Total Synthesis of the C-1 – C-19 Fragment of Phorboxazoles

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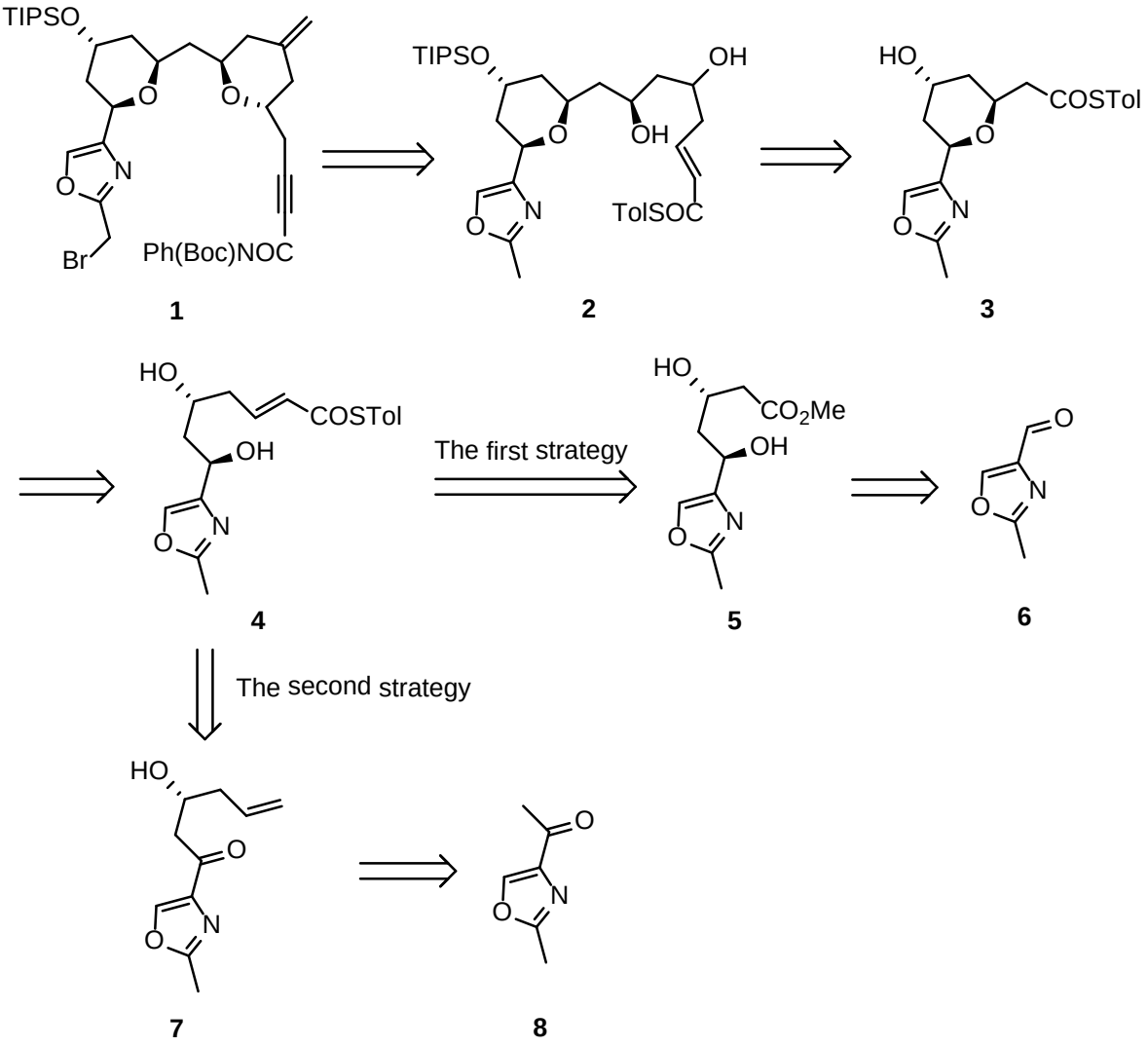
Abstract

Phorboxazoles have become interesting synthetic target, because of their challenging molecular structure and their potent anticancer, antifungal, and antibiotic activity. In this study, two different strategies are used to form two tetrahydropyran rings in the fragment of C-1 – C-19 of phorboxazoles **1**. The first strategy was designed to use oxazole aldehyde **6** as the starting material through Wittig reaction, whereas the second approach was assumed using oxazole methyl ketone **8** by cross metathesis. The key reaction in both strategies will be the application of our developed stereodivergent oxy-Michael reaction methodology.[65]



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At last, I would really thank my friend Haonan Yuan and my parents for supporting me spiritually throughout writing this thesis and my life in general.

Declaration

I declare that this thesis is a presentation of original work and I am the sole author. This work has not previously been presented for an award at this, or any other, University. All sources are acknowledged as References.

1. Background introduction

1.1 Tetrahydropyran (THP) rings

Natural products containing highly substituted THP rings continue to be targets for synthetic organic chemists. The reasons are: (i) the structures of these natural products present several synthetic challenges, (ii) many of these natural products have potent bioactivity in a number of cell assays, and may provide new treatments for various diseases. Within these natural product structures the 4-hydroxy-2,6-disubstituted THP ring is one of the most abundant substitution patterns.[1]

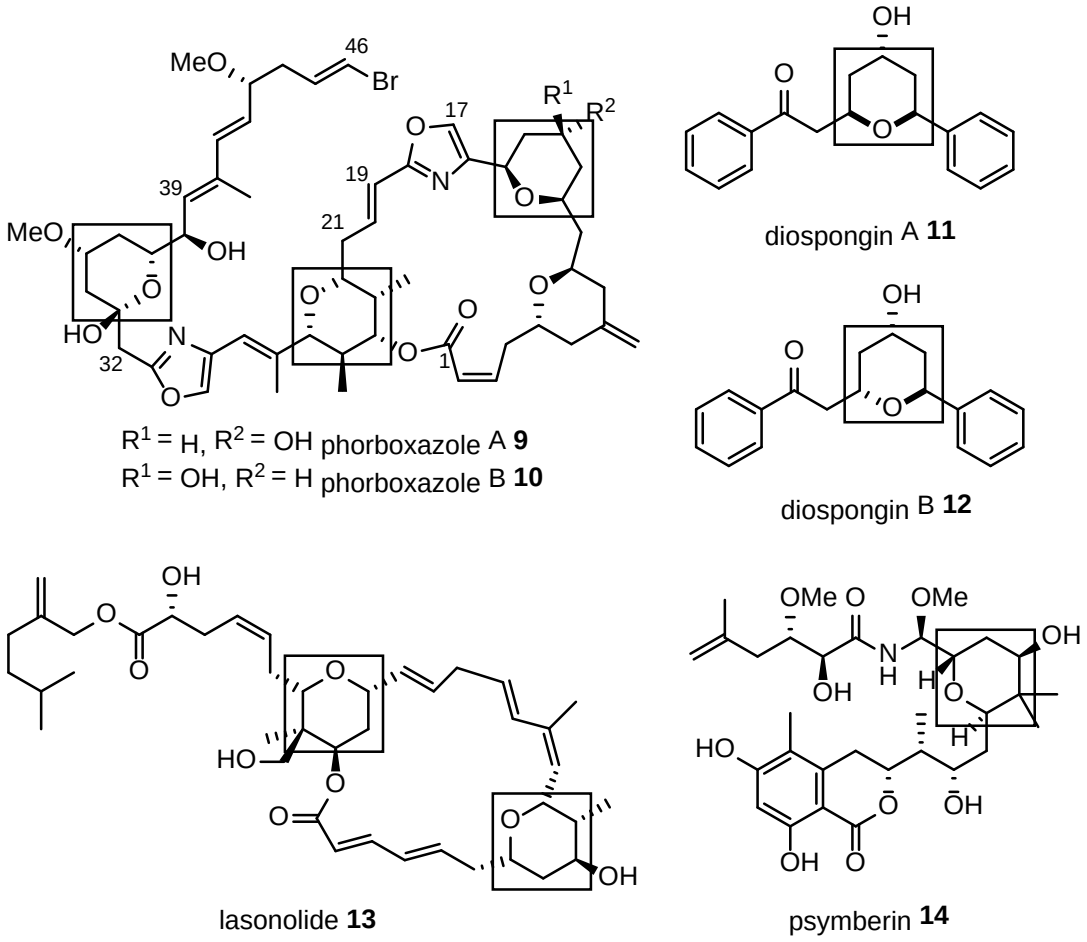


Figure 1. 4-Hydroxy-2,6-disubstituted tetrahydropyran-containing natural products

The phorboxazoles (**9** & **10**) contain three such units and have sub-nanomolar activity against the entire range of the NIH cancer cell lines;[2] lasonolide A **13** has two such motifs and exhibits sub-nanomolar anti-tumour activity;[3] the diospongins (**11** & **12**) have anti-osteoporotic activity and

psymberin **14** is an inhibitor of cancer cell proliferation (**Figure 1**).[4, 5] These biological activities have compelled plenty of work to be done with the propose to efficiently synthesise these molecules and related structures.

1.2 Phorboxazoles A and B

Searle and Molinski reported the isolation of phorboxazoles A and B (**Figure 1**) from the marine sponge *Phorbas sp.*[2] These natural products have become interesting synthetic targets, because of their challenging molecular structure and their potent anticancer, antifungal,[2, 6] and antibiotic activity.[7]

In addition to its antifungal activity, the phorboxazoles displayed antibiotic activity against *saccharomyces carlsberensis.*[2] For both **9** and **10**, bioassays against the National Cancer Institute panel of 60 human solid tumour cell lines revealed excellent activity against the entire panel (GI_{50} = 1.58 × 10^{-9} M).[6a] Some cell lines were completely inhibited at the lowest level tested. Particularly noteworthy, phorboxazole A **9** inhibited the human colon tumour cell line HCT-116 and the breast cancer cell line MCF7 with GI_{50} values of 4.36 × 10^{-10} M and 5.62 × 10^{-10} M, respectively. This data place the phorboxazoles in the company of the spongistatins, collectively the most potent cytostatic agents discovered to date.[8]

Although the biochemical mode of action remains undefined, (+)-phorboxazole A **9** is known to arrest the cell cycle in S phase but does not inhibit tubulin polymerization or interfere with the integrity of microtubules. Unfortunately, further biological analysis was not possible, because access to the producing sponge is currently restricted.[9] Thus, the phorboxazoles will be only available *via* total synthesis.

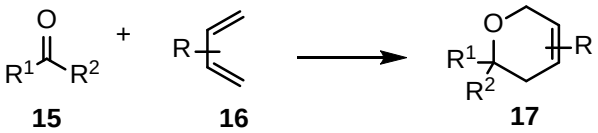
The phorboxazole skeleton is composed of six rings including two 2,4-disubstituted oxazoles and four THP rings, as well as 15 stereocentres organized into a macrolide lactone (C-1 – C-26) and a side chain substructure (C-27 – C-46). This report is concerned with the synthesis of C-1 – C-19 fragment.

Plenty of reactions have been developed for the enantioselective synthesis of substituted THP rings, including hetero-Diels-Alder cyclization,[16] Prins cyclization,[20, 23] Petasis-Ferrier rearrangements,[25] cyclization onto epoxides,[24] the reduction of cyclic hemi-ketals[27] and intramolecular oxy-Michael reactions.[32] The brief review will be shown in the following pages. Most of them will be related to phorboxazoles.

1.3 Strategies used to form THP rings and related natural products

1.3.1 Asymmetric hetero-Diels-Alder reaction

Since its discovery by Diels and Alder,[10] the Diels-Alder reaction has become one of the cornerstone reactions in organic chemistry for the construction of six-membered rings.[11] There are also many variants of the Diels-Alder reaction, including the hetero-Diels-Alder (HDA) reaction, which is a powerful reaction to build up chiral heterocyclic systems (**Scheme 1**).[12]



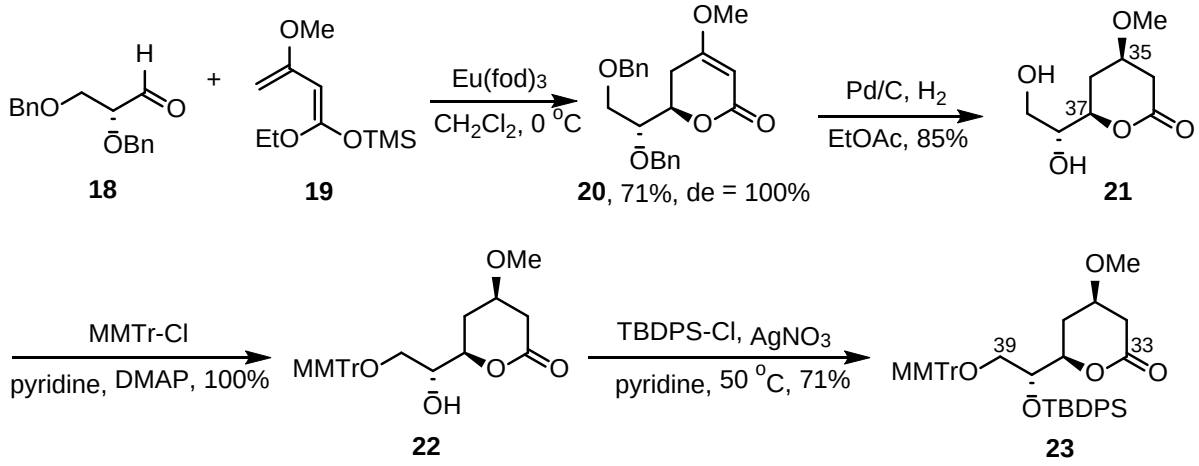
15 **16** **17**

Scheme 1. HDA reaction of carbonyl compounds

In 2007, a total synthesis of phorboxazole B **10** was developed by Burke *et al*. based on a catalytic diastereoselective HDA reaction of a mannitol derived aldehyde with Brassard's diene, as shown in **Scheme 2**.[13]

They discovered an efficient entry to the C-33 – C-39 lactone **23**, which could arise from a chelation-controlled hetero-Diels-Alder reaction of the mannitol-derived aldehyde **18**[14] with Brassard diene **19**.[15] The stereochemical outcome of **20** was predicted based on the work of Midland *et al.*[16] who found the chiral lanthanide shift reagents (LSRs) tris[3-(hepta- fluoropropylhydroxymethylene) d-camphorato]europium (III) ($Eu(hfc)_3$) and other Lewis acid catalysed the cycloadditions of α-alkoxy aldehydes with Brassard's diene **19**. Although the presence of α, β-alkoxy substituents could potentially interfere with the chelation control involving the stereogenic centre at the α position.[17]

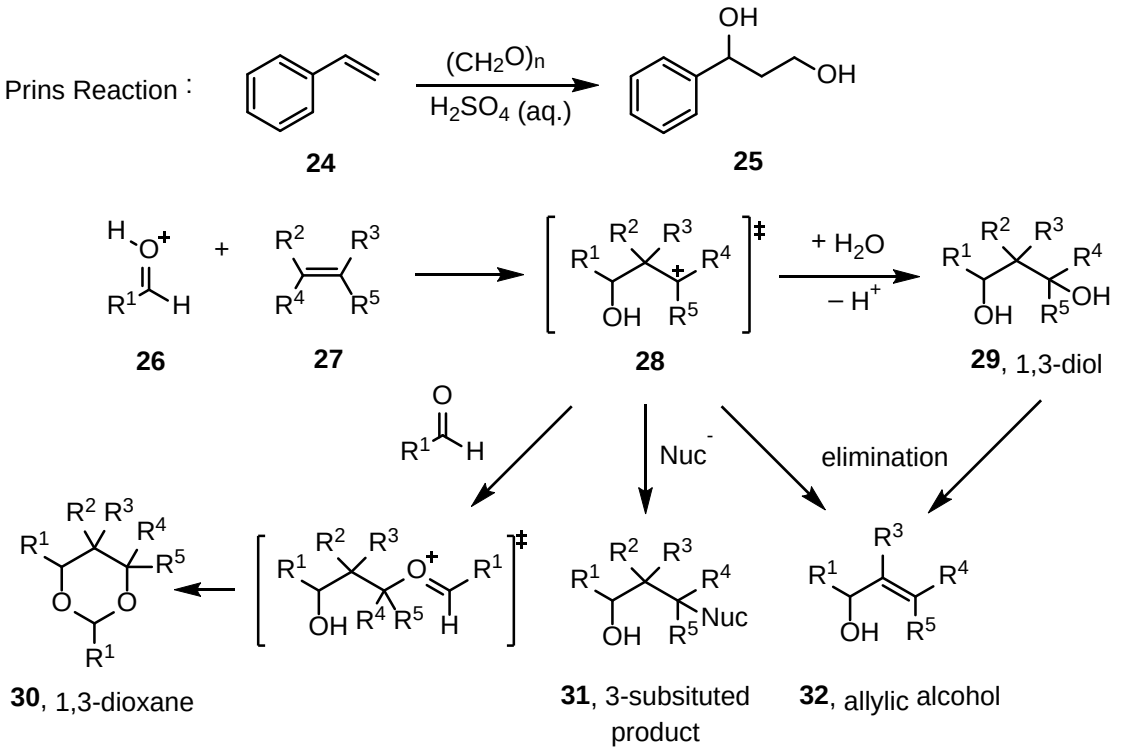
Combination of **18** and **19** to produce **20** proceeded smoothly under Eu^{3+} catalysis.[18] Catalytic hydrogenation, generated both saturated rings and liberated the C-38 and C-39 hydroxy groups, provided crystalline diol **21**. Selective protection of the primary hydroxy group as the monomethoxytrityl ether (MMTr)[19] was accomplished in quantitative yield to afford **22**, followed by installation of the TBDPS ether at C-38 to give the complete C-33 – C-39 lactone **23** in four steps from Brassard's diene **19**.



Scheme 2. Synthesis of *the C-33 – C-39 lactone of* phorboxazole B. fod=tris(6,6,7,7,-8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione), MMTr=monomethoxytriphenylmethyl

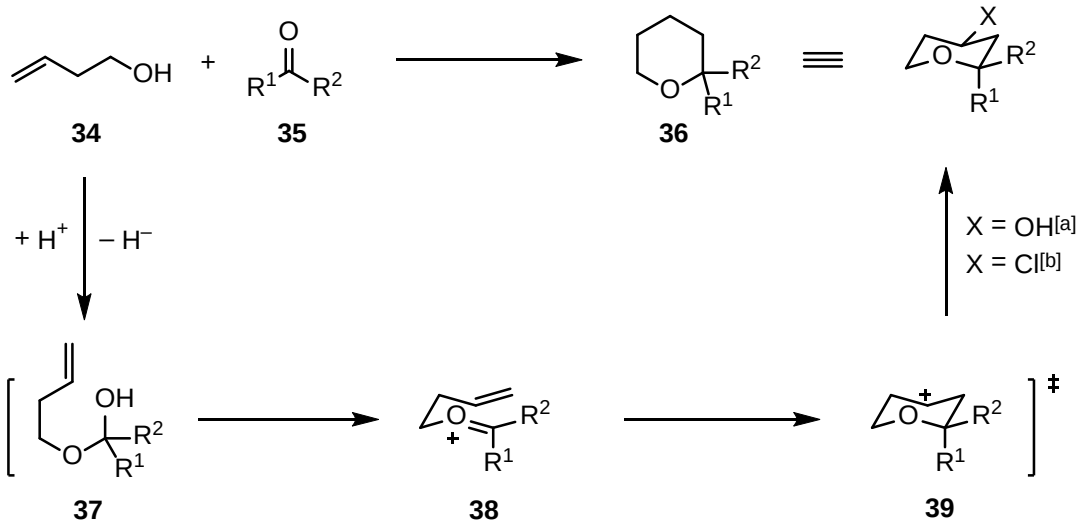
1.3.2 Prins cyclization

In 1911, Hendrik Jacobus Prins reported the acid-catalysed addition of aldehydes to olefinic compounds. The Prins reaction is the acid-catalysed addition of alkenes to aldehydes, and gives different products depending on the reaction conditions. **Scheme 3** shows that the intermediate transition state can be treated by different substrates, and it can also undergo elimination. [20]



Scheme 3. Prins reaction, mechanism and possible reaction pathways. Nuc = nucleophile

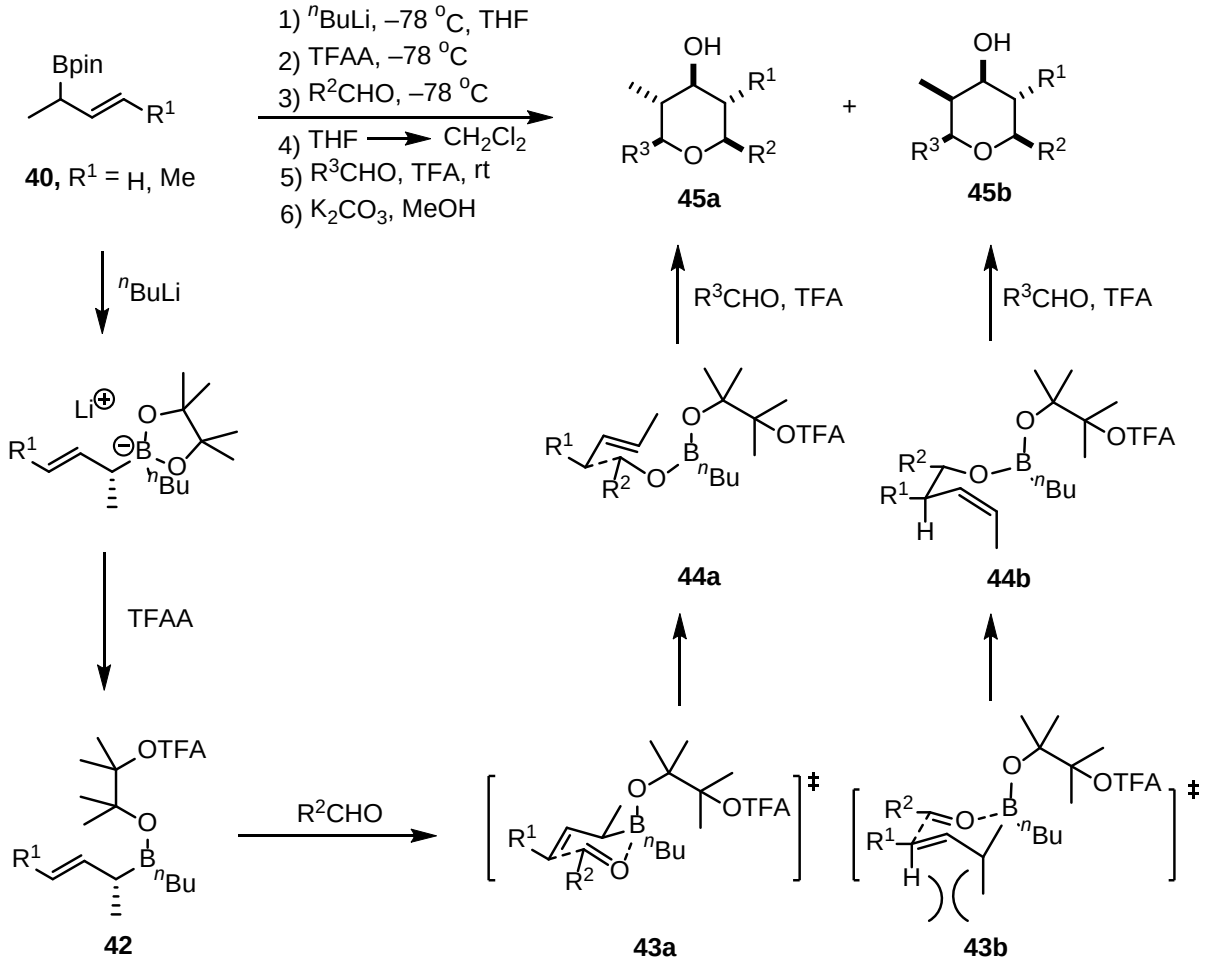
In 1955, Hanschke was the first to report the selective synthesis of THP rings through a Prins reaction by combining 3-buten-1-ol with a variety of aldehydes or ketones in the presence of acid and it was developed and used to form a lot natural products in recent years (**Scheme 4**).[21]



Scheme 4. First report and mechanism of the synthesis of THP rings by the Prins reaction.

[a] when H_2SO_4 was used. [b] When HCl was used

Recently, the Aggarwal group has proved that lithiation-borylation has emerged as a powerful tool for the synthesis of chiral boronic esters including allylic boronic esters. THP rings could be constructed in a highly stereocontrolled way through the three-component allylboration-Prins reaction (**Scheme 5**).

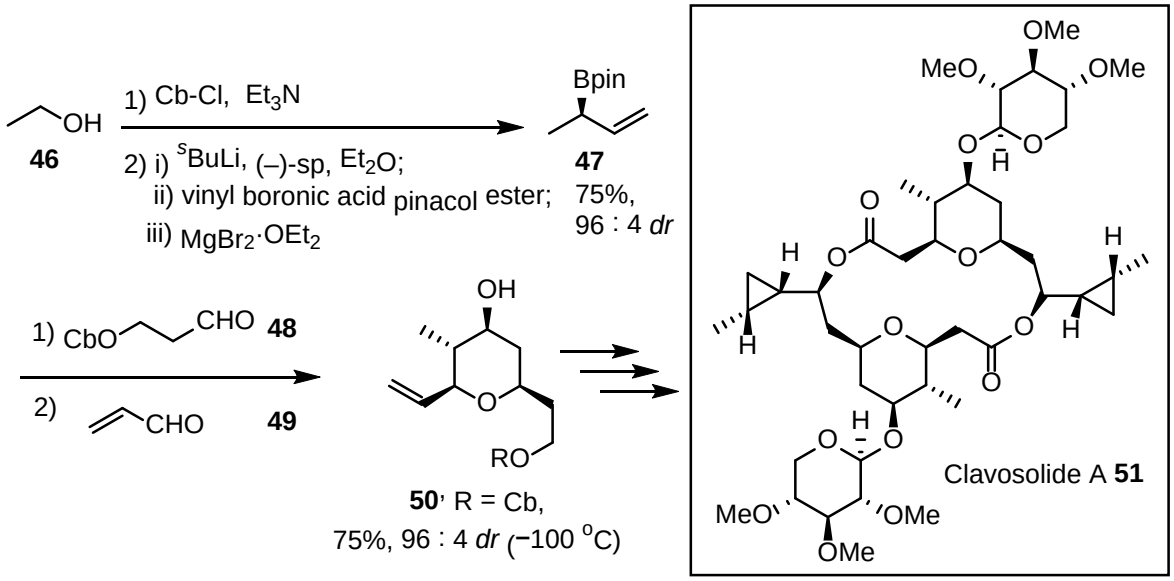


Scheme 5. Three-component allylboration / Prins cyclization

The allylic boronic ester **40** was treated with ^{n}BuLi and TFAA to give intermediate borinic ester **42**, which was reacted with the first aldehyde (R^2CHO) to give intermediate **44 (a** / **b)**. Following solvent exchange to CH_2Cl_2, subsequent reaction with a second aldehyde in TFA followed by acid mediated hydrolysis, furnished the hydroxy THPs **45a** and **45b**. The more reactive borinic ester **42** made the modified allylboration reaction occurs, which reacts with the aldehyde through a Zimmerman-Traxler chair transition state **43**. The reduced steric hindrance around boron in the borinic ester when

compared to the pinacol ester gives the better preference for the reaction to occur *via* transition state **43a**, with the methyl group situated in a *pseudo*-equatorial position, leading to the higher observed diastereoselectivity. The diastereoselectivity of THP **45a** directly reflects the *E/Z* selectivity obtained in the initial allylboration of the aldehyde.[22]

In 2016, this methodology was applied towards the THP core of the macrolide (–)-clavosolide A **51** in a concise and efficient way by Aggarwal group (**Scheme 6**).[23]



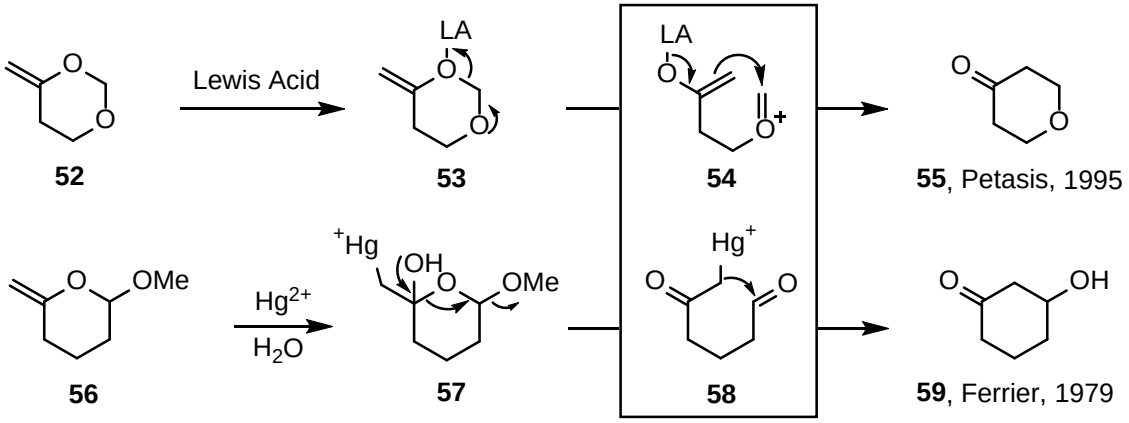
Scheme 6. Synthesis of the THP core. TBS = tert-butyldimethylsilyl; OTIB = 2,4,6-triisopropylbenzoate; sp = sparteine

The allylic boronic ester (*R*)-**47** was constructed using **46** through lithiation-borylation methodology with (–)-sparteine, followed by reacting with aldehyde **48**, and aldehyde **49**. they found that the three component allylboration-Prins reaction worked well when using acrolein, furnishing the THP ring **50** at –100 °C in high yield and good diastereoselectivity (96 : 4 *dr*).

1.3.3 Petasis-Ferrier rearrangements

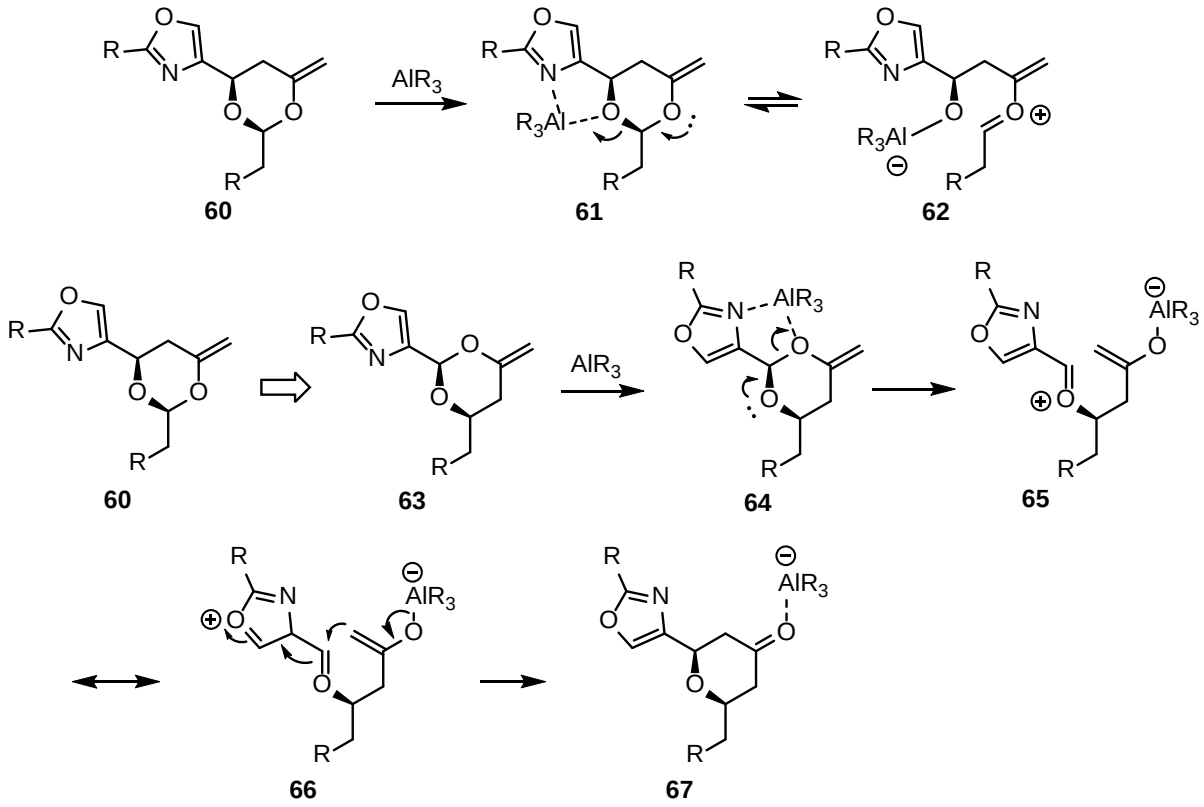
In 1996, Petasis discovered that the acid-promoted rearrangement of enol acetals **52** to tetrahydropyran ones **55** (**Scheme 7**) which proceeds *via* fragmentation, followed by endo cyclization

onto an oxocarbenium **54**.[24] This reaction is closely related to the earlier Ferrier Type-II[25] enol ether rearrangement (**56** to **59**) induced by mercuric ion.



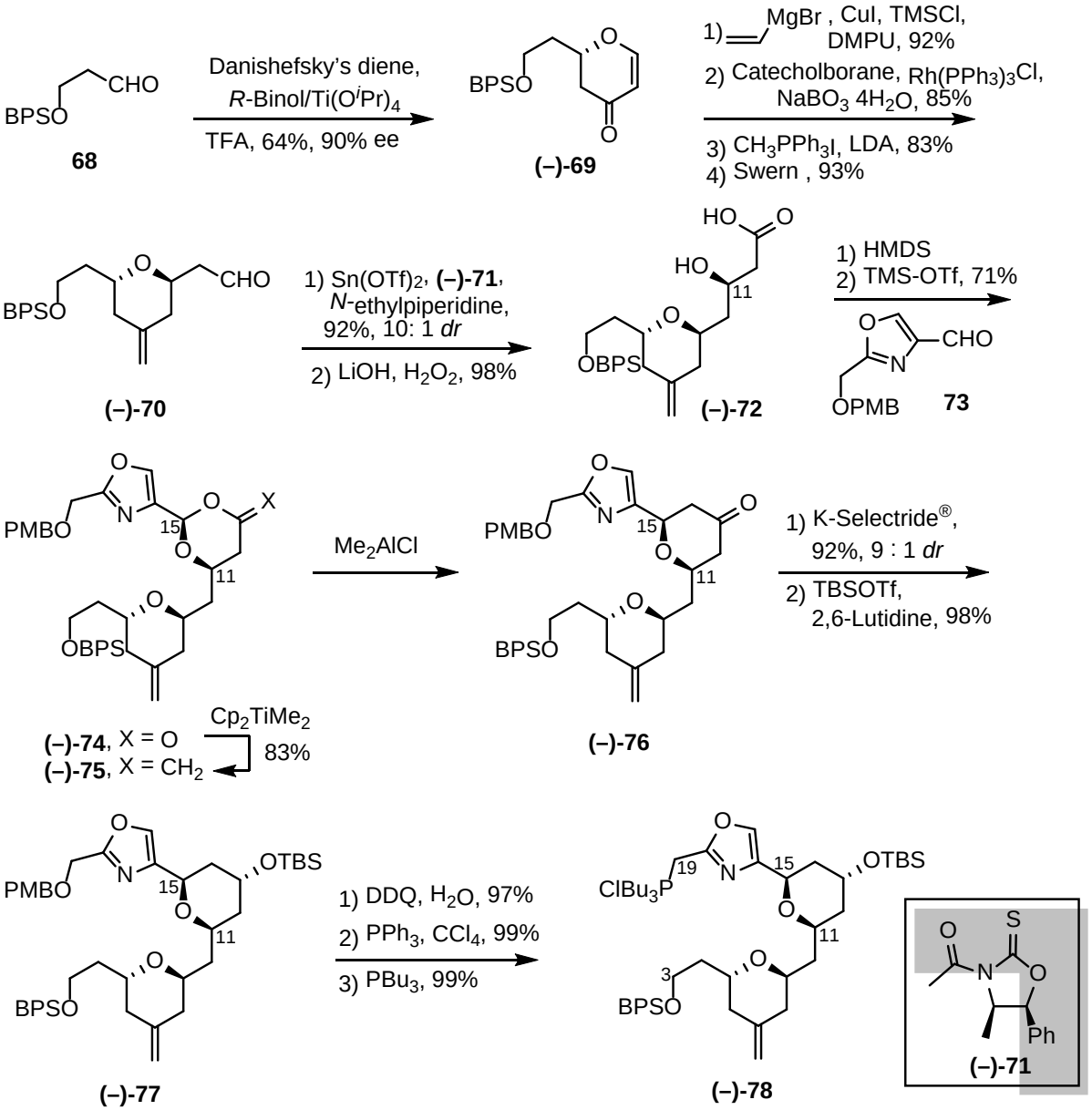
Scheme 7. Petasis-Ferrier rearrangement

Smith III's group reported a modified Petasis-Ferrier rearrangement (**Scheme 8**). The enol ether **60** failed to undergo rearrangement, because the preferred coordination of the aluminium Lewis acid promoter with the conjugated oxazole nitrogen precluded Lewis acid chelation to the requisite enol ether oxygen in **60**, thereby preventing rearrangement. When they changed the rearrangement substrate to **63**, initial coordination of bidentate[26] Lewis acid with the oxazole nitrogen would allow productive activation of the enol ether oxygen **64**, liberating the aluminum enolate, which in turn would rearrange to the tetrahydropyranone **67**.[7]



Scheme 8. Modified Petasis-Ferrier rearrangement

The new bidentate Lewis acid (Me_2AlCl) was explored and used to form the THP rings in phorboxazole A **9** (**Scheme 9**) in 2001. Hetero-Diels-Alder reaction of aldehyde **68** with Danishefsky's diene,[27, 28] promoted by *R*-Binol/Ti(O^iPr)$_4$, furnished enone **69**. Axial addition of vinyl cuprate then furnished *trans*-tetrahydropyranone, which in turn was subjected to hydroboration, Wittig olefination, and Swern oxidation to give aldehyde **70**. A Nagao aldol reaction[29] with tin enolate which derived from **71**, followed by hydrolysis gave β-hydroxy acid **72**.

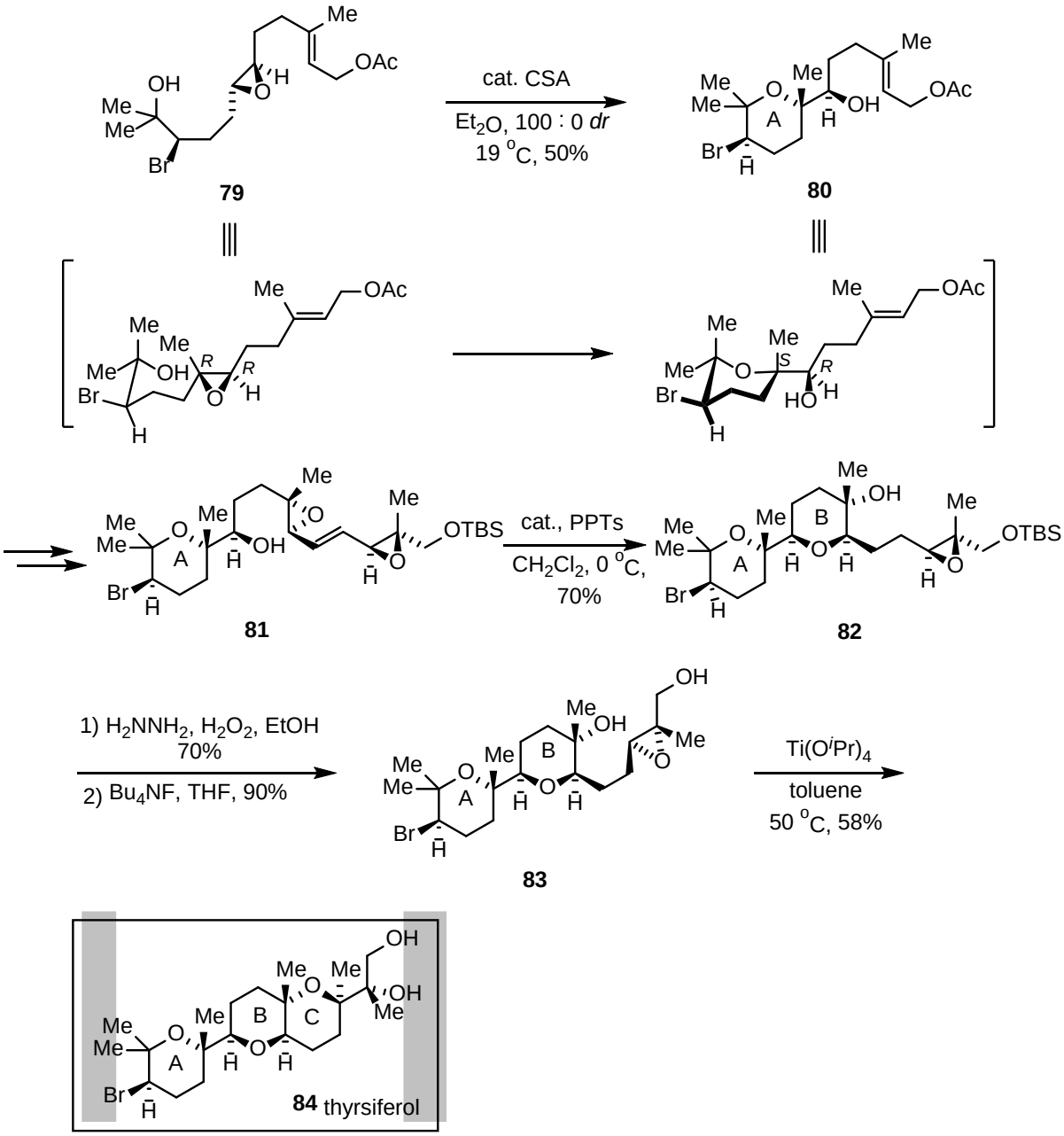


Scheme 9. Synthesis of C-3 – C-19 fragment of phorboxazole A by using Petasis-Ferrier rearrangement. BPS = ^{t}butylbiphenyl

Dioxanone **74** was then constructed *via* the HMDS-promoted bissilylation of **72** and condensation with oxazole aldehyde **73**. Petasis-Tebbe methylenation (Cp_2TiMe_2) provided enol ether **75**. Five steps were required to synthesise the C-3 – C-19 sub target of phorboxazole A **78**: reduction of the C-13 ketone (K-Selectride®), silylation (TBSOTf, 2,6-Lutidine), oxidative removal of the PMB ether (DDQ), generation of the primary chloride (PPh_3, CCl_4) and substitution with tributyl phosphine.

1.3.4 Cyclizing onto epoxides

McDonald group successfully synthesised the thyrsiferol **84** by using cyclization onto epoxides in 2001.[30] Three THP rings (A, B and C) were prepared using acid catalysis (**Scheme 10**).

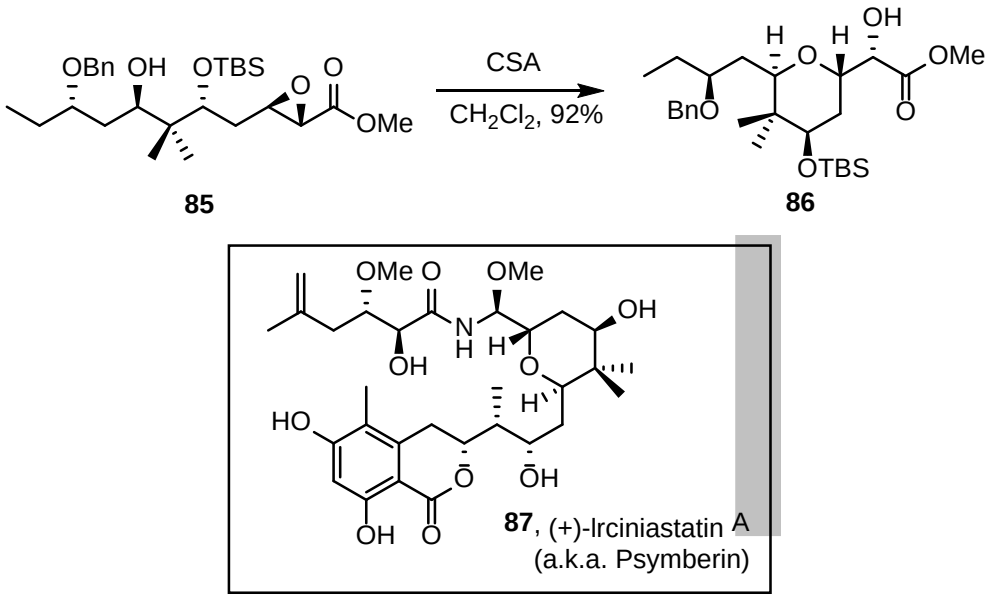


Scheme 10. Completion of three THP rings of thyrsiferol by cyclizing onto epoxides

Brønsted-acid catalysed cyclization of **79** proceeded with complete stereoselectivity for tetrahydropyran formation. Although cyclization in polar solvents such as acetone or THF provided a diastereomeric mixture of the bromotetrahydropyrans **80** (***R*** *&* ***S)***, a kinetic resolution could be

achieved when the acid-catalyzed cyclization of **79** was suspended in diethyl ether. The control of the reaction the temperature and the time resulted in the formation of only one diastereomer, **80*R***. The A ring cyclization product **80** was reacted through several steps, to give hydroxydiepoxide **81**. A second Brønsted-acid catalysed cyclization of the hydroxydiepoxide **81** was performed with good *endo*-regioselectivity for the tetrahydropyran B ring **82**, following with diimide hydrogenation[31] of the alkene, then removing the silyl ether to give the epoxydiol **83**. The epoxydiol **83** then cyclised to synthesise the third THP ring C using the Lewis acid $Ti(O^iPr)_4$ to form thysiferol **84**.

In 2013, Smith III 's group used this strategy to form a 2,6-*trans*-tetrahydropyran in the total synthesis of (+)-irciniastatin A **87**.[32] According to Baldwin's rules, the desired 6-exo-tet and undesired 7-endo-tet cyclisation pathways could complete, however under Lewis acidic conditions the desired 6-exo-tet cyclisation occurred which provided the THP ring in a very high yield (**Scheme 11**).



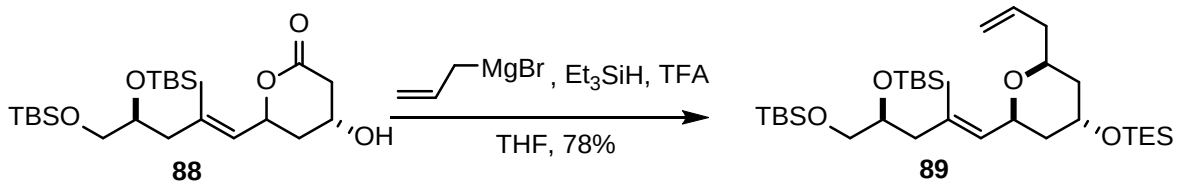
Scheme 11. Completion of the THP ring of (+)-irciniastatin A

1.3.5 Reduction of cyclic hemi-ketals

Reductive cyclisation of hemi-ketals also has proved to be an effective method for the constructing of THP rings in many natural products. These reactions proceed through a cyclic oxocarbenium ion intermediate which is trapped by the incoming nucleophile. Depending on the nucleophile and the

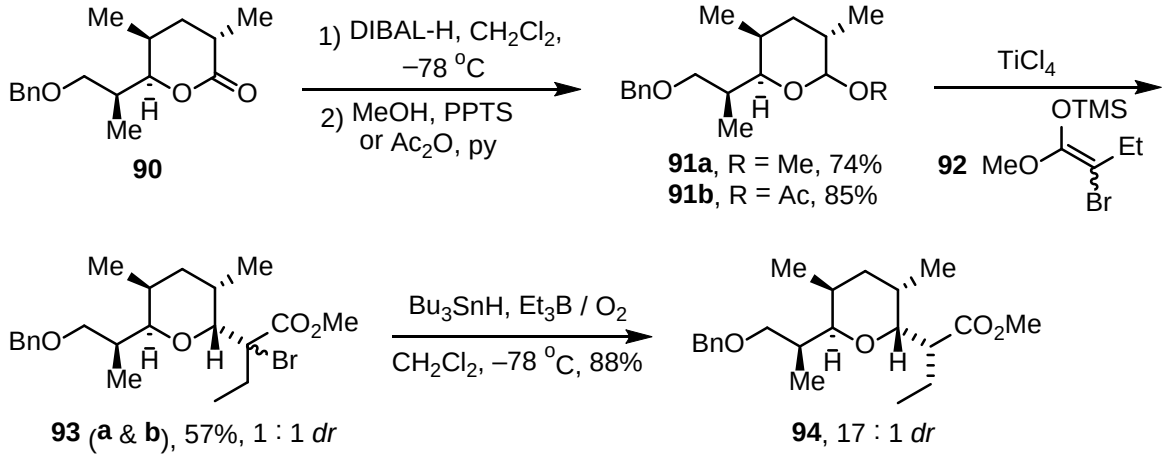
oxocarbenium ion, both 2,6-*cis* or 2,6-*trans* THPs can be accessed. In general, there are two common strategies: those which involve addition to a lactone precursor and those which involve the formation of a cyclic hemi-ketal.[33]

Jennings constructed the THP ring in (–)-dactylolide and (–)-zampanolide **89** by adding the allyl Grignard to **88**, treated with Et_3SiH and TFA (**Scheme 12**).[34] The desired *cis*-isomer was achieved by the *pseudo*-axial attack of the reducing agent on the oxocarbenium ion intermediate.



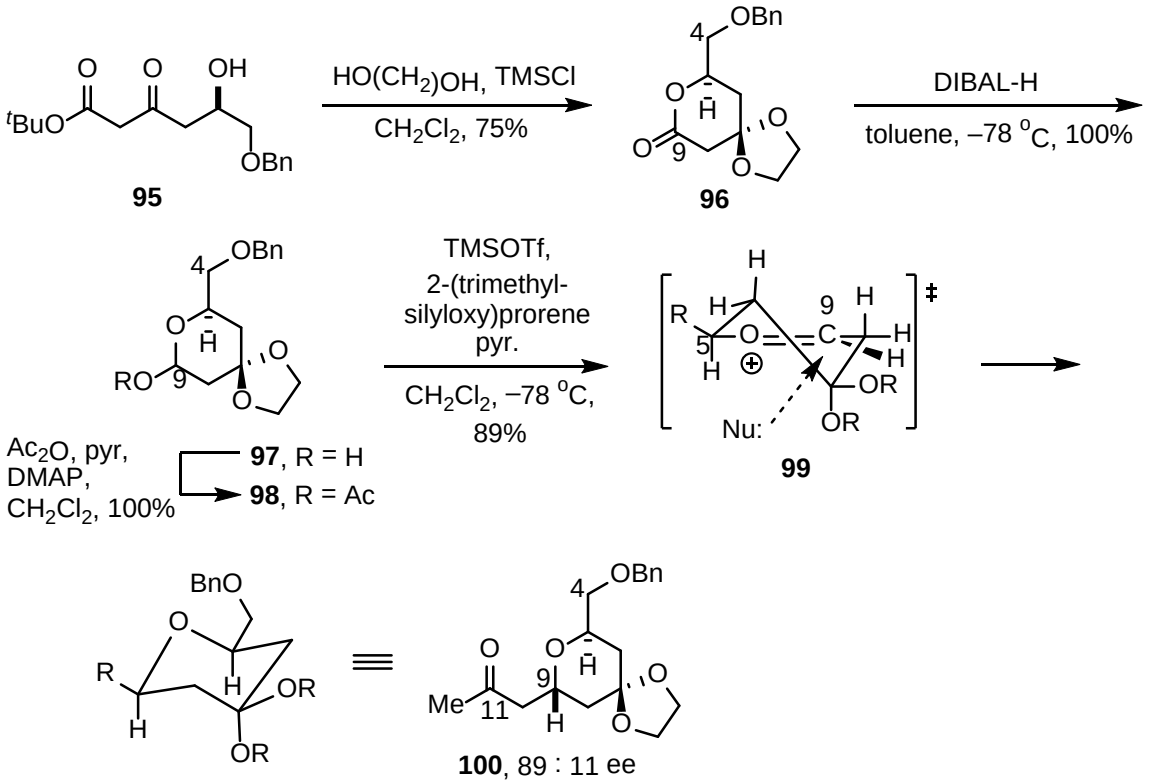
Scheme 12. Synthesis of the THP ring of (–)-dactylolide and (–)-zampanolide

Brazeau *et al.* applied the strategy to form the C-1 – C-17 fragment of narasin.[35] Beginning with the reduction of lactone **90** to form the corresponding acetals (**91 a** & **b**), followed by treatment with $TiCl_4$ and the addition of ketene silyl acetal **92**, the formation of 2,6-*trans* products **93** (**a** & **b**) were constructed. These were then subjected to radical mediated debromination, which gave THP fragment in 88% yield (**Scheme 13**).



Scheme 13. Synthesis of THP ring of C-1 – C-17 fragment of narasin

Evans also applied this methodology to form the C-4 – C-9 subunit of phorboxazole B **10** (**Scheme 14**).[36] δ-Hydroxy-β-ketoester **95** was reacted with ethylene glycol and trimethylsilyl chloride to deliver lactone **96** in 75% yield. Reduction with DIBAL-H and acetylation to give **98**. Following treatment with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and (trimethylsilyloxy)propene, the *trans*-THP ring **100** was formed. The stereochemistry can be rationalised by axial attack of the nucleophile from the bottom face of the oxocarbenium ion derived from **98** *via* a chairlike transition state.

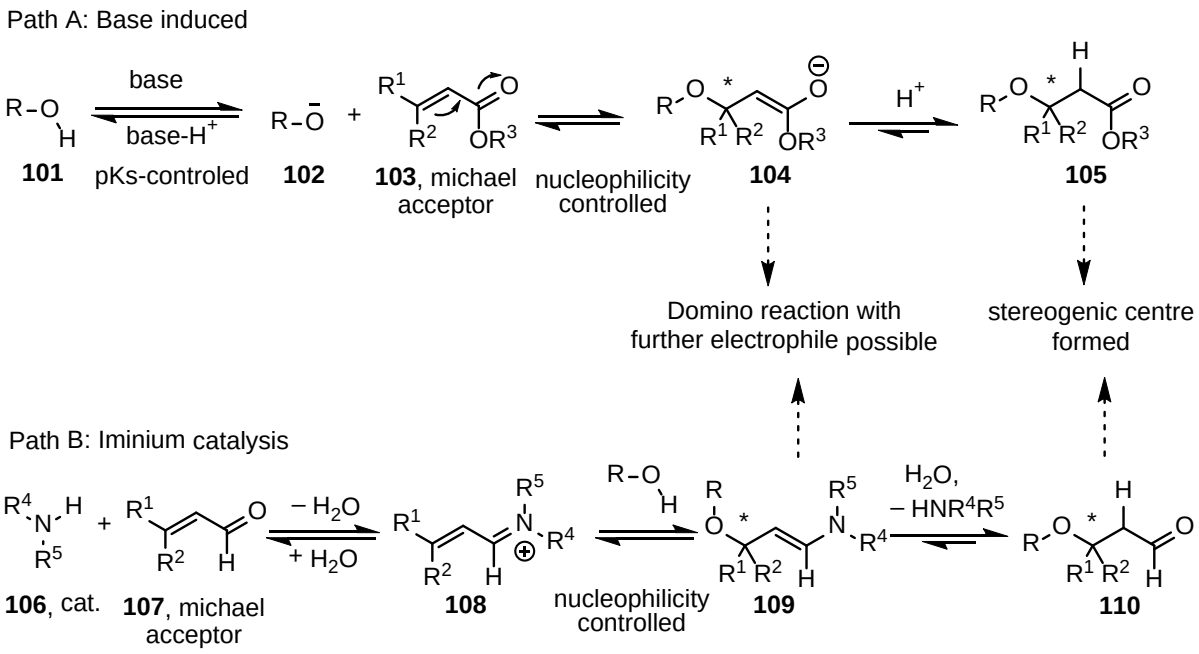


Scheme 14. Synthesis of the C-4 – C-9 fragment of phorboxazoles

1.3.6 Intramolecular oxy-Michael reaction

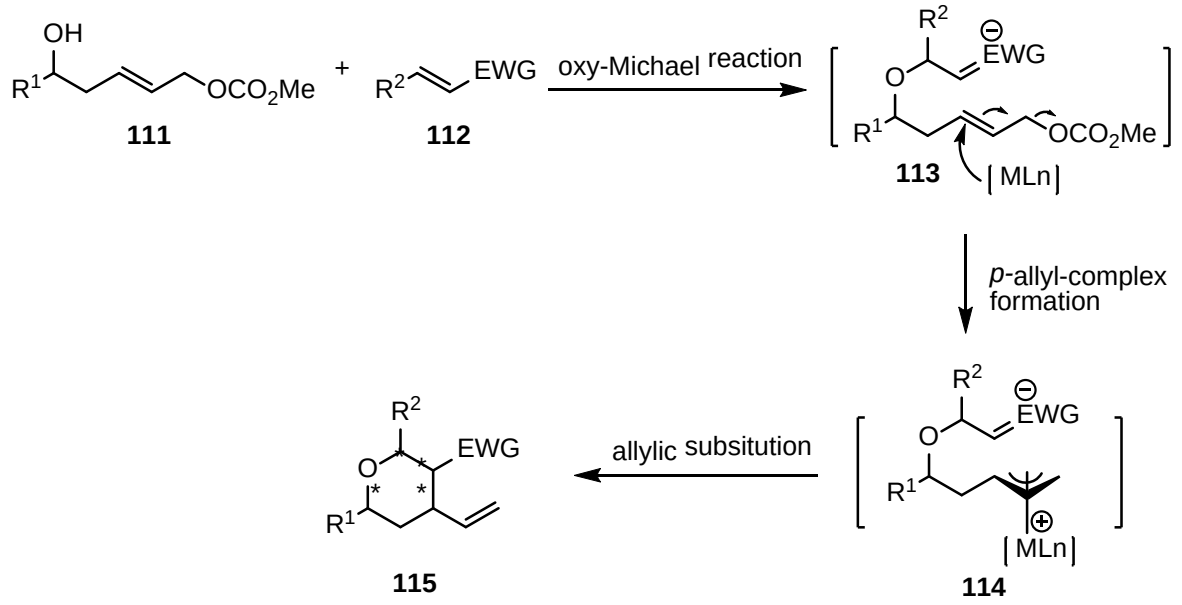
The addition of carbon nucleophiles to conjugate acceptor systems, which is commonly known as Michael addition, is becoming one of the most versatile and widely applied methods in organic synthesis. Over the last decades, tremendous progress has been made in the fields of stereoselective, catalytic or broadly applicable Michael reaction protocols.[37] One of big developments is oxy-Michael addition; oxy-Michael additions are the addition reaction of oxygen nucleophiles to conjugated

systems. Within the last few years, there has been a remarkable increase in publications focussing on method development and application towards natural products. There are two common pathways for oxy-Michael reaction shown below (**Scheme 15**).



Scheme 15. Common pathways of oxy-Michael reaction

As shown in **Scheme 15**, the oxy-Michael reaction is particularly suitable for the rapid generation of molecular complexity when it is embedded in domino reactions. The enolates generated by addition of alkoxides to conjugate acceptors can further react with suitable electrophiles. Menche *et al*. used this reactivity to combine an oxy-Michael reaction with a Tsuji-Trost coupling (**Scheme 16**).[38]



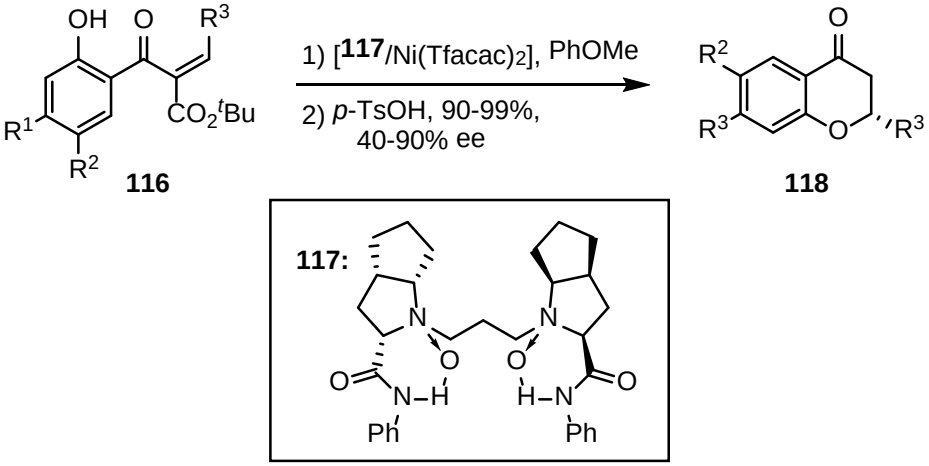
Scheme 16. Oxy-Michael/Tsuji-Trost domino reaction**.** EWG = electron withdrawing group

In this context, readily available homoallylic alcohols **111** react with a conjugate acceptor **112**, giving rise to an intermediate enolate **113**. With the formation of a π-allyl complex out of the olefinic moiety in **113**, an electrophile is generated which reacts with the previously generated enolate in an intramolecular allylic substitution reaction leading to highly substituted tetrahydropyrans **115**.

This protocol not only combines an oxy-Michael reaction with a metal-catalyzed reaction, but also generates four stereogenic centres which rapidly increases molecular complexity. After a lot of experiments, palladium dibenzylideneacetone ($Pd_2(dba)_3$) was identified as one of the suitable palladium sources together with lithium tert-butoxide as a base. A high degree of stereocontrol could be achieved given the fact that up to eight different stereoisomers can potentially be generated in this process.[38]

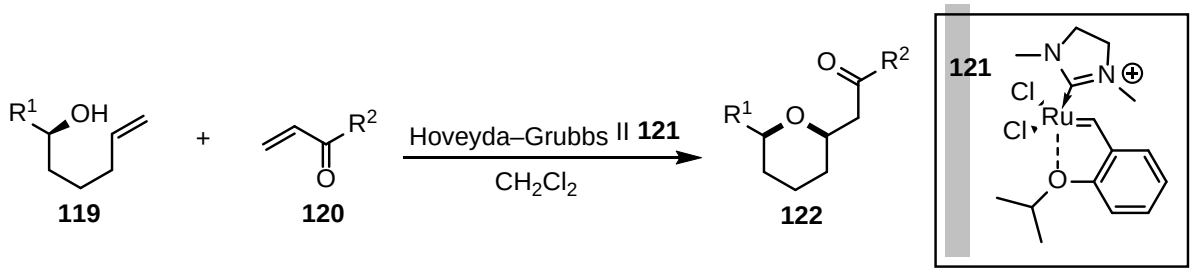
In 2008, Feng and co-workers have developed a highly efficient access to flavanones also using activated α, β-unsaturated ketones **116** and a chiral nickel (II) complex.[39] Optimisation of catalysts and ligands revealed that *N, N'*-dioxide complexes based on proline derivatives as ligands and nickel trifluoroacetylacetonate (Tfacac) as the metal salt gave the best results. Under these conditions, α, β-

unsaturated ketones with variations in the phenolic moiety as well as in the olefinic moiety are suitable substrates for the oxy-Michael reaction (**Scheme 17**).



Scheme 17. Synthesis of flavanones by the Ni(II)-N, N'-dioxide complex

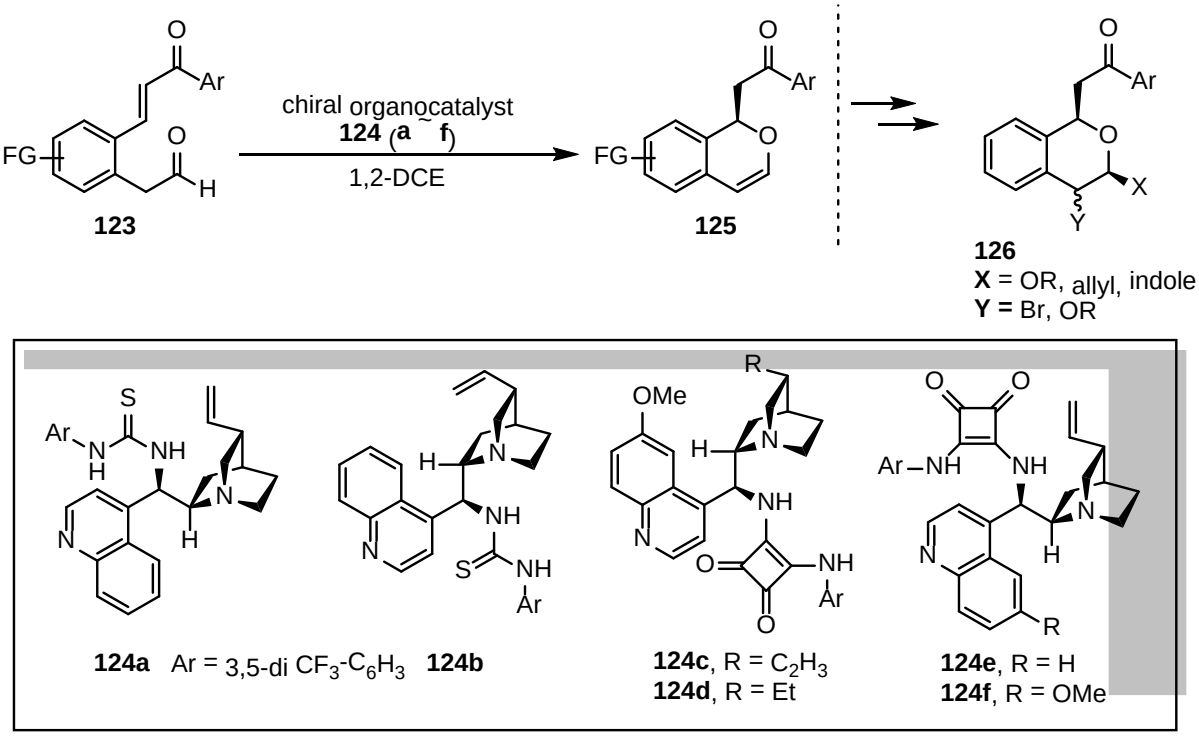
Following decarboxylation in a one-pot procedure, flavanones are obtained in good yields and enantiomeric excesses. Regarding the efficient synthesis of heterocycles, the oxy-Michael reaction has proven to be particularly useful for the synthesis of tetrahydropyrans. Consequently, the reaction has also been used in the total synthesis of complex natural products. Fuwa *et al*. has published a highly efficient synthesis of tetrahydropyrans based on a domino olefin cross metathesis/intramolecular oxy-Michael reaction.[40] The basic concept of this reaction is that cross metathesis between a hydroxy alkene and an enone generates a hydroxy enone which is then capable of intramolecular oxy-Michael addition. At this point it was imaged that promotion of the oxy-Michael reaction step would require an additional base or a Lewis acid to activate the hydroxy function or a carbonyl group.



Scheme 18. Domino cross-metathesis/oxy-Michael reaction

Further study showed that δ-hydroxy olefins **119** and vinyl ketones **120** are transformed directly into the THP rings by using the 2nd generation Hoveyda-Grubbs catalyst **121** and heating the reaction mixture in a microwave oven (**Scheme 18**).

In 2016, Ghorai research group developed a new squaramide-containing tertiary amine based bifunctional organocatalysts **124** (**a – f**) which efficiently activated the *o*-homoformyl chalcones to provide the chiral isochromenes in moderate yields and good to excellent enantioselectivities (**Scheme 19**).[41c]



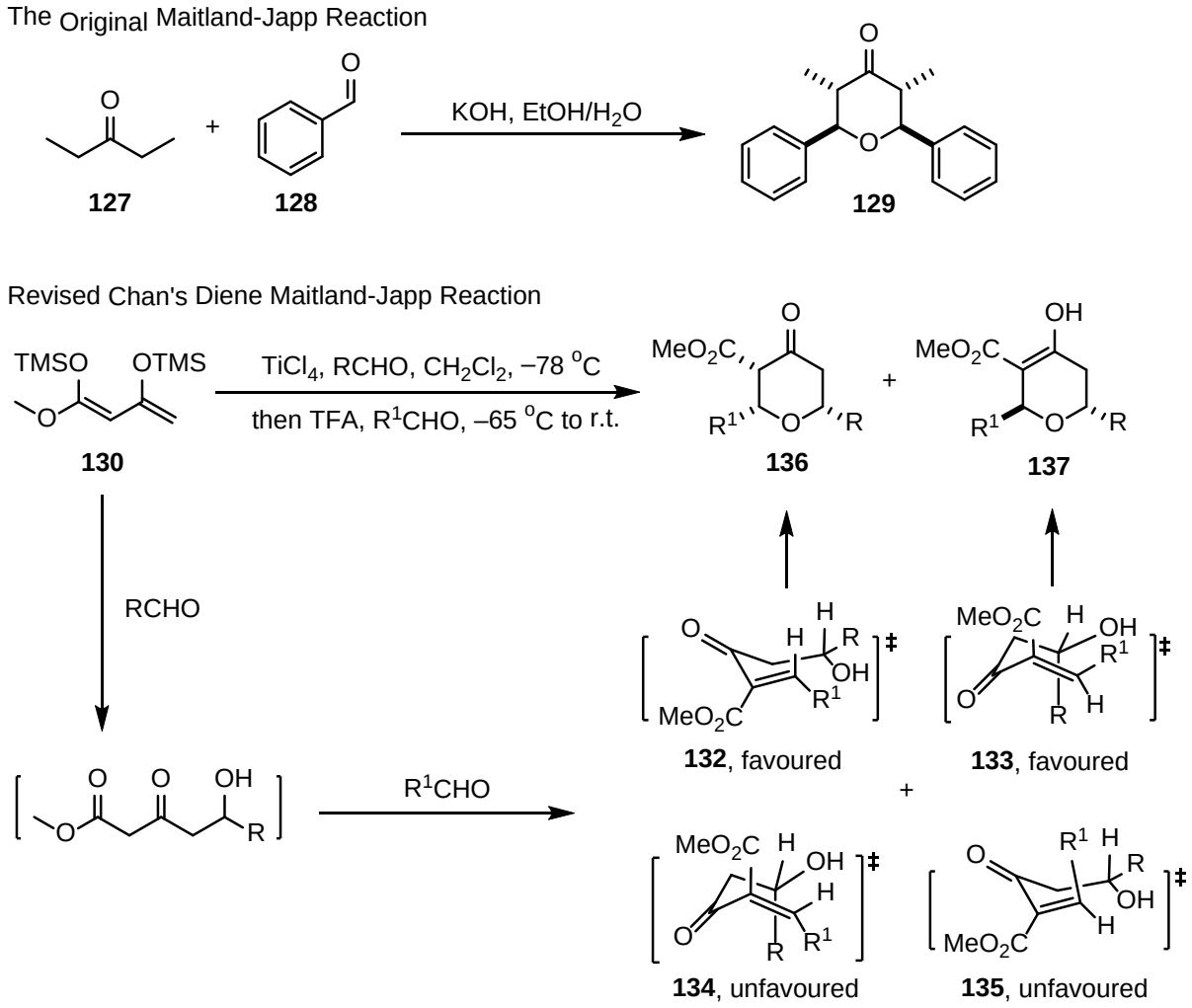
Scheme 19. Synthesis of functionalized isochromans

The Clarke group applied the oxy-Michael reaction towards the phorboxazoles. This will be discussed in the following pages.

1.4 Synthesis of THPs and applications to natural products in Clarke group

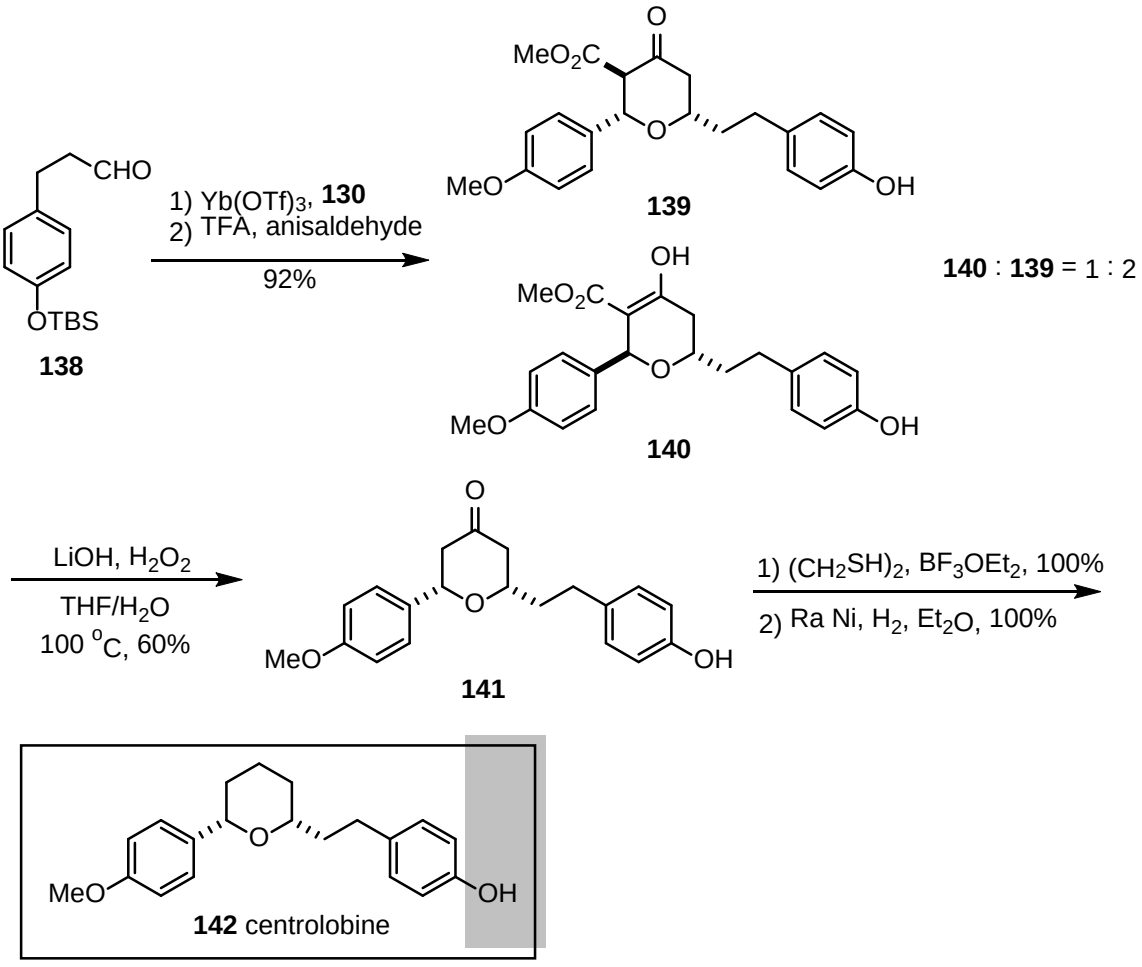
The Clarke group developed several reactions to form THPs and used them in the synthesis of natural products. Research group focused on the Maitland-Japp reaction.[1] The original Maitland-Japp reaction

was the condensation of pentan-3-one **127** with benzaldehyde **128** to give a symmetrical tetrahydropyran-4-one **129** in a low yield (**Scheme 20**).[42] However, this reaction could never be used into a general synthesis of THP rings due to the symmetrical nature of the products produced, and by the use of aromatic aldehydes and a symmetrical ketone. In order to overcome this problem, the pentan-3-one **127** was replaced with the *bis*-silyl enolether of methyl acetoacetate (Chan's diene **130**[43]), which would be performed. An initial aldol reaction would yield δ-hydroxy-β-ketoesters **131** which upon treatment with a second aldehyde would undergo a Knoevenagel condensation at the α-position of the β-ketoester followed by an intramolecular oxy-Michael addition to furnish tri-substituted tetrahydropyranones.



Scheme 20. Original and revised Maitland-Japp reactions

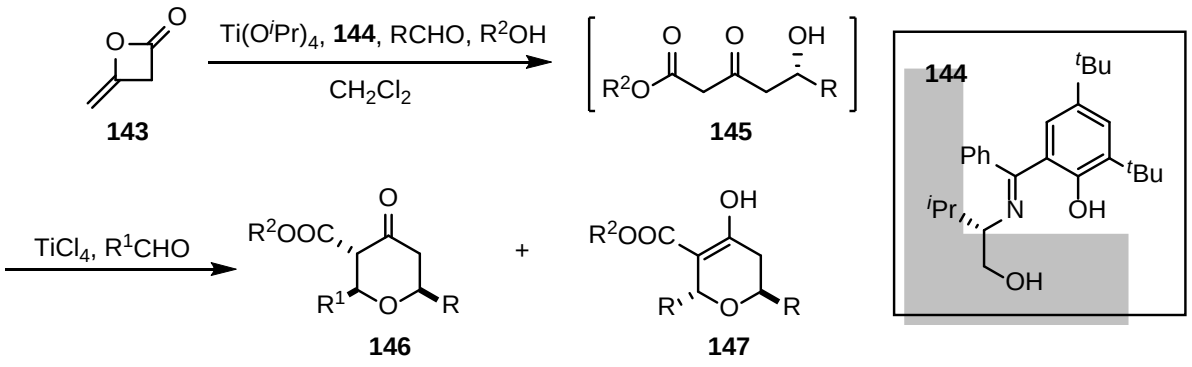
In transition state **136**, Michael addition to the *Z*-enone occurs from the bottom face with the substituents in favourable *pseudo*-equatorial positions leading to 2,6-*cis* THP ring. Addition to the top face of the *Z*-enone as depicted in transition state **135** places R in an unfavourable *pseudo*-axial position leading to 2,6-*trans* THP. In transition state **134**, addition to the bottom face of the *E*-enone leads to both 2- and 6- substituents in axial positions whereas addition to the top face as in transition state **133** leads to R^1 being in a *pseudo*-axial position and the 2,6-*trans* THP being formed. From these transition states, it was rationalised that formation of the *Z*-enone would lead to the 2,6-*cis* THP ring and formation of the *E*-enone would lead to the 2,6-*trans* THP ring. By utilising this procedure, the shortest and highest yield in the synthesis of (±)-centrolobine **142** was achieved (**Scheme 21**).[44]



Scheme 21. Synthesis of the centrolobine

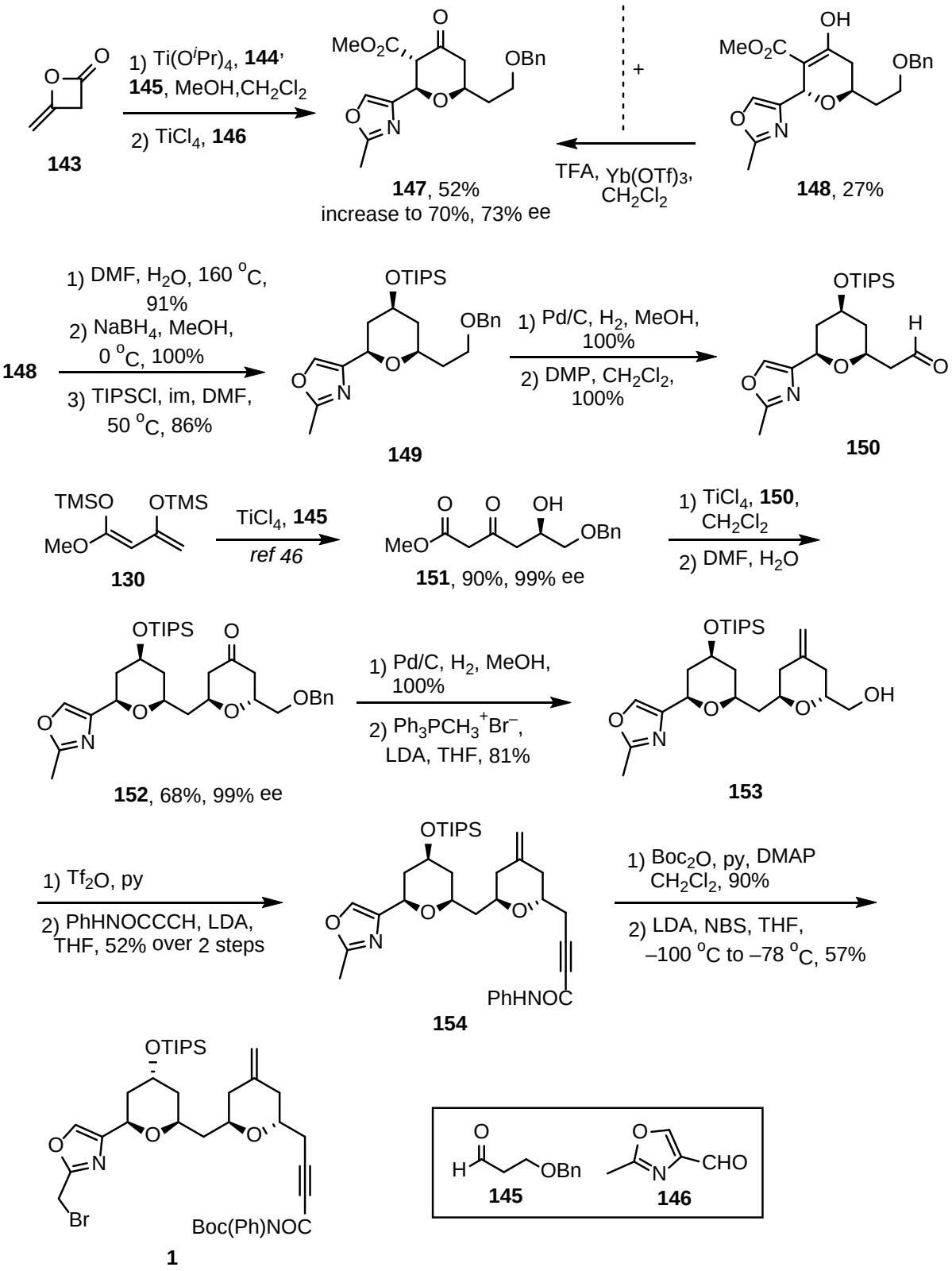
The tautomeric tetrahydropyran-4-ones **139** and **140** were prepared by using the Lewis acid $Yb(OTf)_3$, Chan's diene **130** and two aldehydes in good yield and the ratio is 1 : 2 (**140** : **139**). Surprisingly, the mixture of tautomers were separable by chromatography. The yield of **139** could be maximized by re-equilibration of **140** under Lewis acidic reaction conditions. Therefore, the total yield of **139** increased from 60% to 82%. Decarboxylation of **139** using LiOH and H_2O_2, followed with removal of the carbonyl group by forming a dithiane, then treatment with Raney nickel gave centrolobine **142**.[45]

In the similar way, diketene **143** was used instead of Chan's diene **130**. An asymmetric Maitland-Japp reaction (**Scheme 22**) was developed with the chiral Schiff's base ligand **144**. These reactions were also used to generate the desired δ-hydroxy-β-ketoester in an enantioenriched form. The δ-hydroxy-β-ketoester **145** was cyclised to a THP ring (**146** & **147**) which could be re-cyclised to further increase the enantiopurity of the THP to > 95% ee.[45]



Scheme 22. Asymmetric diketene Maitland-Japp reaction

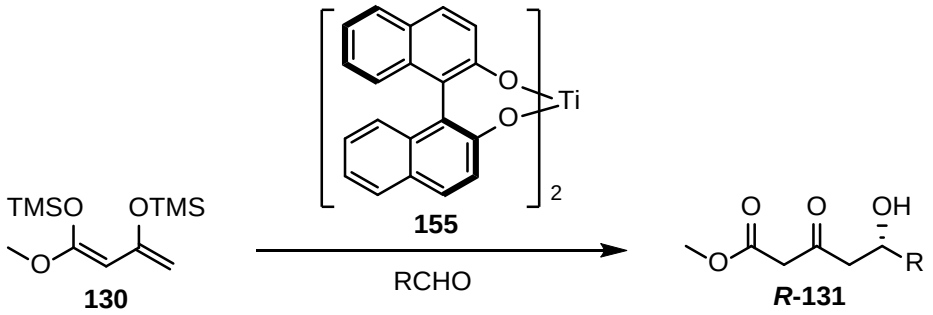
Encouraged by the development of an asymmetric Maitland-Japp reaction and by the observation that the ioselectivities of THPs could be enhanced by recrystallization, an application to the synthesis of the C-1 – C-19 *bis*-pyran unit of the phorboxazoles was achieved. (**Scheme 23**).[45]



Scheme 23. Synthesis of the C-1 – C-19 unit of the phorboxazoles

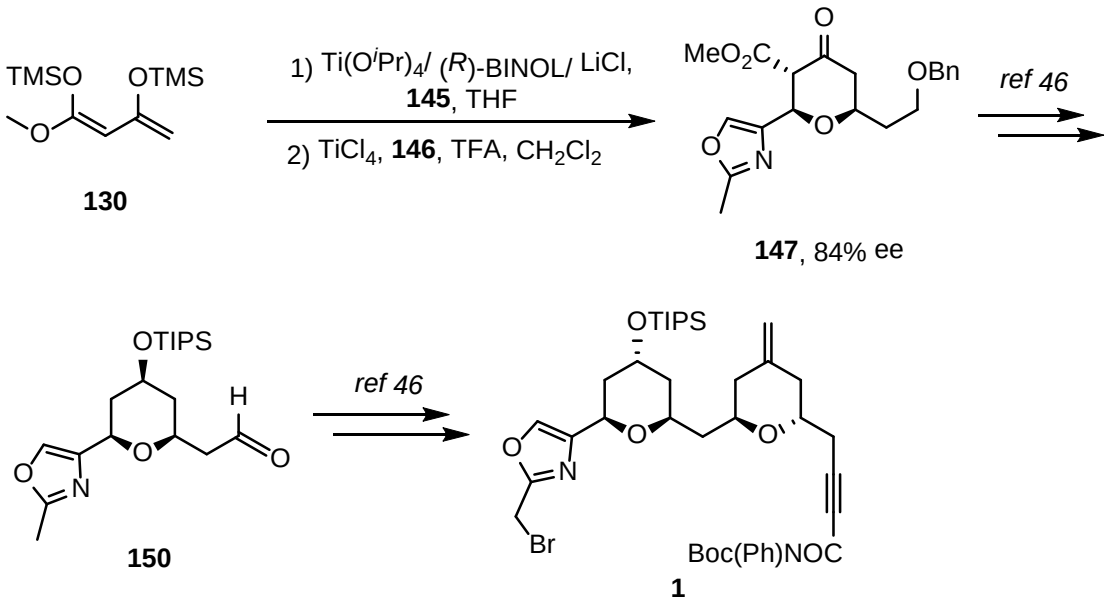
The C-1 – C-19 fragment of the phorboxazoles began with an asymmetric Maitland-Japp reaction of diketene **143** with the first aldehyde **145** and oxazole aldehyde **146**. This generated a mixture of **147** and **148**. Just like compounds **139** and **140**, the mixture were separable by chromatography. It was known that the keto-*cis* and enol-*trans* forms of the THPs generated in the Maitland-Japp reaction are in equilibrium with each other under Lewis acidic conditions, and so **147** could be separated from **148** and re-equilibrated to give a 1 : 2 mixture of **148** : **147** by using $Yb(OTf)_3$. Tetrahydropyran-4-one **147** was decarboxylated under microwave conditions, the ketone was reduced with $NaBH_4$ to afford the stereochemistry required for the synthesis of the phorboxazole B **10**, and the free hydroxyl group protected as a TIPS ether to yield **149**. The benzyl ether of **149** was removed with H_2 over Pd/C and the primary alcohol oxidized with Dess-Martin periodinane to generate aldehyde **150**. Chan's diene **130** was used to form the δ-hydroxy-β-ketoester **151**.[46] Ketoester **151** was subjected to Maitland-Japp cyclization protocol using **76** as the aldehyde partner to form **152**. Removal of the benzyl group of **152** and Wittig olefination generated alcohol **153**, which was converted to the triflate and displaced with the dianion of *N*-phenyl propynamide, to give **154**. The relatively acidic amide NH was protected with a Boc-group and then the oxazole methyl group was brominated by the formation of the anion with LDA and treatment with NBS. This yielded the C-1 – C-19 *bis*-pyran fragment of phorboxazole B **1**, with functionality at either end to allow for coupling to the other fragments of the natural product.

There are a lot of precedents for the asymmetric addition of Chan's diene to aldehydes reported in recent years.[36, 47] A procedure, which was provided by Soriente, was utilised to form different kinds of δ-hydroxy-β-ketoesters (**Scheme 24**).[47]



Scheme 24. Asymmetric addition of Chan's diene to aldehydes

A modification of this reaction was utilised with a Maitland-Japp reaction which resulting in a more efficient new generation synthesis of the C-1 – C-19 unit of phorboxazole B **1** (**Scheme 25**). The yield and ee was better than using diketene. The maximum ee of **147** in this strategy was 84% which will give a better isolation and prevent the loss of the starting materials.

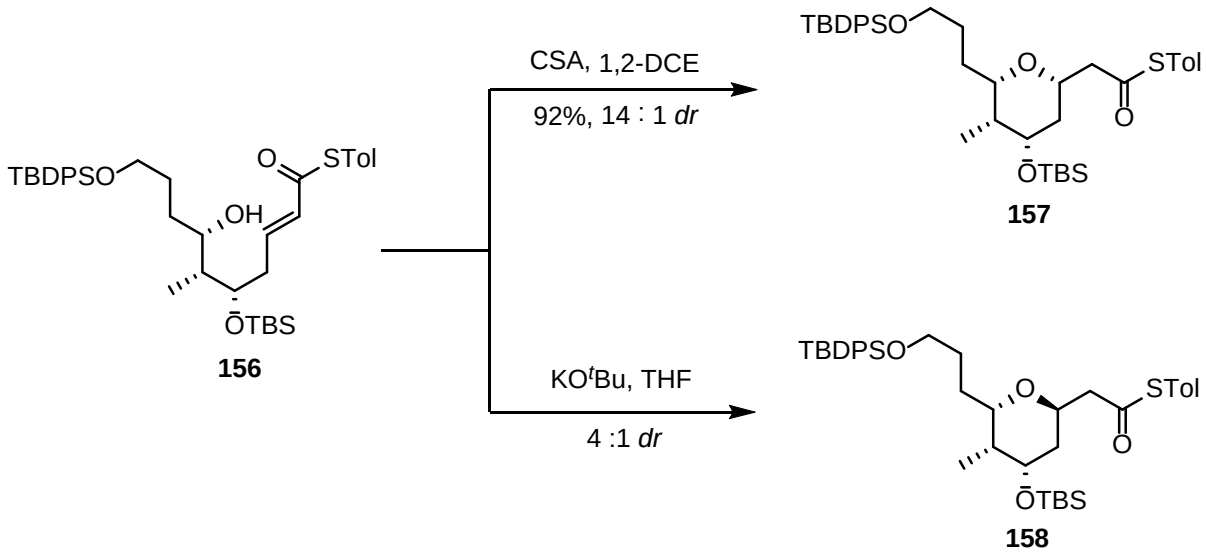


Scheme 25. *S*ynthesis of the C-1 – C-19 unit of phorboxazole B

Generally, 2,6-*trans*-tetrahydropyrans tend to be formed by oxy-Michael reaction under kinetically controlled conditions, while the 2,6-*cis* tetrahydropyrans might be favoured by performing the reaction under thermodynamic conditions. In practice, although 2,6-*cis* tetrahydropyrans might be performed in good yield in higher temperature and longer reaction time, the result often showed

contrary to the expectation. The origin of this is generally accepted as rising from better orbital overlap in the transition state of the base-promoted cyclization leading to the 2,6-*trans* tetrahydropyrans; the reason why the acid-catalysed reaction tends to form the 2,6-*cis* tetrahydropyrans possibly due to the greater stereoelectronic stabilisation of the transition state from both the FMO coefficients of the allylic cation and orbital overlap with the oxygen lone pair.[65]

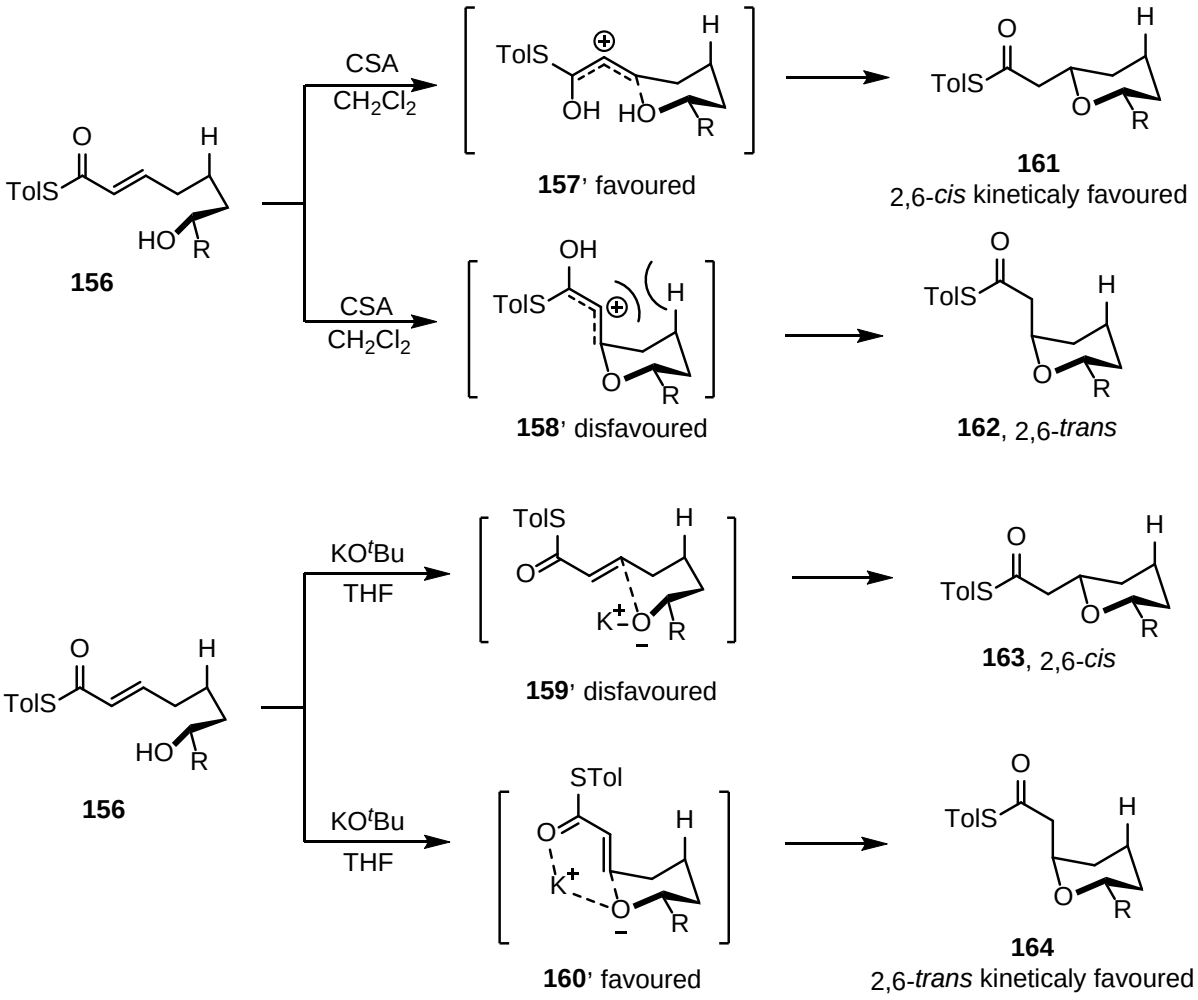
An α, β-unsaturated thioester has been utilised by Fuwa, as an alternative Michael acceptor to form the THP rings (**Scheme 26**).[48] The Brønsted acid-catalysed oxy-Michael reaction gave the *cis*-THP ring in 92% yield and excellent selectivity (14 : 1). When the same substrate was treated with Brønsted base, then the *trans*-THP ring was formed with moderate selectivity (4 : 1). The trend of thermodynamic equilibration to 2,6-*cis* THP ring under the acid condition was stopped by submitting the 2,6-*trans* THP ring to those conditions where it was shown that the formulation of *cis*-product did not occur.



Scheme 26. Fuwa's thioester oxy-Michael cyclisation

For the acid-catalysed reaction, as Fuwa proposed (**Scheme 27**), the transition state **157** is the chair-like transition state and would give the *cis*- product **161**. It would be favoured because all the steric interactions are minimised. In contrast, the chair-like transition state **158** leading to the 2,6-*trans*

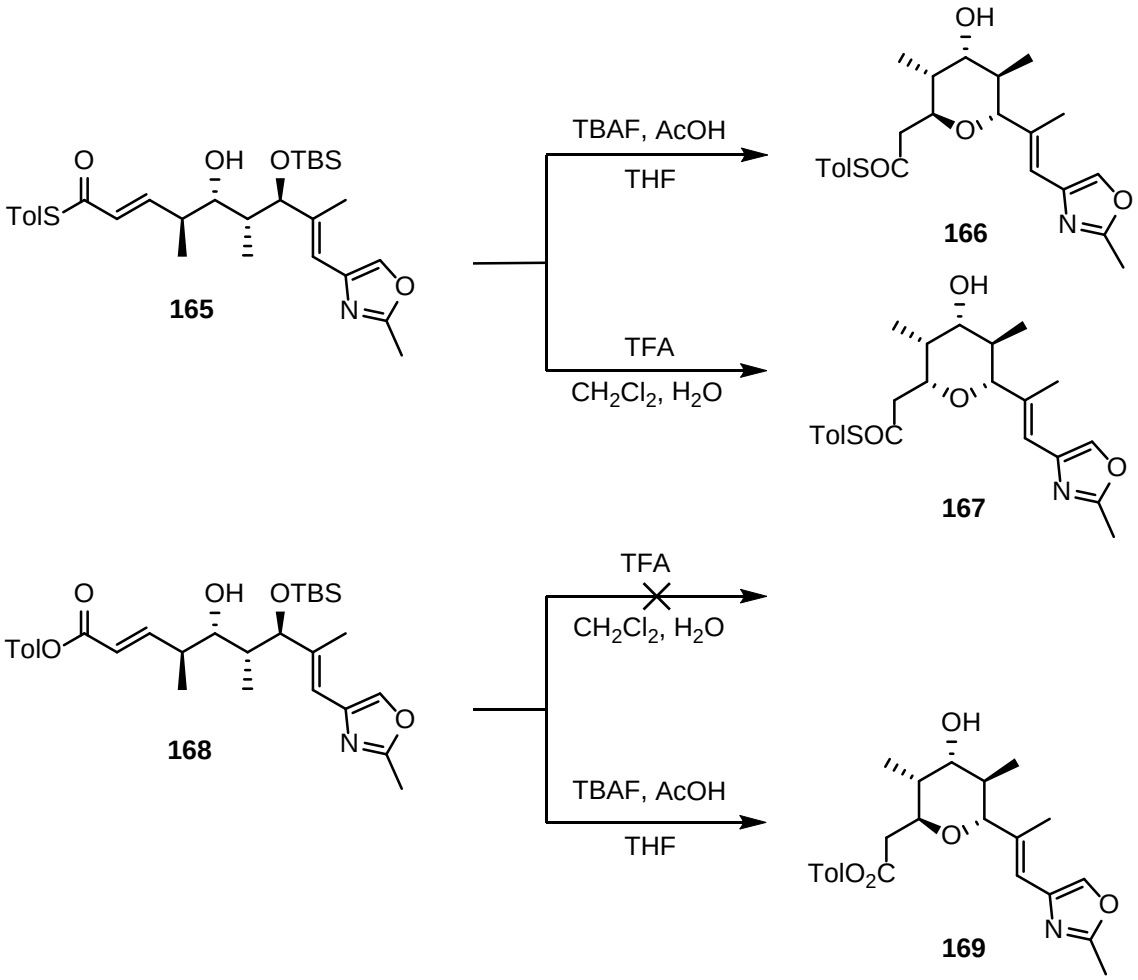
product **162** would be disfavoured because of a steric interaction between the thioester α carbon and the 4-axial hydrogen atom. For the base-catalysed reaction, the main difference in this case is a proposed chelating interaction between the potassium ion and the substrate in the transition state **160** which leads to the 2,6-*trans* product **164**. Fuwa reported that the coordination of the thioester oxygen and the alkoxide to the potassium ion stabilises this transition state in spite of the same unfavourable steric interactions as in the acidic case. In the alternative transition state **159**, the thioester oxygen atom would be too far away for chelation and thus the 2,6-*cis* product **163** would be kinetically disfavoured in these conditions.



Scheme 27. Mechanism of Fuwa's theory

During the Clarke group's synthesis of C-20 – C-32 fragment of phorboxazoles, a remarkable stereodivergent oxy-Michael reaction was uncovered. The stereodivergence occurred when they

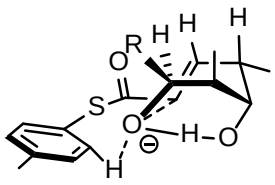
changed the conditions for the deprotection of a TBS-ether. Deprotection of **165** with AcOH buffered TBAF led to form the *trans*-THP ring **166**. When they used the TFA to deprotect **165**, the result would be *cis*-THP ring **167**. However, when they used this methodology to the oxoester **168**, the deprotection with TFA was not successful (**Scheme 28**).



Scheme 28. Stereodivergence in the thioester oxy-Michael cyclization to form the C-20 – C-32 unit of the phorboxazoles

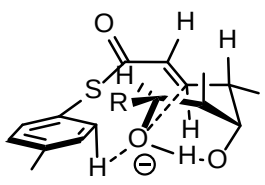
A development of these reactions has been reported by Clarke group. Computational studies indicated that there are two stable transition states in thioester system by Clarke group. According to the previous work in our group, the energy of the transition state **171** of the *trans*-THP ring was lower than the *cis*-THP transition state **170**, which led to **166** (**Figure 2**). A possible reason for the different energy is the eclipsing interaction of the β- and γ- hydrogen atoms of the thioester, which is present

in the *cis*-transition state **170**, not in the *trans*-transition state **171**. However, this could only occupy approximately one third of the energy difference. Another possible reason might be the increased bond strain of thioester in the *cis*- transition state **170**, as double bond orientation is less favourable for the rotation of the tolyl substituent to reach the alkoxide. There also could be some contribution from the *pseudo*-1,3-diaxial interaction between the hydrogen atoms which would be in 2- and 6-positions in the finished product. It might be more incarnated than usual because protons are pointing slightly towards each other to allow the alkoxide attack from a trajectory close to the Bürgi-Dunitz angle.[65]



170

Rel. enthalpy 24.5 kJ/mol
C-O 2.08 Å
O…HO 1.73 Å
O…HAr 2.30 Å

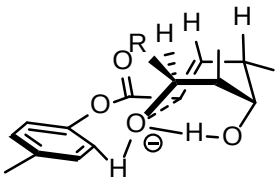


171

Rel. enthalpy 10.0 kJ/mol
C-O 2.13 Å
O…HO 1.73 Å
O…HAr 2.25 Å

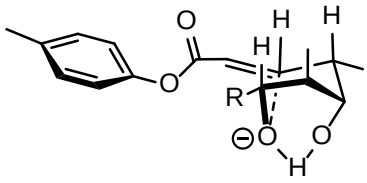
Figure 2. Transition states for TBAF-catalysed thioester cyclisation

In the similar way, the transition states of TBAF-catalysed oxoester cyclization could be analysed (**Figure 3**). The energy of *trans*- transition state **172** is 22.9 kJ/mol, which is higher than in the thioester analogy **170**. However, it is still quite low. The *cis*-transition state **173** is slightly unusual as its tolyl ring is pointing away from the forming ring and has no interaction with the alkoxide. This might be a result of the shorter bond lengths of the oxoester which causes the bond strain to be too large for the induced dipole-anion interaction to give a net reduction of the energy. The *cis*- transition state is 11.5 kJ/mol higher in energy than the *trans*- transition state. Assuming kinetic control, the results again are consistent with the observed diastereoselectivity of this reaction (> 20 : 1 *trans* : *cis*).[65]



172

Rel. enthalpy 22.9 kJ/mol
C-O 1.99 Å
O…HO 1.77 Å
O…HAr 7.44 Å

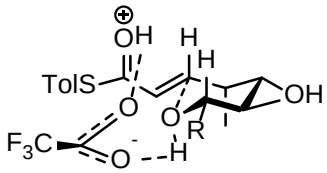


173

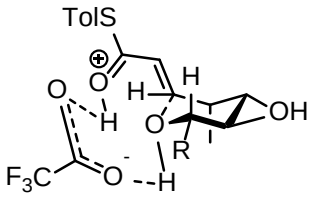
Rel. enthalpy 34.4 kJ/mol
C-O 2.15 Å
O…HO 1.68 Å
O…HAr 5.04 Å

Figure 3. Transition states for TBAF-catalysed oxoester cyclisation

In the acid-catalysed reaction, it was found that the transition states can be stabilized if the proton is removed from the alcohol oxygen in concert with the attack on the conjugated double bond. Two transition states were conformed (**Figure 4**). The energy of *cis*- transition state **174** (14.7 kcal/mol) is 1.9 kcal/mol lower than the *trans*- transition state **175** (16.6 kcal/mol), which result in the stereoselectivity.[65]



174



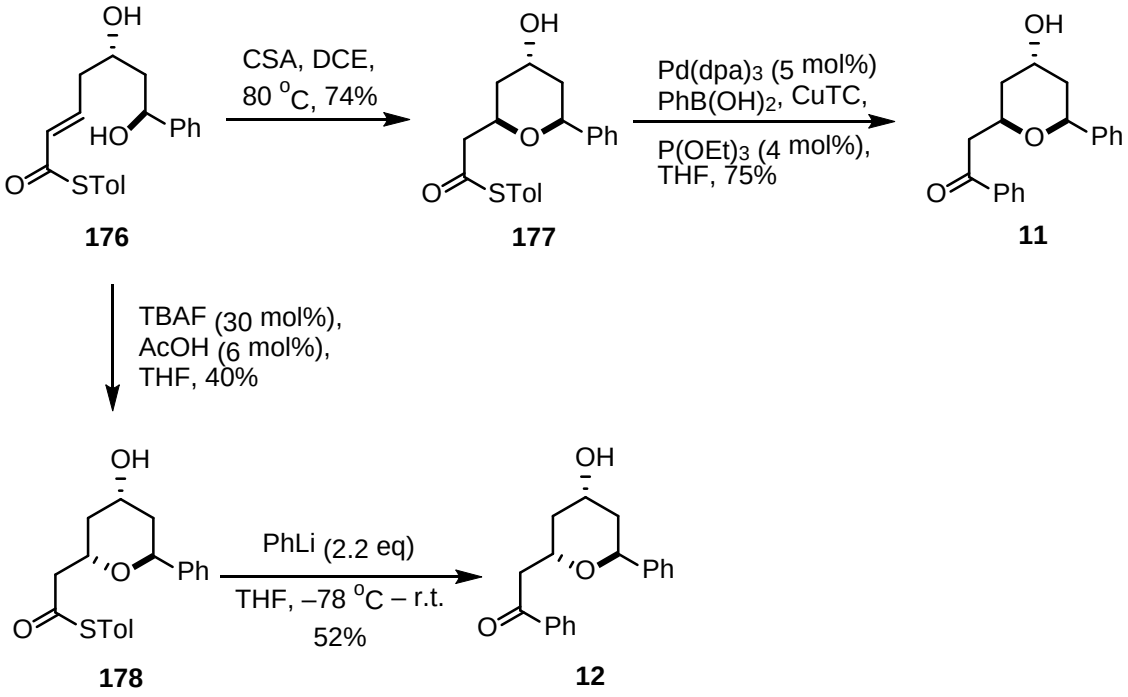
175

Figure 4. Transition states for acid-catalysed reaction

As the hydroxyl nucleophile is the same in both reactions, the only difference between the thioester and the oxoester is the nature of the electrophile. Therefore, any differences in the electronic structure regarding the reactivity of the molecule should present themselves primarily in the LUMO of the substrate. As the similarity of LUMO electron density between two substrates, the only difference should be the overall LUMO energy.[65]

A possible explanation for the difference in the LUMO energies between these two esters might be that the sulfur lone pair has a smaller overlap with the C=O π* orbital of the ester than the oxygen lone pair.[65]

This method was used to form the diospongins A **11** and B **12** successfully in our group (**Scheme 29**). The products of the stereodivergent oxy-Michael reaction **177** and **178** were formed by **176**. Then the Leibeskind-Srogl type coupling reaction of the thioester phenyl boronic acid under $Pd(dpa)_3$ was designed to build the diaspongins **11** and **12** respectively.[65]

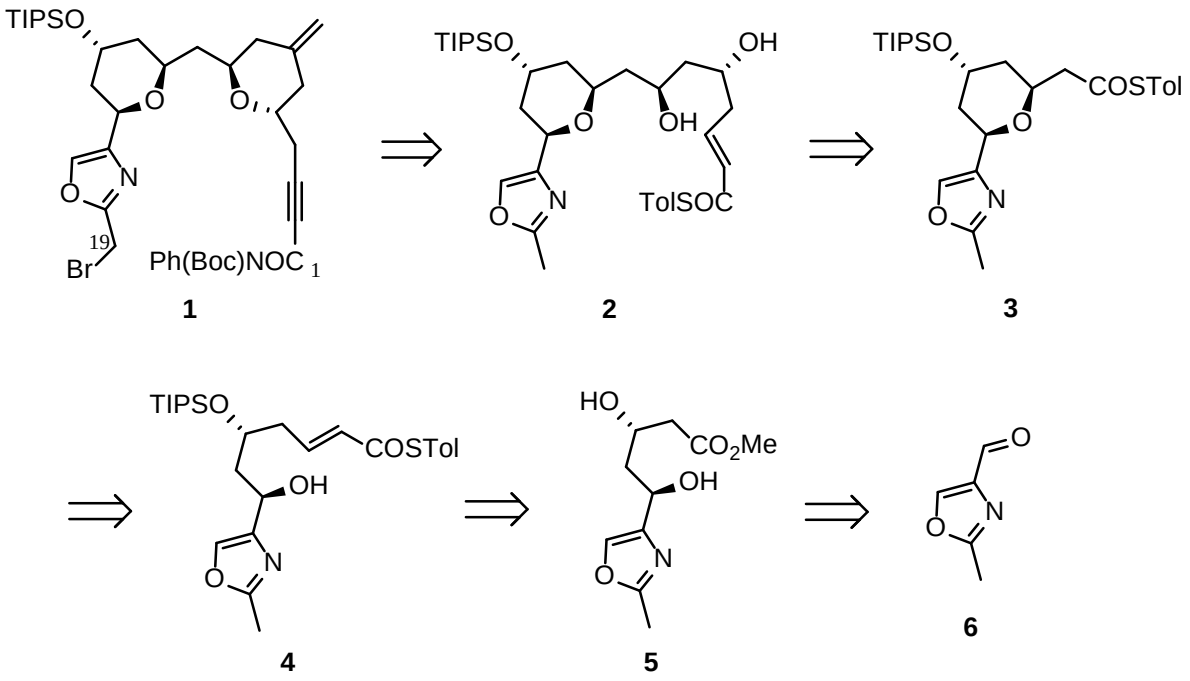


Scheme 29. Stereodivergent synthesis of diospongins A and B

2. Results and discussion

Following the development of the stereodivergent oxy-Michael reaction, we decided to apply it to the synthesis of the *cis*-THP ring in the C-1 – C-19 fragment of phorboxazoles.

2.1 The first strategy



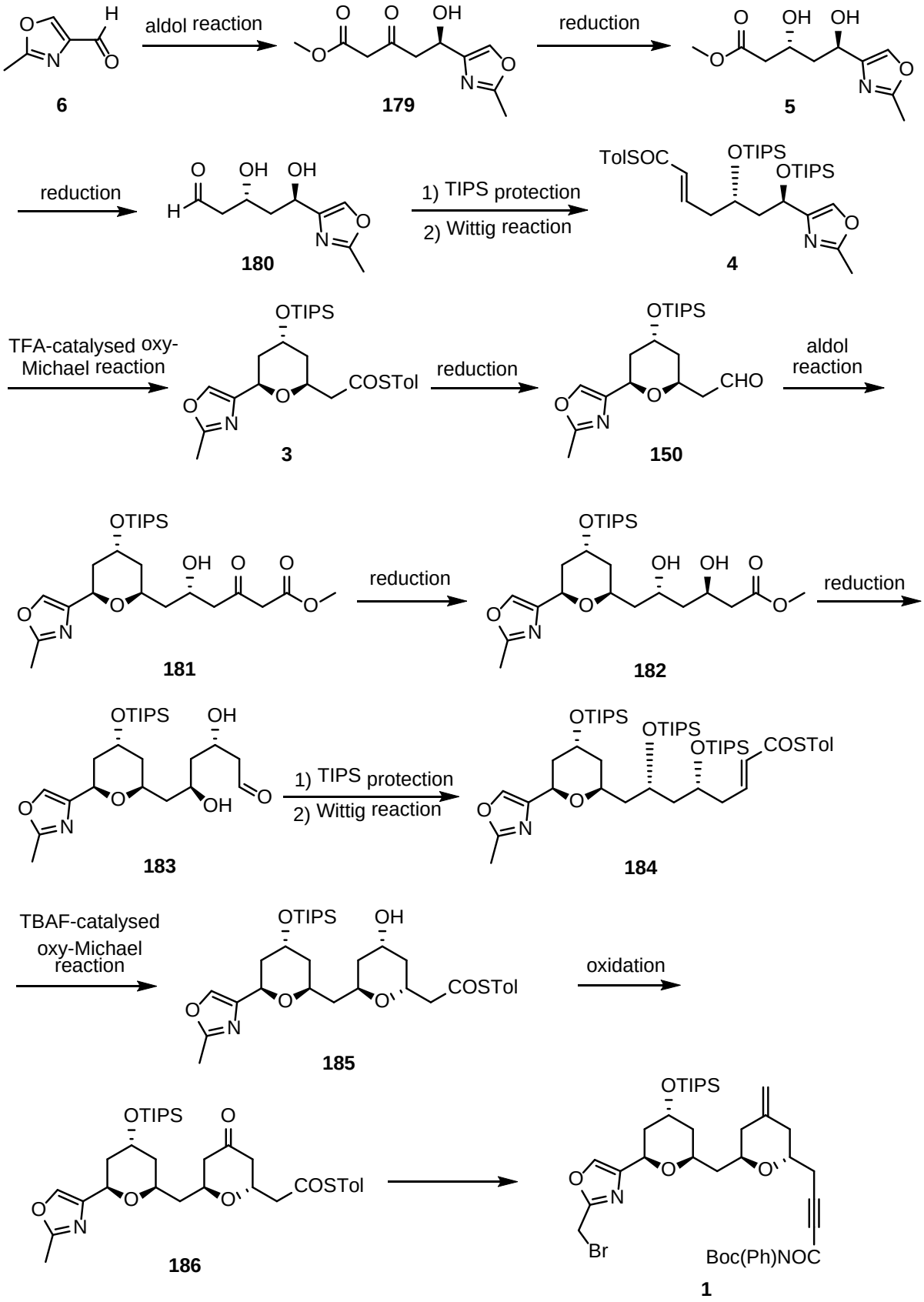
Scheme 30. Retrosynthesis analysis of the fragment of C-1 – C-19 of phorboxazoles

The first approach focused on using the oxazole aldehyde **6** to form the α, β-unsaturated thioester. The fragment of C−1 – C−19 of phorboxazoles **1** is assumed to be derived from **2** which will be prepared using **96** through two steps, reduction and Wittig reaction. The *cis*-THP ring **3** will be synthesised by applying our stereodivergent oxy-Michael reaction from **4**. Thioester **4** can be synthesised from diol ester **5** using the Wittig reaction and the diol ester **5** will be built through aldol reaction and reduction. Because the aldol reaction in this strategy is not stereodivergent, the ee need to be confirmed by using HPLC or ^{1}H NMR. (**Scheme 30**)

A route was proposed to form the fragment of C-1 – C-19 of phorboxazoles **1** (**Scheme 31**). The aldol reaction was used with the oxazole aldehyde **6** to form the δ-hydroxy-β-ketoester **179**. The

formulation of the thioester **4** could be achieved through the chiral controlled reduction, reduction to aldehyde, TIPS protection and Wittig reaction with the thioester ylide. We then planned to use acid, such as CSA or TFA, with this thioester **4**, leading to the first *cis*-THP ring **3**. The thioester THP ring **3** would be reduced to the THP aldehyde **150** for the future use.

Another aldol reaction to make δ-hydroxy-β-ketoester **181** was designed by using the aldehyde **150**. After using the same methodology, the thioester **184** could be prepared with the same methodology, then the buffered fluomide (e.g. TBAF) would be used to form the second *trans*-THP ring **185**. The core fragment **185** should be modified through the oxidation of the hydroxyl; Wittig reaction; reduction of thioester to the aldehyde; another Wittig reaction; Boc-protection and NBS substitution, to synthesise **1**.

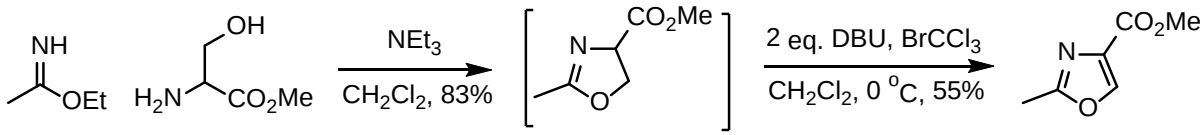


Scheme 31. Route to synthesise the fragment of C-1 – C-19 of phorboxazoles

2.1.1 Synthesis of the oxazole aldehyde

2-Methyl-oxazole-4-carboxaldyde, as known as oxazole aldehyde **6**, is an important starting material in the pharmaceutical industry. A large quantity is required,[9] which means an efficient synthesis is essential for this project. There are several properties which cause this molecule difficult to synthesise. For example, the molecule has low molecular weight; it is unstable in the extreme pH environment; it is very soluble in most solvents including water at level > 1 g/mL; it has the thermal instability issues; and it tends to sublime. Several methods of synthesising the oxazole aldehyde **72** has been reported.[49]

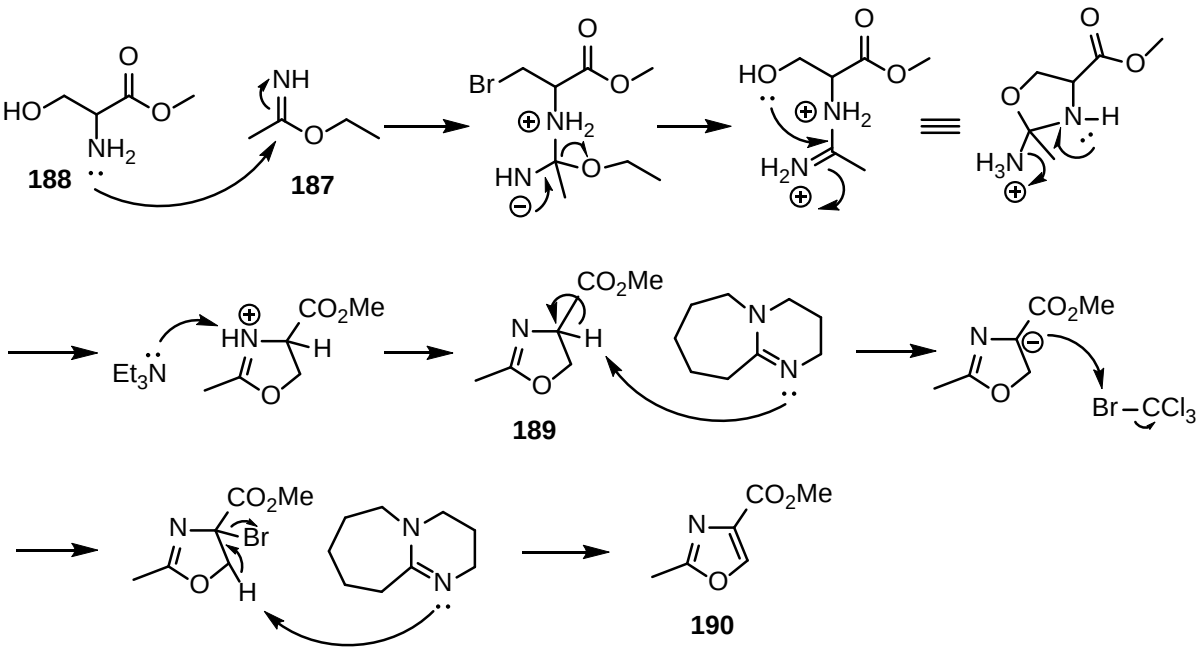
The fundamental way to synthesise the oxazole aldehyde **6** in our group is based on Benoit *et al.*'s work.[49] The intermediate oxazoline **189** was prepared from ethyl acetimidate **187** and serine methyl ester **188**, to give a colourless oil **189**. Adding of 2 equivalent bromotrichloromethane to the mixture of oxazoline and DBU and stirring for 15 minites at 0 °C methyl ester **190** could be isolated by crystallization as a white solid (**Scheme 32**).[50]



187 **188** **189** **190**

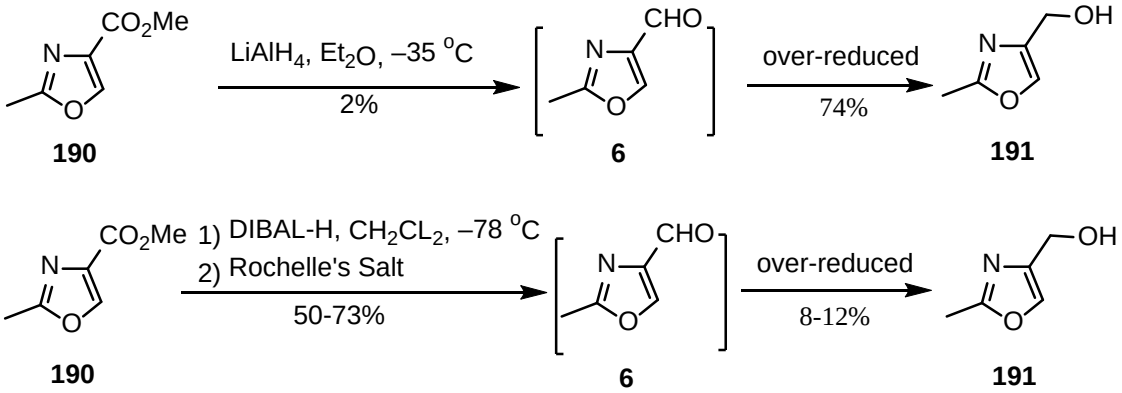
Scheme 32. Route to synthesise the methyl oxazole ester

The yield of this second step was 55 %. Some unidentified polymeric materials were formed as well. The mechanism of these two reaction are shown in **Scheme 33**. The lone pair of NH_2– on the primary amine attacked the C on the imine, which helped form a new imine. After the proton transfer, the leaving group NH_3 was ejected through the double forming in the ring. The extra proton would be carried away by triethylamine. Thus, the intermediate oxazoline **189** was synthesised. DBU, as a non-nucleophilic base, would deprotonate the H– on **189** and treat this enolate would attack the electron-deficient group Br–, and giving the bromo-oxazoline. Deprotonation of H from the adjacent carbon by DBU, eliminates the bromide to form a double bond, giving methyl oxazole ester **190**.



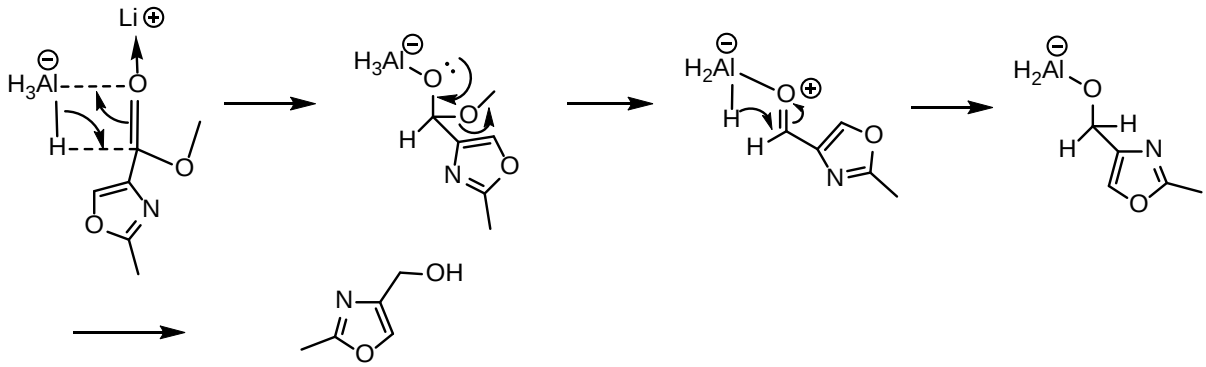
Scheme 33. Mechanism of synthesis of methyl oxazole ester

Direct reduction of ester **190** to aldehyde **6** has been reportedusing either DIBAL or $LiAlH_4$.[51, 52] However, the reduction using $LiAlH_4$ caused the significant over-reduction to alcohol **191** even at very low temperature. Unlike lithium aluminium hydride, DIBAL would not reduce the aldehyde further if only one equivalent was added. Hence, theoretically, the direct reduction of ester **190** could be stopped at the aldehyde stage. In practice, when we used DIBAL to reduce the ester, it easily over-reduced to the alcohol. The best ratio after several attempts was 1 : 5 (**191** : **6**) (**Scheme 34**).



Scheme 34. Strategies of direct reductions

The mechanism of reduction by lithium aluminum hydride is shown below (**Scheme 35**). The nucleophilic H from the hydride reagent adds to the electrophilic C of the carbonyl group of the ester. Electrons from the C=O move to the electronegative O creating an intermediate metal alkoxide complex. The tetrahedral intermediate collapses and displaces the alcohol portion of the ester as a leaving group, this produces an aldehyde as an intermediate. Then the nucleophilic H^- from the hydride reagent adds to the electrophilic C in the polar carbonyl group of the aldehyde. Thus, electrons from the C=O could move to the electronegative O creating an intermediate metal alkoxide complex. At last protonation of the alkoxide oxygen creates the primary alcohol product from the intermediate complex.

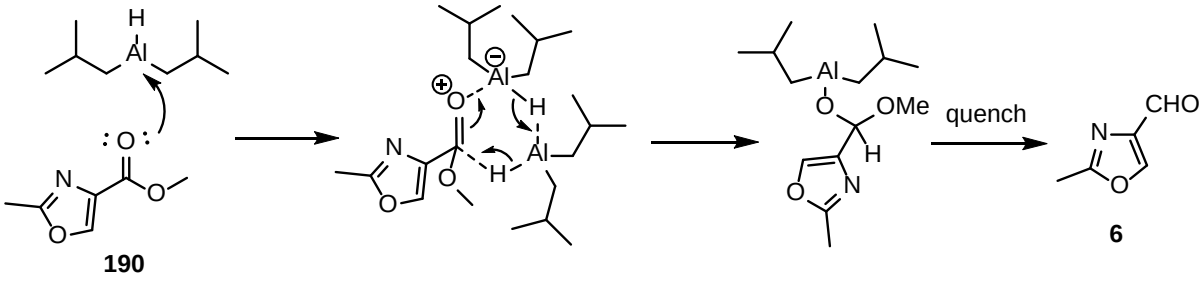


191

Scheme 35. Mechanism of $LiAlH_4$ reduction

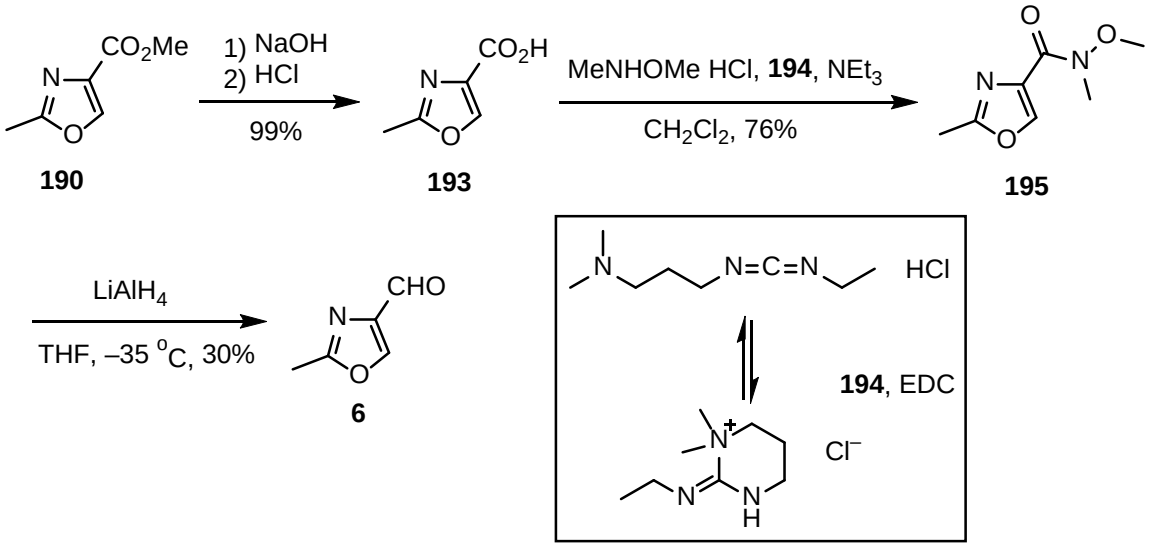
The mechanism for reduction by DIBAL can also be analysed. DIBAL is a little different compared to $LiAlH_4$. Whereas to $LiAlH_4$ is considered a "nucleophilic" reductant, that is, it delivers hydride (H–) directly to a carbonyl carbon, DIBAL is an "electrophilic" reductant. That is, the first step in the reaction is coordination of a lone pair from the carbonyl oxygen (a nucleophile) to the aluminium (electrophile). It is only after coordinating to its carbonyl host that another DIBAL molecule delivers its hydride to the carbonyl carbon, resulting in formation of an alkoxyl hemiacetal intermediate that is stable at low temperatures. Quenching of the reaction then breaks down the hemiacetal, resulting in isolation of the aldehyde (**Scheme 36**). Because the intermediate complex in DIBAL reduction is much more stable

and the condition is easier to controll, direct DIBAL reduction to synthesise the oxazole aldehyde **6** has been successfully achieved.



Scheme 36. Mechanism of DIBAL reduction

DIBAL reduction looks excellent on paper but can sometimes be difficult to achieve in practice, because of its extremely strict control of reaction temperature. In order to sustain –78 °C, slow addition of DIBAL was required. Although the highest yield of aldehyde **6** we achieved is 73%, reproducibility was difficult. Therefore, an alternative way of synthesis of **6** was designed using the Weinreb amide (**Scheme 37**).

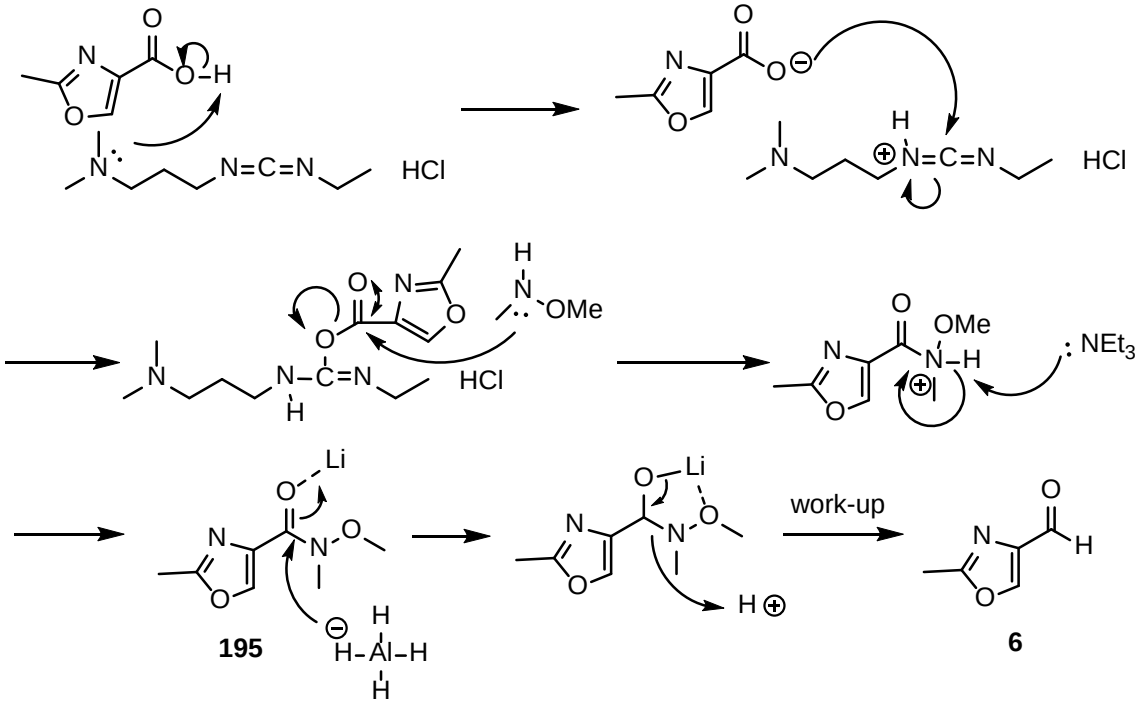


Scheme 37. Route of forming the aldehyde by reducing the Weinreb amide

Hydrolysis of ester **190** to carboxylic acid **193** was carried out by using aqueous NaOH, followed by addition of hydrochloric acid to precipitate the product. Because the carboxylic acid **193** is water

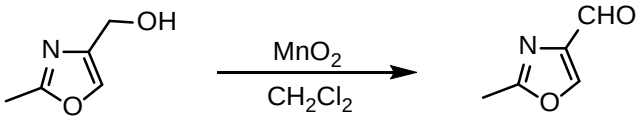
soluble, controlling the amount of water for work-up is important. The Weinreb amide **195** was prepared by using the carboxylic acid **193**, *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (**194**, EDC) and dimethylhydroxylamine hydrochloride under conditions that were tolerance significant levels of water. Theoretically, the Weinreb amide **195** could be cleanly reduced to be aldehyde **6** upon the condition of 0.25 equivalent redundant of $LiAlH_4$ in THF at –35 ^oC. Once the reduction was finished, the excess $LiAlH_4$ was quenched by AcOH. The low yield of this reaction might be due to the lost during the acidic wash.

The mechanism from carboxylic acid **193** in this process is shown below (**Scheme 38**). The lone pair on N atom, as a nucleophile, deprotonated the carboxylic acid. As a result, the enolate group attacked the electrophilic C in EDC, which made adjacent O electrophilic and became a good leaving group. The nucleophilic N in dimethylhydroxylamine added to the carbonyl, which formed the Weinreb amide **195**. The double bond would coordinate the lithium, which helped H^- attack the carbonyl. After the work-up, the aldehyde was synthesised.



Scheme 38. Mechanism of Weinreb amide formulation and reduction

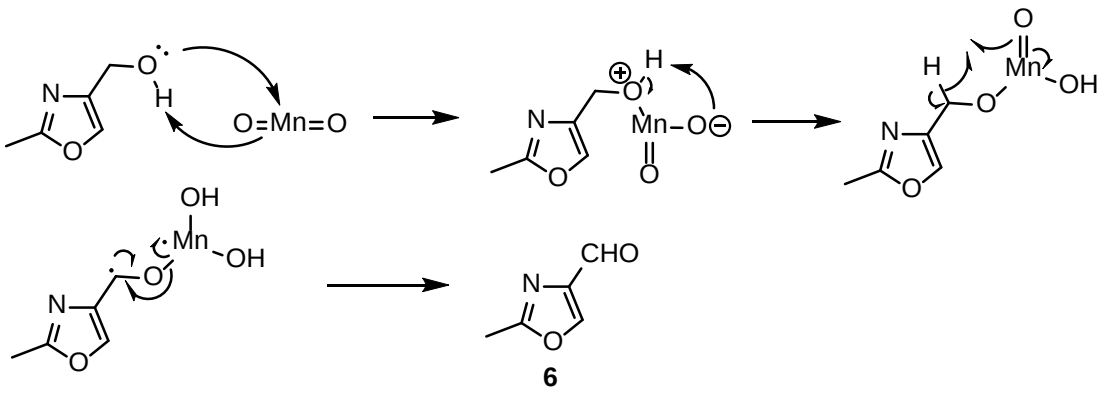
The alcohol **191** could be used to prepare the aldehyde or carboxylic acid *via* oxidation. The oxidation using MnO_2 was used and generated the aldehyde in 23% yield. (**Scheme 39**).



191 **6**, 23%

Scheme 39. Oxidation of the oxazole primary alcohol

The mechanism is shown in **Scheme 40**. MnO_2 is a mild oxidising agent that selectively oxidizes primary or secondary allylic and benzylic alcohols. Primary alcohols yield aldehydes and secondary alcohols form ketones. The mechanism is a bit complex requiring some radical intermediate formation.



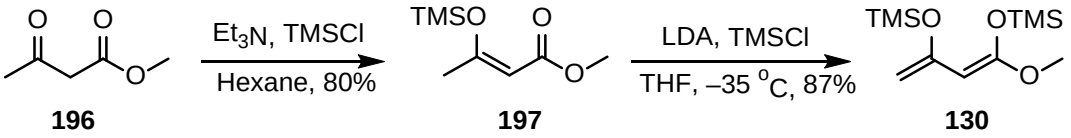
6

Scheme 40. Mechanism of Manganese dioxide oxidation

2.1.2 Synthesis of δ-hydroxy-β-ketoester

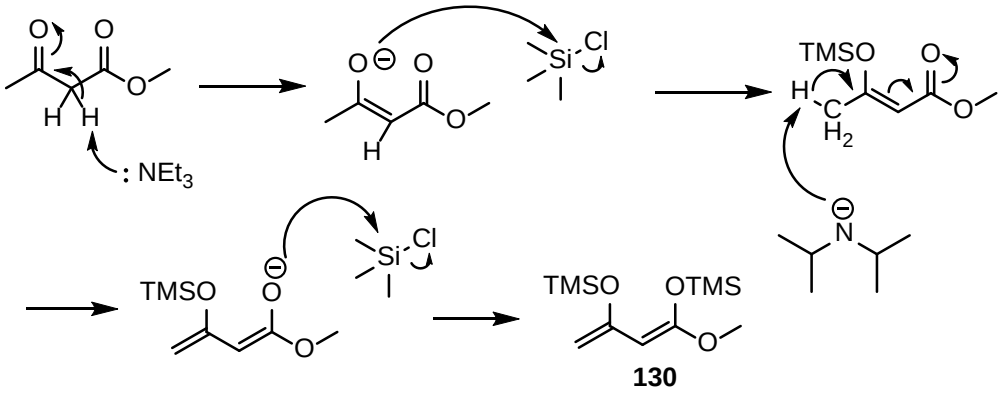
2.1.2.1 Synthesis of Chan's diene

Chan's diene was prepared using the methyl acetoacetate **196**, deprotonated by two different strength of bases through and trapped using chlorotrimethylsilane (TMSCl) to stabilise the enolate to yield to Chan's diene (**Scheme 41**).



Scheme 41. Process of synthesis the Chan's diene

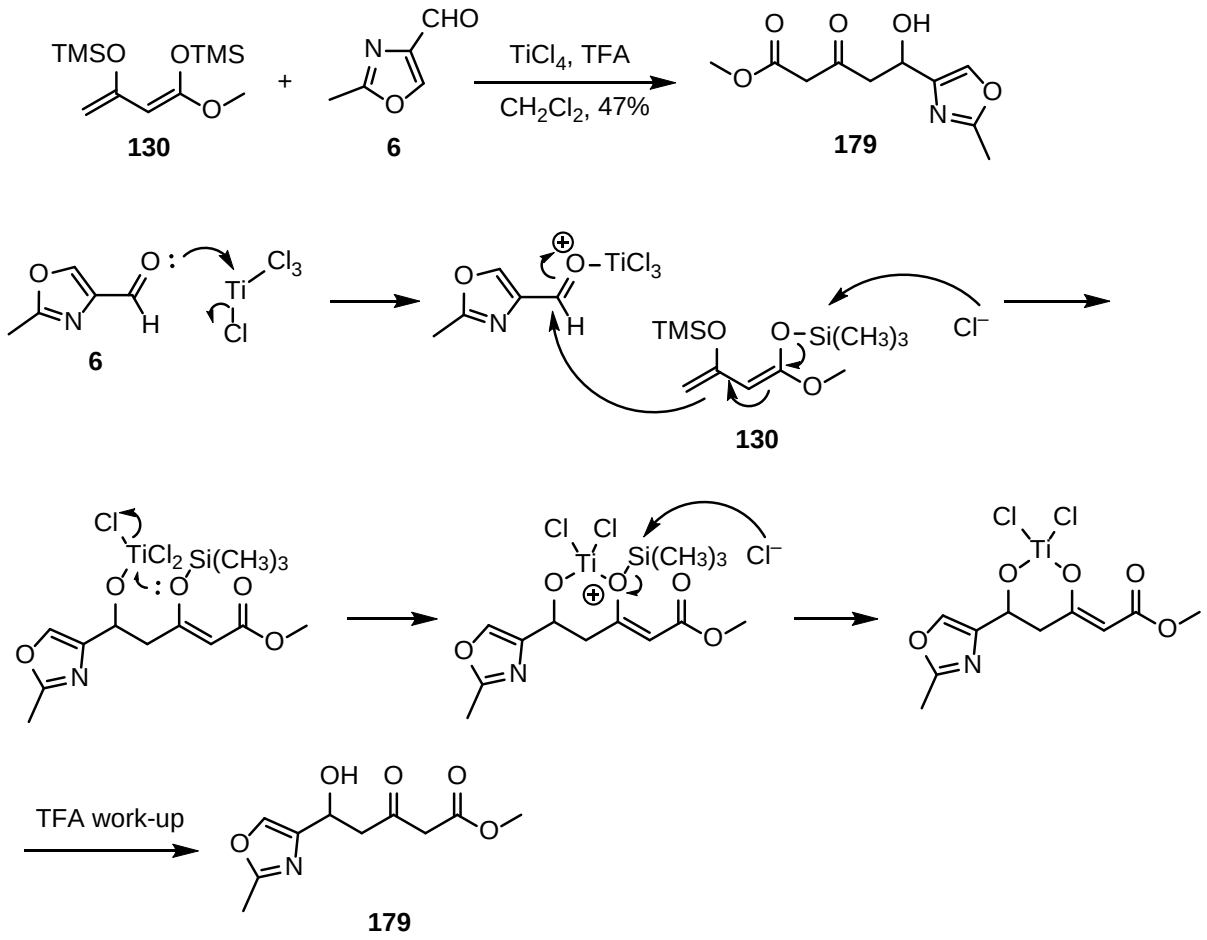
For the first step, in water system, the pK_a of ϒ-H (pK_a = 11) in methyl acetoacetate was lower than α-H (pK_a = 25), so the triethylamine (pK_a of protonated triethylamine is 10.7) could deprotonate the ϒ-H. In the second step, the pK_a of alkene H– (pK_a = 43) was much higher than α-H, therefore, the LDA (the pK_a of *i*-$Pr_2N^+H_2$ is 11.) preferred to deprotonate the α-H rather than alkene H– (**Scheme 42**). Because of its volatile properties, Chan's diene is not easily to store. It was assumed that the aldol reaction was prepared using the fresh Chan's diene.



Scheme 42. Mechanism of forming the Chan's diene

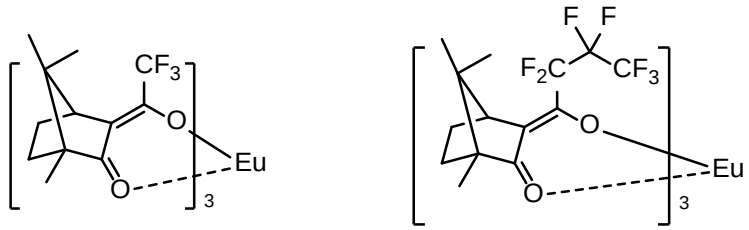
2.1.2.2 The aldol reaction

The original reaction was reported by Mukaiyama in 1973. Chan's diene was used to do the aldol reaction with the oxazole aldehyde (**Scheme 43**). Lewis acid $TiCl_4$ would co-ordinate with the O in the carbonyl of the oxazole aldehyde. Therefore, the Cl^- would be released and then attacked the TMS group which could liberate the enolate. The vinylogous enalate would add to the carbonyl group of the aldehyde-titanium complex and then formed a new titanium complex which would quench with the trifluoroacetic acid (TFA), yielding the δ-hydroxy-β-ketoester **179**. The δ-hydroxy-β-ketoester **179** gave a mixture of *R/S* racemic.



Scheme 43. Chan's diene aldol reaction and its mechanism

Unfortunately, in this study, we failed to test the enantiomeric excess of the mixture **179**. We tried to use the chiral shift reagent, Europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate], [Eu(tfc)$_3$] to do the NMR spectroscopy. However, even though we decreased the usage of Eu(tfc)$_3$ **198** to 5 mol%, the ^{1}H NMR showed that it was still too much, which means that the selected peak was still quite broad. Changing another chiral shift reagent could prove better. For example, Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate], Eu(hfc)$_3$ **199** (**Figure 5**).

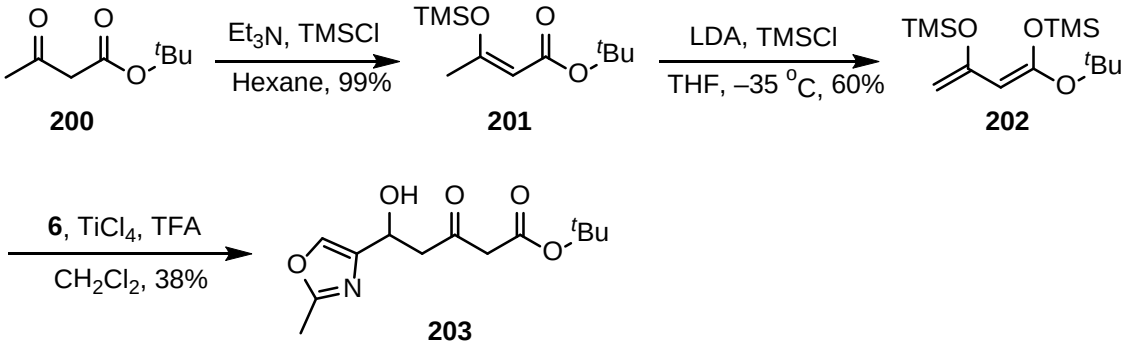


198, $Eu(tfc)_3$ **199**, $Eu(hfc)_3$

Figure 5. Two chiral shift reagents

At the same time, we used the chiral chromatography (HPLC) to confirm the ee, but there were no evident peaks in results. There could be several reasons why we did not get the result by using HPLC. Firstly, the ketoester **179** is not very UV-active; secondly technical issues, for example, the problem with HPLC column; thirdly, the concentration of the solution was not enough for the testing; finally, the solvent system was not good for this ketoester.

Therefore, we tried to form a different δ-hydroxy-β-ketoester which had been synthesised in our group to test the HPLC machine (**Scheme 44**).[66]

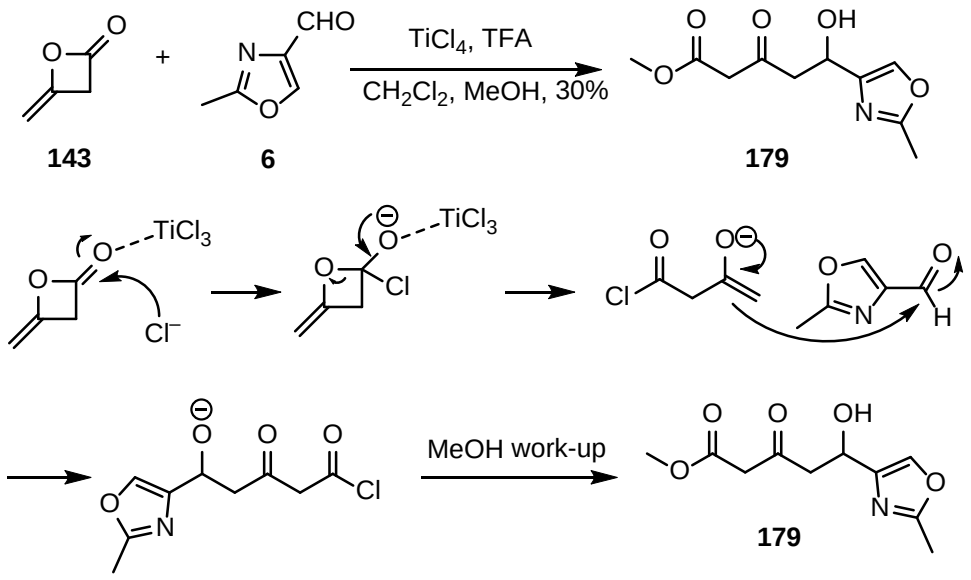


Scheme 44. Asymmetric aldol reaction by using the same methodology

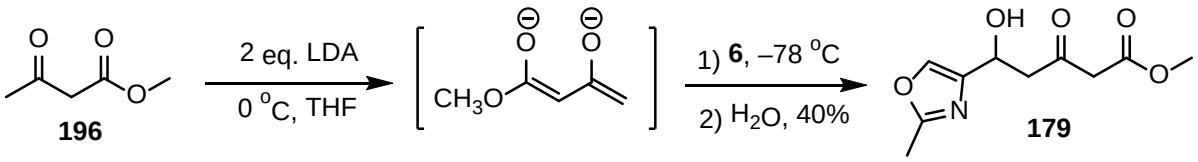
The *tert*-butyl Chan's diene **202** was formed by *tert*-butyl acetoacetate **200** through two steps to do the similar aldol reaction, yielding the δ-hydroxy-β-ketoester **203**. The ee was confirmed that 75% of the enantiomers are the *R* structure according to Mistry's thesis.[66] However, unfortunately, we still did not confirm the ee of **203**. We thought if we could change a HPLC column, the ee of these the δ-hydroxy-β-ketoesters could be tested.

The diketene and Weiler dianion were also used to prepare the δ-hydroxy-β-ketoester **179**. The mechanism of diketene aldol reaction is similar to Chan's diene aldol reaction, which is the Lewis acid conjugating to the carbonyl oxygen of diketene and openning the diketene ring, triggering the addition to the oxazole aldehyde, quenched to yield ketoester **179**. (**Scheme 45**)

In Weiler dianion aldol reaction procedure, two carbonyl groups in methyl acetoacetate would be deprotonated by LDA or NaH, to give the enol and enolate, respectively. Then alkene double bond was forced to add to the carbonyl group on the aldehyde **6**, quenched with H_2O, yielding the ketoester **179** (**Scheme 46**).



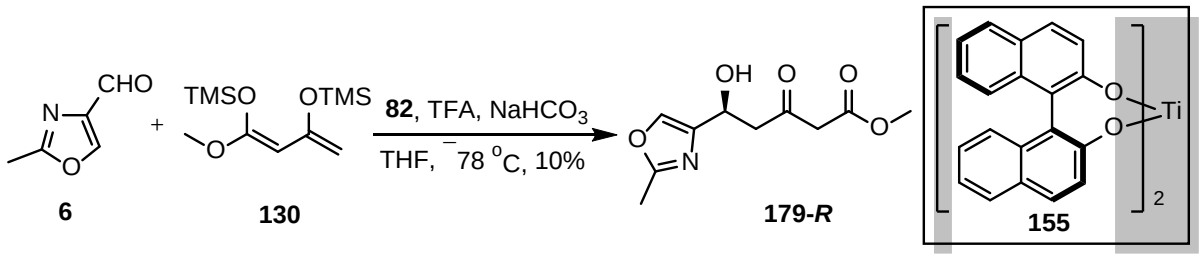
Scheme 45. The diketene aldol reaction and its mechanism



Scheme 46. Route of Weiler dianion aldol reaction

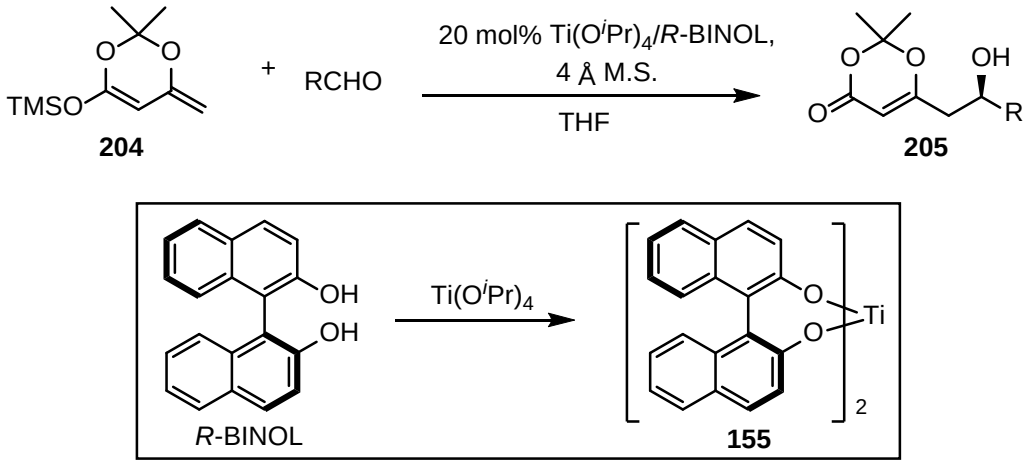
2.1.2.3 Asymmetric aldol reaction

As the development of the organo-etal catalytic asymmetric aldol reaction, in this study, we also tried the Ti-BINOL catalysed aldol reaction. However, the yield was quite poor and we could not confirm the enantiomeric excess of **179** (**Scheme 47**).



Scheme 47. Asymmetric aldol reaction using Ti-BINOL catalyst

The use of Ti(IV)-BINOL as a catalyst for aldol additions is well known and its first reported application to the vinylogous aldol was by Sato and co-workers (**Scheme 48**).[54] The complex was generated *in situ* to catalyse the reaction with diene **204**. Reasonably high though not exceptional enantioselectivities were obtained, however yields of the aldol products were low (**Table 1**).



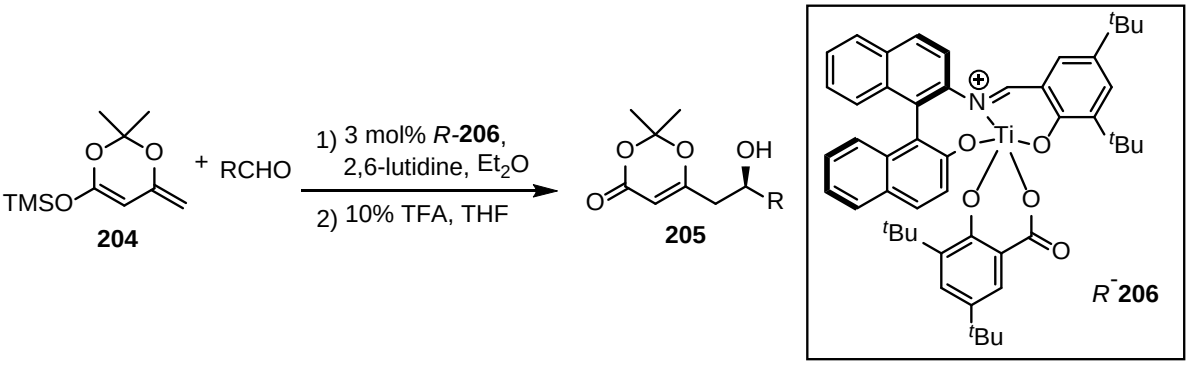
Scheme 48. Sato's asymmetric aldol reaction

R	Yield **205** (%)	ee (%)
Ph	38	88
PhCH=CH	32	33
n-Bu	55	88

Table 1. Sato and co-workers use of Ti(IV)-BINOL to catalyse asymmetric vinylogous aldol reactions

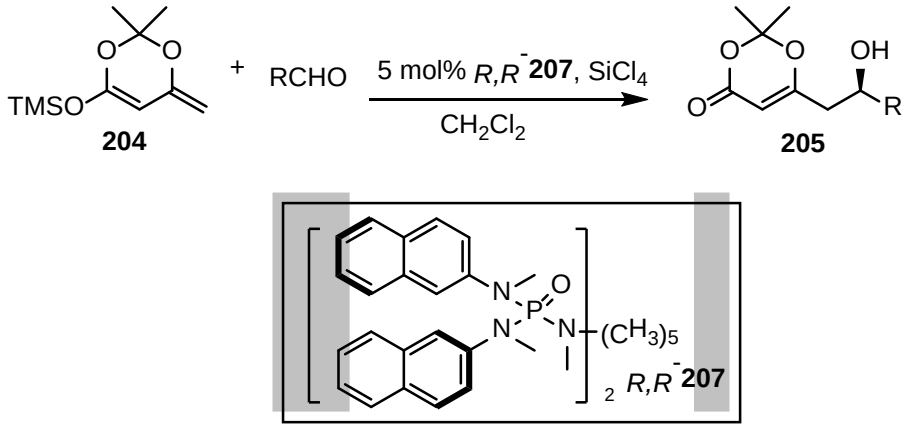
A modified procedure was developed by Scettri and co-workers to expand the scope of the catalytic system (from 20 mol% to 8 mol% of $Ti(O^iPr)_4$).[55] Their studies revealed that cleavage of the silyl protecting group of the aldol product prior to work-up was essential to prevent racemisation of the newly formed stereocentre. Improved yields and enantioselectivities were obtained with a lower catalyst loading in comparison to Sato's results. The complex could also be used to catalyse the reaction with Chan's diene with high yields and selectivities.

Carreira reported the use of chiral Ti(IV)-Schiff base complex **206** to synthesise aldol products in high yields (**Scheme 49**).[56] A wide range of aldehydes including alkynyl aldehydes as well as aromatic, olefinic and aliphatic aldehydes all gave high enantioselectivities. To exhibit the benefits of this catalyst system, it was employed in the total synthesis of macrolactin A.[57]



Scheme 49. Carreira's aldol reaction using Ti(IV)-Schiff base complex

Denmark and co-workers have reported BINAP derived ligand *R*, *R*-**207** which can be used to catalyse asymmetric aldol reactions by a forming complex with $SiCl_4$ (**Scheme 50**).[58] High yields and enantioselectivities were obtained with aliphatic aldehydes than aromatic aldehydes, however, the enantioselectivities reported, while high, are lower than other catalyst systems (**Table 2**). An additional drawback is the ligand must be synthesised in several steps comprising some air-sensitive chemistry. This is not ideal if screening of many catalyst systems is required to find the best enantioselective process to yield a product.



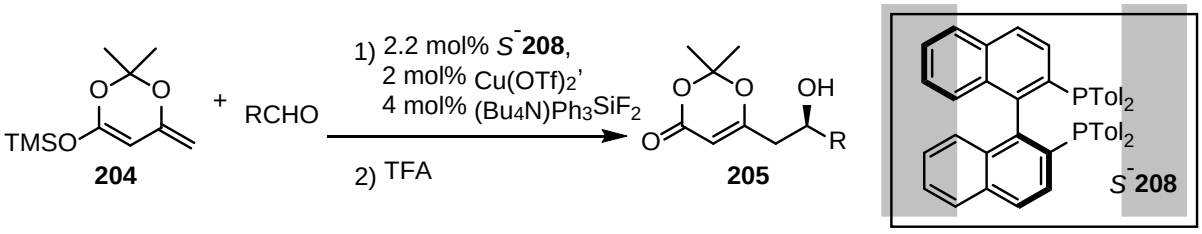
Scheme 50. Denmark's aldol reaction using R,R-**207**

R	Yield **205** (%)	ee (%)
Ph	92	74
PhCH=CH	88	78
$Ph(CH_2)_2$	83	89

Table 2. Results of asymmetric aldol reactions with Denmark's catalyst R, R-**207**

The catalysts which promote the vinylogous asymmetric aldol reactions, that have been described thus far, all catalyse the reaction through activation of the aldehyde in a Mukaiyama-type process. One functioning in an alternate way was reported by Carreira (**Scheme 51**).[59] Following his earlier work

with Ti(IV)-Schiff bases, a Cu(II) fluoride/Tol-BINAP catalyst was constructed for use in the vinylogous aldol reaction. Studies suggest that the reaction is promoted by the formation of a chiral copper dienolate species. The reaction with aromatic aldehyde proceeds to give the products in high yields and enantioselectivities (**Table 3**). However, the complex is less effective with aliphatic aldehydes.



Scheme 51. Carreira's aldol reaction with Cu(II) fluoride/Tol-BINAP catalyst

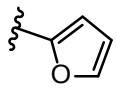
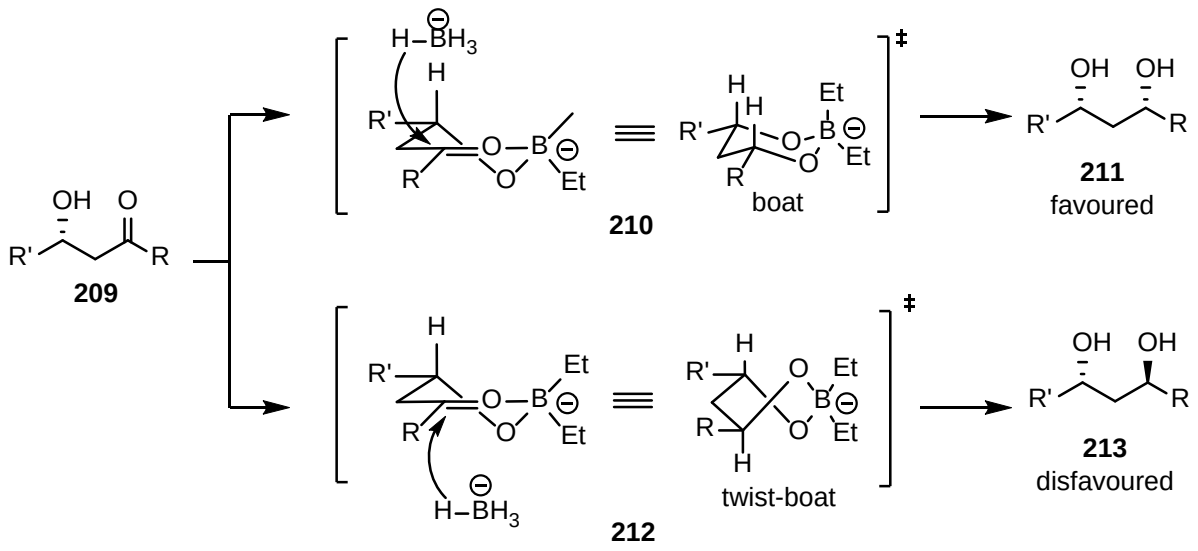
R	Yield **205** (%)	ee (%)
Ph	92	94
PhCH=CH	83	85
MeCH=CH	48	91
	91	94

Table 3: Carreira's use of catalyst S-**208** in the asymmetric vinylogous aldol reaction

2.1.3 Diastereoselective reduction

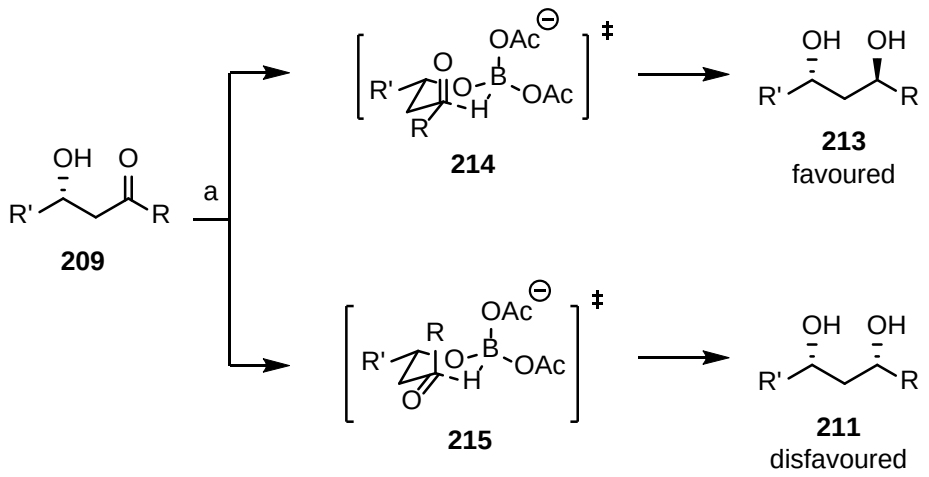
The reduction of the aldol products to the alcohol could potentially produce a mixture of 1,3-*syn* and 1,3-*anti* diastereomers. If this mixture was carried forward, the cyclization could potentially give up to four different diastereomers, which would make the analysis of the results difficult. Thus, it was decided to conduct the cyclizations on diastereomerically pure starting materials. The diastereoselective reductions of β-hydroxyketones is a well-developed area and the general approach to 1,3-*syn* diols is the Narasaka reduction (**Scheme 52**).[60]



Scheme 52. Diastereoselectivity in Narasaka reduction

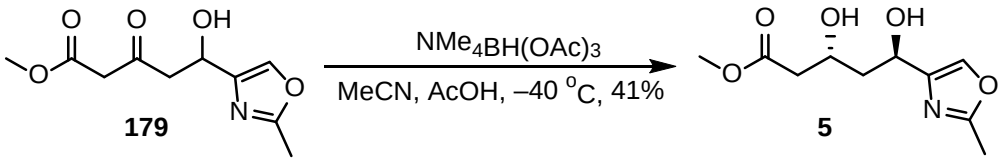
Diethyl alkoxyborane is generated *in situ* and used as a chelating Lewis acids to form some cyclic intermediates. An external hydride source is then used to reduce the ketone. The hydride can attack axially either from the top or the equational attack of the intermediate. Since only an attack from the top would produce an initial chair conformation, the corresponding transition state is lower in energy and therefore the production of the 1,3-*syn* diol **211** is favoured.

The complementary approach to the 1,3-*anti* diols β-hydroxyketones is the Evans-Saksena reduction (**Scheme 53**).[61, 62] In this case, the alcohol is used as a directing group to which the borohydride reducing agent complexes. Hydride is then delivered intramolecularly to the ketone *via* two possible chair-like transition states **214** and **215**. The hydride delivery from the side of the alcohol is preferred as this minimizes any steric interactions in the cyclic transition state. Thus, the transition state **215** is favoured and 1,3-*anti* diol **213** is the major product in the reaction.



Scheme 53. Diastereoselectivity in Evans-Saksena reduction

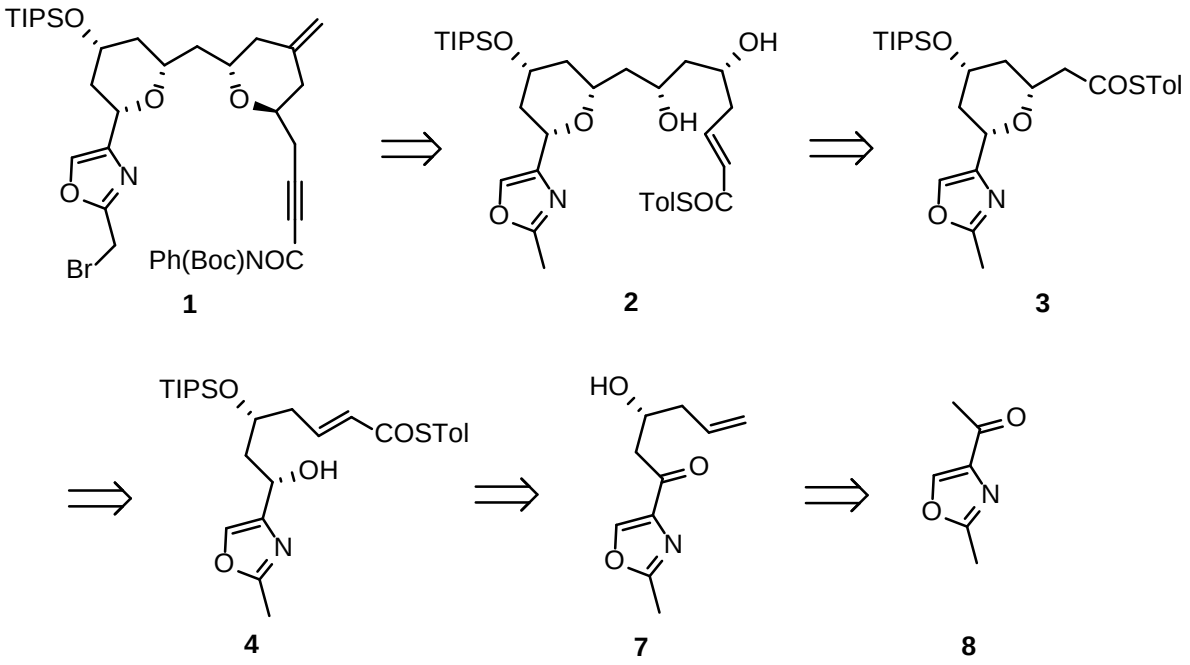
In this case, we tried the *anti*-reduction to the aldol product **179** (**Scheme 54**). The reaction was performed as in the literature.[61] The asymmetric reductant was dissolved in the mixture of AcOH and MeOH, which then stirred for 8 h in –40 °C.



Scheme 54. Asymmetric reduction of the diol ester

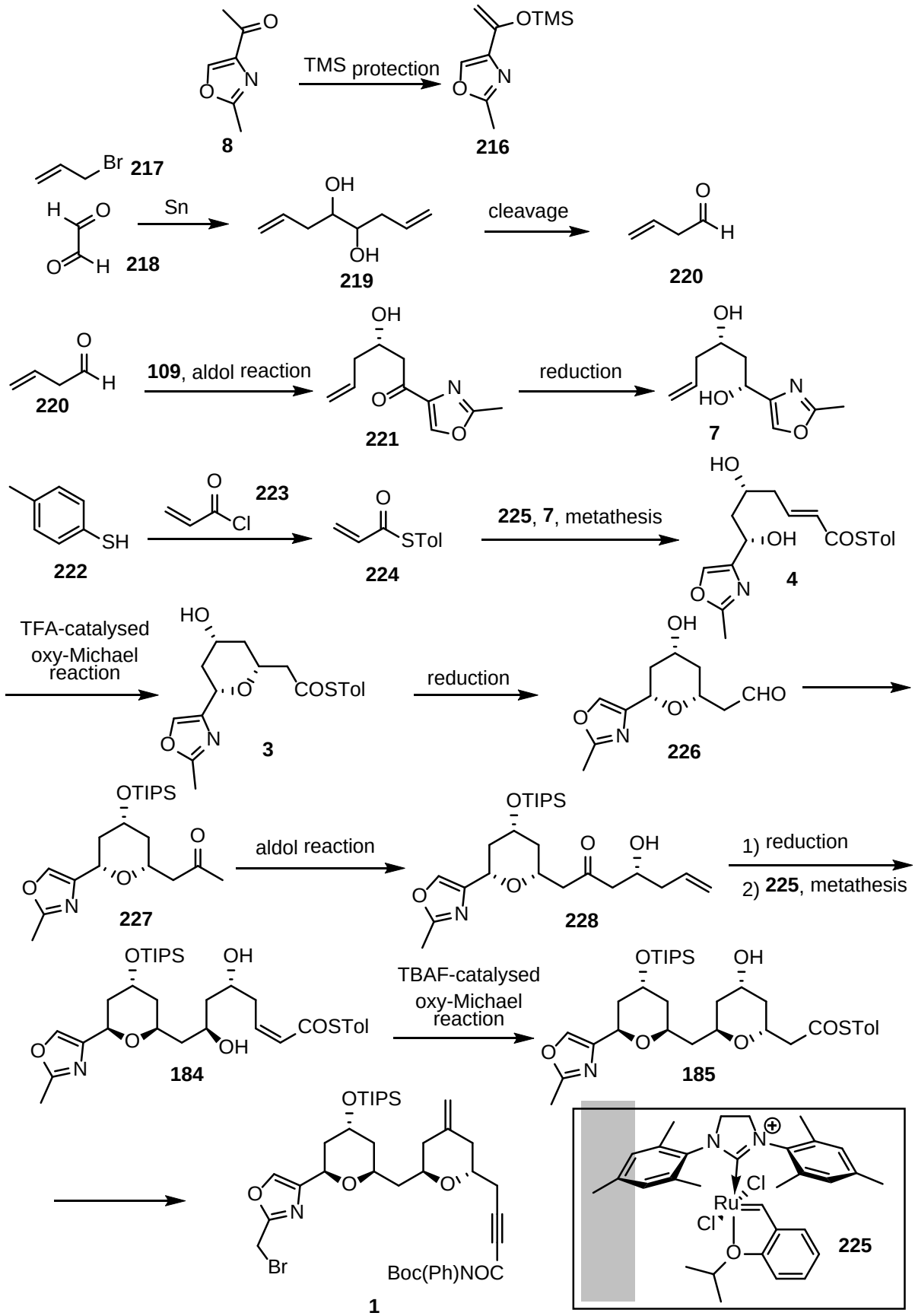
2.2 The second strategy

Because of diol ester **5** was easily decomposed and it was hard to find the satisfied Wittig conditions, we switched to a second synthetic strategy. The key point is to use the silyl enol ether of the methyl oxazole and aldehyde to form the aldol product. The fragment of C-1 – C-19 of phorboxazoles **1** will be accessed *via* **2** through several steps. Thiosester **2** is planned from **3** by using aldol reaction, reduction etc. the *cis* THP ring **3** will be synthesised using our acid-catalysed divergent oxy-Michael reaction from thiosester **4**. A metathesis was planned to convert **7** into **4**, itself made by an aldol reaction from the oxazole ketone **8** (**Scheme 55**).



Scheme 55. Retrosynthesis analysis of the fragment of C-1 – C-19 of phorboxazoles, II

A new route was projected to form the fragment of C-1 – C-19 of phorboxazoles **1**. The Barbier reaction was used to form **219**, followed by reacting with $NaIO_4$ to give the aldehyde **220**. The aldol reaction was assumed by using **220** and silyl enol ether **216** to give **221** which was then reacted with stereodivergent reductant to form diol **7**. The thioacrylate **224** was made and used into metathesis reaction with the 2nd generation Hoveyda-Grubbs catalyst **225**, giving **4**. Then the stereodivergent oxy-Michael reaction with CSA or TFA would build the first *cis*-THP ring. The new ketone **227** would be made through reduction, Grignard addition, DMP oxidation and TIPS protection. After using the same methodology, **184** was made to react with TBAF to build the second *trans*-THP ring **185**. Thus, the fragment of C-1 – C-19 of phorboxazoles **1** was synthesised by using the same method from the first strategy. (**Scheme 56**)

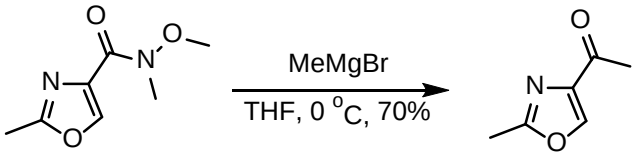


Scheme 56. Route to synthesise the fragment of C-1 – C-19 of phorboxazoles

2.2.1 The aldol reaction

The ketone-based aldol reaction was successfully used to form the diospongins in our group. We also applied the methodology into this study.

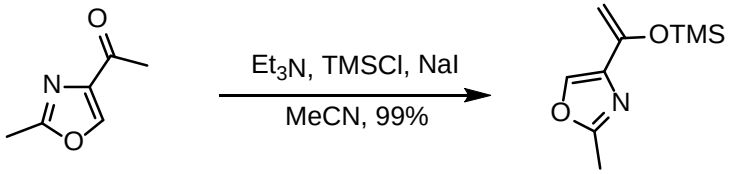
The oxazole ketone **8** was prepared by Weinreb amide **195** and Grignard reagent MeMgBr in THF (**Scheme 57**). The highest yield achieved was 70%, however, the yields normally were 40%, or even lower. The reason for these low yields probably is that the ketone product **8** is water soluble. Therefore, it is difficult to isolate.



195 **8**

Scheme 57. Grignard addition to oxazole ketone

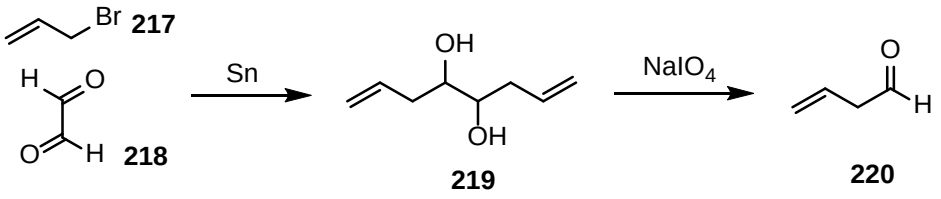
Ketone **8** was used to form silyl enol ether **216** with triethylamine and TMSCl, which gave **216** in 99% yield (**Scheme 58**).



8 **216**

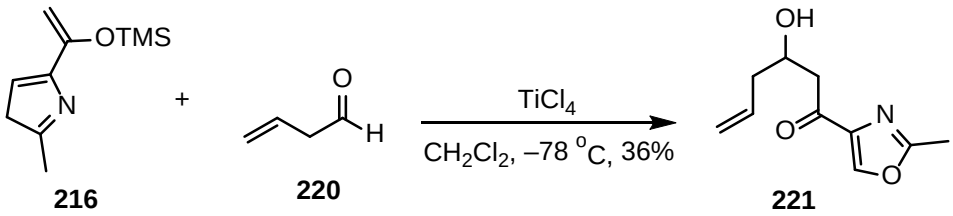
Scheme 58. Synthesis of the silyl enol ether

The Barbier reaction was used to prepare the diol **219**, which gave aldehyde **220** *via* $NaIO_4$-medialised diol cleavage. Many alternative methods (e.g. alcohol oxidation) would likely cause this aldehyde to isomerize to the conjugated aldehyde. The 4-butenal **220** is very volatile and therefore is not usually isolated but used as a solution. (**Scheme 59**)



Scheme 59. Synthesis of 4-butenal

With both starting materials in hand the aldol reaction was carried out and it gave the desired β-hydroxyketone **221** in moderate yield. (**Scheme 60**)



Scheme 60. Aldol reaction to β-hydroxyketone

2.2.2 Olefin metathesis

2.2.2.1 A brief review of olefin metathesis

Within olefin metathesis, three of the most important types, which are ring-opening metathesis polymerization (ROMP), ring-closing metathesis (RCM) and cross metathesis (CM).

ROMP is generally thermodynamically favoured for strained ring systems, such as 3-, 4-, 8- and larger membered compounds. When bridging groups are present (bicyclic olefins) the *Δ*G of polymerization is typically more negative as a result of increased strain energy in the monomer. Block copolymers can be made by sequential addition of different monomers.[63]

RCM can be driven by the loss of ethylene. The development of well-defined metathesis catalysts that are tolerant of many functional groups yet reactive toward a diverse array of olefinic substrates has led to the rapid acceptance of the RCM reaction as a powerful method for forming carbon-carbon double bonds and for macrocyclizations. Where the thermodynamics of the closure reaction are

unfavourable, polymerization of the substrate can occur. This partitioning is sensitive to substrate, catalyst, and reaction conditions.[63]

For the CM, self-dimerization reactions of the more valuable alkene may be minimized using an excess of the more readily available alkene.

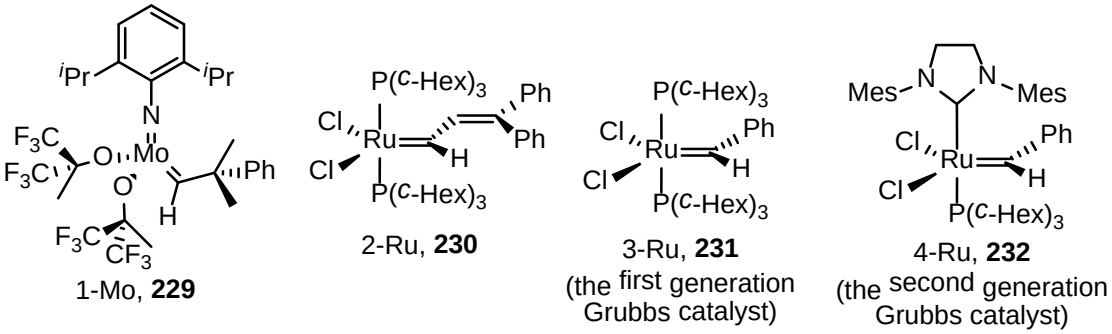
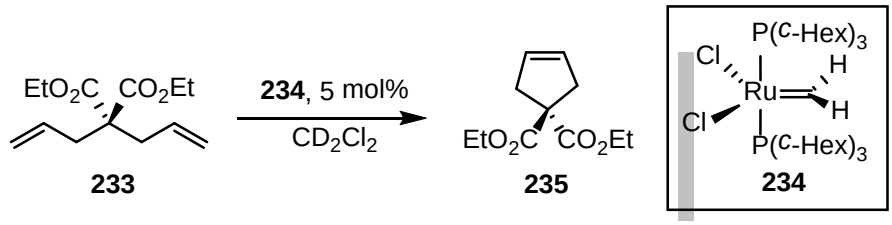


Figure 6. General metathesis catalysts

The well-defined catalysts shown in **Figure 6** have been used widely for the olefin metathesis reaction. Titanium- and tungsten-based catalysts have also been developed but are less used. Schrock's alkoxy imidomolybdenum complex **229** is highly reactive toward a broad range of substrates; however, this Mo-based catalyst has moderate to poor functional group tolerance, high sensitivity to air, moisture or even to trace impurities present in solvents, and exhibits thermal instability. Grubbs' Ru-based catalysts exhibit high reactivity in a variety of ROMP, RCM, and CM processes and show remarkable tolerance toward many different organic functional groups. The electron-rich tricyclohexyl phosphine ligands of the d^6 Ru(II) metal centre in alkylidenes **230** and **231** leads to increased metathesis activity. The NHC ligand in **232** is a strong σ-donor and a poor π-acceptor and stabilizes a 14 e^- Ru intermediate in the catalytic cycle, making this catalyst more effective than **230** or **231**. Ru-based catalysts possibly show little sensitivity to air, moisture, or minor impurities in solvents. These catalysts can be conveniently stored in the air for several weeks without decomposition. All the catalysts above are commercially available, but 1-Mo is significantly more expensive.[63]

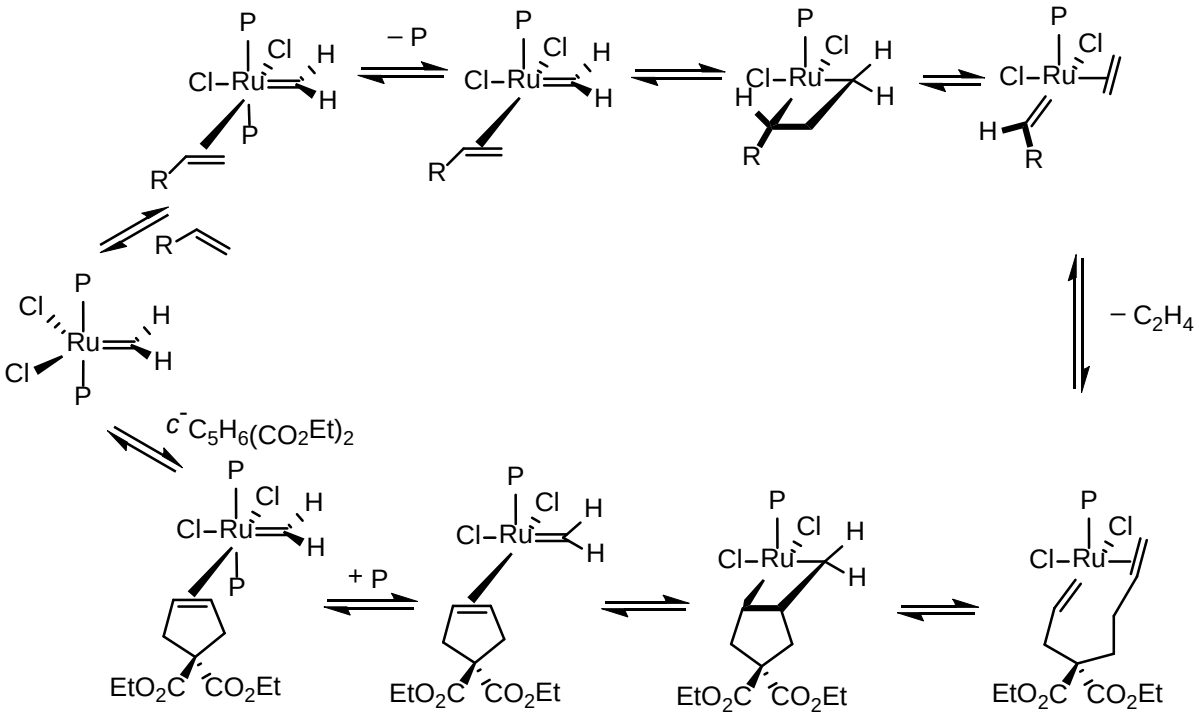
The olefin metathesis reaction was reported as early as 1955 in a Ti(II)-catalyzed polymerization of norbornene. Chauvin first proposed that olefin metathesis proceeds *via* metallacyclobutanes. It is now generally accepted that both cyclic and acyclic olefin metathesis reactions proceed *via* metallacyclobutane and metal-carbene intermediates. A kinetic study of the RCM of diethyl diallylmalonate **233** using a Ru-methylidene **234** (**Scheme 61**) describes two possible mechanisms for olefin metathesis: the “dissociative” mechanism and the “associative” mechanism.[63]



233 **235** **234**

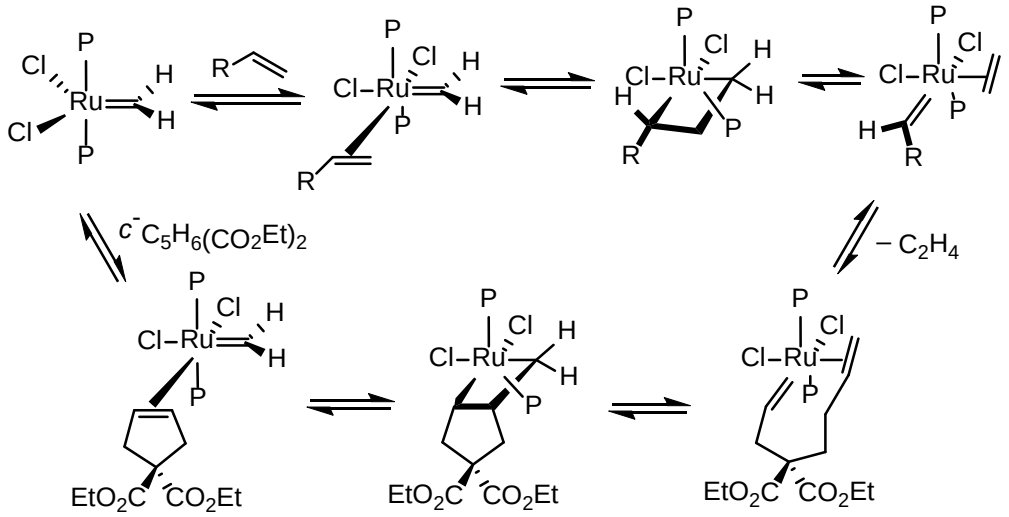
Scheme 61. Metathesis of diethyl diallylmalonate

The "dissociative" mechanism assumes that upon binding of the olefin a phosphine is displaced from the metal center to form a 16-electron olefin complex, which undergoes metathesis to form the cyclised product, regenerating the catalyst upon recoordination of the phosphine (**Scheme 62**).[63]



Scheme 62. The “dissociative” mechanism of RCM

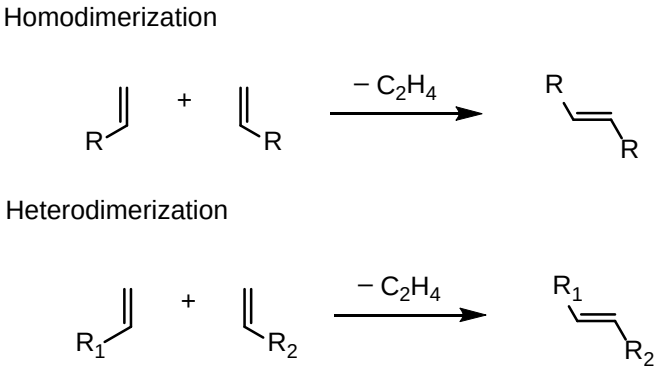
The "associative" mechanism assumes that an 18-electron olefin complex is formed which undergoes metathesis to form the cyclised product (**Scheme 63**). Addition of 1 equivalent of phosphine (with respect to catalyst) decreases the rate of the reaction by as much as 20 times, supporting the dissociative mechanism. It was concluded in this study that the "dissociative" pathway is the dominant reaction manifold (> 95%).[63]



Scheme 63. The “associative” mechanism of RCM

2.2.2.2 Cross metathesis (CM)

Given the various possible alkylidene intermediates and the numerous primary and secondary metathesis pathways involved in a cross metathesis reaction, it is difficult to predict how the complex interplay of steric and electronic factors will determine the ability of various sets of olefins to participate in selective CM reactions.[63c] CM can be divided into two parts: homodimerization CM and heterodimerization CM (**Scheme 64**). The selectivity of these two kinds of reactions will influence the result of CM significantly.



Scheme 64. Homodimerization CM and heterodimerization CM

There are four types of olefins introduced by Grubbs' group, which shows the selectivity in cross metathesis (**Table 4** & **5**).[63c]

Decreasing in olefin reactivity	*Steric congested*	*Electron deficient*		
			Type 1	Rapid homodimerization, homodimers consumable
			Type 2	Slow homodimerization, homodimers sparingly consumable
			Type 3	No homodimerization, active to CM with Type 1 and 2 olefins
			Type 4	Olefins inert to CM, but do not deactivate catalyst (Spectator)

Table 4. Grubbs' model of olefins

Type 1	Statistical (St)			
Type 2	Selective (S)	Non-selective (NS)		
Type 3	Selective (S)	Slow reaction (SI)	Non-selective (NS)	
Type 4	No reaction (NR)	No reaction (NR)	No reaction (NR)	No reaction (NR)
	Type 1	Type 2	Type 3	Type 4

Table 5. Grubbs' model of selectivity

Type 1 olefins are categorized as those able to undergo a rapid homodimerization and whose homodimers can participate in CM as well as their terminal olefin counterpart. Type 2 olefins homodimerize slowly, and unlike Type 1 olefins, their homodimers can only be sparingly consumed in subsequent metathesis reactions. Type 3 olefins are essentially unable to be homodimerized by the catalyst but are still able to undergo CM with Type 1 and Type 2 olefins. Type 4 olefins are not able to participate in CM with a particular catalyst but do not inhibit catalyst activity toward other olefins. Outside these categories are olefins that deactivate the catalyst. In general, a reactivity gradient exists from most active type (Type 1 olefin) to least active Type (Type 4 olefin), with sterically unhindered, electron-rich olefins categorized as Type 1 and increasingly sterically hindered and/or electron-deficient olefins falling into Types 2 through Type 4.[63c]

An olefin's general reactivity (as shown in **Table 4**) with a given catalyst determines the role of secondary metathesis, that is, subsequent reactions of a product olefin with the propagating catalyst. Efficient secondary metathesis occurs when all components in the reaction are readily accessible to the metal alkylidene complex, including homodimers and the CM product. The key to CM reaction selectivity is minimizing the number of undesirable CM side products (such as the homodimers of the starting olefins) either by avoiding their initial formation or by ensuring that they are fully consumed in secondary metathesis events. It is also important that the desired cross product not be redistributed into a statistical product mixture by these same secondary metathesis events.[63c]

Table 6 categorizes most reported CM substrates for the 2nd generation Grubbs catalyst **145**, and this can help us to predict the cross metathesis in our study.

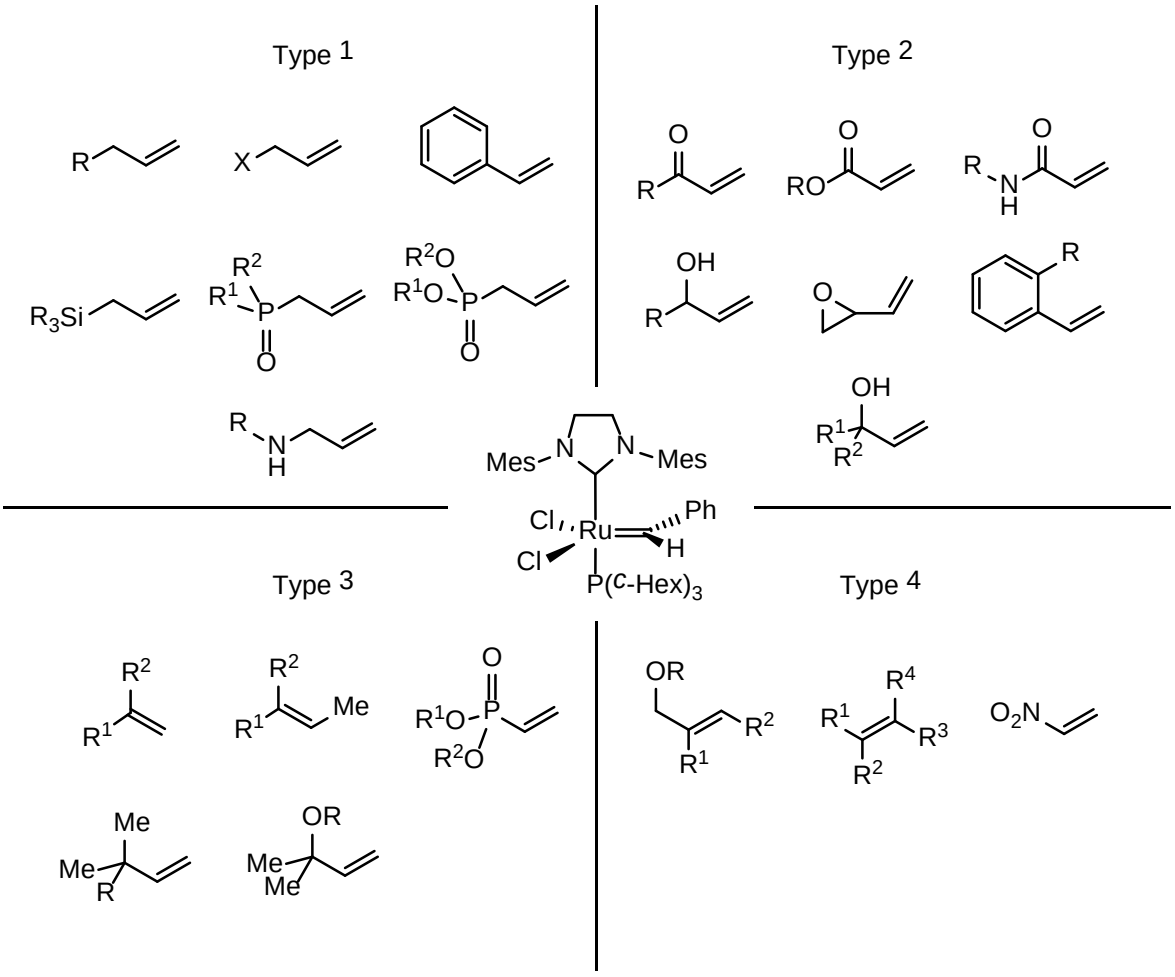
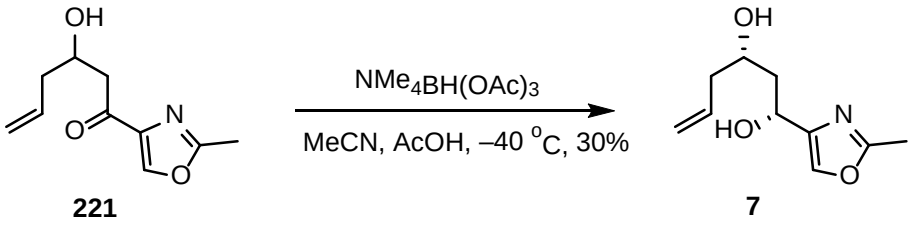


Table 6. Olefin categorization for 2nd Grubbs catalyst

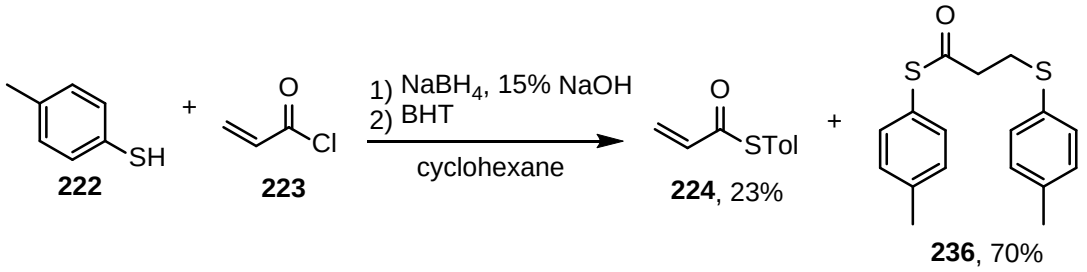
2.2.2.3 Metathesis in our study

We successfully applied our case into the Evans-Saksena reduction, forming the 1,3-*anti* diol **7** (**Scheme 65**). The diol **7** is not very stable in the room temperature, so the it is better to store it in the freezer.



Scheme 65. Asymmetric reduction of β-hydroxyketone

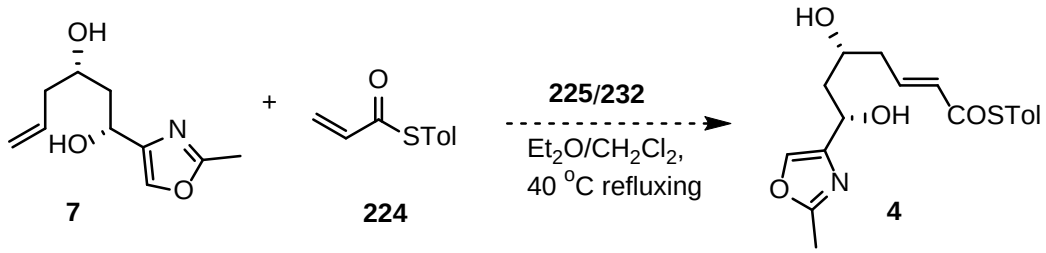
Acryloyl thioester **224** was prepared through a simple reaction and proved to be quite a challenge. Pyridine, triethylamine and sodium hydride were all tested as bases in this reaction and the major product was *bis*-addition product **236** along with large amounts of polymerization products. The highest yield achieved of **224** was 23%, however, this still contained small amounts of **236**, which could impact the metathesis reaction (**Scheme 66**).



Scheme 66. Synthesis of the thioester **224**

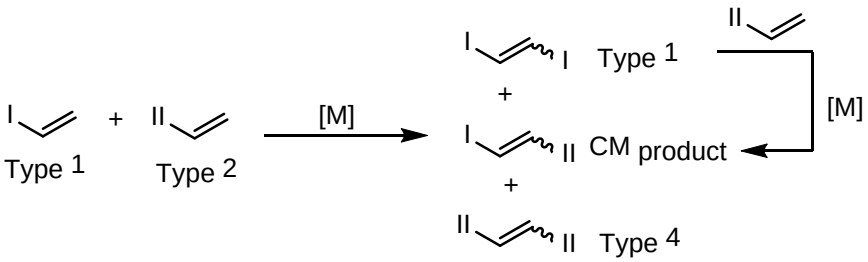
With the starting materials, **7** and **224**, in hand, we attempted to do the cross metathesis several times with the 2nd generation Hoveyda-Grubbs **225** and the 2nd generation Grubbs catalyst **232** in different solvents including Et_2O and CH_2Cl_2. Theoretically, Reactions between Type 1 olefins and Type 2 olefins such as α, β-unsaturated carbonyl olefins result in highly selective CM reactions with high stereoselectivity (*E* / *Z* > 20 : 1).[71] In our study, acryloyl thioester **224** is a Type 2 olefin because it undergoes homodimerization to a small extent under the reaction conditions, allowing for selective reactions with Type 1 olefin **7** (**Scheme 67**). However, neither of them were successful. We could see that the diol spot disappeared and two new spots appeared on TLC when refluxed at 40 °C in the N_2

atmosphere for at least 12 hours. ^{1}H NMR and MS data did not show the evidence that reactions were successful as well.



Scheme 67. Attempts of metathesis

The possible reasons for the result are: product **4** might be cyclised in the reaction process; the product **4** is not stable in the air and room temperature. The possibility of forming the initial homodimer is another important reason for failed cross metathesis. According to the rule of selective CM of Type 1 with Type 2 Olefins (**Scheme 68**), our reactions might stop at the first step – homodimerization CM. Because acryloyl thioester **227** was not stable enough and tend to transfer to **236**, there was lack of **224** in the reaction system to proceed to the next step, which leads to no CM product.



Scheme 68. Primary reactions in CM of Type 1 with Type 2 olefins

3. Conclusion and future work

In this study, several types of aldol reactions were tried, including Chan's diene, diketene and Weiler dianion aldol reaction. We also tried the diastereoselective reduction to diols and the metathesis reaction. Although additional work is needed to achieve the synthesis of C-1 – C-19 fragment of phorboxazoles, the experience we gained will influence the future.

Comparing these two different strategies, the first strategy seems better than the second one. Firstly, most reactions are easier-controlled. Secondly, materials used in the first approach are much cheaper than the second one.

In the future, we may try to find a better condition for the metathesis. For example, protecting two hydroxyl groups in the diol *via* TMSCl, TESOTf, etc., or making it become an acetonide or benzylidene acetal (**Figure 7**).

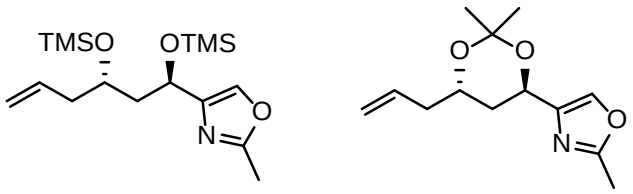
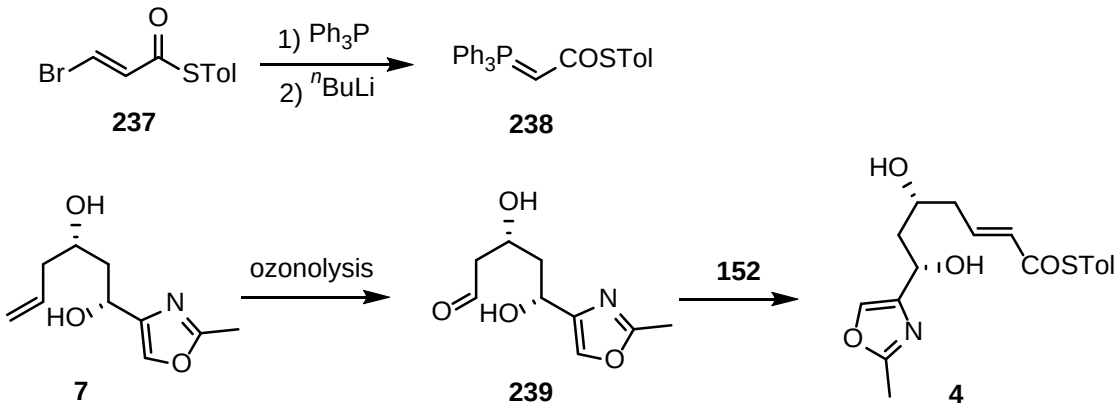


Figure 7. Protection of diol

We also think that use syringe pump slowly adding the diol solution may be benefit to the metathesis. A larger equivalent of acryloyl thioester will be worth to try as well.

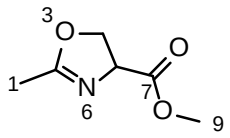
If we still could not solve the problem, we would try the ozonolysis to oxidise the double bond to an aldehyde and then do the Wittig reaction to give the oxy-Michael form product (**Scheme 69**).



Scheme 69. A possible route for future work

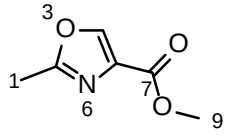
4. Experimental

2-Methyl-4-carbomethoxy ester oxazoline 189



To a solution of *DL*-serine methyl ester hydrochloride (98%) (2.00 g, 12.8 mmol) and ethyl acetimidate hydrochloride (97%) (1.71 g, 13.8 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (≥ 99%) (3.6 mL, 2.57 mmol) over a 20-minute period. The mixture was stirred at room temperature under a N_2 atmosphere for 16 hours. The salts formed were filtered through a pad of Celite and washed with diethyl ether (100 mL). The filtrate was concentrated and the solid formed was washed with diethyl ether (100 mL). The ether extracts were combined and concentrated to give a pale-yellow oil. The material was further purified by Kugelrhor distillation to give a colourless oil (1.53 g, 83 %). The ^{1}H NMR data agreed with the literature.[49] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.72 (1H, ddq, *J* = 10.5, 8.0, 1.0 Hz, H-5), 4.48 (1H, dd, *J* = 8.5, 8.0 Hz, H-4), 4.40 (1H, dd, *J* = 10.5, 8.5 Hz, H-4), 3.78 (3H, s, H - 9), 2.03 (3H, d, *J* = 1.0 Hz, H-1) ppm.

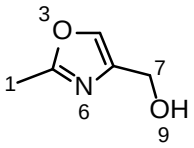
Methyl 2-methyloxazole-4-carboxylate 190



A solution of methyl oxazole **189** (1.50 g, 10.5 mmol) in CH_2Cl_2 (50 mL) stirring at 0 °C under N_2 was treated with DBU (98%) (3.2 mL, 21.0 mmol). The mixture was stirred for 15 minutes and was then treated with $BrCCl_3$ (99%) (1.5 mL, 14.5 mmol) and left to stir for 16 hours at 0 °C gradually warming to room temperature. The mixture was partitioned between ethyl acetate (150 mL) and a 2 M aqueous solution of hydrochloride acid (100 mL). The layers were separated and the aqueous layer washed

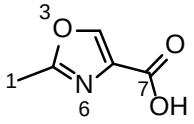
with ethyl acetate (150 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (2 × 200 mL), brine (2 × 200 mL), dried ($MgSO_4$) and concentrated to give an off-white solid. The crude material was purified by flash column chromatography using a 1 : 19 petroleum ether: EtOAc gradient to give a white solid (1.0 g, 70%). The ^{1}H NMR data matched with the literature.[49] **^{1}H NMR** (270 MHz, $CDCl_3$): δ 8.14 (1H, s, H-4), 3.91 (3H, s, H-9), 2.50 (3H, s, H-1) ppm.

(2-Methyloxazol-4-yl)methanol 191



A solution of methyl 2-methyloxazole-4-carboxylate **190** (200 mg, 1.42 mmol) in Et_2O (20 mL) stirring at –35 °C under a N_2 atmosphere was treated with 1.0 M $LiAlH_4$ in THF (3.0 ml, 3.0 mmol). The reaction was stirred for 1 hour after which time the reaction was quenched with an addition of H_2O (0.6 mL) and a 15% aqueous solution of NaOH (0.6 mL). The mixture was stirred at room temperature for 1 hour. To the solution was added $MgSO_4$ (850 mg) and the mixture was left to stir for 30 minutes. The solids were removed by filtration and the filtrate concentrated to give a pale yellow solid (120 mg, 74%). The ^{1}H NMR data agreed with the literature.[49] **^{1}H NMR** (270 MHz, $CDCl_3$): δ 7.48(1H, s, H-4), 4.56 (2H, d, H-7), 2.45 (3H, s, H-1), 2.18 (1H, t, H-9).

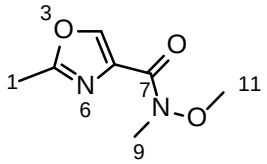
2-Methyloxazole-4-carboxylic acid 193



To a solution of methyl 2-methyloxazole-4-carboxylate **190** (2.00 g, 0.014 mol) in H_2O (5 mL) stirring at room temperature was added a 32% aqueous solution of NaOH (1.80 g, 0.020 mol). The reaction

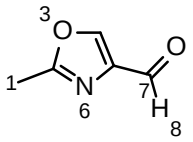
was stirred for 1 hour then was treated with a 37% aqueous solution of HCl (1.56 g, 0.015 mol). The reaction was cooled to 0 °C and left to stand for 1 hour. The solids were filtered and washed with cold H_2O (30 mL) and dried in the oven to give a white solid (1.76 g, 99%). The ^{1}H NMR data agreed with the literature.[49] **^{1}H NMR** (270 MHz, DMSO): δ 8.49 (1H, s, H-4), 2.42 (3H, s, H-1) ppm.

***N*-Methoxy-*N*,2-dimethyloxazole-4-carboxamide 195**



2-Methyoxazole-4-carboxylic acid **193** (1.40 g, 0.011 mol) and *N*, *O*-dimethylhydroxylamine hydrochloride (98%) (1.07 g, 0.011 mol) were dissolved in CH_2Cl_2 (4.5 mL) and H_2O (0.4 mL). The reaction was treated with triethylamine (≥ 99%) (1.51 g, 0.015 mol) and was then stirred at room temperature for 1 hour to give a clear solution which was cooled to 0 °C. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (≥ 99%, AT) (2.50 g, 0.013 mol) was suspended in CH_2Cl_2 (7.5 mL) in another flask and then cooled to 0 °C. The solution of the mixture of carboxylic acid and *N*, *O*-dimethylhydroxylamine hydrochloride was added to the slurry of diimide maintaining the temperature < 10 °C. Once the addition was complete the solution could warm to room temperature and then stirred for 1 hour. A solution of citric acid (≥ 99.5%) (0.9 g) in H_2O (3.6 mL) was added and the layers were separated. The aqueous solution was washed with CH_2Cl_2 (2 × 20 mL). The organic extracts were combined and then washed with H_2O (30 mL) and concentrated to give an orange solid (1.32 g, 71%) which was recrystallized from heptane to give a white solid (896 mg; 46%). The ^{1}H NMR data agreed with the literature.[49] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03 (1H, s, H-4), 3.71 (3H, s, H-11), 3.34 (3H, s, H-9), 2.47 (3H, s, H-1) ppm.

2-Methyloxazole-4-carboxaldehyde 6



From 2-methyl-4-carbomethoxy ester oxazole **190**

A solution of 2-methyl-4-carbomethoxy ester oxazole **190** (1.0 g, 7.1 mmol) in CH_2Cl_2 (100 mL) stirring at –78 °C under a N_2 atmosphere was treated very slowly with 1.0 M DIBAL in hexanes (14 mL, 14 mmol) by using the syringe pump. The reaction was stirred for 3 hours, treated with anhydrous acetone (10 mL) and stirred for 1 hour. A 20% aqueous solution of Rochelle's salt (10 mL) was added and the mixture was stirred overnight gradually warming to room temperature. The mixture was partitioned between Et_2O (100 mL) and H_2O (100 mL). The organic layer was separated and the aqueous layer washed with Et_2O (100 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil (667 mg, 85%). Purification by flash column chromatography afforded a brown solid (531 mg, 66 %). The ^{1}H NMR data agreed with the literature.[49] **^{1}H NMR** (270 MHz, $CDCl_3$): δ 9.89 (1H, s, H-8), 8.15 (1H, s, H-4), 2.52 (3H, s, H-1) ppm.

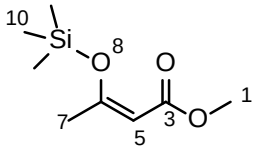
From (2-methyloxazole-4-yl)-methanol **191**

A solution of (2-methyloxazole-4-yl)-methanol **191** (630 mg, 5.57 mmol) and MnO_2 (≥ 99.99% trace metals basis) (9.89 g, 110 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature under a N_2 atmosphere for 24 hours. The mixture was diluted with Et_2O (200 mL) and solids were removed through a pad of Celite and washed with Et_2O (500 mL). The solution was concentrated *in vacuo* to give a brown solid (142 mg, 23%).

*From N-methoxy-N,2-dimethyloxazole-4-carboxamide **195***

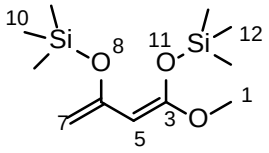
A solution of *N*-methoxy-*N*,2-dimethyloxazole-4-carboxamide **195** (1.0 g, 5.9 mmol) in THF (300 mL) stirring at –35 °C under a N_2 atmosphere was treated with a 1.0 M solution of $LiAlH_4$ in THF (5.9 mL, 5.9 mmol). The reaction was stirred for 1 hour and was treated with a 20% aqueous solution of Rochelle's salt (50 mL). The mixture was warmed to room temperature and stirred for 2 hours. The mixture was partitioned between Et_2O (100 mL) and H_2O (100 mL). The organic layer was separated and the aqueous layer washed with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a brown solid (0.20 g, 30%).

(*Z*)-Methyl 3-((trimethylsilyl)oxy)but-2-enoate 197



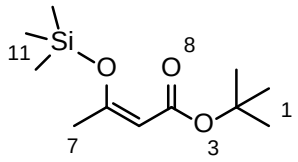
To a solution of methyl acetoacetate (99%) (1.9 mL, 17.2 mmol) and triethylamine (≥ 99%) (3.0 mL, 21.2 mmol) in hexane (250 mL) was added chlorotrimethylsilane (≥ 99%) (3.5 mL, 27.2 mmol). The mixture was stirred at room temperature under a N_2 atmosphere for 12 hours. The salts were filtered through a pad of Celite and washed with hexane (100 mL). The ether extracts were combined and concentrated to give a pale-yellow oil which was purified by Kugelrhor distillation to give a colourless oil (2.59 g, 80%). The ^{1}H NMR data agreed with the literature.[43] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 5.05 (1H, s, H-5), 3.59 (3H, s, H-7), 2.20 (3H, s, H-1), 0.20 (9H, s, H-10) ppm.

(*Z*)-4-Methoxy-2,2,8,8-tetramethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene 130



A solution of LDA was made by using the dried diisopropylamine (2.8 mL, 19.8 mmol) and 2.5 M ^{n}BuLi in hexanes (7.9 mL, 19.8 mmol) in THF (30 mL) at 0 °C under a N_2, then was cooled to –78 °C and stirred for 30 minutes, treated with (*Z*)-methyl 3-((trimethylsilyl)oxy)but-2-enoate **197** (3.34 g, 17.8 mmol) in THF (20 mL) and was left to stir for 15 minutes. The solution was treated with dried chlorotrimethylsilane (≥ 99%) (3.0 mL, 23.8 mmol) and stirred at –78 °C for 10 minutes then warmed to room temperature and left to stir for 16 hours. The yellow solution was concentrated *in vacuo*. The salts were removed by filtration through a pad of Celite and washed with hexanes (100 mL). The filtrate was concentrated to give a crude yellow oil which was used without further purification (4.0 g, 87%). The ^{1}H NMR data agreed with the literature.[43] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.42 (1H, s, H-5), 4.07 (1H, d, H-7), 3.87 (1H, d, H-7), 3.49 (3H, s, H-1), 0.19 (9H, s, H-10), 0.15 (9H, s, H-12) ppm.

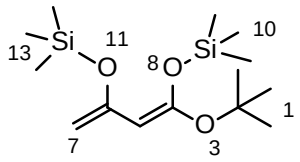
(*Z*)-*tert*-Butyl-3-(trimethylsiloxy)but-2-enoate 201



To a solution of *tert*-butyl acetoacetate (98%) (2.1 mL, 12.6 mmol) and triethylamine (≥ 99%) (2.7 mL, 19.6 mmol) in hexane (100 mL) was added chlorotrimethylsilane (≥ 99%) (3.2 mL, 25.6 mmol). The mixture was stirred at room temperature under a N_2 atmosphere for 12 hours. The salts were filtered through a pad of Celite and washed with petroleum ether (500 mL). The ether extracts were combined and concentrated to give a pale-yellow oil which was purified by Kugelrhor distillation to give a

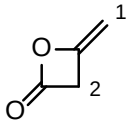
colourless oil (2.88 g, 99%). The ^{1}H NMR data agreed with the literature.[43] **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 4.99 (1H, s, H-5), 2.15 (3H, s, H-7), 1.41 (9H, s, H-1), 0.19 (9H, s, H-11) ppm.

(*Z*)-*tert*-Butoxy-4,6-*bis*-trimethylsilanyloxy-buta-4,6-diene 202



A solution of LDA was made by using the dried diisopropylamine (1.7 mL, 12.0 mmol) and 2.5 M ^{n}BuLi in hexanes (4.8 mL, 12.0 mmol) in THF (30 mL) at 0 °C under a N_2, then was cooled to –78 °C and stirred for 30 minutes. The mixture was treated with (*Z*)-*tert*-butyl 3-(trimethylsiloxy) but-2-enoate **201** (2.3 g, 10.0 mol) in THF (20 mL) and was left to stir for 15 minutes. The solution was treated with chlorotrimethylsilane (≥ 99%) (1.9 mL, 15.0 mmol) and stirred at –78 °C for 10 minutes then warmed to room temperature and left to stir for 16 hours. The yellow solution was concentrated *in vacuo*. The salts were removed by filtration through a pad of Celite and washed with hexanes (100 mL). The filtrate was concentrated to give a crude yellow oil which was used without further purification (1.81 g, 60%). The ^{1}H NMR data agreed with the literature.[43] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.52 (1H, s, H-5), 4.25 (1H, s, H-7), 4.20 (1H, s, H-7), 1.35 (9H, s, H-1), 0.25 (3H, s, H-10), 0.19 (3H, s, H-13) ppm.

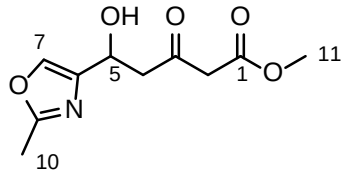
4-Methylideneoxetan-2-one 143



To a solution of acetyl chloride (98%) (4.41 g, 56 mmol) in diethyl ether (10 mL) was added triethylamine (≥ 99%) (3.9 mL, 28 mmol) over 1 min in room temperature. Then the mixture was stirred

for 90 minutes, diluted in small amount of Et_2O (< 10 mL), poured in a small funnel. The product was kept in a dark fume cupboard overnight to give a brown oil. Because it is extremely unstable, we used it directly to the next step. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.52 (d, *J* = 3.87, 1.94 Hz, 1H, H-1), 3.95 (d, *J* = 3.87, 1.36 Hz, 1H, H-1), 3.03 (d, *J* = 1.94, 1.36 Hz, 2H, H-2).

Methyl 5-hydroxy-5-(2-methyloxazol-4-yl)-3-oxopentanoate 179



*From methyl acetoacetate **196***

To a suspension of NaH (60 % dispersion in mineral oil) (414 mg, 10.3 mmol) in THF (20 mL) stirring at 0 °C under a N_2 atmosphere was added methyl acetoacetate (99%) (1.3 mL, 8.62 mmol) over a 20-minute period. The solution was stirred for 15 minutes then was treated with 2.0 M ^{n}BuLi in hexanes (4.74 mL, 9.48 mmol) and left to stir at room temperature for 40 minutes. The mixture was cooled to –78 °C then treated with 2-methyloxazole-4-carbaldehyde **6** (1.05 g, 9.48 mmol) and stirred for 1 hour. The mixture was diluted with EtOAc (50 mL), washed with a 5% aqueous solution of $NaHCO_3$ (3 × 50 mL), brine (2 × 50 mL), dried with $MgSO_4$ and concentrated *in vacuo* to give a brown oil. The crude material was purified by flash column chromatography using a 2 : 3 hexane: EtOAc gradient to give a yellow oil (0.86 g, 40%). **IR** (film): υ_{max} 3192, 3140, 2960, 1749, 1712, 1644 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.44 (s, 3H, H-10), 3.08 (d, *J* = 7.8 Hz, 1H, H-4), 3.09 (d, *J* = 4.6 Hz, 1H, H-4), 3.53 (s, 2H, H-2), 3.75 (s, 3H, H-11), 5.14 (ddd, *J* = 7.8, 4.6, 0.9 Hz, 1H, H-5), 7.49 (d, *J* = 0.9 Hz, 1H, H-7) ppm; **^{13}C NMR** (400 MHz, $CDCl_3$): δ 202.7 (C, C-3), 167.3 (C, C-1), 162.0 (C, C-9), 141.9 (C, C-6), 134.6 (CH, C-7), 63.6 (CH, C-5), 52.6 (CH_3, C-11), 49.7 (CH_2, C-2), 48.7 (CH_2, C-4), 14.1 (CH_3, C-10) ppm; **MS** (ESI): m/z 250.1

(M + Na^+), 228.1 (M + H^+); HRMS: found (M + H^+) 228.0866 $C_{10}H_{14}NO_5$ requires 228.0870, (M + Na^+) 250.0281 $C_{10}H_{13}NNaO_5$ requires 250.0280.

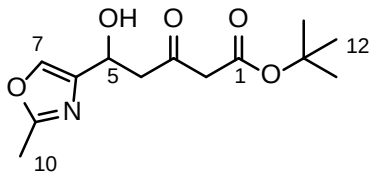
*From (Z)-4-methoxy-2,2,8,8-tetramethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene **130***

To a solution of 2-methyloxazole-4-carbaldehyde **6** (133 mg, 1.20 mmol) in CH_2Cl_2 (5 mL) stirring at –78 °C under a N_2 atmosphere was added 3.0 M $TiCl_4$ in CH_2Cl_2 (333 μL, 1.00 mmol). After stirring for 5 minutes (*Z*)-4-methoxy-2,2,8,8-tetramethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene **130** (300 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) was added. The reaction was stirred for 1 hour and was treated with TFA (99%) (0.15 mL, 2.00 mmol) then warmed to room temperature and stirred for a further 5 minutes. The mixture was partitioned between Et_2O (20 mL) and 5% aqueous solution of $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer washed with Et_2O (20 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and concentrated to give a brown oil that concentrated to give a brown oil that was purified to give an orange oil (0.11 g, 47%).

*From 4-methylideneoxetan-2-one **143***

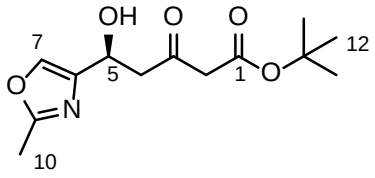
To a solution of 2-methyloxazole-4-carbaldehyde **6** (133 mg, 1.20 mmol) in CH_2Cl_2 (5 mL) stirring at –78 °C under a N_2 atmosphere was added 3.0 M $TiCl_4$ in CH_2Cl_2 (333 μL, 1.00 mmol). After stirring for 5 minutes, diketene **143** (84 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) was added. The reaction was stirred for 1 hour and was treated with TFA (99%) (0.15 mL, 2.00 mmol) then warmed to room temperature and stirred for a further 5 minutes. The mixture was partitioned between Et_2O (20 mL) and 5% aqueous solution of $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer washed with Et_2O (20 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and concentrated to give a brown oil that concentrated to give a brown oil that was purified to give an orange oil (68 mg, 30%).

5-Hydroxy-5-(2-methyloxazole-4-yl)-3-oxo-pentanoic acid *tert*-butyl ester 203



To a solution of 2-methyloxazole-4-carbaldehyde **6** (133 mg, 1.20 mmol) in CH_2Cl_2 (5 mL) stirring at –78 °C under a N_2 atmosphere was added 3.0 M $TiCl_4$ in CH_2Cl_2 (333 μL, 1.00 mmol). After stirring for 5 minutes (*Z*)-*tert*-butoxy-4,6-*bis*-trimethylsilanyloxy-buta-4,6-diene **202** (300 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) was added. The reaction was stirred for 1 hour and was treated with TFA (99%) (0.15 mL, 2.00 mmol) then warmed to room temperature and stirred for a further 5 minutes. The mixture was partitioned between Et_2O (20 mL) and 5% aqueous solution of $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer washed with Et_2O (20 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and concentrated to give a brown oil that was purified to give an orange oil (250 mg, 93%). The ^{1}H NMR data agreed with Mistry's thesis.[66] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.46 (1H, d, *J* = 1.0 Hz, H-7), 5.13 (1H, ddd, *J* = 7.5, 5.0, 1.0 Hz, H-5), 3.41 (2H, s, H-2), 3.07 (2H, dd, *J* = 7.5, 5.0 Hz, H-4), 2.45 (3H, s, H-10), 1.46 (9H, s, H-12) ppm.

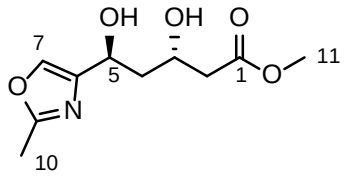
(5*R*)-*tert*-Butyl-3-(2-methyloxazol-4-yl)-3-oxopropanoate 203 (*R*)



4 Å molecular sieves (170 mg) were dried at 180 °C under streaming N_2 for 12 hours. The sieves were cooled to room temperature and treated with THF (1 mL). To this was added $Ti(O^iPr)_4$ (97%) (11 mg, 0.04 mmol) followed by *R*-BINOL (99%) (12 mg, 0.04 mmol) and the mixture was stirred at room temperature for 90 minutes. The mixture was cooled to –78 °C and was treated with a solution of

diene **202** (302 mg, 1.00 mmol) in THF (1.0 mL) followed by a solution of 2-methyloxazol-4-carbaldehyde **6** (56 mg, 0.50 mmol) in THF (0.5 mL). The mixture was warmed to room temperature and left to stir for 24 hours then was quenched with TFA (99%) (0.15 mL, 2.00 mmol) and stirred for a further 5 minutes. The mixture was treated with a 5% aqueous solution of $NaHCO_3$ (5 mL) until effervescence ceased to occur and was diluted in Et_2O (20 mL). The mixture was filtered then the organic layer was separated, washed with brine (2x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a brown oil. The crude material was purified by flash column chromatography using a 2 : 3 hexane: EtOAc gradient to give an orange oil (13 mg, 10%). Because several reasons, including technology issues, we did not have the enantiomeric excess data in our study.

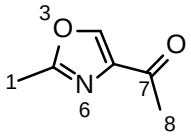
(3S,5S)-Methyl 3,5-dihydroxy-5-(2-methyloxazol-4-yl)pentanoate 5



To a solution of $NMe_4BH(OAc)_3$ (95%) (0.93 g, 3.52 mmol) in dry MeCN (4.4 mL) and AcOH (anhydrous) (4.5 mL) at –35 °C under N_2 atmosphere was added a solution of **98** (100 mg, 0.44 mmol) in dry MeCN (4.4 mL) over a period of 3 minutes. The reaction mixture was stirred for 6 hours at –35 °C and 18 hours at –20 °C. The reaction was quenched with 10% aqueous solution of Rochelle's salt (10 mL) and warmed to room temperature. The mixture was partitioned between ethyl acetate (40 mL) and a saturated aqueous solution of $NaHCO_3$ (40 mL) and the aqueous layer was extracted with ethyl acetate (2 × 40 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated in *vacuo* to give a yellow oil, which was purified by flash silica gel column chromatography (20% to 50% ethyl acetate in hexanes) to give a yellow oil (41 mg, 41%). **IR** (film): υ_{max} 3347.9, 2924.3, 1724.2, 1578.5, 1437.5 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.26 (s, 3H, H-11), 1.90 (dd, *J* = 14.2, 9.5 Hz, 1H, H-4), 2.01 (dt, *J* = 14.2, 3.5 Hz, 1H, H-4), 2.43 (s, 3H, H-10), 2.54 (d, *J* = 1.4 Hz, 1H, –OH) 3.72 (s, 2H, H-2), 4.35 (tdt,

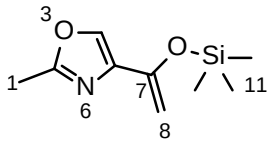
J = 6.9, 5.3, 2.7 Hz, 1H, H-3), 4.94 (dd, *J* = 9.5, 3.5 Hz, 1H, H-5), 7.48 (dd, *J* = 5.3, 0.9 Hz, 1H, H-7) ppm. **^{13}C NMR** (400 MHz, $CDCl_3$): δ 173.2 (C, C-1), 162.0 (C, C-9), 143.4 (C, C-6), 134.6 (CH, C-7), 67.3 (CH, C-5), 65.7 (CH, C-3), 51.9 (CH_3, C-11), 41.1 (CH_2, C-2), 40.6 (CH_2, C-4), 14.2 (CH_3, C-10) ppm; **MS** (ESI): m/z 252.1 (M + Na^+), 230.1 (M + H^+); HRMS: found (M + H^+) 230.1023 $C_{10}H_{16}NO_5$ requires 230.1028, (M + Na^+) 252.0842 $C_{10}H_{15}NNaO_5$ requires 252.0847.

1-(2-Methyloxazol-4-yl)ethanone 8



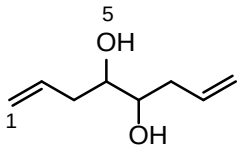
To a solution of *N*-methoxy-*N*,2-dimethyloxazole-4-carboxamide **195** (1.0 g, 5.9 mmol) in THF (30 mL), stirring at 0 °C, was added 1.0M MeMgBr in diethyl ether (7.8 mL, 7.8 mmol). After stirred for 1 hour, water (2 mL) was added to quench the excess Grignard reagent. The mixture was concentrated in *vacuo* and then was treated by ethyl acetate (30 mL) and H_2O (30 mL). The aqueous layer was washed by ethyl acetate (2 × 30mL) and the combined organic solution was concentrated in *vacuo* to give an orange oil. The crude product was purified by a 3 : 2 EtOAc : hexane gradient flash column chromatography to give a pale-yellow solid (0.51g, 70%). The ^{1}H NMR data agreed with the literature.[67] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (1H, s, H-4), 2.45 (3H, s, H-1), 1.51 (3H, s, H-8) ppm.

2-Methyl-4-(1-((trimethylsilyl)oxy)vinyl)oxazole 216



To a solution of **8** (0.2 g, 1.6 mmol) in dry MeCN (2.5 mL) under N_2 was added triethylamine (≥ 99%) (1.2 mL, 8.0 mmol) over a period of 5 minutes. The mixture was stirred and heated to 30 – 35 ^oC, after which trimethylsilyl chloride (≥ 99%) (0.4 mL, 0.32 mmol) was added over 3 minutes. After the mixture was stirred for 30 minutes at the same temperature, a solution of NaI (anhydrous, 99.999% trace metals basis) (0.48 g, 0.32 mmol) in dry MeCN (5 mL) was added over 5 minutes. The reaction temperature was raised to 40 – 45 ^oC and left stirring for 3 hours, after which the reaction was left to cool to room temperature. The reaction mixture was filtered through Celite, extracted with pentane, concentrated *in vacuo*, filtered through Celite again and extracted with hexane. The filtrate was concentrated in *vacuo* to give a pale-yellow oil (0.31 g, 99%). Because it is unstable, we used it directly to the next step. [67] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.42 (1H, s, H-4), 5.00 (1H, s, H-8), 4.33 (1H, s, H-8), δ 2.37 (3H, s, H-1), δ 0.20 – 0.17 (9H, s, H-11) ppm.

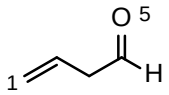
Octa-1,7-diene-4,5-diol 219



Allyl bromide (reagent grade, 97%) (7.15 mL, 82.7 mmol, 2.4 eq.) and 40% aqueous glyoxal (3.94 mL, 34.5 mmol) were dissolved in 1:1 THF/H_2O (35 mL). Tin powder (≥ 99%) (9.82 g, 82.7 mmol) was added and the mixture was sonicated for 6 hours. The reaction was quenched with a 25% KOH solution (28 mL, w:w in H_2O) and diluted with diethyl ether (30 mL). Solid NaCl was added until the aqueous layer was saturated and then the mixture was filtered through Celite. The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organics were dried over $MgSO_4$, filtered and

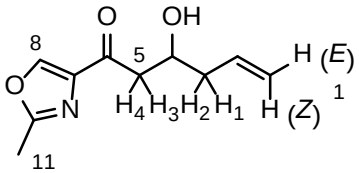
concentrated *in vacuo* to give a yellow oil, which was purified by flash silica gel column chromatography (20% to 50% ethyl acetate in hexanes) to give a yellow oil (3.04 g, 62%). The proton NMR spectrum matched that given in literature.[68] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.93 – 5.78 (2H, m, H-2), 5.19 (2H, ddd, *J* = 8.1, 3.1, 1.6 Hz, H-1), 5.18 – 5.13 (2H, m, H-1), 3.71 – 3.64 (1H, m, H-4), 3.59 – 3.51 (1H, m, H-4), 2.43 – 2.32 (2H, m, H-3), 2.31 – 2.20 (2H, m, H-3), 2.06 (2H, br m, H-5) ppm.

But-3-enal 220



Octa-1,7-diene-4,5-diol **219** (600 mg, 4.22 mmol) was dissolved in DCM (4.5 mL), H_2O (4.5 mL) and cooled to 0 °C. Sodium periodate (≥ 99%) (1.084 g, 5.07 mmol, 1.2 eq.) was added to the mixture in portions after which it was warmed up to room temperature and stirred for 7 hours. The organic layer was washed with water (2 × 5 mL), brine (2 × 5 mL), dried over $MgSO_4$ and filtered to yield **113** as a colourless solution in CH_2Cl_2 (290 mg by NMR, 4.11 mmol, 49 %). The proton NMR spectrum matched that given in literature.[70] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.66 (1H, t, *J* = 1.7 Hz, H-4), 5.92 (1H, ddt, *J* = 17.2, 10.3 and 6.8 Hz, H-2), 5.27 (1H, dd, *J* = 10.3 and 1.5 Hz, H-1), 5.22 (1H, ddd, *J* = 17.2, 3.0 and 1.5 Hz, H-1), 3.17 (2H, ddd, *J* = 6.8, 3.0 and 1.7 Hz, H-3) ppm.

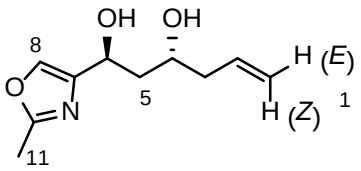
3-Hydroxy-1-(2-methyloxazol-4-yl)hex-5-en-1-one 221



To a solution of silyl enol ether **216** (296 mg, 1.50 mmol) in dry DCM (10 mL) was added a but-3-enal **220** (126 mg, 1.43 mmol) solution in dry DCM over 3 minutes at –78 °C under N_2. After stirring for

15 minutes at the same temperature, a solution of $TiCl_4$ in dry CH_2Cl_2 was added over 3 minutes to the reaction mixture. After leaving the reaction to stir for 4 hours at –78 °C, it was quenched with cold water (7 mL). Saturated $NaHCO_3$ solution (5 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated in *vacuo* to give a yellow oil, which was purified by flash silica gel column chromatography (60% ethyl acetate in hexanes) to give a yellow oil (105 mg, 36%). **IR** (film): υ_{max} 3355.2, 2926.4, 1683.4, 1592.6 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.34 (ddd, *J* = 6.7, 3.0, 1.4 Hz, 1H, H-3 (1)), 2.35 (ddd, *J* = 6.7, 6.4, 1.4 Hz, 1H, H-3 (2)), 2.52 (s, 3H, H-11), 2.99 (dd, *J* = 17.2, 8.9 Hz, 1H, H-5 (4)), 3.10 (dd, *J* = 17.2, 3.0 Hz, 1H, H-5 (3)), 3.20 (d, *J* = 3.4 Hz, 1H, –OH), 4.27 (dddt, *J* = 8.9, 6.4, 3.4, 3.0 Hz, 1H, H-4), 5.15 (br. d, *J* = 10.3 Hz, 1H, H-1 (*E*)), 5.16 (dt, *J* = 16.9, 1.4 Hz, 1H, H-1*Z*), 5.88 (ddt, *J* = 16.9, 10.3, 6.7 Hz, 1H, H-2), 8.15 (s, 1H, H-8). **^{13}C NMR** (400 MHz, $CDCl_3$): δ 194.7 (C, C-6), 162.0 (C, C-10), 142.2 (C, C-7), 134.2 (CH, C-8), 133.8 (CH, C-2), 118.0 (CH_2, C-1), 67.0 (CH, C-4), 46.0 (CH_2, C-5), 41.3 (CH_2, C-3), 14.3 (CH_3, C-11) ppm; **MS** (ESI): m/z 218.1 (M + Na^+), 196.1 (M + H^+); HRMS: found (M + H^+) 196.0968 $C_{10}H_{14}NO_3$ requires 196.0961, (M + Na^+) 218.0788 $C_{10}H_{13}NNaO_3$ requires 218.0795.

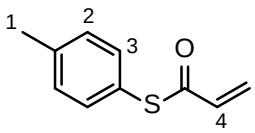
(1S,3R)-1-(2-Methyloxazol-4-yl)hex-5-ene-1,3-diol 7



To a solution of $NMe_4BH(OAc)_3$ (95%) (1.08 g, 4.10 mmol) in dry MeCN (4.4 mL) and AcOH (anhydrous) (4.5 mL) at –35 °C under N_2 atmosphere was added a solution of **221** (100 mg, 0.51 mmol) in dry MeCN (4.4 mL) over a period of 3 minutes. The reaction mixture was stirred for 6 hours at –35 °C and 18 hours at –20 °C. The reaction was quenched with 10% aqueous solution of Rochelle's salt (10 mL) and warmed to room temperature. The mixture was partitioned between ethyl acetate (40 mL) and a saturated aqueous solution of $NaHCO_3$ (40 mL) and the aqueous layer was extracted with ethyl acetate

(2 × 40 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated in *vacuo* to give a yellow oil, which was purified by flash silica gel column chromatography (20% to 50% ethyl acetate in petroleum ether) to give a yellow oil (30 mg, 30%). **IR** (film): υ_{max} 3436.9, 3187.1, 1650.9 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.94 (ddd, *J* = 14.6, 9.2, 3.7 Hz, 1H, H-5), 2.04 (ddd, *J* = 14.6, 7.3, 2.7 Hz, 2H, H- 5), 2.27 (ddt, *J* = 13.7, 7.8, 0.9 Hz, 1H, H-3), 2.34 (ddt, *J* = 14.2, 6.9, 1.4 Hz, 1H, H-3), 2.45 (s, 3H, H-11), 3.99 (dddd, *J* = 9.2, 7.8, 5.0, 3.2 Hz, 1H, H-5), 4.97 (dd, *J* = 7.1, 3.4 Hz, 1H, H-6), 5.16 (dt, *J* = 16.9, 1.4 Hz, 1H, H-1*Z*), 5.16 (dt, *J* = 10.7, 0.9 Hz, 1H, H-1*E*), 5.82 (ddt, *J* = 17.4, 10.5, 7.3 Hz, 1H, H-2), 7.47 (d, *J* = 1.37 Hz, 1H, H-8) ppm; **^{13}C NMR** (400 MHz, $CDCl_3$): δ 162.0 (C, C-10), 143.6 (C, C-7), 134.5 (CH, C-8), 134.3 (CH, C-2), 118.7 (CH_2, C-1), 68.2 (CH, C-6), 65.7 (CH, C-4), 42.2 (CH_2, C-5), 41.4 (CH_2, C-3), 14.1 (CH_3, C-11) ppm; **MS** (ESI): m/z 220.1 ($M + Na^+$), 198.1 ($M + H^+$); HRMS: found ($M + H^+$) 198.1125 $C_{10}H_{16}NO_3$ requires 198.1131, ($M + Na^+$) 220.0944 $C_{10}H_{15}NNaO_3$ requires 220.0950.

***S*-*p*-Tolyl prop-2-enethioate 224**

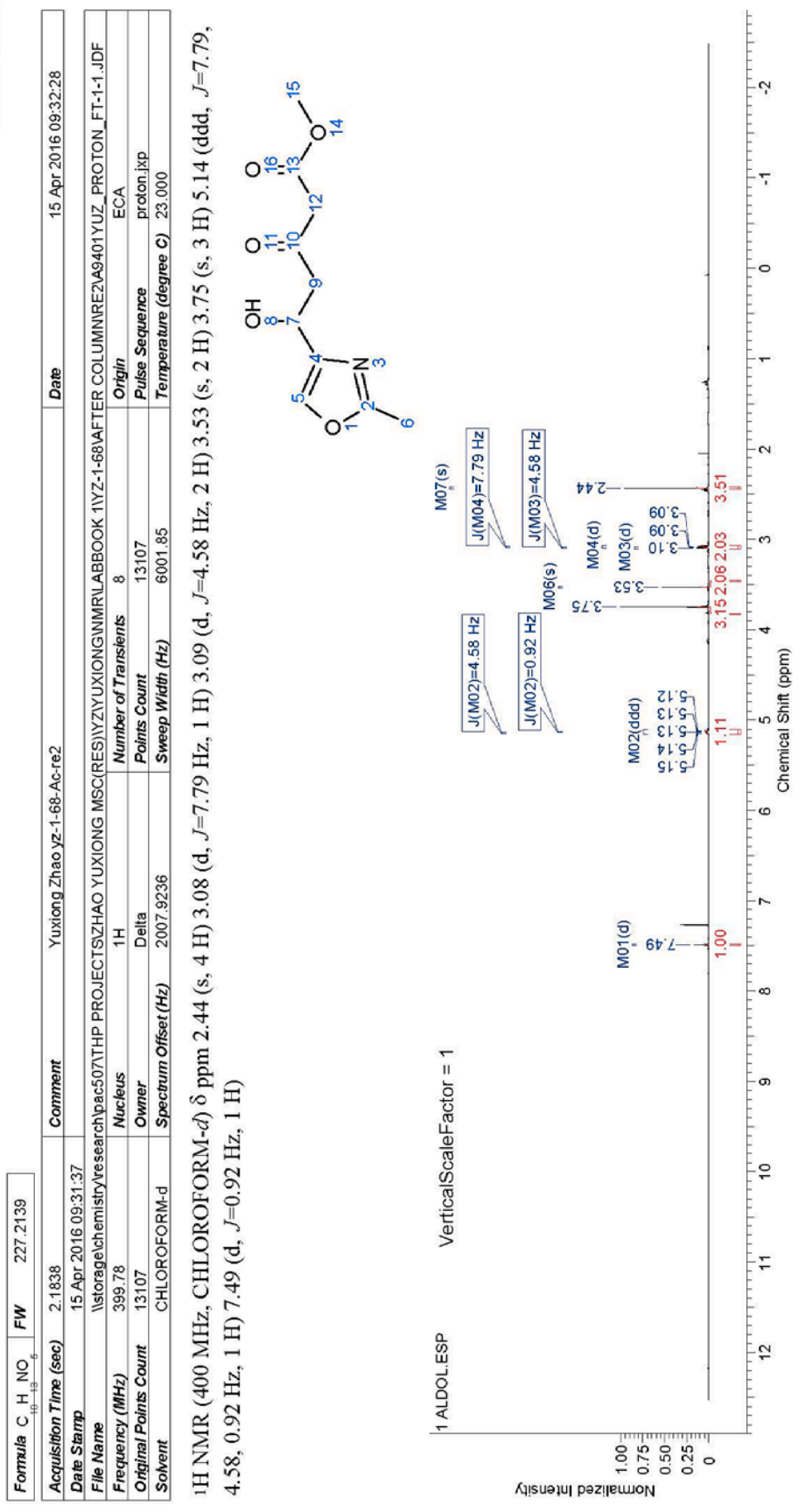


Butylated hydroxytoluene (35.7 mg, 0.162 mmol) and acryloyl chloride (1.34 mL, 16.5 mmol, 1) were dissolved in cyclohexane (7 mL). In a separate flask $NaBH_4$ (13.4 mg, 0.35 mmol) and 4-methylbenzenethiol (1.38 g, 11.0 mmol) were added in order to 15% aq. NaOH (5 mL). This mixture was stirred for 1 hour at room temperature. Under ice-cooling, this mixture was added over a period of 10 minutes to the acryloyl chloride solution. After the reaction mixture was stirred for 30 minutes at 55 – 60 ^oC, it could cool to room temperature and then extracted with diethyl ether (3 x 4 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (3 × 4 mL) and brine (3 × 4 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to a yellow oil, which was purified by flash silica gel column chromatography (3% ethyl acetate in *n*-hexane) to yield **224** as a yellow oil

(690 mg, 45%). The proton NMR spectrum matched that given in literature.[68] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33 (2H, d, *J* = 8.2 Hz, H-2), 7.24 (2H, d, *J* = 8.2 Hz, H-3), 6.46 (1H, dd, *J* = 17.2, 9.6, H-4), 6.38 (1H, dd, *J* = 17.2, 1.6 Hz, H-5), 5.76 (1H, dd, *J* = 9.6, 1.6 Hz, H-5), 2.39 (3H, s, H-1) ppm.

Appendices

Appendix 1: the ^{1}H NMR data of **179**



^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.44 (s, 4 H) 3.08 (d, *J*=7.79 Hz, 1 H) 3.09 (d, *J*=4.58 Hz, 2 H) 3.53 (s, 2 H) 3.75 (s, 3 H) 5.14 (ddd, *J*=7.79, 4.58, 0.92 Hz, 1 H) 7.49 (d, *J*=0.92 Hz, 1 H)

2017/5/9 20:55:48

Formula $C_{10}H_{15}NO_5$	FW	229.2298

Acquisition Time (sec)	2.1838	*Comment*	Yuxiong Zhao yz-2-8-crude			*Date*	20 Apr 2016 15:16:38
Date Stamp	20 Apr 2016 15:15:46						
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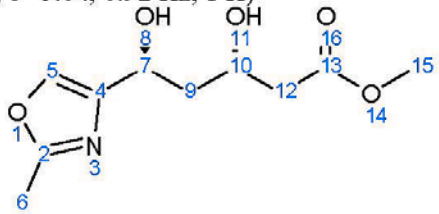
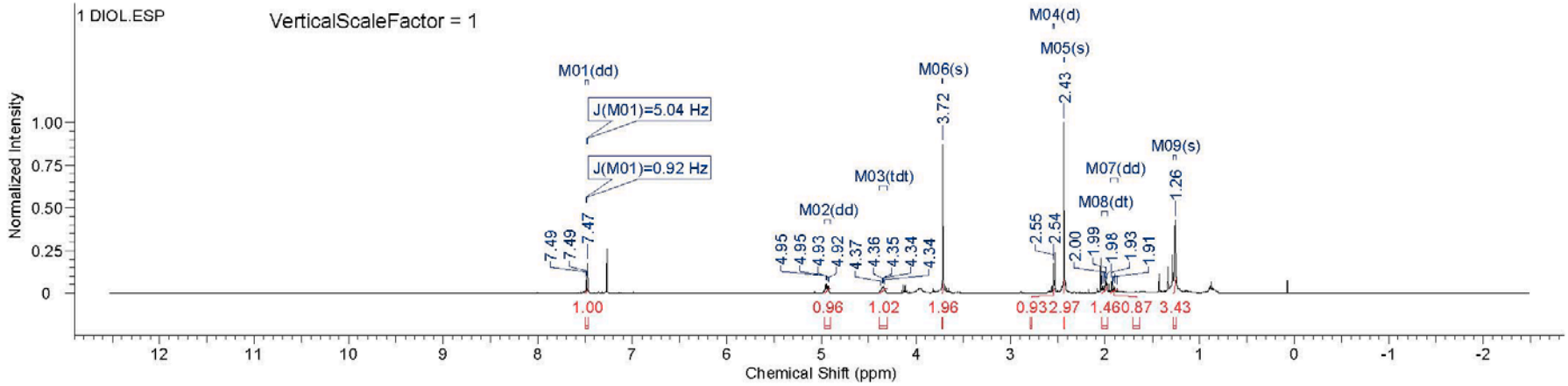
^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.26 (s, 3 H) 1.90 (dd, *J*=14.20, 9.62 Hz, 1 H) 2.01 (dt, *J*=14.20, 3.66 Hz, 1 H) 2.43 (s, 3 H) 2.54 (d, *J*=1.37 Hz, 1 H) 3.72 (s, 2 H) 4.35 (tdt, *J*=6.90, 6.90, 5.50, 2.70, 2.70 Hz, 1 H) 4.94 (dd, *J*=9.39, 3.43 Hz, 1 H) 7.48 (dd, *J*=5.04, 0.92 Hz, 1 H)





2017/5/9 20:59:51

Formula $C_{10}H_{13}NO_3$	FW	195.2151

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Date Stamp	23 Sep 2016 14:28:59						
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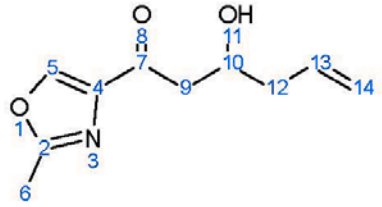
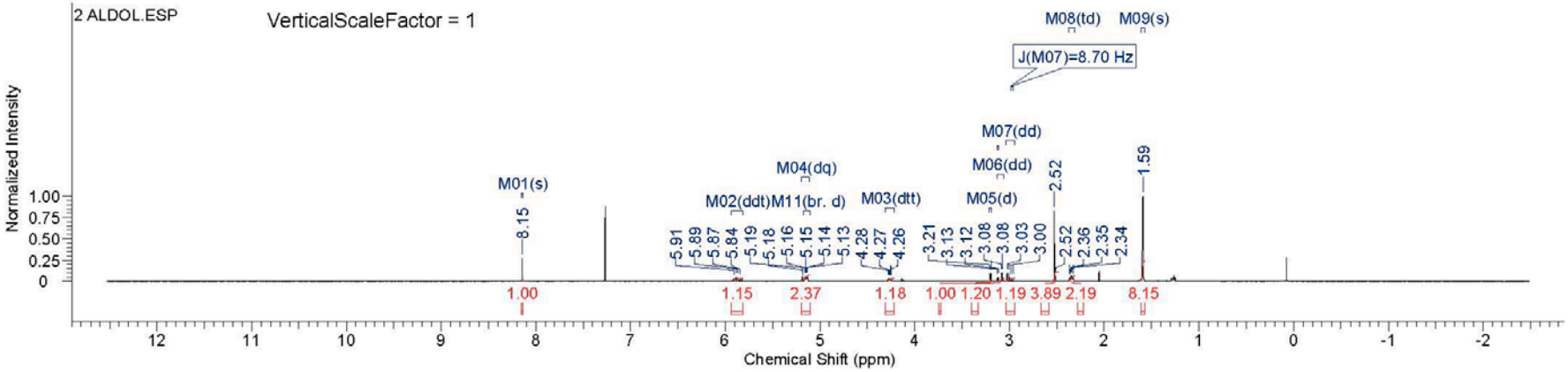
Frequency (MHz)	399.78	*Nucleus*	1H	*Number of Transients*	8	*Origin*	ECA
Original Points Count	13107	*Owner*	Delta	*Points Count*	13107	*Pulse Sequence*	proton.jxp
Solvent	CHLOROFORM-d	*Spectrum Offset (Hz)*	2007.9236	*Sweep Width (Hz)*	6001.85	*Temperature (degree C)*	20.100

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.59 (s, 8 H) 2.34 (ddd, *J*=6.50, 2.70, 1.40 Hz, 1 H) 2.35 (td, *J*=6.50, 1.37 Hz, 2 H) 2.52 (s, 4 H) 2.99 (dd, *J*=16.94, 8.70 Hz, 1 H) 3.10 (dd, *J*=17.40, 2.75 Hz, 1 H) 3.20 (d, *J*=3.66 Hz, 1 H) 4.27 (dtt, *J*=9.20, 6.40, 6.40, 3.20, 3.20 Hz, 1 H) 5.15 (br. d, *J*=10.50 Hz, 1 H) 5.16 (dq, *J*=16.94, 1.37 Hz, 2 H) 5.88 (ddt, *J*=16.94, 10.10, 6.90, 6.90 Hz, 1 H) 8.15 (s, 1 H)





This report was created by ACD/NMR Processor Academic Edition. For more information go to www.acdlabs.com/nmrproc/

2017/5/9 21:02:46

Formula $C_{10}H_{15}NO_3$	*FW*	197.2310					
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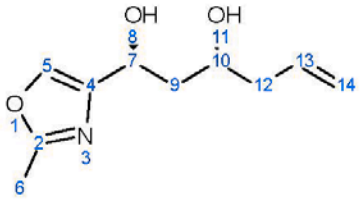
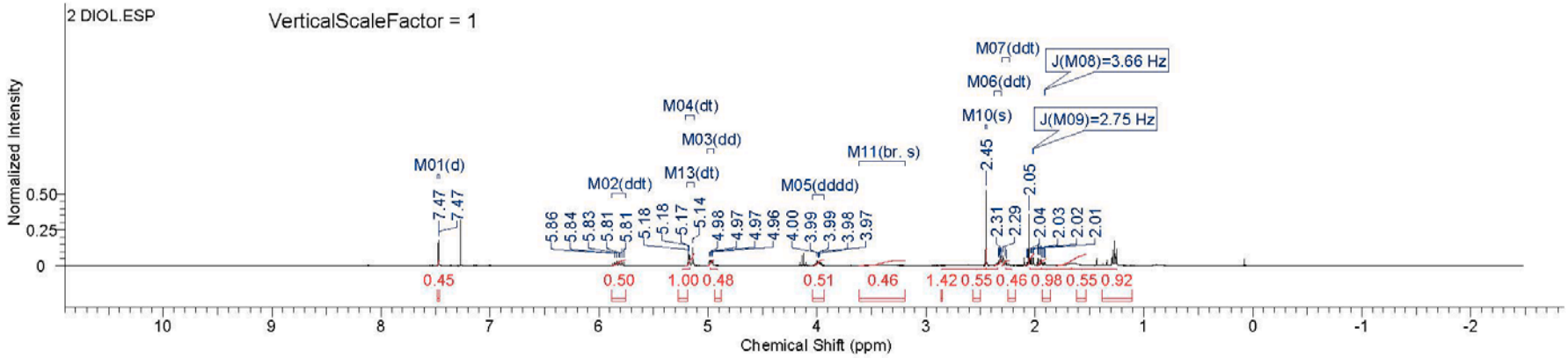
Solvent	CHLOROFORM-d	*Spectrum Offset (Hz)*	2007.9250	*Sweep Width (Hz)*	6001.85	*Temperature (degree C)*	20.500

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.66 (br. s, 2 H) 1.94 (ddd, *J*=14.65, 9.16, 3.66 Hz, 1 H) 2.04 (ddd, *J*=14.65, 7.33, 2.75 Hz, 2 H) 2.27 (ddt, *J*=13.74, 7.79, 0.92, 0.92 Hz, 1 H) 2.34 (ddt, *J*=14.20, 6.90, 1.40, 1.40 Hz, 1 H) 2.45 (s, 3 H) 3.40 (br. s, 1 H) 3.99 (dddd, *J*=9.16, 7.78, 5.04, 3.21 Hz, 1 H) 4.97 (dd, *J*=7.10, 3.43 Hz, 1 H) 5.16 (dt, *J*=10.70, 0.90 Hz, 1 H) 5.16 (dt, *J*=16.80, 1.40 Hz, 8 H) 5.82 (ddt, *J*=17.40, 10.53, 7.33, 7.33 Hz, 1 H) 7.47 (d, *J*=1.37 Hz, 1 H)





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