Chiral Brønsted Acid Catalysed Synthesis of Tetrahydropyrans and Tetrahydrofurans.

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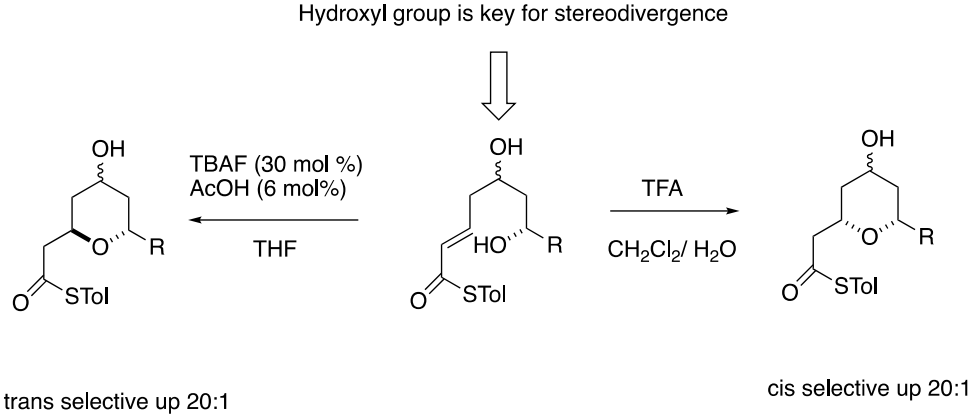
1. Abstract

Tetrahydropyrans are important structural motifs, present in various natural products with significant biological and pharmacological properties. During previous efforts into the synthesis of the C20-C32 core of phorboxazoles, a stereodivergent oxa-Michael reaction was encountered and investigated computationally **(Scheme 1)**.



Scheme 1- The Stereodivergent oxa-Michael Reaction

TFA and CSA have been shown to act as proton shuttles in the cyclisation. The TFA mediated cyclisation doesn't depend on inherent structural features and the use of chiral phosphoric acids, with acidities in the range of TFA and CSA, instead of TFA should make the reaction enantiodivergent. This means that with chiral phosphoric acid and it's (*ent*) form giving the enantiomers from the same cyclisation precursor. This was shown to be feasible by computational analysis, with the mesityl tetrahydropyran cyclisation precursor more enantioselective than the tolyl precursor. To this end, the chiral brønsted acid catalysed cyclisation of the mesityl and tolyl tetrahydropyran and tetrahydrofuran precursors have been carried out under various solvent, catalyst and temperature conditions. For the tetrahydrofuran precursors, the tolyl substrate shows greater enantioselectivity, with the highest ee being 60% using (*R*)-TIPSY. For the tetrahydropyran precursors, the mesityl shows greater enantioselectivity, with the highest ee being 69% using (*R*)-TRIP. Finally, a kinetic resolution of the mesityl tetrahydropyran precursor has been carried out using optimised conditions, resulting in the enantioenrichment of the product at 95%ee and the starting material at 96%ee.

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5. Acknowledgements

At the outset, I would like to thank my supervisor Dr Paul Clarke for giving the opportunity to work on such an exciting project. Over the course of my project, he has provided a lot of valuable advice and feedback about the project and has painstakingly proofread this thesis, being patent with me and always pushing me towards perfection in my presentation. It has been a fun project to be part of, albeit challenging at times, and has given me the chance to hone my lab skills and time management.

I would like to thank my IPM Dr William Unsworth, for giving timely feedback and guidance with the project during my TAP metings, helping to look at the project with a different perspective when things didn't seem to go as planned.

I would also like to thank Heather Fish, for her assistance with acquiring NMR and for patiently reminding me not to overshoot the allotted run time per student in spite of my repeated overstepping. I would also like to thank Karl Heaton for all the help in acquiring mass spectrometry data.

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I finally would like to thank my grandparents, parents and brother for constantly calling me and enquiring about my health and wellbeing, giving constant love and encouragement and not making me feel homesick. In spite of being far away physically, you have been close to my heart every single day and have given me the needed strength to complete this endeavour.

6. Declaration

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

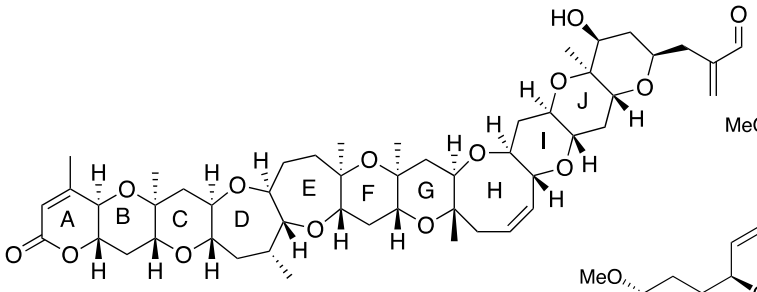
I also declare that the work embodied in this thesis is the result of my own investigations and in the event the work of others has been used this has been fully acknowledged in the text.

7. Introduction

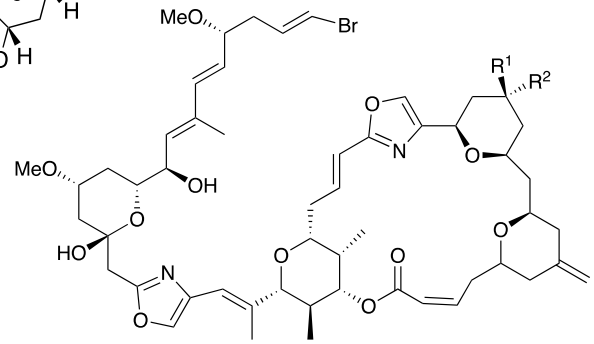
7.1 Tetrahydropyrans in Natural Products

Since ancient times, natural products have been used for medicinal and recreational purposes, and have been a source of fascination and wonder. Over the years, their biological and pharmacological properties have been studied and along with their synthesis, the field of organic chemistry has advanced.

Given that natural products are sources for lead like compounds in drug discovery, consisting of diverse structural motifs that are synthetically challenging to make, methods to construct these motifs in an elegant and efficient manner have been a focus of intense research interest. One such motif occurring regularly in many important natural products is the tetrahydropyran unit. Examples of these include brevetoxin B, [1] phorboxazoles A and B, [2] and leucascandrolide A [3] (**Figure 1**).

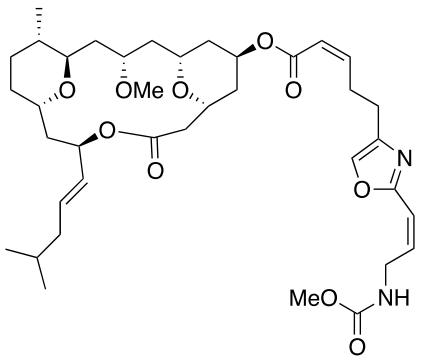


Brevetoxin B (a potent marine toxin)



Phorboxazole A: R^1 = H, R^2 = OH
Phorboxazole B: R^1 = OH, R^2 = H

(a potent antitumor agent)



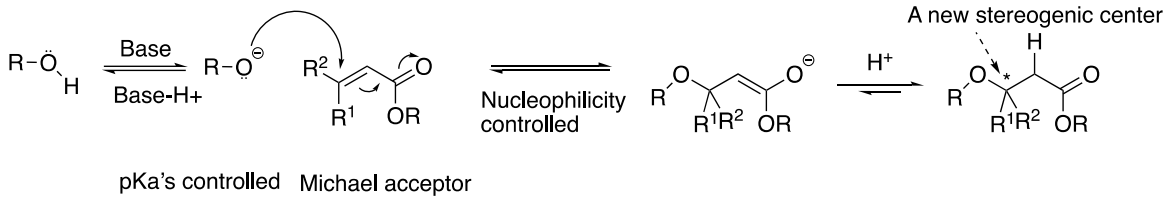
Leucascandrolide A (a potent antifungal)

Figure 1- Natural products containing a tetrahydropyran motif.

The construction of tetrahydropyran rings has been the focus of intense research and various strategies have been adopted, addressing issues of efficiency, stereoselectivity, regioselectivity and yield. Some of these methods include the Prins cyclization, Petasis-Ferrier rearrangement, hetero-Diels Alder reaction (HDA), radical cyclization, transition metal catalyzed cyclization, epoxide mediated cyclization and oxa-Michael reaction, to name a few. [4] The oxa- Michael reaction is of special interest in the Clarke group and hence shall be the sole focus of this review.

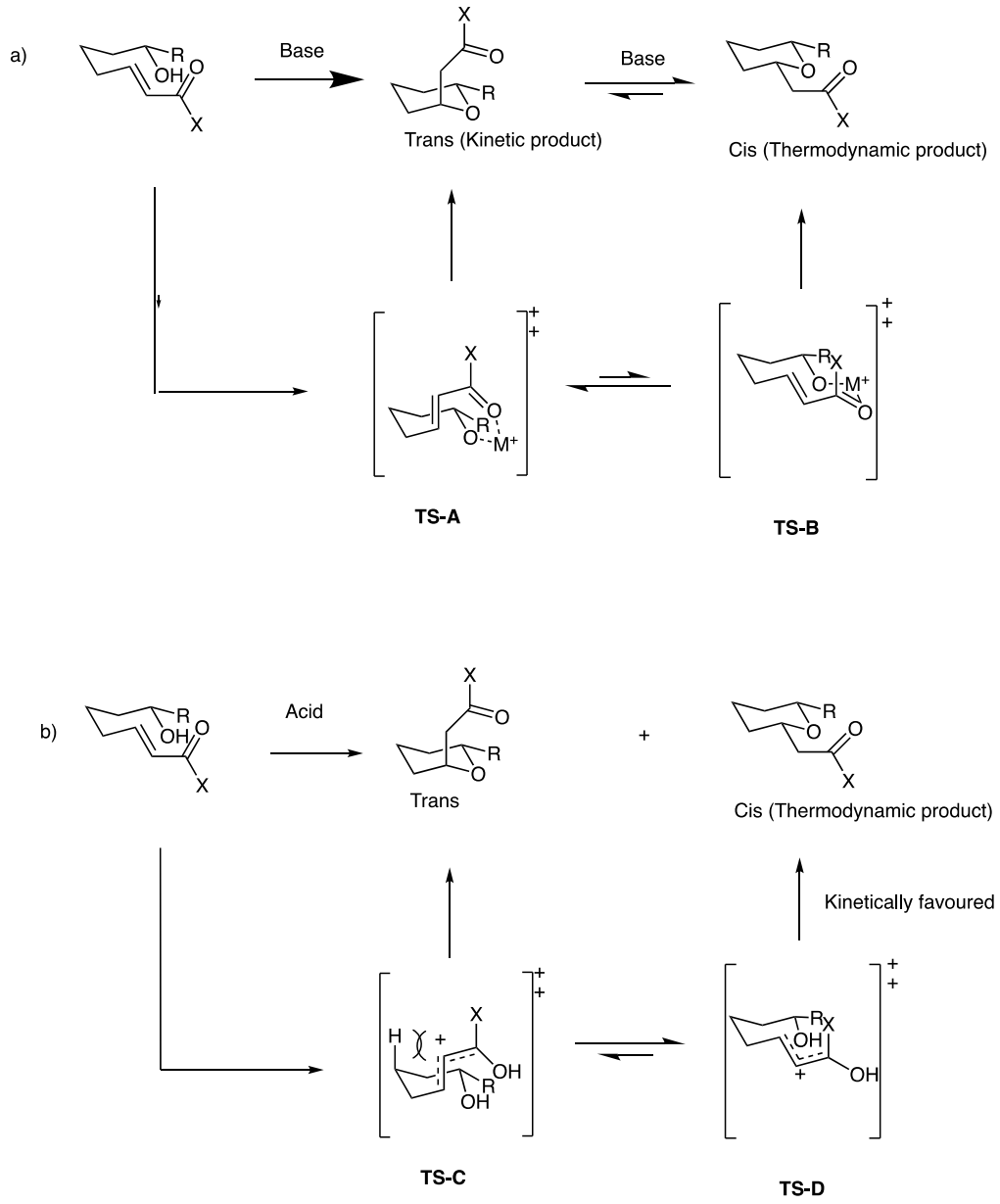
7.2 The Oxa-Michael Reaction

The oxa-Michael reaction involves the addition of oxygen nucleophiles (mainly alcohols) to an acceptor conjugated system forming an intermediate enolate, which on protonation gives rise to β-ether compounds. This generates a new stereogenic center in the β-position of the system (**Scheme 1.1**). [5]



Scheme 1.1 – The Oxa-Michael reaction

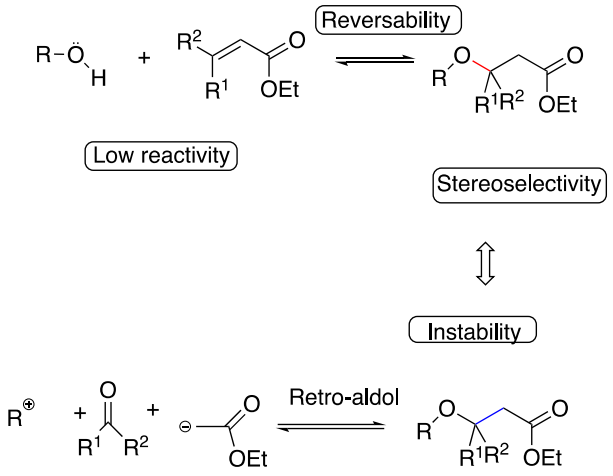
The oxa-Michael reaction can be carried out under basic or acidic conditions. Depending on the conditions, the reaction is under kinetic or thermodynamic control. For example, the intramolecular cyclisation of α,β-unsaturated hydroxyesters, the 2,6-*cis* or 2,6-*trans* disubstituted THP's are generated based on the reaction conditions. In general, under basic conditions, 2,6-*trans* THPs are kinetically favoured at low temperatures (–78 ^{0}C) and short reaction times, whereas 2,6-*cis* THPs are typically thermodynamically favoured at higher temperatures and longer reaction times. This stereoselectivity observed for base-mediated reactions can be explained by the difference in energy and HOMO/LUMO orbital overlap between the s-*cis* (**TS-A** has a lower energy and better orbital overlap) and s-*trans* (**TS-B**, has a higher energy and decreased orbital overlap) TS conformations **(Scheme 1.2a)**. However, under acidic conditions, the transition state **TS-D** leading to the thermodynamic 2,6-*cis* disubstituted tetrahydropyran is now kinetically favoured based on a frontier molecular orbital (FMO) theory argument **(Scheme 1.2b).**



Scheme 1.2 –Stereochemical outcome of intramolecular cyclisation based on reaction conditions.

Inspection of the FMO coefficients of the allylic cationic species and the orbital overlap with the oxygen lone pair indicates greater stereoelectronic stabilization in **TS-D** than **TS-C**. These arguments validate the observed selectivity for simple 2,6-substituted tetrahydropyrans, but the stereochemical outcome of more complex THPs requires conformational analysis of the resultant heterocycle. [6]

F. Loydl reported the first oxa-Michael reaction, en route his synthesis of malic acid, [7] and there have been many uses since. However, there are some serious drawbacks of this reaction. Some of these include low reactivity of the oxygen nucleophile, reversibility of the intermediate enolate, lack of control in stereoselectivity and instability of the final product, which can prone to the retro-aldol reaction (**Scheme 1.3**). [8]



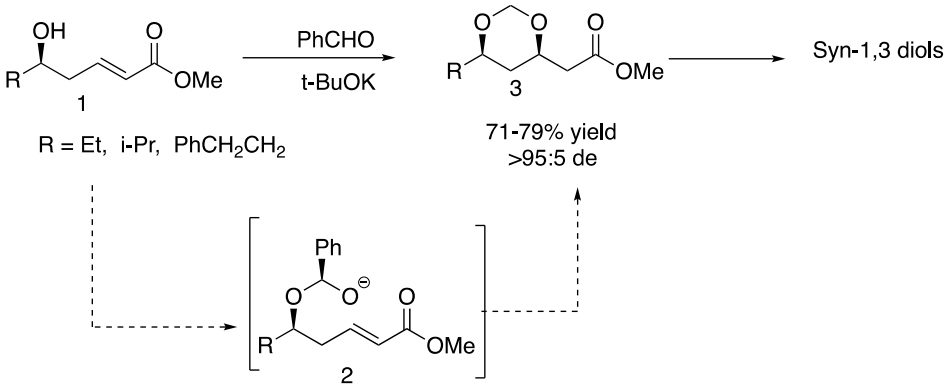
Scheme 1.3 – Challenges of the oxa-Michael reaction

In spite of these challenges, various protocols have been adopted to address these issues and improve the oxa-Michael reaction to make it more synthetically useful.

7.3 Some protocols to overcome the shortcomings of the oxa-Michael Reaction.

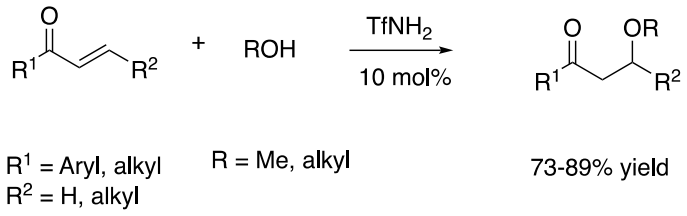
The low reactivity of the alcohol moiety can be attributed to the poor nucleophilicity of the oxygen atom. A way to overcome this drawback is to enhance the nucleophilicity of the alcohol by deprotonating it with a strong base. Further, the lack of reactivity can be overcome by tethering the two reactants, resulting in an intramolecular oxa-Michael reaction. An instructive example for such an intramolecular reaction has been developed by Evans and Gauchet-Prunet. [9] In order to construct *syn*-1,3-diols for the synthesis of polyene macrolide antibiotics in a stereoselective manner, they employed easily accessible homoallylic alcohols **1** as starting materials. Reaction of these alcohols with benzaldehyde in the presence of potassium *tert*-butoxide (t-BuOK) furnished the corresponding benzylidene acetals **3** in high yield and diastereoselectivity. Addition of the deprotonated alcohol to benzaldehyde yields an acetal alkoxide **2** which served as a tethered oxygen nucleophile in the conjugate addition step. The stereochemical outcome of the reaction relies on thermodynamic control

and the fact that the s*yn*-diastereomer is energetically favoured due to all substituents on the dioxane ring being equatorial **(Scheme 1.4).** The substrate scope included unsaturated Weinreb-type amides and, even more interestingly, γ-substituted substrates with equal efficiency.



Scheme 1.4- Stereoselective acetalization of esters

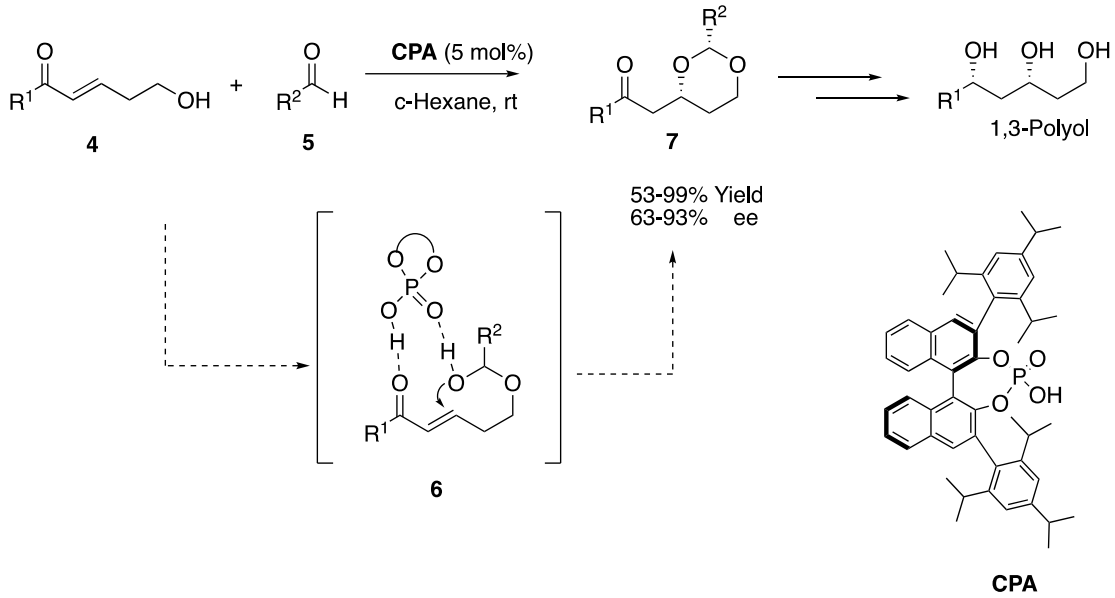
A complementary approach for improving the oxa-Michael reactions involves the activation of the Michael acceptor by acids. An example of this is an interesting reaction developed by Spencer and Wabnitz which employed bis(trifluoromethane)sulfonimide $(Tf_2NH)_2$ as a strong acid catalyst **(Scheme 1.5)**. [10] The reaction involved various α,β-unsaturated ketones as acceptors and alkyl as well as benzyl alcohols. However, phenols are not suitable substrates due to competing Friedel–Crafts-type reactions triggered by the strong acid.



Scheme 1.5- Acid catalyzed oxa-Michael reaction.

A final way of improving the oxa-Michael reaction is by a bifunctional activation pathway, which involves the simultaneous activation of the alcohol and the Michael acceptor. This could be achieved by the use of bifunctional catalysts such as a chiral phosphoric acid or a tertiary amine thiourea. [11, 12] An illustrative example is the chiral phosphoric acid catalyzed asymmetric construction of 1,3-dioxanes by Matsubara *et. al.* [13] In this strategy, the homoallyl alcohol **4** reacts with the aldehyde **5,** to form

the hemiacetal **6.** The dual activation sites of the chiral phosphoric acid **CPA** activate the Michael acceptor and the alcohol to generate 1,3-dioxanes **7** in excellent yields and selectivities. The utility of this strategy is that the produced 1,3-dioxanes **7** can be further manipulated to generate 1,3-polyols, which are useful building blocks in the *de novo* synthesis of optically active polyketides **(Scheme 1.6).**

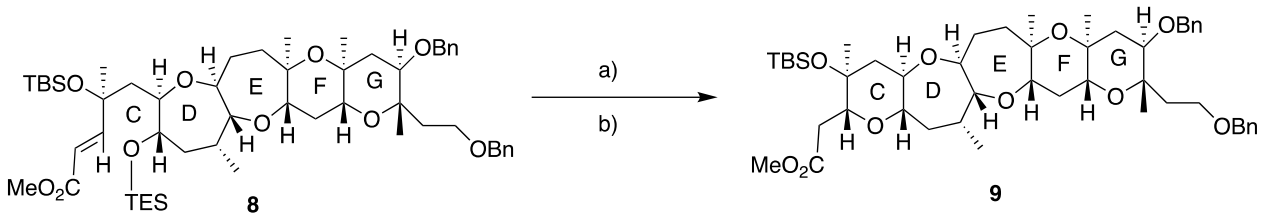


Scheme 1.6- 1,3-Dioxane construction *via* hemiacetalization/intramolecular oxy-Michael addition cascade.

These are just some of the improvements to the oxa-Michael reaction over the years, and as been the subject of intense research interest. This has enabled it to be a useful tool in natural product synthesis.

7.4 Application of the oxa-Michael reaction in the Synthesis of Natural Products.

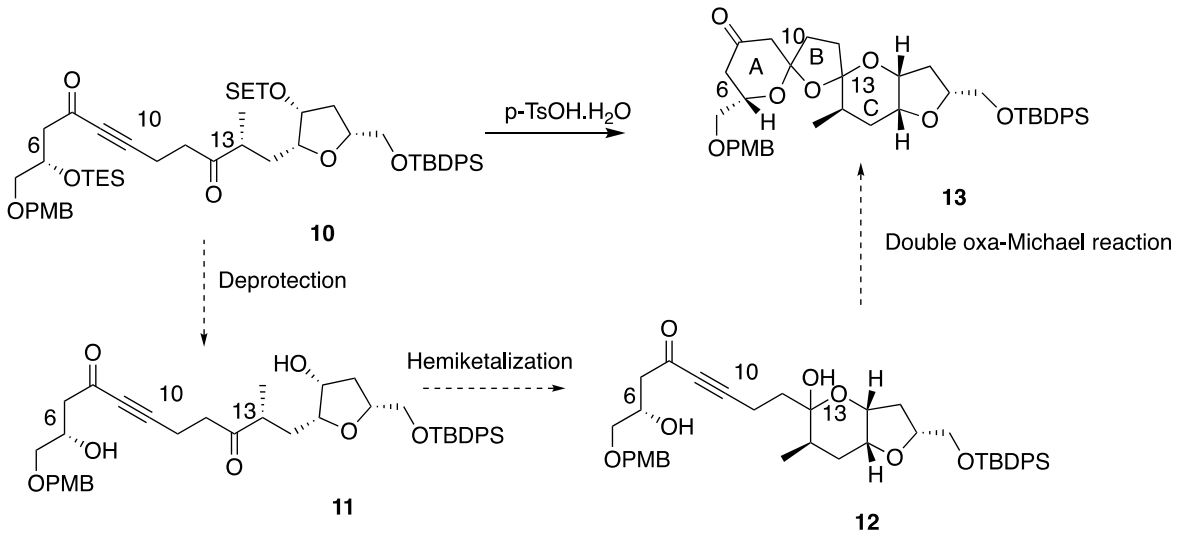
Nicolaou *et al*. employed a late stage intramolecular oxa-Michael reaction in the construction of the CDEFG framework en route to the total synthesis of the marine neurotoxin Brevetoxin B. [14] The framework was completed by the deprotection of the C11 alcohol precursor **8**, which underwent a base catalyzed ring closure in a stereoselective manner with the desired stereochemistry, giving the C ring moiety of the CDEFG framework **9**. The high diastereoselectivity is attributed to the reaction being under thermodynamic control, owing to the reversibility of the cyclisation which results in the more stable thermodynamic product (**Scheme 1.7**).



Reagents and conditions: a) CSA, MeOH b) KH, Et_2O 90% over 2 steps

Scheme 1.7 - Construction of the C ring in the total synthesis of Brevetoxin B

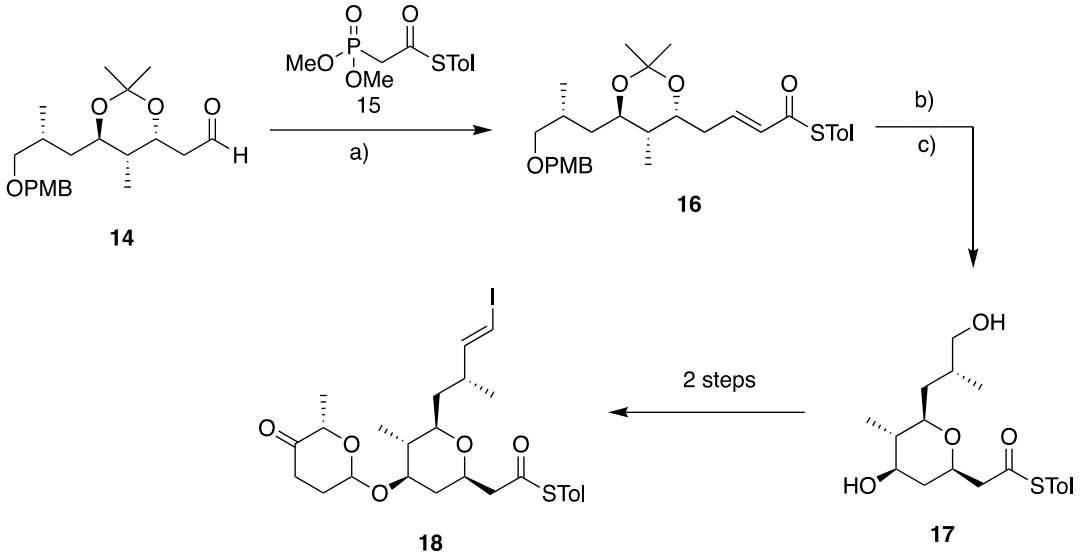
The ABC rings of azaspiracid forms a trioxadispiral motif that poses a significant synthetic challenge, and can be constructed by the efficient use of a double oxa-Michael reaction, as reported by the Forsyth group. [15] The deprotection of the TES-ether molecule **10** gives the free alcohol cyclization precursor **11**. The free alcohol on the furan ring initiates the ring closure at C13 to give the hemiketal **12**, which is followed by the double oxa-Michael attack of the C13 and C6 alcohol onto the alkynone moiety to generate trioxadispiral ABC ring system in a single step with a decent yield of 55% (**Scheme 1.8**). The cyclization is under thermodynamic control and the configuration at the C10 and C13 position is controlled by the configuration of the C6 alcohol.



Scheme 1.8 - Synthesis of the ABC spiroketal ring system of azaspiracid

Patterson completed the synthesis of the C1-C11 subunit (western fragment) of madeirolide A **18** [16] by employing a *cis*-selective oxa-Michael reaction under 'Fuwa' acidic conditions. [17] The key step involves the condensation of aldehyde **14** with the thioester phosphonate **15** under Masamune-Roush

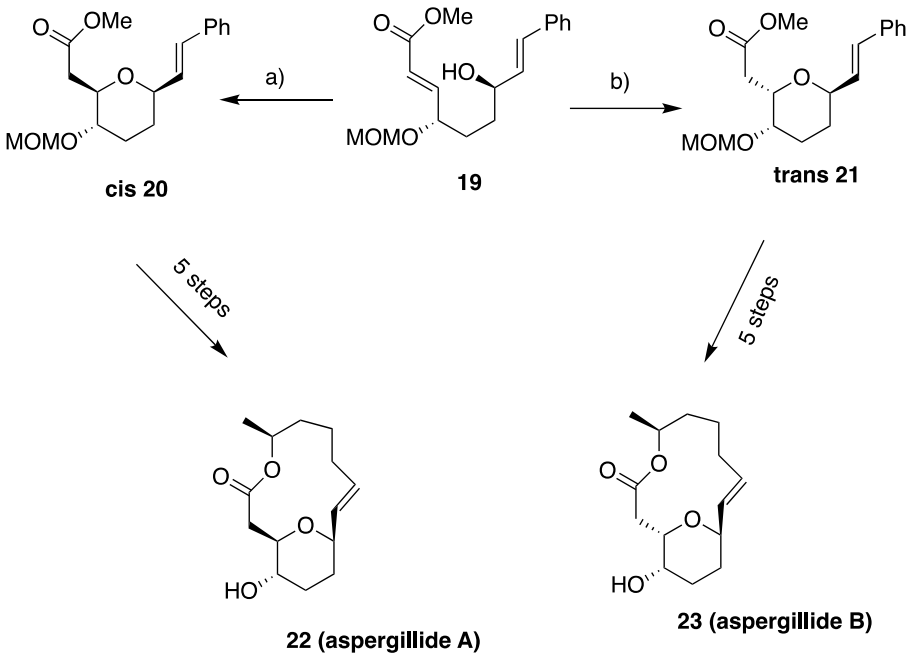
conditions [18] to give the cyclisation precursor **16** in 95% yield. Acetal deprotection by acid treatment facilitated the *cis*-selective cyclisation of the alcohol, followed by PMB deprotection generated the *cis*-tetrahydropyran **17**, which gave the C1-C11 subunit of madeirolide A **18** in 2 steps (**Scheme 1.9**).



Reagents and Conditions: a) LiCl, NEt_3, THF, –15 °C, 40 h (95%), b) TsOH, CH_2Cl_2, 4.5 h, (dr >20:1) c) DDQ, CH_2Cl_2, pH 7 Buff, 0 °C, 1 h (61%).

Scheme 1.9 – Synthesis of the 2,6-cis tetrahydropyran ring of Madeirolide A

Fuwa *et al*. employed a stereodivergent strategy to access aspergillide A **22** and aspergillide B **23** by subjecting the cyclisation precursor **19** to different conditions. [19] Under basic conditions at a lower temperature, the *trans* isomer **trans 21** was synthesized with excellent yield (96%) and selectivity (dr = 17:1), leading to the synthesis of aspergillide B **23** in 5 steps. However, a switch in selectivity was observed at a higher temperature, generating the *cis* isomer **cis 20** with good yield (81%) and selectivity (dr = 11:1), leading to the synthesis of aspergillide A **2.** This change in selectivity can be attributed to the change from kinetic control at lower temperature to the thermodynamic control at a higher temperature (**Scheme 1.10**)



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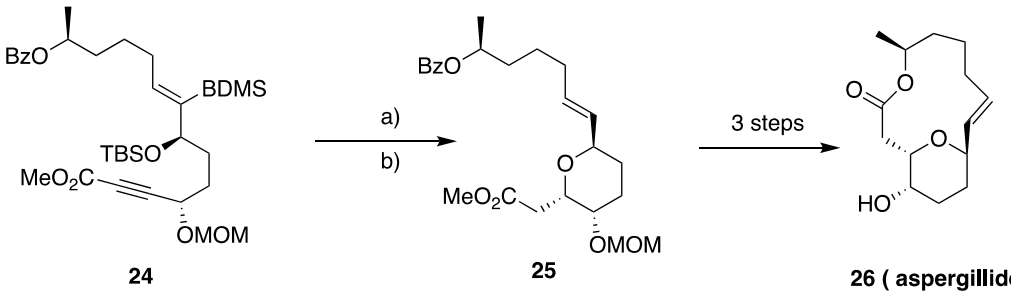
Reagents and conditions: a) DBU, toluene, 135 °C, 36 h (81%) b) t-BuOK, THF, –78 °C, 30 min (96%)

Scheme 1.10 – Stereodivergent strategy employed in the synthesis of aspergillide A and B

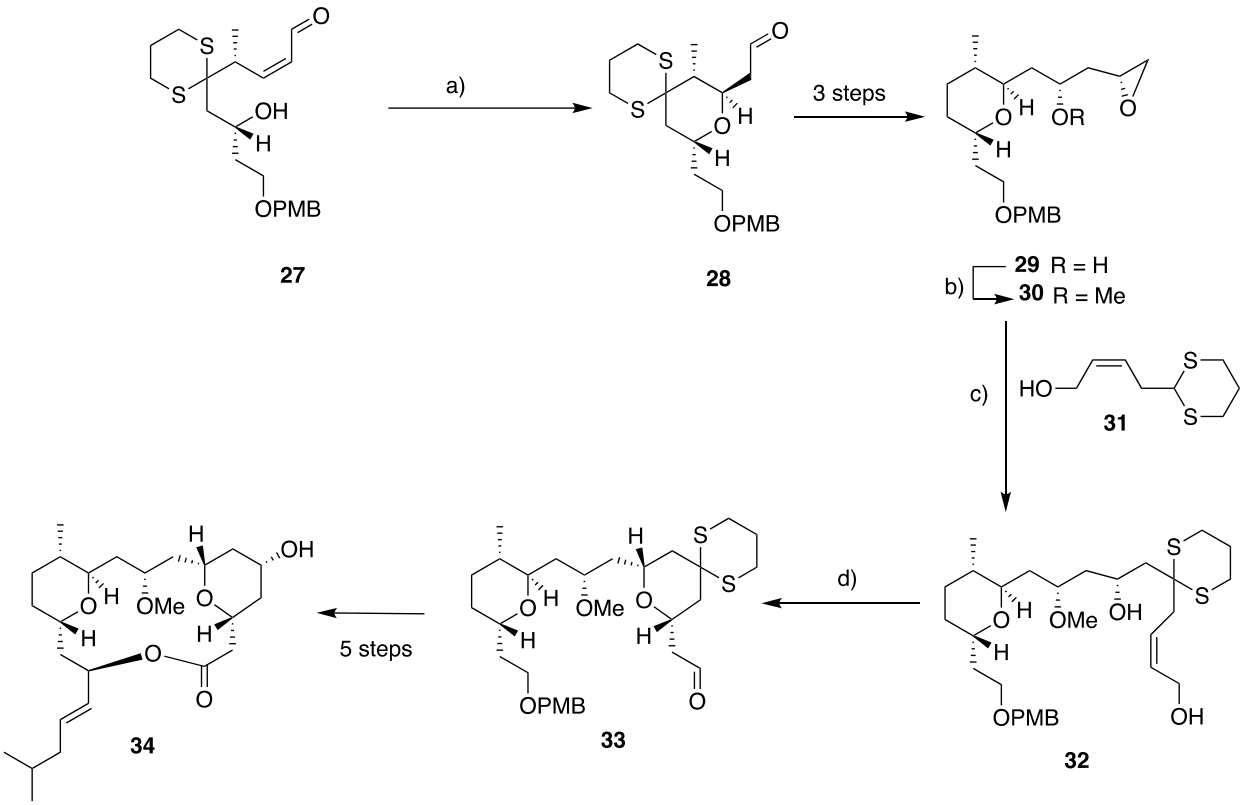
Conversely, Trost employed ruthenium-catalyzed *trans*-hydrosilylation to synthesise the tetrahydropyran ring of aspergillide B. [20] The key step involves chemoselective reduction of alkyne **24** to an *E*-alkene *via* a hydrosilylation/protodesylation, followed by deprotection of the alcohol which facilitates a *trans* selective cyclizsation to construct the tetrahydropyran **25** in 38% yield. This completed the synthesis of aspergillide B **26** in 3 steps (**Scheme 1.11**).



Reagents and conditions: a) $Cp^*Ru(CH_3CN)_3PF_6$, $(EtO)_3SiH$, DCE, 0 °C - rt, 10 h (38%) b) CuI, TBAF, THF, 0 °C - rt, 10 h.

Scheme 1.11 – Synthesis of aspergillide B

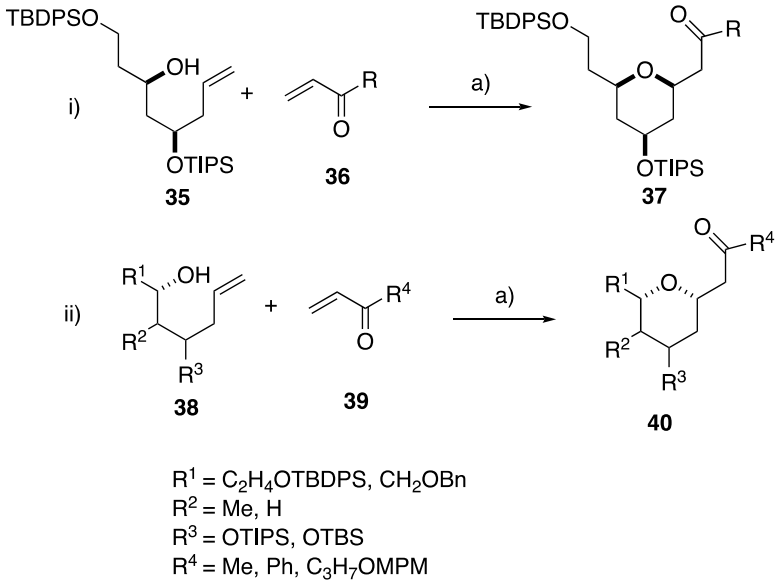
Lee *et al.* constructed the 2,3-*trans*-2,6-*trans*-tetrahydropyran ring **30** and 2,6-*cis*-tetrahydropyran ring **33** of leucascandrolide A macrolactone **34,** using a piperidine catalysed oxa-Micheal reaction and a tandem allylic oxidation/oxa-Michael reaction respectively to afford the synthesis of the macrolactone in 5 steps. The desired *trans* product **28** was formed with good selectivity (dr = 10:1) when aldehyde **27** was subjected to piperidine catalysed conditions at −40 ^{0}C, but was observed to generate the undesired *cis* product at 25 ^{0}C. This observation can be attributed to the shift in control from kinetic to thermodynamic at higher temperatures. Further, the coupling of **31** with **30** facilitated the tandem allylic oxidation/intramolecular oxa-Michael reaction to construct the 2,6-*cis* tetrahydropyran ring in **33.** The synthesis of the macrolactone **34** was completed in 5 steps with an excellent yield of 96 % (**Scheme 1.12**). [21] A similar strategy was employed by Evans to construct the tetrahydropyran rings of **34.** [22]



Reagents and conditions: a) piperidine, –40 °C, 24 h, CH_2Cl_2 (96%) b) NaH, MeI , DMF, 0-25 ^{0}C, 2 h c) t-BuLi, HMPA/THF, –78 °C for 10 min then **25**, –78 °C, 1 h, 92%, d) MnO_2, CH_2Cl_2, 25 °C, 12 h (86%).

Scheme 1.12 – Synthesis of the tetrahydropyran rings of Leucascandrolide A

Fuwa undertook pioneering work in the area of tandem metathesis/ oxa-Micheal cyclization to access substituted tetrahydropyrans in an elegant fashion. A microwave assisted tandem metathesis/oxa-Michael reaction between a δ-hydroxy alkene **35** and a vinyl ketone **36,** catalyzed by the second generation Hovyeds-Grubbs catalyst (HG-II), yielded substituted tetrahydropyrans in good to excellent yields (70-94%) and good diasteteoselectivities (8:1 to 14:1) **(Scheme 1.13, eq (i)).** A broader substrate scope involving a variety of coupling partners (**38 and 39**) under the same conditions gave excellent yields (79-97%) and diastereoselectivities (>20:1) **(Scheme 1.13, eq (ii)).** Interestingly, this process doesn't need any additives and is catalyzed solely by the Hovyeda-Grubbs second generation catalyst. This can be explained by the fact that the substrates are ketones and are far easier to cyclise compared to esters. It was observed that no tandem product was formed at lower temperatures (35 ^{0}C). Several control experiments carried out in the absence and presence of the catalyst revealed that the active ruthenium species responsible for the cyclisation must have been generated *in situ*. Further experiments showed that this species was ruthenium hydride that was generated from the decomposition of the thermally unstable ruthenium methylidene complex, and that the presence of 2,6-dichloro-1,4-benzoquinone slowed down the cyclization and resulted in a lower yield of the tandem product **37** (17%). [23, 24]

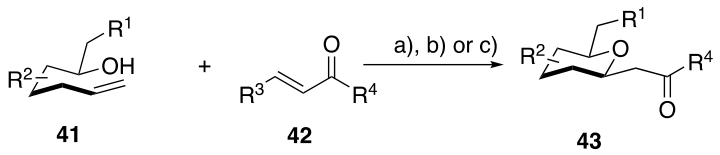


Reagents and conditions: a) **36** (i) **or 39** (ii) (1.5eq), HG-II (10 mol%), CH_2Cl_2, 100 ^{0}C (MW). Yields-i) 70-94% ii) 79-97%

Scheme 1.13- Synthesis of Tetrahydropyrans *via* Tandem Metathesis/ Oxa-Michael reaction

By replacing CH_2Cl_2 with toluene, the substrate scope was widened to include α,β-unsaturated carbonyl compounds **42** and was found to improve the yields and diastereoselectivity. However, the

reaction times also increased. To speed up the tandem process, a brønsted acid like CSA was used. Under CSA conditions, the reaction was observed to occur even at room temperature, giving moderate to good yields (48-80%) of the 2,6-*cis* substituted products with excellent diastereoselectivity (>20:1) **(Scheme 1.14).** [24]

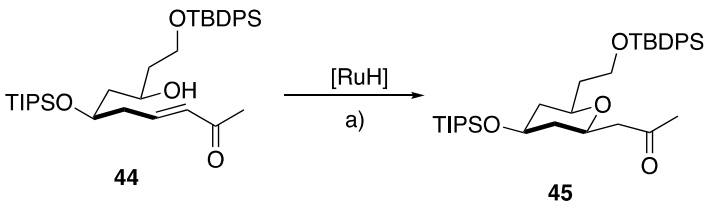


R^1 = OTBDPS
R^2 = OH, OTIPS
R^3 = Me, H
R^4 = OMe, H, 2,5-dimethylpyridinyl

Reagents and conditions: a) HG-II (10 mol%), CH_2Cl_2, 100 ^{0}C (MW), 30 min, 19-98% b) HG-II (10 mol%), Toluene, 80-100 ^{0}C, 11-14 h, 40-73% c) HG-II (10 mol%), CSA (3-10 mol%), CH_2Cl_2, 25-35 ^{0}C, (48-80%)

Scheme 1.14- Improvements to the Tandem Metathesis/ Oxa-Michael reaction

Mechanistic investigations to confirm the nature of the ruthenium species was undertaken. Under reflux conditions in THF, the cyclisation of ζ-hydroxy α,β-unsaturated ketone **44** using various ruthenium hydride complexes was carried out. Using $RuH_2(PPh_3)_4$, the desired product **45** was obtained with a 78% yield and a diastereoselectivity of 8:1. Also, $RuClH(CO)(PPh_3)_3$ and $RuH_2(CO)(PPh_3)_3$ gave the cyclised product in decent yields (45% and 55%, respectively) with a better diastereoselectivity (13:1 and 15:1 respectively). This confirmed the nature of the active ruthenium species as the ruthenium hydride. (**Scheme 1.15**) [24]

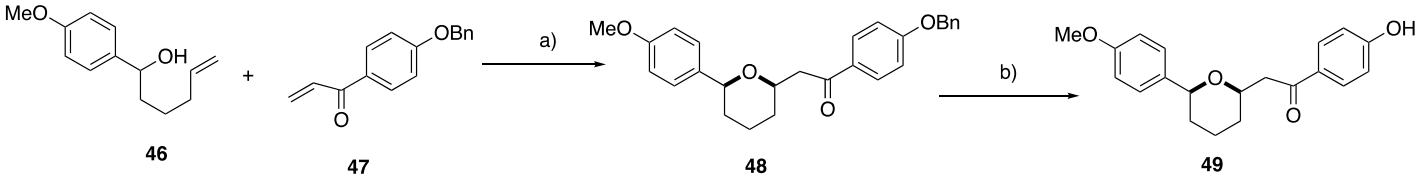


Reagents and conditions: a) THF, Reflux, (45-78%)

Scheme 1.15- Ruthenium Hydride catalyzed Oxa-Michael reaction of ζ-hydroxy α,β-unsaturated ketone **44.**

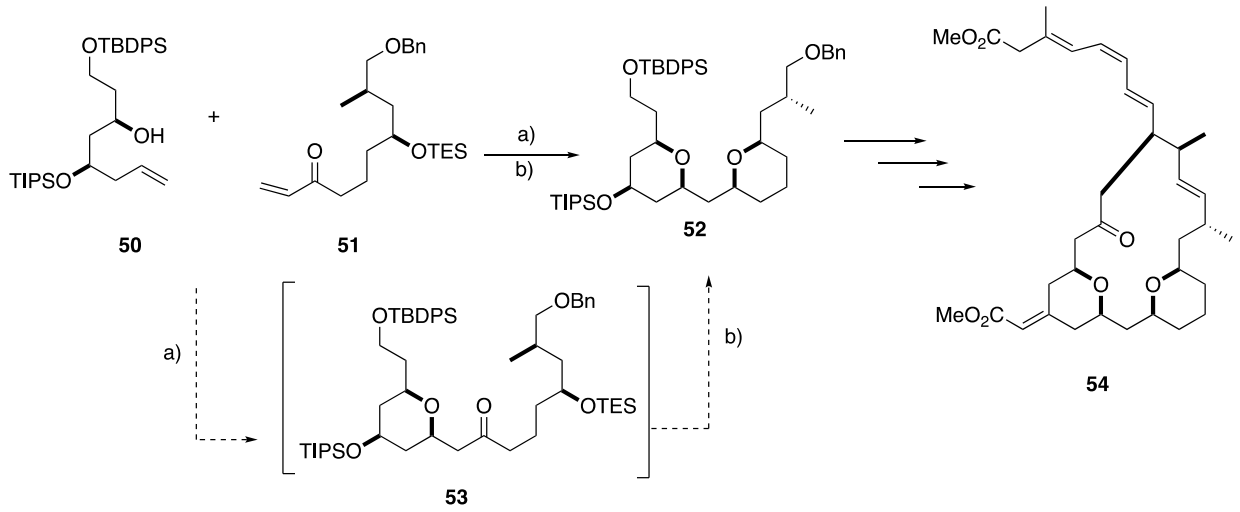
Fuwa employed the tandem metathesis/ oxa-Michael reaction methodology in the synthesis of (±)-centrolobine. The cross metathesis between the hydroxyl alkene **46** and an α,β-unsaturated ketone

47, which was synthesised from readily available p-benzyloxybenzaldehyde, afforded a crude mixture containing the desired 2,6-*cis* disubstituted tetrahydropyran in a ratio of 13:1 with respect to the *trans* isomer. Upon separation, the desired isomer **48** was isolated with a yield of 74%. Deprotection of the benzyl ether group *via* hydrogenolysis yielded (±)-centrolobine **49** in a 68% yield. A domino cross metathesis/ oxa-Michael addition strategy yielded (±)-centrolobine in just four linear steps, starting from commercially available p-benzyloxybenzaldehyde, illustrated the efficiency and utility of this strategy **(Scheme 1.16).** [25]



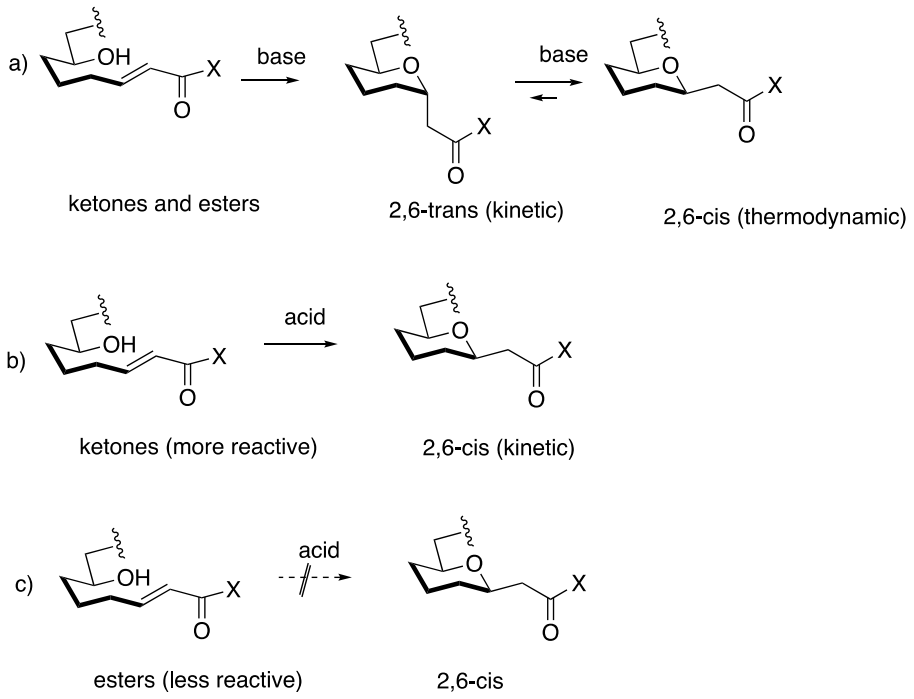
Reagents and conditions: a) HG-II (10 mol%), CH_2Cl_2, 100 ^{0}C (MW), 20 min. b) H_2, Pd/C, THF, rt, (68%).
Scheme 1.16- Fuwa's synthesis of (±)-centrolobine.

Fuwa also employed this strategy in the synthesis of (-)-exiguolide. A microwave assisted cross metathesis was employed between the hydroxyl alkene **50** and an α,β-unsaturated ketone **51**, gave the 2,6-*cis* disubstituted tetrahydropyran intermediate **53**, that was then treated without purification with $BF_3.OEt_2$ and Et_3SiH to afford the methylene *bis*(tetrahydropyran) **52** with an 89% yield and 10:1 diastereoselectivity. (-)-Exiguolide **54** was synthesised from this in subsequent steps. This synthesis highlights the utility and efficiency of this strategy in accessing complex structures **(Scheme 1.17).** [26]



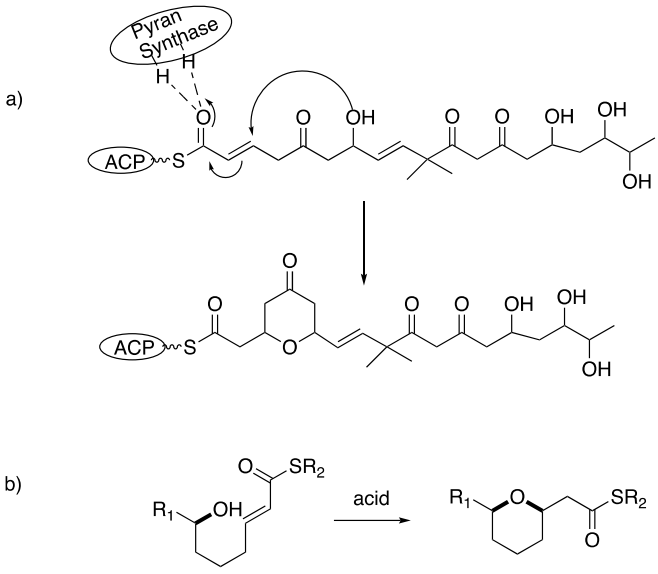
Reagents and conditions: a) HG-II (10 mol%), CH_2Cl_2, 100 ^{0}C (MW), 30 min. b) $BF_3.OEt_2$, Et_3SiH, −60 ^{0}C to −15 ^{0}C, 50 min, (89%)
Scheme 1.17- Fuwa's synthesis of (-)-exiguolide

In spite of being an attractive strategy to construct substituted tetrahydropyrans, a key challenge to the tandem metathesis/ oxa-Michael reaction is lies in controlling the stereoselectivity. The stereoselective synthesis of 2,6-*cis* disubstituted tetrahydropyrans is of particular interest as it occurs extensively in natural products. Fuwa carried out extensive research in the stereoselective synthesis of 2,6-*cis* tetrahydropyrans. [17,27] Under basic conditions, α,β-unsaturated ketones and esters give the kinetic 2,6-*trans* product, which can be converted to the thermodynamic 2,6-*cis* product *via* a base catalyzed ring opening/ring closing sequence. However, under acidic conditions, α,β-unsaturated ketones give the kinetic 2,6-*cis* product and α,β-unsaturated esters generally do not cyclise as they are less reactive **(Scheme 1.18)** [17].



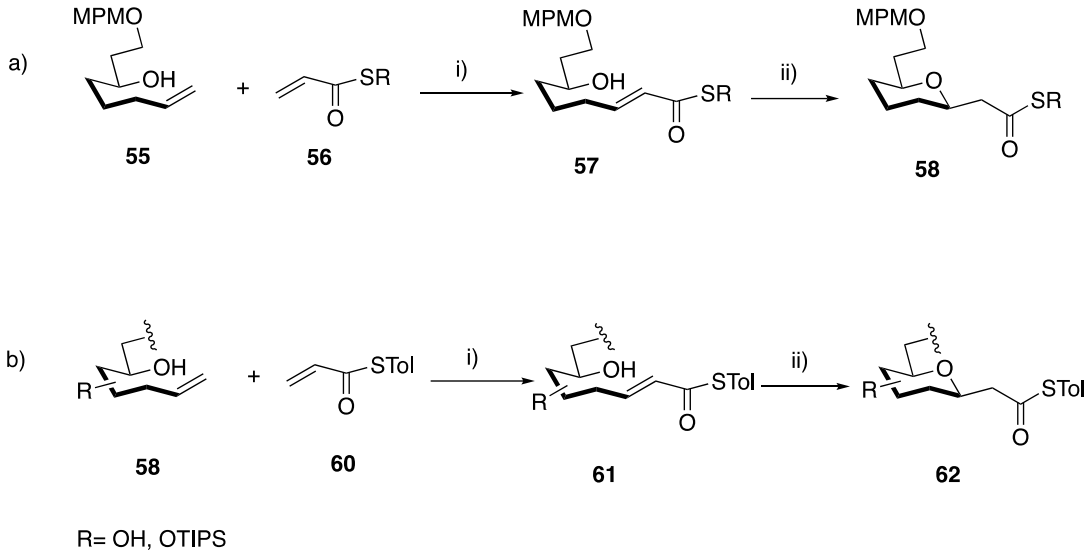
Scheme 1.18- Intramolecular oxa-Michael cyclisation of α,β-unsaturated ketones/esters.

Several studies into the biosynthesis of polyketide containing tetrahydropyrans [28] suggest that tetrahydropyrans are formed *via* a pyran synthase catalyzed intramolecular oxa-Michael cyclisation of α,β-unsaturated thioesters **(Scheme 1.19a)**.[27] Fuwa reasoned that the activation of the carbonyl bond of the α,β-unsaturated thioesters enhanced the reactivity of the thioester and plays a part in making this reaction feasible. Inspired by this, he proposed a biomimetic synthesis of 2,6-*cis* tetrahydropyrans *via* a Brønsted acid catalyzed intramolecular oxa-Michael cyclisation of α,β-unsaturated ester surrogates **(Scheme 1.19b).** [27]



Scheme 1.19- a) Proposed biosynthetic pathway of the synthesis of poleketide tetrahydropyrans b) Biomimetic synthesis of 2,6-*cis* tetrahydropyrans of ester surrogates.

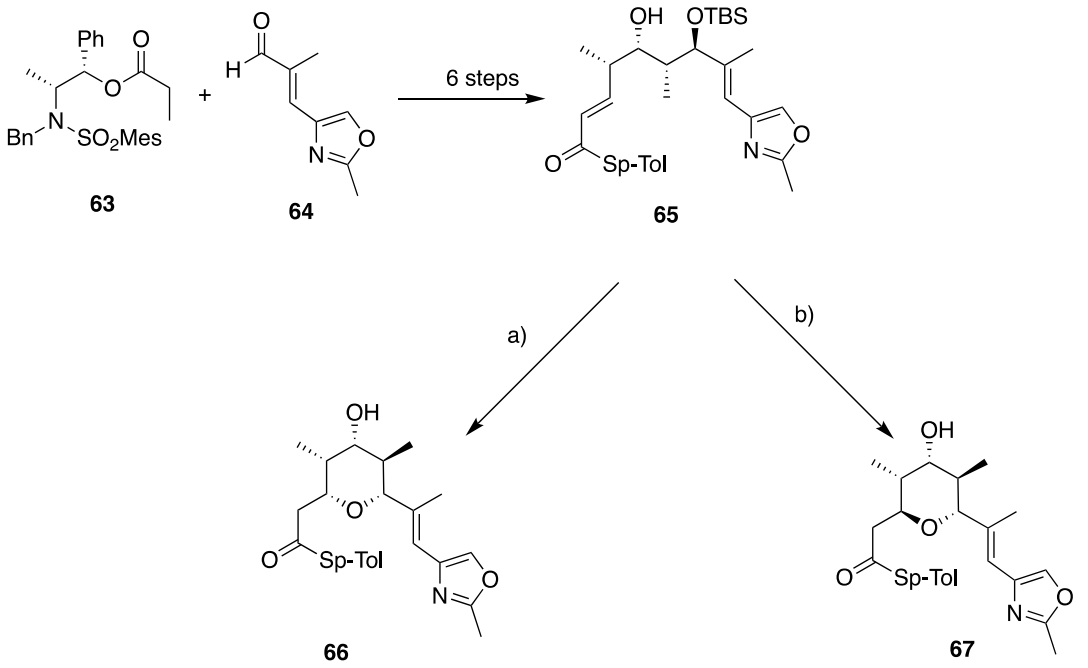
The thioesters were synthesized *via* a HG-II catalyzed metathesis between the hydroxyl alkene **55** and various α,β-unsaturated thioesters **56**. They were then cyclized by a Brønsted acid catalyzed oxa-Michael reaction using CSA. The most reactive tetrahydropyran **58** was obtained using a tolyl thioester **60**, with a yield of 72% and a dr >20:1 **(Scheme 1.20a).** Using the tolyl thioester **60**, a substrate scope was carried out using various hydroxyl alkenes **59** to obtain excellent yields (88-97%) and diastereoselectivities (>20:1) for a variety of tetrahydropyrans **62** (**Scheme 1.20b).** [27] This methodology is especially attractive due to the versatility of the thioesters.



Reagents and conditions: For a) i)HG-II (10 mol%), CH_2Cl_2, 35 ^{0}C. ii) CSA (20 mol%), CH_2Cl_2, rt. (82-94%) For b) i)HG-II (10 mol%), CH_2Cl_2, 35 ^{0}C. ii) CSA (20 mol%), DCE, 70 ^{0}C, (88-97%)

Scheme 1.20- a) Preparation and intramolecular oxa-Michael cyclisation of α,β-unsaturated thioesters. b) Substrate scope

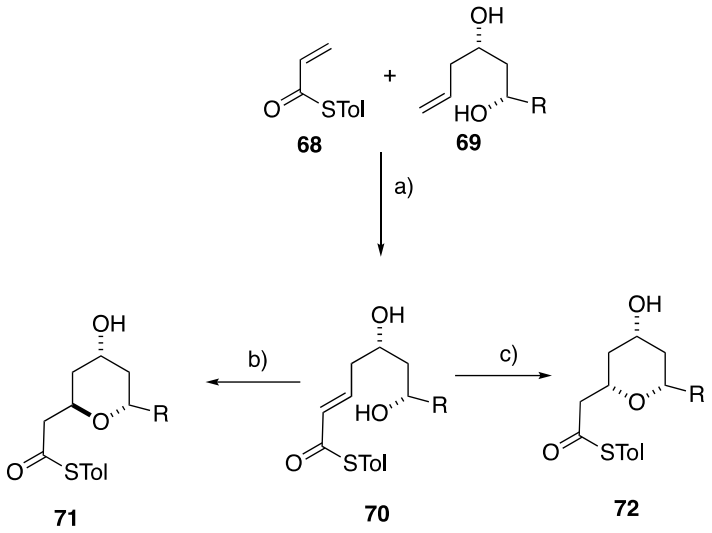
Clarke built on this strategy during his study into the occurrence of stereodivergence while synthesizing the C20-C32 fragmant of the phorboxazoles. [29,30] The Clarke group synthesised the C20-C32 core of the phorboxazoles by employing a silyl ether deprotection/oxa-Michael cyclisation as a key step. Interestingly, they observed that both the *cis* and *trans* products could be generated from **65**, depending on the conditions used. Under acidic conditions, the C20-C32 core **66** was generated while the C22 epimer **67** was generated under buffered fluoride conditions, with an overall yield of 31% over 7 steps (**Scheme 1.21**). [29]



Reagents and conditions: a) TFA, CH_2Cl_2, H_2O, rt b) TBAF, AcOH, THF (31% over 7 steps)

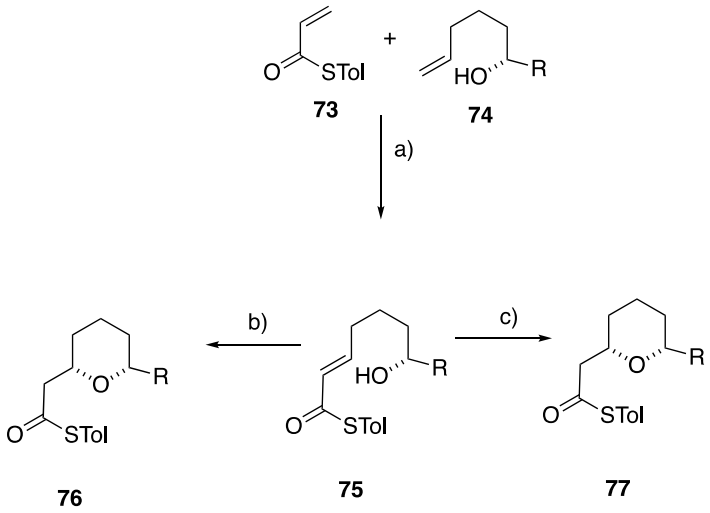
Scheme 1.21- Synthesis of the C20-C32 core of Phorboxazoles

To understand the occurrence of stereodivergence, substrates containing a 4-hydroxy group were synthesized. The synthesis involved a HG-II catalyzed, CuI mediated metathesis between hydroxyl alkenes **69** and thioacrylate **68** in Et_2O under reflux conditions to yield the cyclisation precursor **70**. Unlike Fuwa's work, a copper iodide additive was used, as optimization studies showed that it enhanced the yield. The 2,6-*trans* product **71** was observed predominantly under buffered fluoride conditions, with good yields (40-69%) and good diastereoselectivities (8:1 to 20:1). Under TFA or CSA mediated conditions, the 2,6-*cis* product **72** was observed with better yields (65-74%) and comparable diastereoselectivities (7:1 to 20:1) **(Scheme 1.22)**. When the hydroxyl at the 4 position was removed and the same protocol as above was carried out, the 2,6-*cis* product **76/77** was observed under both the buffered fluoride and acid conditions. While the yields under buffered fluoride conditions (25-53%) were comparable to that of the acid conditions (36-56%), the diastereoselectivities (>20:1) were much better than the acid conditions (4:1 to 8:1) **(Scheme 1.23).** [30]



Reagents and conditions: a) HG-II (10 mol%), CuI (15%), Et_2O, reflux. b) TBAF (30 mol%), AcOH (6%), THF, (40-69%) c) TFA, H_2O, CH_2Cl_2, rt or CSA, DCE, 80 ^{0}C, (65-74%)

Scheme 1.22 - Stereodivergent synthesis of 4-hydroxy containing substrates.

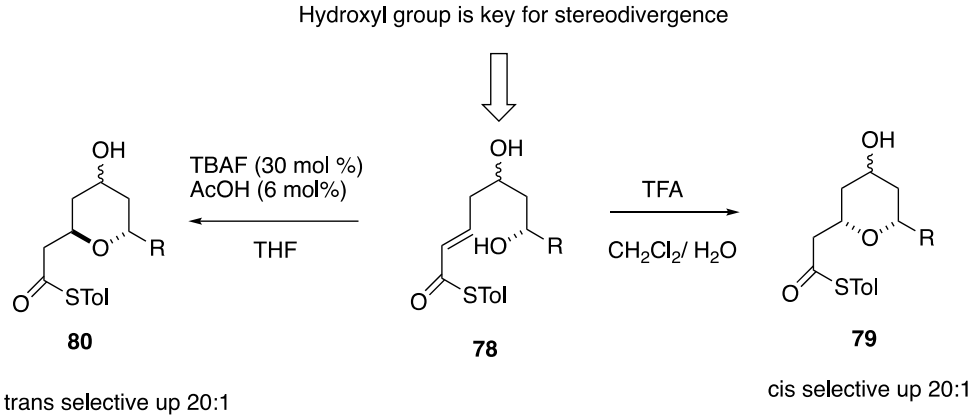


Reagents and conditions: a) HG-II (10 mol%), CuI (15%), Et_2O, reflux. b) TBAF (30 mol%), AcOH (6%), THF, (25-53%) c) TFA, H_2O, CH_2Cl_2, rt or CSA, DCE, 80 ^{0}C,(36-56%)

Scheme 1.23 – Cyclisation of substrates without a 4-hydroxy group.

The general conclusion of the study was that a 4-hydroxyl group was crucial for the occurrence of stereodivergence in the thioester oxa-Michael cyclisation **(Scheme 1.24).** [30] Computational studies were carried out to model the most preferred transition state and understand the underlying mechanism that resulted in the observed stereodivergence. It was found that the flouride mediated

transition state preferred a boat like structure wherein the alkoxide of the cyclizing hydroxyl is involved in hydrogen bonding with the δ hydroxyl. This is not the case with the TFA mediated cyclisation. Here, the molecule adopts a chair- like transition state, with the trifloroacetate acting as a proton shuttle, increasing the nucleophilicity of the alkoxide oxygen and the electrophilicity of the thioester at the same time. The δ-hydroxyl is not involved in the transition state (**Figure 2**). [30]



Scheme 1.24 General outline of the stereodivergent thioester oxy-micheal cyclisation

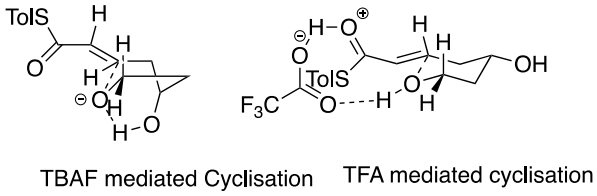
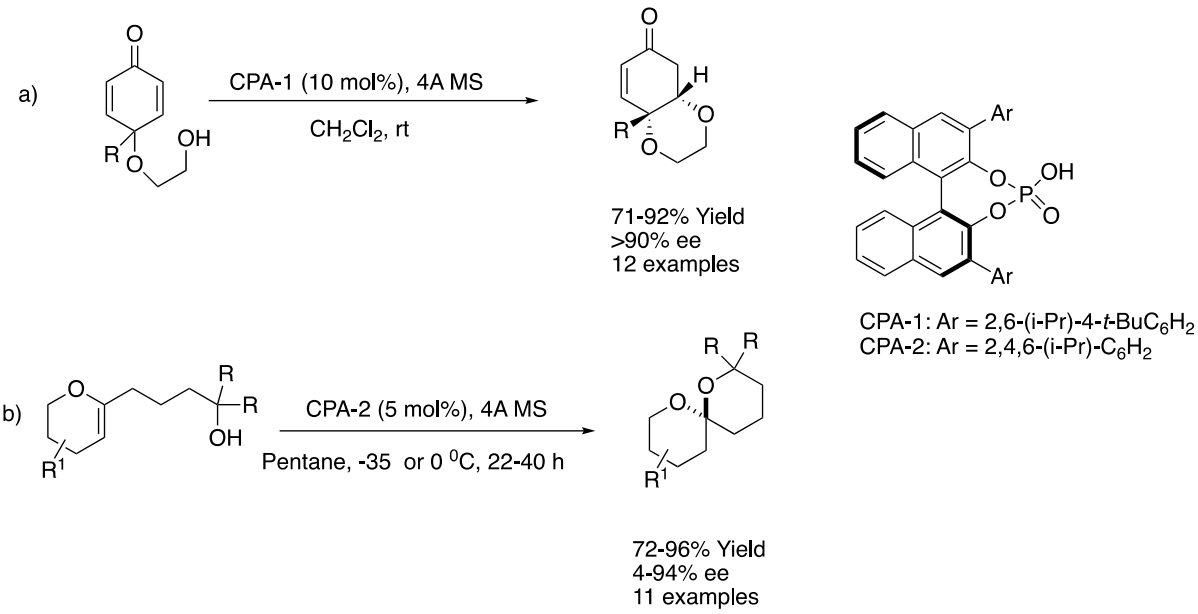


Figure 2- Transition states adopted in the stereodivergent oxy- Micheal cyclisation

7.5 Aim and Scope of the Project.

Chiral Brønsted acids, such as phosphoric acids and their derivatives in particular, have generated a lot of research interest, [31,32] ever since they were reported separately by Akiyama [33] and Terada [34] in 2004. Chiral Brønsted acids have been shown to catalyze desymmetrisation of cyclohexanediones *via* an intramolecular oxy-Micheal reaction **(Scheme 1.25a)** [35] and stereoselective spiroketalisation **(Scheme 1.25 b)** [36] with excellent enantioselectivities.

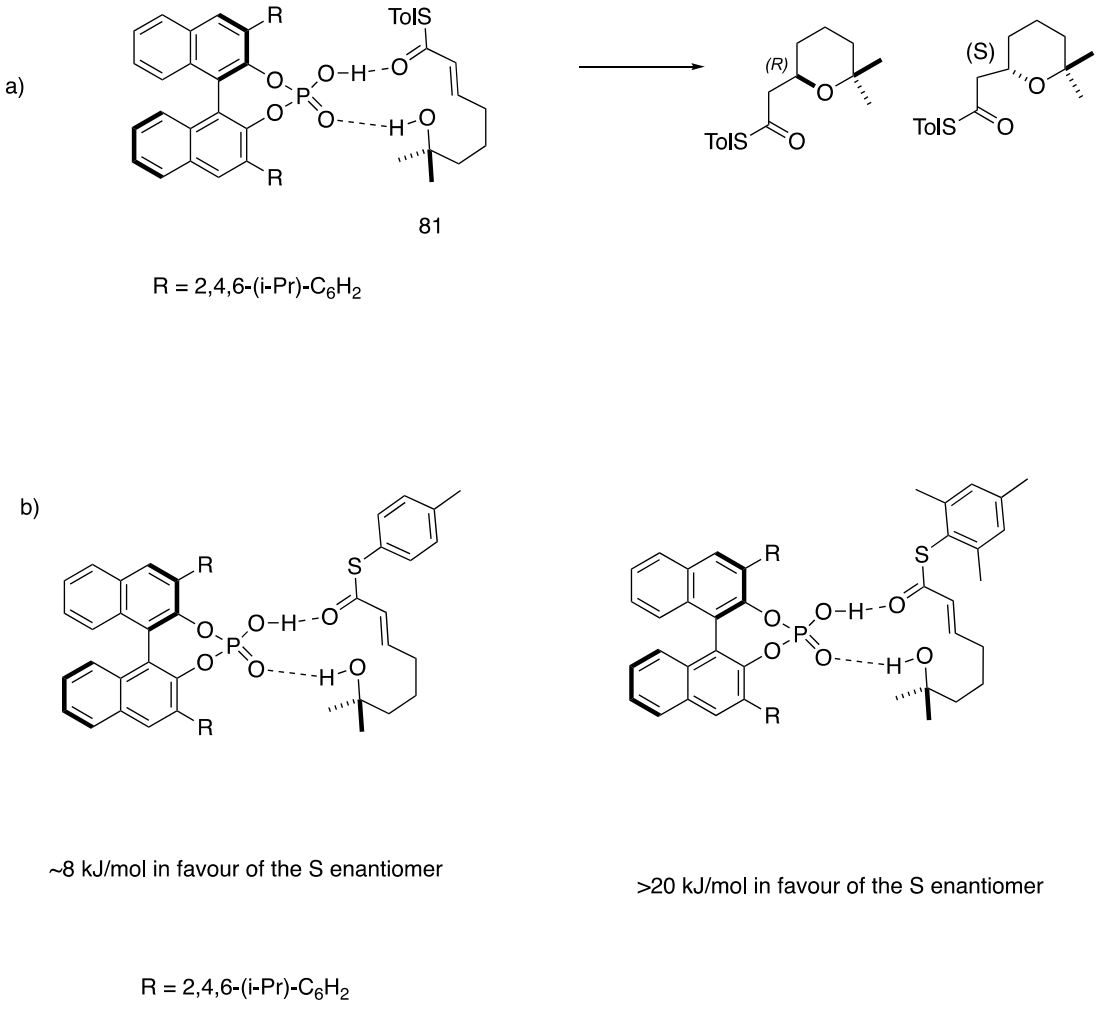


Scheme 1.25- chiral Phosphoric acid catalyzed oxa-Michael cyclisations

As Clarke's TFA mediated cyclisation doesn't depend on any structural features, it can be postulated that a chiral acid which acts as a proton shuttle, can replace TFA, resulting in the enantioselective synthesis of tetrahydropyrans. As TFA (pKa = –0.3) and CSA (pKa = 1.2) act as proton shuttles in the thioester oxy-Micheal reaction, chiral Brønsted acids with similar pKa values should be able to perform the same function. In simple terms, the acid would form one enantiomer while the ent-acid would form the other enantiomer.

Previous computational work in the group, by Kristaps Ermanis,[37] looked into the feasibility of the chiral phosphoric acid catalyzed oxa-Michael cyclisation. Preliminary work modelled the oxa-Michael cyclisation of **81** with the commercially available chiral phosphoric acid (*R*)-TRIP and the energy barrier of formation between the enantiomers was calculated using a conformational search using molecular mechanics with MacroModel and an MMFF force field **(Scheme 1.26a).** It was found that the formation of the *S*-enantiomer was favoured by 8 KJ/mol in case of a tolyl precursor. On changing the tolyl group with a mesityl group, the energy barrier increased to 20 KJ/mol, suggesting that greater enantioselectivities should be observed in cases involving a mesityl precursor **(Scheme 1.26b).** This computational result shows that the cyclisation is feasible and that increasing the acidity of the acid, which is in the range of TFA (pKa = –0.3) and CSA (pKa = 1.2), could favour better enantioselectivities. The aim of this project is to develop an asymmetric oxa-Michael reaction by replacing TFA with a chiral brønsted acid proton shuttle like chiral phosphoric acids, which would lead to the formation of

enantioenriched THP products. The enantioselectivities can be switched by using the ent-form of the chiral acid.

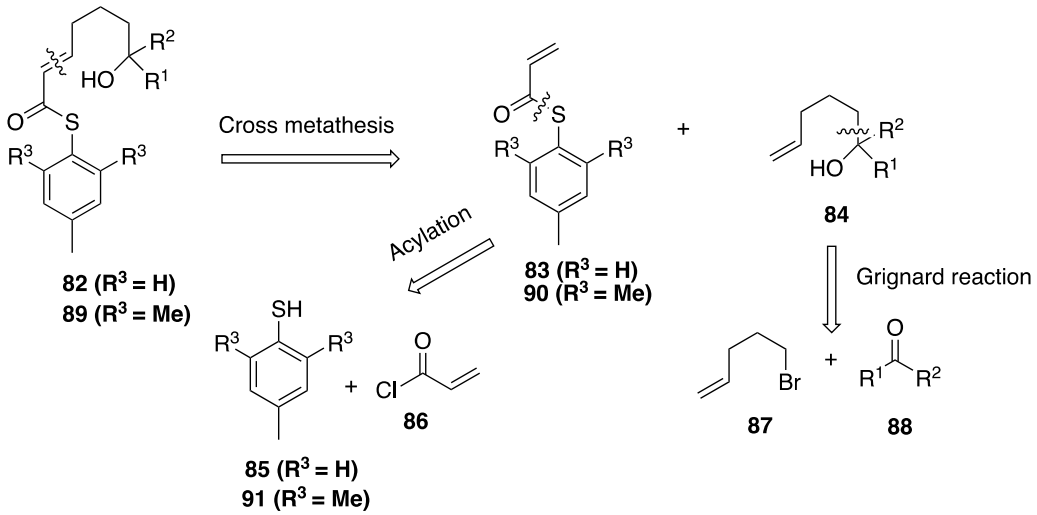


Scheme 1.26- Preliminary computational work into the chiral acid catalyzed oxa-Michael cyclisation.

8. Results and Discussions

8.1 Retrosynthetic Analysis of the Tetrahydropyran Precursors

The cyclisation precursors (tolyl **82** and mesityl **89**) were accessed via a two-step convergent synthetic route starting from readily available starting materials. Performing retrosynthetic analysis on the cyclisation precursors **82** and **89**, they could be simplified to the thioacrylate **83/90** and the alcohol **84** via a cross metathesis reaction. The thioacrylate **83/90** could be prepared via acylation between the thiol **85/91** and acryloyl chloride **86**. The alcohol **84**, on the other hand, could be synthesized *via* a simple Grignard reaction between metallated 5-bromopentene **87** and the corresponding aldehyde/ketone **88** (**Scheme 2.1**).



Scheme 2.1- Retrosynthetic analysis of the cyclisation precursors **82** and **89**.

8.2 Synthesis of the Tetrahydropyran Precursors.

For the purpose of this study, the alcohols used included a primary alcohol **84b**, a secondary alcohol **84c** (with an isopropyl substituent) and a tertiary alcohol **84a** (with a dimethyl substituent), of which **84a** and **84c** were synthesized while **84b** was commercially available (**Figure 3**).

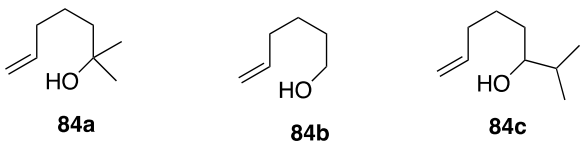
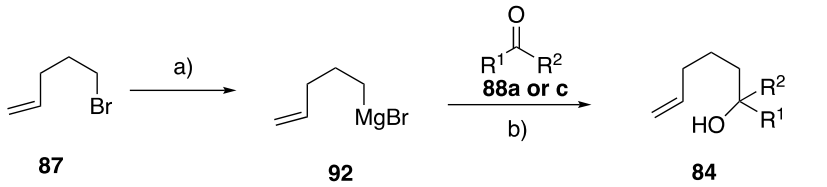


Figure 3- Structures of alcohol **84**.

The forward synthetic route to the cyclisation precursors began with the synthesis of the alcohols **84a**[38] and **84c,** [30] based on literature procedures. The synthesis involved the initial generation of the Grignard reagent **92**, followed by the addition of the corresponding aldehyde **88c**/ketone **88a**, to give the necessary alcohol **84**. Initial attempts at the synthesis of **84a** involved the usage of THF as a solvent, which proved difficult in separation upon work-up, resulting in a loss of product. Upon, switching to Et_2O, the work-up and separation were much easier, resulting in a disappointing yield of 13%. In the synthesis of **84c**, there were no issues involving THF and the synthesis was smooth, resulting in a 25% yield (**Scheme 2.2**)



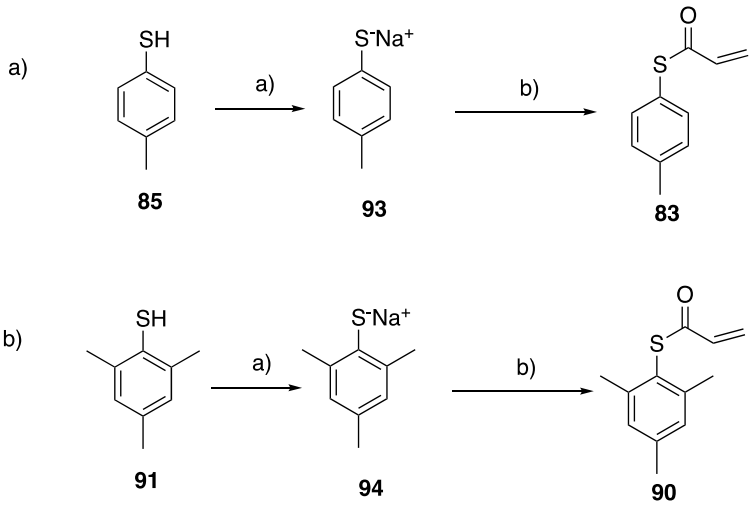
87 **92** **84**

a: $R^1 = R^2 = Me$
c: R^1 = i-Pr, $R^2 = H$

Reagents and conditions: For **84a**: a) Mg/Et_2O, rt, 2 h b) **88a**, rt (13%) and for **84c**: a) Mg/THF, rt, 1 h. b) **88c**, rt, 90 min (25%)

Scheme 2.2- Synthesis of alcohols **84.**

With the synthesis of the alcohols complete, the synthesis of thioacrylate **83** was attempted, based on a literature procedure. [31] The synthesis began with the deprotonation of thiol **85** by dissolving it in a solution of NaOH/$NaBH_4$, to generate the thiolate anion **93**. To this, a solution of acryloyl chloride **86** in cyclohexane, containing the additive BHT, was added, resulting in the synthesis of thioacrylate **83** with a yield of 47% (**Scheme 2.3a**). The thioacrylate **90** was synthesized in an analogous manner with a yield of 50% (**Scheme 2.3b)**.

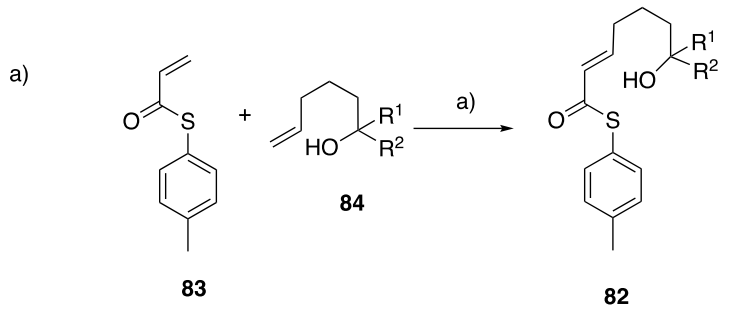


Reagents and conditions: For **83:** a) 15% NaOH, $NaBH_4$, rt, 1 h b) **86**, BHT, cyclohexane, 55 ^{0}C, 30 min, (47%) For **90:** a) 15% NaOH, $NaBH_4$, rt, 1 h b) **86**, BHT, cyclohexane, 55 ^{0}C, 90 min (50%).

Scheme 2.3- Synthesis of Thioacrylate **83** and **90**

The additives play an important role in the efficiency of the synthesis. The addition of $NaBH_4$ to the thiolate **93** prevents the formation of disulfides, while the addition of BHT to the acryloyl chloride **86** prevents radical polymerization. With the synthesis of the thioacrylate **83/90** and the requisite alcohols **84** complete, the synthesis of the cyclisation precursors **82** and **89** was attempted *via* a cross metathesis reaction.

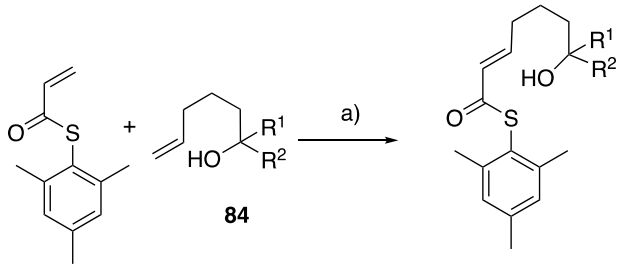
The conditions previously employed by Clarke [30] were used to synthesise our cyclisation precursors **82** and **89** from alcohols **84** and thioacrylate **83** and **91 (Scheme 2.4)**. The metathesis was catalyzed by HG-II and mediated by CuI (1:1 ratio) in Et_2O under reflux conditions, by using the alcohols **84** and the thioacrylate **83/90** in a ratio of 1:3. The synthesis of cyclisation precursor **83** was first attempted. The metathesis occurred smoothly but took longer in the primary and tertiary alcohol cases **(entry 1 and 2) (Scheme 2.4a)** compared to the secondary alcohol **(entry 2)**. The cyclisation precursors were obtained as brown oils and the yields were excellent. In an analogous manner, the Grubbs metathesis between alcohols **84** and the mesitylthioacrylate **90** was carried out under the same conditions used for the tolyl precursors **82**. The synthesis was smooth and the mesityl precursors **89** were made with good to excellent yields **(Scheme 2.4b)** The yield of the isopropyl precursor **89c** (56%) was lower compared to that of **89a** (86%) and **89b** (91%).



83 **84** **82**

Reagents and conditions: a) HG-II (10 mol%), CuI (10%), Et_2O, reflux.

Reaction	Alcohol	R	Cyclisation precursor	Time (h)	Yield (%)
Entry 1	**84a**	$R^1 = R^2 = Me$	**82a**	24	87
Entry 2	**84b**	$R^1 = R^2 = H$	**82b**	24	86
Entry 3	**84c**	$R^1 = H$; $R^2 = i\text{-}Pr$	**82c**	2	85



90 **84** **89**

Reagents and conditions: a) HG-II (10 mol%), CuI (10%), Et_2O, reflux.

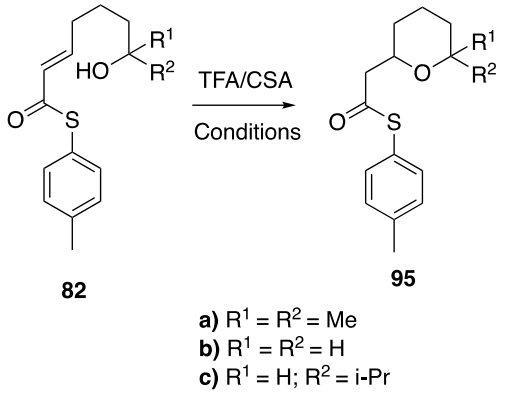
Reaction	Alcohol	R	Cyclisation precursor	Time (h)	Yield (%)
Entry 1	**84a**	$R^1 = R^2 = Me$	**89a**	18	86
Entry 2	**84b**	$R^1 = R^2 = H$	**89b**	24	91
Entry 3	**84c**	$R^1 = H$; $R^2 = i\text{-}Pr$	**89c**	16	56

Scheme 2.4 – Synthesis of cyclisation precursors **82** and **89**.

With the synthesis of the cyclisation precursors **82** and **89** complete, the Brønsted acid catalyzed cyclisation was ready to be attempted.

8.3 Brønsted Acid Catalyzed Cyclisation of Tetrahydropyran Precursors.

The general scheme for the Brønsted acid catalyzed cyclisation involves the use of TFA or CSA as acids. The cyclisation of tolyl precursors **82** to generate 2,6 disubstituted tetrahydropyrans **95** was first attempted **(Scheme 2.5)**.



Scheme 2.5 – General scheme for Brønsted Acid Catalyzed Cyclisation

The objectives of carrying out Brønsted acid catalyzed cyclisation of precursors **82** was twofold. Firstly, it was done to observe the reactivity trends of the precursors **82** to acid cyclisation and use that information to carry out the chiral Brønsted acid catalyzed asymmetric cyclisation of the same. Secondly, the generated racemic samples would be used for HPLC analysis and screen conditions for effective resolution, which would be used to determine the %ee of the enantioenriched samples from the asymmetric cyclisation.

We began with the TFA catalyzed cyclisation of **82a**, using the conditions employed by Clarke. [30] The initial precursor concentration for all cyclisations was kept at standard of 0.06 M. To this, TFA and H_2O were added. The TFA used was also 0.06 M and the ratio of TFA and H_2O was maintained at 9:1. The total amount of TFA and H_2O were scaled up accordingly **[Table1].**

Reaction	Solvent	Temperature (^{0}C)	Time (h)	(TFA: H_2O) (mL)	Conversion (%)
Entry 1	DCM	rt	24	0.9:0.1	nil
Entry 2	DCE	50	24	0.9:0.1	32
Entry 3	DCE	50	24	1.8:0.2	32
Entry 4	DCE	50	24	3.6:0.4	31
Entry 5$^{\perp}$	DCE	50	24	0.9:0.1	60
Entry 6$^{\perp}$	DCE	50	24	neat	83
Entry 7*	DCM	rt	24	20 mol%	11
Entry 8*	TFE	rt	24	20 mol%	10
Entry 9*	HFIP	rt	24	20 mol%	13

$\perp$ solvent evaporated before addition. $*$ No water added

Table 1- Cyclisation of **82a** under TFA conditions.

Similar to previous work in the Clarke group, [30] the cyclisation of **82a** was attempted at room temperature, but no cyclisation product was observed even after 24 h **(entry 1)**. As there was no reaction observed at room temperature, it was reasoned that given the low reactivity of the substrate, increasing the temperature might help overcome the lack of reactivity. The solvent was switched to DCE and the reaction was carried out at 50 ^{0}C. Maintaining the same amount of TFA and H_2O, some conversion of the substrate to the product was observed **(entry 2)**. The next parameter that could be altered was the amount of TFA and H_2O. The amount was doubled **(entry 3)** and subsequently quadrupled **(entry 4)** with respect to **entry 1**, but the conversion appeared to remain constant. It appears that the cyclisation was unaffected by the amount of acid. The next parameter to change was the amount of solvent. In effect, by removing the solvent, the effective concentration of the precursor increases. To alter this, a 0.06 M solution of the substrate in DCM was prepared and the solvent was evaporated, prior to addition of the acid. To this, TFA and H_2O were added in a ratio of 9:1 (1 mL combined) and reacted. Interestingly, the conversion doubled **(entry 5)** with respect to **entry 2**. Encouraged by this result, the reaction was carried out neat in TFA i.e. without the presence of H_2O. This improved the conversion to 83% **(entry 6)**. Seeing that the absence of water gave the best conversion, the effect of catalyst loading and more polar solvents on the reaction was studied. To this end, the reaction was carried out at room temperature without the presence of H_2O, with an initial precursor concentration of 0.06 M, and a TFA loading of 20 mol% **(entry 7)**. Next, DCM was replaced by TFE **(entry 8)** and HFIP **(entry 9)**. Surprisingly, there was similar conversions, showing that

decreasing the loading in the absence of H_2O does form some product, unlike **entry 1 [Table-1]**. The cyclisation of **82a** was then attempted using CSA, under the conditions employed by Clarke. [30] In this reaction, CSA was used in 3 eq and the cyclisation was carried out at 80 ^{0}C for 24 h. The conversion (75%) was higher than a typical TFA cyclisation.

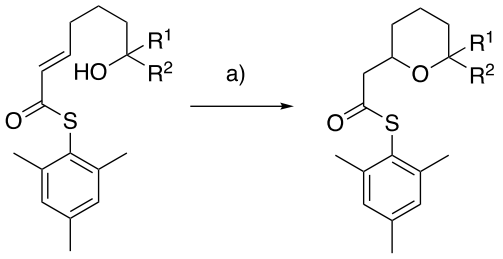
With the cyclisation of **82a** complete, the focus shifted to **82b**. The TFA cyclisation was attempted first **(Table 2)**.

Reaction	Solvent	Temperature (^{0}C)	Time (h)	(TFA: H_2O) (mL)	Conversion (%)
Entry 1	DCM	rt	24	0.9:0.1	13
Entry 2	DCE	60	24	2.7:0.3	41
Entry 3	DCE	80	24	2.7:0.3	36

Table 2- Cyclisation of **82b** under TFA conditions.

Similar to **82a**, the cyclisation was first attempted at room temperature, starting with a precursor concentration of 0.06 M. However, the conversion was only 13% **(entry 1)**. Subsequently, the temperature was increased to 60 ^{0}C and instead of a 0.06 M solution of substrate, a 0.02 M one was taken and the amount of TFA and H_2O were tripled **(entry 2)** with respect to **entry 1**. In essence, two parameters namely temperature and amount of catalyst were varied at the same time. The temperature was further increased to 80 ^{0}C, keeping the amount of acid and H_2O the same **(entry 3)**. Interestingly, the conversion tripled compared to the first attempt, and gave a more modest conversion of 41% and 36% at 60 ^{0}C and 80 ^{0}C respectively **[Table-2]**. Following this, a CSA catalyzed cyclisation of **82b** was attempted analogous to that of **82a**. The cyclisation was carried out at 80 ^{0}C, using 3eq of CSA, for 24 h. The conversion (94%) was excellent, compared to the TFA cyclisation attempts of **82b**.

Finally, the TFA cyclisation of substrate **82c** was carried out, based on a literature procedure [31] In the procedure, the precursor concentration was 0.06 M, and the amount of TFA and H_2O used were 0.9 mL and 0.1 mL respectively. The reaction was quenched after 5.5 h. While the conversion was not reported, it was assumed to have undergone complete conversion. However, in our attempt analogous to the procedure, there was still unreacted starting material. Prolonged reaction time of 48 h gave only a 64% conversion.



89 **96**

a) $R^1 = R^2 = Me$
c) $R^1 = H$; $R^2 = i\text{-}Pr$

Reagents and conditions: a) TFA (1.8 mL)/ H_2O (0.2 mL), DCE, 50 ^{0}C, 24 h. Yield- **96a** (41%) and **96c** (52%)

Scheme 2.6- Cyclisation of **89** under TFA conditions.

The cyclisation of mesityl precursors **89** to generate 2,6 disubstituted tetrahydropyrans **96** was then attempted **(Scheme 2.6)**. Observing that when H_2O was present, the amount of TFA and H_2O used had no effect on the conversion, it was decided that a screen similar to the tolyl precursors **82** would not be undertaken. Instead, it was decided that one set of conditions would be chosen to prepare the racemic samples needed for HPLC analysis. To this effect, the cyclisation of **89a** and **89c** at 50 ^{0}C in DCE, using TFA/ H_2O (1.8 mL : 0.2 mL) and a precursor concentration of 0.06 M was carried out. The conversions for **89a** and **89c** were 44% and 89% respectively.

With the synthesis of cyclized products **95** and **96** complete, attempts were made to resolve the enantiomers of the racemic mixtures**.** Since the next part of the study involved the asymmetric oxa-Michael cyclisation using chiral phosphoric acids and determining the enantioselectivities of the cyclized products, conditions to resolve these mixtures in a chiral fashion was of paramount importance. Hence, conditions determined from the successful separation of enantiomers in a racemic mixture could be applied to resolving chiral mixtures.

Chiral HPLC is a very useful technique to resolve complex mixtures and finds wide application in analytical labs and industry. The principle involves the differential retention times of the components in a mixture upon elution on a chiral column, leading to successful chiral resolution. After testing various columns using different eluant concentration (Hexane:IPA) and flow rates, the cyclisation products **95** and **96** were resolved using a CHIRALCEL AD-H column **(Figure 4) [Table 3]**.

Cyclisation Product	(Hexane:IPA)	Peak 1 (min)	peak 2 (min)	Flowrate (mL/min)
95a	95/5	3.763	4.484	1.0
95b	95/5	12.200	13.213	1.0
95c	95/5	3.314	3.581	1.0
96a	95/5	4.280	4.891	0.9
96c	97/3	9.897	12.369	0.9

Table 3- HPLC retention times of cyclised products **95** and **96**.

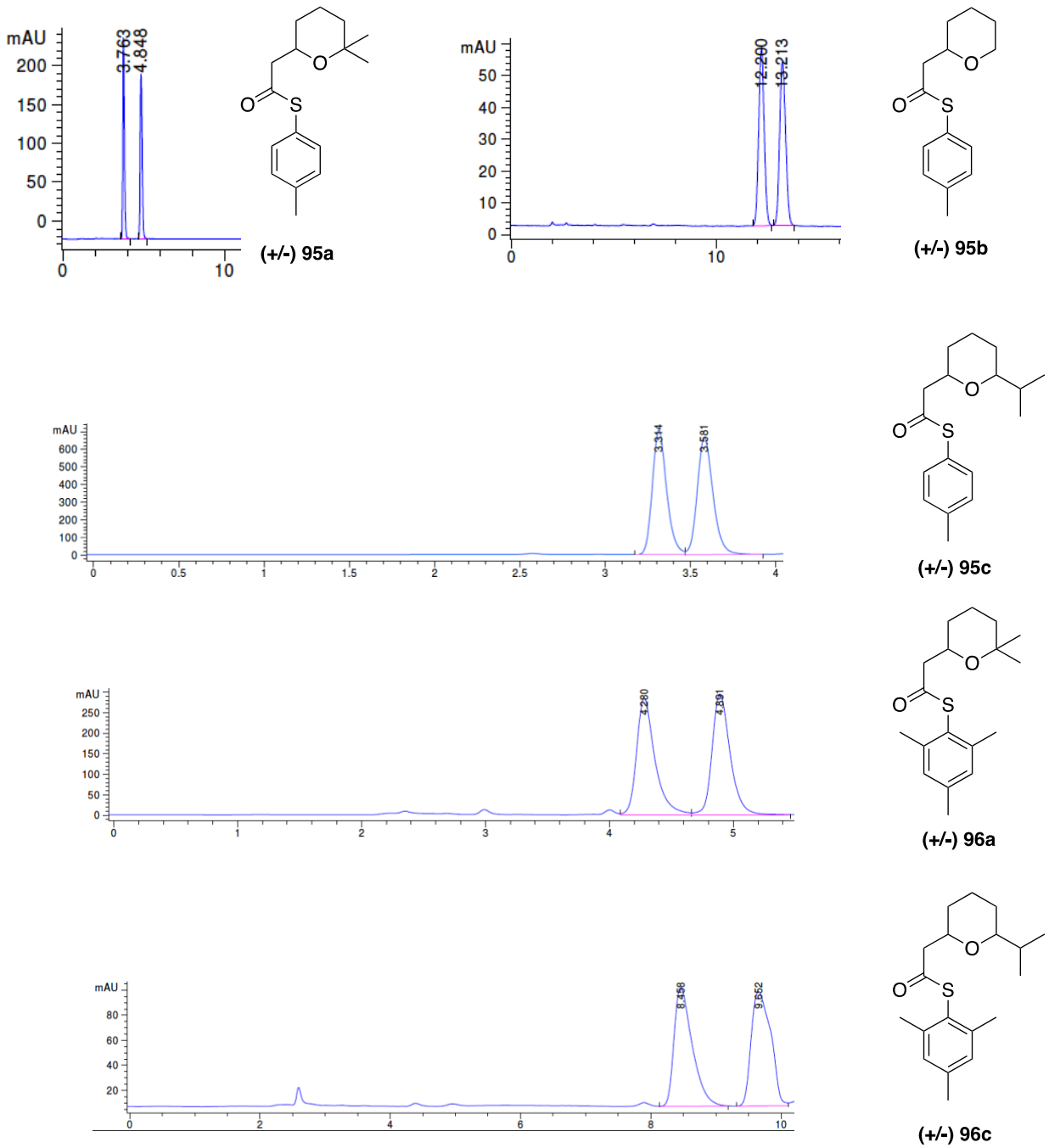


Figure 4- HPLC traces of cyclised products **95** and **96**.

Based on the Brønsted acid catalyzed cyclisations of precursors **82** and **89**, it was observed that the amount of acid used had little effect on conversion and that there was no marked improvement in the conversion. This could be attributed to the lower reactivity of thioesters, compared to ketones, to acid cyclisation due to lower activation of the Michael acceptor. Another factor could be the rate of cyclisation itself, which is a 6-exo-trig cyclisation here. It is known that 5-exo-trig cyclisations involving tetrahydrofurans are faster than the 6-exo-trig cyclisations involving tetrahydrofurans. It can thus be reasoned that the conversions of the corresponding tetrahydrofuran precursors under the conditions tested should be better than the tetrahydropyran precursors **82** and **89**. To this end, the synthesis of the corresponding tetrahydrofuran precursors was attempted.

8.4 Synthesis of Tetrahydrofuran Precursors.

The synthesis of the tolyl tetrahydrofuran precursors followed the same strategy as the tetrahydropyran precursors. The synthesis began with the preparation of the corresponding alcohols **97.** The alcohols **97a** and **97c** were synthesized while **97b** was commercially available **(Figure 5**).

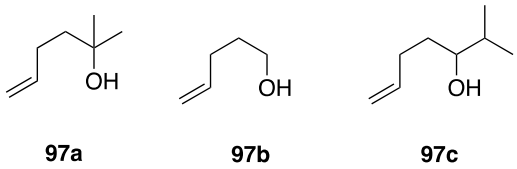
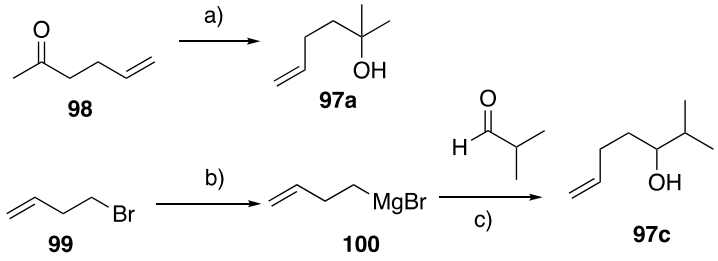


Figure 5- Structures of alcohol **97**

The forward synthetic route to the tetrahydrofuran precursors began with the synthesis of the alcohols **97a** [39] and **97c**[30], analogous to literature procedures **(Scheme 2.7)**.

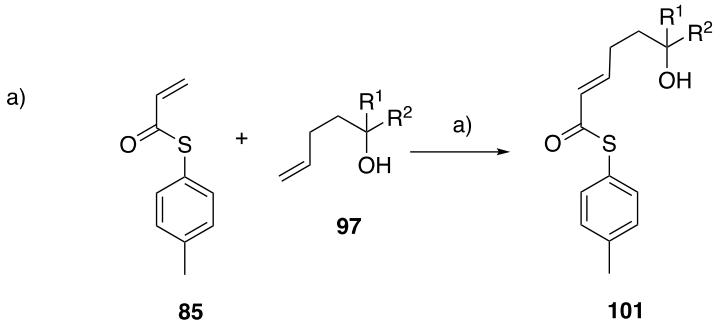


Reagents and conditions: a) MeMgBr/Et_2O, rt, 1 h (39%) b) Mg/THF, rt, 2.5 h c) rt, 2 h (49%)

Scheme 2.7- Synthesis of alcohols **97**

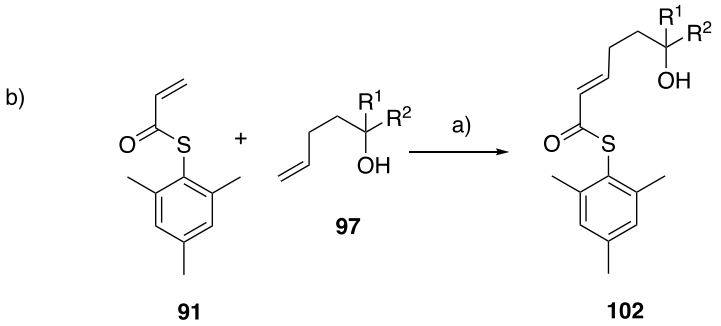
The synthesis of both **97a** and **97c** occurred smoothly with a yield of 39% and 49% respectively. The synthesis of the tolyl cyclisation precursor **101** was first attempted. The metathesis between the

alcohols **97** and thioacrylate **85** was carried using similar conditions as the tetrahydropyran precursors **(Scheme 2.8)**. The metathesis occurred smoothly with similar times for all three precursors and were obtained as brown oils with excellent yields **(Scheme 2.8a)**. Similarly, the synthesis of the mesityl precursors **102** was attempted. Using mesitylthioacrylate **91**, the Grubbs metathesis between alcohols **97** and the mesitylthioacrylate **91** was carried out under the same conditions. The synthesis was smooth and the mesityl precursors **102** were made with good to excellent yields **(Scheme 2.8b)**. The yields were comparable to the tolyl precursors, with **102a** and **102b** having a yield of 88% and 82% respectively. The synthesis of the isopropyl precursor **102c** was not attempted.



Reagents and conditions: a) HG-II (10 mol%), CuI (10%), Et_2O, reflux

Reaction	Alcohol	R	Cyclisation precursor	Time (h)	Yield (%)
Entry 1	**97a**	$R^1 = R^2 =$ Me	**101a**	20	87
Entry 2	**97b**	$R^1 = R^2 =$ H	**101b**	18	79
Entry 3	**97c**	$R^1 =$ H; $R^2 =$ i-Pr	**101c**	16	74



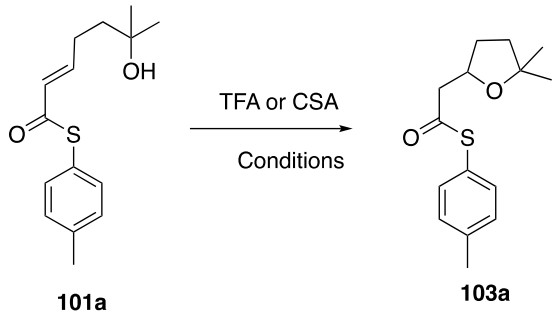
Reagents and conditions: a) HG-II (10 mol%), CuI (10%), Et_2O, reflux

Reaction	Alcohol	R	Cyclisation precursor	Time (h)	Yield (%)
Entry 1	**97a**	$R^1 = R^2 =$ Me	**102a**	18	88
Entry 2	**97b**	$R^1 = R^2 =$ H	**102b**	18	82

Scheme 2.8 – Synthesis of cyclisation precursors **101** and **102**.

8.5 Brønsted acid Catalyzed Cyclisation of Tetrahydrofuran Precursors.

The general scheme for the Brønsted acid catalyzed cyclisation involves the use of TFA or CSA as acids. The cyclisation of tolyl precursors **101a** to generate 2,6 disubstituted tetrahydrofuran **103a** was first attempted **(Scheme 2.9)**.



Scheme 2.9 – Cyclisation of **101a** under acid conditions

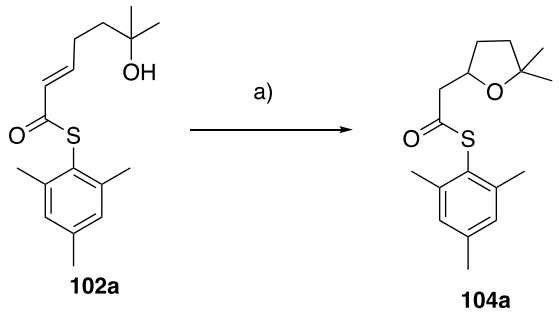
Reaction	Solvent	Temperature (^{0}C)	Time (h)	(TFA: H_2O) (mL)	Conversion (%)
Entry 1	DCM	rt	24	1.8:0.2	6
Entry 2	DCE	50	24	0.9:0.1	68
Entry 3	DCE	50	24	1.8:0.2	37
Entry 4	DCE	50	24	3.6:0.4	38
Entry 5$^{\perp}$	DCE	50	24	9:1	46
Entry 6$^{\perp}$	DCE	50	24	neat	93
Entry 7$^{\perp}$	DCE	50	24	1:1	4

$\perp$ solvent evaporated before addition

Table 4 – Cyclisation of **101a** under TFA conditions

The first cyclisation attempted was the TFA catalyzed cyclisation of **101a**.The precursor concentration for all cyclisations was kept at standard of 0.06 M. The TFA used was also 0.06 M and the ratio of TFA and H_2O was maintained 9:1. The total amount of TFA and H_2O were scaled up accordingly **(Table 4)**. Unlike the tolyl tetrahydropyran precursor **82a**, the cyclisation at room temperature was attempted with 1.8 mL of TFA. This gave very little conversion and the separation was not clean, with a lot of grease accompanying the product **(entry 1)**. Reverting back to using 0.9 mL of TFA, the solvent was switched to DCE and the reaction was carried out at 50 ^{0}C. Interestingly, a drastic increase in

conversion (68%) was observed **(entry 2)**. The next parameter that could be altered was the amount of TFA and H_2O. The amount was then doubled **(entry 3)** and quadrupled **(entry 4)** with respect to **entry 2**. However, the conversion (37%) in **entry 3** almost halved and remained the same (38%) for **entry 4** with respect to **entry 2**, in spite of increasing the amount of TFA and H_2O**.** The next parameter to change was the amount of solvent. It appears that the cyclisation was unaffected by the amount of acid. The next parameter to change was the amount of solvent. In effect, by removing the solvent, the effective concentration of the precursor increases. To alter this, a 0.06 M solution of the substrate in DCM was prepared and the solvent was evaporated before addition of the acid. To this, TFA and H_2O were added in a ratio of 9:1 (1 mL combined) and reacted. However, there was only a marginal increase in the conversion (46%) **(entry 5)**. When the reaction was carried out neat i.e. without the presence of H_2O, the conversion (93%) doubled **(entry 6)** with respect to **entry 5**. Finally, TFA and H_2O were added in a 1:1 ratio (1 mL combined) after evaporating DCM. Interestingly, a similar result as the room temperature condition of poor conversion and purification was observed **(entry 7) [Table-4]**. The cyclisation of **101a** was then attempted using CSA, under similar conditions as the toll tetrahydropyran precursor **82a**. In the reaction, CSA was used in 3 eq and the cyclisation was carried out at 80 ^{0}C for 24 h. It was observed that the conversion (97%) was near quantitative.



102a **104a**

Reagents and conditions: a) TFA (1.8 mL)/ H_2O (0.2 mL), DCE, 50 ^{0}C, 24 h (68%)

Scheme 2.10- Cyclisation of **102a** under TFA conditions.

The cyclisation of mesityl precursors **102** to generate 2,6 disubstituted tetrahydropyrans **104** was then attempted **(Scheme 2.10)**. Observing that when H_2O was present, the amount of TFA and H_2O used had no effect on the conversion, it was decided that a screen similar to the tolyl precursors **101** would not be undertaken. Instead, it was decided that one set of conditions would be chosen to prepare the racemic samples needed for HPLC analysis. To this effect, the cyclisation of **102a** at 50 ^{0}C in DCE, using TFA/ H_2O (1.8 mL : 0.2 mL) and a precursor concentration of 0.06 M was carried out. The conversions for **102a** was 77%.

With the synthesis of cyclized products **103a** and **104a** complete, attempts were made to resolve the enantiomers of the racemic mixtures**.** Similar HPLC conditions as the tetrahydropyran precursors **95** and **96** were employed, using the CHIRALCEL AD-H column as before. The cyclisation products **103a** and **104a** were resolved **(Figure 6) [Table 5]**.

Cyclisation Product	(Hexane:IPA)	Peak 1 (min)	peak 2 (min)	Flowrate (mL/min)
103a	97/3	15.319	16.966	0.9
104a	95/5	4.983	5.866	0.9

Table 5- HPLC retention times of cyclised products **103a** and **104a.**

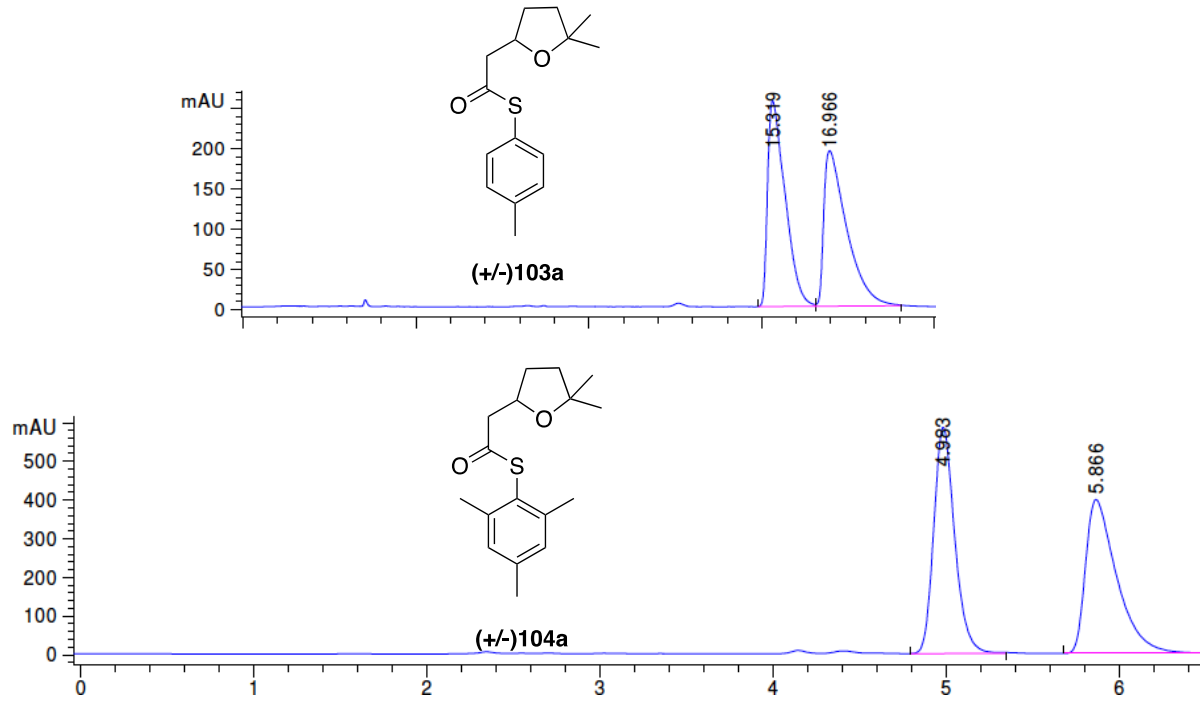
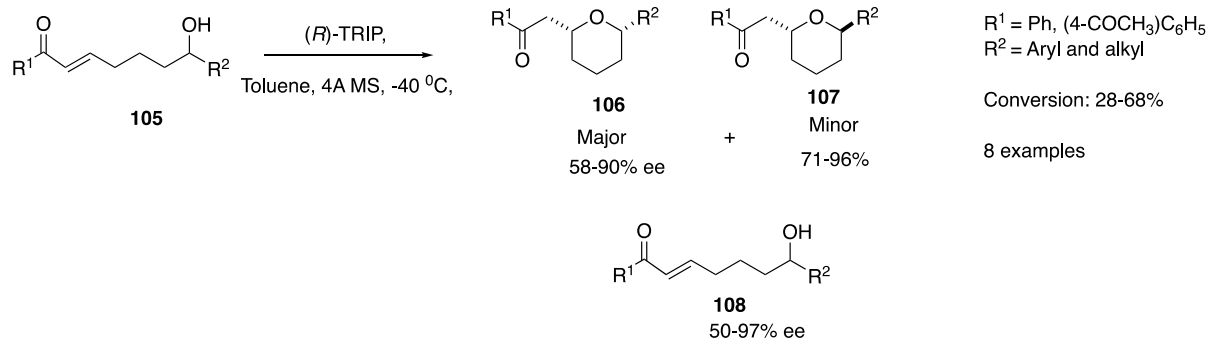


Figure 6- HPLC traces of cyclised products **103a** and **104a.**

Comparing the Brønsted acid mediated cyclisation trends between the tetrahydropyran precursor **82a** and **101a**, the anticipated improvement in conversion of a tetrahydrofuran precursor **101a** with respect to the tetrahydropyran precursor **82a** was not found**.** It was found that the amount of acid had only a marginal effect on conversion. Clarke's conditions [36] were concluded to be suboptimal for carrying out asymmetric cyclisations and there was a need for different conditions. This was affirmed by the fact that increasing the polarity of the solvent from DCE to the use of TFE and HFIP had no

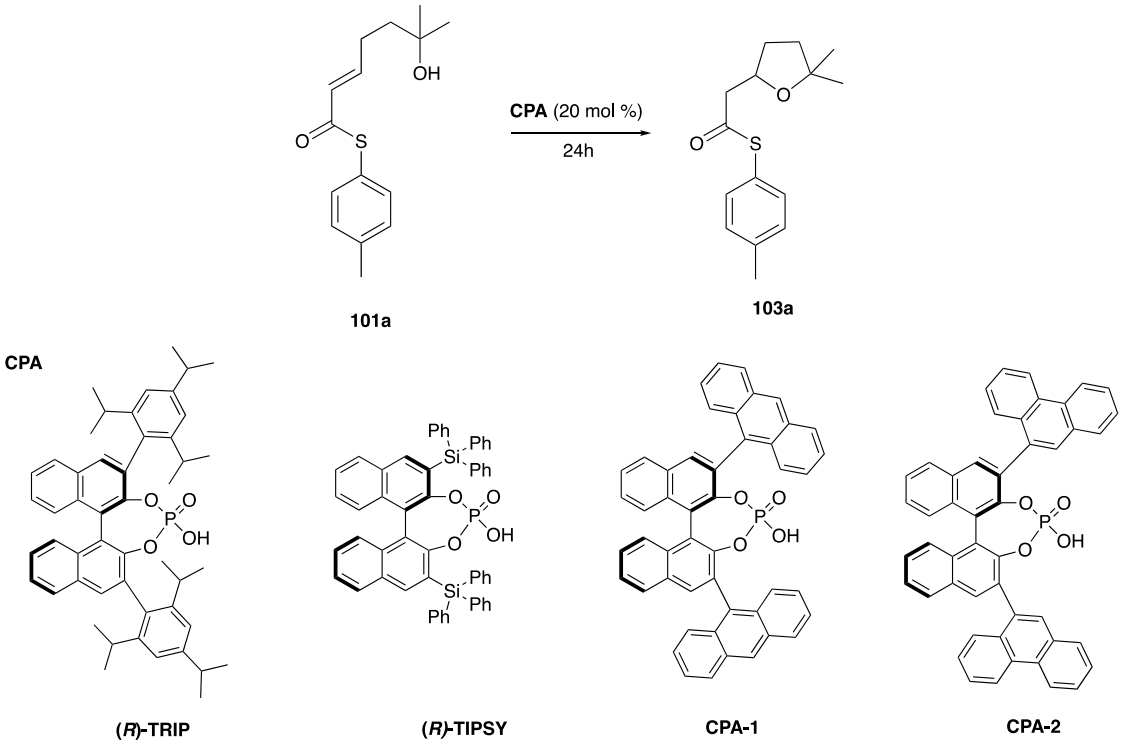
improvement on conversion **[Table1]**. The reason we increased polarity was the assumption that a more polar solvent might stabilize the transition state of a chiral Brønsted acid catalyzed cyclisation. This pointed to the possible important role the solvent might play in the asymmetric cyclisation. Given that increase in polarity didn't improve conversion, we hypothesized that a decrease in polarity might just improve it. Upon a literature search, we came across the enantioselective synthesis of 2,6-*cis* tetrahydropyrans using a chiral phosphoric acid via an oxa-Michael cyclisation reported by Yoneda **(Scheme 2.11)**. [40] In his study, he carried out novel asymmetric cycloetherification, which was then accompanied by the kinetic resolution of secondary and tertiary alcohols to synthesise tetrahydropyrans bearing two chiral centers with excellent enantioselectivities and high s-factors.



Scheme 2.11- Kinetic resolution of secondary alcohols

What interested us was the use of toluene to achieve such high enantioselectivities. This indicated that our reasoning was in the right direction and we hypothesized that the use of solvents with similar or lower polarity and dielectric constant to that of toluene would enhance enantioselectivities in an asymmetric cyclisation. The dielectric constant of toluene is 2.38. To this end, solvents with dielectric constants similar to or lower than toluene were chosen-1,4-dioxane (2.21) and cyclohexane (2.02). An important thing to note in the paper was the presence of the α,β-unsaturated ketone functionality in all the substrates. This has a higher reactivity towards cyclisation compared to thioesters, and hence the reaction occurred at very low temperatures. The substrate scope was limited to only α,β-unsaturated aryl ketones. We wanted to employ these conditions to the chiral Brønsted acid catalyzed cyclisation of the thioester precursors which are more versatile than α,β-unsaturated ketones as they can be converted to other functional groups.[17,27] Reasoning that the cyclisation involving tetrahydrofuran precursors **101** and **102** might be faster than tetrahydropyran precursors **82** and **89**, we felt that the chiral Brønsted acid catalyzed cyclisation of the tetrahydrofuran precursors **101** and **102** might be a good place to start**.**

8.6 Chiral Brønsted Acid Catalyzed Cyclisation of Tetrahydrofuran Precursors.



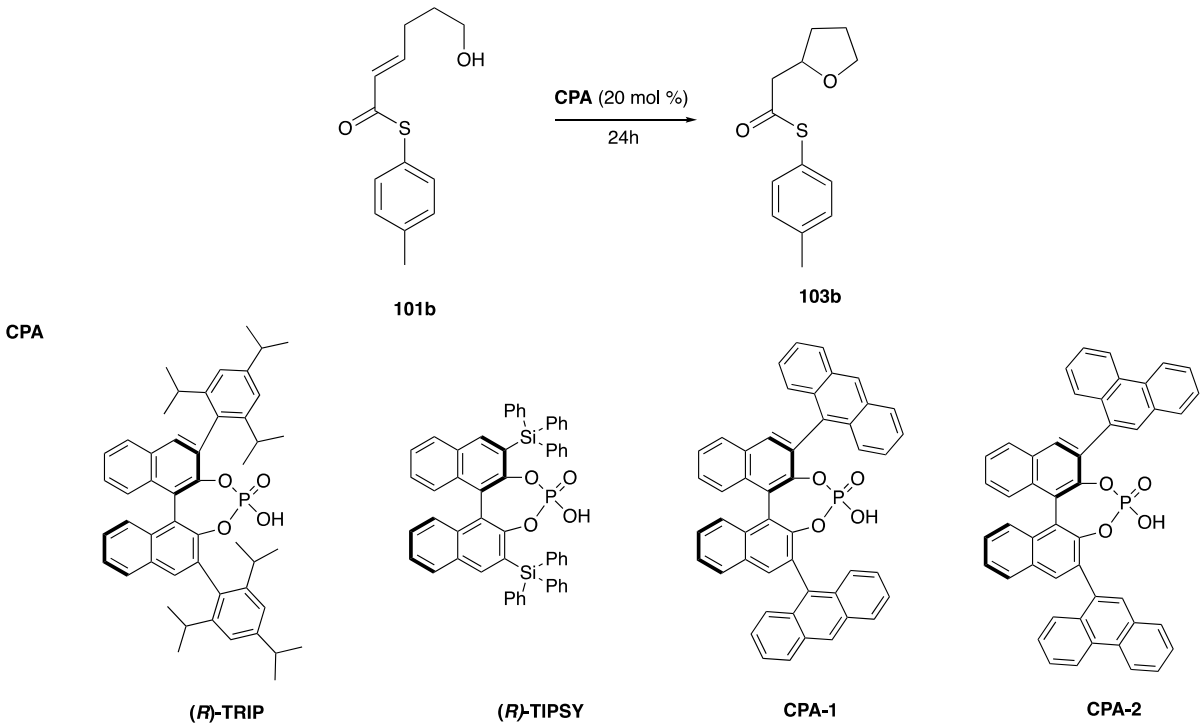
Scheme 2.12– Chiral Brønsted Acid Catalyzed Cyclisation of **101a** using **CPA**.

	Temperature (^{0}C)	**Solvent**	**Catalyst**	**Conversion (%)**	ee (%)
Entry 1	rt	DCM	(*R*)-TRIP	11	29
Entry 2	rt	1,4-Dioxane	(*R*)-TRIP	-	14
Entry 3	rt	Toluene	(*R*)-TRIP	10	26
Entry 4	rt	Cyclohexane	(*R*)-TRIP	18	43
Entry 5	50	Toluene	(*R*)-TRIP	74	42
Entry 6	50	Cyclohexane	(*R*)-TRIP	99	45
Entry 7	75	Cyclohexane	(*R*)-TRIP	99	46
Entry 8	50	Cyclohexane	(*R)*-TIPSY	89	60
Entry 9	50	Cyclohexane	CPA-1	99	15
Entry 10	50	Cyclohexane	CPA-2	12	3
Entry 11	50	Toluene	CPA-2	6	3

Table 6– Chiral Brønsted Acid Catalyzed Cyclisation of **101a** using **CPA**.

We began with the investigation of the chiral Brønsted acid catalyzed cyclisation of **101a**. An initial solvent, catalyst and temperature screen was first undertaken using (***R*)-TRIP**, (***R*)-TIPSY**, **CPA-1** and **CPA-2**. The temperature was varied from room temperature to 50 ^{0}C and subsequently 75 ^{0}C and a catalyst loading of 20 mol% was chosen. The initial precursor concentration was maintained at

0.06 M **(Scheme 2.12)**. The initial solvent screen involving the chosen solvents was attempted at room temperature and was compared to that involving DCM. As expected, the conversion (11%) was low with DCM and the ee was 29% **(entry 1)**. The reaction in dioxane produced multiple products and the conversion could not be ascertained. However, the ee (14%) was observed to decrease by half **(entry 2)**. Interestingly, the conversion (10%) and ee (26%) in toluene **(entry 3)** was similar to that of **entry 1**. Finally, in cyclohexane, an improvement in the ee (43%) was observed **(entry 4).** The cyclisation was then attempted at 50 ^{0}C, to increase the conversion. In toluene, there was a significant improvement in the conversion (74%), and no reduction in the ee (42%) **(entry 5)**. Switching to cyclohexane, a quantitative conversion (99%) was observed and the ee (40%) was maintained **(entry 6)**. Increasing the temperature to 75 ^{0}C in cyclohexane had no demonstrative effect, with the ee (46%) remaining essentially the same **(entry 7)**. This was a surprising result, as one would expect the %ee to drop with increase in temperature. When (*R*)-TRIP was replaced with (*R*)-TIPSY in cyclohexane, there was a slight drop in conversions (99% to 89%). Interestingly, there was an increase in the ee (60%) **(entry 8)**. In the case of **CPA-2**, the conversion (99%) improved by 10%, but the ee (15%) dropped by 75% compared to (*R*)-TIPSY **(entry 9)**. Finally, **CPA-3** was used and found to have solubility issues in cyclohexane, giving a very poor conversion (12%) and rendering the product essentially racemic **(entry 10)**. On using toluene, conversion (6%) dropped by half with no improvement of the ee **(entry 11)**. The best conditions were determined to be using (*R*)-TIPSY in cyclohexane at 50 ^{0}C which gave a 60% ee **[Table 6]**.



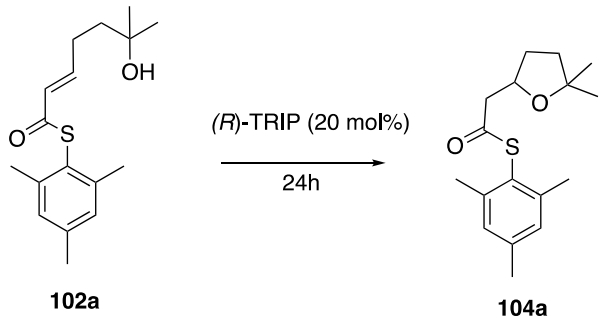
Scheme 2.13– Chiral Brønsted Acid Catalyzed Cyclisation of **101b** using **CPA.**

	Temperature (^{0}C)	Solvent	Catalyst	Conversion (%)	ee (%)
Entry 1	rt	Cyclohexane	(*R*)-TRIP	10	10
Entry 2	50	Cyclohexane	(*R*)-TRIP	80	33
Entry 3	75	Cyclohexane	(*R*)-TRIP	97	40
Entry 4	50	Cyclohexane	(*R*)-TIPSY	60	14
Entry 5	50	Cyclohexane	CPA-1	81	2
Entry 6	50	Cyclohexane	CPA-2	6	24
Entry 7	50	Toluene	CPA-2	7	1

Table 7– Chiral Brønsted Acid Catalyzed Cyclisation of **101b** using **CPA**

Next, the cyclisation of **101b** was investigated **(Scheme 2.13**). Seeing that cyclohexane and toluene gave better results than 1,4-dioxane and owing to multiple products generated in it, its use was discontinued. At room temperature, the conversion (10%) in cyclohexane was very low with only a 10% ee **(entry 1)**. Upon increasing the temperature to 50 ^{0}C, a marked improvement in the conversion (80%) was observed and the ee was 33% **(entry 2)**. At 75 ^{0}C, a near quantitative conversion (97%) was observed **(entry 3)**, but the ee (40%) improved only marginally compared to **entry 2**. Interestingly, (*R*)-TIPSY resulted in a decrease in the conversion (60%) **(entry 4)** and a marked decrease in the ee (14%) compared to **entry 2**. When, **CPA-1** was used, the product was essentially racemic **(entry 5)**, but improvements in the conversion (81%) was observed. Finally, **CPA-2** was used and found to have solubility issues in cyclohexane and difficulty in purification, giving a poor conversion (6%). But an improvement in the ee (24%) **(entry 6)**. On using toluene instead of cyclohexane for **CPA-2**, similar issues as **entry 6** were faced and the product was essentially racemic **(entry 7) [Table 7]**.

With the investigation into the chiral acid catalyzed cyclisation of tolyl tetrahydrofuran precursors **101**, completed, to focus was shifted to the asymmetric cyclisation of the mesityl tetrahydrofuran precursors **102**. The choice of solvent was restricted to cyclohexane, as it gave the highest conversions and ee. The choice of catalyst was restricted to (*R*)-TRIP.



102a **104a**

Scheme 2.14 – Chiral Brønsted Acid Catalyzed Cyclisation of **102a** using (*R*)-TRIP

	Temperature (^{0}C)	Solvent	Conversion (%)	ee (%)
Entry 1	rt	Cyclohexane	23	14
Entry 2	50	Cyclohexane	98	31
Entry 3	75	Cyclohexane	98	21

Table 8 – Chiral Brønsted Acid Catalyzed Cyclisation of **102a** using (*R*)-TRIP.

The chiral Brønsted catalyzed cyclisation of **102a** using (R)-TRIP in cyclohexane was investigated **(scheme 2.14)**. At room temperature, the conversion (23%) was low with only a 14% ee **(entry 1)**. Upon increasing the temperature to 50 ^{0}C, a near quantitative conversion (98%) was observed and the ee more than doubled to 31% **(entry 2)**. However, increasing the temperature to 75 ^{0}C, decreased the ee (21%), but maintained the conversion (98%) **(entry 3) [Table 8]**.

102b **104b**

Scheme 2.15 – Chiral Brønsted Acid Catalyzed Cyclisation of **102b** using (*R*)-TRIP.

	Temperature (^{0}C)	Solvent	Conversion (%)	ee (%)
Entry 1	rt	Cyclohexane	9	10
Entry 2	50	Cyclohexane	89	10
Entry 3	75	Cyclohexane	95	4

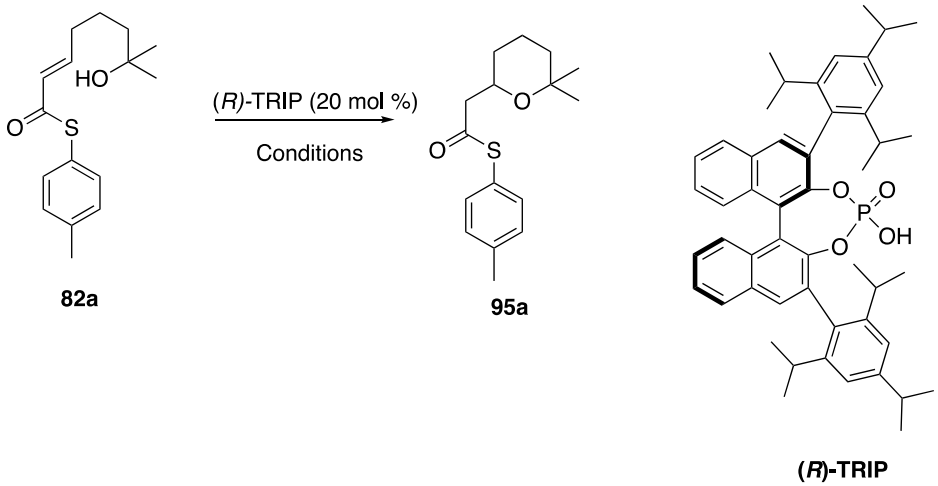
Table 9 – Chiral Brønsted Acid Catalyzed Cyclisation of **102b** using (*R*)-TRIP.

Finally, the chiral Brønsted catalyzed cyclisation of **102b** using (*R*)-TRIP in cyclohexane was investigated **(Scheme 2.15)**. At room temperature, the conversion (9%) and ee (10%) were low **(entry 1)**. Upon increasing the temperature to 50 ^{0}C, a 10-fold increase in the conversion (89%) was observed but it had no effect on the ee (10%) **(entry 2)**. However, increasing the temperature to 75 ^{0}C, gave a near quantitative conversion (95%) but the product was essentially racemic. **(entry 3) [Table 9]**.

The asymmetric cyclisation of precursors **101** and **102** confirms that the role played by the solvent is crucial to the enantioselectivity. It reinforces our hypothesis that solvents with lower dielectric

constants improve the conversion and enantioselectivity to a large extent. The best conditions were found to be using (*R*)-TRIP in cyclohexane at 50 ^{0}C. The conversions are now almost quantitative, and the ee doesn't decrease with increase in temperature. This concludes the asymmetric cyclisation of tetrahydrofuran precursors **101** and **103**. The main conclusion that could be drawn from this study is the role of the solvent in asymmetric cyclisation of tetrahydrofuran precursors **101** and **103**, and that this hypothesis would be further reinforced if a similar trend (increase in conversion and ee with a decrease in polarity of the solvent) was observed in the asymmetric cyclisation of tetrahydropyran precursors **82** and **89**. To this end, the chiral Brønsted acid catalyzed cyclisation of tetrahydropyran precursors **82** and **89** was investigated.

8.7 Chiral Brønsted Acid Catalyzed Cyclisation of the Tetrahydropyran Precursors



Scheme 2.16 – Chiral Brønsted Acid Catalyzed Cyclisation of **82a** using (*R*)-TRIP.

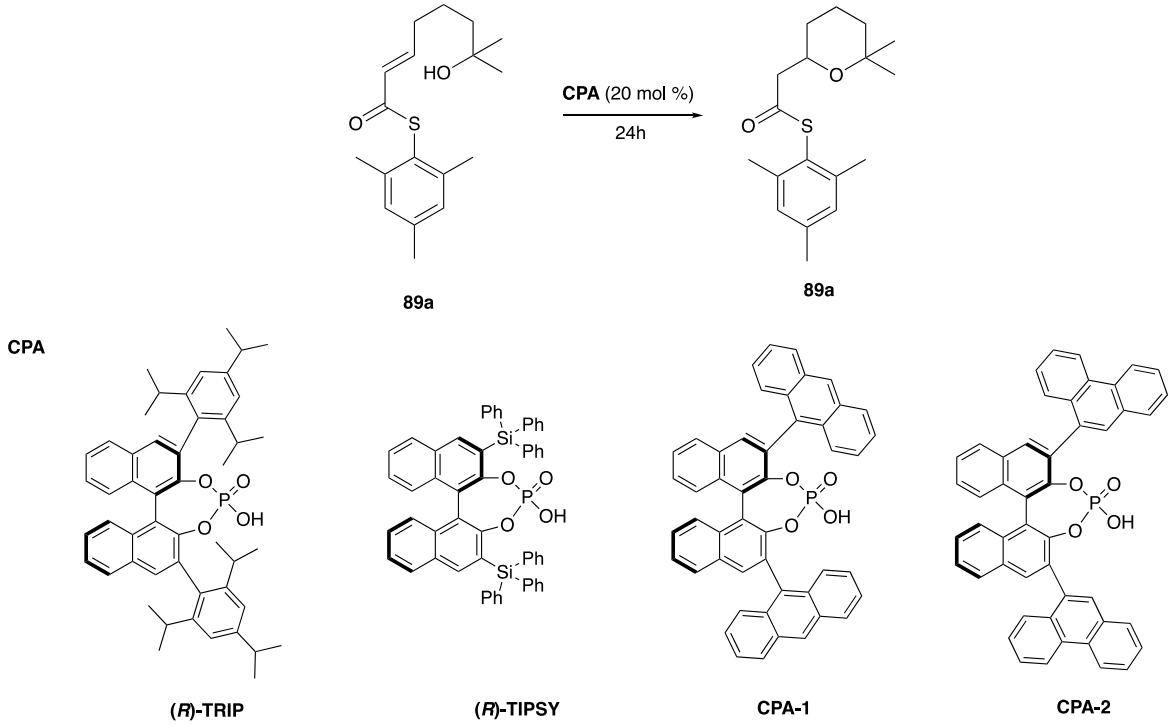
The chiral Brønsted acid catalyzed cyclisation of **82a** was attempted first. The catalyst of choice was (*R*)-TRIP, with a catalyst loading of 20 mol%. The concentration of the precursor was maintained at 0.06 M **(Scheme 2.16)**. To test our hypothesis about the effect the polarity of the solvent had on conversion and ee, initial cyclisations focused on more polar solvents. Initial attempts were carried out at room temperature in DCM. As expected, the conversion (9%) was low and the product was essentially racemic (3% ee). Reasoning that H_2O was present in the TFA mediated cyclisation of **82a**, it was added at a 5% loading to see if it played any role in the cyclisation. The cyclisation appeared to have shut off, with no observed conversion even after 96 h. The cyclisation was then attempted in less polar solvents like toluene and cyclohexane **[Table 10]**.

	Temperature (^{0}C)	Solvent	Conversion (%)	ee (%)
Entry 1	rt	Toluene	6	-
Entry 2	50	Toluene	30	13
Entry 3	50	Cyclohexane	77	18

Table 10- Chiral Brønsted Acid Catalyzed cyclisation of **82a** using (*R*)-TRIP.

An initial attempt at room temperature in toluene gave a very low conversion (6%) and the product was essentially racemic **(entry 1)**. On raising the temperature to 50 ^{0}C, there was a marked improvement in conversion (31%) with the %ee of 13% **(entry 2)**. Finally, toluene was replaced with cyclohexane, and as expected, the conversion improved to 77%. However, there was only a marginal improvement in the ee (18%) **(entry 3) [Table 10]**. While the conversions improved markedly in less polar solvents, the ee was poor. Due to this, the focus shifted to the chiral Brønsted acid catalyzed cyclisation of mesityl precursors **89a** and **89b**.

With the choice of cyclohexane and toluene as solvents, a catalyst and temperature screen was decided to be undertaken. The catalysts screened involved (***R*)-TRIP**, (***R*)-TIPSY**, **CPA-1** and **CPA-2**. The temperature at which the reactions were carried out at were room temperature, 50 ^{0}C and subsequently 75 ^{0}C. The initial precursor concentration was maintained at 0.06 M. Initially, cyclisation of **89a** was carried out **(Scheme 2.17)**.



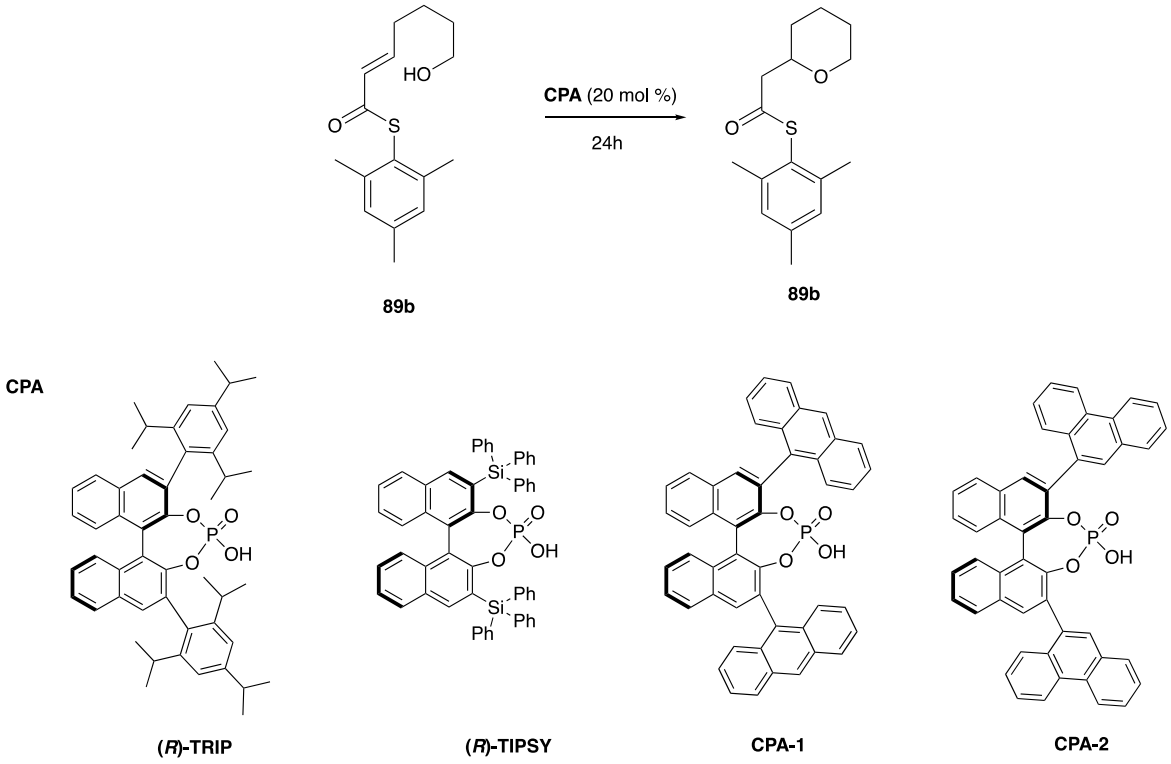
Scheme 2.17– Chiral Brønsted Acid Catalyzed Cyclisation of **89a** using **CPA**

	Temperature (^{0}C)	Solvent	CPA	Conversion (%)	ee (%)
Entry 1	rt	Toluene	(*R*)-TRIP	10	10
Entry 2	50	Toluene	(*R*)-TRIP	69	60
Entry 3	75	Toluene	(*R*)-TRIP	97	61
Entry 4	rt	Cyclohexane	(*R*)-TRIP	10	44
Entry 5	50	Cyclohexane	(*R*)-TRIP	96	69
Entry 6	75	Cyclohexane	(*R*)-TRIP	100	66
Entry 7	50	Cyclohexane	(*R*)-TIPSY	23	40
Entry 8	50	Cyclohexane	CPA-1	96	21
Entry 9	50	Cyclohexane	CPA-2	3	2
Entry 10	50	Toluene	CPA-2	4	12

Table 11– Chiral Brønsted Acid Catalyzed Cyclisation of **89a** using CPA.

Initial attempts at room temperature in toluene gave poor conversion (10%) and ee (10%) **(entry 1)**.The reaction was then carried out at 50 ^{0}C. Interestingly, the conversion improved (69%) and there was a marked improvement to the ee (60%) **(entry 2)**. Finally, the cyclisation was done at 75 ^{0}C. A near quantitative conversion (97%) was observed with the ee (61%) essentially unchanged **(entry 3)**. This was an interesting result as the enantioselectivity was independent of temperature, contrary to the expectation that it would decrease. It was reasoned that the energetic barrier to induce erosion of enantioselectivity must be higher for the mesityl precursor compared to the tolyl one, and could explain the poor enantioselectivities of the tolyl precursors at higher temperatures. The solvent was changed to cyclohexane and the experiments were repeated at these three temperatures. A marked increase in the %ee (10% to 42%) was observed at room temperature **(entry 4)** compared to **entry 1**. At 50 ^{0}C, the conversion was near quantitative (96%) **(entry 5)** and there was a marginal increase in ee (60% to 69 %) compared to **entry 2**. At 75 ^{0}C, the conversion was quantitative **(entry 6)** but the ee only slightly improved (61% to 66 %) compared to **entry 3**. As the increase in temperature had no marked effect of the ee, the catalyst screen was carried out at 50 ^{0}C using cyclohexane. When (*R*)-TRIP was replaced with (*R*)-TIPSY, there was a significant drop in conversion (96% to 23%) **(entry 7)** and the ee markedly decreased (69% to 40%) in comparison to **entry 5**. In the case of **CPA-1**, the conversion (96%) were similar to **entry 5**, but a drastic fall in ee (69% to 21%) was observed **(entry 8)**. Finally, **CPA-2** was used and found to have solubility issues in cyclohexane, giving very poor conversion (3%) and rendering the product essentially racemic **(entry 9)**. On replacing cyclohexane with toluene, there was no change in conversion (4%) **(entry 10)** and only a marginal improvement in ee (4% to 12 %) with respect to **entry 9** was observed**.** The best conditions were determined to be using (*R*)-TRIP in

cyclohexane at 50 ^{0}C to give a 69% ee **[Table 11]**. The fluctuations in the %ee at 50 ^{0}C and 75 ^{0}C are down to errors in measurement.



Scheme 2.18– Chiral Brønsted Acid Catalyzed Cyclisation of **89b** using **CPA**.

	Temperature (^{0}C)	**CPA**	**Solvent**	**Conversion (%)**	**ee (%)**
Entry 1	50	(*R*)-TRIP	Cyclohexane	98	44
Entry 2	50	(*R*)-TIPSY	Cyclohexane	56	58
Entry 3	50	CPA-1	Cyclohexane	83	5
Entry 4	50	CPA-2	Cyclohexane	11	1
Entry 5	50	CPA-3	Toluene	7	5

Table 12– Chiral Brønsted Acid Catalyzed Cyclisation of **89b** using **CPA**.

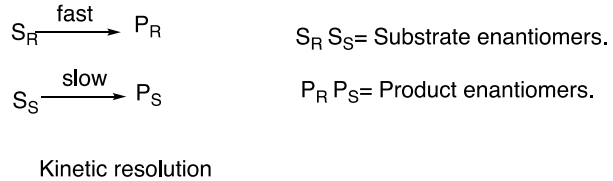
Using these conditions, the cyclisation of **89b** was investigated **(Scheme 2.18**). Starting with (*R*)-TRIP, a near quantitative conversion (98%) was observed and the ee was 44% **(entry 1)**. Interestingly, *(R)*-TIPSY gave a lower conversion (56%) but showed a marked improvement in the ee (58%) compared to (*R*)-TRIP **(entry 2)**. However, when **CPA-1** was used, there was a sharp dip in ee (44% to 5%) compared to (*R*)-TRIP, while a marginal dip in the conversion (98% to 83%) was observed **(entry 3)**. Finally, **CPA-2** was used and found to have solubility issues in cyclohexane, giving very poor conversion (11%) and the product formed was essentially racemic **(entry 4)**. On replacing cyclohexane with

toluene, only a marginal improvement in ee (5%) was observed **(entry 5) [Table 12]**. The general trend observed was that the best enantioselectivity was observed while using *(R)*-TRIP and that it was independent of temperature. Our hypothesis regarding solvent polarity was reinforced, with the cyclisation of the mesityl precursor **89a** in cyclohexane at 50 ^{0}C giving the best ee of 69%. Further, the trends indicated by the preliminary computation by Kristaps are observed. The ee of **82a** under these conditions is 18% while the ee of **89a** is 69%, confirming that the mesityl precursor **89a** is more enantioselective compared to the tolyl precursor **82a (Scheme 1.27b)**. With the best sets of conditions identified, we were now in a position to investigate the kinetic resolution of the tetrahydropyran and tetrahydrofuran precursors using *(R)*-TRIP as the chiral acid.

Among the tetrahydropyran precursors, the mesityl precursors **89** exhibited better enantioselectivities, in contrast to the tolyl precursors **101** among tetrahydrofurans. Hence, it was reasoned that the tolyl isopropyl tetrahydrofuran precursor **101c** and mesityl isopropyl tetrahydropyran precursor **89c** would be better suited for a kinetic resolution. It is known that under acidic conditions, the tetrahydropyran precursor **82c** gave predominantly *cis* products. [36] A similar behavior can be expected from the mesityl precursor **89c**. If that *cis*-selectivity holds for the tetrahydrofuran precursor **101c** as well, the kinetic resolution could be attempted for both **101c** and **89c** using (*R*)-TRIP as the catalyst in cyclohexane at 50 ^{0}C.

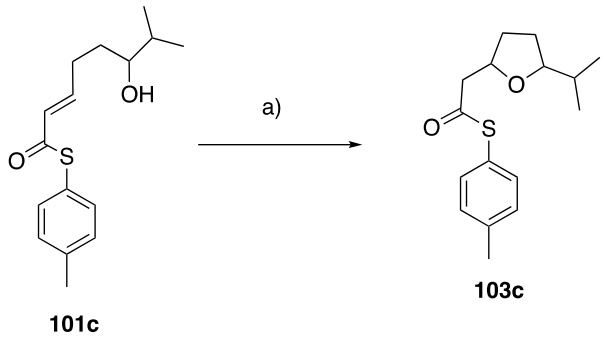
8.8 Kinetic Resolution of the Tetrahydropyran and Tetrahydrofuran Precursors

The synthesis of enantiomerically pure compounds is a major challenge in organic chemistry and various strategies have been devised to address this issue. An important process to address this issue is the kinetic resolution of racemates to generate enantiomerically enriched compounds. Kinetic resolution is a process in which one enantiomer interacts with a chiral catalyst and forms the product, *via* a diastereomeric transition state, faster than the other enantiomer. As a result, in an ideal reaction, the product and substrate are at 50% conversion. This is a classical kinetic resolution and the main drawback is that the maximum theoretical yield is 50%. **(Scheme 2.19)**. [41]



Scheme 2.19- A Classical Kinetic resolution

To the best of our knowledge, the only example of the enantioselective synthesis of 2,6-*cis* tetrahydropyrans using a chiral phosphoric acid via an oxa-Michael cyclisation and kinetic resolution was reported by Yoneda **(Scheme 2.11)**.[41] In his study, he carried out novel asymmetric cycloetherification, which was then accompanied by the kinetic resolution of secondary and tertiary alcohols to synthesise tetrahydropyrans bearing two chiral centers with excellent enantioselectivities and high s-factors. As there was α,β-unsaturated aryl ketone functionality in all the substrates, the substrate scope was limited and didn't include esters. To the best of our knowledge, no study has addressed the kinetic resolution of esters or thioesters. This calls for a much-needed focus into the resolution of esters and we believe that this kinetic resolution of **101c** and **89c** is a step in that direction. To ascertain if **101c** exhibited *cis*-selectivity under Brønsted acid conditions, the TFA catalyzed cyclisation of **101c** at 50 ^{0}C, using a 1.8 : 0.2 mL ratio of TFA and H_2O was attempted **(Scheme 2.20)**.



101c **103c**

Reagents and conditions: a) TFA (1.8 mL)/ H_2O (0.2 mL), DCE, 50 ^{0}C, 24 h (58%) (dr = 1.41:1)

Scheme 2.20 – Cyclisation of **101c** under TFA conditions

Unfortunately, an inseparable diastereomeric mixture (dr = 1.41:1) was obtained in 58% yield. It showed that the *cis* selectivity of tetrahydropyran precursors under these conditions doesn't hold for tetrahydrofuran precursors. The mixture was resolved by chiral HPLC and as expected, four peaks corresponding to the four stereoisomers were observed **(Figure 7)**. The major and minor peaks were identified. Taking the ratio between the area under the peaks, the dr was determined to be 1.4:1 and was in good agreement with the NMR **[Table 13]**. However, it was disappointing as the acid may have changed the diastereoselectivity as well. Consequently, attempts to kinetically resolve **101c** was abandoned.

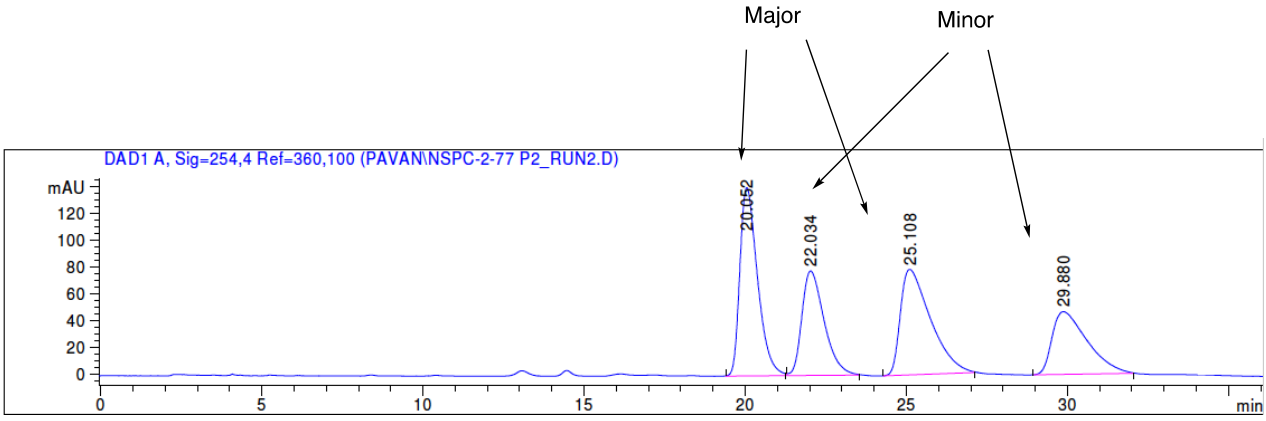
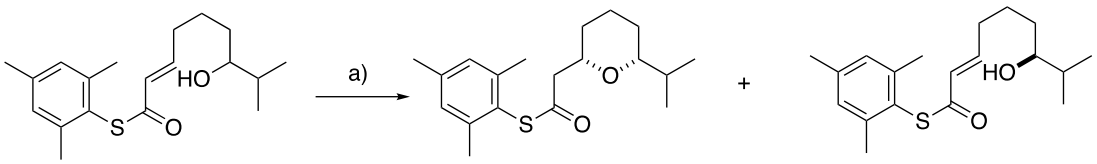


Figure 7 – HPLC trace of **101c**

	(Hexane:IPA)	Major isomer (min)	Area (%)	Minor isomer (min)	Area (%)	Flowrate (mL/min)	dr
101c	96/4	20.052	59	22.034	41	0.9	1.4:1
		25.108		29.880			

Table 13– HPLC data of **101c**

The kinetic resolution of **89c** was attempted using (*R*)-TRIP in cyclohexane at 50 ^{0}C. In the ideal resolution of the racemic mixture of **89c**, under these conditions, one enantiomer would convert completely to the corresponding 2,6-*cis* product **96c**, leaving behind enantioenriched starting material **89c (Scheme 2.21)**.



89c **96c** **89c**

Reagents and conditions: a) (*R*)-TRIP (20 mol%) , cyclohexane, 50 ^{0}C,

Scheme 2.21- Kinetic resolution of **89c**

Time (h)	Conversion (%)	Starting Material (SM) ee (%)	Product (P) ee (%)
0	0	0	0
1	13	17	80
2	32	36	90
3	39	54	91
4	48	67	93
5	47	78	91
6	52	85	91

Table 14- Conversion and ee of **P** and **SM**

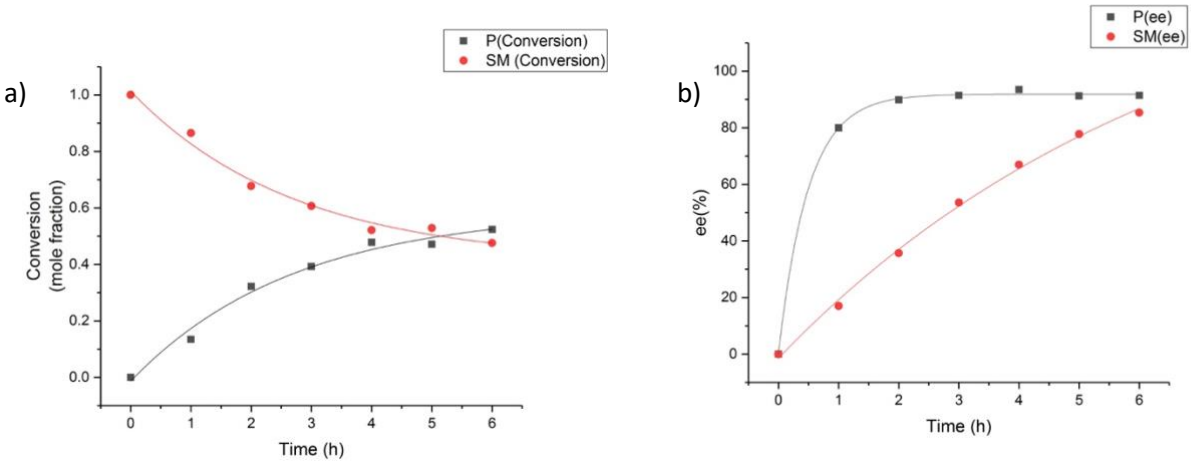


Figure 8- a) Conversion of P vs SM b) ee of P vs SM

To a 0.15 M solution of **89c**, (*R*)-TRIP (20 mol %) was added and heated at 50 ^{0}C. At regular intervals, aliquots (0.25 mL) were taken, dissolved in cyclohexane (0.25 mL) and quenched with Et_3N (0.2 mL). The aliquots were filtered through a silica pad and analysed by HPLC using an AD-H column (95:5 to 90:10 of Hexane:IPA). Triplicate measurements of each aliquot was undertaken and averaged. The formation of the product **(P)** and the consumption starting material **(SM)** was monitored by HPLC **(Figure 8a)**. The reaction was quenched when 52% of the starting material was consumed. The ee was simultaneously monitored and gave interesting observations. Rapid enantioenrichment of the product was observed after 1 h, with a massive jump in ee of the product from 0 to 80%. Simultaneously, the starting material enrichment improved gradually to 85% after 6 h. The apparent increase in conversion of the starting material at t = 4 h (48%) compared to t = 5 h (47%) was a wobble in the

baseline, which enhanced the integration of the starting material. This can be put down to an instrumental error **(Figure 8b) [Table 14]**. To confirm this observation, the quenched reaction mixture was purified and the product **96c** (10.0mg) and starting material **89c** (2.9mg) were isolated. The ee of the cyclized product **96c** should correspond to 91% and the starting material **89c** to 85%. To our delight, the ee of the product (96%) and starting material (95%) were within experimental error **[Table 15]**. This was compared to the corresponding racemic products **(Figure 9)**. The NMR of enriched **96c** matched that of the racemic mixture **82c**, indicating that the product **96c** is predominantly *cis* and that no *trans* product was observed.

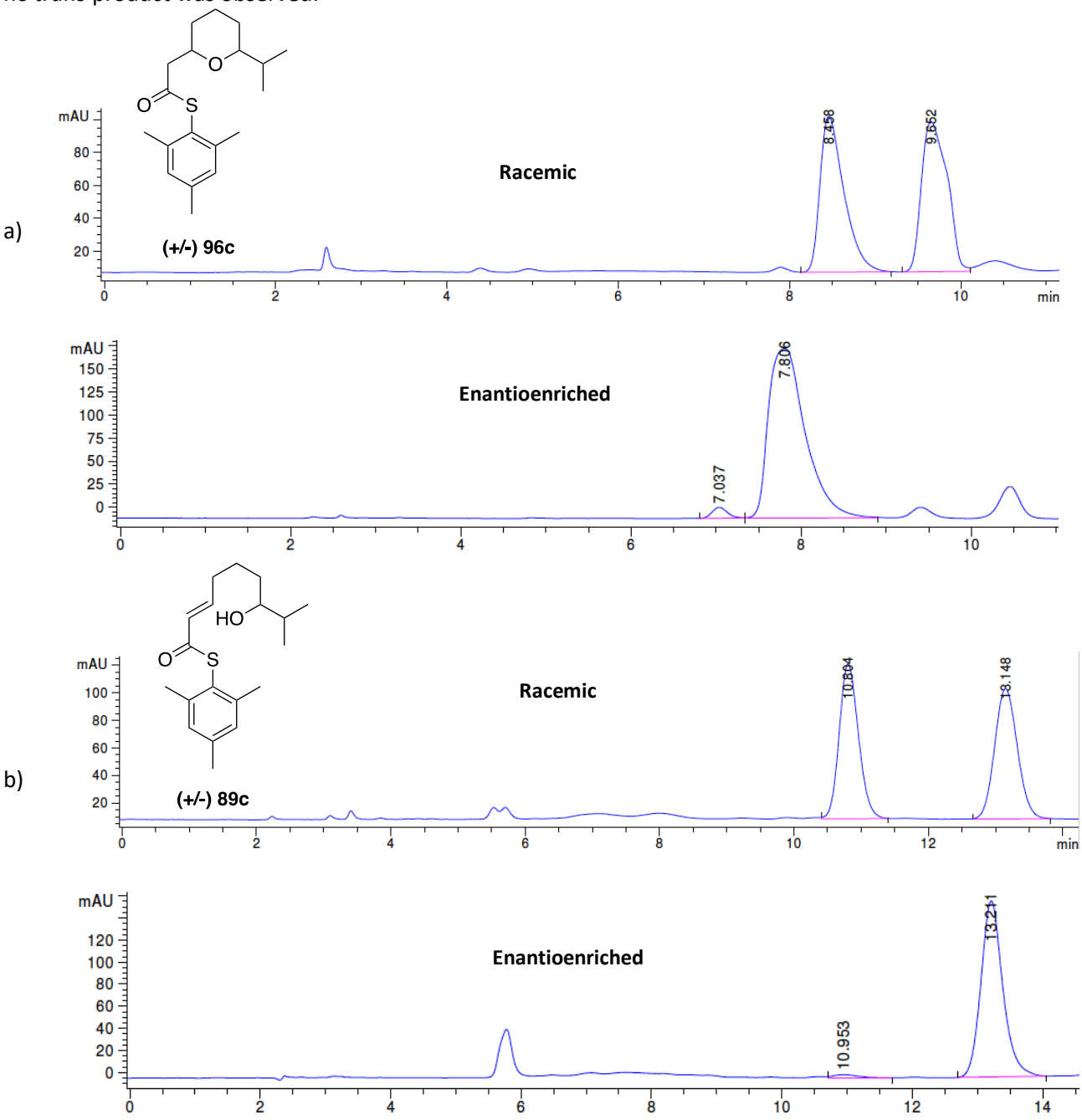


Figure 9- a) HPLC trace of **96c** b) HPLC trace of **89c**

	(Hexane:IPA)	Minor peak (min)	Major Peak (min)	Flowrate (mL/min)	ee (%)
96c	96/4	7.037	7.806	0.9	95
89c	90/10	10.953	13.211	0.9	96

Table 15- HPLC data of **96c** and **89c**

It was observed that the retention times of the racemic and enantioenriched samples of **96c** are different. This can be explained by different temperature gradients present during measurement, as the temperature control of the HPLC was not functional. This concludes the studies into the chiral resolution of thioesters using (*R*)-TRIP in cyclohexane at 50 ^{0}C, and an enantioerchment of 95% with respect to the product was achieved. This level of enantioenrichment is better than the one reported by Yoneda [44] (58-90%). This is of importance because it gives us access to a variety of enantioenriched functionalities owing to the versatility of thioesters. This is a very encouraging result and a step in the right direction in making the oxa-Michael cyclisation of thioesters more enantioselective.

8.9 Conclusion and future work.

The synthesis of tetrahydropyran cyclisation precursors **82** and **89** was achieved in excellent yields, *via* a Hovyeda-Grubbs catalyzed metathesis reaction between readily synthesized alcohols **84** and thioacrylate **83/90 (Scheme 2.4)**. Their Brønsted acid catalyzed cyclisation using TFA and CSA was studied using the conditions used by Clarke **(Scheme 2.45 and 2.6)**. [36] It was found that the increase in temperature or the amount of catalyst has only a moderate effect on cyclisation, with it often not reaching completion even after 24 hours. It was reasoned that a 5-exo-trig cyclisation involving tetrahydrofuran precursors was faster than the 6-exo-trig cyclisation involving tetrahydropyran precursors and that the conversion should increase. To this end, the corresponding tetrahydrofuran precursors **101** and **103** were synthesized in excellent yields **(Scheme 2.8)**. The Brønsted acid catalyzed cyclisation using TFA and CSA was studied and it was found to display similar reactivity trends as the tetrahydropyran precursors **(Scheme 2.9 and 10)**.

It was reasoned that the nature of the solvent might be a factor and lowering the polarity and dielectric constant of the solvent might improve conversion. This hypothesis was supported by a study by Yoneda [44] wherein he used toluene to achieve excellent enantioselectivities for the chiral Brønsted acid catalyzed synthesis of 2,6-*cis* tetrahydropyrans. Reasoning that thioesters were more versatile

than ketones, and the cyclisatisation to form tetrahydrofurans was faster than that of tetrahydropyrans, solvents with dielectric constants similar to or lower than toluene were employed for the asymmetric cyclisation. The asymmetric cyclisation using chiral phosphoric acids like (*R*)-TRIP, (*R)*-TIPSY and other commercially available acids under various solvent and temperature conditions were applied to the tolyl precursors **82** and mesityl precursors **89** of tetrahydrofurans. The tolyl substrates showed more promise, exhibiting moderate ee (15-60%), while the mesityl precursors were exhibiting disappointing ee's (4-30%) **(Scheme 2.12 and 2.13)**. Solvents having a low dielectric constant, like toluene and cyclohexane, were found to favour cyclisation, with 50 ^{0}C being the ideal temperature to achieve good conversions and %ee.

The solvent hypothesis was further reinforced when poor conversions and ee were obtained for the asymmetric cyclisation of the tolyl tetrahydropyran precursor **82a (Scheme 2.16)**. It was concluded that toluene and cyclohexane were the better choices for solvents. Analogous to the tetrahydropyran precursors, the asymmetric cyclisation of the mesityl tetrahydropyran precursor **89** using chiral phosphoric acids like (*R*)-TRIP, (*R)*-TIPSY and other commercially available acids under various solvent and temperature conditions were carried out. The best result (69%ee) was obtained for the precursor **89a** at 50 ^{0}C in cyclohexane using (*R*)-TRIP **(Scheme 2.17 and 2.18)**.

As the precursors **89** and **101** showed the most promise, it was reasoned that **101c** and **89c** would be suitable for a kinetic resolution using these conditions. Attempts at kinetically resolving the tolyl tetrahydrofuran precursor **101c** were abandoned due to lack of stereoselectivity (dr = 1.41:1) towards the *cis* isomer under acid conditions. The kinetic resolution of **89c** was attempted under the cyclohexane conditions. The conversion was monitored using HPLC, which resulted in a 95% enrichment of the *cis* product **96c** after 6 h with a 52% conversion **(Scheme 2.21)**. To the best of our knowledge, this is the first example of kinetic resolution of thioester substrates using a chiral phosphoric acid.

In conclusion, optimal solvent, temperature and catalyst conditions were identified for the chiral Brønsted acid catalyzed oxa-Michael cyclisation. Future work would involve a broader substrate scope and attempts at kinetic resolution of other tetrahydropyran precursors under the identified conditions. Additionally, attempts at identifying the absolute stereochemistry of all enantioenriched products, including the *cis* isomer **96c**, through a crystal structure would be carried out. This would be supported by computational work into the mechanism of the chiral Brønsted acid cyclisation and the level of agreement between the two would be ascertained.

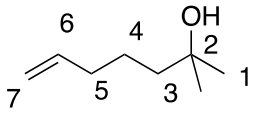
9. **Experimental**

9.1 General experimental

Unless otherwise noted all compounds were bought from commercial suppliers and used without further purification. Nuclear magnetic resonance spectra were recorded on a Jeol ECS-400 spectrometer at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: chloroform-d, 7.26 ppm for ^{1}H NMR; chloroform-d, 77.0 ppm for ^{13}C NMR. Coupling constants (*J*) are quoted in Hertz. Infra-red absorbances were recorded on a PerkinElmer UATR Two FT-IR spectrometer using NaCl plates. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI) technique. Optical rotations were carried out using a JASCO-DIP370 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg.cm^2.g^{-1}. Thin layer chromatography was performed on aluminium sheets coated with Merck Silica gel 60 F_{254}. The plates were developed using ultraviolet light, basic aqueous potassium permanganate or ethanolic anisaldehyde. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Sigma-Aldrich. Dry solvents were acquired from a PureSolv PS-MD7 solvent tower. High Performance Liquid Chromatography (HPLC) was performed using an Agilent 1200 series instrument using the chiral columns indicated and a range of wavelengths from 210-280 nm for detection. All other solvents and reagents were used as received from commercial suppliers. All numbering on the structures below is for the benefit of characterisation and does not necessarily conform to IUPAC rules.

9.2 Experimental Procedures

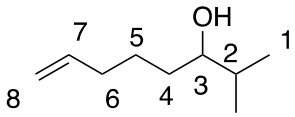
2-Methylhept-6-en-2-ol (84a)



A degassed solution of 5-bromo-1-pentene (5.1 mL, 43 mmol) in Et_2O (20 mL) was added dropwise over an hour, to a mixture of magnesium turnings (1.20 g, 49.4 mmol) in dry Et_2O (40 mL) under a nitrogen atmosphere. The reaction mixture was left to stir at room temperature for two hours. The solution of Grignard reagent was added dropwise, over 5 minutes, to a solution of dry acetone (3.1 mL, 44 mmol) in Et_2O (20 mL). A white precipitate formed immediately. The reaction mixture was then quenched with excess saturated aq NH_4Cl solution and the white precipitate was filtered. The organic layer was separated and washed with H_2O, dried over anhydrous Na_2SO_4 and filtered. It was then concentrated *in vacuo* to give a colourless oil. The oil was purified by flash column chromatography on silica with ethyl acetate /n-hexane (1:7) to yield **84a** as a colourless oil (0.68 g, 13%). *Data was consistent with those reported in the literature*. [38]

^{1}H NMR (400 MHz, $CDCl_3$): δ5.80 (1H, ddt, J = 17.1 Hz, 10.4 Hz, 6.6 Hz, H-6), 4.99 (1H, ddt, J = 17.1 Hz, 2.0 Hz, 1.4 Hz, H-7_{trans}), 4.94 (1H, ddt, J = 10.4 Hz, 2.0 Hz, 1.4 Hz, H-7_{cis}), 2.10-2.00 (2H, m, H-5), 1.50-1.40 (4H, m, H-3 + H-4), 1.27 (1H, s, OH), 1.19 (6H, s, H-1) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ138.9, 114.7, 71.1, 43.5, 34.3, 29.4, 23.8 ppm. **IR** (film, NaCl): v_{max} 3369, 3078, 2971, 1641, 1467, 1377, 1151, 992, 908, 764 cm^{-1}. **ESI-MS**: m/z calcd for $C_8H_{16}O$ (M^+-CH_3) 113.0966; found 113.0958

2-Methyloct-7en-3-ol (84c)

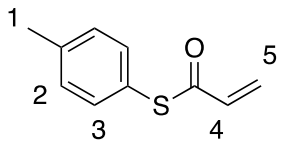


To a suspension of magnesium turnings (296 mg, 12 mmol) in dry THF (20 mL), a solution of 5-bromo-1-pentene (1.79 g, 12 mmol, 1.4 mL) in dry THF (4.0 mL) was added over a period of 5 minutes under a nitrogen atmosphere at 0 °C. After stirring the mixture for 60 minutes at room temperature, the Grignard reagent (11.3 mL, 1.5 eq.) was added over a period of 5 minutes to a solution of isobutyraldeyhde (292 mg, 4 mmol, 0.37 mL) in dry THF (2 mL) at 0 °C. The solution was stirred for 90 minutes at room temperature, then quenched with ice water (15 mL) and treated with dilute H_2SO_4 (5 M, 4 mL) until the magnesium salt dissolved. After separating the phases, the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and

concentrated *in vacuo* to give a yellow oil. This was then purified by column chromatography on silica with 10 % ethyl acetate in petroleum ether to yield **84c** as a yellow oil (142.8 mg, 25 %). *Data was consistent with that reported in literature*. [30]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 (1H, ddt, *J* = 17.1 Hz, 10.2 Hz, 6.8 Hz, H-7), 5.03-4.97 (1H, ddt, J = 17.1 Hz, 2.0 Hz, 1.8 Hz, H-8), 4.96-4.92 (1H, ddt, *J* = 10.2 Hz, 2.0 Hz, 1.2 Hz, H-8), 3.35 (1H, ddd, *J* = 8.5 Hz, 5.1 Hz, 3.5 Hz, H-3), 2.14-1.98 (2H, m, H-6), 1.69 – 1.52 (2H, m, H-4), 1.51-1.43 (1H, m, H-2), 1.40-1.32 (2H, m, H-5), 0.90 (3H, d, *J* = 4.1 Hz, H-1), 0.89 (3H, d, *J* = 4.1 Hz, H-1) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 138.9, 114.7, 76.8, 33.9, 33.7, 25.5, 19.0, 17.2 ppm. **IR** (film, NaCl): ν_{max} 3370, 3077, 2958, 2934, 2873, 1698, 1641, 1461, 1384, 1367, 1260, 992, 908 cm^{-1}. **ESI-MS**: m/z calcd for $C_9H_{19}O^+$ ($M+H^+$) 147.1430; found 147.1422

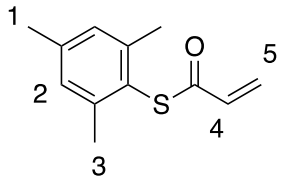
_S-p_-Tolyl prop-2-enethioate (83)



$NaBH_4$ (27.0 mg, 0.70 mmol, 0.03 eq) and 4-methylbenzenethiol (2.74g, 22 mmol) were added in that order to 15% aqueous NaOH solution (10 mL) and stirred at room temperature for an hour and then cooled to 0 ^oC before use. In a separate flask, butylated hydroxytoluene (72.0 mg, 0.327 mmol, 0.015 eq) and acryloyl chloride (2.7 mL, 33 mmol, 1.5 eq) were dissolved in cyclohexane (15 mL). To this solution under cooling at 0^oC, the borohydride solution was added over a period of 10 minutes. The resultant solution was then stirred at 55 ^0C for 30 minutes. The reaction mixture was then cooled to room temperature and extracted with Et_2O (3 x 10 mL). The organics were washed with saturated $NaHCO_3$ solution (3x5 mL) and brine solution (3 x 5 mL), dried over anhydrous $MgSO_4$, and filtered. A portion of butylated hydroxytoluene (36.2 mg) was added prior to evaporation to prevent polymerisation. The reaction mixture was then concentrated *in vacuo* to give a yellow oil. This was purified by column chromatography on silica using 3% ethyl acetate in hexane to yield **83** as a yellow oil (1.86 g, 47%). *Data was consistent with that reported in literature*. [30]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (2H, d, J = 8.0 Hz, H-2), 7.24 (2H, d, J = 8.0 Hz, H-3), 6.44 (1H, dd, J = 17.2 Hz, 9.6 Hz, H-4), 6.37 (1H, dd, J = 17.2 Hz, 1.6 Hz, H-5_{trans}), 5.75 (1H, dd, J = 9.6 Hz, 1.6 Hz, H-5_{cis}), 2.37 (3H, s, H-1) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ189.2, 139.9, 134.7, 134.5, 130.2, 127.4, 123.7, 21.5 ppm **IR** (film NaCl): ν_{max} 3027, 2922, 2863, 1683, 1612, 1494, 1394, 1161, 988, 941, 807, 722 cm^{-1}. **ESI-MS**: m/z calcd for $C_{10}H_{10}NaOS^+$ ($M+Na^+$) 201.0350; found 201.0353

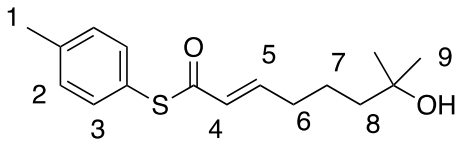
_S_-Mesityl prop-2-enethioate (90)



$NaBH_4$ (12.8 mg, 0.338 mmol, 0.03 eq) and 2,4,6-trimethylbenzenethiol (1.7mL, 2.74g, 11.3 mmol, 1.0 eq) were added in that order to 15% aqueous NaOH solution (5 mL) and stirred at room temperature for an hour and then cooled to 0 ^oC before use. In a separate flask, butylated hydroxytoluene (25.0 mg, 0.113 mmol, 0.01 eq) and acryloyl chloride (1.4 mL, 17.23 mmol, 1.53 eq) were dissolved in cyclohexane (7 mL). To this solution under cooling at 0 ^oC, the borohydride solution was added over a period of 10 minutes. The resultant solution was then stirred at 55 ^0C for an hour. The reaction mixture was then cooled to room temperature and extracted with Et_2O (3 x 15 mL). The organics were washed with saturated $NaHCO_3$ solution (3x5 mL) and brine solution (3 x 5 mL), dried over anhydrous $MgSO_4$, and filtered. A portion of butylated hydroxytoluene (42.3 mg) was added prior to evaporation to prevent polymerisation. The reaction mixture was then concentrated *in vacuo* to give a yellow oil. This was purified by column chromatography on silica using 2% ethyl acetate in hexane to yield **90** as a yellow oil (1.17 g, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00-6.97 (2H, m, H-2), 6.47 (1H, dd, J = 17.2 Hz, 9.6 Hz, H-4), 6.38 (1H, dd, J = 17.2 Hz, 1.6 Hz, H-5_{trans}), 5.73 (1H, dd, J = 9.6 Hz, 1.6 Hz, H-5_{cis}), 2.30 (1H, s, H-3) 2.28 (1H, s, H-1) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ188.3, 142.8, 140.2, 134.7, 129.4, 127.0, 123.1, 21.7, 21.3 ppm **IR** (film NaCl): ν_{max} 3027, 2922, 2863, 1683, 1612, 1494, 1394, 1161, 988, 941, 807, 722 cm^{-1}. **ESI-MS**: m/z calcd for $C_{12}H_{15}OS^+$ ($M+H^+$) 207.0838; found 207.0840

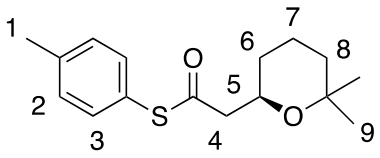
(_E_)-_S_-_p_-Tolyl 7-hydroxy-7-methyloct-2-enethioate (82a)



2-Methylhept-6-en-2-ol (102.4 mg, 0.8 mmol, 1.0 eq) and _S-p_-tolylprop-2-enethioate (427.2 mg, 2.4 mmol, 3.0 eq) were dissolved in dry Et_2O (5 mL) under a nitrogen atmosphere. To this, copper (I) iodide (15.3 mg, 0.08 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (50.2mg, 0.08 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 ^0C for 24 hours. The mixture was then concentrated and purified by column chromatography on silica using 10-15 % ethyl acetate in petroleum ether to yield **82a** as a brown oil (192.7 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.31 (2H, d, J = 8.0 Hz, H-2), 7.21 (2H, d, J = 8.0 Hz, H-3), 6.96 (1H, dt, J = 15.6 Hz, 7.0 Hz, H-5), 6.18 (1H, dt, J = 15.6 Hz, 1.4 Hz, H-4), 2.36 (3H, s, H-1), 2.24 (2H, qd, J = 7.0 Hz, 1.4 Hz, H-6), 1.62-1.48 (4H, m, H-7 + H-8), 1.22 (6H, s, H-9) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ188.7, 146.3, 139.8, 134.8, 130.2, 128.2, 124.2, 71.0, 43.4, 32.8, 29.5, 23.0, 21.5 ppm. **IR** (film NaCl): ν_{max} 3383, 2964, 2924, 2853, 1687, 1631, 1494, 1464, 1398, 1376, 1284, 1160, 1017, 972, 807 cm^{-1}. **ESI-MS**: m/z calcd for $C_{16}H_{22}NaO_2S^+$ ($M+Na^+$) 301.1233; found 301.1230

_S-p-T_olyl-2-(6,6-dimethyltetrahydro-_2H_-pyran-2-yl)ethanethioate (95a)



Acid conditions:

TFA

(*E*)-*S*-*p*-Tolyl 7-hydroxy-7-methyloct-2-enethioate (15.0 mg, 0.054 mmol) was dissolved in DCE (0.9 mL) and H_2O (0.4 mL) was added and cooled in ice. To this, a solution of TFA in DCE (3.6 mL, 0.06 M) was added over three minutes. The reaction mixture was then heated at 50 ^{0}C for 24 hours. The reaction mixture was then quenched with saturated $NaHCO_3$ solution (5 mL) and diluted with DCM (2 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a crude yellow oil. The oil was purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield **95a** as a yellow oil (4.2. mg, 28%).

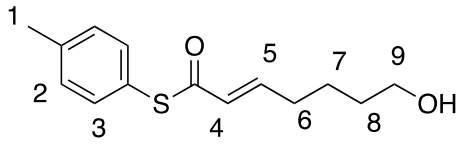
CSA

To a solution of (*E*)-*S*-*p*-tolyl 7-hydroxy-7-methyloct-2-enethioate (28.9 mg, 0.104 mmol) in DCE (5 mL), a portion of CSA (73.0 mg, 0.314 mmol, 3 eq) was added and heated under reflux at 80 ^{0}C for 24 hours. The reaction was quenched with Et_3N (1.0 mL), washed with $NaHCO_3$ solution (2 x 5 mL) and brine solution (2 x 5 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to give a crude yellow oil. The oil was purified by column chromatography on silica with dichloromethane to yield **95a** as a yellow oil (13.0 mg, 45 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.27 (d, 2H, J = 8.1 Hz, H-2), 7.19 (2H, d, J = 8.1 Hz, H-3), 4.04 (1H, dtd, J = 11.4 Hz, 6.6 Hz, 2.1 Hz, H-5), 2.82 (1H, dd, J = 14.8 Hz, 6.6 Hz, H-4), 2.64 (1H, dd, J = 14.8 Hz, 6.6 Hz, H-4), 2.36 (3H, s, H-1), 1.68-1.61 (3H, m, 2x H-6 + H-7), 1.48-1.30 (2H, m, H-8), 1.19 (3H, s, H-9), 1.18 (3H, s, H-9), 1.13 (1H, m, H-7) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ196.1, 139.7, 134.6, 130.1, 124.6, 72.5, 67.7, 50.8, 35.9, 31.9, 31.3, 21.9, 21.5, 19.9 ppm. **IR** (film NaCl): ν_{max} 2973, 2928, 1707, 1494,

1460, 1379, 1360, 1281, 1213, 1137, 1065, 1043, 974, 900, 867, 806, 746 cm^{-1}. **ESI-MS**: m/z calcd for $C_{16}H_{22}NaO_2S^+$ ($M+Na^+$) 301.1233; found 301.1227

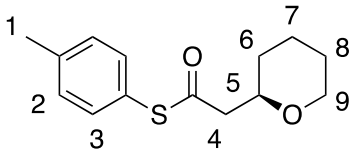
(*E*)-*S*-*p*-Tolyl 7-hydroxyhept-2-enethioate (82b)



5-Hexen-1-ol (40.1 mg, 0.4 mmol, 1.0 eq) and *S*-*p*-tolylprop-2-enethioate (213.6 mg, 1.2 mmol, 3.0 eq) were dissolved in dry Et_2O (5 mL) under a nitrogen atmosphere. To this, copper (I) iodide (7.6 mg, 0.04 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (25.1 mg, 0.04 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 ^{0}C for 24 hours. The mixture was then concentrated and purified by column chromatography on silica using 10-15 % ethyl acetate in petroleum ether to yield **82b** as a brown oil (86.0 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.30 (2H, d, J = 8.0 Hz, H-2), 7.20 (2H, d, J = 8.0 Hz, H-3), 6.95 (1H, dt, J = 15.6 Hz, 7.0 Hz, H-5), 6.17 (1H, dt, J = 15.6 Hz, 1.4 Hz, H-4), 3.70-3.60 (2H, m, H-9), 2.36 (3H, s, H-1), 2.25 (2H, qd, J = 7.0 Hz, 1.4 Hz, H-6), 1.64-1.52 (4H, m, H-7 + H-8) ppm. **^{13}C NMR** 101 MHz, $CDCl_3$): δ188.7, 146.2, 139.8, 134.7, 130.1, 128.2, 124.1, 62.6, 32.2, 32.1, 24.3, 21.5 ppm. **IR** (film NaCl): ν_{max} 3387, 3030, 2928, 2863, 1682, 1631, 1495, 1456, 1384, 1376, 1214, 1184, 1051, 998, 808 cm^{-1}. **ESI-MS**: m/z calcd for $C_{14}H_{18}NaO_2S^+$ ($M+Na^+$) 273.0920; found 273.0911

***S*-*p*-*T*olyl-2-(tetrahydro-*2H*-pyran-2-yl)ethanethioate (95b)**



Acid conditions:

TFA

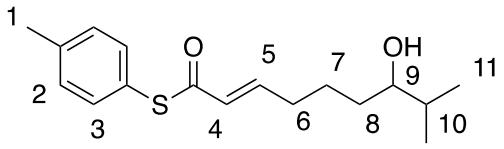
(*E*)-*S*-*p*-Tolyl 7-hydroxyhept-2-enethioate (17.4 mg, 0.070 mmol) was dissolved in DCE (3 mL) and H_2O (0.3 mL) was added and cooled in ice. To this, a solution of TFA in DCE (2.7 mL, 0.06 M) was added over three minutes. The reaction mixture was then heated at 60 ^{0}C for 24 hours. The reaction mixture was then quenched with saturated $NaHCO_3$ solution (3 mL) and diluted with DCM (2 mL). The phases were separated and the aqueous layer was extracted with DCM (2 x 3 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a crude yellow oil. The oil was purified by column chromatography on silica using DCM to yield **95b** as a yellow oil (6.1 mg, 35%).

CSA

To a solution of (*E*)-*S*-*p*-tolyl 7-hydroxyhept-2-enethioate (14.0 mg, 0.056 mmol) in DCE (5 mL), a portion of CSA (39.0 mg, 0.168 mmol, 3 eq) was added and heated under reflux at 80 ^{0}C for 24 hours. The reaction was quenched with Et_3N (1.0 mL), washed with $NaHCO_3$ solution (2 x 5 mL) and brine solution (2 x 5 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to give a crude yellow oil. The oil was purified by column chromatography on silica with DCM to yield **95b** as a yellow oil (5.7 mg, 41 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.28 (d, 2H, J = 8.1 Hz, H-2), 7.20 (2H, d, J = 8.1 Hz, H-3), 3.95 (1H, dt, J = 11.4 Hz, 2.2 Hz, H-9), 3.79 (1H, dddd, J = 10.6 Hz, 7.8 Hz, 5.4 Hz, 2.2 Hz, H-5), 3.43 (1H, td, J = 11.4 Hz, 2.2 Hz, H-9), 2.86 (1H, dd, J = 14.9 Hz, 7.8 Hz, H-4), 2.65 (1H, dd, J = 14.9 Hz, 5.4 Hz, H-4), 2.35 (3H, s, H-1), 1.62-1.44 (6H, m, H-6 + H-7 + H-8) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ195.9, 139.8, 134.5, 130.1, 124.4, 74.6, 68.8, 50.3, 31.7, 25.8, 23.4, 21.5 ppm **IR** (film NaCl): ν_{max} 2926, 2852, 1708, 1494, 1440, 1377, 1360, 1272, 1195, 1180, 1089, 1046, 1005, 965, 807, 742 cm^{-1}. **ESI-MS**: m/z calcd for $C_{14}H_{18}NaO_2S^+$ (M+Na$^+$) 273.0920; found 273.0934.

(*E*)-*S*-*p*-Tolyl 7-hydroxy-8-methylnon-2-enethioate (82c)

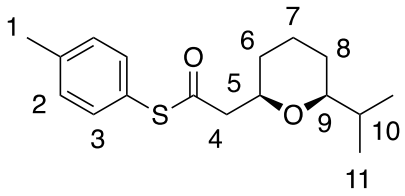


2-Methyloct-7-en-2-ol (24.2 mg, 0.170 mmol, 1.0 eq) and *S*-*p*-tolylprop-2-enethioate (92.0 mg, 0.511 mmol, 3.0 eq) were dissolved in dry Et_2O (5 mL) under a nitrogen atmosphere. To this, copper (I) iodide (5.0 mg, 0.026 mmol, 15 mol%) and Hovyeda-Grubbs 2nd generation catalyst (10.7 mg, 0.017 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 ^{0}C for 2 hours. The mixture was then concentrated and purified by column chromatography on silica using 10-15 % ethyl acetate in petroleum ether to yield **82c** as a brown oil (42.2 mg, 85%). *Data was consistent with those reported in the literature*. [30]

^{1}H NMR (400 MHz, $CDCl_3$): δ7.30 (2H, d, J = 7.9 Hz, H-2), 7.21 (2H, d, J = 7.9 Hz, H-3), 6.96 (1H, dt, J = 15.6 Hz, 6.9 Hz, H-5), 6.18 (1H, dt, J = 15.6 Hz, 1.4Hz, H-4), 3.35 (2H, ddd, J = 8.6 Hz, 5.2Hz, 3.2 Hz, H-9), 2.36 (3H, s, H-1), 2.29-2.21 (2H, m, H-6), 1.71-1.60 (2H, m, H-8), 1.52-1.38 (3H, m, H-7 + H-10), 0.91 (3H, d, *J* = 3.7 Hz, H-11), 0.89 (3H, d, *J* = 3.7 Hz, H-11) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ188.7, 146.4, 139.7, 134.7, 130.1, 128.1, 124.2, 76.6, 33.7, 32.4, 24.6, 21.5, 19.0, 17.2 ppm. **IR** (film NaCl):

ν_{max} 3438, 2959, 2927, 2870, 1678, 1631, 1494, 1461, 1384, 1277, 1211, 1140, 1036, 982, 807 cm^{-1}. **ESI-MS**: m/z calcd for $C_{17}H_{25}NaO_2S^+$ ($M+Na^+$) 315.1389; found 315.1380

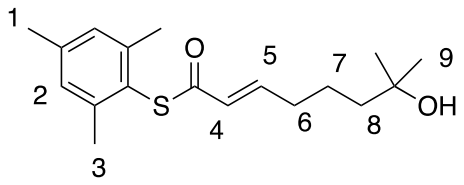
_S-p-T_olyl-2-(6-isopropyltetrahydro-_2H_-pyran-2-yl)ethanethioate (95c)



(*E*)-*S*-*p*-Tolyl 7-hydroxy-8-methylnon-2-enethioate (15.0 mg, 0.051 mmol) was dissolved in DCM (1 mL) and H_2O (0.1 mL) was added and cooled in ice. To this, a solution of TFA in DCM (0.9 mL, 0.06 M) was added over three minutes. The reaction mixture stirred at room temperature for 48 hours. The reaction mixture was then quenched with saturated $NaHCO_3$ solution (3 mL) and diluted with DCM (2 mL). The phases were separated and the aqueous layer was extracted with DCM (2 x 3 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a crude yellow oil. The oil was purified by column chromatography on silica using DCM to yield **95c** as a yellow oil (6.5 mg, 43%). *Data was consistent with those reported in the literature*. [30]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (2H, d, *J* = 8.2 Hz, H-2), 7.19 (2H, *J* = 8.2 Hz, H-3), 3.78 (1H, dddd, J = 11.1 Hz, 8.2 Hz, 4.9 Hz, 1.8 Hz, H-5), 2.95 (1H, ddd, *J* = 11.1 Hz, 6.9 Hz, 1.8 Hz, H-9), 2.85 (1H, dd, *J* = 14.4 Hz, 8.2 Hz, H-4), 2.64 (1H, dd, *J* = 14.4Hz, 4.9 Hz, H-4), 2.37 (3H, s, H-1), 1.84-1.74 (1H, m, H-10), 1.65 – 1.43 (6H, m, H-6 + H-7 + H-8), 0.94 (3H, d, *J* = 6.8 Hz, H-11), 0.86 (3H, d, *J* = 6.8 Hz, H-11) ppm **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 196.3, 139.7, 134.6, 130.1, 124.6, 83.4, 75.0, 50.5, 33.6, 31.5, 28.2, 23.7, 21.5, 18.9 ppm. **IR** (film, NaCl): ν_{max} 2928, 2857, 1706, 1494, 1457, 1339, 1274, 1203, 1071, 1048, 996, 806 cm^{-1}. **ESI-MS**: m/z calcd for $C_{17}H_{25}NaO_2S^+$ ($M+Na^+$) 315.1389; found 315.1381

(*E*)-*S*-Mesityl 7-hydroxy-7-methyloct-2-enethioate (89a)

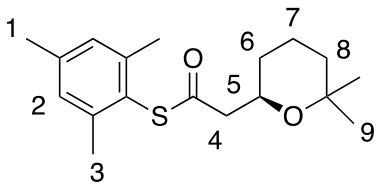


2-Methylhept-6-en-2-ol (76.8 mg, 0.6 mmol, 1.0 eq) and *S*-mesityl prop-2-enethioate (373 mg, 1.81 mmol, 3.02 eq) were dissolved in dry Et_2O (20 mL) under a nitrogen atmosphere. To this, copper (I) iodide (11.5 mg, 0.06 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (37.6mg, 0.06 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 ^{0}C for 18

hours. The mixture was then concentrated and purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield **89a** as a brown oil (157.7 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (3H, m, H-2 + H-5), 6.22 (1H, dt, J = 15.6 Hz, 1.6 Hz, H-4), 2.30 (6H, s, H-3), 2.28 (3H, s, H-1), 2.24 (2H, dtd, J = 7.3 Hz, 7.3 Hz, 1.5 Hz, H-6), 1.60-1.55 (4H, m, H-7 + H-8), 1.22 (6H, s, H-9) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ187.8, 145.9, 142.8, 140.0, 129.3, 128.3, 123.6, 71.0, 43.5, 32.8, 29.5, 23.0, 21.8, 21.5 ppm. **IR** (film NaCl): ν_{max} 3412, 2969, 2940, 1684, 1631, 1464, 1375, 1284, 1156,1040, 972, 907, 851, 799, 765, 715 cm^{-1}. **ESI-MS**: m/z calcd for $C_{18}H_{26}NaO_2S^+$ ($M+Na^+$) 329.1546; found 329.1551

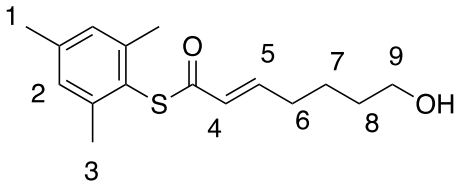
***S*-Mesityl 2-(6,6-dimethyltetrahydro-2H-pyran-2-yl)ethanethioate (96a)**



(*E*)-*S*-Mesityl 7-hydroxy-7-methyloct-2-enethioate (18.5 mg, 0.060 mmol) was dissolved in DCE (1.0 mL) and H_2O (0.2 mL) was added and cooled in ice. To this, a solution of TFA in DCE (1.8 mL, 0.06 M) was added over three minutes. The reaction mixture was then heated at 50 ^{0}C for 24 hours. The reaction mixture was then quenched with saturated $NaHCO_3$ solution (2 mL) and diluted with DCM (2 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a crude yellow oil. The oil was purified by column chromatography on silica using 5% ethyl acetate in petroleum ether to yield **96a** as a yellow oil (7.5 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ6.97 (2H, s , H-2), 4.10-4.00 (1H, m, H-5), 2.82 (1H, dd, J = 14.2 Hz, 7.8 Hz, H-4), 2.64 (1H, dd, J = 14.2 Hz, 5.0 Hz, H-4), 2.30 (6H, s, H-3), 2.37 (3H, s, H-1), 1.70-1.60 (3H, m, 2x H-6 + H-7), 1.45-1.35 (3H, m, 2x H-8 + H-7), 1.16 (6H, s, H-9) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ195.4, 142.6, 139.9, 129.3, 124.1, 72.3, 68.2, 50.8, 35.9, 31.8, 31.3, 21.9, 21.8, 21.3, 20.0 ppm **IR** (film NaCl): ν_{max} 2972, 2926, 1702, 1461, 1377, 1364, 1278, 1138, 1063, 1043, 978, 901, 849, 797, 737, 717 cm^{-1}. **ESI-MS**: m/z calcd for $C_{18}H_{26}NaO_2S^+$ ($M+Na^+$) 329.1546; found 329.1548.

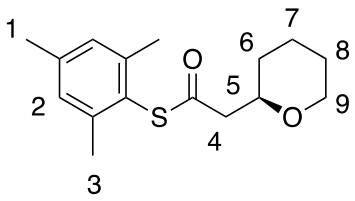
(*E*)-*S*-Mesityl 7-hydroxyhept-2-enethioate (89b)



5-Hexen-1-ol (60.1 mg, 0.6 mmol, 1.0 eq) and *S*-mesityl prop-2-enethioate (378.1 mg, 1.84 mmol, 3.06 eq) were dissolved in dry Et_2O (20 mL) under a nitrogen atmosphere. To this, copper (I) iodide (11.6 mg, 0.06 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (38.0 mg, 0.06 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 ^{0}C for 24 hours. The mixture was then concentrated and purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield **89b** as a brown oil (151.0 mg, 91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.00-6.90 (3H, m, H-2, H-5), 6.22 (1H, dt, J = 15.3 Hz, 1.7 Hz, H-4), 3.67 (2H, t, J = 5.7 Hz, H-9), 2.30 (6H, s, H-3), 2.28 (3H, s, H-1), 2.26-2.23 (2H, m, H-6), 1.65-1.55 (4H, m, H-7 + H-8) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ187.8, 145.8, 142.8, 140.0, 145.7, 142.8, 140.0, 129.3, 128.4, 123.6, 62.7, 32.3, 32.1, 24.3, 21.8, 21.3 ppm. **IR** (film NaCl): ν_{max} 3357, 2928, 2860, 1683, 1631, 1456, 1376, 1298, 1135, 1049, 996, 850, 803, 745, 715 cm^{-1}. **ESI-MS**: m/z calcd for $C_{16}H_{22}NaO_2S^+$ ($M+Na^+$) 301.1233; found 301.1230

***S*-Mesityl 2-(tetrahydro-2H-pyran-2-yl)ethanethioate (96b)**



(*E*)-*S*-Mesityl 7-hydroxyhept-2-enethioate (12.0 mg, 0.043 mmol) was dissolved in cyclohexane (2.1 mL). To this, (*R*)-TRIP (6.5 mg, 0.009 mmol, 20mol %) was added and stirred at 50 ^{0}C under a nitrogen atmosphere for 24 hours. The reaction mixture was then concentrated *in vacuo* and purified by column chromatography on silica using 5% ethyl acetate in petroleum ether to yield **116b** as a yellow oil (10.8 mg, 90%).

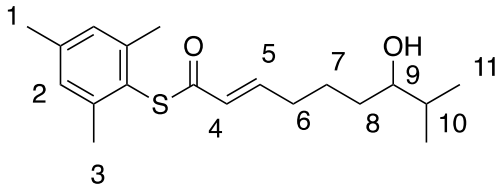
^{1}H NMR (400 MHz, $CDCl_3$): δ6.96 (2H, s, H-2), 3.96 (1H, dt, J = 11.4 Hz, 2.2 Hz, H-9), 3.80 (1H, dddd, J = 10.6 Hz, 7.8 Hz, 5.3 Hz, 2.3 Hz, H-5), 3.43 (1H, td, J = 11.4 Hz, 2.2 Hz, H-9), 2.86 (1H, dd, J = 14.7 Hz, 7.8 Hz, H-4), 2.65 (1H, dd, J = 14.7 Hz, 5.3 Hz, H-4), 2.28 (6H, s, H-3), 2.27 (3H, s, H-1), 1.66-1.45 (6H, m, H-6 + H-7 + H-8) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ195.1, 142.6, 140.0, 129.3, 123.9, 75.1, 68.7, 50.3, 31.7, 25.8, 23.4, 21.7, 21.5 ppm **IR** (film NaCl): ν_{max} 2925, 2852, 1701, 1602, 1571, 1463, 1440,

1376, 1352, 1288, 1196, 1174, 1089, 1046, 1005, 967,901, 850, 800, 742 cm^{-1}. **ESI-MS**: m/z calcd for $C_{16}H_{22}NaO_2S^+$ ($M+Na^+$) 301.1233; found 301.1235.

$[\alpha]_D^{25.0}$ +53.0 (c = 0.51, $CHCl_3$) for the mixture.

HPLC (Chiralpak AD-H, 5% IPA, 95% hexane, 0.9 mL/min, λ = 254): t_R (minor) = 6.4, t_R (major) = 7.0, ee - 44%

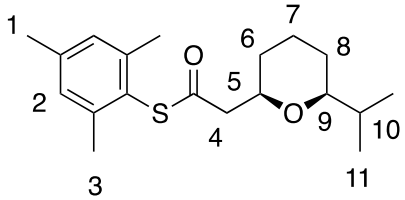
(*E*)-*S*-Mesityl 7-hydroxy-8-methylnon-2-enethioate (89c)



2-Methyloct-7-en-2-ol (130.6 mg, 0.92 mmol, 1.0 eq) and *S*-Mesityl prop-2-enethioate (590.4 mg, 2.87 mmol, 3.12 eq) were dissolved in dry Et_2O (30 mL) under a nitrogen atmosphere. To this, copper (I) iodide (17.6 mg, 0.092 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (57.7 mg, 0.092 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 ^{0}C for 16 hours. The mixture was then concentrated and purified by column chromatography on silica using 20 % ethyl acetate in petroleum ether to yield **89c** as a brown oil (166.0 mg, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.10-6.93 (3H, m, H-2 + H-5), 6.22 (1H, dt, J = 15.5 Hz, 1.4Hz, H-4), 3.37 (1H, m, H-9), 2.30 (6H, s, H-3), 2.28 (3H, s, H-1), 2.29-2.20 (2H, m, H-6), 1.73-1.60 (2H, m, H-8), 1.53-1.49 (3H, m, H-7 + H-10), 0.92 (3H, d, *J* = 3.7 Hz, H-11), 0.90 (3H, d, *J* = 3.7 Hz, H-11)ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ188.0, 142.8, 140.0, 129.3, 128.3, 123.6, 76.6, 33.7, 32.4, 24.6, 21.8, 21.3, 19.0, 17.2 ppm. **IR** (film NaCl): ν_{max} 3444, 2955, 2929, 2871, 1684, 1630, 1460, 1375, 1298, 1280, 1139, 1033, 982, 850, 801, 715 cm^{-1}. **ESI-MS**: m/z calcd for $C_{19}H_{28}NaO_2S^+$ ($M+Na^+$) 343.1702; found 343.1704

***S*-Mesityl 2-(6-isopropyltetrahydro-2H-pyran-2-yl)ethanethioate (96c)**

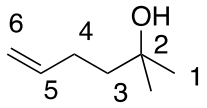


(E)-*S*-mesityl 7-hydroxy-8-methylnon-2-enethioate (19.2 mg, 0.06 mmol) was dissolved in DCE (1 mL) and H_2O (0.2 mL) was added and cooled in ice. To this, a solution of TFA in DCE (1.8 mL, 0.06 M) was

added over three minutes. The reaction mixture stirred at 50 ^{0}C for 24 hours. The reaction mixture was then quenched with saturated $NaHCO_3$ solution (2 mL). The aqueous layer was extracted with DCM (3 x 10 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a crude yellow oil which was purified by column chromatography on silica using 5% ethyl acetate in hexane to yield **96**c as a yellow oil (10.0 mg, 52%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.96 (2H, *s,* H-2), 3.82 (1H, dddd, J = 11.1 Hz, 8.2 Hz, 4.9 Hz, 1.8 Hz, H-5), 2.97 (1H, ddd, *J* = 11.0 Hz, 6.9 Hz, 1.8 Hz, H-9), 2.88 (1H, dd, *J* = 14.7 Hz, 7.8 Hz, H-4), 2.65 (1H, dd, *J* = 14.7 Hz, 4.6 Hz, H-4), 2.28 (6H, s, H-3), 2.27 (3H, s, H-1), 1.89-1.81 (1H, m, H-10), 1.68-1.45 (6H, m, H-6 + H-7 + H-8), 0.91 (3H, d, *J* = 6.4 Hz, H-11), 0.85 (3H, d, *J* = 6.4 Hz, H-11) ppm **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 195.2, 142.6, 140.0, 129.3, 124.1, 83.3, 75.0, 50.5, 33.4, 31.5, 28.0, 23.7, 21.8, 21.3, 18.9, 18.7 ppm. **IR** (film, NaCl): ν_{max} 2925, 2854, 1703, 1464, 1376, 1274, 1088, 849, 744 cm^{-1}. **ESI-MS**: m/z calcd for $C_{19}H_{28}NaO_2S^+$ ($M+Na^+$) 343.1702; found 343.1707.

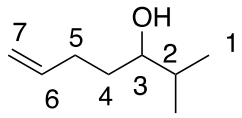
2-Methylhex-5-en-2-ol (97a)



A solution of 3M MeMgBr solution in ether (6.3 mL, 19 mmol, 1.1 eq) was charged into a 250 mL round bottom flask and diluted with dry Et_2O (11 mL) under a nitrogen atmosphere. To this, 5-Hexen-2-one (2.0 mL, 17 mmol, 1.0 eq) was added dropwise over 10 minutes and stirred at room temperature for 1h. The reaction mixture was quenched with sat. NH_4Cl solution (5.5 mL), followed by 1M soln of $NaHSO_4$ solution (4 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous $MgSO_4$ and filtered. It was then concentrated in vacuo to give a yellow oil. The oil was purified by flash column chromatography on silica with 1% MeOH in DCM to yield **97a** as a colourless oil (0.748 g, 39%). *Data was consistent with those reported in the literature*. [39]

^{1}H NMR (400 MHz, $CDCl_3$): δ5.84 (1H, ddt, J = 17.1 Hz, 10.4 Hz, 6.6 Hz, H-4), 5.03 (1H, ddt, J = 17.1 Hz, 2.0 Hz, 1.4 Hz, H-5_{trans}), 4.95 (1H, ddt, J = 10.4 Hz, 2.0 Hz, 1.4 Hz, H-5_{cis}), 2.17-2.10 (2H, m, H-3), 1.60-1.54 (2H, m, H-2), 1.22 (6H, s, H-1) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ139.1, 114.6, 71.1, 43.0, 34.3, 29.4, 29.0 ppm. **IR** (film, NaCl): ν_{max} 3342, 3045, 2936, 1641, 1453, 1376, 1290, 1221, 1153, 994, 908, 772, 630 cm^{-1}

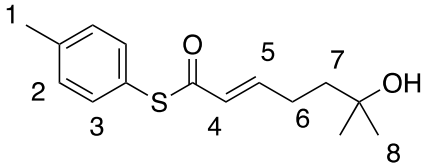
2-Methylhept-6-en-3-ol (97c)



To a suspension of magnesium turnings (601 mg, 25 mmol) in dry Et_2O (27 mL), a solution of 4-bromo-1-butene (2.54mL, 25 mmol) in dry Et_2O (4.0 mL) was added over a period of 5 minutes under a nitrogen atmosphere at 0 °C. After stirring the mixture for 2.5 h at room temperature, the Grignard reagent (20.0 mL, 1.5 eq.) was added over a period of 5 minutes to a solution of isobutyraldeyhde (0.76 mL, 8.3 mmol) in dry Et_2O (5 mL) at 0 °C. The solution was stirred for 2 hours at room temperature, then quenched with sat. NH_4Cl solution (25 mL) until the magnesium salt dissolved. After separation of the phases, the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a yellow oil. This was then purified by column chromatography on silica with 10 % ethyl acetate in petroleum ether to yield **97c** as a yellow oil (519.4 mg, 49 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (1H, ddt, *J* = 17.1 Hz, 10.2 Hz, 6.7 Hz, H-6), 5.04 (1H, ddt, J= 17.1 Hz, 2.0 Hz, 1.8 Hz, H_{trans}), 4.96 (1H, ddt, J = 10.2 Hz, 2.0 Hz, 1.2 Hz, H-7_{cis}), 3.37 (1H, ddd, *J* = 8.8 Hz, 5.2 Hz, 3.4 Hz, H-3), 2.30-2.20 (1H, m, H-4), 2.19-2.10 (1H, m, H-4), 1.70-1.55 (3H, m, H-5 + H2), 0.90 (3H, d, *J* = 3.2 Hz, H-1), 0.89 (3H, d, *J* = 3.2 Hz, H-1) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 138.9, 114.9, 76.4, 33.9, 33.7, 30.1, 18.9, 17.3 ppm. **IR** (film, NaCl): ν_{max} 3354, 3078,2959, 2938, 2875, 1641, 1469, 1450, 1414, 1387, 1368, 1269, 1179, 1095, 1057, 1018, 992, 956, 908, 850, 833, 805, 770, 644 cm^{-1}. ESI-MS: m/z calcd for $C_8H_{17}O^+$ ($M+H^+$) 129.1274; found 129.1272

(*E*)-*S*-*p*-Tolyl 6-hydroxy-6-methylhept-2-enethioate (101a)

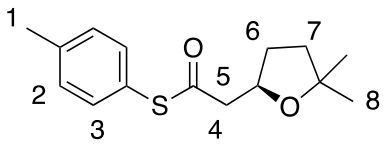


2-Methylhex-5-en-2-ol (68.4 mg, 0.6 mmol, 1.0 eq) and *S*-*p*-tolylprop-2-enethioate (327.5 mg, 1.84 mmol, 3.1 eq) were dissolved in dry Et_2O (10 mL) under a nitrogen atmosphere. To this, copper (I) iodide (11.5 mg, 0.06 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (37.6 mg, 0.06

mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 ^{0}C for 20 hours. The mixture was then concentrated in vacuo and purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield **101a** as a brown oil (137.5 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.30 (2H, d, J = 8.2 Hz, H-2), 7.21 (2H, d, J = 8.2 Hz, H-3), 7.00 (1H, dt, J = 15.6 Hz, 6.8 Hz, H-5), 6.19 (1H, dt, J = 15.6 Hz, 1.6 Hz, H-4), 2.36 (3H, s, H-1), 2.35-2.30 (2H, m, H-6), 1.66-1.60 (2H, m, H-7), 1.24 (6H, s, H-8) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ188.7, 146.7, 139.8, 134.6, 130.1, 127.9, 124.2, 70.7, 41.7, 29.5, 27.5, 21.5 ppm. **IR** (film NaCl): ν_{max} 3409,2970, 2925, 1686, 1631, 1494, 1450, 1378, 1211, 1140, 1034, 997, 925, 906, 808, 705 cm^{-1}. **ESI-MS**: m/z calcd for $C_{15}H_{20}NaO_2S^+$ ($M+Na^+$) 287.1076; found 287.1080; $C_{15}H_{21}O_2S^+$ ($M+H^+$) 265.1257; found 265.1258

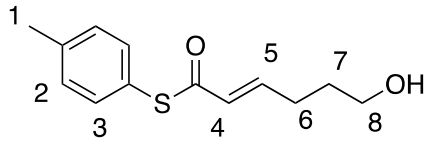
***S*-*p*-*T*olyl-2-(5,5-dimethyltetrahydrofuran-2-yl)ethanethioate (103a)**



(*E*)-*S*-*p*-Tolyl 6-hydroxy-6-methylhept-2-enethioate (19.2 mg, 0.073 mmol) was dissolved in DCE (1.2 mL) and H_2O (0.2 mL) was added and cooled in ice. To this, a solution TFA in DCE (1.8 mL, 0.06 M) was added over three minutes. The reaction mixture was heated at 50 ^{0}C for 24 hours. The reaction mixture was then quenched with saturated $NaHCO_3$ solution (1 mL) and diluted with DCM (2 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a crude yellow oil. The oil was purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield **103a** as a yellow oil (6.9mg, 36%).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.27 (d, 2H, J = 8.1 Hz, H-2), 7.19 (2H,d, J = 8.1 Hz, H-3), 4.40-4.33 (1H, m, H-5), 2.99 (1H, dd, J = 14.8 Hz, 7.3Hz, H-4), 2.64 (1H, dd, J = 14.8 Hz, 5.7Hz, H-4), 2.35 (3H, s, H-1), 2.20-2.10 (m, 1H, H-6) 1.80-1.70 (3H, m, H-6 + 2x H-7), 1.26 (3H, s, H-8), 1.22 (3H, s, H-9) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ195.8, 139.8, 134.6, 130.1, 124.3, 81.3, 75.0, 50.3, 38.3, 31.8, 29.3, 28.2, 21.5 ppm **IR** (film NaCl): ν_{max} 2960, 2924, 2853, 1705, 1463, 1439, 1365, 1260, 1141, 1055, 1002, 806, 758 cm^{-1}. **ESI-MS**: m/z calcd for $C_{15}H_{20}NaO_2S^+$ ($M+Na^+$) 287.1076; found 287.1078.

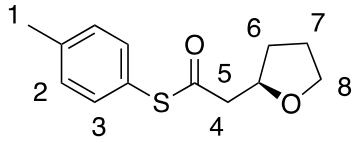
(*E*)-*S*-*p*-Tolyl 6-hydroxyhex-2-enethioate (101b)



Pent-4-en-1-ol (43.1 mg, 0.5 mmol, 1.0 eq) and *S*-*p*-tolylprop-2-enethioate (274.0 mg, 1.54mmol, 3.08 eq) were dissolved in dry Et_2O (20 mL) under a nitrogen atmosphere. To this, copper (I) iodide (9.6 mg, 0.05 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (31.4 mg, 0.05 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 ^{0}C for 18 hours. The mixture was then concentrated *in vacuo* and purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield **101b** as a brown oil (93.5 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.30 (2H, d, J = 8.2 Hz, H-2), 7.21 (2H, d, J = 8.2 Hz, H-3), 6.97 (1H, dt, J = 15.5 Hz, 7.0 Hz, H-5), 6.20 (1H, dt, J = 15.5 Hz, 1.6 Hz, H-4), 2.36 (3H, s, H-1),3.65 (2H, t, J = 6.4 Hz, 6.4 Hz, H-8), 2.36 (3H, s, H-1), 2.32 (2H, dtd, J = 7.0 Hz, 7.0 Hz, 1.6 Hz, H-6), 1.76-1.70 (2H, m, H-7) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ188.7, 145.9, 139.8, 134.7, 130.1, 128.2, 124.1, 62.0, 30.9, 28.7, 21.4 ppm. **IR** (film NaCl): ν_{max} 3382, 3024, 2924, 2870, 1684, 1631, 1493, 1445, 1303, 1278, 1210, 1180, 1135, 1048, 990, 971, 868, 807 cm^{-1}. **ESI-MS**: m/z calcd for $C_{13}H_{16}NaO_2S^+$ ($M+Na^+$) 259.0763; found 259.0767

***S*-*p*-*T*olyl-2-(tetrahydrofuran-2-yl)ethanethioate (103b)**



(*E*)-*S*-*p*-Tolyl 6-hydroxyhex-2-enethioate (12.8 mg, 0.054 mmol) was dissolved in cyclohexane (2.6 mL). To this, (*R*)-TRIP (8.2 mg, 0.011 mmol, 20 mol %) was and stirred at 75 ^{0}C under a nitrogen atmosphere for 24 hours. The reaction mixture was then concentrated *in vacuo* and purified by column chromatography on silica using 5% ethyl acetate in petroleum ether to yield **103b** as a yellow oil (10.8 mg, 84%).

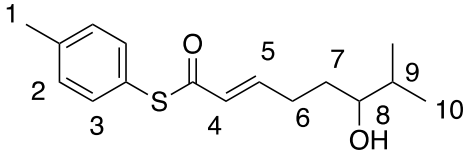
^{1}H NMR (400 MHz, $CDCl_3$): δ7.28 (2H, d, J = 8.1 Hz, H-2), 7.20 (2H,d, J = 8.1 Hz, H-3), 4.32-4.24 (1H, m, H-5), 3.89 (1H, dt, *J* = 8.0 Hz, 6.6 Hz, H-8), 3.75 (1H, td, *J* = 8.0 Hz, 6.6 Hz, H-8), 2.95 (1H, dd, J = 14.9 Hz, 6.7 Hz H-4), 2.76 (1H, dd, J = 14.9 Hz, 6.2 Hz, H-4), 2.36 (3H, s, H-1), 2.12-2.04 (1H, m, H-6), 1.96-1.84 (2H, m, H-7), 1.64-1.57 (1H, m, H-6) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ195.9, 139.9, 134.6, 130.2, 124.2, 75.6, 68.2, 49.4, 31.4, 25.7, 21.5 ppm **IR** (film NaCl): ν_{max} 2924, 2584, 1705, 1495, 1461, 1378,

1261, 1181, 1068, 1014, 807, 750 cm^{-1}. **ESI-MS**: m/z calcd for $C_{13}H_{16}NaO_2S^+$ ($M+Na^+$) 259.0763; found 259.0765.

$[\alpha]_D^{25.0}$ −14.3 (c = 0.50, $CHCl_3$) for the mixture.

HPLC (Chiralpak AD-H, 5% IPA, 95% hexane, 0.9 mL/min, λ = 254): t_R (major) = 14.1, t_R (minor) = 17.7, ee - 40%

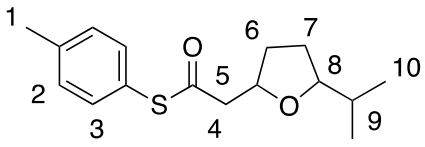
(*E*)-*S*-*p*-Tolyl 6-hydroxy-7-methyloct-2-enethioate (101c)



2-Methylhept-6-en-3-ol (129.0 mg, 1.01 mmol, 1.0 eq) and *S*-*p*-tolylprop-2-enethioate (550.1 mg, 3.09 mmol, 3.06 eq) were dissolved in dry Et_2O (20 mL) under a nitrogen atmosphere. To this, copper (I) iodide (19.2 mg, 0.101 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (63.2 mg, 0.101 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 ^{0}C for 16 hours. The mixture was then concentrated and purified by column chromatography on silica using 15 % ethyl acetate in hexane to yield **101c** as a brown oil (206.4 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.30 (2H, d, J = 8.0 Hz, H-2), 7.22 (2H, d, J = 8.0 Hz, H-3), 7.00 (1H, dt, J = 15.6 Hz, 6.9 Hz, 6.9 Hz, H-4), 6.21 (1H, dt, J = 15.6 Hz, 1.4 Hz, 1.4 Hz, H-5), 3.37 (1H, br s, OH), 2.50-2.40 (1H, m, H-8), 2.36 (3H, s, H-1), 2.35-2.25 (1H, m, H-9), 1.70-1.50 (4H, m, H-6 + H-7), 0.92 (3H, d, *J* = 3.7 Hz, H-10), 0.91 (3H, d, *J* = 3.7 Hz, H-10) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ186.7, 146.5, 139.8, 134.8, 130.2, 128.1, 124.2, 76.1, 34.0, 32.4, 29.1, 21.5, 18.9, 17.3 ppm. **IR** (film NaCl): ν_{max} 3448, 3025, 2958, 2870, 1677, 1631, 1494, 1461, 1385, 1282, 1210, 1138, 1029, 990, 807 cm^{-1}. **ESI-MS**: m/z calcd for $C_1H_{22}NaO_2S^+$ ($M+Na^+$) 301.1233; found 301.1234

***S*-*p*-Tolyl 2-(5-isopropyltetrahydrofuran-2-yl)ethanethioate (103c)**

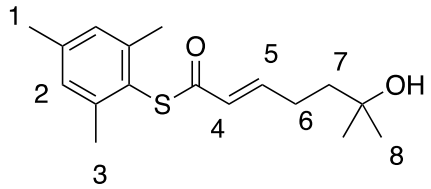


(*E*)-*S*-*p*-Tolyl 6-hydroxy-7-methyloct-2-enethioate (16.5 mg, 0.059 mmol) was dissolved in DCE (1 mL) and H_2O (0.2 mL) was added and cooled in ice. To this, a solution of TFA in DCE (1.8 mL, 0.06 M) was

added over three minutes. The reaction mixture was heated at 50 ^{0}C for 24 hours. The reaction mixture was then quenched with saturated $NaHCO_3$ solution (2 mL). The aqueous layer was extracted with DCM (3 x 10 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a crude yellow oil. The oil was purified by column chromatography on silica using 5% ethyl acetate in hexane to yield **103c** as an inseparable diastereomeric mixture (dr = 1.41:1) (9.4 mg, 58%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27 (4H, d, *J* = 8.2 Hz, H-2), 7.22 (4H, *J* = 8.2 Hz, H-3), 4.37-4.32 (1H, m, H-5_{major}), 4.31-4.24 (1H, m, H-5_{minor}), 3.56-3.50 (1H, m, H-8_{major}), 3.66-3.44 (1H, m, H-8_{minor}), 3.00-2.80 (2H, m, H-4_{major} + H-4_{minor}), 2.80-2.70 (2H, m, H-4_{major} + H-4_{minor}), 2.36 (6H, s, H-1_{major} + H-1_{minor}), 2.14-2.02 (2H, m, H-9_{major} + H-9_{minor}), 1.98-1.85 (2H, m, H-6_{major} + H-6_{minor}), 1.73-1.57 (6H, m, 2x H-7_{major} + H-6_{major} + 2x H-7_{minor} + H-6_{minor}), 0.96-0.94 (6H, m, H-10_{major} + H-10_{minor}), 0.86-0.82 (6H, m, H-11_{major} + H-11_{minor}) ppm **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 196.9, 139.8, 134.6, 130.1, 124.3, 85.3, 84.7, 75.4, 75.3, 50.0, 49.7, 33.3,33.2, 32.3, 31.2, 29.3, 28.3, 21.5, 19.5, 18.5, 18.4 ppm. **IR** (film, NaCl): ν_{max} 2958, 2925, 2872, 1705, 1494, 1468, 1380, 1270, 1166, 1070, 987, 806, 753 cm^{-1}. **ESI-MS**: m/z calcd for $C_{17}H_{25}NaO_2S^+$ ($M+Na^+$) 315.1389; found 315.1381

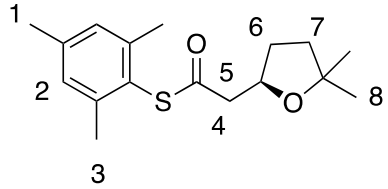
(*E*)-*S*-Mesityl 6-hydroxy-6-methylhept-2-enethioate (102a)



2-Methylhex-5-en-2-ol (68.4 mg, 0.6 mmol, 1.0 eq) and *S*-mesityl prop-2-enethioate (372.1 mg, 1.81 mmol, 3.01 eq) were dissolved in dry Et_2O (20 mL) under a nitrogen atmosphere. To this, copper (I) iodide (11.5 mg, 0.06 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (37.6mg, 0.06 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 ^{0}C for 18 hours. The mixture was then concentrated *in vacuo* and purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield **102a** as a brown oil (154.0 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.03-6.95 (3H, m, H-2 + H-5), 6.23 (1H, dt, J = 15.5 Hz, 1.4 Hz, H-4), 2.36-2.31 (2H, m, H-7), 2.30 (6H, s, H-8), 2.28 (3H, s, H-1), 1.68-1.64 (2H, m, H-6) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ187.8, 146.2, 142.8, 140.0, 129.3, 128.1, 123.6, 70.7, 41.8, 29.5, 27.4, 21.7, 21.3 ppm. **IR** (film NaCl): ν_{max} 3414, 2969, 2924, 1671, 1631, 1465, 1375, 1213, 1157, 1030, 996, 926, 850, 808 cm^{-1}. **ESI-MS**: m/z calcd for $C_{17}H_{24}NaO_2S^+$ ($M+Na^+$) 315.1389; found 315.1394

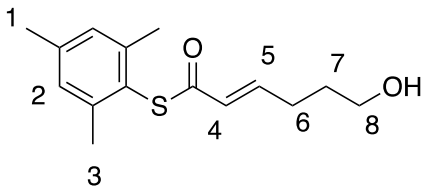
_S_-Mesityl 2-(5,5-dimethyltetrahydrofuran-2-yl)ethanethioate (104a)



(*E*)-*S*-Mesityl-6-hydroxy-6-methylhept-2-enethioate (19.0 mg, 0.065 mmol) was dissolved DCE (1.1 mL) and H_2O (0.2 mL) was added and cooled in ice. To this, a solution of TFA in DCE (1.8 mL, 0.06M) was added over three minutes. The reaction mixture was then heated at 50 ^{0}C for 24 hours. The reaction mixture was then quenched with saturated $NaHCO_3$ solution (2 mL) and diluted with DCM (2 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a crude yellow oil. The oil was purified by column chromatography on silica using 5% ethyl acetate in petroleum ether to yield **104a** as a yellow oil (13.0 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (2H, s, H-2), 4.40-4.33 (1H, m, H-5), 2.99 (1H, dd, J = 14.2 Hz, 6.0 Hz H-4), 2.73 (1H, dd, J = 14.2 Hz, 7.8 Hz, H-4), 2.29 (H, s, H-3), 2.27 (3H, s, H-1), 2.20-2.10 (1H, m, H-6) 1.80-1.70 (3H, m, H-6 + 2x H-7), 1.26 (3H, s, H-8), 1.21 (3H, s, H-9) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ195.8, 142.6, 140.0, 129.3, 123.9, 81.2, 75.3, 50.3, 38.3, 31.8, 29.3, 28.1, 21.7, 21.3 ppm **IR** (film NaCl): ν_{max} 2967, 2925, 2855, 1701, 1601, 1460, 1439, 1365, 1249, 1141, 1056, 1000, 980, 909, 849, 806, 737 cm^{-1}. **ESI-MS**: m/z calcd for $C_{17}H_{25}NaO_2S^+$ ($M+Na^+$) 293.1570; found 293.1571.

(*E*)-*S*-Mesityl 6-hydroxyhex-2-enethioate (102b)

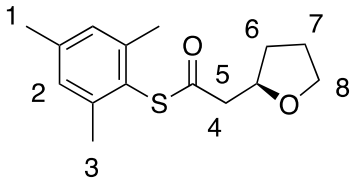


Pent-4-en-1-ol (34.5 mg, 0.4 mmol, 1.0 eq) and *S*-mesityl prop-2-enethioate (250.5 mg, 1.22 mmol, 3.04eq) were dissolved in dry Et_2O (20 mL) under nitrogen atmosphere. To this, copper (I) iodide (7.7 mg, 0.04 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (25.1 mg, 0.04 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 ^{0}C for 18 hours. The mixture was then concentrated *in vacuo* and purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield **102b** as a brown oil (86.8 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ7.02-6.92 (2H, m, H-2 + H-5), 6.24 (1H, dt, J = 15.6 Hz, 1.4 Hz, H-4), 3.69 (2H, t, J = 6.2 Hz, H-8), 2.36-2.32 (2H, m, H-6), 2.30 (6H, s, H-3), 2.28 (3H, s, H-1), 1.80-1.74 (2H, m, H-7) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ187.8, 145.3, 142.8, 129.3, 128.5, 123.5, 62.1, 30.9, 28.7, 21.8, 21.3 ppm. **IR** (film NaCl): ν_{max} 3357, 2923, 2855, 1682, 1631, 1437, 1375, 1315, 1280, 1210, 1175,

1136, 1044, 990, 971, 850, 798, 715 cm^{-1}. **ESI-MS**: m/z calcd for $C_{15}H_{20}NaO_2S^+$ ($M+Na^+$) 287.1076; found 287.1079

_S_-Mesityl 2-(tetrahydrofuran-2-yl)ethanethioate (104b)



(*E*)-*S*-Mesityl 6-hydroxyhex-2-enethioate (15.7 mg, 0.0595 mmol) was dissolved in cyclohexane (3 mL). To this, (*R*)-TRIP (9.0 mg, 0.012 mmol, 20 mol %) was added and stirred at 50 ^{0}C under a nitrogen atmosphere for 24 hours. The reaction mixture was diluted with DCM (3 mL) and quenched with saturated $NaHCO_3$ solution (2 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organics were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and purified by column chromatography on silica using 5% ethyl acetate in petroleum ether to yield **104b** as a yellow oil (11.5 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ6.96 (2H, s, H-2), 4.32-4.24 (1H, m, H-5), 3.89 (dt, *J* = 8.1 Hz, 6.6 Hz, 1H, H-8), 3.74 (td, *J* = 8.1 Hz, 6.6 Hz, 1H, H-8), 2.97 (1H, dd, J = 14.7 Hz, 6.4 Hz, H-4), 2.75 (1H, dd, J = 14.7 Hz, 6.5 Hz, H-4), 2.30 (6H, s, H-3), 2.27 (3H, s, H-1), 2.14-2.05 (m, 1H, H-6), 2.00-1.85 (2H, m, H-7), 1.66-1.50 (1H, m, H-6) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ195.0, 142.6, 140, 129.3, 123.8, 75.9, 68.1, 49.4, 31.2, 25.7, 21.7, 21.5 ppm **IR** (film NaCl): ν_{max} 2953, 2922, 2869, 1700, 1602, 1460, 1376, 1298, 1177, 1068, 1004, 850, 751, 715 cm^{-1}. **ESI-MS**: m/z calcd for $C_{15}H_{20}NaO_2S^+$ ($M+Na^+$) 287.1076; found 287.1073.

$[\alpha]_D^{25.0}$ −6.1 (c = 0.525, $CHCl_3$) for the mixture.

HPLC (Chiralpak AD-H, 5% IPA, 95% hexane, 0.9 mL/min, λ = 254): t_R (major) = 9.6, t_R (minor) = 12.5, ee - 10%

10. Abbreviations

Å	Ångstrom
Ac	acetyl
BHT	butylated hydroxy toluene (2,6-di-t-butyl-4-methylphenol)
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DMF	dimethylformamide
dr	diastereomeric ratio
ee	enantiomeric excess
eq	equivalent
ESI	electrospray ionization
Et	ethyl
FMO	Frontier Molecular Orbital
g	gram
h	hour
HFIP	1,1,1,3,3,3-Hexaflouro-2-propanol
HG-II	Hoveyda-Grubbs 2nd generation catalyst
HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i-Pr	isopropyl
IPA	isopropanol
IR	Infrared spectroscopy
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant (Hz)
kJ	kilojoule
LUMO	lowest unoccupied molecular orbital
M	molar
Me	methyl

mg	milligram
mL	milliliter
MHz	megahertz
MMFF	Merck Molecular Force Field
MOM	methoxymethyl
MS	molecular sieves
MW	microwave
NMR	nuclear magnetic resonance spectroscopy
Ph	phenyl
PMB	p-methoxybenzyl
rt	room temperature
TBAF	tetra-n-butylammonium fluoride
TBDPS	t-butyldiphenylsilyl
TBS	t-butyldimethylsilyl
t-Bu	tert-butyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
TFE	2,2,2-Triflouroethanol
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TIPSY	3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diylhydrogenphospate
TLC	thin layer chromatography
Tol	p-tolyl
TRIP	3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diylhydrogenphosphate
TS	transition state
v	vibration frequency (cm^{-1})

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