maitland-Japp reaction (**Scheme 72, 73**).

2.9. Conclusion and future work

Preliminary work showed that the single diastereomeric *cis*-THP was synthesized by L-selectride reduction of a DHP. In order to demonstrate the DHP was also a promising precursor for the *trans*-THP formation, the DHP **179** was synthesized from δ-hydroxy-β-ketoester **177** and *N,N*-dimethyl formamide **178** in 43% yield. The *trans*-THP products enol-**180** and keto-**181** were generated by treating with Gilman reagent in 31% yield (**Scheme 40**).

Although the methodology investigation of DHP from δ-hydroxy-β-ketoester and thioamide was not successful (**Scheme 41**), the product acquired after the reaction was a DHT, therefore a new synthetic strategy for DHT formation was discovered.

From the screening of Lewis acids to promote the reaction, $TiCl_4$ and $Yb(OTf)_3$ were found to be able to encourage the DHT reaction (**Table 11, 12**). It was found that $Yb(OTf)_3$ was a more suitable Lewis acid over $TiCl_4$, because it gave cleaner reaction, so no side product contamination happened to the desired DHT. The reaction catalyzed by $Yb(OTf)_3$ tolerated a much higher reaction temperature than $TiCl_4$, thus a high boiling point solvent, 1,4-dioxane was adopted as the solvent to carry out the reaction under reflux. It was found that the yield of the reaction was not closely related to the type of the solvents, but the rate of the reaction was dependent on the reaction temperature.

With a high reaction temperature, such as 101 ^{o}C in refluxing 1,4-dioxane, the time required for complete conversion of starting material was shortened effectively to one hour instead of 16 hour at 35 ^{o}C in THF (**Table 12, Entry b, h**). It was believed that the high reaction temperature needed to promote the loss of hydroxyl group of the δ-hydroxy-β-ketoester to generate an enone, and then the sulfur atom underwent a conjugated addition on the enone to form the DHT.

This elimination and conjugated addition mechanism was supported by formation of DHT from an enone **196**, which was synthesized from the δ-hydroxy-β-ketoester **186** and Yb(OTf)$_3$, and thioacetamide in the presence of Yb(OTf)$_3$ (**Scheme 47**). The another possible intramolecular S$_N$2 mechanism was ruled out, because the DHT reaction with an enantiomercally-enrich δ-hydroxy-β-ketoester (*R*)-**194** resulted in a racemic mixture of DHT products with 0% *ee*, the loss of stereochemical information should be due to the loss of the hydroxyl group and thus destroyed the stereocentre (**Scheme 46**).

A thiopyran containing natural product called citreothiopyran A **209** was synthezied successfully *via* DHT reaction. Two synthetic pathways were proposed, one was to convert the ester group of the DHT **211** obtained from δ-hydroxy-β-ketoester **210** and thioacetamide to the ketone group, but this did not work (**Scheme 51**). Another pathway was to start with 4,6-dihydroxyhept-3-en-2-one **215** formed by dianionic aldol reaction, as a starting material which already possessed a ketone group, but self-cyclization of this compound occurred. Whereas, the problem was solved by converting the 4,6-dihydroxyhept-3-en-2-one to a tosylate with TsCl, and then treating it with thioacetamide and Yb(OTf)$_3$, citreothiopyran A was achieved in 4% yield over three steps (**Scheme 52**).

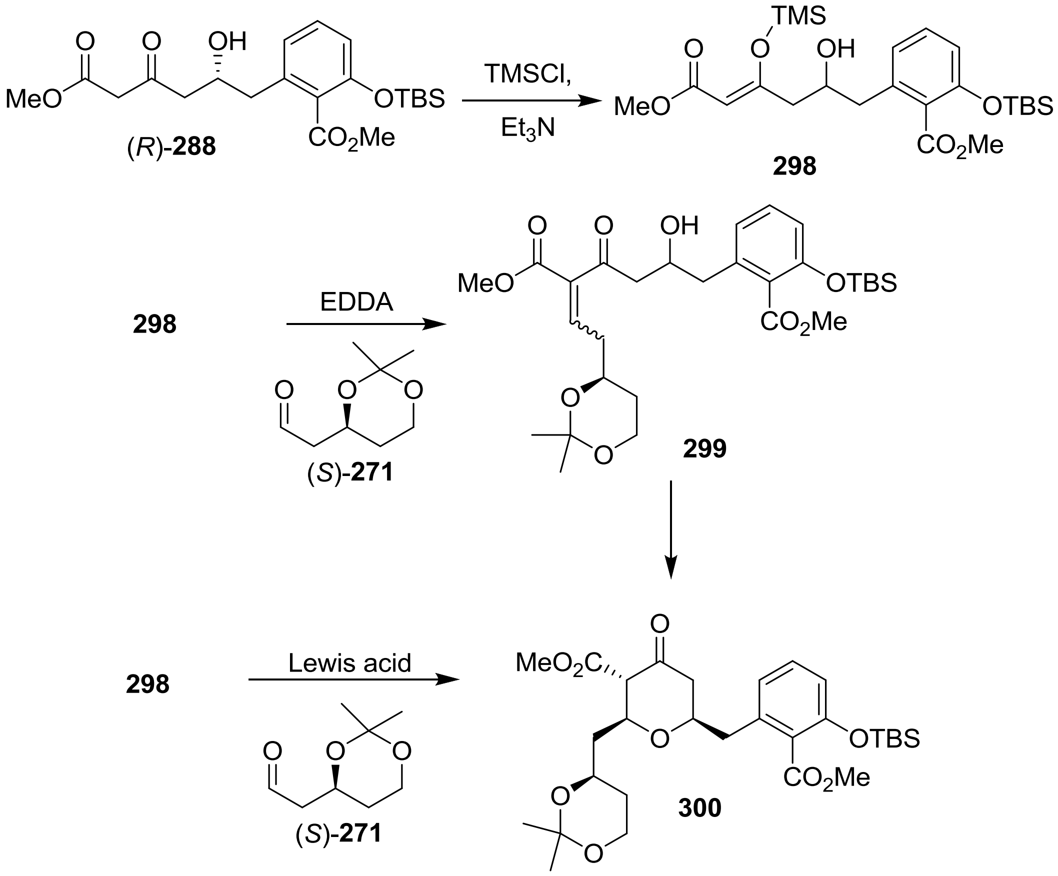
A number of citreothiopyran A analogs were also synthesized by modifing the substitution group at C6 position of the DHT framework (**Scheme 53**). Different aldol products **219a** – **219f** were formed by the same dianionic aldol reaction, and then converted to the corresponding tosylates, in which the dehydrated compounds were also formed, these compounds were treated with thioacetamde and Yb(OTf)$_3$ to give the desired citreothiopyran A analogs in 4% to 19% yield over two steps (**Table 16**).

It was also tried to modified the C2 substitution group of DHT *via* the reaction between δ-hydroxy-β-ketoester and different thioamides (**Scheme 48, Table 15**). But, only the unfuntionalized ^{n}hexyl group was successful introduced to the DHT **193d** with the hexanethioamide **191c**.

A study of diketene addition to aldehyde for δ-hydroxy-β-ketoester formation triggered by nucleophilic organocatalysts including NHC and quinuclidine was performed. Unfortunately, both of these organocatalysts were fail to promote the diketene addition reaction, and no δ-hydroxy-β-ketoester was produced. The NHC only encouraged the formation of methyl acetoacetonate by activating the methanol to undergo transesterfication reaction.

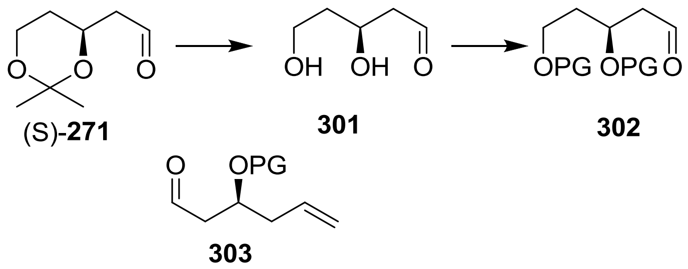
It was anticipated that the TiCl$_4$-promoted diketene addition reaction involved a chelation of the Ti metal to the carbonyl group of the diketene, and the neighbouring chloride anions acted as nucleophile to initiate the tranesterfication reaction giving the enolate for addition to aldehydes. In the study of the organocatalysts, we could not ensure how the organocatalysts interact with the diketene, and hence the reaction between the diketene and organocatalysts may not generate the required enolate ion to react with aldehydes. Based on these results, it may be neccessary to have a functional organocatalyst to interact with the diketene in the same manner as TiCl$_4$ so as to ensure the nucleophilic nitrogen atom to attack the diketene to generate the essential enolate for the desired diketene addition reaction.

An investigation of (-)-apicularen A synthesis was also conducted. It was decided to construct the THP core of apicularen A *via* asymmetric Maitland-Japp reaction with Chan's diene and aldehydes **270** and (*S*)-**271**. Unfortunately, the Maitland-Japp reaction was unsuccessful because of the unstable ketal protecting group of aldehyde (*S*)-**271** and δ-hydroxy-β-ketoester (*S*,*S*)-**290** in the acidic medium (**Scheme 72, 73**) which is a requirement for the Maitland-Japp reaction to proceed. When the δ-hydroxy-β-ketoester (*R*)-**288** was treated isobutaraldehyde and Yb(OTf)$_3$, the desired THP products **296** and **297** were formed in 75% yield (**Scheme 76**), this showed the Maitland-Japp reaction should be a promising strategy for the THP core of apicularen formation, but the ketal protecting group was too vulnerable to the reaction conditions. Although the ketal protecting group was very unstable, the δ-hydroxy-β-ketoester (*S*,*S*)-**290** was obtained in around 50% yield *via* the asymmetric aldol reaction, in which Lewis acids were involved in the reaction. This was because that the Chan's diene was the most reactive reagent in that reaction, and the Lewis acid may tend to interact with the most reactive molecule but not destroy the ketal protecting group. Therefore, in order to prevent the ketal protecting group from being affected in the Maitland-Japp reaction, it may be worth converting the δ-hydroxy-β-ketoester **288** to an activated silyl enol ether **298** before being treated with the aldehyde (*S*)-**271** and Lewis acid to give the THP **300** or converted to the Knoevenagel product **299** (**Scheme 77**).



Scheme 77: Proposed formation of THP from silyl enol ether and aldehyde.

Also, one could change the protecting group to a more acidic resistant one, such as a benzyl or TBS protecting group, or otherwise, the aldehyde (*S*)-**271** could be altered, such as in compound **303** (**Scheme 78**).



Scheme 78: Possible replacement of (*S*)-**271**.

3. Experimental

3.1. General Information

^{1}H NMR and ^{13}C NMR spectra were recorded on a Jeol ECX-400, Jeol ECS400 (400 MHz) at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: chloroform-*d*, 7.26 ppm (^{1}H NMR), 77.0 ppm (^{13}C NMR), Benzene d6, 7.16 ppm (^{1}H NMR), 127.4 ppm (^{13}C NMR); Coupling constants (*J*) are quoted in Hertz (Hz). Mass spectrometric data are acquired from the University of York mass spectrometry service using electrospray ionization (ESI) technique which was conducted with a Bruker microTOF MS-Agilent series 1200 LC. Infra-red (IR) spectra were recorded on a ThermoNicolet IR 100 spectrometer using NaCl plates. Optical rotations were carried out using a JASCO-DIP370 polarimeter; concentrations are given in g 100 ml^{-1} and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. High-performance liquid chromatography was carried out on an Agilent 1100 Series system using a Chiralcel OD-H column with hexanes/isopropanol as the mobile phase. Melting points were measured by using a Stuart SMP3 apparatus. Thin layer chromatography was performed on glass-backed plates coated with Merck Silica gel 60 F$_{254}$. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate, basic aqueous potassium permanganate or ethanolic anisaldehyde. Preparative thin layer chromatography was performed using Machery-Nagel UV$_{254}$ pre-coated plates with concentration layer. The plates were developed using ultraviolet light, acidic aqueous ceric ammonium molybdate, basic aqueous potassium permanganate or ethanolic anisaldehyde.

All numbering on the structures below is for the benefit of characterisation and does not conform to IUPAC rules. However, the compound names are standardised and correspond to IUPAC rules.

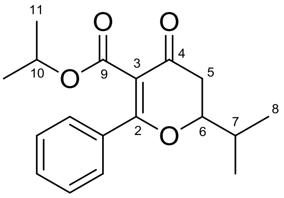
3.2. Materials

All of the aldehydes were distilled before use and the other chemicals were used as supplied without further purification. Dichloromethane was distilled from calcium chloride, methanol was distilled from magnesium turnings/iodine and tetrahydrofuran was distilled from sodium/benzophenone ketyl unless otherwise stated. Reactions which involve moisture sensitive reagents were done under an atmosphere of nitrogen. All glassware was flame dried and cooled down under an atmosphere of nitrogen.

3.3. Synthesis of dihydropyran-4-one

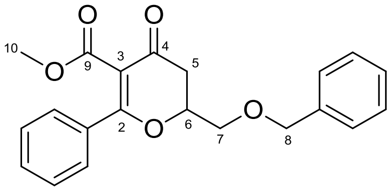
General procedure of dihydropyran-4-one formation: Dimethyl acetal of *N,N*-dimethyl benzamide (4 mmol, 0.78 g) was added to a solution of δ-hydroxy-β-ketoester (0.4 mmol), prepared according to the literature[40], in dry toluene (1 ml). The reaction mixture was stirred at room temperature for 16 hours. After which the solvent of the crude reaction was removed in vacuo and purified by flash column chromatography on silica gel.

3-(2-Methyl-ethanoate)-6-(2-methyl-ethyl)-4-oxo-2-phenyl-5,6-dihydro-2H-pyran (170a)



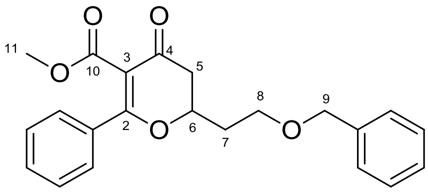
(64 mg, 53 %), brown oil; **IR** υ$_{max}$ (solution, CH_2Cl_2): 3056, 2878, 1721, 1667, 1601, 1565, 1491, 1450, 1386, 1341, 1315, 1266, 1148, 1106, 1071, 967, 937, 897, 841, 823cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.63 – 7.38 (5H, m, Ph), 4.99 (1H, sept, *J* = 6.2 Hz, H_{10}), 4.38 (1H, ddd, *J* = 14.1, 6.3, 3.3 Hz, H_6), 2.65 (1H, dd, *J* = 16.4, 14.1 Hz, H_{5a}), 2.55 (1H, dd, *J* = 16.4, 3.3 Hz, H_{5e}), 2.08 (1H, d sept, *J* = 6.8, 6.6 Hz, H_7), 1.16 (3H, d, *J* = 6.2 Hz, H_{11}), 1.11 (3H, d, *J* = 6.6 Hz, H_8), 1.06 (3H, d, *J* = 6.8 Hz, H_8), 0.90 (3H, d, *J* = 6.2 Hz, H_{11}) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 189.7, 172.5, 165.5, 133.5, 131.9, 128.6, 128.5, 112.8, 84.4, 68.8, 38.5, 32.1, 21.8, 21.1, 18.1 ppm. **MS** (ESI): *m/z* 325 (100%, M + Na$^+$), 303 (30%, M + H$^+$), HRMS: found (M + H$^+$) 303.1595 $C_{18}H_{23}O_4$ requires 303.1591, (M + Na$^+$) 325.1411 $C_{18}H_{22}NaO_4$ requires 325.1410. Flash column chromatography on silica gel (3:1 ratio of petroleum ether and ethyl acetate).

3-Methylmethanoate-6-(benzyloxy-methyl)-4-oxo-2-phenyl-5,6-dihydro-2H-pyran (172a)



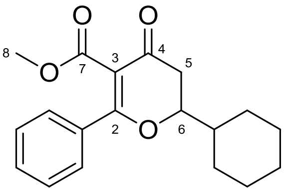
(15.5 mg, 11%), brown oil. **IR** υ$_{max}$ (solution, CH_2Cl_2): 3055, 2868, 1729, 1669, 1590, 1564, 1435, 1384, 1345, 1100, 1065, 1030, 896 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.53 – 7.21 (10H, m, Ph), 4.73 (1H, m, H_6), 4.55 (2H, d, *J* = 5.8 Hz, H_8), 3.76 (1H, dd, *J* = 11.0, 3.7 Hz, H_7), 3.71 (1H, dd, *J* = 11.0, 4.9 Hz, H_7), 3.54 (3H, s, H_{10}), 2.79 (1H, dd, *J* = 16.5, 13.7 Hz, H_{5a}), 2.49 (1H, dd, *J* = 16.5, 3.7 Hz, H_{5e}) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 188.6, 172.1, 166.3, 132.0, 128.4, 128.3, 127.9, 127.6, 112.1, 78.4, 73.4, 70.2, 53.4, 52.2, 37.3 ppm. **MS** (ESI): *m/z* 375 (100%, M + Na$^+$), 353 (42%, M + H$^+$), HRMS: found (M + Na$^+$) 375.1197 $C_{21}H_{20}NaO_5$ requires 375.1203, (M + H$^+$) 353.1381 $C_{21}H_{21}O_5$ requires 353.1384. Flash column chromatography on silica gel (1:1 ratio of petroleum ether and ethyl acetate).

3-Methylmethanoate-6-(benzyloxy-ethyl)-4-oxo-2-phenyl-5,6-dihydro-2H-pyran (172e)



(60 mg, 41%), brown oil. **IR** υ$_{max}$ (solution, CH_2Cl_2): 3055, 2868, 1729, 1669, 1590, 1564, 1435, 1384, 1345, 1100, 1065, 1030, 896 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.52 – 7.31 (10H, m, Ph), 4.89 (1H, m, H_6), 4.58 (1H, d, *J* = 11.9 Hz, H_9), 4.53 (1H, d, *J* = 11.9 Hz, H_9), 3.80 – 3.62 (2H, m, H_8), 3.62 (3H, s, H_{11}), 2.67 (1H, dd, *J* = 16.8, 11.3 Hz, H_{5a}), 2.62 (1H, dd, *J* = 16.8, 5.5 Hz, H_{5e}), 2.25 – 2.03 (2H, m, H_7) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 192.6, 175.9, 170.2, 141.6, 136.7, 135.7, 132.2, 132.0, 131.5, 131.5, 115.9, 77.0, 68.9, 55.9, 44.6, 38.3 ppm. **MS** (ESI): *m/z* 389 (100%, M + Na$^+$), 367 (51%, M + H$^+$), HRMS: found (M + Na$^+$) 389.1359 $C_{22}H_{22}NaO_5$ requires 389.1359, (M + H$^+$) 367.1541 $C_{22}H_{23}O_5$ requires 367.1540. Flash column chromatography on silica gel (2:3 ratio of petroleum ether and ethyl acetate).

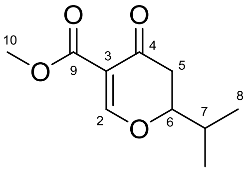
3-Methylmethanoate-6-cyclohexyl-4-oxo-2-phenyl-5,6-dihydro-2H-pyran (172f)



(41.5 mg, 33%), brown oil; **IR** υ$_{max}$ (solution, CH_2Cl_2): 3055, 2933, 2857, 2306, 1729, 1667, 1590, 1564, 1423, 1384, 1342, 1120, 1058, 896 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.56 – 7.40 (5H, m, Ph), 4.38(1H, ddd, *J* = 13.7, 6.1, 3.4 Hz, H_6), 3.62 (3H, s, H_8), 2.65 (1H, dd, *J* = 16.5, 13.7 Hz, H_{5a}), 2.56 (1H, dd, *J*= 16.5, 3.4 Hz, H_{5e}), 2.05-1.20 (11H, m, Cy) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 189.6, 172.8, 166.6, 133.1, 132.0, 128.5, 128.3, 111.85, 83.8, 52.2, 41.4, 38.4, 28.2, 26.1, 25.7 ppm. **MS** (ESI): *m/z* 337 (100%, M + Na$^+$), 315 (34%, M + H$^+$), HRMS: found (M + Na$^+$) 337.1410 $C_{19}H_{22}NaO_4$ requires 337.1410, (M + H$^+$) 315.1588 $C_{19}H_{23}O_4$ requires 315.1591. Flash column chromatography on silica gel (7:3 ratio of petroleum ether and ethyl acetate).

3.4. Synthesis of single diastereomeric 2,6-*trans*-tetrahydropyran-4-one

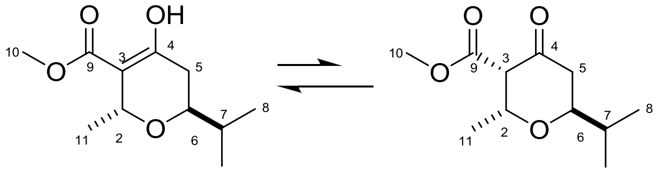
3-Methylmethanoate-6-(2-methylethyl)-4-oxo-5,6-dihydro-2H-pyran (179)



Dimethylacetal *N*,*N*-dimethylformamide (4.2 ml, 31.8 mmol) was added to a solution of δ-hydroxy-β-ketoester (0.6 g, 3.18 mmol) in freshly distilled toluene (9 ml). The reaction mixture was stirred for 3 hours at room temperature. The reaction was diluted with diethyl ether (20 ml), washed with sat. $NaHCO_3$ (3 x 5 ml), and the aqueous layer was extracted with ethyl acetate (3 x 5 ml), then the combined organic lay was washed with brine (3 x 5 ml), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (7:3 ratio of petroleum ether: ethyl acetate) to give 280 mg (43.4%) of **179** as a brown oil. **IR** υ_{max} (solution, $CHCl_3$): 2925, 1712, 1674, 1560, 1416, 1368, 1280, 1131, 1058 cm^{-1}. **^{1}H NMR** (400 MHz,

$CDCl_3$) δ: 8.37 (1H, s, H_2), 4.29 (1H, ddd, *J* = 13.4, 5.8, 3.6 Hz, H_6), 3.80 (3H, s, H_{10}), 2.59 (1H, dd, *J* = 16.2, 13.4 Hz, H_{5a}), 2.50 (1H, dd, *J* = 16.2, 3.6 Hz, H_{5e}), 2.05 (1H, m, H_7), 1.04 (3H, d, *J* = 6.7 Hz, H_8), 1.00 (3H, d, *J* = 6.7 Hz, H_8) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 187.7, 171.7, 164.2, 110.5, 85.6, 51.8, 38.9, 31.6, 17.7, 17.5 ppm. **MS** (ESI): *m/z* 221 (100%, M + Na^+), 199 (4%, M + H^+), HRMS: found (M + Na^+) 221.0787 $C_{10}H_{14}NaO_4$ requires 221.0784, (M + H^+) 199.0966 $C_{10}H_{15}O_4$ requires 221.0784.

(2*R*,6*S*)-3-Methylmethanoate-2-methyl-6-(2-methylethyl)-4-hydroxy-5,6-dihydro-2H-pyran (180) and (2*R*,6*S*)-3-methylmethanoate-2-methyl-6-(2-methylethyl)-4-oxo-tetrahydropyran (181)



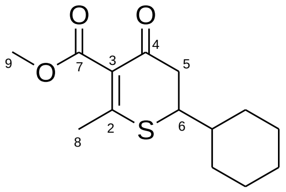
A 1.35M solution of MeLi in diethyl ether (0.38 ml, 1.62 mmol) was added to CuI (0.154 g, 0.81 mmol) in freshly distilled THF (2 ml) at 0°C, The reaction mixture was stirred for 1 hour. Freshly distilled TMSCl (0.32 ml, 2.52 mmol) and 2-ene-3-methylmethanoate-6-(2-methylethyl)-4-oxo-dihydro-pyran (100 mg, 0.5 mmol) were added to the reaction at -78 °C, and the reaction mixture was stirred for 3 hours. The reaction was quenched by adding sat. NH_4Cl (2ml). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 10 ml), the combined organic layer was washed with brine (3 x 3 ml), dried over

$MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (9.5:0.5 ratio of petroleum ether and ethyl acetate to 7:3 ratio of petroleum ether and ethyl acetate) to give 33 mg (31 %) of enol **180** and keto **181** tautomers in 10:1 ratio as a brown oil. **IR** υ_{max} (solution, CH_2Cl_2): 3435, 3055, 2686, 1660, 1623, 1441, 1422, 1366, 1222, 1071, 896 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 12.0 (1H, s, enol), 4.65 (1H, quart, *J* = 6.4 Hz, H_{2enol}), 4.51 (1H, pent, *J* = 6.4 Hz, H_{2keto}), 3.75 (3H, s, H_{10enol}), 3.74 (3H, s, H_{10keto}), 3.52 (1H, ddd, *J* = 10.7, 7.0, 4.3 Hz, H_{6enol}), 3.17 (1H, dd, *J* = 6.4, 1.2 Hz, H_{3keto}), 2.61 (1H, dd, *J* = 14.0, 6.4 Hz, H_{5eketo}), 2.51 (1H, dd, *J* = 14.0, 4.9, 1.2 Hz, H_{5eketo}), 2.25 (1H, dd, *J* = 17.7, 10.4 Hz, H_{5eenol}), 2.16 (1H, dd, *J* = 17.7, 4.0 Hz, H_{5aenol}), 1.67 (1H, d, sept, *J* = 6.4, 6.7 Hz, H_7), 1.33 (3H, d, *J* = 6.4 Hz, H_{11enol}), 1.27 (3H, d, *J* = 6.4 Hz, H_{11keto}), 0.95 (3H, d, *J* = 6.7 Hz, H_{8enol}), 0.95 (3H, d, *J* = 6.4 Hz, H_{8keto}), 0.90 (3H, d, *J* = 6.7 Hz, H_{8enol}), 0.87 (3H, d, *J* = 6.7 Hz, H_{8keto}) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 171.0, 170.0, 101.9, 71.1, 67.3, 51.4, 32.7, 32.0, 19.8, 18.5, 17.9 ppm. **MS** (ESI): *m/z* 237 (100%, M + Na^+), 215 (20%, M + H^+), HRMS: found (M + Na^+) 237.1099 $C_{11}H_{18}NaO_4$ requires 237.1097, (M + H^+) 215.1274 $C_{11}H_{19}O_4$ requires 215.1278.

3.5. Synthesis of dihydrothiopyran

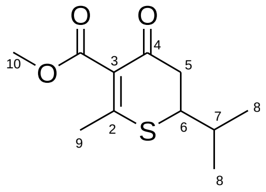
General procedure of dihydrothiopyran formation: Ytterbium triflate (370 mg, 0.6 mmol) was added to a solution of δ-hydroxy-β-ketoester (0.6 mmol) and thioacetamide (90 mg, 1.2 mmol) in 1,4-dioxane (30 ml) at room temperature. The reaction mixture was stirred under reflux for 1 hour. Then the crude reaction was diluted with Et_2O (60 ml) and washed with sat. $NaHCO_3$ solution (3 x 15ml), the aqueous layer was extracted with ethyl acetate (3 x 10 ml). The combined organic layer was washed with brine (3 x 10 ml), and then dried over $MgSO_4$, filtered and concentrated in vacuo, the crude product was purified by flash column chromatography on silica gel.

3-Methylmethanoate-6-cyclohexyl-2-methyl-4-oxo-5,6-dihydro-2H-thiopyran (187)



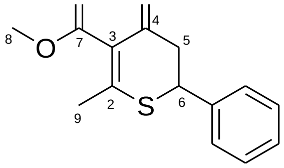
(69 mg, 42%), brown oil; **IR** υ_{max} (solution, CH_2Cl_2): 3055, 2987, 1729, 1656, 1572, 1423, 1015, 896 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.81 (3H, s, H_9), 3.33(1H, ddd, *J* = 12.8, 6.4, 3.4 Hz, H_6), 2.77 (1H, dd, *J* = 15.9, 3.4 Hz, H_{5e}), 2.64 (1H, dd, *J* = 15.9, 12.8 Hz, H_{5a}), 2.19 (3H, s, H_8), 1.9 – 1.0 (11H, m, Cy) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 192.0, 167.0, 161.0, 128.0, 52.3, 48.0, 40.9, 40.7, 30.1, 29.8, 26.0, 22.5 ppm. **MS** (ESI): *m/z* 291 (100%, M + Na^+), 269 (58%, M + H^+), HRMS: found (M + Na^+) 291.1025 $C_{14}H_{20}NaO_3S$ requires 291.1025, (M + H^+) 269.1204 $C_{14}H_{21}O_3S$ requires 291.1025. Flash column chromatography on silica gel (7:3 ratio of petroleum ether and ethyl acetate).

3-Methylmetanoate-2-methyl-6-(2-methyl-ethyl)-4-oxo-5,6-dihydro-2H-thiopyran (192e)



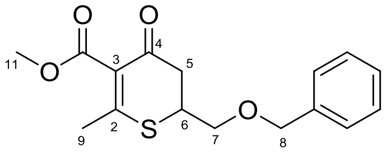
(31.5 mg, 23%), brown oil. **IR** υ$_{max}$ (solution, CH_2Cl_2): 3054, 1729, 1656, 1572, 1423, 1332, 1057, 1015, 896 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.83 (3H, s, H_{10}), 3.33(1H, ddd, *J* = 13.2, 6.2, 3.4 Hz, H_6), 2.76 (1H, dd, *J* = 15.9, 3.4 Hz, H_{5e}), 2.61 (1H, dd, *J* = 15.9, 13.2 Hz, H_{5a}), 2.20 (3H, s, H_9), 1.94 (1H, d sept, *J* = 6.7, 6.2 Hz, H_7), 1.05 (3H, d, *J* = 6.4 Hz, H_8), 1.03 (3H, d, *J* = 6.4 Hz, H_8) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 191.6, 166.5, 160.9, 127.8, 52.4, 48.9, 40.8, 31.4, 22.5, 19.5, 19.4 ppm. **MS** (ESI): *m/z* 251 (100%, M + Na$^+$), 229 (31%, M + H$^+$), HRMS: found (M + Na$^+$) 251.0712 $C_{11}H_{16}NaO_3S$ requires 251.0712, (M + H$^+$) 229.0891 $C_{11}H_{17}O_3S$ requires 229.0893. Flash column chromatography on silica gel (7:3 ratio of petroleum ether and ethyl acetate).

3-Methylmethanoate-2-methyl-4-oxo-6-phenyl-5,6-dihydro-2H-thiopyran (192f)



(13 mg, 8%), brown oil. **IR** υ$_{max}$ (solution, CH_2Cl_2): 3054, 1731, 1657, 1434, 1325, 1013, 909 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.42 – 7.33 (5H, m, Ph), 4.66 (1H, dd, *J* = 14.0, 3.4 Hz, H_6), 3.86 (3H, s, H_8), 3.11 (1H, dd, *J* = 15.8, 14.0 Hz, H_{5a}), 2.96 (1H, dd, *J* = 15.8, 3.4 Hz, H_{5e}), 2.20 (3H, s, H_9) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 190.8, 166.4, 160.5, 137.0, 129.2, 128.8, 127.4, 52.3, 46.1, 43.6, 22.0 ppm. **MS** (ESI): *m/z* 285 (100%, M + Na$^+$), 263 (35%, M + H$^+$), HRMS: found (M + Na$^+$) 285.0548 $C_{14}H_{14}NaO_3S$ requires 285.0556, (M + H$^+$) 263.0731 $C_{14}H_{15}O_3S$ requires 263.0731. Flash column chromatography on silica gel (4:1 ratio of petroleum ether and ethyl acetate).

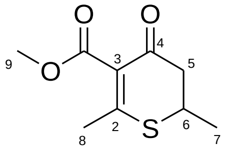
3-Methylmethanoate-6-(benzyloxy-methyl)-2-methyl-4-oxo-5,6-dihydro-2H-thiopyran (192g)



(35.2 mg, 19%), brown oil. **IR** υ$_{max}$ (solution, CH_2Cl_2): 3054, 1729, 1659, 1574, 1423, 1108, 1025, 896 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.38 – 7.30 (5H, m, Ph), 4.57 (1H, d, *J* = 12. 2 Hz, H_8), 4.54 (1H, d, *J* = 12.2 Hz, H_8), 3.82 (3H, s, H_{11}), 3.72 (1H, m, H_6), 3.64 (1H, dd, *J* = 9.8, 8.0 Hz, H_7), 3.62 (1H, dd, *J* = 10.0, 9.8 Hz, H_7), 2.78 (1H, dd, *J* = 16.2, 4.6 Hz, H_{5e}), 2.71 (1H, dd, *J* = 16.2, 10.4 Hz, H_{5a}), 2.19 (3H, s, H_9) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 190.2, 166.3, 159.8, 128.5,128.0, 127.7, 73.4, 70.3, 52.3, 41.5, 39.3, 22.3 ppm. **MS** (ESI): *m/z* 329 (100%, M + Na$^+$), 307 (11%, M + H$^+$), HRMS: found (M + Na$^+$) 329.0810 $C_{16}H_{18}NaO_4S$ requires 329.0818, (M + H$^+$) 307.0994 $C_{16}H_{19}O_4S$ requires

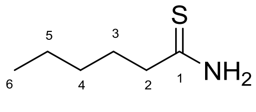
307.0999. Flash column chromatography on silica gel (1:1 ratio of petroleum ether and ethyl acetate).

3-Methylmethanoate-2,6-dimethyl-4-oxo-5,6-dihydro-2H-thiopyran (192h)



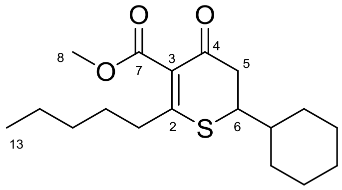
(15.6 mg, 13%), brown oil. **IR** υ_{max} (solution, CH_2Cl_2): 3054, 1729, 1657, 1573, 1423, 1028, 896 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.83 (3H, s, H_9), 3.56 (1H, m, H_6), 2.78 (1H, dd, *J* = 15.9, 3.4 Hz, H_{5e}), 2.55 (1H, dd, *J* = 15.9, 11.9 Hz, H_{5a}), 2.18 (3H, s, H_8), 1.40 (3H, d, *J* = 7.0 Hz, H_7) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 191.1, 166.5, 160.2, 127.8, 52.4, 44.8, 36.7, 22.1, 19.6 ppm. **MS** (ESI): *m/z* 223 (100%, M + Na^+), 201 (17%, M + H^+), HRMS: found (M + Na^+) 223.0401 $C_9H_{12}NaO_3S$ requires 223.0399, (M + H^+) 201.0581 $C_9H_{13}O_3S$ requires 201.0580. Flash column chromatography on silica gel (7:3 ratio of petroleum ether and ethyl acetate).

Thiohexamide (191c)



Lawesson reagent (1.23g, 3mmol) was added to a solution of hexanyl amide (0.7 g, 6mmol) in THF (7 ml) at room temperature. The reaction was stirred at room temperature for 1 hour. The solvent of the reaction was removed in vacuo, and the residuel was directly purified by flash column chromatography on silica gel (1:1 ratio of petroleum ether and ethyl acetate) to give 605 mg (76.8%) of **189c** as a white solid. **mp** 49.0 – 50.5^{o}C. **IR** υ_{max} (solution, CH_2Cl_2): 3436, 3389, 2916, 2887, 2818, 1582, 1383, 1304 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.75 (1H, s, NH), 6.97 (1H, s, NH), 2.65 (2H, t, *J* = 7.6 Hz, H_2), 1.76 (2H, q, *J* = 7.6 Hz, H_3), 1.39 – 1.28 (4H, m, H_4 and H_5), 0.89 (3H, t, *J* = 7.0 Hz, H_6) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 211.0, 45.4, 31.0, 28.8, 22.3, 13.9 ppm. **MS** (ESI): *m/z* 132 (100%, M + H^{+}), HRMS: found (M + H^{+}) 132.0843 $C_6H_{14}NS$ requires 132.0841.

3-Methylmethanoate-6-cyclohexyl-2-(*n*-hexyl)-4-oxo-5,6-dihydro-2H-thiopyran (193d)



Ytterbium triflate (370 mg, 0.6 mmol) was added to a solution of δ-hydroxy-β-ketoester (137 mg, 0.6 mmol) and thiohexamide **191c** (90 mg, 1.2 mmol) in 1,3-dioxane (30 ml) at room temperature. The reaction mixture was stirred under reflux for 1 hour. Then the crude reaction was diluted with Et_2O (60 ml) and washed with sat. $NaHCO_3$ solution (3 x 15ml), the aqueous layer was extracted with ethyl acetate (3 x 10 ml). The combined organic layer was washed with brine (3 x 10 ml), and then dried over $MgSO_4$, filtered and concentrated in vacuo, the crude product was purified by flash column chromatography on silica gel (9:1

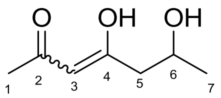
ratio of petroleum ether and ethyl acetate) to give 44.8 mg (23%) of **193d** as a brown oil. **IR** υ_{max} (solution, CH_2Cl_2): 3055, 2932, 2857, 1728, 1654, 1563, 1424, 1329, 1014, 896 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.82 (3H, s, H_8), 3.12 (1H, ddd, J = 13.1, 6.4, 3.4 Hz, H_6), 2.76 (1H, dd, J = 16.2, 3.4 Hz, H_{5e}), 2.61 (1H, dd, J = 16.2, 13.1 Hz, H_{5a}), 2.42 (2H, m, cy), 1.80 – 1.0 (17H, m, cy, ^{n}hexyl), 0.89 (3H, t, J = 6.7 Hz, H_{13}) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 192.1, 166.8, 165.6, 138.3, 127.5, 52.3, 47.8, 40.9, 40.9, 36.6, 31.4, 30.1, 29.8, 29.1, 26.1, 26.0, 22.2, 13.8 ppm. **MS** (ESI): *m/z* 347 (100%, M + Na^+), 325 (89%, M + H^+), HRMS: found (M + Na^+) 347.1651 $C_{18}H_{28}NaO_3S$ requires 347.1651, (M + H^+) 325.1834 $C_{18}H_{29}O_3S$ requires 325.1832.

3.6. Synthesis of citreothiopyrane A and analogous

General procedure for dianionic aldol reaction: A 2.35M solution of ^{n}BuLi in hexane (18.2 ml, 42.85 mmol) was added to a solution of dry diisopropyl amine (6.6 ml, 46.74 mmol) in dry THF (40 ml) at -78°C. The reaction mixture was stirred at 0 °C for 30 min. After which a solution of acetylacetone (2 ml, 19.48 mmol) in THF (5 ml) was added, and the reaction mixture was stirred at 0 °C for 30 min. Then, a solution of aldehyde (19.48 mmol) in THF (5 ml) was added, the reaction mixture was stirred at 0 °C for 1 hour. The reaction was quenched by adding sat. NH_4Cl solution (10 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 15 ml), the combined organic layer was washed with sat. NH_4Cl solution (3 x 5 ml), brine (3 x 5 ml), dried over

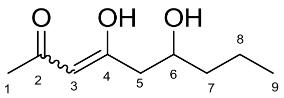
$MgSO_4$, filtered and concentrated in vacuo. The crude reaction was purified by flash column chromatography on silica gel.

4,6-dihydroxyhept-3-en-2-one (215)



(955 mg, 34%), brown oil. **IR** υ_{max} (solution, $CHCl_3$): 3394, 2933, 2889, 1697, 1597, 1394, 1279, 1089, 1036, 1012, 962, 917 cm^{-1}. **^{1}H NMR** (400 MHz, Benzene d6) δ: 5.01 (1H, s, H_3), 4.07 – 3.98 (1H, m, H_6), 2.13 (1H, dd, J = 15.2, 9.5 Hz, H_5), 2.01 (1H, dd, J = 15.2, 4.0 Hz, H_5), 1.57 (3H, s, H_1), 1.03 (3H, d, J = 7.0 Hz, H_7) ppm. **^{13}C NMR** (400 MHz, Benzene d6) δ: 194.4, 188.9, 100.4, 64.3, 47.1, 23.2, 22.6 ppm. **MS** (ESI): m/z 167 (100%, M + Na^+), 145 (42%, M + H^+), HRMS: found (M + Na^+) 167.0672 $C_7H_{12}NaO_3$ requires 167.0679, (M + H^+) 145.0859 $C_7H_{13}O_3$ requires 145.0859. Flash column chromatography on silica gel (1:1 ratio of petroleum ether and ethyl acetate).

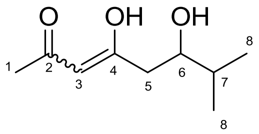
4,6-dihydroxynon-3-en-2-one (219a)



(1.98 g, 59%), brown oil. **IR** υ_{max} (solution, $CHCl_3$): 3389, 2972, 2916, 2889, 2830, 1688, 1596, 1395, 1278, 1103, 1054, 1007, 914 cm^{-1}. **^{1}H NMR** (400 MHz, Benzene d6) δ: 5.04 (1H, s, H_3), 3.90 (1H, m, H_6), 2.14 (1H, dd, J = 15.2, 7.9 Hz,

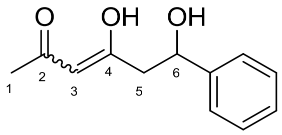
H_5), 2.08 (1H, dd, *J* = 15.2, 4.3 Hz, H_5), 1.58 (3H, s, H_1), 1.50 – 1.14 (4H, m, H_7 and H_8), 0.86 (3H, t, *J* = 7.0 Hz, H_9) ppm. **^{13}C NMR** (400 MHz, Benzene d6) δ: 194.9, 188.5, 100.4, 67.7, 45.7, 38.9, 23.1, 18.4, 13.6 ppm. **MS** (ESI): *m/z* 195 (100%, M + Na$^+$), HRMS: found (M + Na$^+$) 195.0996 $C_9H_{16}NaO_3$ requires 195.0992. Flash column chromatography on silica gel (7:3 ratio of petroleum ether and ethyl acetate).

4,6-dihydroxy-7-methyloct-3-en-2-one (219b)



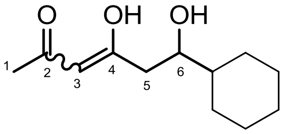
(1.42 g, 42.3%), brown oil. **IR** υ_{max} (solution, $CHCl_3$): 3383, 2920, 1692, 1597, 1445, 1439 cm^{-1}. **^{1}H NMR** (400 MHz, Benzene d6) δ: 5.04 (1H, s, H_3), 3.69 (1H, dt, *J* = 7.6, 5.2 Hz, H_6), 2.12 (1H, d, *J* = 5.2 Hz, H_5), 2.11 (1, s, H_5), 1.58 (3H, s, H_1), 1.58 – 1.41 (1H, m, H_7), 0.88 (3H, d, *J* = 7.0 Hz, H_8), 0.82 (3H, d, *J* = 7.0 Hz, H_8) ppm. **^{13}C NMR** (400 MHz, Benzene d6) δ: 195.8, 188.1, 100.5, 72.6, 42.8, 33.2, 23.0, 18.1, 16.9 ppm. **MS** (ESI): *m/z* 195 (100%, M + Na$^+$), 173 (87%, M + H$^+$), HRMS: found (M + Na$^+$) 195.0992 $C_9H_{16}NaO_3$ requires 195.0992, (M + H$^+$) 173.1172 $C_9H_{17}O_3$ requires 173.1172. Flash column chromatography on silica gel (7:3 ratio of petroleum ether and ethyl acetate).

4,6-dihydroxy-6-phenylhex-3-en-2-one (219c)



(1.53 g, 38.2%), brown oil. **IR** υ$_{max}$ (solution, $CHCl_3$): 3394, 2973, 1697, 1596, 1432, 1398 cm^{-1}. **^{1}H NMR** (400 MHz, Benzene d6) δ: 7.30 – 7.03 (5H, m, Ph), 5.02 (1H, dd, *J* = 9.2, 3.6 Hz, H_6), 4.96 (1H, s, H_3), 2.46 (1H, dd, *J* = 15.6, 9.2 Hz, H_5), 2.33 (1H, dd, *J* = 15.6, 3.6 Hz, H_5), 1.51 (3H, s, H_1) ppm. **^{13}C NMR** (400 MHz, Benzene d6) δ: 194.1, 188.5, 143.6, 141.3, 128.0, 125.4, 100.5, 70.3, 47.8, 23.0 ppm. **MS** (ESI): *m/z* 229 (100%, M + Na$^+$), HRMS: found (M + Na$^+$) 229.0828 $C_{12}H_{14}NaO_3$ requires 229.0835. Flash column chromatography on silica gel (7:3 ratio of petroleum ether and ethyl acetate).

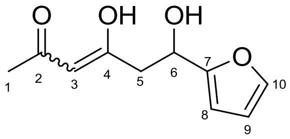
6-cyclohexyl-4,6-dihydroxyhex-3-en-2-one (219d)



(1.41g, 34%), brown oil. **IR** υ$_{max}$ (solution, $CHCl_3$): 3429, 2885, 2812, 1696, 1596, 1428, 1400, 1022, 914 cm^{-1}. **^{1}H NMR** (400 MHz, Benzene d6) δ: 5.07 (1H, s, H_3), 3.70 (1H, dt, *J* = 7.0, 5.2 Hz, H_6), 2.16 – 2.14 (2H, m, H_5), 1.57 (3H, s, H_1), 1.83 – 1.50 (5H, m, Cy), 1.30 – 0.80 (6H, m, Cy) ppm. **^{13}C NMR** (400 MHz, Benzene d6) δ: 196.0, 188.0, 100.4, 72.0, 43.1, 42.9, 28.7, 27.5, 26.2, 26.0, 25.8, 23.0 ppm. **MS** (ESI): *m/z* 213 (100%, M + H$^+$), 235 (49%, M + Na$^+$), HRMS:

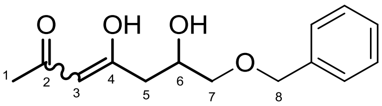
found (M + H$^+$) 213.1491 $C_{12}H_{21}O_3$ requires 213.1485, (M + Na$^+$) 235.1307 $C_{12}H_{20}NaO_3$ requires 235.1305. Flash column chromatography on silica gel (7:3 ratio of petroleum ether and ethyl acetate).

6-(furan-2-yl)-4,6-dihydroxyhex-3-en-2-one (219e)



(2.18 g, 57%), brown oil. **IR** υ_{max} (solution, $CHCl_3$): 3530, 2973, 1701, 1596, 1400, 1132, 997, 913 cm^{-1}. **^{1}H NMR** (400 MHz, Benzene d6) δ: 7.06 (1H, dd, *J* = 1.8, 0.9 Hz, H_{10}), 6.11 (1H, d, *J* = 3.4 Hz, H_8), 6.05 (1H, dd, *J* = 1.8, 3.4 Hz, H_9), 5.07 (1H, dd, *J* = 8.8, 4.3 Hz, H_6), 4.99 (1H, s, H_3), 2.62 (1H, dd, *J* = 15.6, 8.8 Hz, H_5), 2.53 (1H, dd, *J* = 15.6, 4.3 Hz, H_5), 1.51 (3H, s, H_1) ppm. **^{13}C NMR** (400 MHz, Benzene d6) δ: 193.6, 188.4, 155.8, 141.4, 109.9, 105.7, 100.4, 64.3, 44.0, 22.9 ppm. **MS** (ESI): *m/z* 219 (100%, M + Na$^+$), HRMS: found (M + Na$^+$) 219.0629 $C_{10}H_{12}NaO_4$ requires 219.0628. Flash column chromatography on silica gel (1:1 ratio of petroleum ether and ethyl acetate).

7-(benzyloxy)-4,6-dihydroxyhept-3-en-2-one (219f)

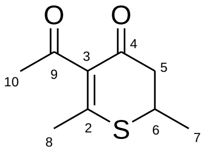


(1.79 g, 36.8%), brown oil. **IR** υ_{max} (solution, $CHCl_3$): 3385, 2822, 1696, 1597, 1432, 1400, 1342, 1099, 1012, 914, 689 cm^{-1}. **^{1}H NMR** (400 MHz, Benzene d6) δ: 7.26 – 7.06 (5H, m, Ph), 5.09 (1H, s, H_3), 4.24 (1H, s, H_8), 4.23 (1H, s, H_8), 4.25 – 4.14 (1H, m, H_6), 3.24 (2H, m, H_7), 2.31 (1H, dd, J = 15.0, 7.6 Hz, H_5), 2.26 (1H, dd, J = 15.0, 5.2 Hz, H_5), 1.55(3H, s, H_1) ppm. **^{13}C NMR** (400 MHz, Benzene d6) δ: 193.4, 189.0, 138.1, 128.0, 127.3, 127.2, 100.5, 73.3, 72.7, 67.3, 42.2, 23.2 ppm. **MS** (ESI): *m/z* 251 (100%, M + H^+), 273 (90%, M + Na^+), HRMS: found (M + H^+) 251.1272 $C_{14}H_{19}O_4$ requires 251.1278, (M + Na^+) 273.1090 $C_{14}H_{18}NaO_4$ requires 273.1097. Flash column chromatography on silica gel (1:1 ratio of petroleum ether and ethyl acetate).

General procedure for tosylate formation: 4-Tolenesulfonyl chloride (0.6 g, 3.12 mmol) was added to a solution of dianionic aldol product (0.3 g, 2.08 mmol) in freshly distilled pyridine (4.2 ml) at 0^{o}C. The reaction mixture was stirred fro 16 hours at room temperature. The reaction mixture was poured into ice-cooled water (8 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 5 ml), the combined organic layer was washed with sat. CuSO4 solution (3 x 1 ml), and brine (3 x 1 ml), and then dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was used in the next step without further purification.

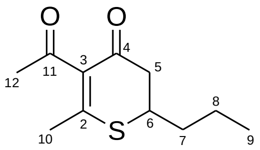
General procedure for citreothiopyrane A and analogous formation: Ytterbium triflate (1.29 g, 2.08 mmol) was added to a solution of the crude tosylate (2.08 mmol) and thioacetamide (310 mg, 4.16 mmol) in freshly distilled 1,4 dioxane (40 ml) at room temperature. The reaction mixture was stirred under reflux for 1 hour. After which the reaction mixture was diluted with diethyl ether (80 ml) and washed with sat. $NaHCO_3$ solution (3 x 15ml), the aqueous layer was extracted with ethyl acetate (3 x 15 ml). The combined organic layer was washed with brine (3 x 10 ml), and then dried over $MgSO_4$, filtered and concentrated in vacuo, the crude product was purified by flash column chromatography on silica gel.

Citreothiopyrane A (209)



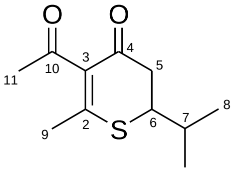
(46 mg, 12% over 2 steps), brown oil. **IR** υ_{max} (solution, CH_2Cl_2): 3008, 1668, 1629, 1527, 1400, 882 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.56 (1H, m, H_6), 2.78 (1H, dd, J = 15.9, 3.4 Hz, H_{5e}), 2.58 (1H, dd, J = 15.9, 11.9 Hz, H_{5a}), 2.36 (3H, s, H_{10}), 2.16 (3H, s, H_8), 1.39 (3H, d, J = 7.0 Hz, H_7) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 201.9, 192.9, 161.5, 134.5, 45.3, 36.6, 31.7, 22.3, 19.6 ppm. **MS** (ESI): *m/z* 207 (100%, M + Na^+), 185 (41%, M + H^+), HRMS: found (M + Na^+) 207.0450 $C_9H_{12}NaO_2S$ requires 207.0450, (M + H^+) 185.0630 $C_9H_{13}O_2S$ requires 188.0631. Flash column chromatography on silica gel (7:3 ratio of petroleum ether and ethyl acetate).

3-Acetyl-2-methyl-6-propyl-4-oxo-5,6-dihydro-2H-thiopyran (222a)



(84 mg, 19% over 2 steps), brown oil. **IR** υ$_{max}$ (solution, $CHCl_3$): 2918, 1627, 1506, 1403, 1297 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.42 (1H, m, H_6), 2.79 (1H, dd, *J* = 15.9, 3.4 Hz, H_{5e}), 2.59 (1H, dd, *J* = 15.9, 11.9 Hz, H_{5a}), 2.36 (3H, s, H_{12}), 2.17(3H, s, H_{10}), 1.70 – 1.62 (2H, m, H_7), 1.49 – 1.40 (2H, m, H_8), 0.94 (3H, t, *J* = 7.3 Hz, H_9) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 201.9, 193.0, 161.6, 134.6, 43.7, 41.5, 35.8, 31.7, 22.5, 19.6, 13.6 ppm. **MS** (ESI): *m/z* 213 (100%, M + H$^+$), 235 (36%, M + Na$^+$), HRMS: found (M + H$^+$) 213.0939 $C_{11}H_{17}O_2S$ requires 213.0944, (M + Na$^+$) 235.0753 $C_{11}H_{16}NaO_2S$ requires 235.0763. Flash column chromatography on silica gel (4:1 ratio of petroleum ether and ethyl acetate).

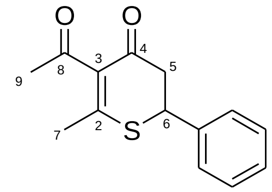
3-Acetyl-6-isopropyl -2-methyl-4-oxo-5,6-dihydro-2H-thiopyran (222b)



(66 mg, 15% over 2 steps), brown oil. **IR** υ$_{max}$ (solution, $CHCl_3$): 2922, 1666, 1518, 1443, 1402, 1352, 1332, 1309, 1286 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.30 (1H, ddd, *J* = 12.8, 6.4, 3.4 Hz, H_6), 2.75 (1H, dd, *J* = 15.9, 3.4 Hz, H_{5e}),

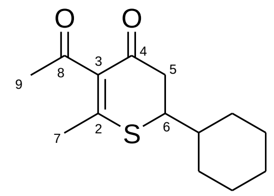
2.64 (1H, dd, *J* = 15.9, 12.8 Hz, H_{5a}), 2.36 (3H, s, H_{11}), 2.19(3H, s, H_9), 1.94 (1H, m, H_7), 1.05 (3H, d, *J* = 5.9 Hz, H_8), 1.03 (3H, d, *J* = 5.9 Hz, H_8) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 201.8, 193.4, 162.2, 134.5, 48.6, 31.7, 31.4, 22.6, 19.5, 19.4 ppm. **MS** (ESI): *m/z* 213 (100%, M + H^+), 235 (68%, M + Na^+), HRMS: found (M + H^+) 213.0955 $C_{11}H_{17}O_2S$ requires 213.0944, (M + Na^+) 235.0771 $C_{11}H_{16}NaO_2S$ requires 235.0763. Flash column chromatography on silica gel (4:1 ratio of petroleum ether and ethyl acetate).

3-Acetyl-2-methyl-6-phenyl-4-oxo-5,6-dihydro-2H-thiopyran (222c)



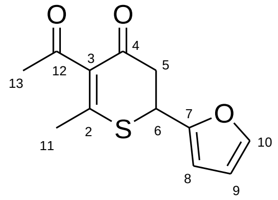
(20.5 mg, 4% over 2 steps), brown oil. **IR** υ_{max} (solution, $CHCl_3$): 2973, 1670, 1628, 1501, 1402, 915 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.45 – 7.28 (5H, m, Ph), 4.63(1H, dd, *J* = 14.0, 3.4 Hz, H_6), 3.12 (1H, dd, *J* = 15.9, 14.0 Hz, H_{5a}), 2.94 (1H, dd, *J* = 14.0, 3.4 Hz, H_{5e}), 2.40 (3H, s, H_9), 2.20 (3H, s, H_7) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 201.8, 192.6, 161.7, 137.0, 134.8, 129.1, 128.9, 128.8, 127.5, 127.4, 45.8, 31.8, 22.1, 22.1 ppm. **MS** (ESI): *m/z* 247 (100%, M + H^+), 269 (61%, M + Na^+), HRMS: found (M + H^+) 247.0777 $C_{14}H_{15}O_2S$ requires 247.0787, (M + Na^+) 269.0596 $C_{14}H_{14}NaO_2S$ requires 269.0607. Flash column chromatography on silica gel (4:1 ratio of petroleum ether and ethyl acetate).

3-Acetyl-6-cyclohexyl -2-methyl-4-oxo-5,6-dihydro-2H-thiopyran (222d)



(52.5 mg, 10% over 2 steps), brown oil. **IR** υ$_{max}$ (solution, CH_2Cl_2): 2884, 2810, 1630, 1565, 1426, 1353, 1298, 1171, 1122, 1026, 942, 842 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 3.30 (1H, ddd, *J* = 12.5, 6.4, 3.4 Hz, H_6), 2.76 (1H, dd, *J* = 15.6, 3.4 Hz, H_{5e}), 2.65 (1H, dd, *J* = 15.6, 12.5 Hz, H_{5a}), 2.36 (3H, s, H_9), 2.19 (3H, s, H_7), 1.85 – 1.00 (11H, m, Cy) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 201.9, 193.6, 162.4, 134.6, 47.8, 41.3, 41.0, 31.8, 30.1, 29.9, 26.0, 22.7 ppm. **MS** (ESI): *m/z* 253 (100%, M + H$^+$), 275 (29%, M + Na$^+$), HRMS: found (M + H$^+$) 253.1261 $C_{14}H_{21}O_2S$ requires 253.1257, (M + Na$^+$) 275.1072 $C_{14}H_{20}NaO_2S$ requires 275.1076. Flash column chromatography on silica gel (7:3 ratio of petroleum ether and ethyl acetate).

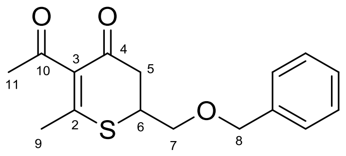
3-Acetyl-6-furan-2-yl-2-methyl-4-oxo-5,6-dihydro-2H-thiopyran (222e)



(24.6 mg, 5% over 2 steps), brown oil. **IR** υ$_{max}$ (solution, $CHCl_3$): 2973, 1612, 1596, 1519, 1411, 1002, 949, 914, 870 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.40

(1H, dd, *J* = 1.8, 1.0 Hz, H_{10}), 6.35 (1H, dd, *J* = 3.4, 1.8 Hz, H_9), 6.27 (1H, d, *J* = 3.4 Hz, H_8), 4.67 (1H, dd, *J* = 10.0, 4.6 Hz, H_6), 3.11 (1H, dd, *J* = 16.2, 10.0 Hz, H_{5a}), 3.03 (1H, dd, *J* = 16.2, 4.6 Hz, H_{5e}), 2.38 (3H, s, H_{13}), 2.17 (3H, s, H_{11}) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 201.4, 191.8, 160.0, 150.2, 143.2, 134.8, 110.8, 108.2, 41.4, 38.6, 31.9, 22.2 ppm. **MS** (ESI): *m/z* 237 (100%, M + H^+), 259 (69%, M + Na^+), HRMS: found (M + H^+) 237.0583 $C_{12}H_{13}O_3S$ requires 237.0580, (M + Na^+) 259.0399 $C_{12}H_{12}NaO_3S$ requires 259.0399. Flash column chromatography on silica gel (4:1 ratio of petroleum ether and ethyl acetate).

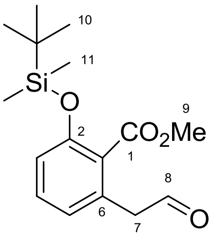
3-Acetyl-6-(benzyloxymethyl)-2-methyl-4-oxo-5,6-dihydro-2H-thiopyran (222f)



(90.6 mg, 15% over 2 steps), brown oil. **IR** υ_{max} (solution, CH_2Cl_2): 2819, 1668, 1627, 1516, 1432, 1402, 1335, 1292, 1087, 1012, cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.39 – 7.27 (5H, m, Ph), 4.55 (2H, s, H_8), 3.75 – 3.55 (3H, m, H_6 and H_7), 2.78 (1H, dd, *J* = 15.8, 5.0 Hz, H_{5e}), 2.73 (1H, dd, *J* = 15.8, 9.0 Hz, H_{5a}), 2.33 (3H, s, H_{11}), 2.17 (3H, s, H_9) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 201.7, 192.2, 161.0, 137.3, 134.7, 128.6, 128.5, 128.1, 127.8, 127.7, 73.5, 70.6, 41.5, 40.0, 31.8, 22.5 ppm. **MS** (ESI): *m/z* 313 (100%, M + Na^+), 291 (30%, M + H^+), HRMS: found (M + Na^+) 313.0854 $C_{16}H_{18}NaO_3S$ requires 313.0869, (M + H^+) 291.1042 $C_{16}H_{19}O_3S$ requires 291.1049. Flash column chromatography on silica gel (1:1 ratio of pentane and diethyl ether).

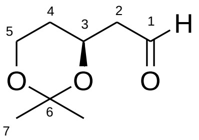
3.7. Synthesis of apicularen A THP core

Methyl 2-(*tert*-butyl-dimethyl-silanyloxy)-6-(2-oxo-ethyl)-benzoate (270)



2,6-Lutidine (0.96 g, 8.92 mmol) was added to a solution of **277**[61a] (1 g, 4.46 mmol) in DCM (17 ml). Then, TBSOTf (1.2 g, 4.9 mmol) was added to the reaction mixture at 0°C, the reaction mixture was stirred at room temperature for 6 hours. After which, water (17 ml) was added to the reaction mixture, the layers were separated. The aqueous layer was extracted with DCM (3 x 5 ml). The combined organic layer was washed with 10% aqueous HCl (5 ml) and brine (3 x 2 ml), dried over $MgSO_4$ and concentrated in vacuo. The cude **278** was used in the next step without further purification. A 1 M solution of DIBALH in cyclohexane (4.46 ml, 4.46 mmol) was added to a solution of crude **278** in DCM (25 ml) at -78°C. The reaction mixture was stirred at -78°C for 2 hours. After which, the reaction was quenched by adding ethyl acetate (2 ml) to the reaction mixture. The reaction mixture was poured into a sat. aqueous solution of sodium potassium tartrate (25 ml) at 0°C. The resulting reaction mixture was stirred for 4 hours at room temperature. After which the layers were separated, and the aqueous layer was extracted with DCM (3 x 10 ml). The combined organic layer was washed with brine (3 x 5 ml), dried over $MgSO_4$, filtered and concentrated in vacuo. The cude product was purified by flash column chromatography on silica gel (3:1 ratio of petane and diethyl ether) to give 1.08 g of **270** (78%) as a colourless oil over two steps. **IR** υ$_{max}$ (solution, $CHCl_3$): 2908, 2816, 1707, 1569, 1443, 1412, 1275, 1096, 1053, 1026, 988, 829 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.68 (1H, t, *J* = 2.0 Hz, H_8), 7.29 – 7.24 (1H, m, Ph), 6.83 – 6.80 (2H, m, Ph), 3.85 (3H, s, H_9), 3.64 (2H, d, *J* = 2.0 Hz H_7), 0.97 (9H, s, H_{10}) 0.23 (6H, s, H_{11}) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 198.9, 168.1, 153.5, 131.8, 131.0, 126.6, 123.4, 118.7, 52.2, 48.6, 25.6, 18.1, -4.3 ppm. **MS** (ESI): *m/z* 331 (100%, M + Na$^+$), 309 (40%, M + H$^+$), HRMS: found (M + Na$^+$) 331.1327 $C_{16}H_{24}NaO_4Si$ requires 331.1336, (M + H$^+$) 309.1506 $C_{16}H_{25}O_4Si$ requires 309.1517.

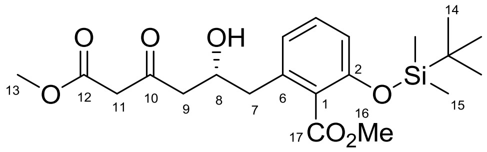
(*S*)-2-(6, 6-Dimethyl-3, 5-dioxan-4-yl)ethanol ((*S*)-271)



Compound (*S*)-**271** was prepared according to the procedure described in the literature in 25% yield over 10 steps as colourless oil.[62] **[α]$_D$^{25}** +13.6 (c 1.05, $CHCl_3$), 96% *ee*; **IR** υ$_{max}$ (solution, $CHCl_3$): 2832, 1699, 1360, 1146, 1082, 1033, 952, 920, 832 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 9.78 (1H, t, *J* = 2.0 Hz, H_1), 4.40 – 4.47 (1H, m, H_3), 4.01 (1H, dt, *J* = 11.9, 2.0 Hz, H_5), 3.86 (3H, ddd, *J* = 11.9, 5.5, 1.8 Hz, H_5), 2.63 (1H, ddd, *J* = 16.8, 7.3, 2.5 Hz, H_2), 2.49 (3H, ddd, *J* = 16.8, 5.2, 2.0 Hz, H_2) 1.49 – 1.72 (2H, m, H_4), 1.48 (3H, s, H_7), 1.37 (3H, s, H_7) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 200.9, 98.6, 64.5, 59.6, 49.9, 30.9, 29.8, 19.1 ppm. **MS** (ESI): *m/z* 181 (100%, M + Na$^+$), 159 (23%, M + H$^+$), HRMS:

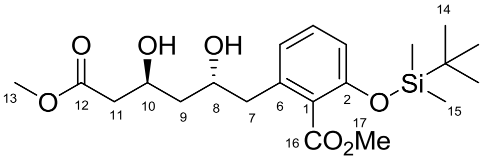
found (M + Na$^+$) 181.0833 $C_8H_{14}NaO_3$ requires 181.0835, (M + H$^+$) 159.1017 $C_8H_{15}O_3$ requires 159.1016.

(*R*)-methyl-2-(*tert*-butyl-dimethyl-silanyloxy)-6-(2-hydroxy-6-methoxy-4,6-dioxo-hexyl)-benzoate ((*R*)-288)



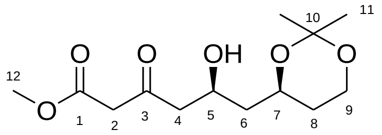
Neat Ti(^{i}OPr)$_4$ (28 mg, 0.1 mmol) was added to a solution of (*S*)-Binol (29 mg, 0.1 mmol) in THF (10 ml) and stirred for 20 min at room temperature under a N_2 atmosphere. After this time dry LiCl (8 mg, 0.2 mmol) was added and the reaction mixture was stirred for a further 30 min. After this time a solution of aldehyde **270** (1.54 g, 5 mmol) in THF (3 ml) was added and the reaction mixture was stirred at room temperature for 20 min. A solution of Chan's diene (2.6 g, 10 mmol) in THF (3 ml) was added slowly *via* a syringe pump at a rate of 30 ml/h. When the addition was complete the reaction mixture was stirred at room temperature for 16 hours. The solvent was removed in vacuo and the residue dissolved in dry MeOH (10 ml), to which was added PPTS (255 mg, 1 mmol) and the mixture was stirred at -12 ^oC for 2 hours. After this time the volatiles were removed in vacuo and the residue was dissolved in ethyl acetate (15 ml) and washed successively with sat. $NaHCO_3$ solution (3 x 5 ml) and brine (3 x 5 ml). The organics were then dried over $MgSO_4$, filtered and concentrated in vacuo to give a brownish oil. The residue was purified by flash column chromatography on silica gel (6:4 ratio of petroleum ether and ethyl acetate) to give (*R*)-**288** in 190 mg (8%) as a colourless oil. **[α]$_D$^{25}** +1.8 (c 1.1, $CHCl_3$); **IR** υ_{max} (solution, $CHCl_3$): 2908, 2816, 1707, 1569, 1443, 1412, 1275, 1096, 1053, 1026, 988, 829 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.22 (1H, t, *J* = 7.9 Hz, H_4), 6.87 (1H, m, H_3), 6.74 (1H, m, H_5), 4.28 (1H, m, H_8), 3.88 (3H, s, H_{13}), 3.73 (3H, s, H_{16}) 3.49 (2H, s, H_{11}), 3.15 (1H, d, *J* = 4.3 Hz, H_7), 2.78 – 2.70 (3H, m, H_7 and H_9), 0.96 (9H, s, H_{14}), 0.21 (6H, s, H_{15}) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 202.8, 169.3, 167.2, 152.7, 136.8, 130.5, 126.7, 122.8, 117.4, 68.5, 52.4, 52.3, 49.6, 49.2, 40.2, 25.5, 18.0, -4.4 ppm. **MS** (ESI): *m/z* 447 (100%, M + Na^+), 425 (63%, M + H^+), HRMS: found (M + Na^+) 447.1797 $C_{21}H_{32}NaO_7Si$ requires 447.1810, (M + H^+) 425.1977 $C_{21}H_{33}O_7Si$ requires 425.1990. 80% *ee* as determined from diol (2*R*,4*S*)-**289** resulting from anti reduction.

Methyl-2-(*tert*-Butyl-dimethyl-silanyloxy)-6-((2*R*,4*S*)-2,4-dihydroxy-6-methoxy-6-oxo-hexyl)-benzoate ((2*R*,4*S*)-289)



A solution of tetramethylammonium acetoxyborohydride (76 mg, 0.29 mmol) in acetic acid (0.6 ml) was added to a pre-cooled (-35 °C) solution of (*R*)-**288** (20 mg, 0.041 mmol) in acetonitrile (0.8 ml) over a period of 5 min. After 2 hours the reaction mixture was kept stirring at – 20 °C for 13 hours. The reaction was then quenched by addition of a sat. aqueous solution of Rochelle`s salts (4 ml) and then warmed to room temperature. The reaction mixture was diluted with ethyl acetate (5 ml) and washed with sat. Na_2CO_3 (3 x 1 ml), the aqueous layer was extracted with ethyl acetate (3 x 1 ml). The combined organic layer was washed with brine (3 x 1 ml), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (1:1 ratio of petroleum ether and ethyl acetate) to give 17.3 mg (98%) of (2*R*,4*S*)**-289** as a colourless oil. **$[\alpha]_D^{25}$** +32.2 (c 1.0, $CHCl_3$); **IR** υ_{max} (solution, $CHCl_3$): 2908, 2816, 1707, 1569, 1443, 1412, 1275, 1096, 1053, 1026, 988, 829 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 7.15 (1H, t, *J* = 7.8 Hz, H_4), 6.79 (1H, m, H_3), 6.66 (1H, m, H_5), 4.29 (1H, m, H_{10}), 4.06 (1H, m, H_8), 3.81 (3H, s, H_{13}), 3.64 (3H, s, H_{17}) 3.35 (1H, d, *J* = 4.3 Hz, H_7), 2.95 (1H, d, *J* = 4.3 Hz, H_7), 2.71 (1H, dd, *J* = 13.9, 4.5 Hz, H_{11}), 2.62 (1H, dd, *J* = 13.9, 8.6 Hz, H_{11}), 2.47 – 2.44 (2H, m, H_9), 0.89 (9H, s, H_{14}), 0.15 (3H, s, H_{15}) 0.14 (3H, s, H_{15}) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 173.3, 169.6, 152.9, 137.8, 130.6, 126.7, 122.9, 117.4, 69.8, 65.8, 52.4, 51.9, 42.3, 41.5, 41.2, 25.6, 18.1, -4.3 ppm. **MS** (ESI): *m/z* 449 (100%, M + Na^+), 427 (63%, M + H^+), HRMS: found (M + Na^+) 449.1957 $C_{21}H_{34}NaO_7Si$ requires 449.1966, (M + H^+) 427.2136 $C_{21}H_{33}O_7Si$ requires 427.2147. 80% ee as determined by HPLC: CHIRACEL OD-H, hexane/isopropanol 95:5, flow rate = 0.4 ml/min, T = 20 °C, t_r anti-(8*R*, 10*R*) minor = 47.1 min, t_r anti-(8*R*, 10*S*) major = 53.0 min; formation of syn diol was not detected.

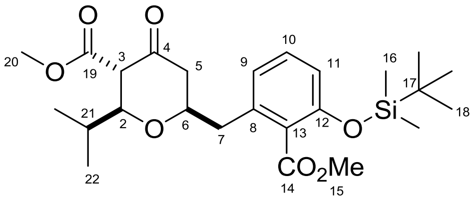
(*S*)-Methyl 6-((*S*)-2,2-dimethyl-1,3-dioxan-4-yl)-5-hydroxy-3-oxo-hexanoate ((*S*,*S*)-290)



Neat Ti(O^{i}Pr)$_4$ (7 mg, 0.025 mmol) was added to a solution of (*R*)-Binol (8.0 mg, 0.028 mmol) in THF (2 ml) and stirred for 20 min at room temperature under a N_2 atmosphere. After this time dry LiCl (2.1 mg, 0.05 mmol) was added and the reaction mixture was stirred for a further 30 min. After this time a solution of aldehyde (*S*)-**271** (200 mg, 1.3 mmol) in THF (1 ml) was added and the reaction mixture was stirred at room temperature for 20 min. A solution of Chan's diene (660 mg, 2.5 mmol) in THF (1 ml) was added slowly *via* a syringe pump at a rate of 30 ml/h. When the addition was complete the reaction mixture was stirred at room temperature for overnight. The solvent was removed in vacuo and the residue dissolved in dry MeOH (4 ml), to which was added PPTS (64 mg, 0.25 mmol) and the mixture was stirred at -12 ^{o}C for 2 hours. After this time the volatiles were removed in vacuo and the residue was dissolved in ethyl acetate (15 ml) and washed successively with sat. $NaHCO_3$ solution (3 x 1 ml) and brine (3 x 1 ml). The organics were then dried over $MgSO_4$, filtered and concentrated in vacuo to give a brownish oil. The residue was purified by flash column chromatography on silica gel (6:4 ratio of petroleum ether and ethyl acetate) to give (*S*,*S*)-**290** in 173 mg (50%) as a colourless oil. **$[\alpha]_D^{25}$** +23.3 (c 1.0, $CHCl_3$); **IR** υ_{max} (solution, $CHCl_3$): 3435, 2909, 2833, 1719, 1689, 1415, 1362, 1302, 1145, 1083, 951, 859, 802 cm^{-1}. **^{1}H NMR** (400 MHz, Benzene d_6) δ: 4.20 (1H, m,

H_9), 3.75(1H, m, H_9), 3.53 – 3.51 (2H, m, H_5 and H_7), 3.30 (3H, s,H_{12}), 3.18 (2H, m, H_2), 2.50 (1H, dd, *J* = 16.2, 7.6 Hz, H_4), 2.28 (1H, dd, *J* = 16.2, 4.9 Hz, H_4), 1.65 – 1.30 (2H, m, H_6), 1.34 (3H, s, H_{11}), 1.30 – 1.20 (1H, m, H_8), 1.19 (3H, s, H_{11}), 0.84 – 0.75 (1H, m, H_8) ppm. **^{13}C NMR** (400 MHz, Benzene d_6) δ: 201.4, 166.9, 97.7, 68.6, 66.8, 59.0, 50.1, 49.5, 49.3, 42.3, 30.9, 29.5, 18.6 ppm. **MS** (ESI): *m/z* 297 (100%, M + Na^+), HRMS: found (M + Na^+) 297.1312 $C_{13}H_{22}NaO_6$ requires 297.1309.

3-Methylmethanoate-6-(2-(tert-butyldimethylsilyloxy-2-(methoxycarbonyl)benzyl)-2-(2-methylethyl)-4-oxo-tetrahydropyran (296)



Solid $Yb(OTf)_3$ (130 mg, 0.21 mmol) was added to a stirred solution of aldol product *rac*-**288** (100 mg, 0.21 mmol) and isobutaraldehyde (16.4 mg, 0.22 mmol) in dry THF (2 ml) and the reaction mixture was stirred for 1.5 h. After this time, the reaction mixture was diluted with diethyl ether (4 ml) and the organics washed successively with sat. $NaHCO_3$ solution (3 x 1 ml). The aqueous layer was extracted with ethyl acetate (3 x 1 ml), and the combined organic layer was washed with brine (3 x 1 ml), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (9:1 ratio of petroleum ether and ethyl acetate) to give 75 mg (75%) of THP predominated with *cis*-keto THP **296** (19:1 selectivity). **IR** υ_{max} (solution,

$CHCl_3$): 3372 (enol isomer), 2912, 1692, 1443, 1413, 1258, 1095, 1063, 831 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) 7.18 (1H, t, *J* = 7.9 Hz, H_{10}), 6.88 (1H, d, *J* = 7.9 Hz, H_9), 6.72 (1H, d, *J* = 7.9 Hz, H_{11}), 3.91 – 3.81 (1H, m, H_2), 3.85 (3H, s, H_{15}), 3.80 – 3.69 (1H, m, H_6), 3.73 (3H, s, H_{20}), 3.36 (1H, d, *J* = 10.7 Hz, H_3), 2.93 (1H, dd, *J* = 14.4, 7.4 Hz, H_7), 2.74 (1H, dd, *J* = 14.4, 5.2 Hz, H_7), 2.43 (1H, dd, *J* = 14.4, 2.4 Hz, H_{5eq}), 2.25 (aH, dd, *J* = 14.4, 11.6 Hz, H_{5a}), 1.69 (1H, m, H_{21}), 0.96 (9H, s, H_{18}), 0.96 – 0.93 (6H, m, H_{22}), 0.21 (6H, s, H_{16}) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$) δ: 203.8, 168.72, 168.66, 152.5, 135.8, 129.8, 126.8, 123.2, 117.3, 82.1, 60.6, 52.08, 52.04, 46.6, 39.6, 31.4, 25.5, 19.6, 18.0, 15.3, -4.40, -4.36 ppm. **MS** (ESI): *m/z* 501 (100%, M + Na^+), 479 (40%, M + H^+), HRMS: found (M + Na^+) 501.2264 $C_{25}H_{38}NaO_7Si$ requires 501.2279, (M + H^+) 479.2442 $C_{25}H_{39}O_7Si$ requires 479.2460.

4. Appendix

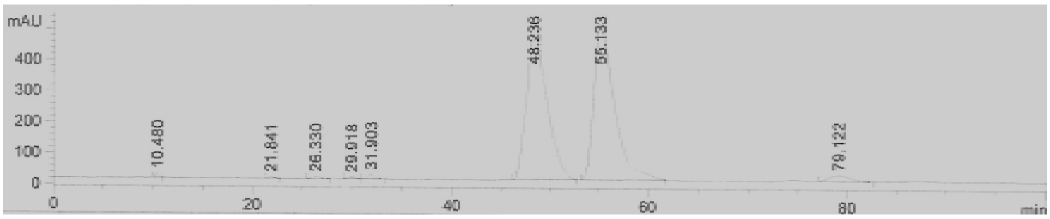


Figure 11: HPLC experiment of diol *rac*-**289**.

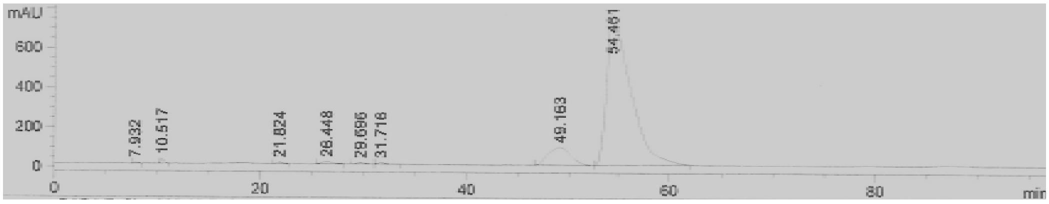


Figure 12: HPLC experiment of diol *(2R,4S)*-**289**.

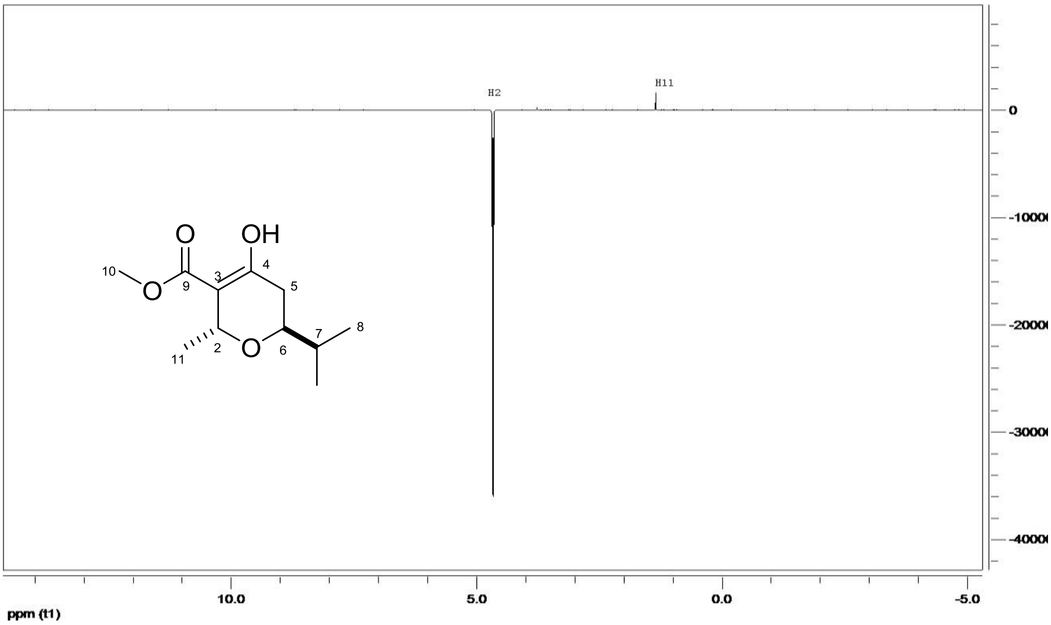


Figure 13: NOE experiment with irradiation at H2.

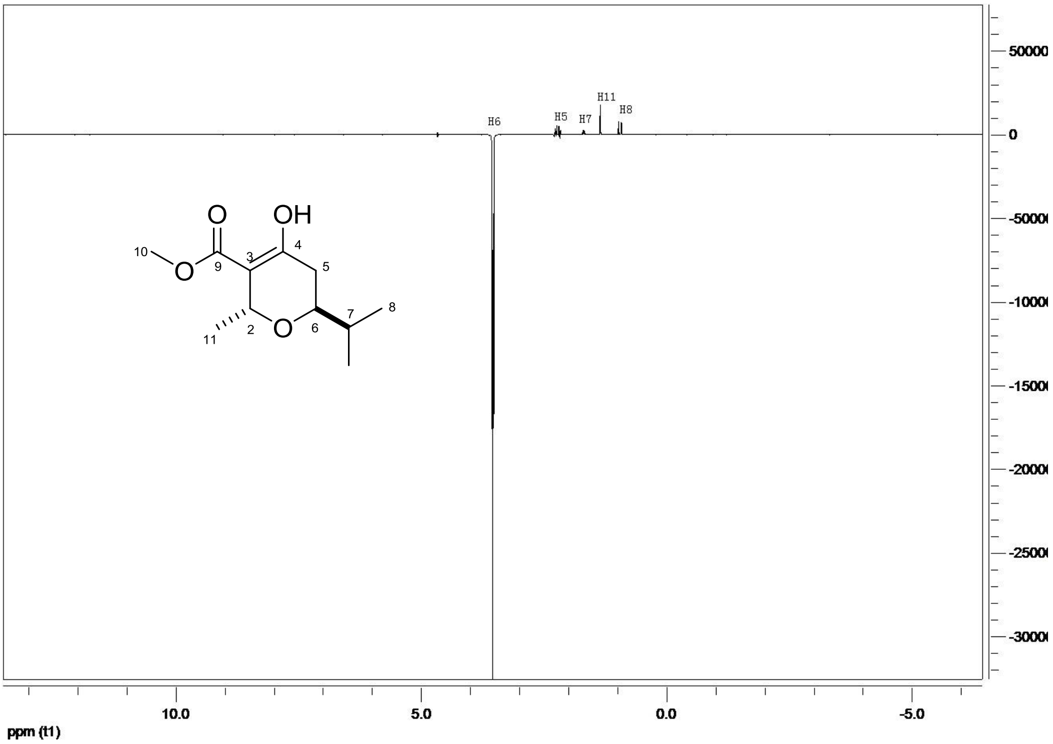


Figure 14: NOE experiment with irradiation at H6.

5. Abbreviations

AIBN	azobisisobutyronitrile
Bn	benzyl
BPS	*t*-butyldiphenylsilane
CPME	cyclopentyl methyl ether
CSA	Camphorsulfonic acid
Cy	cyclohexyl
DCM	dichloromethane
DHP	dihydropyran
DHT	dihydrothiopyran
DIBALH	diisobutylaluminium hydride
2,6-DTBMP	2,6-di-*tert*-butyl-4-methyl pyridine
DMAP	*N*,*N*-4-dimethylaminopyridine
dr	diastereomeric ratio
EDDA	ethylene diamine diacetate
ee	enantiomeric excess
eq	equivalent
HAD	hetero Diels-Alder
hr	hour
HMDS	hexamethyldisilazane
Hz	Hertz
^{i}Pr	isopropyl
O^{i}Pr	isopropoxyl
IR	infra-red
LDA	lithium diisopropylamide

LA	Lewis acid
Me	methyl
MHz	megaHertz
NHC	*N*-heterocyclic carbene
NMO	N-methylmorpholine-N-oxide
OAc	acetate anion
Ph	phenyl
ppt	precipitate
PG	protecting group
pyr	pyridine
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
rt	room temperature
THF	tetrahydropyran
TLC	thin-layer chromatography
TMS	trimethylsilyl
O^tBu	*tert*-butoxide
TPAP	tetrapropylammonium perruthenate
Ts	tosyl (toluenesulfonyl)

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