# Two-Directional Asymmetric “Clip-Cycle” Synthesis of 3,5-Disubstituted Pyrrolizidines and Indolizidines

Lee Charles Duff

Master of Science (by Research)

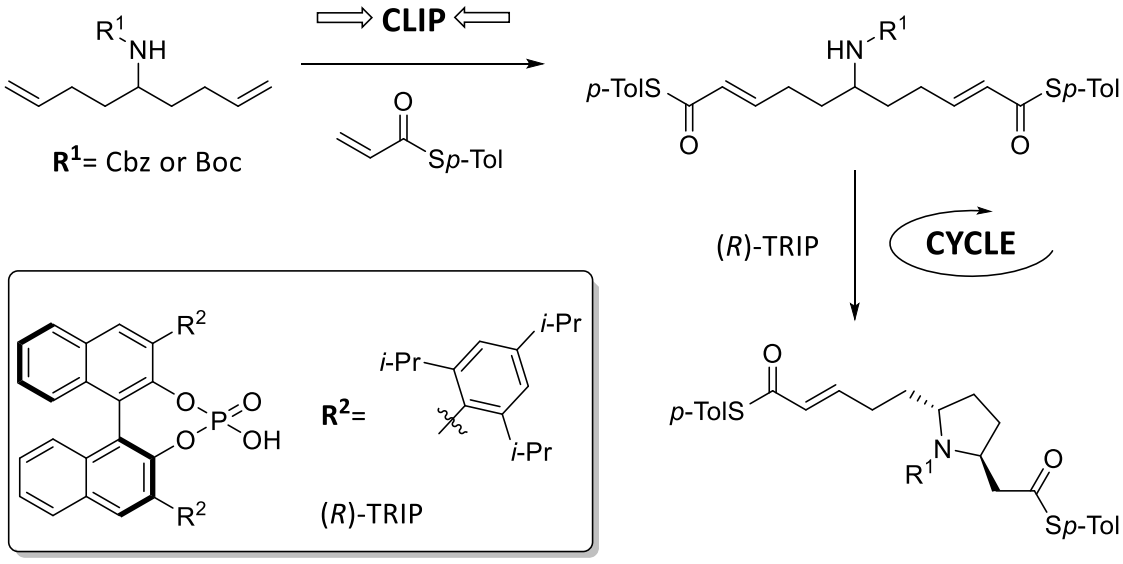
University of York

Chemistry

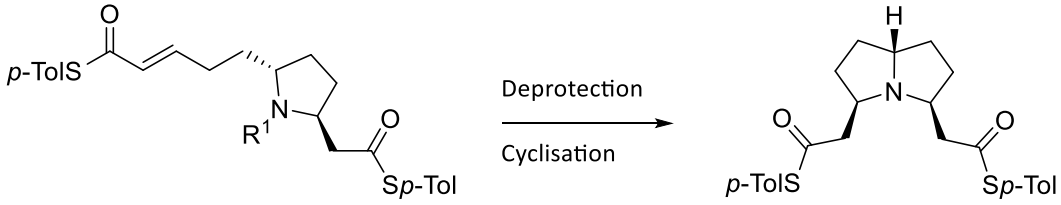
April 2021

# 1. Abstract

Two-directional synthesis is an effective strategy employed in the synthesis of 3,5-disubstituted pyrrolizidine and indolizidine alkaloids. This thesis reports the use of a two-directional approach coupled with a "clip-cycle" methodology to access the pyrrolizidine motif *via* an asymmetric pathway. The method involves clipping a linear protected amino-diene with an α,β-unsaturated thioester *via* a double alkene cross metathesis, followed by an asymmetric intramolecular Michael cyclisation catalyzed by a chiral phosphoric acid catalyst ((*R*)-TRIP). The use of an α,β-unsaturated thioester as the Michael acceptor in the intramolecular aza-Michael reaction allowed the chiral pyrrolidines to be obtained with high enantioselectivities and yields. Subsequent deprotection and cyclisation led to the formation of a *meso*-pyrrolizidine with a *cis-cis* configuration.




**Scheme 1.** Asymmetric "clip-cycle" synthesis




**Scheme 2.** Deprotection-cyclisation to form a 3,5-disubstituted pyrrolizidine

# 2. Contents

# 3. List of Figures

# 4. List of Schemes

# 5. List of Tables

# 6. Acknowledgements

Firstly, I would like to thank my supervisor Prof. Paul Clarke for welcoming me back into his group and offering me a wonderful opportunity to get back into chemistry after nine years away. I would like to thank Paul for his patience and support in helping me to readjust to working in a research laboratory again and for always being available to provide advice and guidance with my project, even during the difficult time brought about by the COVID-19 pandemic. I would also like to thank Paul for proofreading my thesis even when I failed to provide work to him in a timely fashion!

I would like to thank all the current members of the Clarke group for all their help and support in the lab and for creating a friendly and enjoyable atmosphere. A special thank-you to Chris and Saikiran for being my mentors and having an abundance of patience in answering all my stupid questions, of which there were many!

I would also like to thank Heather Fish for her help with obtaining NMR data and Karl Heaton for his help obtaining MS data, both of whom were always happy to answer any queries I had.

Finally, I would like to thank my family for all their help and support during my time at university, especially during lockdown when things were particularly difficult.

# 7. Declaration

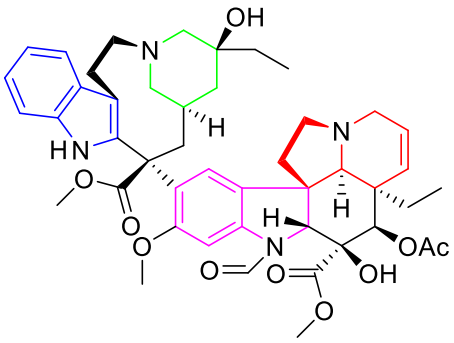
I hereby declare that the substance of this thesis has not been submitted, nor is currently being submitted, in candidature for any other degree.

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 as references.

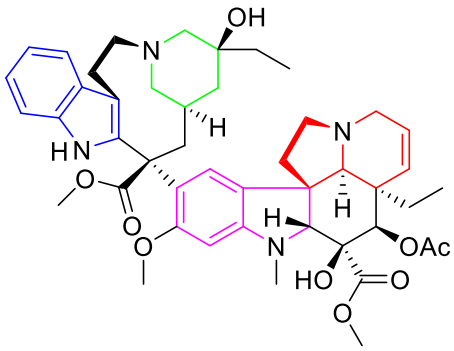
# 8. Introduction

## 8.1. Pyrrolizidine and Indolizidine Alkaloids

Natural products have become an appealing starting point for the discovery and development of new drug molecules. This is mainly due to their structural and chemical diversity and seemingly abundant occurrence in Nature, as new natural products are discovered frequently.[1] Within many of the drugs currently in use today *N*-heterocycles are the most commonly observed moiety, contributing to 59% of U.S. FDA approved pharmaceuticals.[2] A good example is the anticancer drugs Vincristine and Vinblastine extracted from the Madagascar Periwinkle plant (**Figure 1**).[3] Both compounds contain a piperidine (green), an indole (blue), an indoline (purple) and an indolizidine (red). Often it is difficult to extract natural products on a large enough scale to meet medical demands, and so synthetic routes for pharmaceutically important molecules must be established.




Vincristine




Vinblastine

**Figure 1.** Anticancer drugs Vincristine and Vinblastine

Herein, the focus is on the synthesis of the pyrrolizidine and indolizidine moiety found in many naturally occurring alkaloids. Pyrrolizidines have two five-membered rings fused together whereas indolizidines have a five-membered ring fused to six-membered ring, with both motifs sharing a common nitrogen atom. Pyrrolizidine and indolizidine alkaloids have been isolated from a wide range of sources in Nature, from poison dart frogs and ants to plants and trees (**Figure 2**).[4]

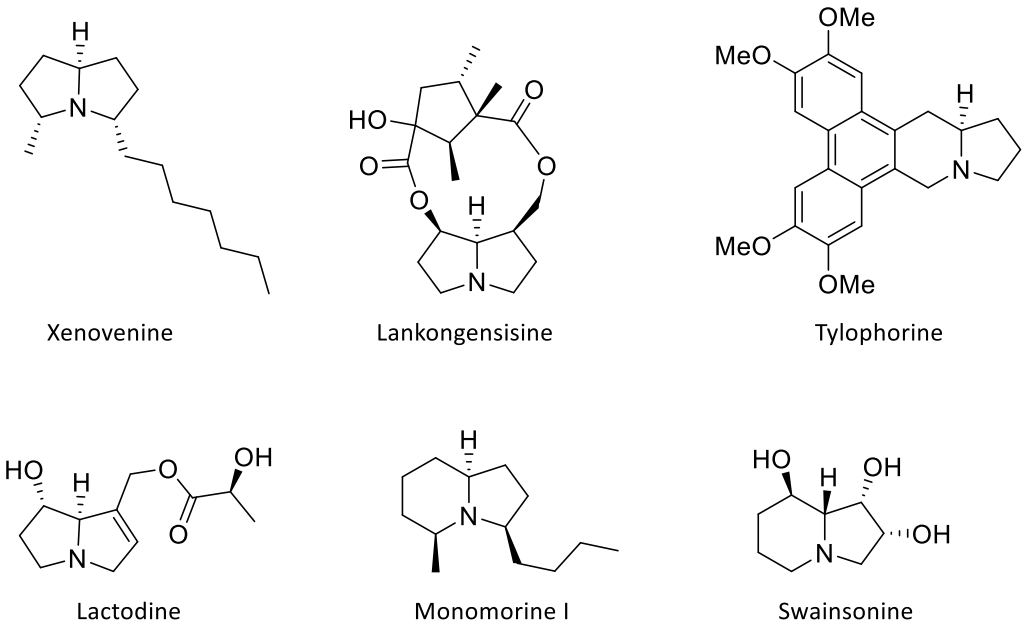



**Figure 2.** Representative examples of naturally occurring pyrrolizidine and indolizidine alkaloids

Many of these natural products have been shown to exhibit significant biological activity and have therefore garnered interest within the pharmaceutical industry as potential lead compounds for new drug discovery.[5] Mitomycin C, castanospermine and its analogue celgosivir are examples of the potential of small molecule pyrrolizidine and indolizidine alkaloids with medicinal properties (**Figure 3**). Mitomycin C has been used to treat a number of cancers due to its antitumor and antibiotic activity.[6] Castanospermine has been shown to inhibit the dengue virus found in mosquitoes,[7] whereas celgosivir is a potential treatment for the hepatitis C virus.[8] Numerous synthetic strategies have been developed for the synthesis of natural and unnatural pyrrolizidine and indolizidine alkaloids.[9]

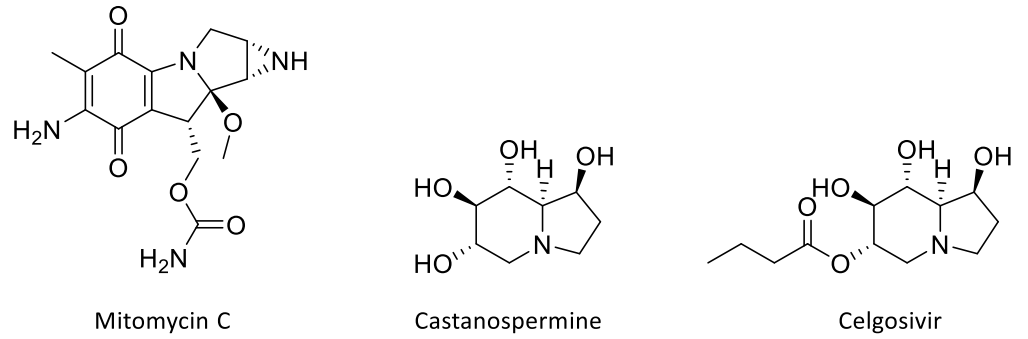


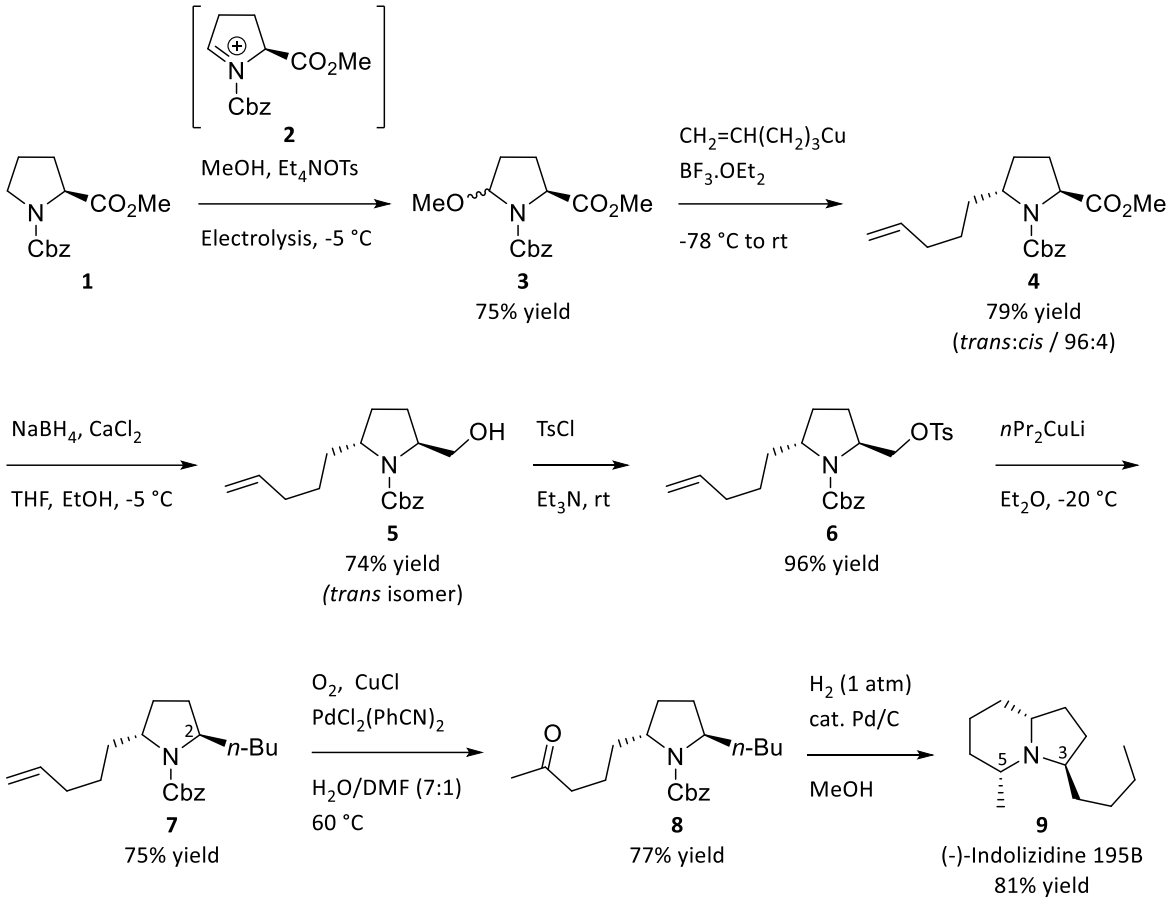

**Figure 3.** Pyrrolizidine mitomycin C and indolizidines castanospermine and celgosivir

## 8.2. Synthesis of 3,5-disubstituted Pyrrolizidine and Indolizidine Alkaloids

As a large number of pyrrolizidine and indolizidine alkaloids have now been isolated from Nature and many of them exhibit biological activities of interest to the pharmaceutical industry,[10] numerous methodologies towards the total synthesis of these important alkaloids have been developed.[9] Herein, we discuss a selection of synthetic approaches employed in the total synthesis of 3,5-disubstituted pyrrolizidine and indolizidine alkaloids.

A common strategy to enantioenriched alkaloids is the use of chiral pool synthesis, which utilizes enantiomerically pure starting materials that are cheap and readily available in Nature. Amino acids, hydroxy acids, carbohydrates and terpenes are the most frequently used naturally occurring molecules for this methodology. The strategy involves carrying forward the structure and inbuilt chirality of the starting material to the target molecule.[11] The amino acid proline has been shown to be an effective chiral synthon in the synthesis of pyrrolizidines and indolizidines.[12]

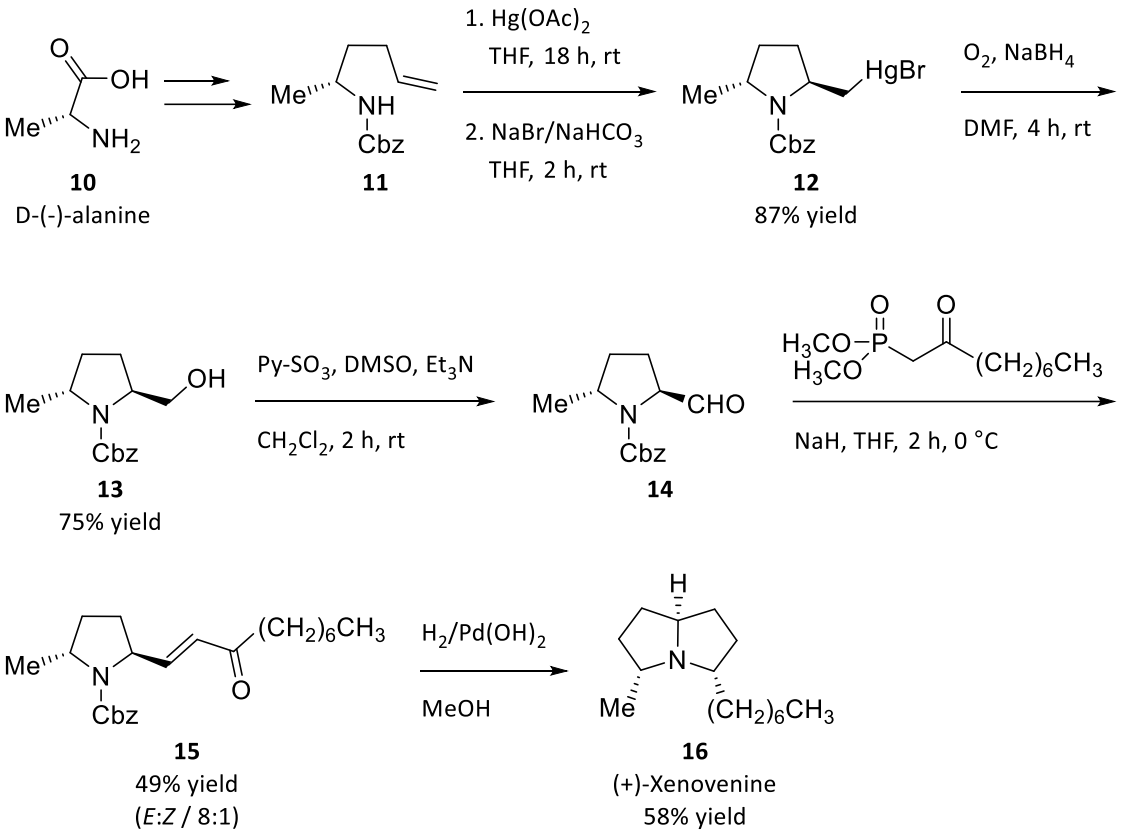
Lhommet *et. al*. demonstrate the use of (*S*)-proline for the total synthesis of (-)-indolizidine 195B.[13] The first key step involves an anodic α-methoxylation at the 5 position on the Cbz protected (*S*)-proline methyl ester **1** to form **3**, which proceeds via iminium ion intermediate **2** (**Scheme 3**). The second key step is the boron trifluoride mediated coupling of pent-4-enyl copper to generate **4**, which was achieved with a high diastereoselectivity towards the *trans* diastereomer (96:4). To install the butyl functionality located at the 3 position of (-)-indolizidine 195B, compound **4** underwent chemoselective reduction of the methyl ester using sodium borohydride to give alcohol **5**. At this stage the diastereomers could be separated allowing the *trans* isomer to be obtained in a 73% yield. Alcohol **5** was then tosylated to **6** before undergoing homologation by nucleophilic displacement of the tosylate group in the presence of excess *n*-$Pr_2CuLi$ to give **7**. This gave the desired butyl group at the 2 position of the pyrrolidine whilst the chirality of the stereocenter had been retained. Compound **7** was then converted into (-)-indolizidine 195B **9** in two steps. Firstly, oxidation of the terminal alkene to form ketone **8** *via* the Wacker process. Secondly, deprotection of the Cbz group *via* hydrogenolysis using $H_2$ and Pd/C, which led to the intramolecular cyclization to form (-)-indolizidine 195B **9** with an 81% yield. Overall, **9** was obtained with a 19% yield over 7 steps starting from **1**.




**Scheme 3**. Total synthesis of (-)-indolizidine 195B form (*S*)-proline[13]

Alternatively, Takahata and co-workers have accomplished the total synthesis of the pyrrolizidine alkaloid (+)-xenovenine using D-alanine as a chiral synthon.[14] Their synthesis began from *N*-alkenylurethane **11** which is readily available from D-alanine **10** (**Scheme 4**). Again, the chirality of **11** is carried through the synthesis to the final product and in this case no further manipulations to the methyl group were required. The first step involved the intramolecular cyclization of **11** to form the organomercury pyrrolidine **12** using mercury acetate. The reaction was found to be stereoselective towards the *trans* diastereomer, as after demecuration of **12** *via* oxidation gave only the *trans* diastereomer of alcohol **13** with a 75% yield. Primary alcohol **13** then underwent oxidation to aldehyde **14** using the Parikh-Doering oxidation method.[15] Without purification, elongation of aldehyde **14** was achieved *via* a Horner-Wadsworth-Emmons reaction, generating compound **15** in an overall yield of 49% from alcohol **13** with selectivity towards the *E*-alkene (*E*:*Z* / 8:1). Compound **15** then underwent simultaneous Cbz deprotection and alkene hydrogenation of the α,β-unsaturated ketone using $H_2$ with palladium hydroxide as a catalyst. This led to the

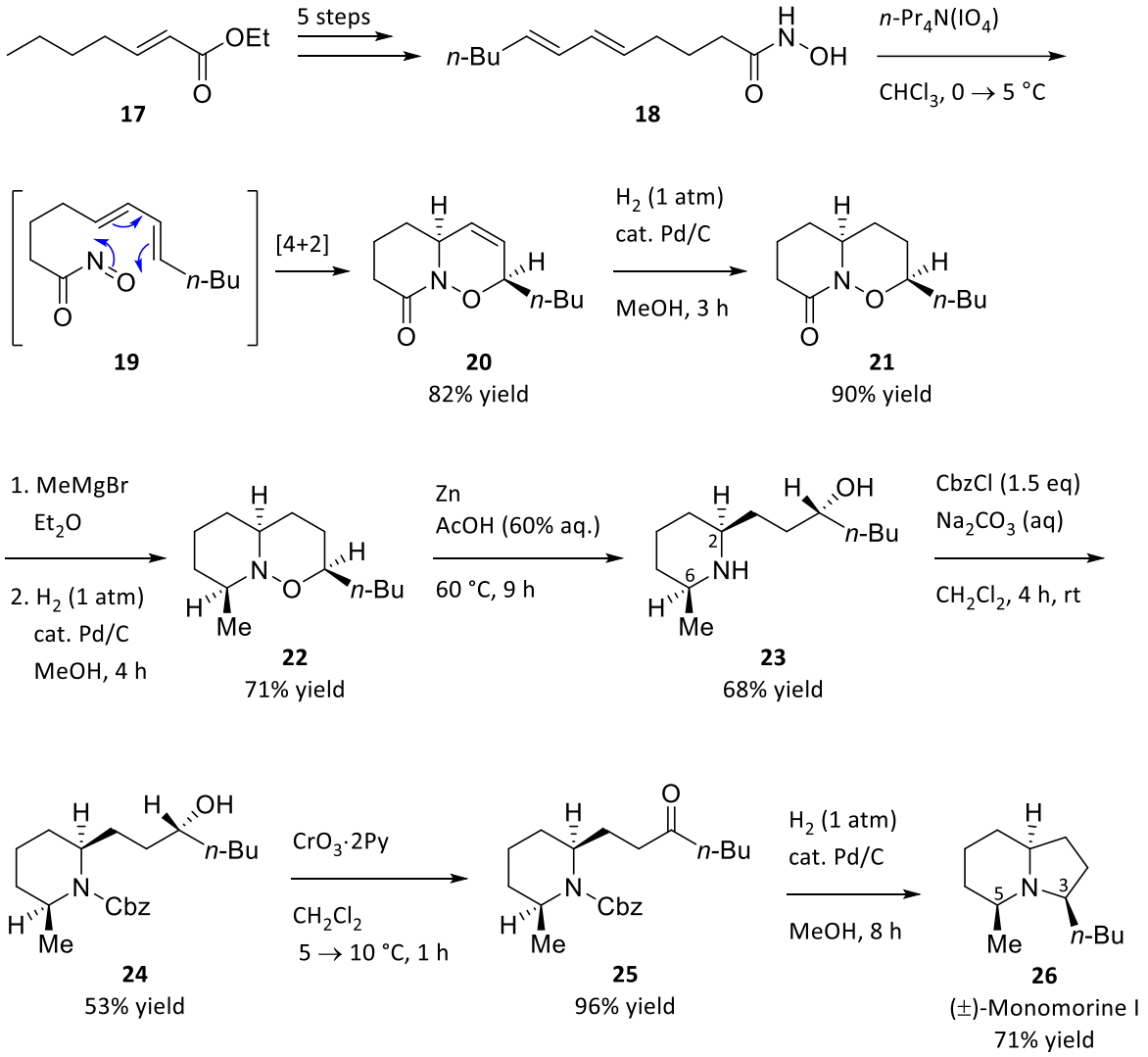
stereoselective intramolecular cyclization to form (+)-xenovenine **16** with a yield of 58%. Overall, **16** was obtained with a 21% yield over 5 steps starting from **11**.




**Scheme 4**. Total synthesis of (+)-xenovenine from D-alanine[14]

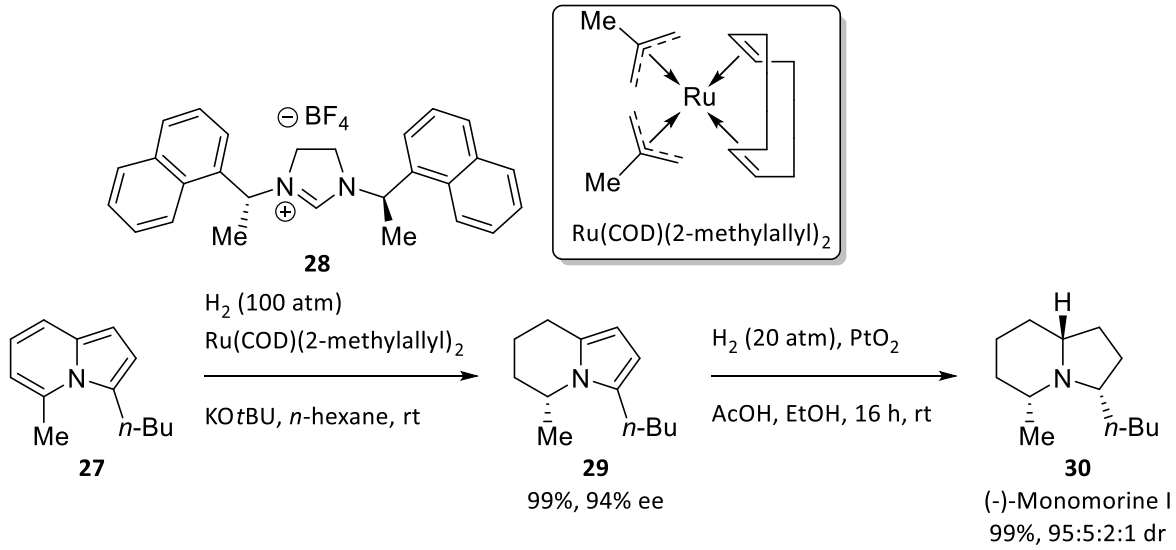
Another approach utilized for the synthesis of indolizidines is the application of the [4+2] cycloaddition reaction in forming six-membered rings. The intramolecular [4+2] cycloaddition reaction has been shown to be a useful method employed in the synthesis of natural products.[16] Watanabe *et*. *al*. report the total synthesis of (±)-monomorine using an intramolecular nitroso [4+2] cycloaddition reaction as a key step in the reaction sequence (**Scheme 5**).[17] Starting from hydroxamic acid **18**, obtained in 5 steps from (*E*)-2-heptenoate **17**, the bicyclic oxazine **20** was obtained *via* an *in-situ* [4+2] cycloaddition (**19**) after periodate oxidation. Oxazine **20** was isolated as a single diastereomer with a good yield of 82%. Here the nitroso group acts as the dienophile in the [4+2] cycloaddition reaction. Oxazine **20** is then converted to oxazine **21** by hydrogenation of the alkene using $H_2$ with Pd/C as the catalyst. To install the methyl functionality located at the 5 position of monomorine I, oxazine **21** underwent a Grignard reaction with methyl magnesium bromide followed by catalytic hydrogenation to give oxazine **22** as a single isomer with a yield of

71%. Reductive cleavage of the N-O bond using zinc dust in aqueous acetic acid led to the stereoselective formation of the 2,6-disubstituted piperidine **23**, which had the desired *cis* configuration. Piperidine **23** was then Cbz protected with benzyl chloroformate before undergoing a Collins oxidation of the secondary alcohol to form the ketone (**25**). With the ketone functionality installed, Cbz deprotection of piperidine **25** using $H_2$ with Pd/C as the catalyst allowed for the intramolecular cyclization to form monomorine I **26** racemically, with a yield of 71%.




**Scheme 5**. Total synthesis of (±)-monomorine I *via* a [4+2] cycloaddition reaction[17]

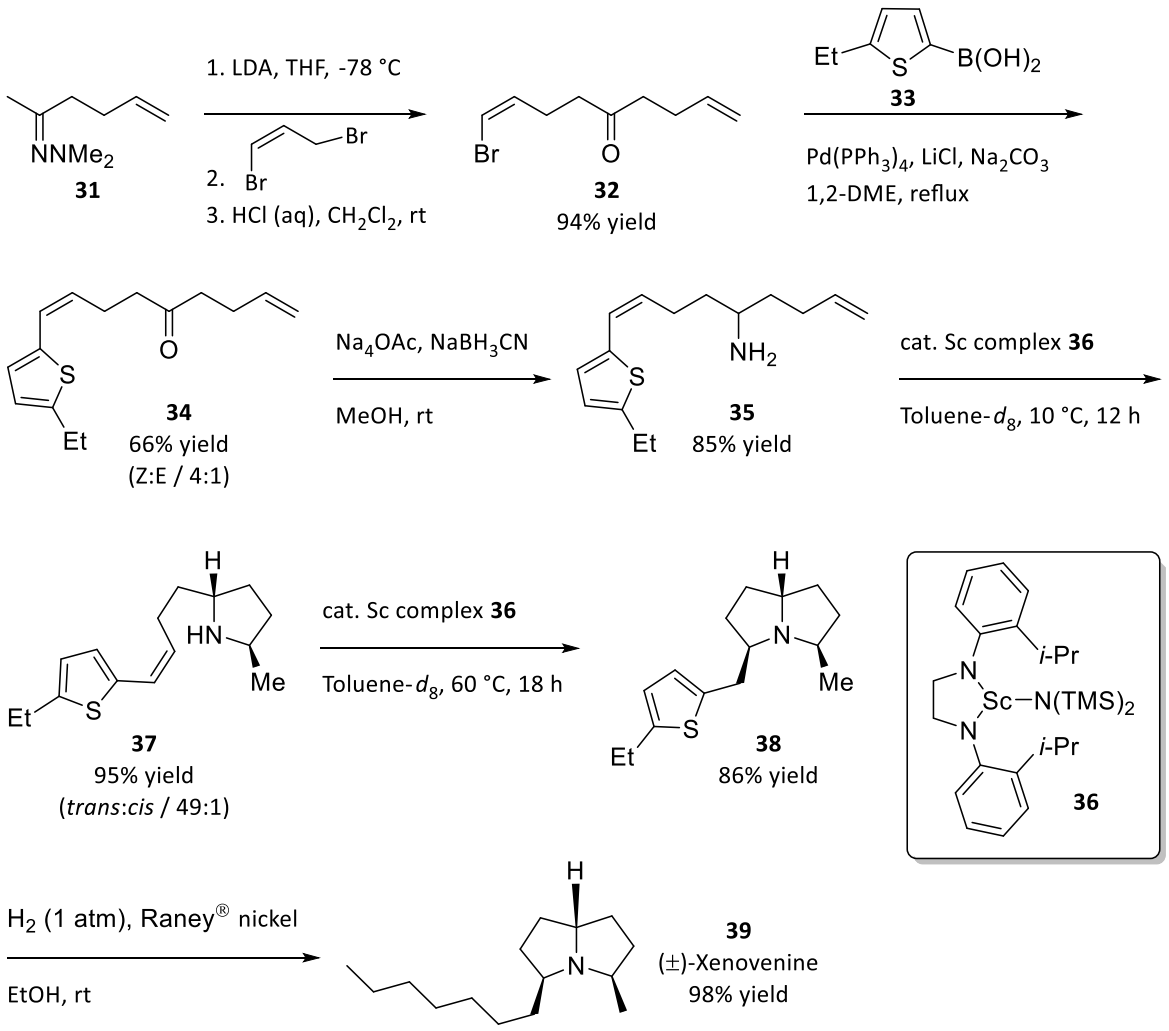
Recently, Glorius and co-workers have investigated a more direct route to indolizidines via catalytic hydrogenation of substituted indolizines using a chiral ruthenium complex with an *N*-heterocyclic carbene ligand. They have demonstrated the effectiveness of this strategy in the asymmetric synthesis of unnatural (-)-monomorine I (**Scheme 6**).[18] The use of chiral ligand **28** with the ruthenium complex allowed the hydrogenation of 3-butyl-5-methylindolizine **27** to form compound **29** in near quantitative yield. The reaction is both regioselective, only the six-membered ring is hydrogenated, and stereoselective generating **29** with an enantiomeric excess of 94%. Compound **29** was then subjected to a second catalytic hydrogenation using $H_2$ and Adams catalyst (platinum oxide) to generate monomorine I **30** in near quantitative yield with high diastereoselectivity (95:5:2:1 dr). The major product was determined to be the unnatural (-)-monomorine I **30**.




**Scheme 6**. Synthesis of (-)-monomorine I *via* catalytic hydrogenation[18]

Another strategy widely employed for the synthesis of pyrrolizidines and indolizidines is the use of transition metals to catalyze the intramolecular cyclization reaction to form six-membered or five-membered *N*-heterocycles with a high degree of stereoselectivity. This method is particularly useful for the stereocontrolled formation of new C-N bonds required for the synthesis of pyrrolizidines and indolizidines.[9] Livinghouse *et*. *al*. have reported a diastereoselective synthesis of (±)-xenovenine using a scandium complex to catalyze an intramolecular hydroamination cyclization (**Scheme 7**).[19] Starting from hydrazone **31,** ketone **32** was obtained *via* a 3 step one-pot reaction involving lithiation with LDA followed by alkylation and finally hydrolysis of the hydrazone. Ketone **32** was then coupled with 5-ethylthiophene-2-boronic acid (**33**) to form ketone **34**, which was

obtained as a mixture of *Z*- and *E*- isomers (4:1). The cyclization precursor **35** was then acquired *via* reductive amination of **34**. The importance of the alkylthiophene substituent becomes apparent during the second intramolecular cyclization, it not only activates the alkene allowing the cyclization to proceed at a lower temperature and reaction time, but also can be reduced to give the alkyl chain present in xenovenine.

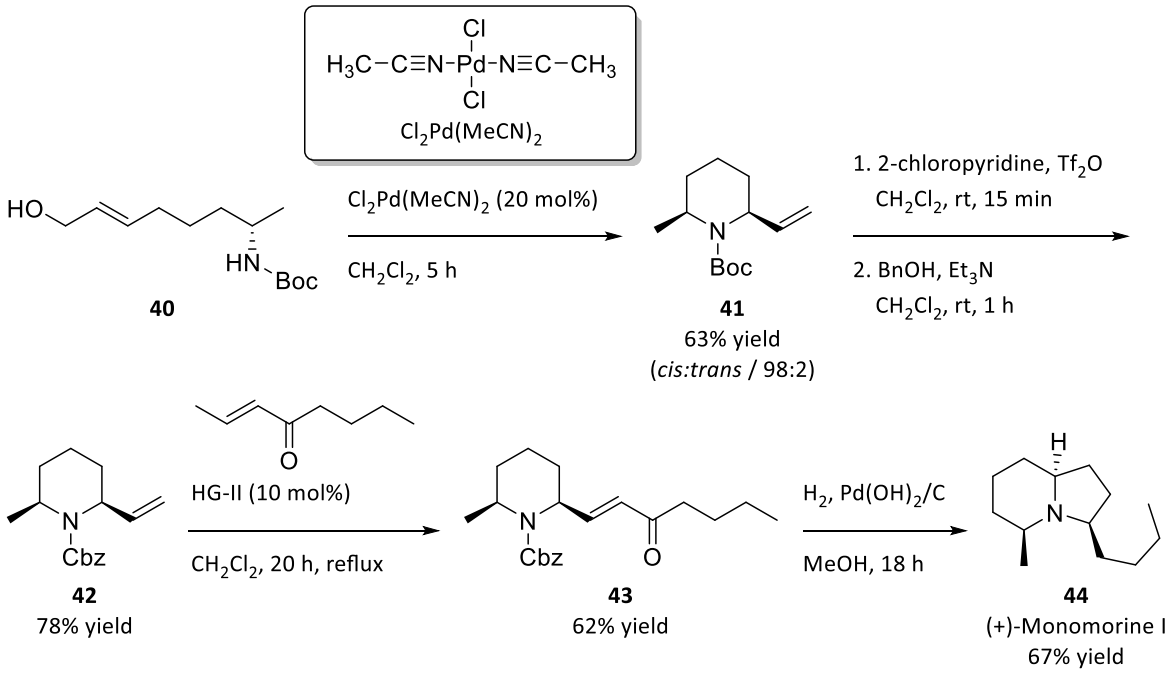



**Scheme 7**. Synthesis of (±)-xenovenine *via* transition metal catalyzed hydroamination[19]

Treatment of precursor **35** with the scandium complex **36** in deuterated toluene at 10 °C allowed the diastereoselective intramolecular cyclization to form pyrrolidine **37** in a high yield of 95%, with the *trans*-diastereomer as the major product (*trans*:*cis* / 49:1). The second cyclization to form pyrrolizidine **38** from pyrrolidine **37** was achieved by increasing the reaction temperature from 10 °C to 60 °C, they also noted that **38** could be obtained directly from **35** by running the reaction from

the start at 60 °C. Finally, reduction of the alkylthiophene substituent using Raney® nickel gave xenovenine **39** racemically in a 98% yield. Overall, (±)-xenovenine **39** was synthesized with a 44% yield in 5 steps starting from hydrazone **31**.

Makabe et. al. have reported an asymmetric synthesis of (+)-monomorine *via* a diastereoselective intramolecular aminopalladation.[20] Intramolecular aminopalladation involves the activation of an alkene by coordination of a palladium complex, the resulting alkene-palladium complex can then undergo nucleophilic attack by the nitrogen to form a heterocycle. This method has been shown to be a useful strategy in the synthesis of *N*-heterocycles in particular pyrrolidines and piperidines.[21] Makabe and coworkers utilize the intramolecular aminopalladation method to form a 2,6-disubstituted piperidine (**41**) diastereoselectively, as the key step in the synthesis of (+)-monomorine I (**Scheme 8**).




**Scheme 8**. Asymmetric synthesis of (+)-monomorine I *via* diastereoselective aminopalladation[20]

The reaction time was found to be an important factor in achieving the desired stereochemistry of the piperidine. When the reaction was run for 30 min piperidine **41** was obtained in a ratio of 67:33 in favor of the *cis*-diastereomer with a 49% yield. Whereas, increasing the reaction time to five hours allowed the formation of piperidine **41** in a ratio of 98:2 in favor of the *cis*-diastereomer with a 63% yield. They rationalized this result by proposing two transition states which are in equilibrium

as shown in **Figure 4**. Transition state **45** is more stable due to the chelation between the oxygen atom of the Boc group and the alcohol group with palladium and the absence of any steric clash between these groups shown in transition state **46**, which led to the 2,6-*trans*-piperidine **47**. Therefore, the favored route is via transition state **45** leading to the formation of the 2,6-*cis*-piperidine **41** as the major product.

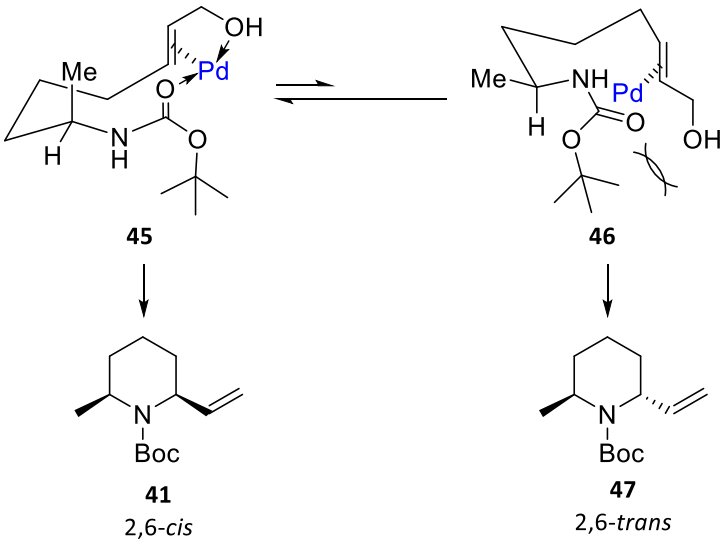


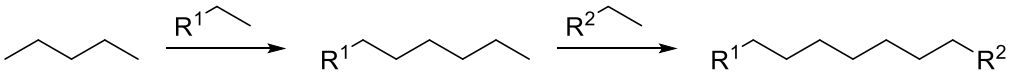

**Figure 4**. Preposed transition states for the selective formation of the 2,6-*cis*-piperidine[20]

The Boc group on piperidine **41** was then converted to a Cbz group to give piperidine **42**. Cross metathesis of piperidine **42** with 2-octen-4-one, using Hoveyda-Grubbs Catalyst™ 2nd generation, gave the desired chain elongation to form piperidine **43**. Simultaneous alkene hydrogenation and deprotection of **43** using $H_2$ and Pearlman's catalyst ($Pd(OH)_2/C$) allowed for the intramolecular cyclization to form (+)-monomorine I **44** with a 67% yield. The reason for changing the protecting group was because when the Boc protected piperidine was carried forward through the metathesis and subsequent alkene reduction, Boc deprotection and intramolecular cyclization a complex mixture was formed.

## 8.3. Two-Directional Synthesis of 3,5-disubstituted Pyrrolizidines and Indolizidines

Two- directional synthesis is a strategy employed for extending the chain of a linear substrate. this can be done sequentially, from either end of the substrate, or simultaneously, extending both ends *via* the same reaction (**Figure 5**). The two-directional strategy has been shown to be a useful approach in the synthesis of natural products.[22]

1. Sequential two-directional synthesis




2. Simultaneous two-directional synthesis

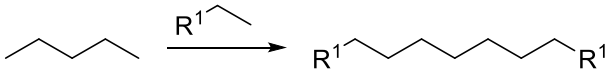
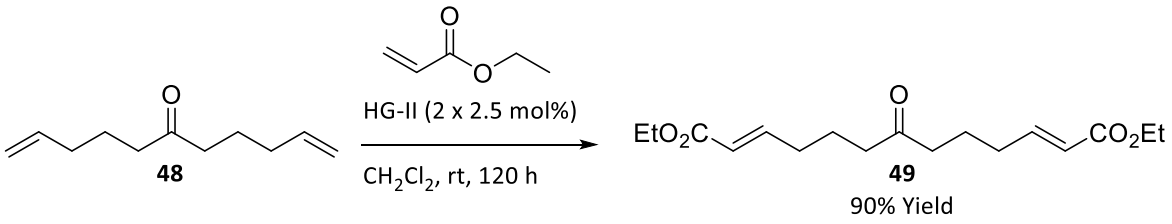



**Figure 5**. Two-directional synthesis of a linear substrate

An effective method utilized for the simultaneous two-directional synthesis is the double alkene cross metathesis reaction of linear dienes. Investigations into the two-directional cross metathesis reaction conducted by Stockman *et. al*.[23] showed that the reaction can be catalyzed by Hoveyda-Grubbs Catalyst™ 2nd generation at room temperature for a number of different alkenes. Their results demonstrated that the corresponding metathesis products could be obtained in high yields with selectivity towards the *E*,*E*-dienes (**Scheme 9**).

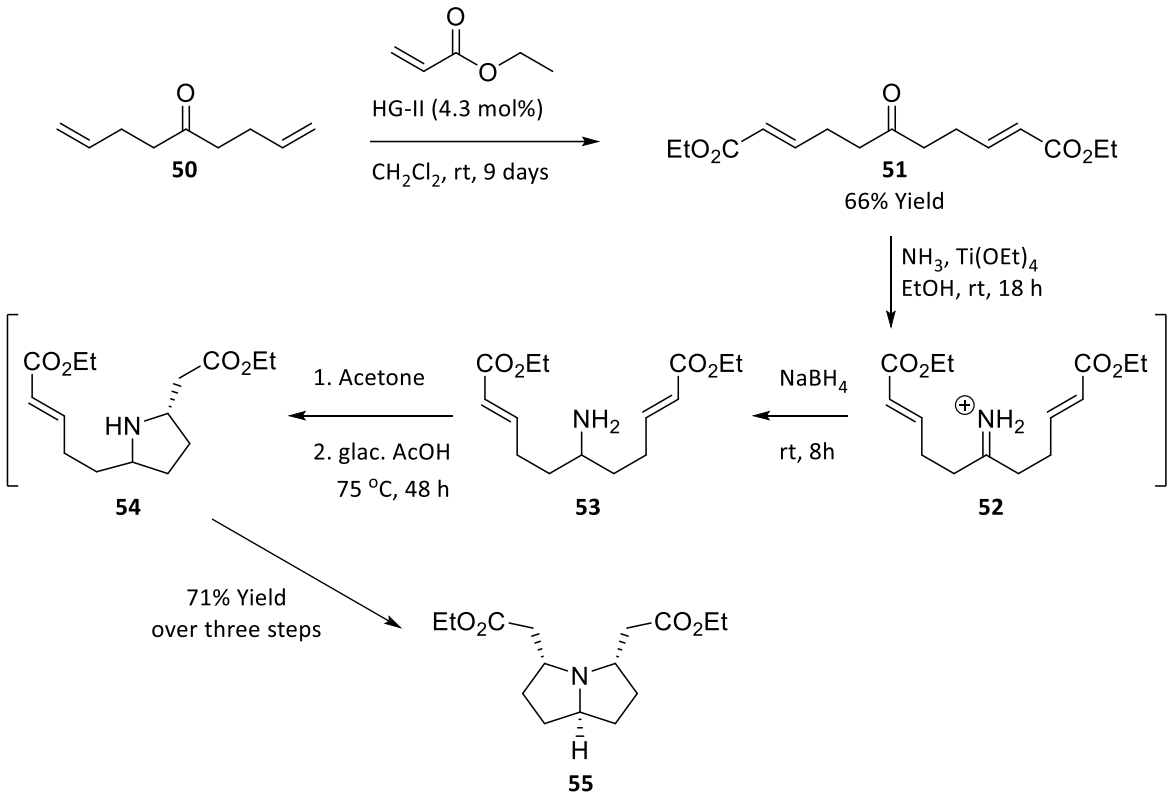



**Scheme 9**. Representative example for a two-directional cross metathesis[23]

The example in **Scheme 9** shows the two-directional double alkene cross metathesis between symmetrical diene **48** and 6 equivalents of ethyl acrylate, with 5 mol% of Hoveyda-Grubbs Catalyst™ 2nd generation to generate ketodiester **49** with an excellent yield of 90%. It is worth noting that

due to the long reaction time (5 days) they found that adding the catalyst in two portions (2nd portion after 24 h) gave the best results.

Stockman and co-workers have developed a strategy using the two-directional cross metathesis method coupled with tandem cyclisation reactions to access 3,5-disubstituted pyrrolizidines and reported the first total synthesis of pyrrolizidine alkaloid *cis*-223B.[24] For the initial method towards 3,5-disubstituted pyrrolizidines they utilized a tandem reaction involving a reductive amination followed by a double intramolecular aza-Michael cyclization over three steps in one pot (**Scheme 10**).

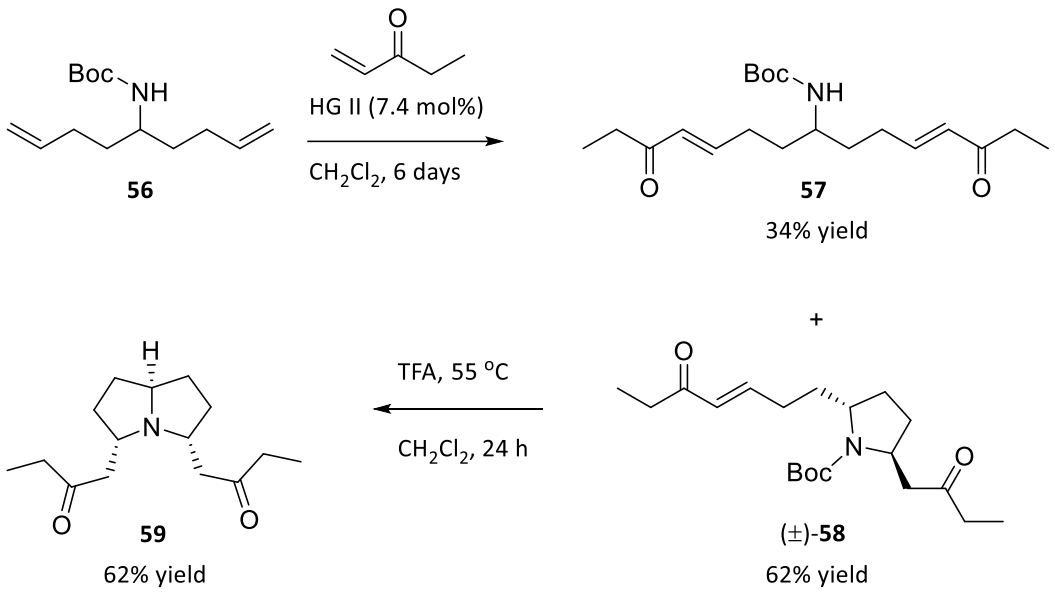



**Scheme 10**. Two-directional synthesis coupled with a tandem reductive amination-double Michael addition for the synthesis of pyrrolizidines[24]

The forward synthesis proceeded *via* a two-directional double alkene cross metathesis between symmetrical diene **50** and ethyl acrylate, catalyzed by Hoveyda-Grubbs Catalyst™ 2nd generation. This installed the α,β-unsaturated diethyl esters as the Michael acceptors required for the intramolecular cyclizations. Although the ketodiester **51** was isolated with a good yield of 66% a drawback to the metathesis would be the long reaction time of 9 days. They achieved the reductive

amination step by treating ketodiester **51** with ammonia which undergoes nucleophilic attack at the ketone to form a hemiaminal followed by elimination of water to form the iminium ion **52**. These steps are reversible and so titanium ethoxide was added to remove the water and drive the reaction towards the iminium ion, which was then reduced with sodium borohydride to form amine **53**. Excess sodium borohydride was removed by reacting it with added acetone before amine **53** underwent a double intramolecular aza-Michael cyclization catalyzed by glacial acetic acid. This was accomplished at a high temperature of 75 °C over a period of 48 hours. The resulting *meso*-pyrrolizidine **55** was isolated as a single diastereomer with a *cis*-*cis* configuration, with respect to the substituents and the bridgehead hydrogen, and in a yield of 71% over the three steps.

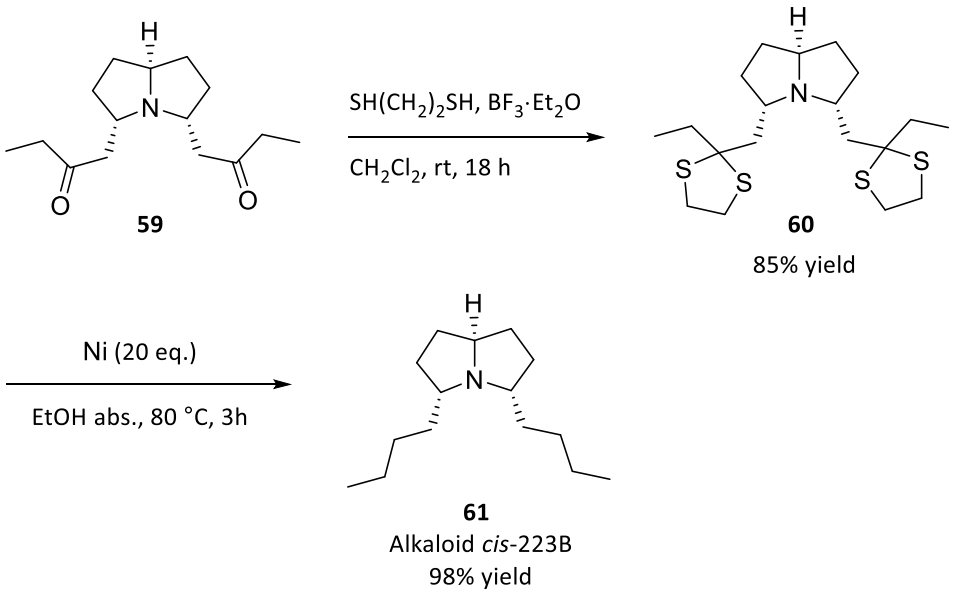
For the total synthesis of pyrrolizidine alkaloid *cis*-223B they changed the Michael acceptor to an enone in order install a diketone functionality to the pyrrolizidine which could then be reduced to form the alkaloid. As a result, they surmised that the tandem reductive amination-Michael addition method would not be appropriate due to the similar reactivity of the enones and the ketone. Instead they chose to use a Boc protected amino-diene (**Scheme 11**).




**Scheme 11**. Two-directional synthesis coupled with a tandem acid catalyzed double Michael addition for the synthesis of pyrrolizidine **59**[24]

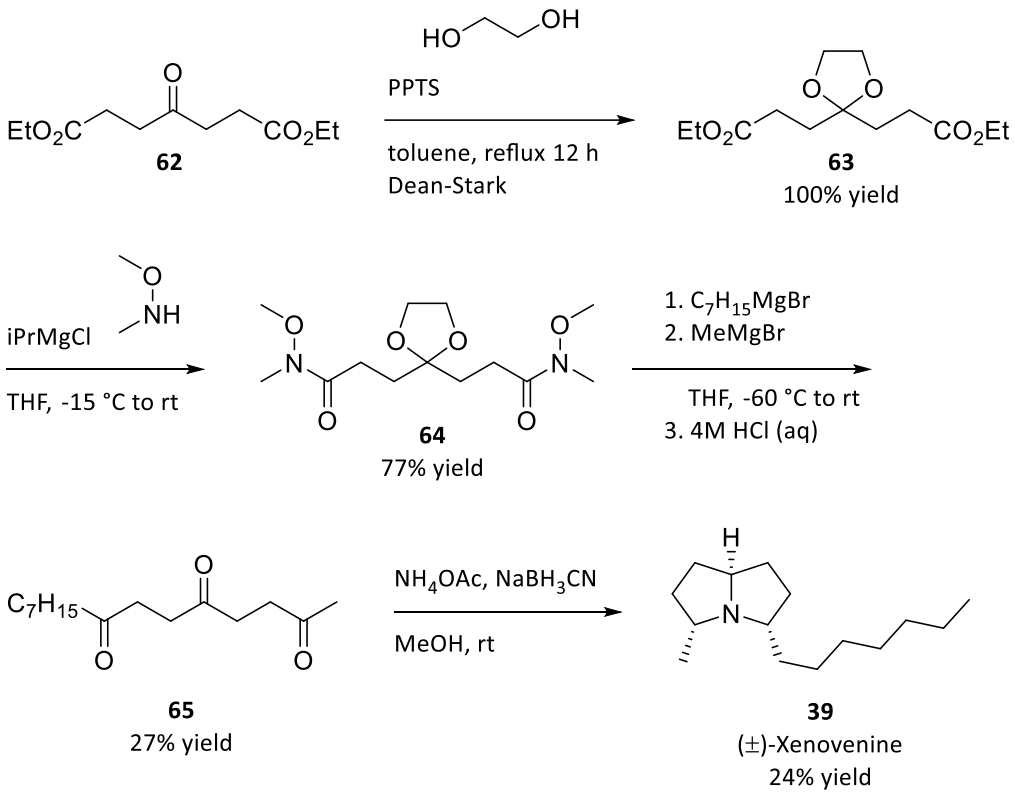
Interestingly, the metathesis between amino-diene **56** and 1-penten-3-one gave the racemic pyrrolidine **58** as the major product, demonstrating the increased reactivity of the α,β-unsaturated ketone compared to the α,β-unsaturated diethyl ester when used as Michael acceptors. The

subsequent deprotection and cyclisation of **57** and **58**, catalyzed by trifluoroacetic acid, generated the *meso*-pyrrolizidine **59** as a single diastereomer. Pyrrolizidine alkaloid *cis*-223B **61** was obtained from the reduction of the diketone functionality (**Scheme 12**). This was achieved by converting diketone **59** to dithioacetal **60** followed by reduction using Raney® nickel. The total synthesis of pyrrolizidine alkaloid *cis*-223B **61** was accomplished in 7 steps with an overall yield of 43%.



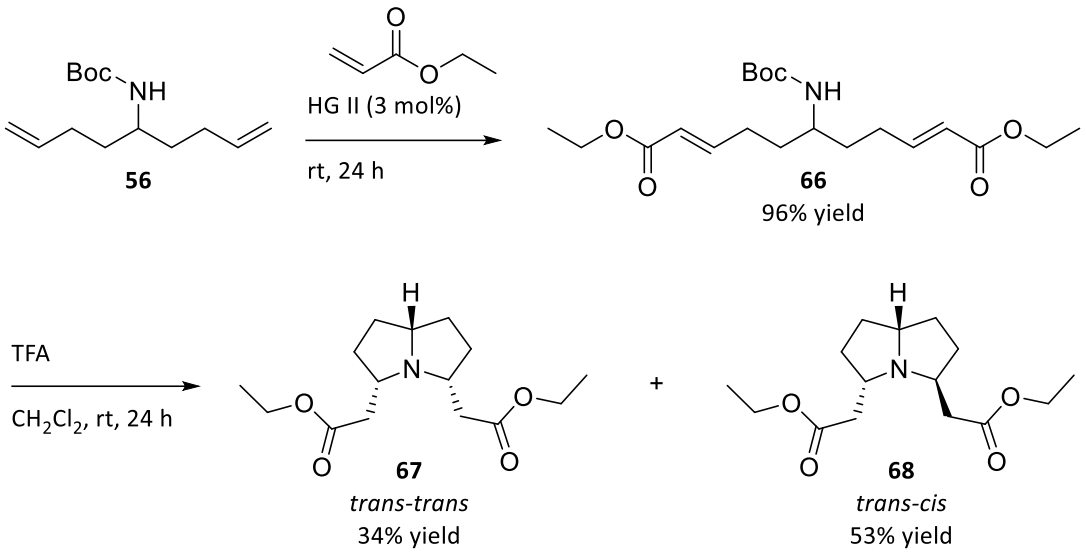

**Scheme 12**. Reduction of diketone **59** to give pyrrolizidine alkaloid *cis*-223B **61**[24]

Thus far, the two-directional tandem cyclisation methodology has led to the formation of symmetrical (*meso*) pyrrolizidines. Stockman *et*. *al*. has also reported a two-directional approach coupled with a tandem triple amination for the total synthesis of unsymmetrical 3,5-disubstituted pyrrolizidines.[25] The strategy was used for the diastereoselective synthesis of (±)-xenovenine (**Scheme 13**). The key steps involve the simultaneous formation of Weinreb diamide **64** followed by sequential Grignard reactions to install the alkyl chain at one end and a methyl group at the other, forming triketone **65**. Triple reductive amination of **65** using ammonium acetate and sodium borohydride generated the racemic pyrrolizidine xenovenine **39** as a single diastereomer. The total synthesis of (±)-xenovenine **39** was achieved in 4 steps with an overall yield of 5%.



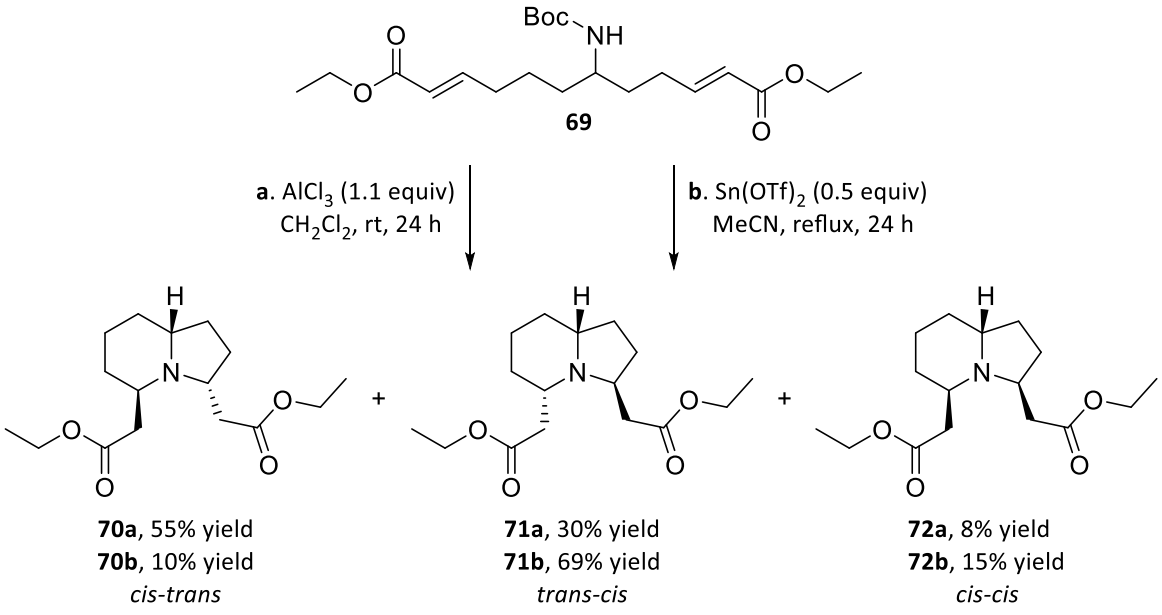

**Scheme 13**. Total synthesis of (±)-xenovenine **39** via a triple reductive amination[25]

Spring *et*. *al*. have also demonstrated the use of a two-directional approach to synthesize 3,5-disubstituted pyrrolizidines and indolizidines.[26] For the pyrrolizidines they use the same method as Stockman and co-workers used for Boc protected amino-dienes,[24] with the difference being the choice of the Michael acceptor utilized for the intramolecular double aza-Michael cyclizations. Instead of using an α,β-unsaturated ketone they used an α,β-unsaturated diethyl ester (**Scheme 14**). Interestingly this led to the formation of two different stereoisomers, the *trans-trans meso*-pyrrolizidine **67** and the *trans-cis* pyrrolizidine **68** with the latter being the major product. Also, the cross metathesis was accomplished with a shorter reaction time of 24 hours with an excellent yield of 96% and without the formation of the racemic pyrrolidine.




**Scheme 14**. Two-directional synthesis coupled with a tandem acid catalyzed double Michael addition for the synthesis of pyrrolizidines[26]

For the synthesis of the indolizidines, Lewis acids were used to catalyze the intramolecular double aza-Michael cyclization to achieve a degree diastereoselectivity, with each reaction generating a mixture of diastereomers (**Scheme 15**).

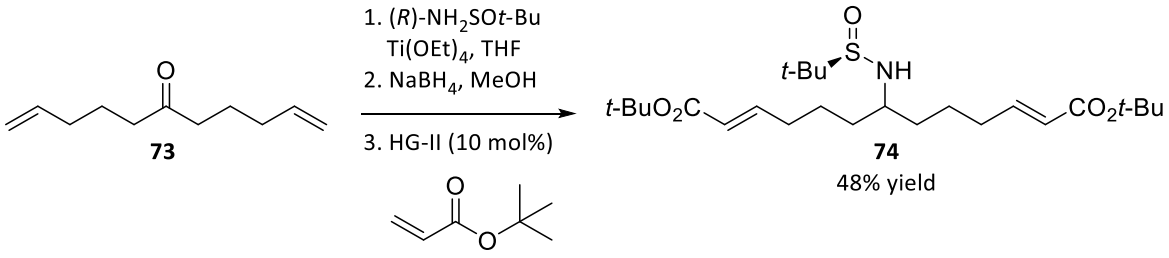



**Scheme 15**. Lewis acid catalyzed cyclization for the synthesis of indolizidines[26]

When the unsymmetrical amino-diene **69** was treated with aluminium trichloride the *cis*-*trans* indolizidine **70a** was generated as the major product (55% yield), whereas treating **69** with scandium triflate gave the *trans*-*cis* indolizidine **71b** as the major product (69% yield). In each case the *cis*-*cis* indolizidine **72a-b** was isolated as a minor product, suggesting that the formation of the *trans*-fused indolizidines were more thermodynamically stable than *cis*-fused indolizidine.

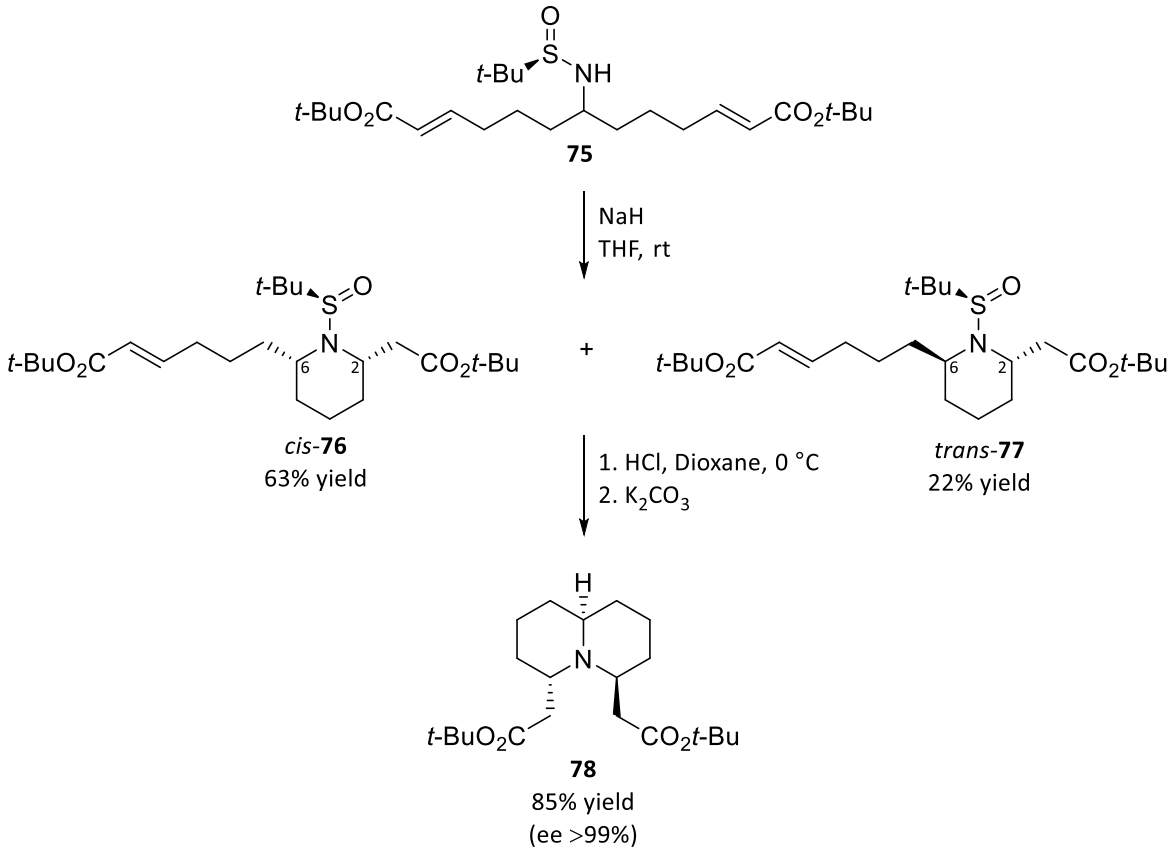
The work reported by Stockman *et*. *al*.[24/25] and Spring *et*. *al*.[26] has demonstrated successfully the diastereoselective synthesis of 3,5-disubstituted pyrrolizidines and indolizidines using a two-directional approach. However, to synthesize 3,5-disubstituted pyrrolizidines and indolizidines asymmetrically using this methodology would pose a greater challenge. Introduction of a chiral reagent would be needed to catalyze the first intramolecular aza-Michael reaction and control the enantioselectivity of the resulting chiral pyrrolidine. The choice of Michael acceptor would also be critical as to avoid the formation of the racemic pyrrolidine from the metathesis step and the effect it has on the enantioselectivity of the intramolecular cyclization.

A recent report by Fustero *et*. *al*. showed that it is possible to synthesize enantiomerically pure quinolizidines asymmetrically using a chiral sulfinyl amine as a chiral auxiliary and a source of nitrogen. The asymmetric reaction involves desymmetrization of a linear substrate *via* an intramolecular aza-Michael cyclization.[27] The method was utilized for the total synthesis of (-)-hippodamine and (+)-epi-hippodamine. The symmetrical cyclization precursor was synthesized by firstly installing Ellman's chiral auxiliary *via* reductive amination of ketodiene **73** followed by a two-directional double alkene cross metathesis with *tert*-butyl acrylate to give the diester **74** (**Scheme 16**).



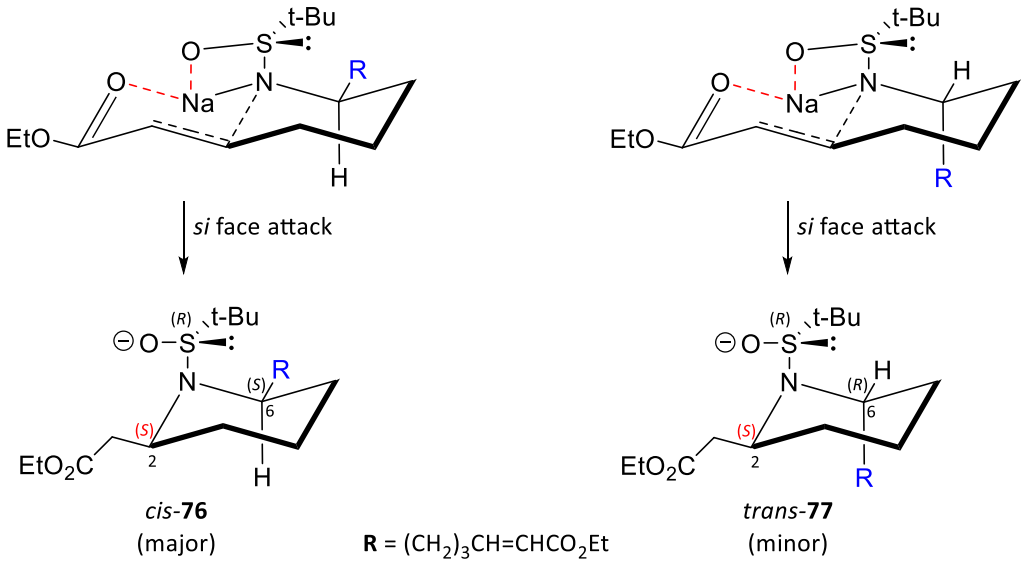

**Scheme 16**. Synthesis of quinolizidine cyclization precursor[27]

The initial intramolecular cyclisation using sodium hydride gave a mixture of the 2,6-*cis* and 2,6-*trans* disubstituted piperidines **76** and **77** (3:1), with the *cis* as the major product. Although the two diastereomers could be separated by flash column chromatography, this was not necessary as further cyclisation of both diastereomers led to the enantiomerically pure quinolizidine **78** (**Scheme 17**). Further manipulations of quinolizidine **78** over 3 steps gave access to a mixture of (-)-hippodamine and (+)-epi-hippodamine.[27]



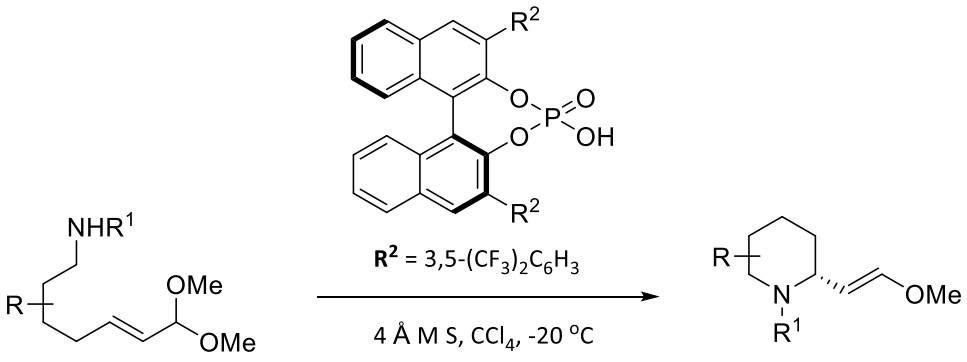

Scheme 17. Asymmetric synthesis of quinolizidine **78**[27]

The importance of the selectivity from the first intramolecular cyclization was not the *cis* or *trans* stereochemistry, but the fact that both diastereomers shared the same stereochemistry at the 2 position on the piperidine ring and the stereochemistry at the 6 position did not affect the second intramolecular cyclisation. The stereoselectivity of the first intramolecular cyclization was rationalized by two proposed transition states which showed *si* face attack of the nitrogen nucleophile and the importance of the sulfinyl auxiliary in directing the stereochemistry (**Scheme 18**). The major *cis* product arises from the bulky *tert*-butyl group (R) being in the equatorial position.




**Scheme 18**. Proposed transition states for the formation of piperidines **76** and **77**[27]

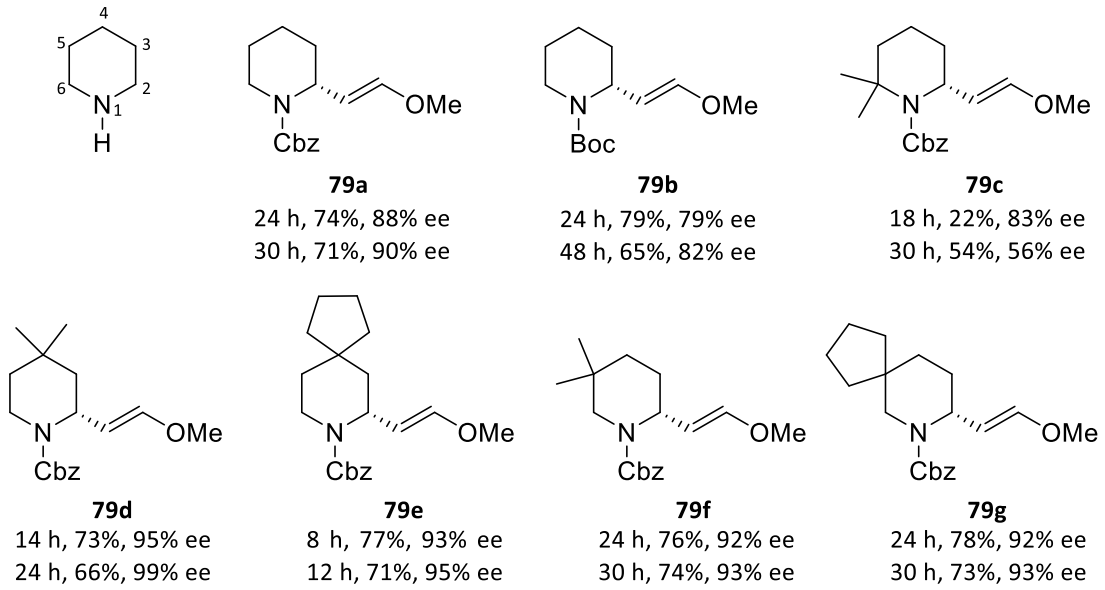
An alternative method for the synthesis of *N*-heterocycles *via* an asymmetric intramolecular aza-Michael reaction is the use of chiral Brønsted acid catalysts to induce enantioselectivity. Nagorny *et*. *al*. reported an enantioselective synthesis of functionalized chiral piperidines using an α,β-unsaturated dimethyl acetal, as the Michael acceptor, and a chiral phosphoric acid (CPA) to catalyze the intramolecular aza-Michael cyclization (**Scheme 19**).[28]




**Scheme 19**. General scheme for the CPA catalyzed synthesis of chiral piperidines[28]

The enantioselectivity of the resulting chiral piperidines was found to be highly dependent upon the polarity of the solvent, the temperature and the catalyst loading. Nonpolar solvents and low temperatures gave the best selectivity and yields. Using carbon tetrachloride as the solvent at -20

°C with a catalyst loading of 15 mol% were found to be the optimal conditions for these reactions. The procedure was found to be tolerant of substitution at the 4 and 5 positions on the piperidine ring (**79d-g**) and changes to the protecting group (**79a-b**), generating high yields and ees (**Figure 6**).




**79a**
24 h, 74%, 88% ee
30 h, 71%, 90% ee

**79b**
24 h, 79%, 79% ee
48 h, 65%, 82% ee

**79c**
18 h, 22%, 83% ee
30 h, 54%, 56% ee

**79d**
14 h, 73%, 95% ee
24 h, 66%, 99% ee

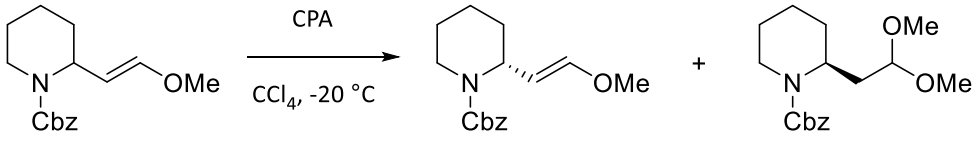
**79e**
8 h, 77%, 93% ee
12 h, 71%, 95% ee

**79f**
24 h, 76%, 92% ee
30 h, 74%, 93% ee

**79g**
24 h, 78%, 92% ee
30 h, 73%, 93% ee

**Figure 6**. Representative examples for the CPA catalyzed synthesis of chiral piperidines[28]

Interestingly, increasing the reaction time led to enantioenrichment in all cases except for substitution at the 6 position (**79c**), which led to an increase in yield but a decrease in enantioselectivity. The enantioenrichment was assumed to arise from a CPA catalyzed reaction between the minor enantiomer and methanol (a by-product of the reaction) leading to the formation of an acetal (**80**). This was demonstrated by subjecting racemic **79a** to the optimized reaction conditions (**Scheme 20**). Chiral piperidine **79a** was recovered with an increase in enantiomeric excess (53% ee).




(±)-**79a**

**79a**
41%, 53% ee

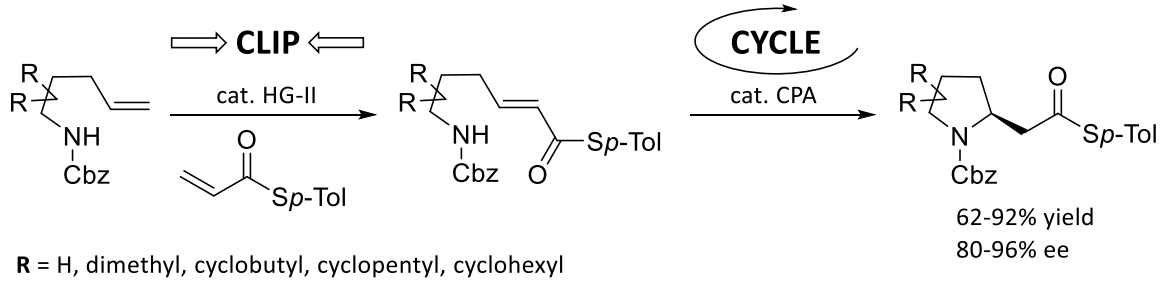
**80**
50%, 41% ee

**Scheme 20**. Enantioenrichment of racemic **79a**[28]

DFT computational analysis determined that the cyclisation proceeds *via* a two-step mechanism involving the formation of a mixed chiral phosphate acetal first which then undergoes a concerted asynchronous $S_N2'$-like mechanism to yield the chiral piperidines.[28] Although high yields and enantioselectivities were achieved, the method is not without its disadvantages such as the use of undesirable reaction conditions (-20 °C) and the high toxicity of carbon tetrachloride.

## 8.4. Brønsted Acid Catalyzed Synthesis of Chiral Pyrrolidines

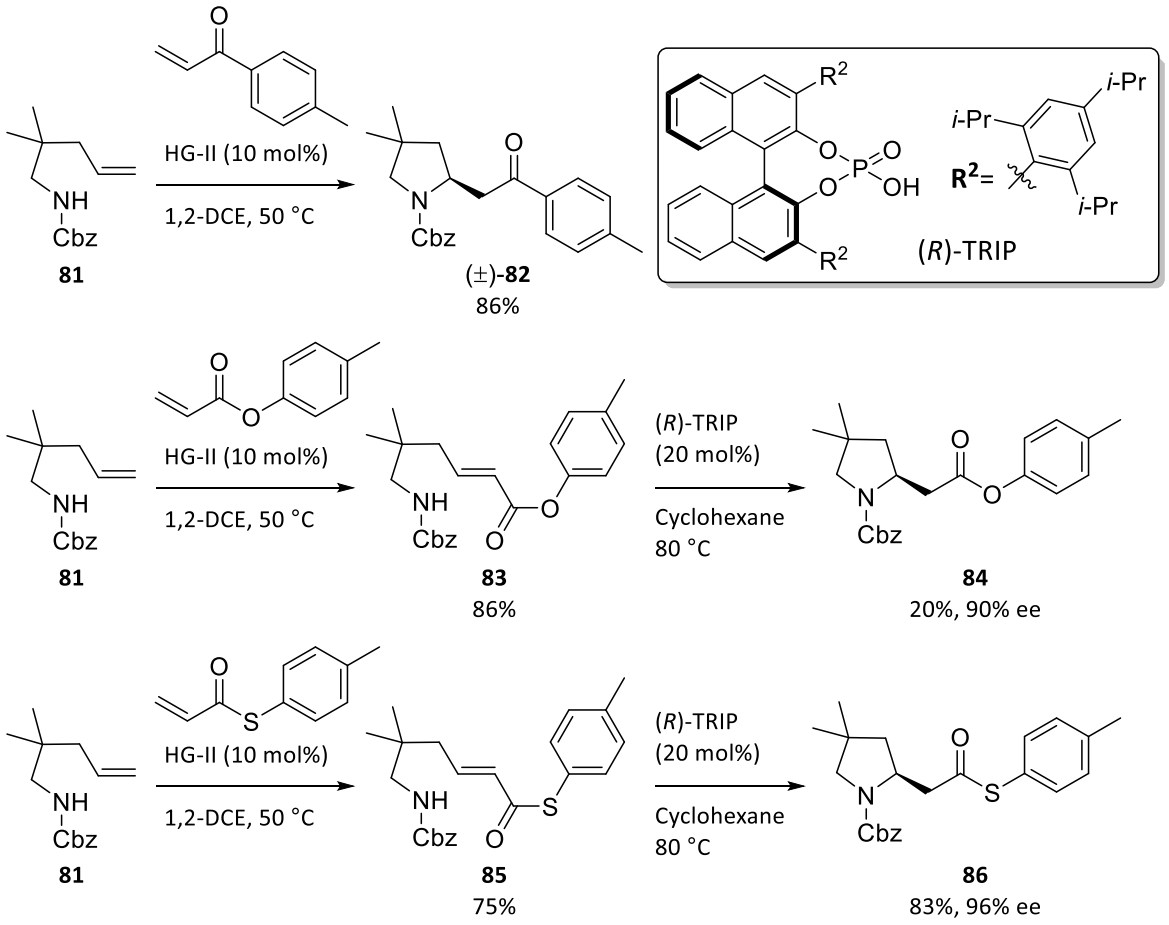
To investigate the potential of chiral phosphoric acid catalysts (CPAs) for the asymmetric synthesis of *N*-heterocycles, Clarke *et*. *al*. have developed an asymmetric "clip-cycle" strategy for the synthesis of 2,2- and 3,3-disubstituted pyrrolidines and spiropyrrolidines.[29] The "clip-cycle" methodology involves clipping a Cbz-protected amine with an α,β-unsaturated thioester *via* an alkene cross metathesis catalyzed by Hoveyda-Grubbs Catalyst™ 2nd generation. This is followed by an asymmetric intramolecular aza-Michael cyclisation, catalyzed by a CPA, to generate chiral pyrrolidines in high yields and ees (**Scheme 21**).




**Scheme 21**. General scheme for the "clip-cycle" synthesis of chiral pyrrolidines[29]

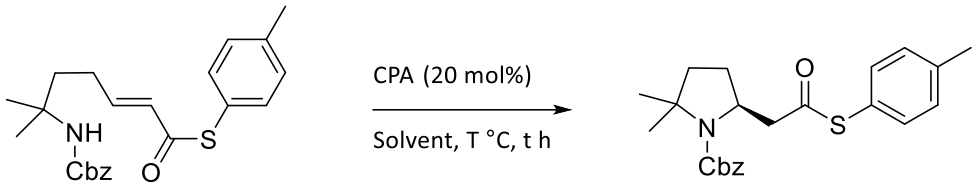
Selection of the α,β-unsaturated thioester as the Michael acceptor was critical for achieving high yields and enantioselectivities. Alternative Michael acceptors were tested for their suitability (**Scheme 22**). Cbz-protected amine **81** was clipped separately with an α,β-unsaturated ketone, an α,β-unsaturated oxoester and an α,β-unsaturated thioester before being cyclized with the CPA (*R*)-TRIP. The α,β-unsaturated ketone was found to be far too reactive producing the corresponding racemic 3,3-disubstituted pyrrolidine **82** directly from the cross metathesis. The α,β-unsaturated oxoester gave the metathesis product **83** in a high yield (86%) but upon cyclization only generated the 3,3-disubstituted pyrrolidine **84** with a yield of 20%, despite having a good enantiomeric excess

of 90%. However, the α,β-unsaturated thioester gave a good balance between reactivity and selectivity generating the metathesis product **85** with a yield of 75% and the 3,3-disubstituted pyrrolidine **86** with a yield of 83% and an enantiomeric excess of 96%.




**Scheme 22**. Comparison of Michael acceptors for the "clip-cycle" synthesis of chiral pyrrolidines[29]

The optimal conditions utilized to achieve high yields and ees for the chiral pyrrolidines from the asymmetric cyclisation were the result of extensive screening within the Clarke group.[30] The solvent, temperature, reaction time and CPA catalyst were all investigated using cyclisation precursor **87** to form the 2,2-dimethyl substituted pyrrolidine **88** (**Table 1** and **Figure 7**).




**87** **88**

| | **CPA** (20 mol%) | **Solvent** | **Temperature** (°C) | **Time** (h) | **Yield** (%) | **ee** (%) |
|---|---|---|---|---|---|---|
| **1** | (*R*)-TRIP | Cyclohexane | 80 | 24 | 77 | 92 |
| **2** | (*R*)-TRIP | Cyclohexane | 50 | 24 | 38 | 90 |
| **3** | (*R*)-TRIP | Cyclohexane | 50 | 48 | 46 | 94 |
| **4** | (*R*)-TRIP | Toluene | 50 | 24 | 18 | 92 |
| **5** | (*R*)-TRIP | 1,2-DCE | 50 | 24 | 12 | 90 |
| **6** | (*R*)-TiPSY | Cyclohexane | 80 | 24 | 22 | 58 |
| **7** | (*R*)-phen-cat | Cyclohexane | 80 | 24 | 21 | 46 |
| **8** | (*R*)-anth-cat | Cyclohexane | 80 | 24 | 99 | 62 |

**Table 1**. Reaction conditions screened for the cyclization of **87**[30]

The change in temperature resulted in a dramatic effect on the yield but only a minor effect on the ee. Using (*R*)-TRIP **89** at 80 °C gave a 77% yield whereas running the same reaction at 50 °C gave a 38% yield (entries 1 and 2). Increasing the reaction time did not result in a significant change in either yield or ee when the reaction was run at 50 °C for 24 hours and 48 hours (entries 2 and 3). Entries 2, 4 and 5 show that the CPA catalyzed reaction favored non-polar solvents with cyclohexane generating the highest yield (38%) compared to toluene (18%) and 1,2-DCE (12%). Interestingly the solvent had little effect on the enantioselectivity. However, changing the CPA had an effect on both the yields and ees. For (*R*)-TiPSY **90** and (*R*)-phen-cat **91** a substantial drop in both yield and ee was observed when compared to (*R*)-TRIP **89** (entries 1, 6 and 7). Whereas, (*R*)-anth-cat **92** showed a significant increase in yield but a decrease in ee when compared to (*R*)-TRIP **89** (entries 1 and 8). Overall, it was determined that using (*R*)-TRIP **89** in cyclohexane at 80 °C for 24

hours are the optimal reaction conditions for the synthesis of chiral pyrrolidines using the "clip-cycle" methodology (entry 1, highlighted blue).

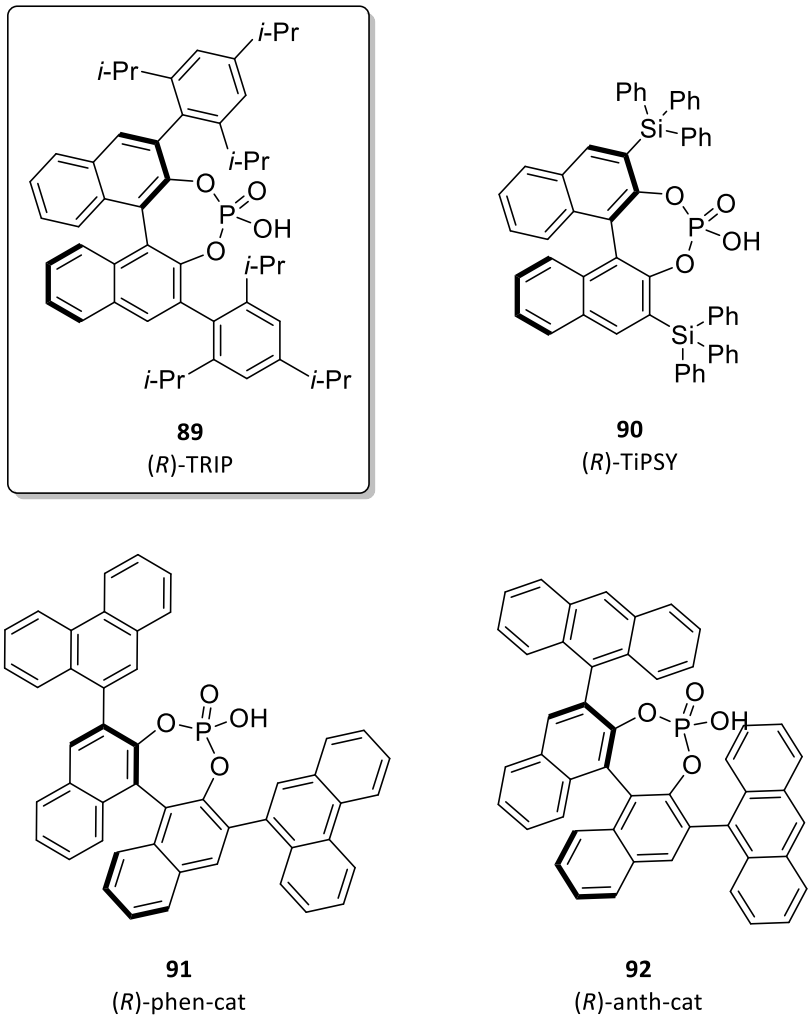



**Figure 7**. Chiral phosphoric acids tested for the asymmetric cyclization

Applying the optimized conditions in the "clip-cycle" methodology allowed chiral pyrrolidines and spiropyrrolidines to be synthesized with good yields and high enantioselectivities which was demonstrated for a range of substitutions at the 2 and 3 positions on the pyrrolidine ring (**Figure 8**).[29] For the synthesis of unsubstituted chiral pyrrolidine **93** (*R*)-TiPSY **90** was used as the catalyst to give the highest ee. The methodology could also be used as an effective strategy for the total synthesis of natural products. Pyrrolidine alkaloids (*R*)-bgugaine **96** and (*R*)-irnidine **97** were synthesized enantioselectively in 6 steps with overall yields of 33% and 18% respectively.[31]

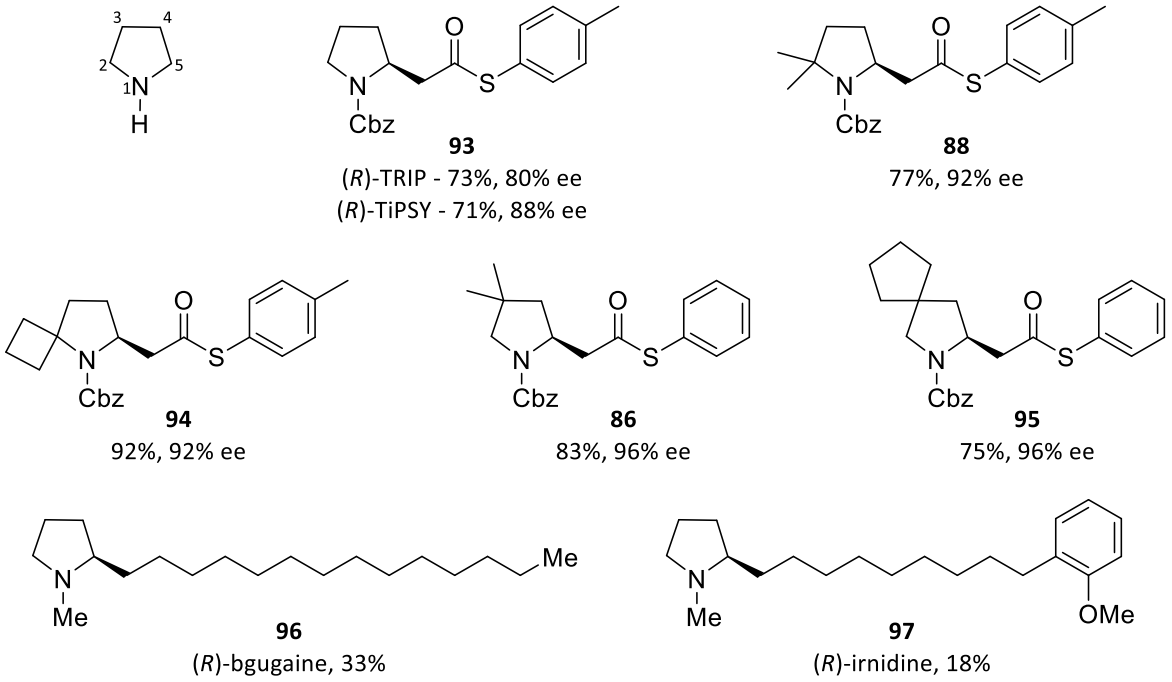
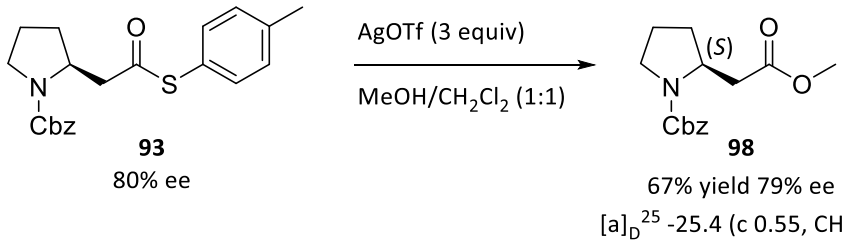



**Figure 8**. Representative examples of chiral pyrrolidines synthesized using the "clip-cycle" methodolgy[29/31]

The absolute stereochemistry of the CPA catalyzed cyclisation was determined by converting the unsubstituted chiral pyrrolidine **93** to a methyl ester *via* transesterification using silver triflate in methanol (**Scheme 23**).[32] As there was no erosion of the ee from the functional group transformation, comparison of the optical rotation of **98** with that of the same compound reported in the literature confirmed the stereochemistry to be (*S*) for the major enantiomer.[33]




**Scheme 23**. Transesterification of **93** to form the methyl ester[30]

DFT computation analysis of the CPA catalyzed cyclization has been conducted within the Clarke group.[29] The results showed that the CPA acts as a proton shuttle and proceeds *via* an aminoenol which tautomerizes to give the cyclized product. The intermediate aminoenol can adopt either an *S,E* configuration or an *R,Z* configuration. As shown in **Figure 9**, the *S*,*E* pathway is lower in energy

than the *R,Z* pathway and therefore the favored route for the cyclisation. This was attributed to the steric effect of the thioester α-proton which points inward, towards the catalyst pocket, for the *R,Z* pathway and outwards for the *S,E* pathway. Overall, the CPA catalyzed cyclization was determined to be the rate- and stereochemistry-determining step.

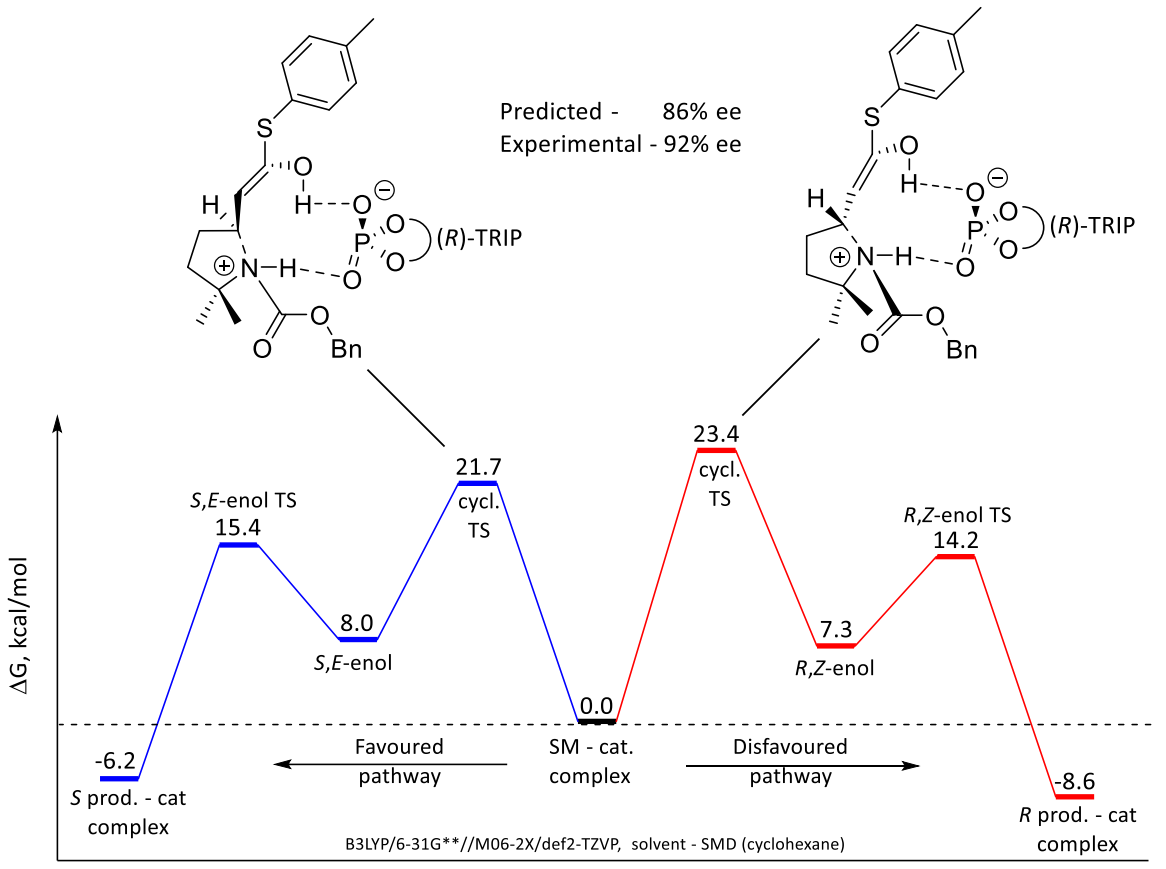
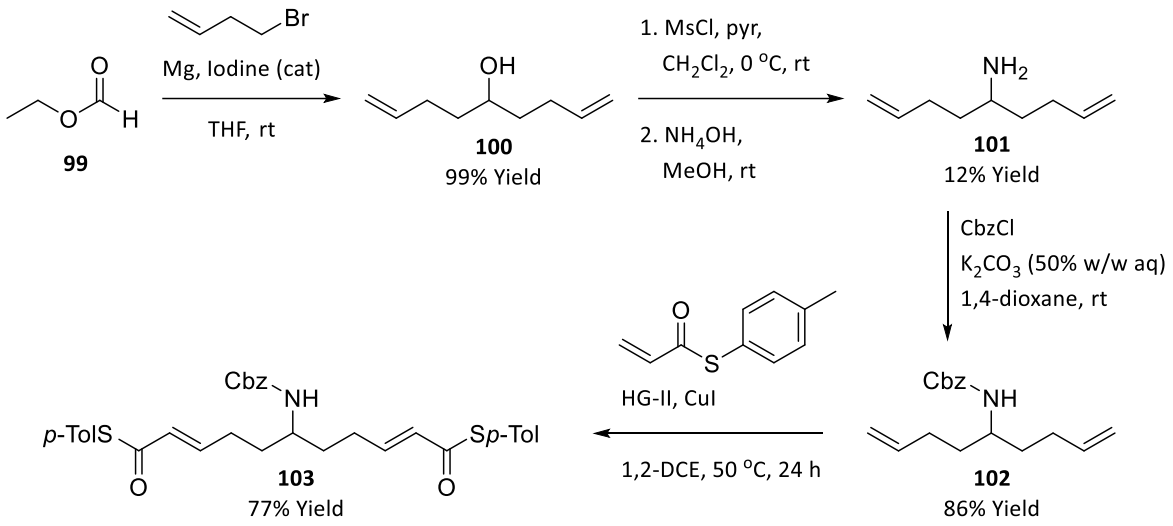



**Figure 9**. Computational analysis for the asymmetric cyclisation[29]

## 8.5. Background Work

Encouraged by the high enantioselectivities achieved for the synthesis of 2,2- and 3,3-disubstituted pyrrolidines and spiropyrrolidines, work has been done within the Clarke group to adapt the "clip cycle" methodology for the synthesis of bicyclic *N*-heterocycles.[30/34] The strategy involves the CPA catalyzed desymmetrization of an achiral symmetrical precursor to form a chiral unsymmetrical product, which could then undergo further cyclisation to form a bicyclic heterocycle. The initial approach for the synthesis of the desymmetrization precursor is outlined below (**Scheme 24**). The

synthesis began by treating ethyl formate **99** with 4-butenyl magnesium bromide (Grignard reagent) to give the secondary alcohol **100** in a near quantitative yield of 99%. Alcohol **100** was then converted to amino-diene **101** over 2 steps in one pot. The procedure involves treating **100** with methanesulfonyl chloride (MsCl) to form an alkyl mesylate, which then undergoes nucleophilic attack from ammonia to generate amine **101** and mesylate (excellent leaving group). Amine **101** was isolated in a very low yield of 12%. Benzyl chloroformate was then used to Cbz protect **101** before undergoing a two-directional double alkene cross-metathesis with an α,β-unsaturated *p*-tolyl thioester, to give the desymmetrization precursor **103** with a 77% yield.

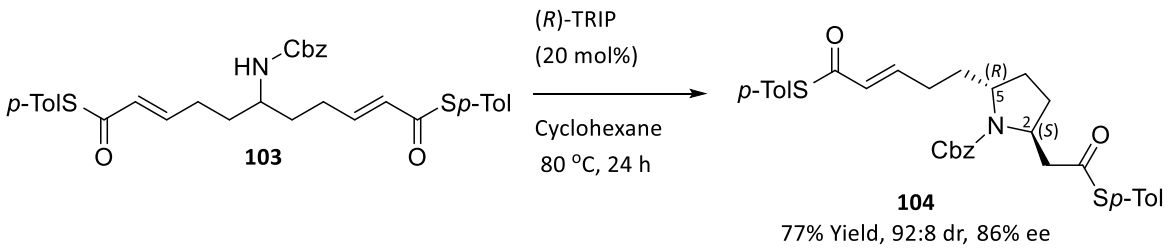



**Scheme 24**. Synthesis of the desymmetrization precursor[30/34]

The optimized conditions used for the cross metathesis were previously developed in the Clarke group for the synthesis of 2,2- and 3,3-disubstituted pyrrolidines and spiropyrrolidines.[30] Hoveyda-Grubbs Catalyst™ 2nd generation was used to catalyze the reaction in the presence of a copper iodide co-catalyst. Studies conducted by Lipshultz *et*. *al*. have demonstrated the importance of the addition of copper iodide in cross metathesis reactions when using acrylates.[35] The addition of copper iodide allowed the Hoveyda-Grubbs Catalyst to be used in catalytic quantities (10 mol%) and also aided in increasing the rate of the reaction.[36] This was attributed to the ability of the iodine ion to stabilize the catalyst, as well as the ability of copper(I) to scavenge the phosphine ligand.

Precursor **103** was then cyclized using the optimized conditions, (*R*)-TRIP (20 mol%) in cyclohexane at 80 °C for 24 hours (**Scheme 25**). The 2,5-disubstituted pyrrolidine **104** was obtained as a mixture of diastereomers (92:8) with a yield of 77% and the major diastereomer was determined to have

an enantiomeric excess of 86%. As the same asymmetric cyclisation conditions had been used for the synthesis of 2,2- and 3,3-disubstituted pyrrolidines and spiropyrrolidines, the stereochemistry was assigned as the (*S*) configuration at the 2 position for the major diastereomer.



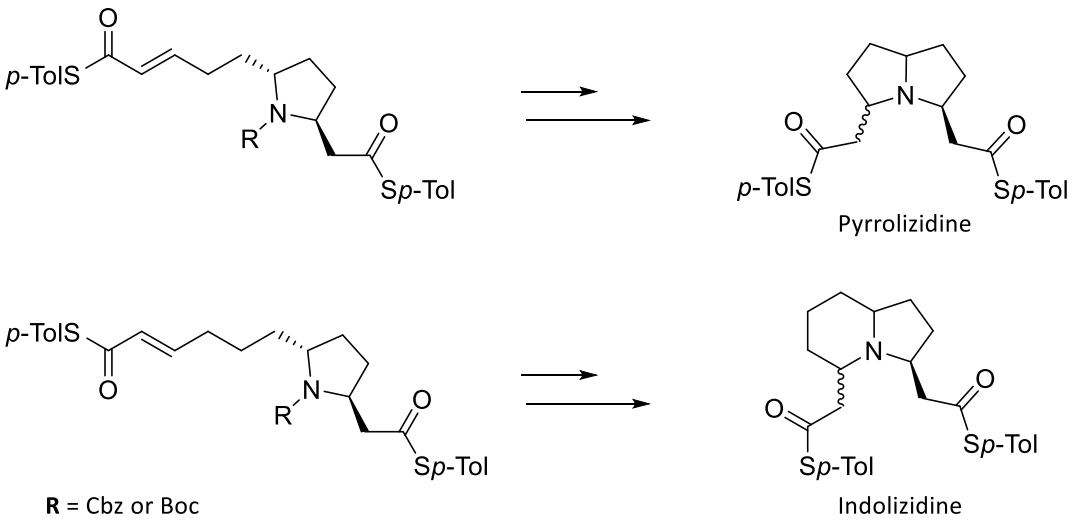

**Scheme 25**. Asymmetric cyclisation of **103** using (*R*)-TRIP[30]

Determination of the stereochemistry at the 5 position and to ascertain whether or not the major diastereomer of pyrrolidine **104** has a *cis* or *trans* configuration has yet to be accomplished. However, a literature comparison has been done between a 2,5-disubstituted pyrrolidine previously synthesized in the Clarke group[37] (using the "clip-cycle" methodology) and a similar compound reported by Farwick *et*. *al*.[38] (**Figure 10**). Pyrrolidine **106** reported in the literature was Boc protected and was determined to have a *trans* configuration, whereas pyrrolidine **105** synthesized in the Clarke group was Cbz protected. The process involved synthesizing the Cbz protected pyrrolidine **105** using the procedure reported by Farwick and co-workers and comparing the $^{1}$H NMR data to the Boc protected pyrrolidine **106**. The $^{1}$H NMR data was found to be consistent and so the protecting group did not affect the stereochemistry of the chiral pyrrolidine being formed in the reaction. Comparison of the $^{1}$H NMR data of both Cbz-pyrrolidines (synthesized using "clip-cycle" methodology and the Farwick procedure) was also consistent suggesting that pyrrolidine **105** has a *trans* configuration. Although this does not confirm the absolute stereochemistry of pyrrolidine **104**, we can surmise that the *trans* configuration forms preferentially from the cyclization using the "clip-cycle" methodology. Therefore, the stereochemistry for pyrrolidine **104** can be assigned as shown in **Scheme 25** with a degree of confidence, however definitive proof would need to be obtained through X-ray crystallography.


**Figure 10**. Chiral pyrrolidines used for determining the cis or trans stereochemistry

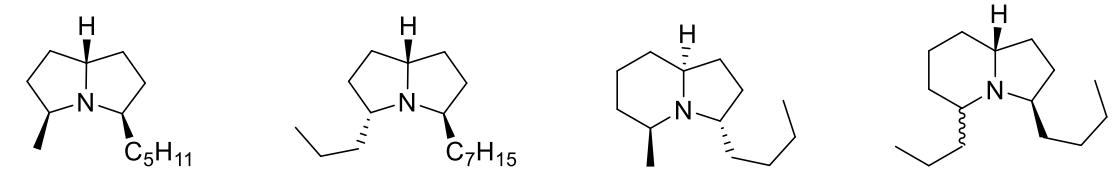
## 8.6. Aim and Scope of the Project

The aim of the project is to continue working towards synthesizing bicyclic heterocycles *via* a two-directional approach utilizing the "clip-cycle" methodology developed within the Clarke group. Work within the group has shown that 2,5-disubstituted pyrrolidines can be generated with high yields and enantioselectivities[30/37] and the potential for further cyclisation to the bicyclic heterocycles has yet to be investigated. The focus will be on the synthesis of the pyrrolizidine and indolizidine motifs *via* an asymmetric pathway using linear substrates and determining the absolute stereochemistry of resulting 3,5-disubstituted pyrrolizidines and indolizidines (**Scheme 26**).




**Scheme 26**. Deprotection-cyclisation to form pyrrolizidines and indolizidines

Attempts will also be made to selectively functionalize the saturated thioester formed from the initial asymmetric cyclisation to the pyrrolidine, to enable access to naturally occurring 3,5-disubstituted pyrrolizidine and indolizidine alkaloids asymmetrically (**Figure 11**).



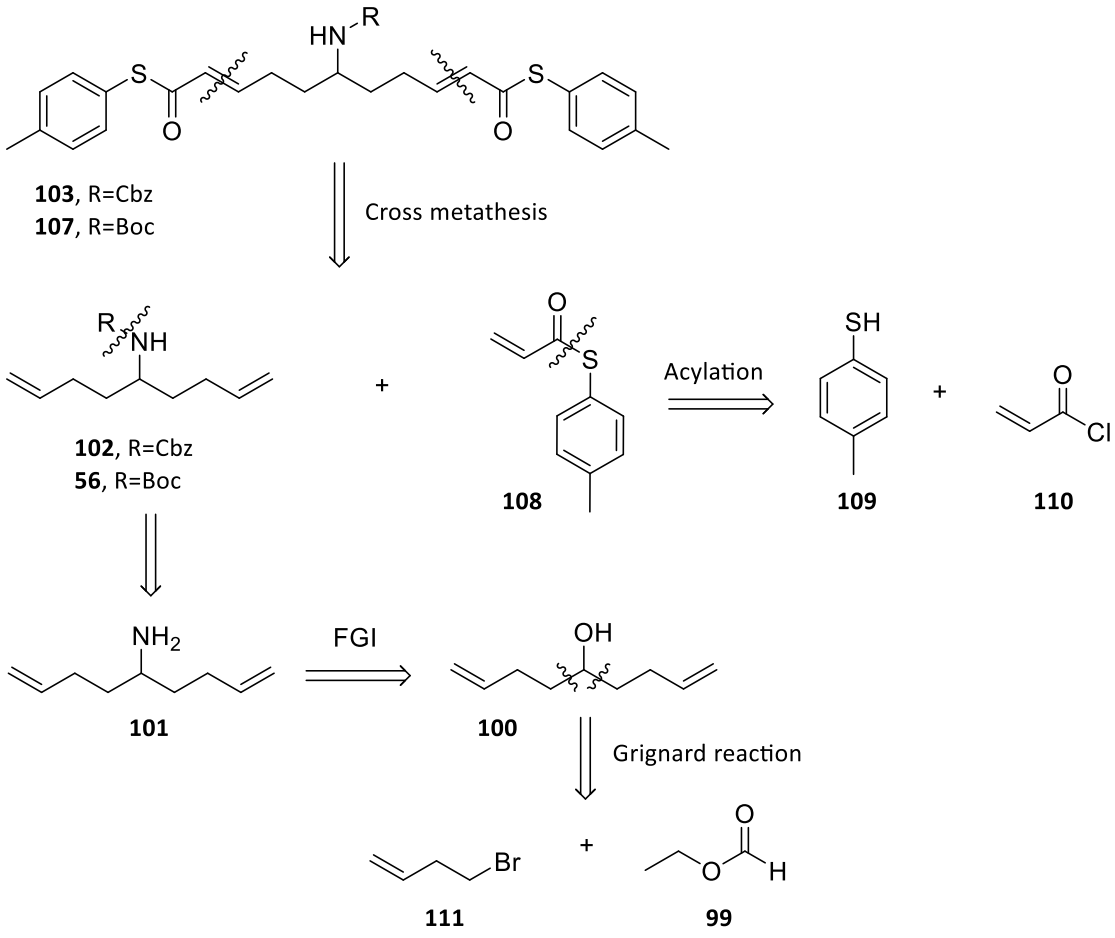

Pyrrolizidine **195F** | Pyrrolizidine **251O** | Indolizidine **195B** | Indolizidine **223AB**

**Figure 11**. Potential pyrrolizidine and Indolizidine alkaloid targets

# 9. Results and Discussion

## 9.1. Retrosynthetic Analysis of the Pyrrolizidine Precursor

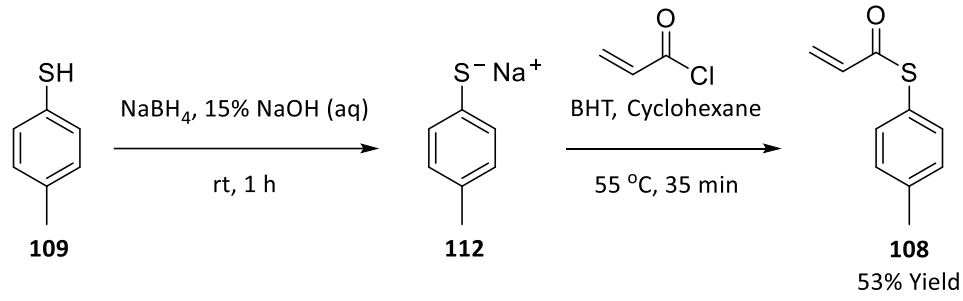
Retrosynthetic analysis of the cyclization precursor demonstrates a synthetic route *via* commercially available starting materials (**Scheme 27**). Cyclisation precursors **103** and **107** can be synthesized from the protected amines **102** and **56** using thioacrylate **108** *via* a two-directional double alkene cross metathesis reaction. Acylation of thiol **109** with acryloyl chloride **110** can be used to prepare thioacrylate **108**. Functional group interconversion of secondary alcohol **100** to the primary amine **101** can be achieved *via* a Mitsunobu reaction, the amine can then be Cbz or Boc-protected. Secondary alcohol **100** can be easily obtained from a Grignard reaction between two equivalents of metalated 4-bromobutene **111** and ethyl formate **99**.




**Scheme 27**. Retrosynthetic analysis of cyclisation precursors **103** and **107**

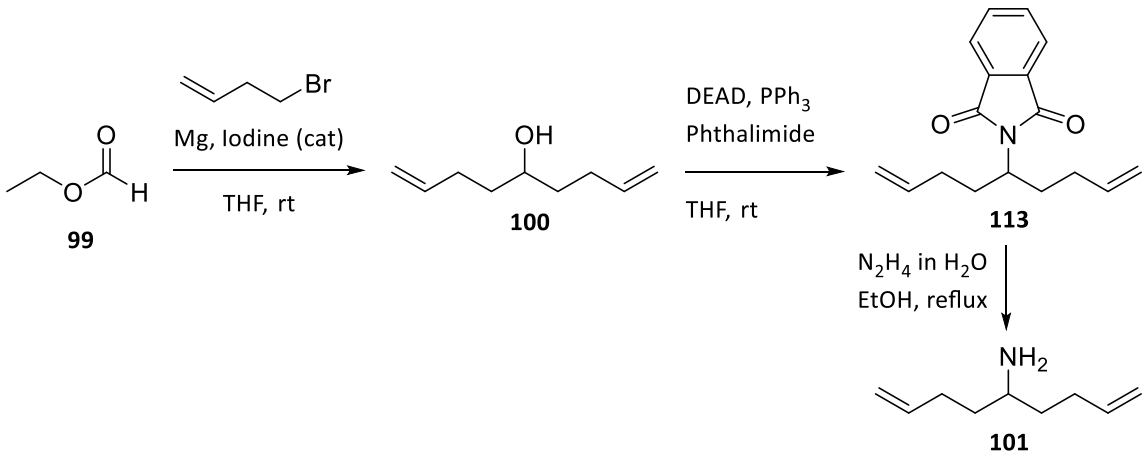
## 9.2. Synthesis of Pyrrolizidine Precursors

The forward synthesis began with the synthesis of the α,β-unsaturated *p*-tolyl thioester **108** using a previously published procedure (**Scheme 28**).[39] The method involved treating *p*-thiocresol **109** with an aqueous solution of NaOH to form the sodium salt **112**, this was done in the presence of sodium borohydride to prevent the formation of disulfides. The sodium salt then underwent acylation after being added to a solution of acryloyl chloride and BHT in cyclohexane, which generated thioester **108** in a moderate yield of 53%. BHT was added at this stage and during purification to prevent radical polymerization. Although the product was contaminated with BHT, it was found that it did not interfere with cross-metathesis reactions and the yield was easily calculated from the $^{1}$H NMR spectrum.



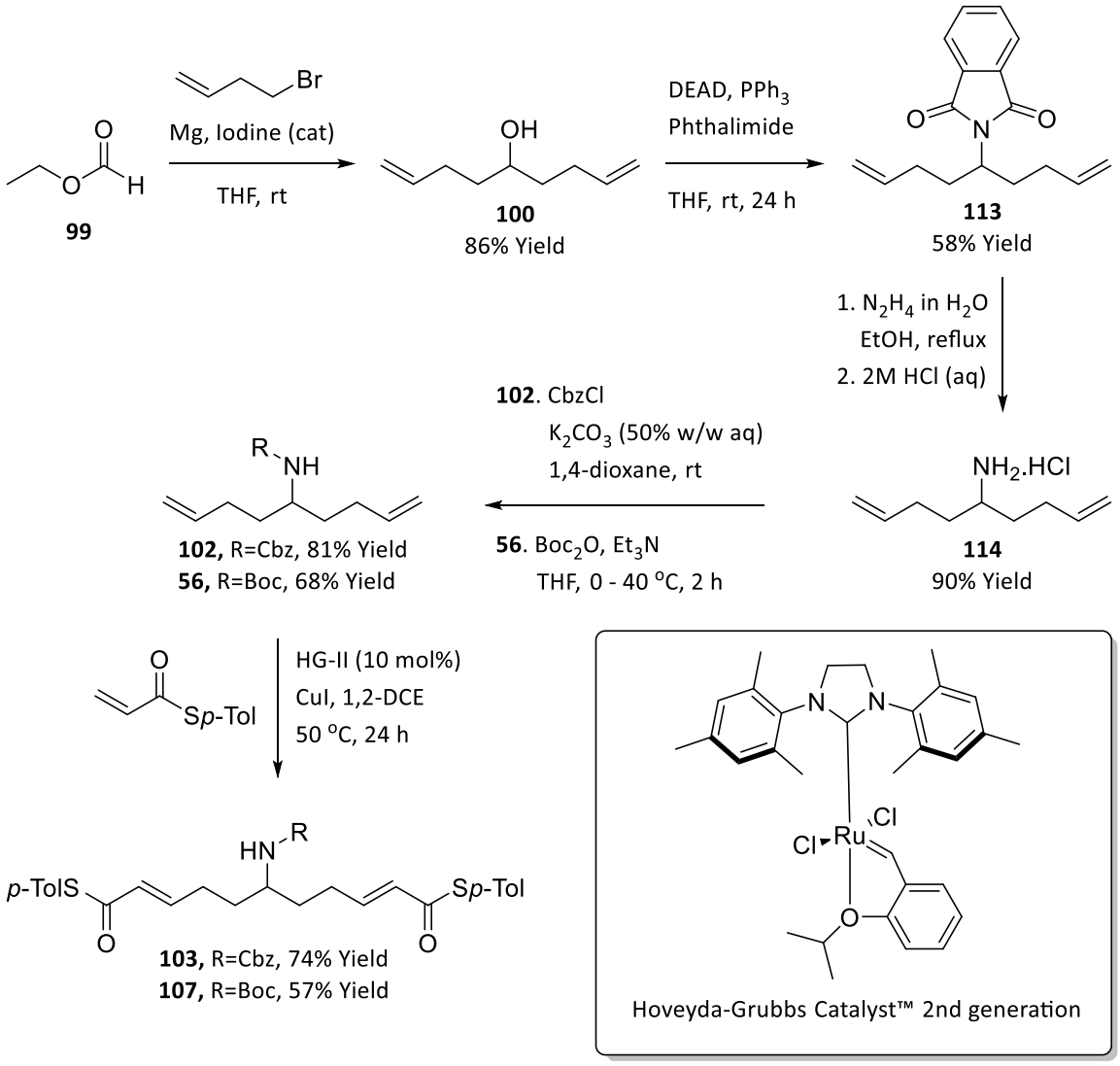

**Scheme 28**. Synthesis of α,β-unsaturated p-tolyl thioester **108**

The next step was to synthesize the symmetrical amino-diene **101** *via* a 3-step synthesis based on a literature procedure (**Scheme 29**).[40]




**Scheme 29**. Literature procedure for the synthesis of amine **101**[40]

This procedure was utilized in preference to the method already employed by the Clarke group, as previously discussed (**Scheme 24**).[34] This was due to the poor yield of amine **101** (12%) and the need to increase the available material for subsequent reactions. The forward synthesis began with a Grignard reaction between 4-butenyl magnesium bromide and ethyl formate **99** to generate alcohol **100** in a good yield of 86% (**Scheme 30**).




**Scheme 30**. Synthesis of pyrrolizidine cyclisation precursors **103** and **107**

Converting alcohol **100** to the amine salt **114** was achieved through a Mitsunobu reaction. The Mitsunobu reaction is more commonly used for the conversion of primary and secondary alcohols to esters (esterification), with inversion of the stereochemistry *via* a $S_N2$-mechanism, which can then be hydrolyzed to give the inverted alcohol.[41] Here, the Mitsunobu method is utilized to

generate a tertiary amine from a secondary alcohol using a phthalimide as the *N*-nucleophile. The reaction proceeds by activation of the alcohol **100** and phthalimide by a zwitterionic intermediate formed from diethyl azodicarboxylate (DEAD) and triphenylphosphine. The resulting nucleophilic substitution generated *N*-alkyl phthalimide **113** in a moderate yield of 58% and triphenylphosphine oxide as a byproduct.

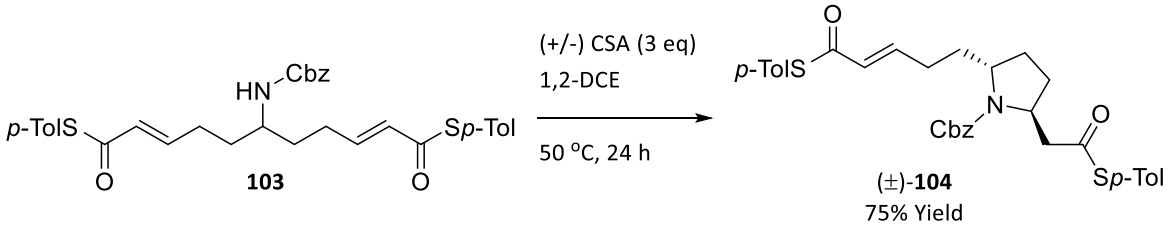
*N*-Alkyl phthalimide **113** then underwent hydrazinolysis with hydrazine hydrate, using the Ing-Manske procedure,[42] to generate the free amine. Due to the high volatility of the amine, a 2M HCl aqueous solution was used during workup to form the amine salt **114** which was isolated with an excellent yield of 90%. Amine salt **114** was then either Cbz-protected[43] with benzyl chloroformate or Boc-protected[44] with di-*tert*-butyl dicarbonate. This allowed for the investigation into the effect of the protecting group on the Brønsted acid catalyzed cyclisation reactions. The Cbz-protected amine **102** was isolated with a good yield of 81% whereas the Boc-protected amine **56** was isolated with a lower yield of 68%.

The final step involved "clipping" of the protected amines **102** and **56** with *p*-tolyl thioester **108** *via* a two-directional double alkene cross-metathesis reaction using the optimized conditions developed in the Clarke group.[30] The double cross-metathesis was performed using Hoveyda-Grubbs Catalyst™ 2nd generation (10 mol%) and CuI as a co-catalyst, with 6 equivalents of *p*-tolyl thioester **108** in 1,2-dichloroethane at 50 °C for 24 hours. The double cross metathesis was found to be selective towards the *E*,*E*-dienes.[23] This was clearly observed in the $^{1}$H NMR spectrums which showed coupling constants of *J*=14.4 Hz for **103** and *J*=15.5 Hz for **107** due to the $^{3}J$ *trans* coupling of the alkene protons. The Cbz-amino thioester **103** was obtained in a much higher yield of 74% than the Boc-amino thioester **107** with a yield of 57%. Each metathesis reaction was run for 24 hours and although we observed complete conversion of the starting material in both reactions (by TLC), the mass spectra for the Boc-amino thioester **107** showed the presence of the mono metathesis product. Running the reaction for 48 hours had little effect on the yield, so we surmised the that the catalyst was no longer active and increasing the catalyst loading may increase the yield of the desired product. With the cyclisation precursors successfully prepared our attention turned to the Brønsted acid catalyzed cyclisation reactions utilized in the "clip-cycle" methodology.

## 9.3. Brønsted Acid Catalyzed Cyclisation of Pyrrolizidine Precursors

With the cyclisation precursors in hand and applying the optimized conditions established in the Clarke group,[30] we advanced with the Brønsted acid catalyzed desymmetrisation cyclizations. These proceeded *via* an intramolecular aza-Michael reaction to generate the corresponding pyrrolidines racemically and asymmetrically. Firstly, each precursor was cyclized with racemic camphorsulfonic acid (CSA), in order to establish the HPLC conditions required to separate the two enantiomers of the major diastereomer. This would enable the determination of the enantiomeric excess (ee) obtained from each asymmetric cyclisation. Secondly, each precursor was cyclized asymmetrically using the chiral phosphoric acid catalyst (*R*)-TRIP.

The Cbz-protected precursor **103** was investigated first. Precursor **103** was cyclised using 3 equivalents of CSA in 1,2-dichloroethane at 50 °C for 24 hours (**Scheme 31**). Complete conversion to the corresponding racemic pyrrolidine **104** was observed and it was isolated in a good yield of 75% for the major diastereomer. Pyrrolidine **104** is shown to have *trans* stereochemistry for the major diastereomer, although at this stage we did not know whether the major diastereomer was *trans* or *cis*. However, after the second cyclisation and NMR analysis of the resulting pyrrolizidine (as discussed in section 9.4), we could confirm that **104** formed with *trans* stereochemistry.




**Scheme 31**. Racemic cyclisation of **103** using CSA

The enantiomers were separated *via* chiral HPLC analysis using a CHIRALPAK IG column with a hexane/IPA (50:50) solvent system, at 25 °C and a flow rate of 0.7 ml/min. This gave good separation of the enantiomers with retention times of 52 min and 59 min and peak areas of 50.7% and 49.3% respectively, indicating a racemic mixture (**Figure 12**, **Table 2**). Small Peaks at 38 min and 50 min were shown in the HPLC trace. These may have been due to small amounts of the minor diastereomer being present but this did not affect our ability to identify the retention times for the enantiomers of the major diastereomer.

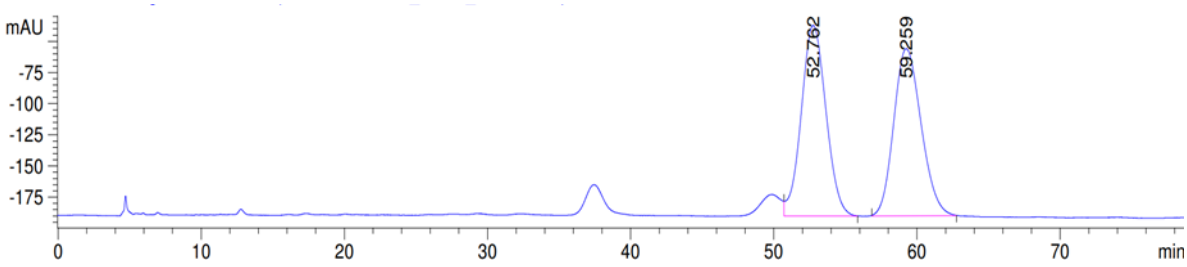
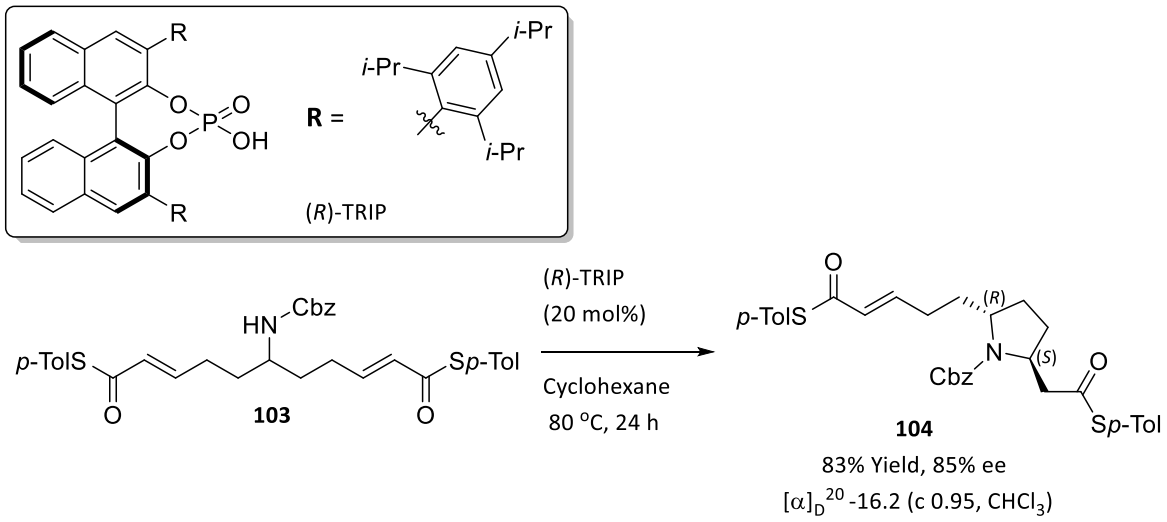



**Figure 12**. HPLC trace of the racemic Cbz-pyrrolidine **104**

| **Peak** | **Retention Time** (min) | **Area** (%) |
|---|---|---|
| **1** | 52.762 | 50.7031 |
| **2** | 59.259 | 49.2969 |

**Table 2**. HPLC retention times and peak areas for the racemic Cbz-pyrrolidine **104**

Precursor **103** was then cyclized asymmetrically with (*R*)-TRIP (20 mol%) in cyclohexane at 80 °C for 24 hours (**Scheme 32**). Under these conditions we achieved a 100% conversion to the corresponding Cbz-pyrrolidine **104**, which was isolated in an excellent yield of 83%.




**Scheme 32**. Asymmetric cyclisation of **103** using (R)-TRIP

The enantiomers were again separated *via* chiral HPLC analysis using the same conditions as for the racemic cyclisation, CHIRALPAK IG column with a hexane/IPA (50:50) solvent system, at 25 °C and a flow rate of 0.7 ml/min. This gave retention times of 53 min for minor enantiomer and 59 min for the major enantiomer, with peak areas of 7.3% and 92.7% respectively, giving an enantiomeric excess of 85% (**Figure 13**, **Table 3**). The stereochemistry for pyrrolidine **104** can be assigned as the *trans* pyrrolidine with an (*R,S*) configuration for the major diastereomer, as shown in **Scheme 32**. The assignment is in line with the work conducted in the Clarke group for determining the stereochemistry of substituted pyrrolidines synthesized using the same CPA conditions, as previously discussed (**Scheme 23** and **Figure 10**).[30/37]

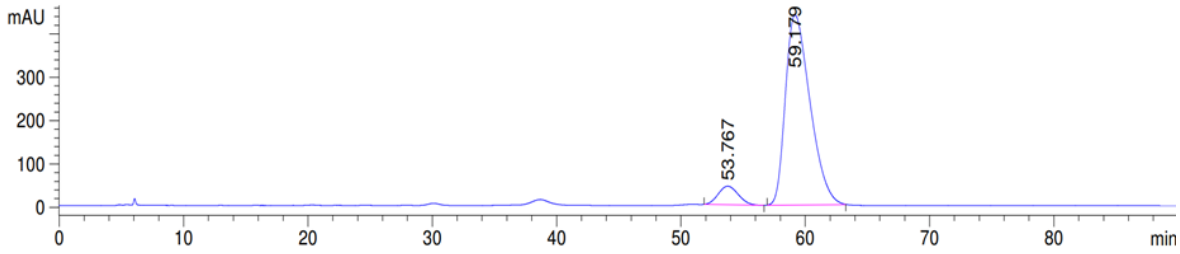



**Figure 13**. HPLC trace of the chiral pyrrolidine **104**

| **Peak** | **Retention Time** (min) | **Area** (%) |
|---|---|---|
| **1** | 53.767 | 7.3342 |
| **2** | 59.179 | 92.6658 |

**Table 3**. HPLC retention times and peak areas for the chiral pyrrolidine **104**

NMR analysis was used to confirm the synthesis of pyrrolidine **104**. The $^{1}$H NMR analysis was made more complicated due to the mixture of rotamers (1:1 ratio) observed in the spectrum, which were caused by the Cbz group. The assignment of the aromatics and the $CH_3$ groups were straightforward. The aromatics gave a multiplet between 7.43 ppm and 7.18 ppm for 13 protons (H-1,2,3,9,10,24,25) and the $CH_3$ groups gave a singlet at 2.37 ppm for 6 protons (H-7,27) (**Figure 14**). The $CH_2$ from the Cbz group could also be easily assigned as the multiplet between 5.30 ppm and 5.07 ppm (2 protons, H-5), since there was no coupling observed for this $CH_2$ in the 2D COSY

spectrum (**Figure 17**). The other $CH_2$ groups were assigned to the multiplets between 2.39 ppm and 1.37 ppm for 8 protons (H-15,16,18,19), with the exception of the $CH_2$ at H-21 which will be discussed later.

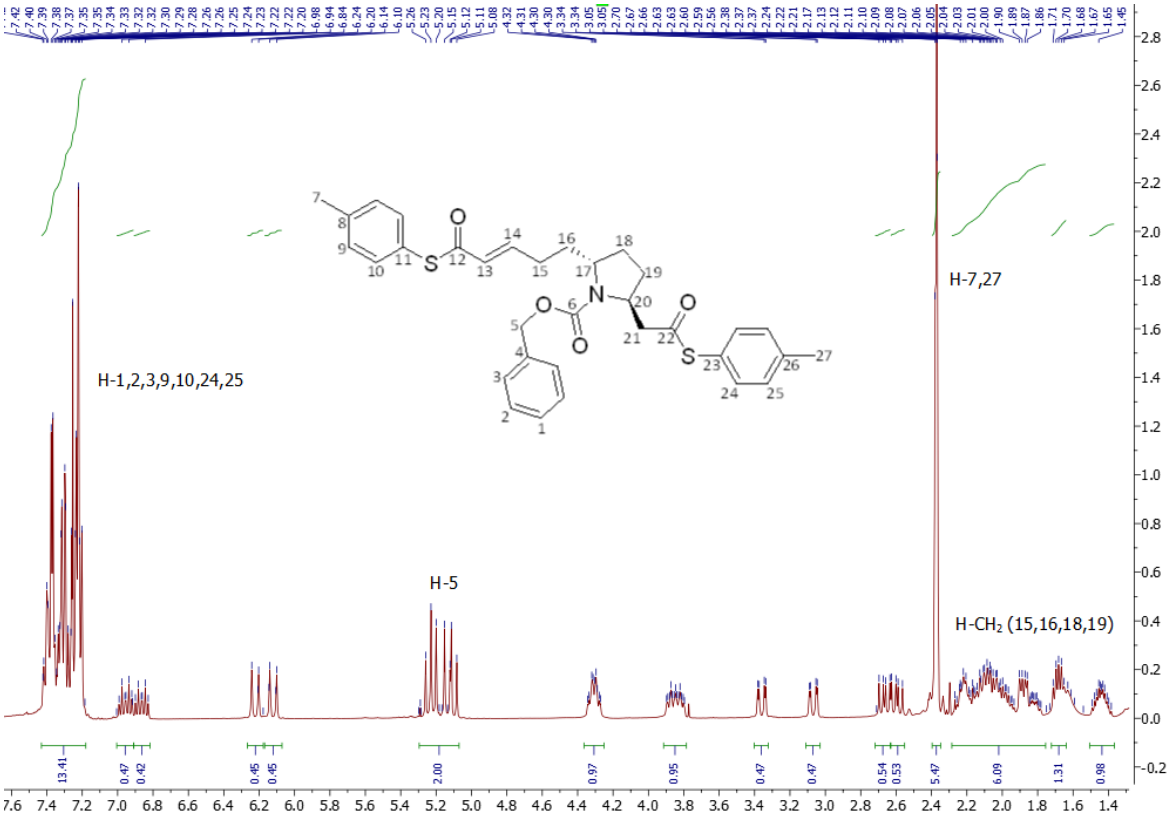



**Figure 14**. $^1$H NMR spectrum for pyrrolidine **104**

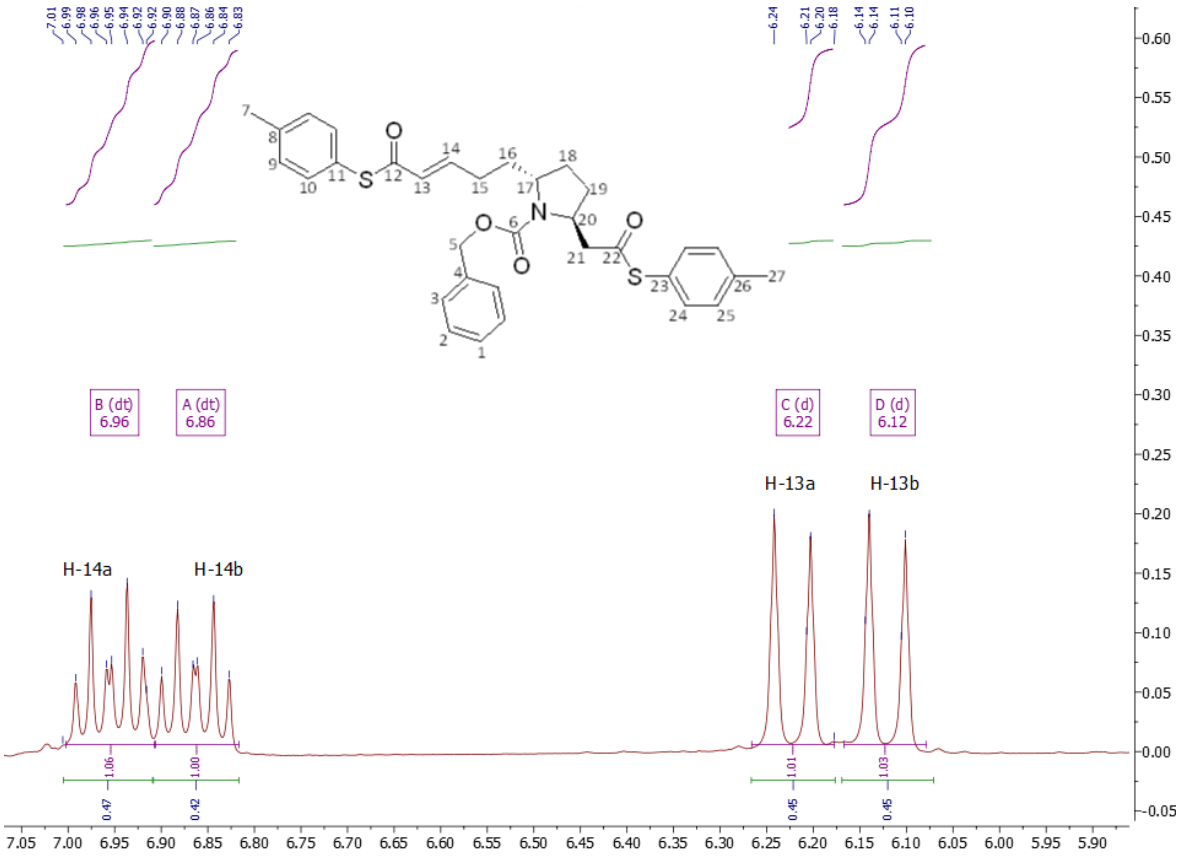



**Figure 15**. $^{1}$H NMR spectrum for pyrrolidine **104** showing the splitting for the alkene protons

The alkene protons appeared as mix of rotamers in a 1:1 ratio (**Figure 15**). H-13 showed as two doublets at 6.22 ppm (H-13a) and 6.12 ppm (H-13b) each with a coupling constant of *J*=15.6 Hz, which is due to the $^{3}J$ *trans* coupling with H-14. H-14 gave two doublet of triplets at 6.96 ppm (H-14a) and 6.86 ppm (H-14b) with coupling constants of *J*=15.7 Hz for the $^{3}J$ *trans* coupling to H-13, and *J*=6.6 Hz for the $^{3}J$ coupling to H-15 ($CH_2$).

In order to assign the peaks between 3.36 ppm and 2.59 ppm (**Figure 16**), we needed to look at the quaternary carbons at each carbonyl C-6, C-12 and C-22. Each quaternary carbon produces two peaks close together in the $^{13}$C spectrum (due to rotamers) and a 2D HMBC spectrum was used to assign them (**Figure 18**). The peaks at 159.9 ppm and 156.1 ppm were assigned to C-6 as they correlate to the $CH_2$ of the Cbz group (H-5). The peaks at 188.4 ppm and 188.6 ppm were assigned to C-12 as they correlate to the alkene protons H-13 and H-14. The peaks at 195.9 ppm and 196.1 ppm can be assigned to C-22 and they correlate to the peaks between 3.36 ppm and 2.59 ppm in the $^{1}$H NMR spectrum, which can now be assigned to H-21 ($CH_2$). As the H-21 protons are next to a

stereocentre they are nonequivalent and so generate double doublets, they are also shown in **figure 16** as a mix of rotamers (1:1 ratio). One H-21 proton produces a double doublet at 3.36 ppm and 3.07 ppm (H-21a and H-21b) which have a $^{2}J$ coupling constant of $J$=14.8 Hz (coupled to H-21) and a $^{3}J$ coupling constant of $J$=3.2 Hz (coupled to H-20). The other H-21 proton produces a double doublet at 2.67 ppm and 2.59 ppm (H-21c and H-21d) which have a $^{2}J$ coupling constant of $J$=15.0 Hz (coupled to H-21) and a $^{3}J$ coupling constant of $J$=9.8 Hz (coupled to H-20). From the 2D COSY spectrum (**Figure 17**), H-21 couples to the mutiplet between 4.37 ppm and 4.25 ppm which can now be assigned as H-20. By process of elimination the mutiplet between 3.91 ppm and 3.78 ppm must be assigned to H-17.

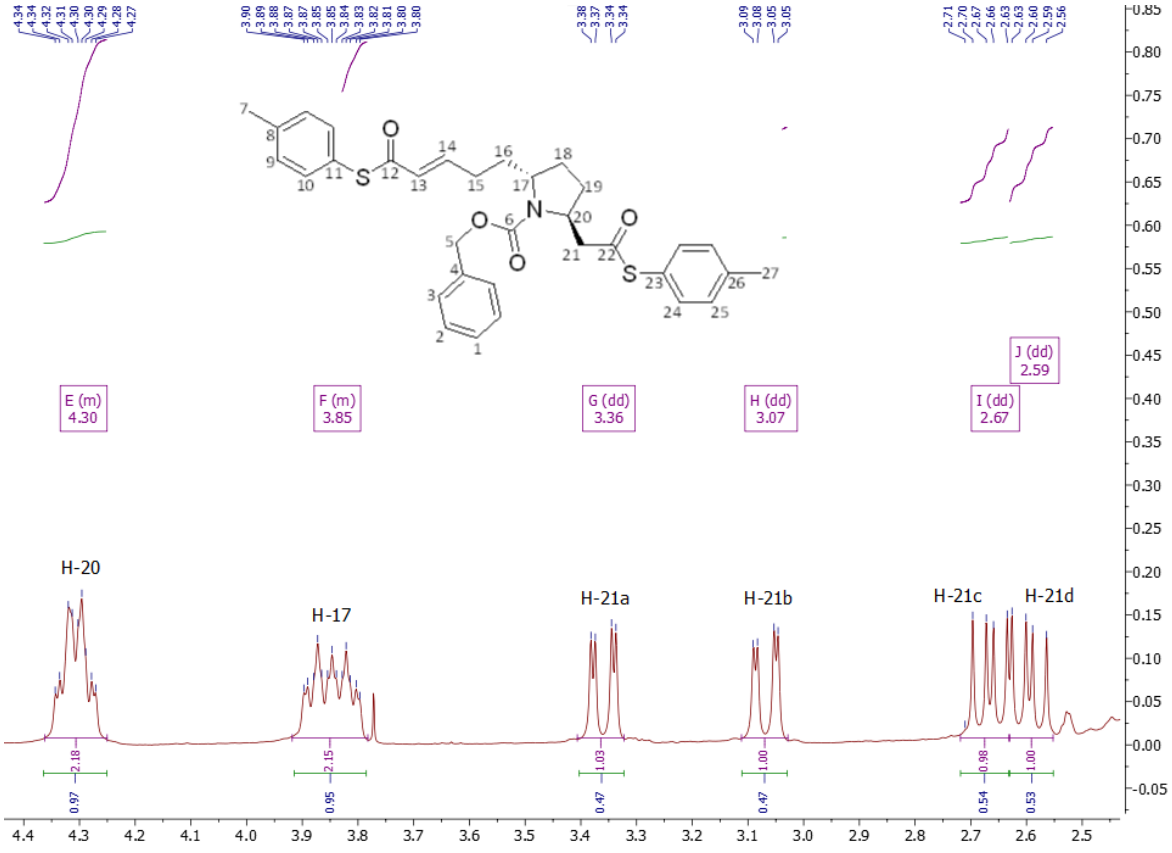



**Figure 16**. $^{1}$H NMR spectrum for pyrrolidine **104**

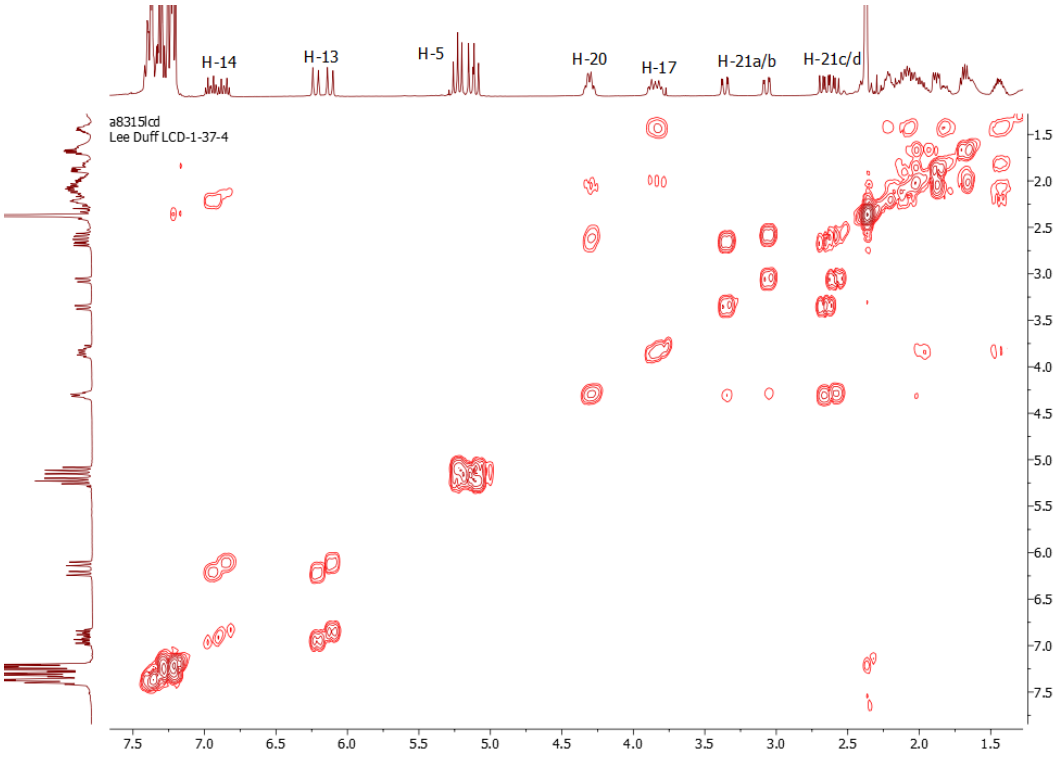



**Figure 17**.2D COSY spectrum for pyrrolidine **104**

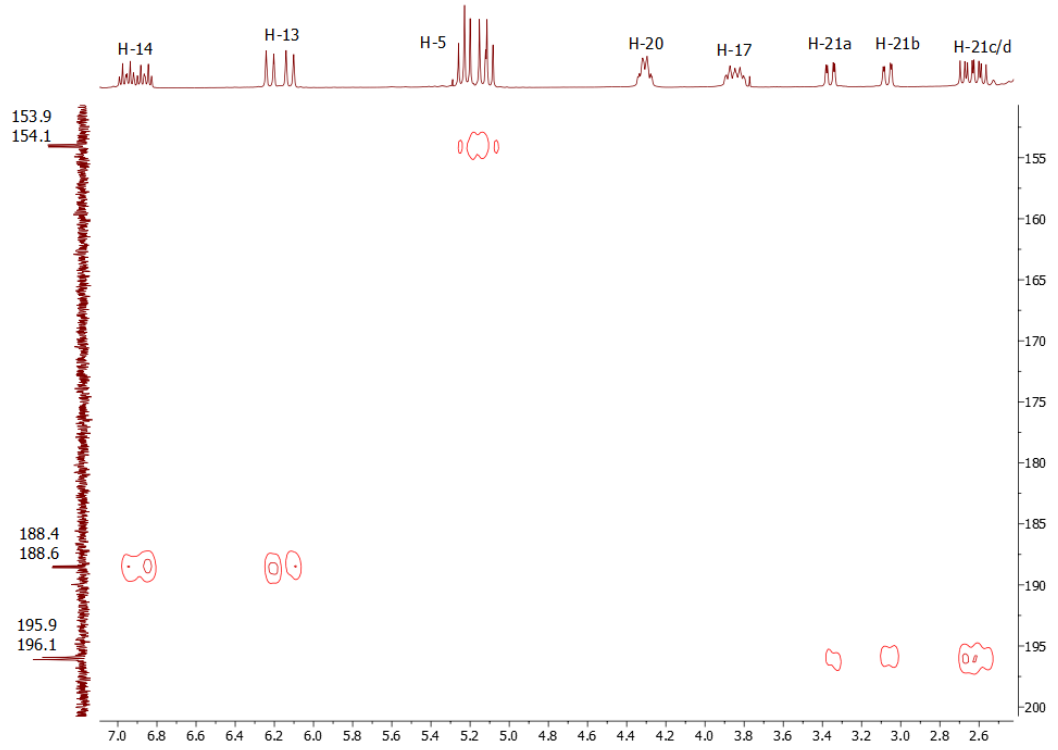
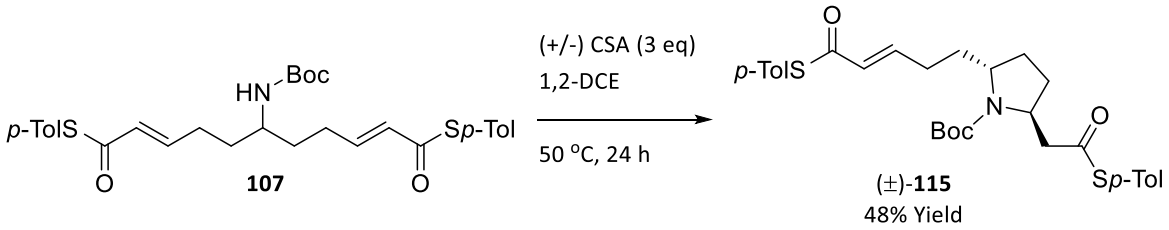



**Figure 18**. 2D HMBC spectrum for pyrrolidine **104**

Next, we investigated the cyclisation reactions for the Boc-protected precursor **107**. Precursor **107** was cyclised racemically using the same conditions, 3 equivalents of CSA in 1,2-dichloroethane at 50 °C for 24 hours (**Scheme 33**). A 100% conversion of precursor **107** to the corresponding racemic Boc-pyrrolidine **115** was observed by TLC, however **115** was isolated in a much lower yield of 48% for the major diastereomer. We surmised that the acidic conditions of the reaction may have been strong enough to remove the Boc-protecting group, which would lead to further cyclisation to the pyrrolizidine.




**Scheme 33**. Racemic cyclisation of **107** using CSA

The enantiomers were separated *via* chiral HPLC analysis using a CHIRALPAK IG column with a hexane/IPA (90:10) solvent system, at 25 °C and a flow rate of 0.7 ml/min. This gave good separation of the enantiomers with retention times of 55 min and 59 min and peak areas of 49.4% and 50.6% respectively, indicating a racemic mixture (**Figure 19**, **Table 4**).

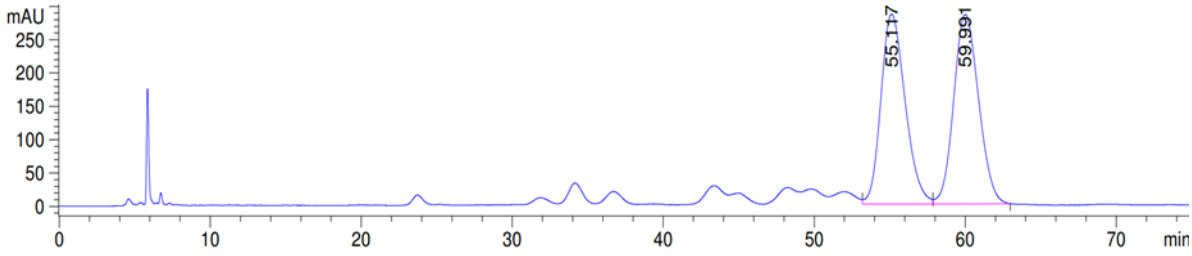



**Figure 19**. HPLC trace of the racemic pyrrolidine **115**

| Peak | Retention Time (min) | Area (%) |
|---|---|---|
| **1** | 55.117 | 49.4286 |
| **2** | 59.991 | 50.5714 |

**Table 4**. HPLC retention times and peak areas for the racemic pyrrolidine **115**

The racemic Boc-pyrrolidine **115** was not isolated cleanly from the flash column chromatography (**Figure 20**) and this would account for the number of small peaks that show up in the HPLC trace. However, these peaks did not affect our ability to identify the retention times for the enantiomers of the major diastereomer and show that **115** had been generated racemically.

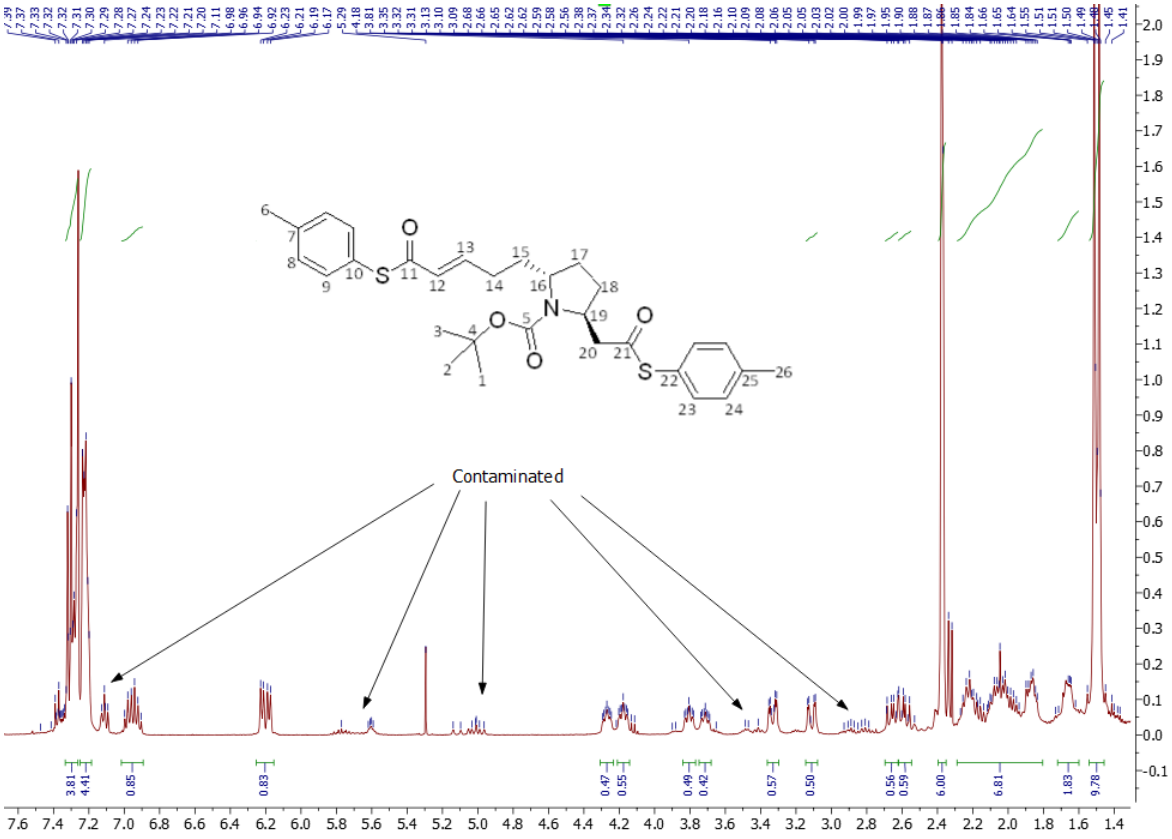
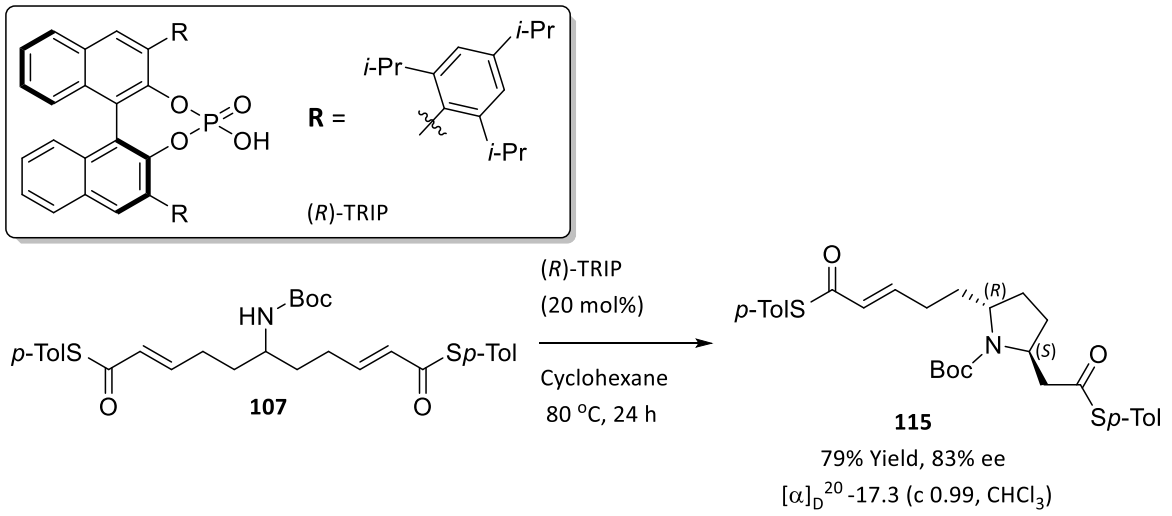



**Figure 20**. $^{1}$H NMR spectrum for the racemic pyrrolidine **115**

Precursor **107** was then cyclised asymmetrically with (*R*)-TRIP (20 mol%) in cyclohexane at 80 °C for 24 hours (**Scheme 34**). 100% conversion to the corresponding chiral pyrrolidine **115** was achieved with a good yield of 79% for the major diastereomer. The enantiomers were again separated *via* chiral HPLC analysis using the same conditions as for the racemic cyclisation, CHIRALPAK IG column with a hexane/IPA (90:10) solvent system, at 25 °C and a flow rate of 0.7 ml/min. This gave retention times of 55 min for minor enantiomer and 59 min for the major enantiomer, with peak areas of 8.6% and 91.4% respectively, giving an enantiomeric excess of 83% (**Figure 21**, **Table 5**).




**Scheme 34**. Asymmetric cyclisation of **107** using (R)-TRIP

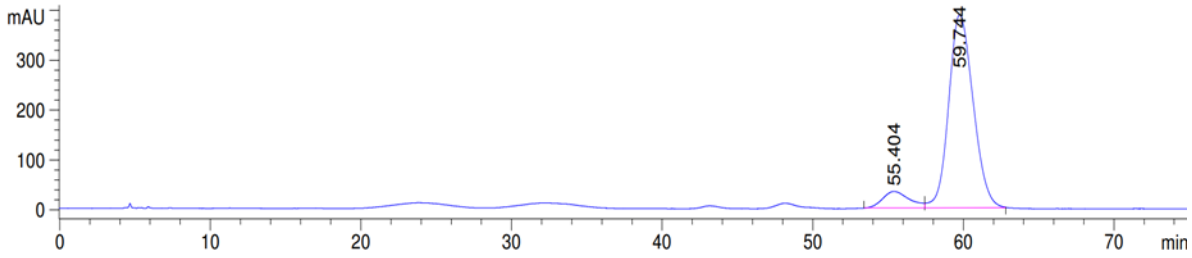



**Figure 21**. HPLC trace of the asymmetric pyrrolidine **115**

| **Peak** | **Retention Time** (min) | **Area** (%) |
|---|---|---|
| **1** | 55.404 | 8.5719 |
| **2** | 59.744 | 91.4281 |

**Table 5**. HPLC retention times and peak areas for asymmetric pyrrolidine **115**

We were pleased to observe that the asymmetric cyclisations were consistent for both the Cbz and Boc precursors, with only a small reduction in yield and %ee for the Boc protected pyrrolidine **115**. This showed that the protecting groups employed had little effect on the asymmetric cyclisation when using (*R*)-TRIP as the catalyst. The NMR analysis for the Boc-pyrrolidine was the same as for the Cbz-pyrrolidine with the exception of additional rotamers caused by the Boc group. The protons at each stereocenter (H-16 and H-19) now gave a mix of rotamers with a 1:1 ratio (**Figure 22**). The methyls from the Boc group also show as rotamers, generating two singlets at 1.48 ppm and 1.51 ppm for the 9 protons.

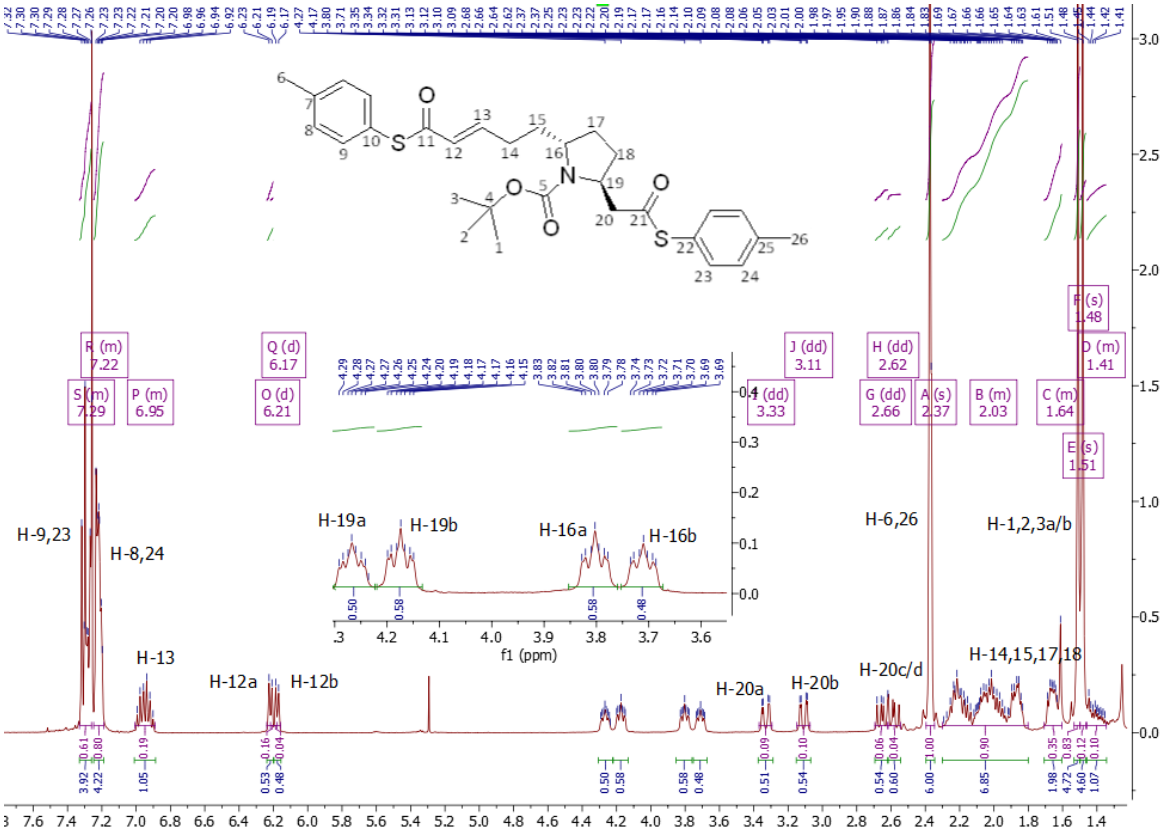



**Figure 22**. $^{1}$H NMR spectrum for pyrrolidine **115**

## 9.4. Cyclisation from the Pyrrolidine to the Pyrrolizidine

With the asymmetric cyclisation to pyrrolidines **104** and **115** in high yields and ees accomplished, we turned our attention to the deprotection and subsequent intramolecular aza-Michael cyclisation to form the pyrrolizidine motif found in 3,5-disustituted pyrrolizidine alkaloids. We envisaged this could be achieved *via* a one-pot deprotection-cyclisation reaction. Since at this stage we did not know whether **104** had trans or cis stereochemistry, three possible diastereomers could be generated from the deprotection-cyclisation reaction (**Figure 23**). In relation to the bridgehead proton, two *meso*-pyrrolizidines **116** and **117** with *cis-cis* or *trans-trans* configurations and a chiral pyrrolizidine **118** with a *trans-cis* configuration are the possible diastereomers. In order to determine which of these pyrrolizidines is obtained from the deprotection-cyclisation we would need to analyze the relationship between the bridgehead proton and the protons at each stereocentre.

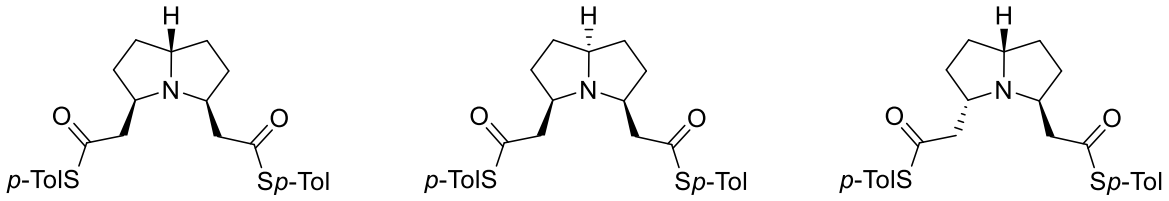
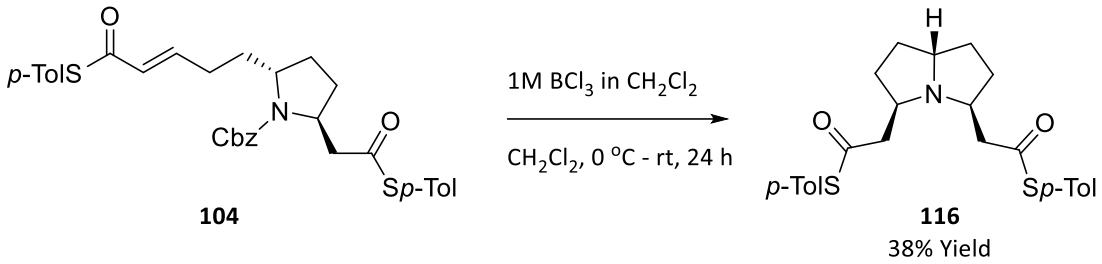



**Figure 23**. Possible pyrrolizidine diastereomers

The deprotection of the Cbz protecting group posed the greatest challenge as traditional methods of cleaving the Cbz group could not be used due to the functionality present in pyrrolidine **104**. Hydrogenolysis with $H_2$ over a palladium catalyst could also lead to competitive reduction of the alkene, which would prevent the desired intramolecular cyclisation to form the pyrrolizidine. In a similar fashion HBr could undergo electrophilic addition to the alkene.

The strong Lewis acid boron trichloride ($BCl_3$) has been shown to cleave the benzyl ether (OBn) protecting group[45] and was successfully utilized within the Clarke group in the studies towards the synthesis of hexacyclinic acid.[46] This was done in the presence of an alkene and ester functional groups. The benzyl ether protecting group is also more commonly removed using $H_2$, Pd/C or HBr. We envisaged that $BCl_3$ could be used in the same way to deprotect the Cbz group. Treating pyrrolidine **104** with a 1M solution of $BCl_3$ in DCM was successful in cleaving the Cbz group. The

subsequent cyclisation to pyrrolizidine **116** was achieved with a yield of 38% and **116** was isolated as a single diastereomer (**Scheme 35**).




**Scheme 35**. Cbz deprotection and cyclisation of pyrrolidine **116** using $BCl_3$

The $^1$H NMR spectrum for pyrrolizidine **116** (**Figure 24**) showed a quintet at 3.62 ppm for the bridgehead proton (H-11) and a multiplet at 3.27 ppm for the protons at each stereocentre (H-8,14). This was comparable to the data reported by Stockman *et. al.*[24] for the diethyl ester pyrrolizidine **55**, with the bridgehead proton giving a quintet at 3.59 ppm and the protons at the stereocentres giving a multiplet at 3.18 ppm (**Figure 25**).

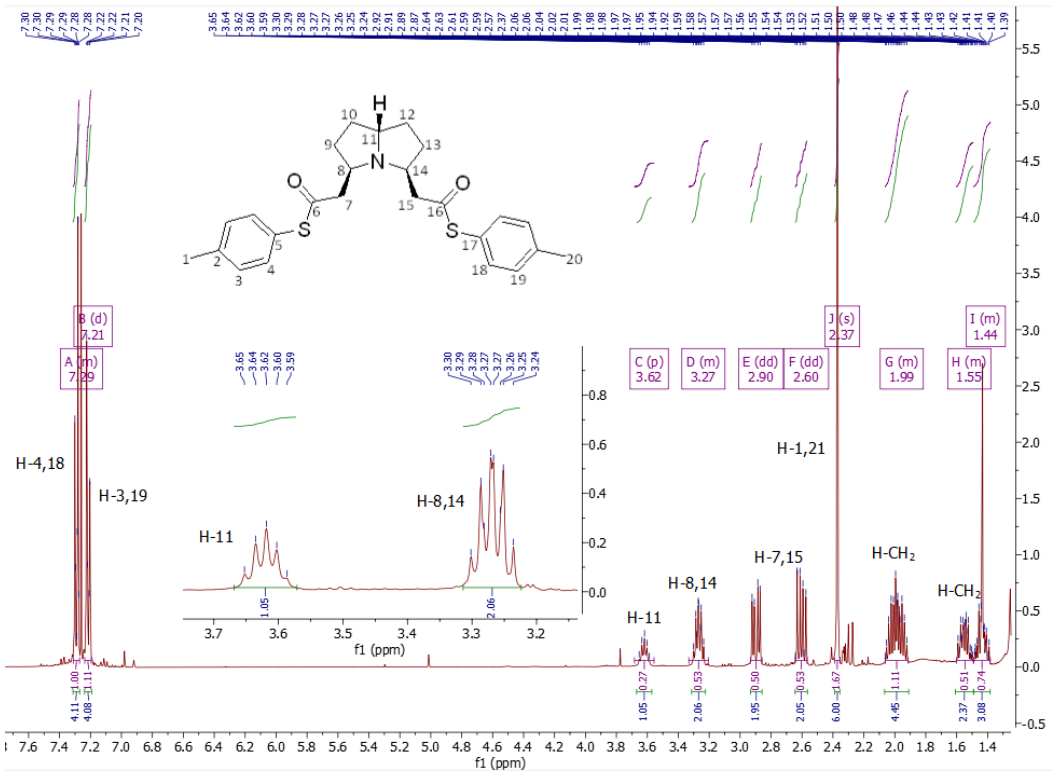



**Figure 24**. $^1$H NMR spectrum for pyrrolizidine **116**

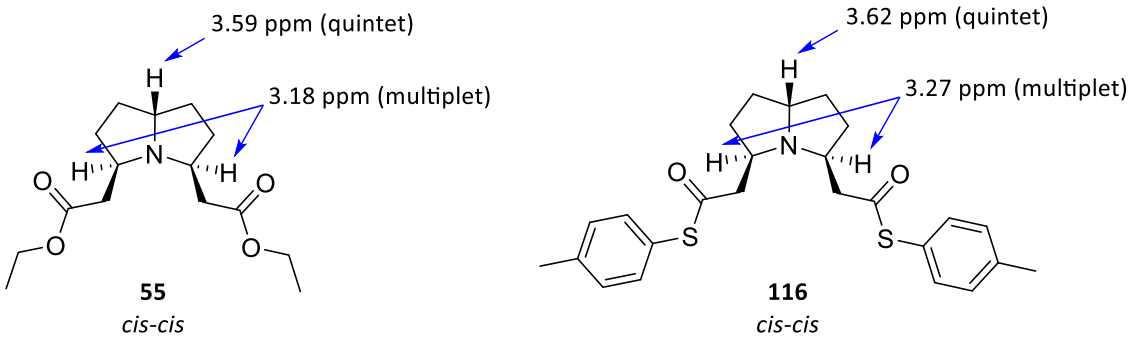
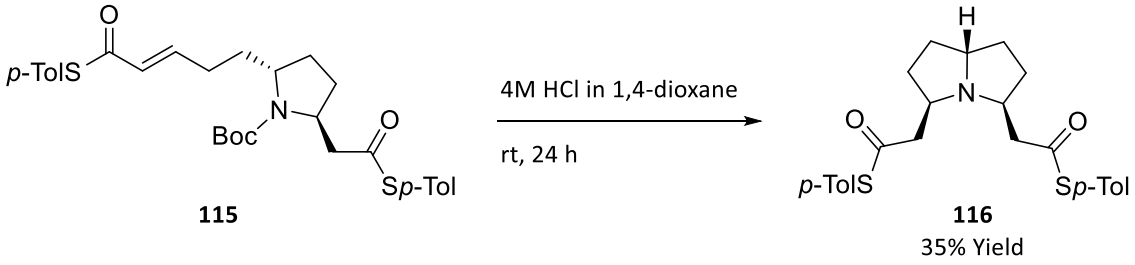



**Figure 25**. Comparison of the diethyl ester pyrrolizidine **55** with pyrrolizidine **116**

Pyrrolizidine **116** also gave an $[\alpha]_D$ reading of zero, therefore we initially assumed the stereochemistry to be that of the *meso*-pyrrolizidine with a *cis-cis* configuration. If this assumption was correct, it meant that the ee of pyrrolidine **104**, achieved through the asymmetric cyclisation, was inconsequential when forming the *meso*-pyrrolizidine **116**.

Deprotecting the Boc-protected pyrrolidine **115** was more straightforward, as the Boc group can be easily removed using an acid. Pyrrolidine **115** was treated with 4M HCl in 1,4-dioxane under dry conditions. This also generated the same *cis-cis* pyrrolizidine **116** as a single diastereomer with a yield of 35% (**Scheme 36**). The $^1$H NMR spectrum for the Boc deprotection-cyclization matched with the $^1$H NMR spectrum for the Cbz deprotection-cyclisation, therefore the same pyrrolizidine diastereomer was forming in each case.




**Scheme 36**. Boc deprotection and cyclisation of pyrrolidine **115** using 4M HCl in dioxane

To confirm the stereochemistry of pyrrolizidine **116** we decided to synthesize the diethyl ester pyrrolizidine **55** and compare our data with that previously published in the literature. Three diastereomers for the diethyl ester pyrrolizidine have been reported (**Figure 26**). Stockman *et. al*.[24] reported the *cis-cis* pyrrolizidine **55** and Spring *et. al*.[26] reported the *trans-trans* **67** and the *trans-cis* **68** pyrrolizidines.

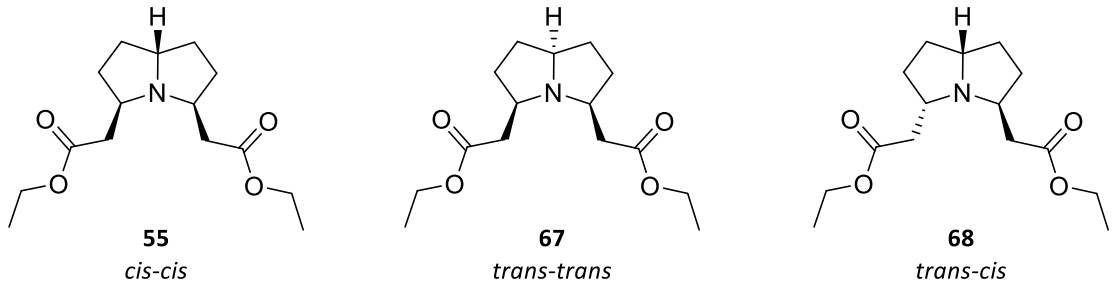
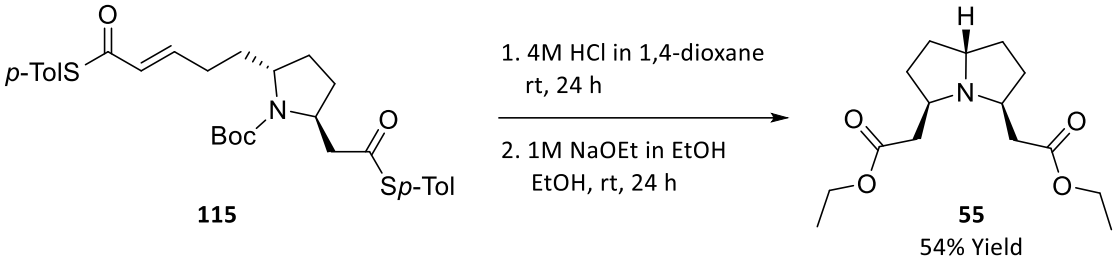



**Figure 26**. Reported diastereomers of the diethyl ester pyrrolizidine

The diethyl ester pyrrolizidine was obtained *via* a two-step one-pot synthesis involving the treatment of pyrrolidine **115** with 4M HCl in 1,4-dioxane to form pyrrolizidine **116**, followed by transesterification of the thioesters using a 1M solution of sodium ethoxide in EtOH (**Scheme 37**). The diethyl ester pyrrolizidine **55** was isolated as a single diastereomer with a good yield of 54%.




**Scheme 37**. Boc deprotection and transesterification of pyrrolidine **115**

The $^{1}$H NMR data for the diethyl ester pyrrolizidine **55** was assigned as shown in **Figure 27**. The ethyl groups were assigned first, with H-1 and H-15 giving a triplet at 1.25 ppm with a $^{3}J$ coupling constant of $J$=7.3 Hz for 6 protons, and H-2 and H-14 giving a quartet at 4.11 ppm with a $^{3}J$ coupling constant of $J$=7.3 Hz for 4 protons. The multiplets at 1.45 ppm and 1.96 were assigned to the $CH_2$ groups around the pyrrolizidine ring (H-6,7,9 and 10). The 2D COSY spectrum (**Figure 28**) shows that the single proton at 3.58 ppm couples to the $CH_2$ groups to give a quintet with a $^{3}J$ coupling constant of $J$=6.5 Hz, therefore this proton was assigned as the bridgehead proton H-8. The multiplet at 3.18 ppm was assigned to the protons at each stereocenter, H-5 and H-11, as they couple to the $CH_2$ groups and the peaks at 2.24 ppm and 2.54 ppm. The remaining protons at H-4 and H-12 are assigned to the double doublets at 2.24 ppm and 2.54 ppm which have $^{3}J$ coupling constants of $J$=15.0, 8.2 Hz and $J$=15.0, 6.0 Hz respectively. The splitting patern of H-4 and H-12 is due to the protons being nonequivalent as there is a stereocentre in the molecule.

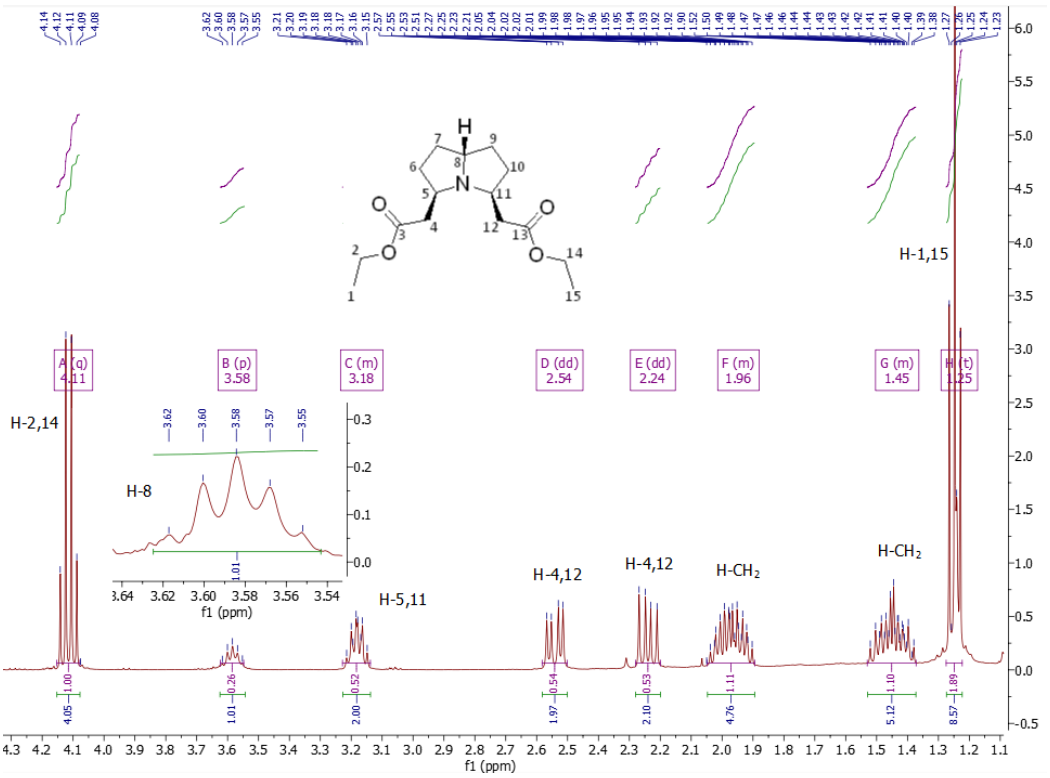



**Figure 27**. $^{1}$H NMR spectrum for pyrrolizidine **55**

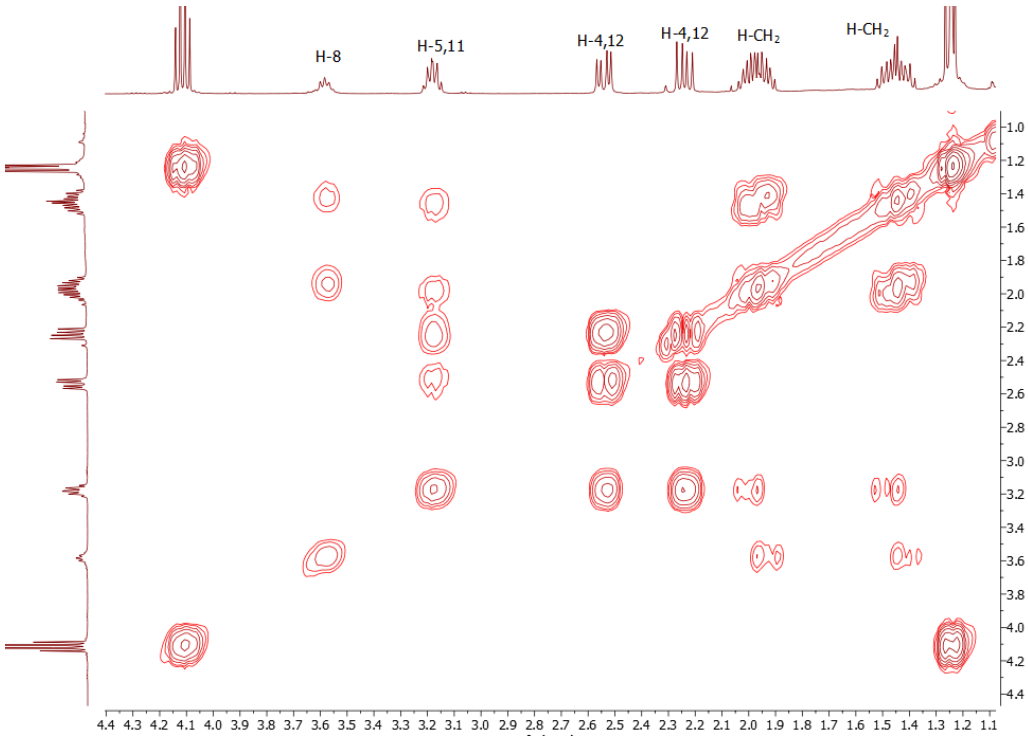
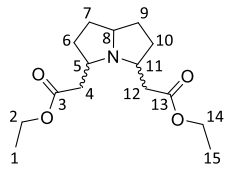
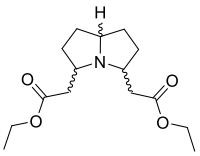
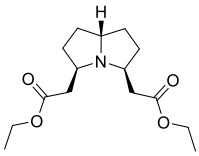
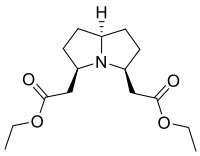
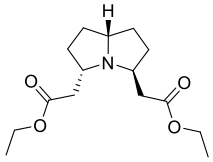



**Figure 28**. 2D COSY spectrum for pyrrolizidine **55**

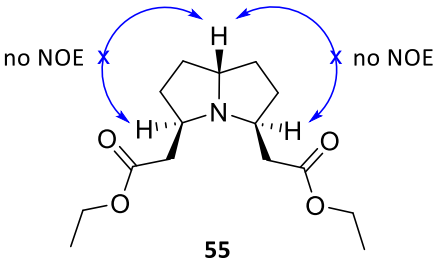
We then proceeded to compare our $^{1}H$ and $^{13}C$ NMR data with the data reported in the literature for the three possible pyrrolizidines (**Table 6**). Straight away we could rule out the chiral pyrrolizidine with the *trans-cis* configuration (highlighted orange), as there are significant differences between our data and the reported data. The three differences that stand out the most are shown in entries 4, 5 and 6. H-4 and H-12 give four double doublets in the $^{1}H$ NMR and two peaks in the $^{13}C$ NMR for the *trans-cis* pyrrolizidine, whereas our data gives two double doublets in the $^{1}H$ NMR and one peak in the $^{13}C$ NMR (Entry 4). The protons at the stereocenters (H-5 and H-11) give a multiplet at 3.18 ppm in our $^{1}H$ NMR data, but they are split into two peaks at 3.37 ppm (pentet) and 3.55 ppm (multiplet) for the *trans-cis* pyrrolizidine (Entry 5). H-6, 7, 9 and 10 give four multiplets and one triplet of doublet of doublets in the $^{1}H$ NMR and four peaks in the $^{13}C$ NMR for the *trans-cis* pyrrolizidine, whereas our data gives two multiplets in the $^{1}H$ NMR and two peaks in the $^{13}C$ NMR (Entry 6).

The data comparison between our data and the two *meso*-pyrrolizidines (*cis-cis* and *trans-trans*) were very similar with only two minor differences (highlighted blue). The *trans-trans* pyrrolizidine gives a pentet for the protons at the stereocenters, H-5 and H-11, and a multiplet for the bridgehead proton H-8, whereas our data and the data for the *cis-cis* pyrrolizidine give a multiplet for H-5 and H-11 and a pentet for H-8. Although our data matches best with that of the *cis-cis* pyrrolizidine we cannot say for certain that we have not formed the *trans-trans* pyrrolizidine. In order to distinguish between the two *meso*-pyrrolizidines we ran a 2D NOSEY experiment to analyze the relationship between the bridgehead proton and the protons at the stereocenters. For the *trans-trans* pyrrolizidine we would expect to see through space interactions between these protons whereas the *cis-cis* pyrrolizidine would show no NOE interactions. The NOESY spectrum for pyrrolizidine **55** (**Figure 29**) showed no NOE interactions between the bridgehead proton (H-8) and the protons at the stereocenters (H-5 and H-11), and so we are confident in reporting the stereochemistry of pyrrolizidine **55** as the *meso*-pyrrolizidine with a *cis-cis* configuration.

| | |  | |  (our data) | |  (*cis-cis*) | |  (*trans-trans*) | |  (*trans-cis*) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Assignment** | **$^{1}$H** (ppm) | **$^{13}$C** (ppm) | **$^{1}$H** (ppm) | **$^{13}$C** (ppm) | **$^{1}$H** (ppm) | **$^{13}$C** (ppm) | **$^{1}$H** (ppm) | **$^{13}$C** (ppm) |
| **1** | 1 and 15 | 1.25 t | 14.4 | 1.26 t | 14.2 | 1.26 t | 14.6 | 1.26 t | 14.6 |
| **2** | 2 and 14 | 4.11 q | 60.3 | 4.13 q | 60.2 | 4.13 q | 60.6 | 4.16 m | 60.7<br>60.9 |
| **3** | 3 and 13 | N/A | 172.5 | N/A | 172.2 | N/A | 172.0 | N/A | 172.4<br>172.5 |
| **4** | 4 and 12 | 2.24 dd<br>2.54 dd | 41.7 | 2.24 dd<br>2.54 dd | 41.4 | 2.25 dd<br>2.55 dd | 42.0 | 2.27 dd<br>2.33 dd<br>2.53 dd<br>2.85 dd | 37.0<br>42.7 |
| **5** | 5 and 11 | 3.18 m | 63.0 | 3.18 m | 62.9 | 3.20 p | 63.3 | 3.37 p<br>3.55 m | 55.1<br>58.6 |
| **6** | 6,7,9 and 10 | 1.45 m<br>1.96 m | 31.2<br>31.5 | 1.46 m<br>1.97 m | 31.1<br>31.3 | 1.47 m<br>1.98 m | 31.6<br>31.8 | 1.38 m<br>1.62 m<br>1.88 m<br>2.02 m<br>2.12 tdd | 30.5<br>32.4<br>32.6<br>34.4 |
| **7** | 8 | 3.58 p | 64.5 | 3.59 p | 64.3 | 3.59 m | 64.8 | 3.65 m | 66.5 |

*t - triplet, q - quartet, p - pentet, dd - double doublet, tdd – triplet of doublet of doublets and m - multiplet

**Table 6**. $^{1}$H NMR and $^{13}$C NMR data comparison




**55**

*cis-cis*

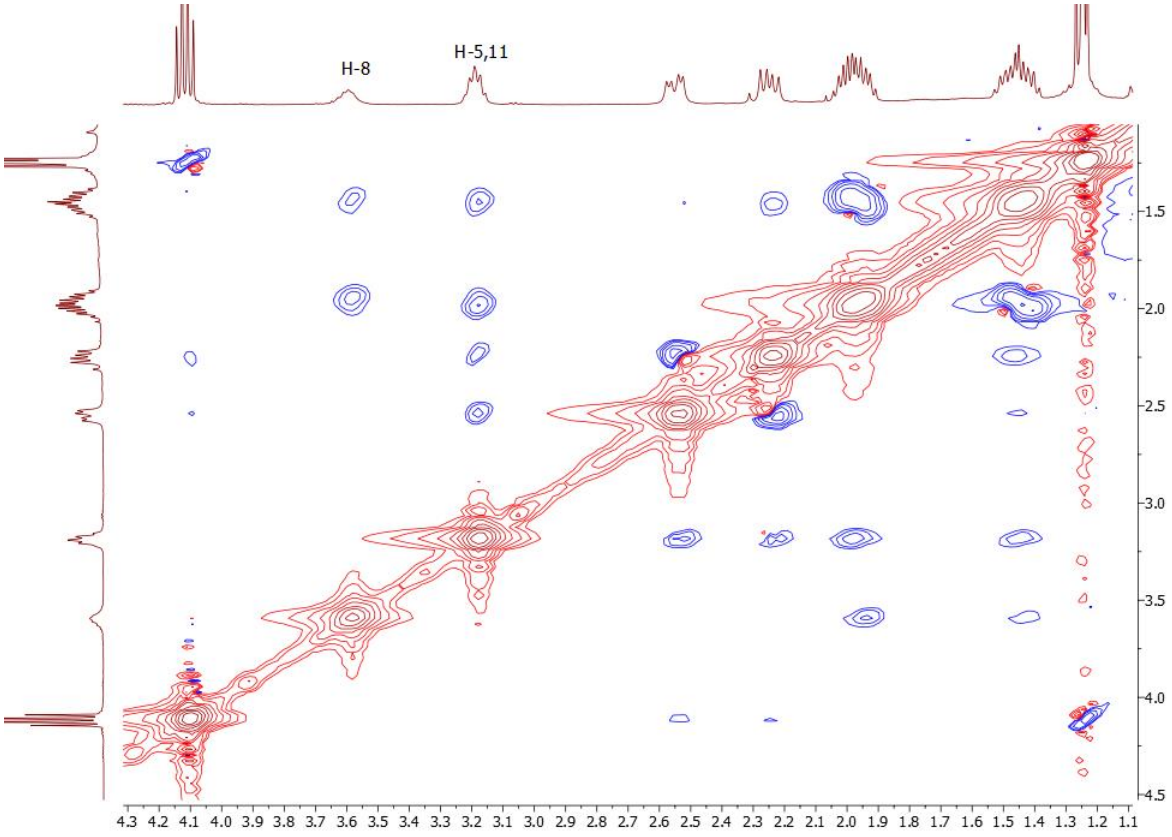
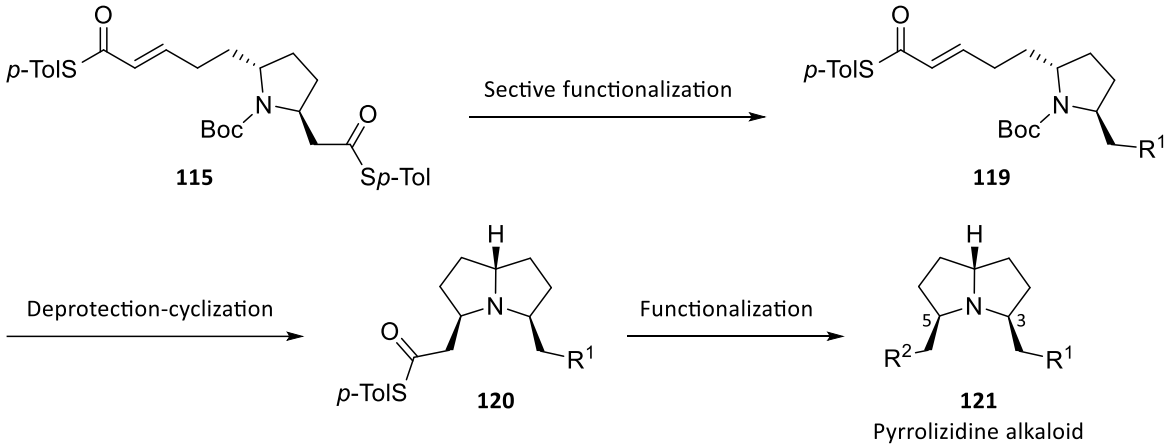



**Figure 29**. 2D NOESY spectrum for pyrrolizidine **55**

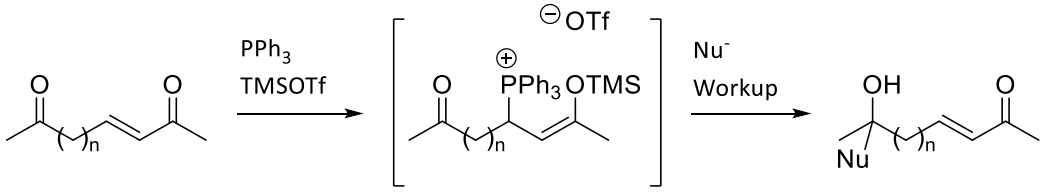
## 9.5. Selective Reduction of the Saturated Thioester

With the synthesis of a pyrrolizidine successfully accomplished, we turned are attention to attempting to selectively reduce and functionalize the saturated thioester. This was to negate the problem of generating a *meso*-pyrrolizidine from a chiral starting material with a high ee and to install the functionality found in 3,5-disubstituted pyrrolizidine alkaloids. Once the saturated thioester had been functionalized (**Scheme 38**), we could proceed with the deprotection-cyclization which would generate an unsymmetrical chiral pyrrolizidine **120.** The thioester on pyrrolizidine **120** can then be functionalized to generate a 3,5-disubstituted pyrrolizidine alkaloid **121**. For this part of the investigation, we decided that the Boc protected pyrrolidine **115** would be taken forward. This was to avoid the use of $BCl_3$ due to its acute toxicity and the ease with which the Boc group can be removed.



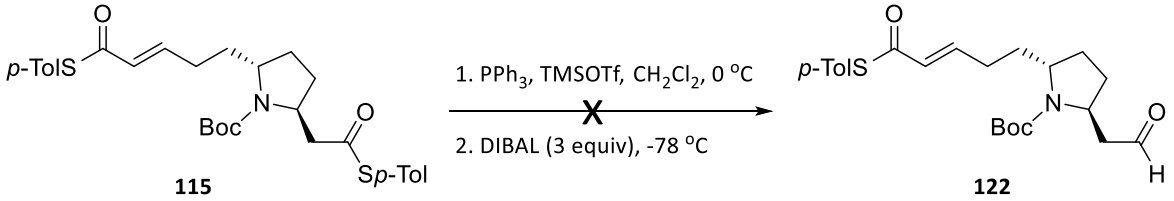

**Scheme 38**. Selective functionalization for the synthesis of pyrrolizidine alkaloids

The challenge we were faced with for this functional group transformation was how to selectively reduce the saturated thioester in the presence of the unsaturated thioester. Work published by Fujioka *et. al.*[47] presented us with a possible solution. Their work demonstrated the selective reduction of carbonyl functionalities in the presence of *α,β*-unsaturated ketones. The two-step procedure involved the *in-situ* protection of the enone using $PPh_3$ and TMSOTf to form a phosphonium silyl enol ether. The other carbonyl functional group could then be treated with the desired nucleophile, and once the reaction was complete the temporary protection could be easily removed during work-up (**Scheme 39**).



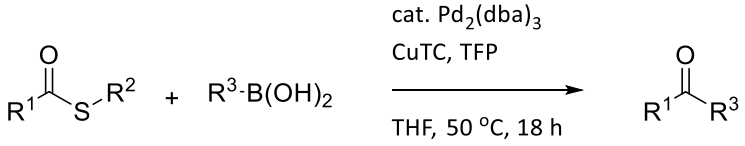

**Scheme 39**. General scheme for the in-situ protection and reduction methodology reported by Fujioka et. al.[47]

We attempted the reduction using 1.5 equivalents of $PPh_3$ and TMSOTf in DCM at 0 °C, to form the in-situ protection, followed by 3 equivalents of DIBAL at -78 °C (**Scheme 40**). Disappointingly, the mass spectra of the crude reaction material did not show the presence of aldehyde **122** and the $^1H$ NMR spectrum showed no sign of an aldehyde peak in the 8-10 ppm region. We surmised that the in-situ protection was not occuring which may be due to the sterically hindered position of the enone in relation to the Boc group and the bulky $PPh_3$. The enones utilized by Fujioka *et. al.* were all sterically unhindered.



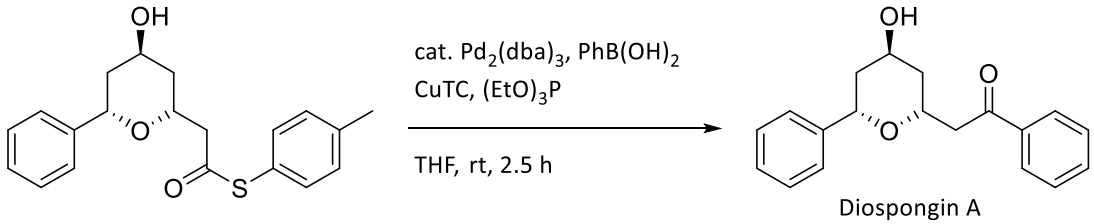

**Scheme 40**. Selective reduction of the saturated thioester to the aldehyde

An alternative method was to use a palladium catalyzed cross-coupling reaction developed by Liebeskind and Srogl.[48] The reaction involves a palladium catalyzed cross-coupling of a thioester with a boronic acid, mediated by a copper co-catalyst to generate the corresponding ketone (**Scheme 41**).



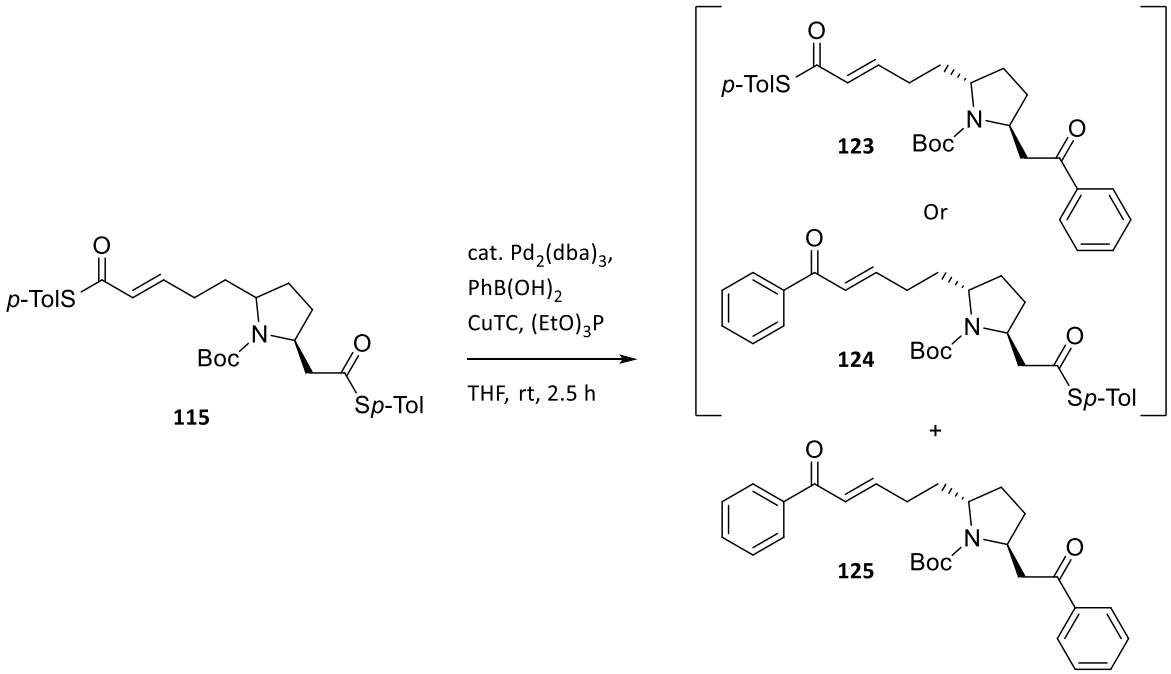

**Scheme 41**. General scheme for the palladium catalysed cross-coupling reaction reported by Liebeskind and Srogl.[48]

The Liebeskind-Srogl reaction was successfully utilised in the Clarke group for the synthesis of diospongin A,[49] where they used a procedure reported by Fuwa *et*. *al*.[50] to convert the saturated thioester to an aryl ketone (**Scheme 42**).




**Scheme 42**. Liebeskind-Srogl reaction utilised for the synthesis of diospongin A[49]

Following the same procedure, we attempted to convert the saturated thioester to the aryl ketone. This was done using 10 mol% of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$, 3 equivalents of copper(I) thiophene-2-carboxylate (CuTC) and 1 equivalent of phenylboronic acid. The starting material was consumed in 2.5 hours as shown by TLC (**Scheme 43**).

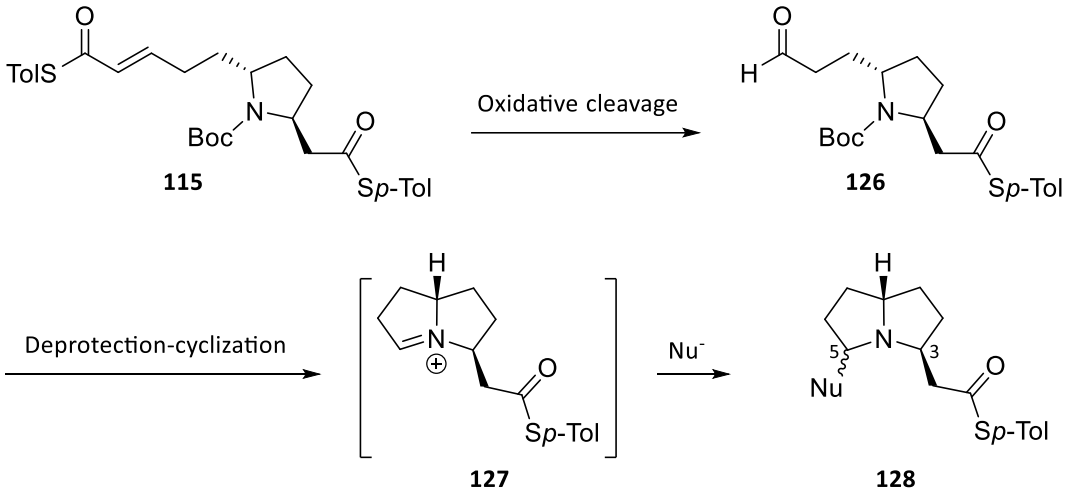



**Scheme 43**. Liebeskind-Srogl cross-coupling reaction using phenylboronic acid

Unfortunately, the reaction was not selective towards the saturated thioester, the mass spectra of the crude reaction material showed that the cross-coupling had taken place at the unsaturated thioester as well as the saturated thioester giving the double addition product **125**. The mass

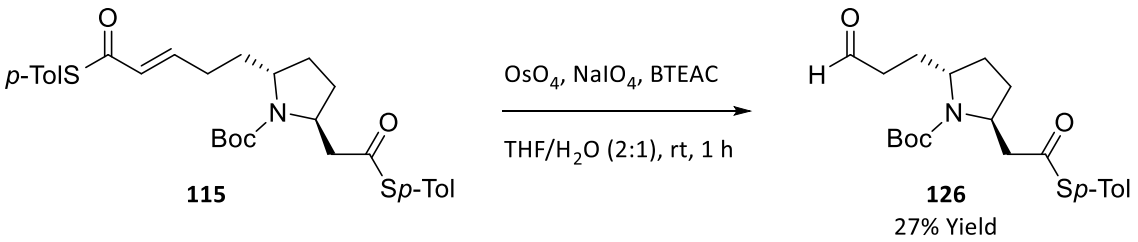
spectra also showed that we had formed a single addition product, which could be the functionalization of the saturated thioester **123** or the unsaturated thioester **124** or a mixture of both. Disappointingly, we were unable to separate the mixture of compounds by flash column chromatography.

Unable to selectively functionalize the saturated thioester we turned our attention to the unsaturated thioester (**Scheme 44**). Oxidative cleavage of the alkene in **115** should lead to the aldehyde **126** which could then undergo intramolecular cyclisation on removal of the Boc group. This would generate the iminium ion intermediate **127** which could be treated with an appropriate nucleophile to install functionality at the 5 position on the pyrrolizidine ring **128**.




**Scheme 44**. Proposed oxidative cleavage of the unsaturated thioester

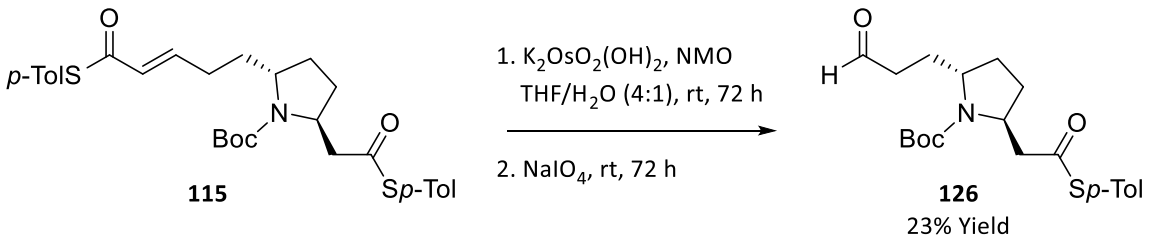
Initially we performed the oxidative cleavage using the Lemieux-Johnson oxidation.[51] Following a literature procedure,[52] pyrrolidine **115** was treated with osmium tetroxide (0.5 mol%) and sodium *meta*periodate (2 equiv) in a mixture of THF and water (2:1) for 1 hour (**Scheme 45**). Benzyl triethyl ammonium chloride (BTEAC) was added to aid the reaction in bi-phasic conditions.




**Scheme 45**. Oxidative cleavage of **115** via a Lemieux-Johnson oxidation

The two step reaction proceeds via dihydroxylation of the alkene by osmium tetroxide to form the diol, followed by oxidative cleavage with sodium *meta*periodate to form the aldehyde. Sodium *meta*periodate also re-oxidises osmium tetroxide from Os(VI) to Os(VIII) and so the osmium tetroxide can be used in catalytic amounts. Although the reaction was successful, aldehyde **126** was isolated with a 27% yield.

In an attempt to increase the yield of aldehyde **126** and avoid using the volatile and toxic osmium tetroxide, we decided to use an Upjohn dihydroxylation reaction[53] to form the diol, before adding sodium *meta*periodate to cleave the diol and form the aldehyde. Here osmium tetroxide is generated *in-situ* from potassium osmate by the oxidising agent *N*-methylmorpholine-*N*-oxide (NMO), which also re-oxidises osmium tetroxide from Os(VI) to Os(VIII). Following a literature procedure,[54] pyrrolidine **115** was added to potassium osmate (10 mol%) and a stoichiometric quantity of NMO in a THF and water mixture (4:1) at room temperature. The reaction was followed by TLC and took 72 hours for the starting material to be consumed. Sodium *meta*periodate (2 equiv) was then added and the reaction run for a further 72 hours at room temperature (**Scheme 46**).




**Scheme 46**. Oxidative cleavage of **115** via an Upjohn dihydroxylation and sodium metaperiodate

After 72 hours the reaction was stopped because the mass spectra of the crude reaction mixture showed that over oxidation of **126** to form the peroxyacid was occurring. Unfortunately, considering the long reaction time, aldehyde **126** was only isolated with a yield of 23%. Alternatively, the diol formed from the dihydroxylation step could be isolated and purified before being treated with sodium *meta*periodate. Studies into the cyclisation of **126** will be the subject of future work.

## 9.6. Synthesis of the Indolizidine precursor

The two-directional asymmetric "clip-cycle" methodology employed herein for the synthesis of pyrrolizidines can be extended towards the synthesis of indolizidines. The strategy would involve using an unsymmetrical chiral precursor for the CPA catalyzed intramolecular aza-Michael cyclization to form the chiral pyrrolidine, which could then undergo further cyclization to the indolizidine. As the chiral precursor is racemic, kinetic resolution studies would need to be performed in order to generate an enantioenriched CPA cyclized product. Kinetic resolutions are dependent upon one enantiomer of the substrate reacting faster than the other and so as the reaction proceeds an enantiopure product is formed while the enantiomeric excess (ee) of the chiral precursor increases.[55] Ideally running the reaction to 50% conversion will give an ee >99% for both the product and the recovered starting material, with a maximum yield of 50% (**Figure 30**).

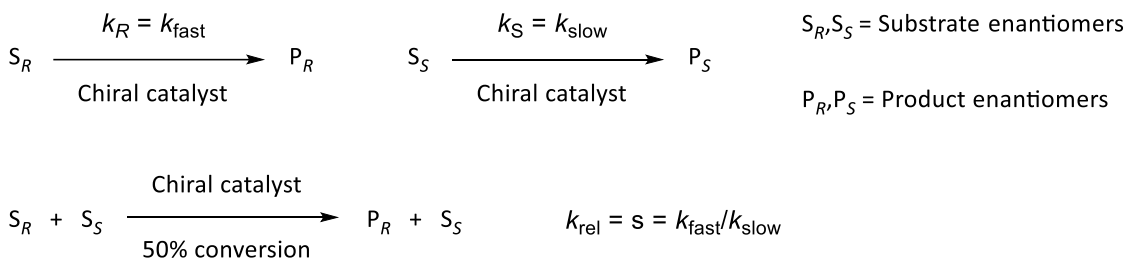
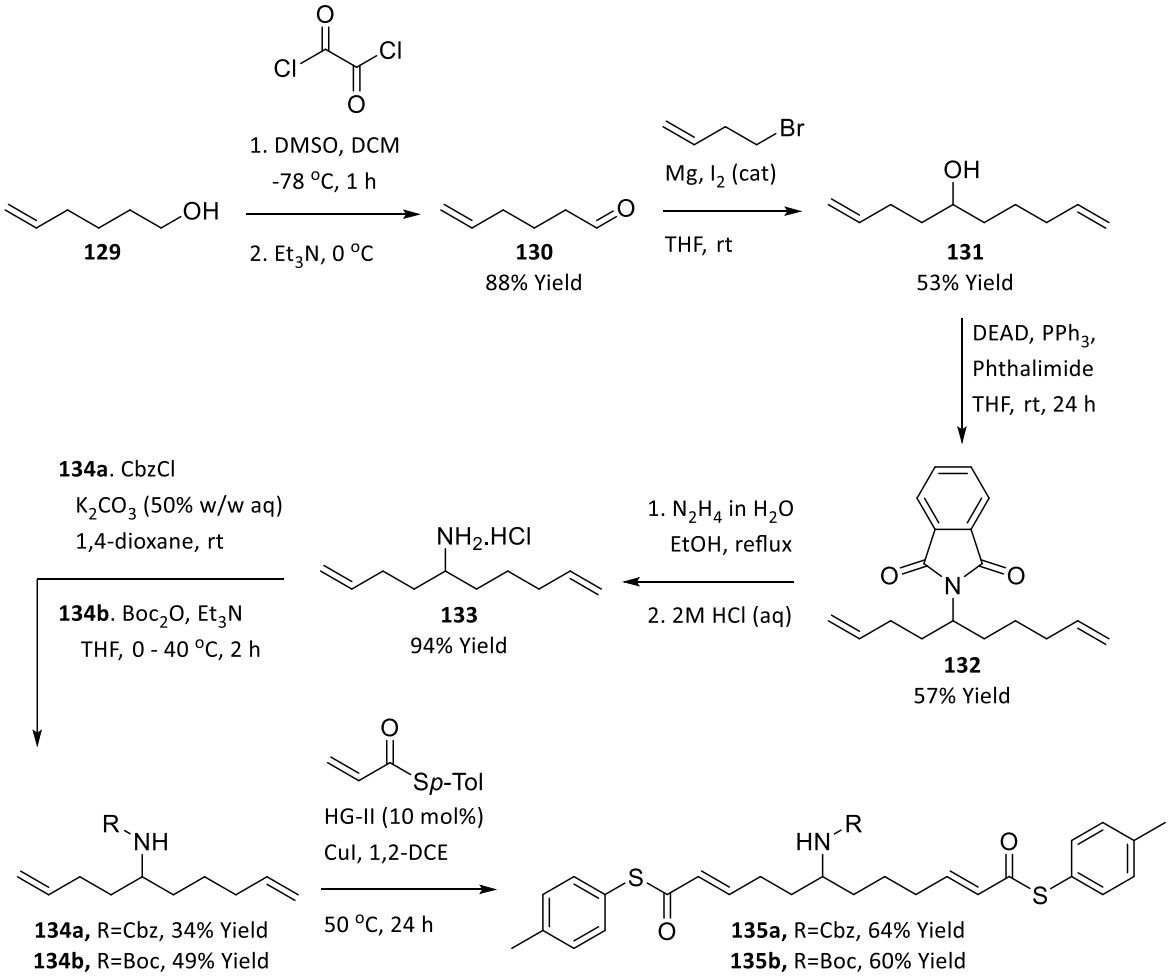



**Figure 30**. Catalytic kinetic resolution[55]

The s-factor, which equates to the relative rate of reaction ($k_{rel}$), is a measure of the selectivity of the kinetic resolution, and is calculated by dividing the rate of reaction of the substrate enantiomer that reacts fast ($k_{fast}$) by the rate of reaction of the substate enantiomer that reacts slow ($k_{slow}$). A high s-factor is required to generate the product with a high ee. Another consideration that needs to be made is the potential of the unsymmetrical chiral precursor cyclizing to the piperidine as well as the pyrrolidine. According to Baldwin's rules[56] both the 5-*exo*-*trig* cyclization to form the pyrrolidine and the 6-*exo*-*trig* cyclisation to form the piperidine are favored. Although 5-membered rings are slightly less stable than 6-membered rings due to ring strain, we would expect the 5-membered ring to form in preference to the 6-membered ring as a result of kinetic control. The activation energy barrier $\Delta G^{‡}$ (Gibbs free energy) for 5-membered rings is lower than the $\Delta G^{‡}$ for 6-membered rings. This can be explained by the relation of $\Delta G^{‡}$ to the enthalpy of activation $\Delta H^{‡}$ and the entropy of activation $\Delta S^{‡}$ which is represented by the equation $\Delta G^{‡} = \Delta H^{‡} - T\Delta S^{‡}$. As there is a

small difference between the $\Delta H^{\ddagger}$ value for 5 and 6 membered rings the important factor is the $\Delta S^{\ddagger}$ value. There is more disorder in the chain that cyclizes to the 6-membered ring than the chain that cyclizes to the 5-membered ring and so the $\Delta S^{\ddagger}$ is larger and negative for the formation of the 6-membered ring leading to a larger $\Delta G^{\ddagger}$. The 5-membered ring being the kinetic product will form faster than the 6-membered ring which would be the thermodynamic product.

The forward synthesis for unsymmetrical chiral precursor required an extra step compared with that of the pyrrolizidine precursor, as 5-hexenal **130** was not commercially available (**Scheme 47**).




**Scheme 47**. Synthesis of indolizidine cyclisation precursors **135a-b**

The synthesis began with a Swern oxidation converting primary alcohol **129** to aldehyde **130** following a literature proceedure.[57] The reaction proceeds *via* acylation between DMSO and oxalyl chloride to form a chlorosulfonium ion which then reacts with the alcohol. The resulting

alkoxysulfonium salt is deprotonated with $Et_3N$ to give a sulfur ylide which decomposes to give the aldehyde and dimethyl sulfide. Aldehyde **130** was obtained in a good yield of 88%. However because **130** was highly volatile it was kept in a solution of pentane/$Et_2O$ after flash column chromatography. The yield was calculated by determining the percentage by weight of the product and the solvents ($Et_2O$ and pentane) in the solution. This was achieved by inputting the peak integrations from the $^1H$ NMR spectra into an NMR residual solvents calculator (**Figure 31** and **Table 7**). The percentage by weight calculated for the product could then be used to calculate the percentage yield (**Figure 32**).

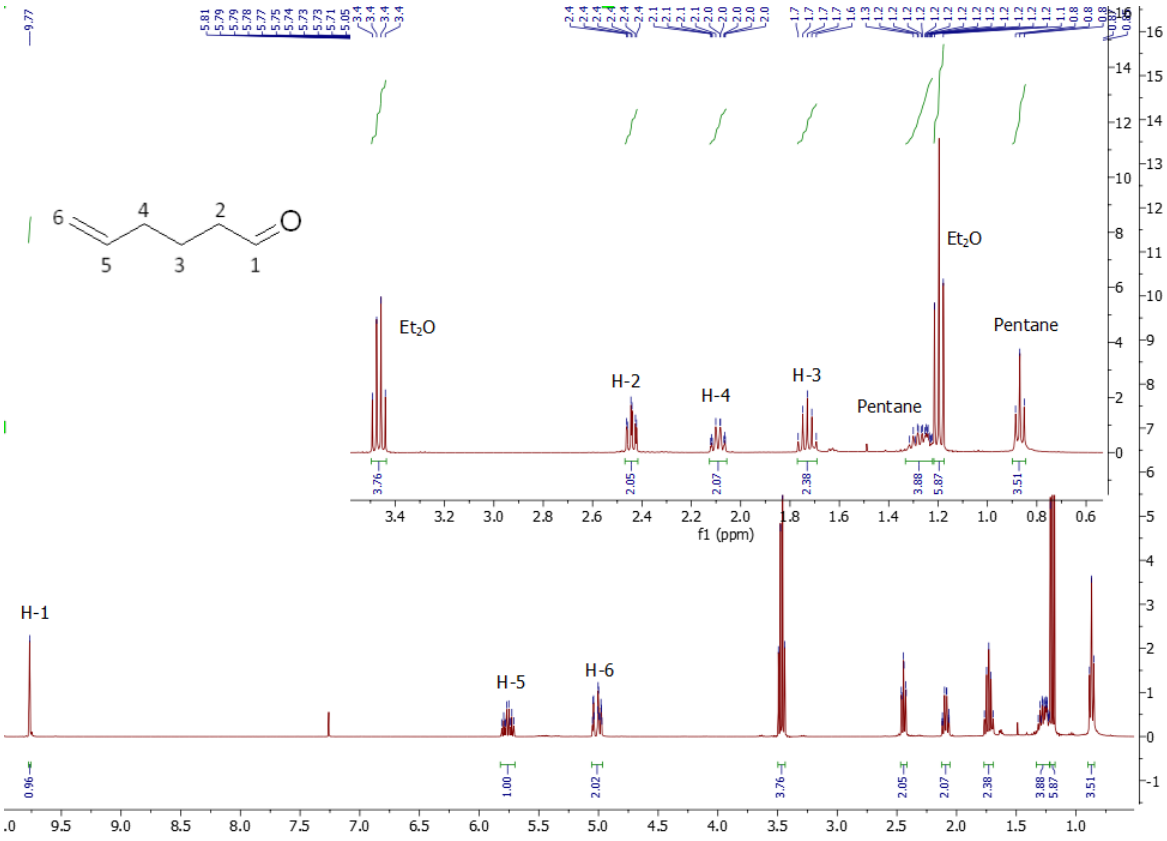



**Figure 31**. $^1H$ NMR spectrum of the aldehyde solution

| | Product | $Et_2O$ | Pentane |
|---|---|---|---|
| **Peak integration** | 1 | 3.76 | 3.88 |
| **Protons in peak** | 1 | 4 | 6 |
| **MW (g/mol)** | 98.15 | 74.12 | 72.15 |
| **% by weight** | 46.16 | 31.90 | 21.94 |

**Table 7**. NMR product and residual solvent percentages

Weight of solution = 3.89 g

% by weight of aldehyde **130** = 46.16%

MW of aldehyde **130** = 98.15 g/mol

MW of alcohol **129** = 100.16 g/mol

$$\text{Weight of aldehyde } \mathbf{130} \text{ in solution} = \frac{3.89\text{ g} \times 46.16}{100} = 1.80\text{ g}$$

$$\text{Moles of aldehyde } \mathbf{130} = \frac{1.80\text{ g}}{98.15\text{ g/mol}} = 18.34\text{ mmol} \qquad \text{Moles of alcohol } \mathbf{129} = \frac{2.09\text{ g}}{100.16\text{ g/mol}} = 20.87\text{ mmol}$$

$$\text{Yield of aldehyde } \mathbf{130} = \frac{18.34\text{ mmol} \times 100}{20.87\text{ mmol}} = 87.87\%$$

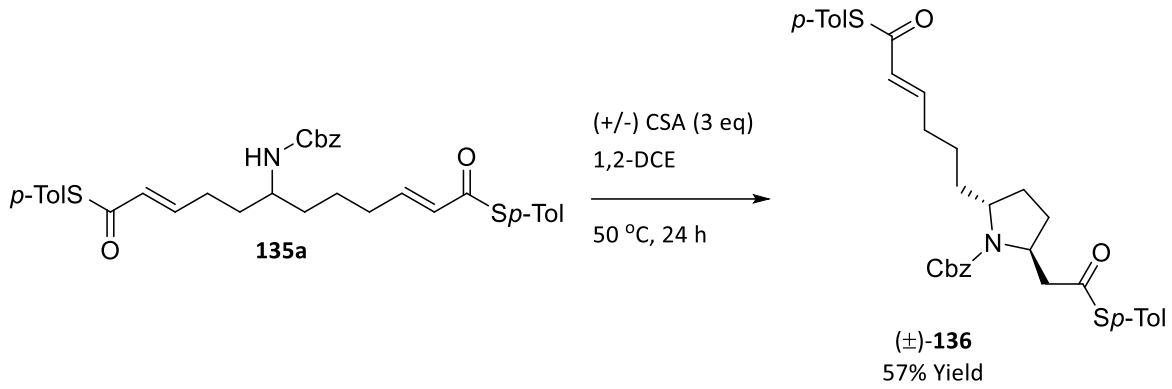
**Figure 32**. Yield calculation for aldehyde **130**

Next, the Grignard reaction between 4-butenyl magnesium bromide and aldehyde **130** generated chiral secondary alcohol **131** in a moderate yield of 53%. Converting **131** to the amine salt **132** was achieved through a Mitsunobu reaction using phthalimide as the *N*-nucleophile, followed by hydrazinolysis with hydrazine hydrate and an aqueous acid work-up. The amine salt **132** was obtained in an excellent yield of 94%. Amine salt **132** was then either Cbz protected with benzyl chloroformate or Boc protected with di-*tert*-butyl dicarbonate. Disappointingly the isolated yields for **134a** and **134b** were much lower, 34% and 49% respectively, compared to the symmetrical dienes **56** and **102**. Finally protected amines **134a-b** were "clipped" with *p*-tolyl thioester **108** *via* a two-directional double alkene cross-metathesis reaction using the optimised conditions. The metatheses were performed using Hoveyda-Grubbs catalyst™ 2nd generation (10 mol%) and CuI as a co-catalyst, with 6 equivalents of *p*-tolyl thioester **108** in 1,2-dichloroethane at 50 °C for 24 hours.

Both amino thioesters **135a** and **135b** were isolated in moderate yields of 64% and 60% respectively.

Precursors **135a** and **135b** were then cyclized racemically using the optimized conditions of 3 equivalents of CSA in 1,2-dichloroethane at 50 °C for 24 hours (**Schemes 48** and **49**). Complete conversion to the corresponding racemic pyrrolidines **136** and **137** was observed by TLC, but the isolated yields were significantly lower, 57% and 38% respectively, than compared to the racemic cyclisation of the symmetrical precursors **104** and **115**. We surmised that this could be due to the formation of the six membered rings (piperidine) although they were not isolated from the crude reaction material. The $^{1}$H-NMR data for **136** and **137** was consistent with the $^{1}$H NMR data for the pyrrolidines generated from the desymmetrization cyclizations. The key peaks for the protons at each stereocentre resonate at 4.29 ppm (H-21) and 3.82 ppm (H-18) for **136** (**Figure 33**), which is consistent with the resonance of the same protons from the pyrrolidine formed from the desymmetrization (4.30 ppm and 3.85 ppm). The same is true for **137** (**Figure 34**). We are confident that the pyrrolidines have formed as the major product in each case.

The next step would be to find HPLC conditions for the unsymmetrical precursors and the racemic pyrrolidines, which could then be used to conduct kinetic resolution studies on the asymmetric cyclizations. Unfortunately, due to time constraints caused by the COVID-19 pandemic, the kinetic resolution studies were not attempted and are the subject of future work.




**Scheme 48**. Racemic cyclisation of **135a** using CSA

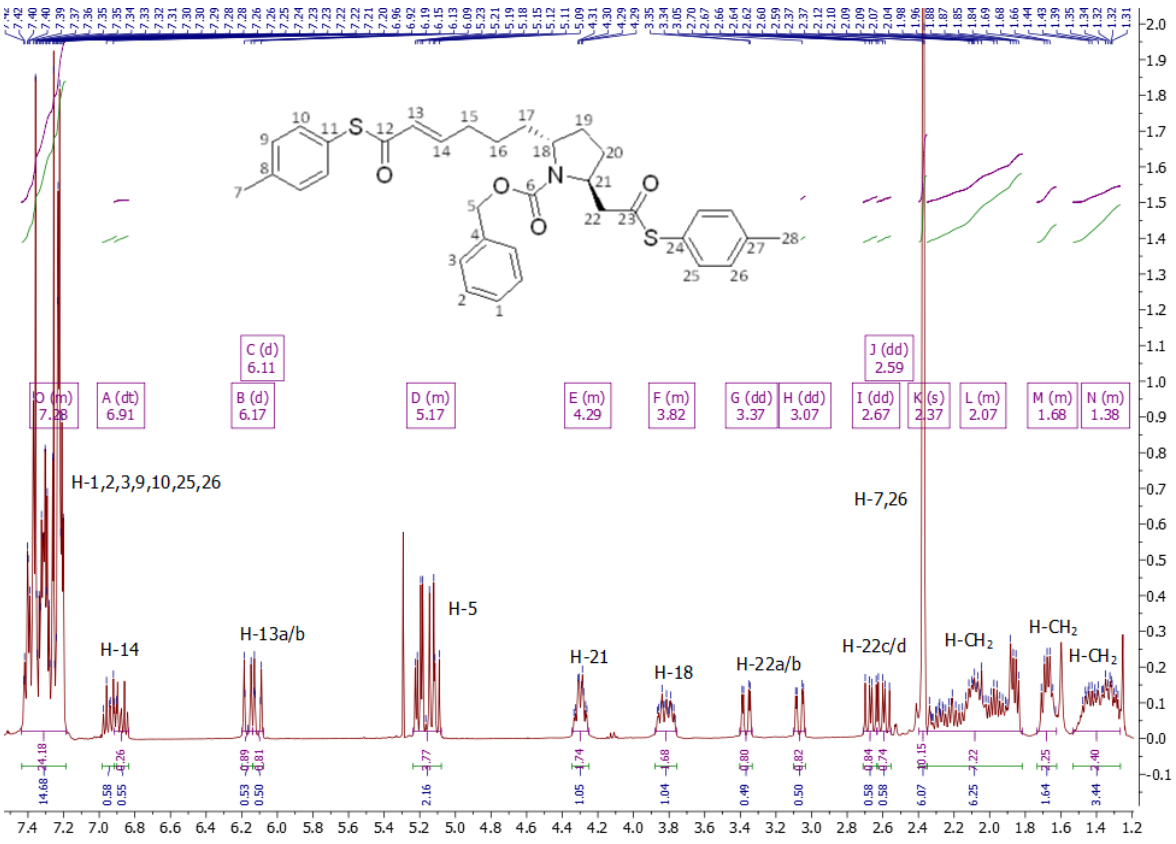
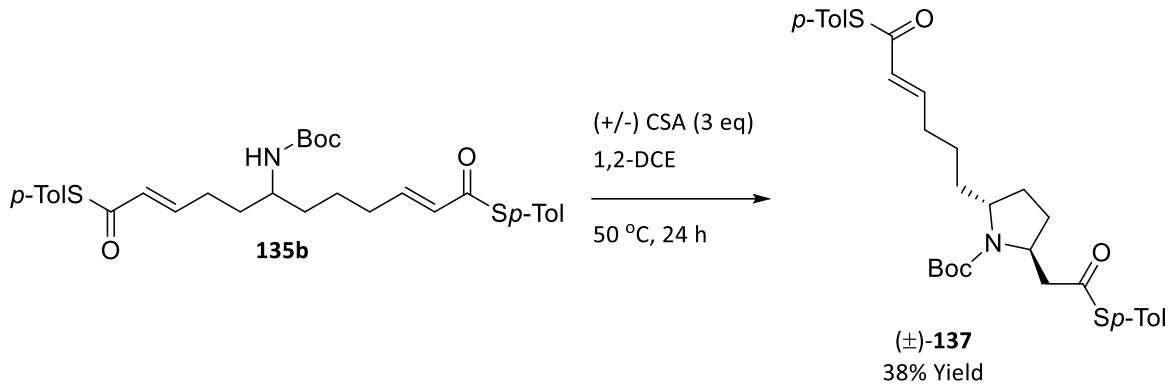



**Figure 33**. $^{1}$H NMR spectrum of racemic pyrrolidine **136**




**Scheme 49**. Racemic cyclisation of **135b** using CSA

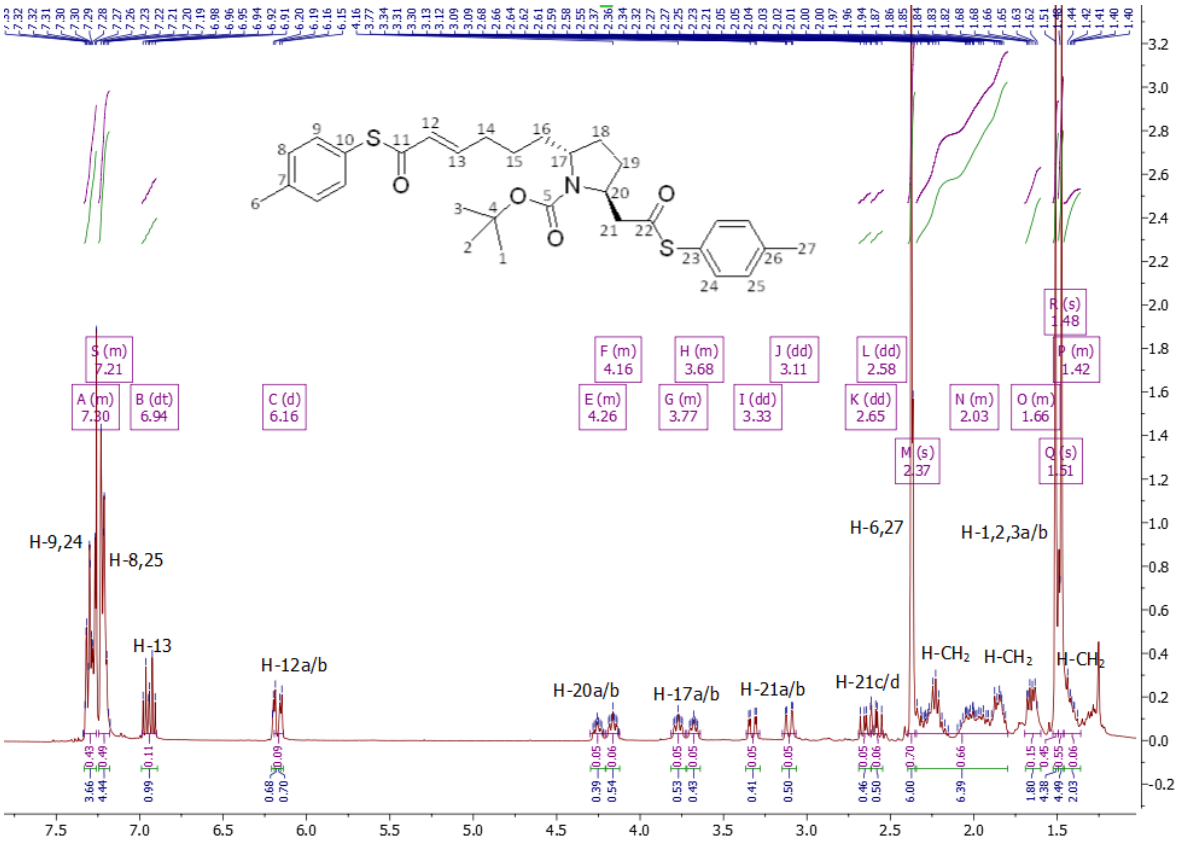



**Figure 34**. $^{1}$H NMR spectrum of racemic pyrrolidine **137**

## 9.7. Conclusion and Future Work

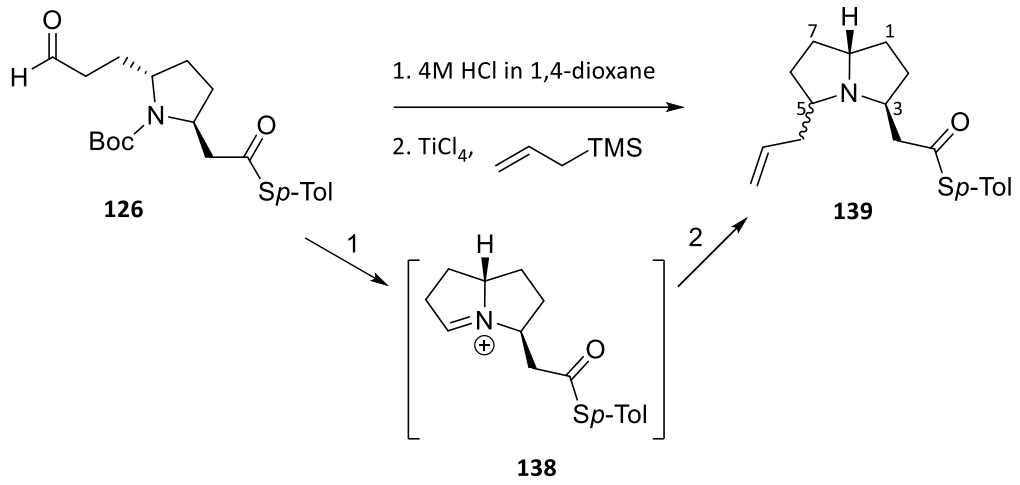
The synthesis of the symmetrical and unsymmetrical linear cyclisation precursors (**103**,**107** and **135a-b**) was achieved effectively using a two-directional approach over 5 steps and 6 steps respectively. The double alkene cross metathesis reactions, between the Cbz and Boc protected amino dienes and thioacrylate **108**, catalyzed by Hoveyda-Grubbs catalyst™ 2nd generation gave good yields (57% - 74%) and selectivity towards the *E*,*E*-dienes. The yields for the Boc protected precursors were found to be lower in each case. The asymmetric cyclizations catalyzed by the chiral Brønsted acid catalyst (*R*)-TRIP generated chiral pyrrolidines **104** and **115** with high yields and ees for the major diastereomers. Only a slight reduction in yield and ee was observed for the Boc protected pyrrolidine compared to the Cbz protected pyrrolidine.

Both the Cbz and Boc protected chiral pyrrolidines (**104** and **115**) were successfully deprotected and cyclized to form pyrrolizidine **55** as a single diastereomer. Confirmation of the absolute stereochemistry was determined by comparison of $^{1}$H NMR data published in the literature for stereoisomers of the 3,5-disutituted diethyl ester pyrrolizidine and 2D NOESY experiment. The stereochemistry was found to be that of the *meso*-pyrrolizidine with a *cis*-*cis* configuration. Unfortunately, the high ees obtained for pyrrolidines **104** and **115** *via* the asymmetric cyclisation reactions, were inconsequential when forming the *meso*-pyrrolizidine (**116**) in the second cyclisation. Initial attempts to selectively functionalize the saturated thioester present in the chiral pyrrolidine **115** met with failure. However, oxidative cleavage of the alkene contained in the unsaturated thioester to form aldehyde **126** were successful, although only with a low yield.

In conclusion, coupling a two-directional approach with the “clip-cycle” methodology developed in the Clarke group for the synthesis of substituted chiral pyrrolidines, can be used to synthesize the pyrrolizidine motif found in natural alkaloids. Although this resulted in the *meso*-pyrrolizidine, further studies towards the selective functionalization of the saturated thioester could mitigate this problem and allow the chirality of the pyrrolidine obtained from the asymmetric cyclization to be retained.

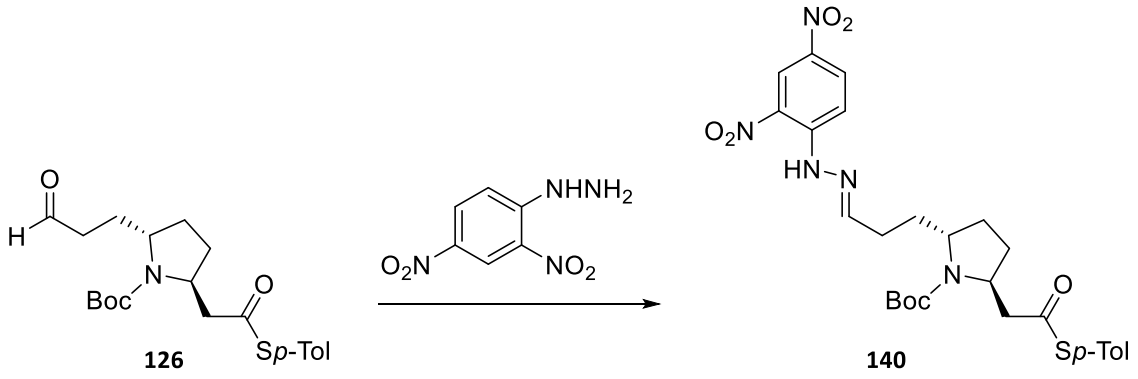
Future work would focus on the deprotection and cyclisation of aldehyde **126** obtained from the oxidative cleavage of pyrrolidine **115**. This would generate an iminium ion intermediate which could then be treated with an appropriate nucleophile to install functionality at the 5 position on the

pyrrolizidine ring. For example, following the deprotection of pyrrolidine **115** the resulting iminium ion intermediate **138** could be treated with allyl trimethyl silane and titanium tetrachloride *via* a Sakurai reaction (**Scheme 50**). After determining the stereochemistry at the 5 position on the resulting pyrrolizidine **139**, the saturated thioester could be functionalized *via* a Liebeskind-Srogl reaction and the alkene reduced by $H_2$ over a palladium catalyst.




**Scheme 50**. Plausible functionalization *via* a Sakurai reaction

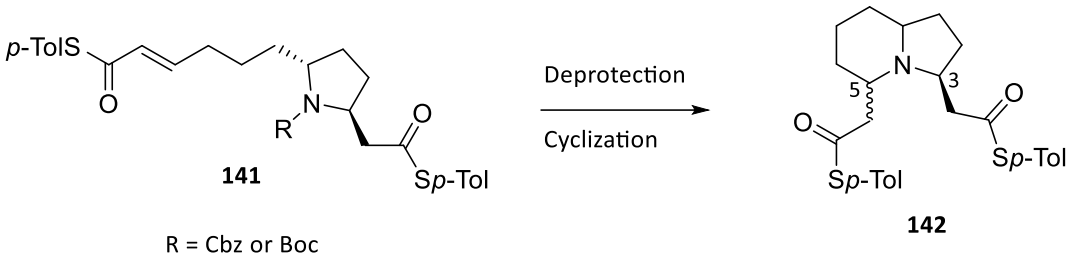
Aldehyde **126** could also be trapped with dinitrophenyl hydrazine (2,4-DNP) to form a hydrazone **140** which may crystalize, allowing the absolute stereochemistry of the chiral pyrrolidine to be determined by X-ray crystallography (**Scheme 51**).




**Scheme 51**. Conversion of **126** into a hydrazone

Future work would also include kinetic resolution studies of the asymmetric CPA catalyzed cyclisation of the unsymmetrical chiral precursors, with the view to generating enantiopure chiral

pyrrolidines. The process would involve finding the HPLC conditions for a 50:50 mixture of the precursors and the racemic pyrrolidines, which can then be used to conduct kinetic resolutions for the asymmetric cyclizations. The resulting chiral pyrrolidines could then be deprotected and cyclized to the corresponding indolizidines (**Scheme 52**). Unlike with the pyrrolizidine the indolizidines formed cannot be *meso* compounds. Determination of the stereochemistry at the 5 position would need to be done first, before attempting to functionalize either the saturated or unsaturated thioesters of the chiral precursors in order to synthesis 3,5-disustituted indolizidine alkaloids.




R = Cbz or Boc

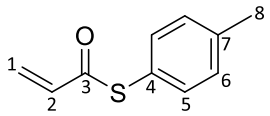
**Scheme 52**. Deprotection-cyclisation to form an indolizidine

# 10. Experimental

## 10.1. General Experimental

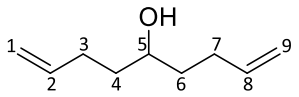
Unless otherwise noted all compounds were bought from commercial suppliers and used without further purification. Nuclear magnetic resonance spectra were recorded on a Jeol ECS-400 spectrometer at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: chloroform-d, 7.26 ppm for $^{1}H$ NMR; chloroform-d, 77.00 ppm for $^{13}C$ NMR. Coupling constants (*J*) are quoted in Hertz. Infra-red spectra were recorded on an ATI Mattson Genesis FT-IR spectrometer. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionization (ESI) and atmospheric-pressure chemical ionization (APCI) techniques. Optical rotations were carried out using a Billingham and Stanley $ADP_{450}$ 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 $F_{254}$ or neutral aluminium oxide 60 $F_{254}$. The plates were developed using ultraviolet light, basic aqueous potassium permanganate or acidic aqueous ceric ammonium molybdate. 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 or neutral aluminium oxide 60 (40-300 µm) supplied by Acros. Dry solvents were acquired from PureSolv alumina columns from Innovative Technologies. 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 characterization and does not necessarily conform to IUPAC rules.

## 10.2. Experimental Procedures



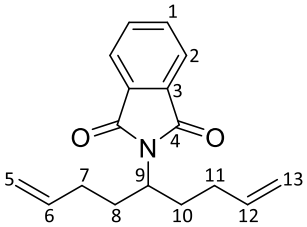

***S*-*p*-tolyl prop-2-enethioate** (**108**)

Sodium borohydride (0.05 g, 1.32 mmol) and *p*-thiocresol (5.46 g, 44.0 mmol) were added to a solution of NaOH (15% w/w aq. 20 ml) and the resulting solution was stirred at room temperature for 1 hour to form the sodium salt of *p*-thiocresol (*p*-$CH_3C_6H_4S^-Na^+$). In a separate flask, BHT (0.136 g, 0.616 mmol) and acryloyl chloride (5.97 g, 66.0 mmol) were dissolved in cyclohexane (40 ml). Both solutions were ice-cooled before use. The *p*-$CH_3C_6H_4S^-Na^+$ solution was then added over 10 mins to the solution of acryloyl chloride and the resulting mixture was stirred at 55 °C for 35 mins. The reaction was cooled to room temperature and extracted with diethyl ether (100 ml). The organic layer was washed with 5% aqueous $NaHCO_3$ solution and brine, dried over $Na_2SO_4$ and concentrated *in vacuo* (a portion of BHT (0.136 g) was added to the filtrate to prevent polymerization during the evaporation of the solvent). The crude product was purified by flash column chromatography ($SiO_2$, 2% $Et_2O$/hexane) to afford **108** as a colourless oil (4.18 g, 23.0 mmol, 53% yield). **TLC ($SiO_2$)** $R_f$ = 0.29 (5% $Et_2O$/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.32 (2 H, d, *J* = 7.9 Hz, H-5), 7.24 (2 H, d, *J* = 7.9 Hz, H-6), 6.44 (1 H, dd, *J* = 17.2, 9.5 Hz, H-2), 6.37 (1 H, dd, *J* = 17.2, 1.7 Hz, H-1), 5.75 (1 H, dd, *J* = 9.5, 1.7 Hz, H-1), 2.38 (3 H, s, H-8) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$); δ 189.1 (C-3), 139.9 (C-7), 134.7 (C-5), 134.5 (C-2), 130.2(C-6), 127.4 (C-1), 123.7 (C-4), 21.5 (C-8) ppm; **IR (ATR)**: $\nu_{max}$ 3024, 2922, 1682, 1612, 1494, 1447, 1394, 1304, 1210, 1160, 1117, 987, 941, 807, 722, 628, 528, 471 $cm^{-1}$; **HRMS (APCI)** 179.0521 ($M + H^+$. $C_{10}H_{11}OS$ requires 179.0525).




**Nona-1,8-dien-5-ol** (**100**)

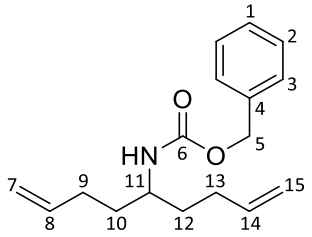
Magnesium turnings (1.22 g, 50.0 mmol) and iodine (1 crystal) were added to a flame dried flask under $N_2$, which was warmed until the iodine sublimed. The flask was allowed to cool to room temperature before the addition of dry THF (40 ml). To this mixture, 4-bromo-1-butene (5.08 ml, 50.0 mmol) was added slowly at room temperature (the flask was placed in a water bath to control the temperature). The resulting reaction mixture was then stirred at room temperature for 1 h to form the Grignard reagent. The reaction was then cooled to 0 °C before the addition of ethyl formate (1.62 ml, 20.0 mmol) in dry THF (10 ml) over 10 mins. The reaction mixture was then stirred at room temperature overnight. The reaction mixture was cooled to 0 °C and quenched with saturated $NH_4Cl$ solution (50 ml). The aqueous phase was then extracted with $Et_2O$ (3 x 50ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 5% EtOAc/hexane) to afford secondary alcohol **100** as a yellow oil (2.42 g, 17.3 mmol, 86% yield). *Data was consistent with those reported in the literature*.[40] **TLC ($SiO_2$)** $R_f$ = 0.19 (10% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 5.84 (2H, ddt, *J* = 16.9, 10.1, 6.8 Hz, H-2,8), 5.05 (2H, ddd, *J* = 17.3, 3.6, 1.4 Hz, H-1,9), 4.97 (2H, dd, *J* = 10.1, 1.4 Hz, H-1,9), 3.69 – 3.61 (1H, m, H-5), 2.27 – 2.07 (4H, m, $CH_2$), 1.63 – 1.47 (5H, m, $CH_2$ and OH) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$); δ 138.7 (C-2,8), 114.9 (C-1,9), 71.1 (C-5), 36.6 (C-4,6), 30.2 (C-3,7) ppm; **IR (ATR)**: $\nu_{max}$ 3342, 3078, 2978, 2933, 1641, 1449, 1416, 1314, 1079, 992, 908, 639, 556 $cm^{-1}$; **HRMS (APCI)** 141.1271 ($M + H^+$. $C_9H_{17}O$ requires 141.1274).




**2-(nona-1,8-dien-5-yl)isoindoline-1,3-dione** (**113**)

Phthalimide (1.44 g, 9.80 mmol) and triphenylphosphine (2.57 g, 9.80 mmol) were dissolved in THF (50 ml). Secondary alcohol **100** (1.10 g, 7.84 mmol) was then added followed by DEAD (5 ml, 11.0

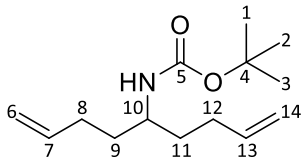
mmol) at room temperature over 20 min. The reaction mixture was stirred at room temperature for 24 h. The solvent was then removed under reduced pressure and the resulting crude oil triturated with hexane/$Et_2O$ (2:1 mixture) until complete removal of the solids. The combined organic layers were concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 2% EtOAc/pentane) to afford *N*-alkyl phthalimide **113** as a colourless oil (1.23 g, 4.56 mmol, 58% yield). **TLC ($SiO_2$)** $R_f$ = 0.29 (5% EtOAc/pentane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.82 (2H, dd, *J* = 5.5, 3.2 Hz, H-2), 7.71 (2H, dd, *J* = 5.5, 3.1 Hz, H-1), 5.75 (2H, ddt, *J* = 17.0, 10.1, 6.7 Hz, H-6,12), 4.96 (2H, ddd, *J* = 17.0, 3.3, 1.4 Hz, H-5,13), 4.90 (2H, dd, *J* = 10.1, 1.4, Hz, H-5,13), 4.23 (1H, m, H-9), 2.28 – 2.17 (2H, m, $CH_2$), 2.10 – 1.95 (4H, m, $CH_2$), 1.85 – 1.75 (2H, m, $CH_2$) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$); δ 168.9 (C-4), 137.6 (C-6,12), 134.0 (C-1), 131.9 (C-3), 123.3 (C-2), 115.3 (C-5,13), 51.4 (C-9), 31.7 (C-8,10), 31.0 (C-7,11) ppm; **IR (ATR)**: $\nu_{max}$ 3078, 2929, 1772, 1704, 1641, 1613, 1468, 1453, 1393, 1368, 1334, 1172, 1068, 992, 911, 880, 794, 719, 699, 641, 609, 550, 531, 510, $cm^{-1}$; **HRMS (APCI)** 270.1479 ($M + H^+$. $C_{17}H_{20}NO_2$ requires 270.1489).




**Benzyl nona-1,8-dien-5-ylcarbamate** (**102**)

Phthalimide **113** (2.00 g, 7.46 mmol) was dissolved in EtOH (70 ml). Hydrazine hydrate (1.08 ml, 22.28 mmol) was then added and the reaction mixture was refluxed overnight, during this time a white solid precipitated. The reaction was cooled to room temperature and quenched with concentrated HCl (37% w/w, 28ml). The solvent was removed under reduced pressure and the residual aqueous solution was diluted with $H_2O$ (80 ml) and then washed with $Et_2O$ (3 x 80ml). The aqueous layer was treated with NaOH until pH 12 and then extracted with $Et_2O$ (3 x 80ml). The combined organic layers were washed with 2M HCl (aq, 5 x 80 ml). The aqueous layer was concentrated *in vacuo* to give the amine HCl salt **114** (1.18 g, 6.72 mmol, 90% yield). To the amine HCl salt **114** (188 mg, 1.07 mmol) was added $K_2CO_3$ (50% w/w, aq, 0.37 ml, 2.67 mmol) and 1,4-dioxane (5 ml) and the resulting mixture was stirred for 15 min to generate the free amine. Benzyl chloroformate (0.18 ml, 1.28 mmol) was then added. The reaction mixture was stirred at room

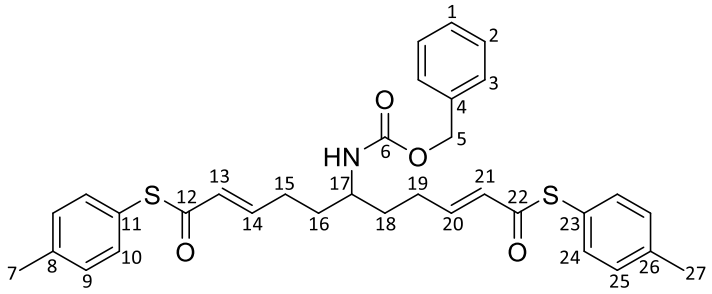
temperature for 5 h. The reaction was quenched with $H_2O$ (5 ml) and extracted with DCM (3 x 10ml). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 10% EtOAc/hexane) to afford Cbz-Amine **102** as a white solid (237 mg, 0.87 mmol, 81% yield). **TLC ($SiO_2$)** $R_f$ = 0.21 (10% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.41 – 7.28 (5H, m), 5.81 (2H, ddt, *J* = 17.2, 10.1, 6.6 Hz, H-8,14), 5.09 (2H, s, H-5), 5.01 (2H, bd, *J* = 17.2 Hz, H-7,15), 4.96 (2H, bd, *J* = 10.1 Hz, H-7,15), 4.52 (1H, d, *J* = 9.2 Hz, H-NH), 3.75 – 3.58 (1H, m, H-11), 2.18 – 2.02 (4H, m, $CH_2$), 1.64 – 1.55 (2H, m, $CH_2$), 1.53 – 1.42 (2H, m, $CH_2$) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$); δ 156.2 (C-6), 138.1 (C-8,14), 136.8 (C-4), 128.7 (C-1/2/3), 128.2 (C-1/2/3), 115.1 (C-7,15), 66.7 (C-5), 50.8 (C-11), 34.8 (C-10,12), 30.2 (C-9,13) ppm; **IR (ATR)**: $\nu_{max}$ 3321, 3075, 2935, 2852, 1692, 1640, 1532, 1452, 1415, 1330, 1230, 1243, 1215, 1046, 1028, 994, 910, 774, 736, 696, 642, 458, $cm^{-1}$; **HRMS (ESI)** 296.1616 ($M + Na^+$. $C_{17}H_{23}NNaO_2$ requires 296.1621).




***tert*-butyl nona-1,8-dien-5-ylcarbamate** (**56**)

Phthalimide **113** (2.00 g, 7.46 mmol) was dissolved in EtOH (70 ml). Hydrazine hydrate (1.08 ml, 22.28 mmol) was then added and the reaction mixture was refluxed overnight, during this time a white solid precipitated. The reaction was cooled to room temperature and quenched with concentrated HCl (37% w/w, 28ml). The solvent was removed under reduced pressure and the residual aqueous solution was diluted with $H_2O$ (80 ml) and then washed with $Et_2O$ (3 x 80ml). The aqueous layer was treated with NaOH until pH 12 and then extracted with $Et_2O$ (3 x 80ml). The combined organic layers were washed with 2M HCl (aq, 5 x 80 ml). The aqueous layer was concentrated *in vacuo* to give the amine HCl salt **114** (1.18 g, 6.72 mmol, 90% yield). To a solution of amine HCl salt **114** (500 mg, 2.85 mmol) and di-*tert*-butyl dicarbonate (747 mg, 3.42 mmol) in THF (12 ml) at 0 °C was added $Et_3N$ (1.00 ml, 7.13 mmol) in THF (7 ml) over 10 min. The reaction mixture was allowed to warm to room temperature before being heated at 40 °C for 2 h. The reaction was cooled to room temperature and the salts removed by filtration before being concentrated *in vacuo*. The residue was dissolved in DCM (40 ml) and washed with a saturated

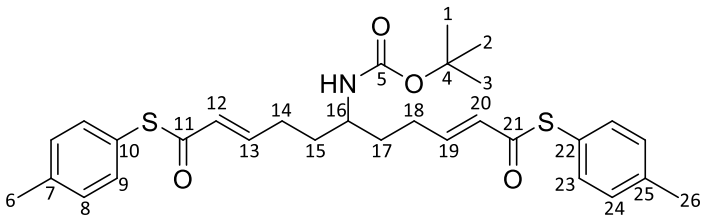
solution $NH_4Cl$ (aq), a saturated solution $NaHCO_3$ (aq) and brine. The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 10% $Et_2O$/hexane) to afford Boc-amine **56** as a white solid (492 mg, 1.93 mmol, 68% yield). *Data was consistent with those reported in the literature*.[40] **TLC ($SiO_2$)** $R_f$ = 0.33 (20% $Et_2O$/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 5.81 (2H, ddt, *J* = 16.8, 10.1, 6.5 Hz, H-7,13), 5.01 (2H, ddd, *J* = 17.1, 3.3, 1.3 Hz, H-6,14), 4.95 (2H, dd, *J* = 10.1, 1.9 Hz, H-6,14), 4.27 (1H, bd, *J* = 9.5 Hz, H-NH), 3.66 – 3.53 (1H, m, H-10), 2.18 – 2.01 (4H, m, $CH_2$), 1.62 – 1.52 (2H, m, $CH_2$), 1.48 – 1.39 (2H, m, $CH_2$), 1.43 (9H, s, H-1,2,3) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$); δ 155.7 (C-5), 138.3 (C-7,13), 114.9 (C-6,14), 79.0 (C-4), 50.0 (C-10), 34.9 (C-9,11), 30.3 (C-8,12), 28.5 (C-1,2,3) ppm; **IR (ATR)**: $\nu_{max}$ 3336, 3078, 2978, 2931, 2859, 1684, 1641, 1524, 1451, 1391, 1366, 1301, 1247, 1172, 1046, 1024, 993, 909, 874, 777, 640, $cm^{-1}$; **HRMS (ESI)** 262.1778 ($M + Na^+$. $C_{14}H_{25}NNaO_2$ requires 262.1777).




**(2*E*,9*E*)-*S*,*S*-di-*p*-tolyl 6-(((benzyloxy)carbonyl)amino)undeca-2,9-dienebis(thioate)** (**103**)

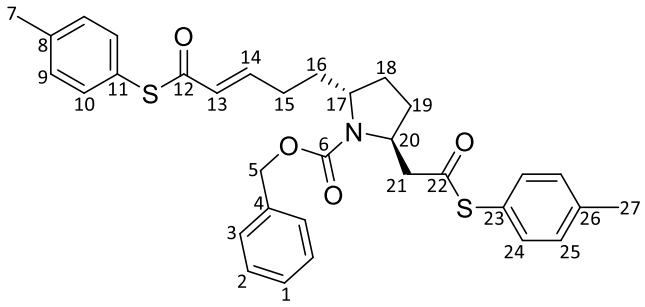
Thioester **108** (587 mg, 3.29 mmol) was dissolved in 1,2-DCE (10 ml) and placed under $N_2$. Cbz-amine **102** (150 mg, 0.549 mmol) was dissolved in 1,2-DCE (10 ml) and placed under $N_2$. To a flame dried flask under $N_2$ were added Hoveyda-Grubbs Catalyst™ 2nd generation (34.0 mg, 0.0549 mmol) and copper iodide (105 mg, 0.549 mmol), followed by the solutions of thioester and Cbz-amine. The flask was then degassed and backfilled with $N_2$ (x3). The reaction mixture was heated to 50 °C for 24 h. The reaction was then cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 10%-50% EtOAc/hexane) to afford amino-thioester **103** as a brown oil (235 mg, 0.409 mmol, 74% yield). **TLC ($SiO_2$)** $R_f$ = 0.13 (20% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.38 – 7.28 (9H, m, H-1,2,3,10,24), 7.21 (4H, d, *J* = 8.1 Hz, H-9,25), 6.93 (2H, dt, *J* = 15.6, 6.9 Hz, H-14,20), 6.18 (2H, bd, *J* = 15.5 Hz, H-13,21), 5.20 – 5.00 (2H, m, H-5), 4.53 (1H, d, *J* = 9.5 Hz, H-NH), 3.75 – 3.62 (1H, m, H-17), 2.37 (6H, s, H-7,27), 2.35

– 2.20 (4H, m, $CH_2$), 1.74 – 1.63 (2H, m, $CH_2$), 1.59 – 1.48 (2H, m, $CH_2$) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 188.6 (C-12/22), 156.2 (C-6), 145.1 (C-14,20), 139.8 (C-8,26), 134.7 (C-10,24), 130.1 (C-9,25), 128.7/128.4 (C-1,2,3), 128.3 (C-13,21), 124.1 (C-11,23), 67.1 (C-5), 51.0 (C-17), 34.1 (C-16,18), 29.0 (C-15,19), 21.5 (C-7,27) ppm; **IR (ATR)**: $\nu_{max}$ 3347, 3031, 2922, 2859, 1682, 1630, 1525, 1494, 1449, 1400, 1337, 1287, 1236, 1181, 1141, 1090, 1053, 1017, 974, 807, 736, 698, 649, 536, 475 $cm^{-1}$; **HRMS (ESI)** 596.1890 ($M + Na^+$. $C_{33}H_{35}NNaO_4S_2$ requires 596.1900).




**(2*E*,9*E*)-*S*,*S*-di-*p*-tolyl 6-((*tert*-butoxycarbonyl)amino)undeca-2,9-dienebis(thioate)** (**107**)

Thioester **108** (684 mg, 3.89 mmol) was dissolved in 1,2-DCE (10 ml) and placed under $N_2$. Boc-amine **56** (150 mg, 0.549 mmol) was dissolved in 1,2-DCE (10 ml) and placed under $N_2$. To a flame dried flask under $N_2$ were added Hoveyda-Grubbs Catalyst™ 2nd generation (40.1 mg, 0.0639 mmol) and copper iodide (122 mg, 0.639 mmol), followed by the solutions of thioester and Boc-amine. The flask was then degassed and backfilled with $N_2$ (x3). The reaction mixture was heated to 50 °C for 24 h. The reaction was then cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 10%-50% EtOAc/hexane) to afford amino-thioester **107** as a brown oil (198 mg, 0.367 mmol, 57% yield). **TLC ($SiO_2$)** $R_f$ = 0.18 (20% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.31 (4H, d, *J* = 8.0 Hz, H-9,23), 7.21 (4H, d, *J* = 7.9 Hz, H-8,24), 6.95 (2H, dt, *J* = 15.5, 6.9 Hz, H-13,19), 6.19 (2H, dd, *J* = 15.6, 1.6 Hz, H-12,20), 4.28 (1H, d, *J* = 9.6 Hz, H-NH), 3.69 – 3.56 (1H, m, H-16), 2.38 (6H, s, H-6,26), 2.35 – 2.25 (4H, m, $CH_2$), 1.73 – 1.62 (2H, m, $CH_2$), 1.59 – 1.51 (2H, m, $CH_2$), 1.46 (9H, s, H-1,2,3) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 188.6 (C-11,21), 155.7 (C-5), 145.4 (C-13,19), 139.8 (C-7,25), 134.7 (C-9,23), 130.2 (C-8,24), 128.3 (C-12,20), 124.1 (C-10,22), 79.7 (C-4), 50.4 (C-16), 34.3 (C-15,17), 29.1 (C-14,18), 28.5 (C-1,2,3), 21.5 (C-6,26) ppm; **IR (ATR)**: $\nu_{max}$ 3374, 2976, 2924, 1710, 1683, 1631, 1598, 1514, 1494, 1449, 1391, 1365, 1288, 1245, 1169, 1091, 1052, 1017, 975, 935, 863, 807, 705, 648, 618, 536, 475 $cm^{-1}$; **HRMS (ESI)** 562.2065 ($M + Na^+$. $C_{30}H_{37}NNaO_4S_2$ requires 562.2056).

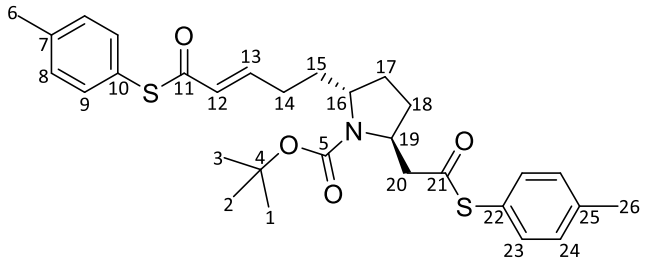


**(2*S*,5*R*)-benzyl 2-(2-oxo-2-(*p*-tolylthio)ethyl)-5-((*E*)-5-oxo-5-(p-tolylthio)pent-3-en-1-yl)pyrrolidine-1-carboxylate** (**104**)

For the racemic cyclisation, amino-thioester **103** (16.0 mg, 0.028 mmol) dissolved in 1,2-DCE (1.4 ml) was added to racemic CSA (20.0 mg, 0.084 mmol) under $N_2$. The reaction mixture was the heated to 50 °C for 24 h. The reaction was cooled to room temperature, quenched with $Et_3N$ (0.15 ml), diluted with DCM (10 ml) and then washed with saturated $NaHCO_3$. The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 10% EtOAc/hexane) to afford Cbz-pyrrolidine **104** as a colourless oil (12.3 mg, 0.021 mmol, 75% yield).

For the asymmetric cyclisation, amino-thioester **103** (89.0 mg, 0.155 mmol) dissolved in cyclohexane (10 ml) was added to (R)-TRIP (23.3 mg, 0.031 mmol) under $N_2$. The reaction mixture was the heated to 80 °C for 24 h. The reaction was cooled to room temperature, quenched with $Et_3N$ (0.6 ml) and then concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 5%-10% EtOAc/hexane) to afford Cbz-pyrrolidine **104** as a colourless oil (86.8 mg, 0.151 mmol, 97% yield (73.2 mg, 0.128 mmol, 83% yield, 86% ee, major diastereomer)) as a 1:1 mixture of rotamers. **TLC ($SiO_2$)** $R_f$ = 0.22 (20% EtOAc/hexane).$^1$**H NMR** (400 MHz, $CDCl_3$); δ 7.43 – 7.18 (13H, m, H-1,2,3,9,10,24,25), 6.96 (1H, dt, *J* = 15.7, 6.6 Hz, H-14, *rotamer 1*), 6.86 (1H, dt, *J* = 15.7, 6.6 Hz, H-14, *rotamer 2*), 6.22 (1H, d, *J* = 15.6 Hz, H-13, *rotamer 1*), 6.12 (1H, d, *J* = 15.6 Hz, H-13, *rotamer 2*), 5.30 – 5.07 (2H, m, H-5), 4.37 – 4.25 (1H, m, H-20), 3.91 – 3.78 (1H, m, H-17), 3.36 (1H, dd, , *J* = 14.8, 3.2 Hz, H-21, *rotamer 1*), 3.07 (1H, dd, , *J* = 14.8, 3.2 Hz, H-21, *rotamer 2*), 2.67 (1H, dd, , *J* = 15.0, 9.8 Hz, H-21, *rotamer 1*), 2.59 (1H, dd, , *J* = 15.0, 9.8 Hz, H-21, *rotamer 2*), 2.37 (6H, s, H-7,27), 2.29 – 1.75 (6H, m, $CH_2$), 1.73 – 1.64 (1H, m, $CH_2$), 1.51 – 1.37 (1H, m, $CH_2$) ppm; $^{13}$**C NMR** (101 MHz, $CDCl_3$) δ 196.1/195.9 (C-22), 188.6/188.4 (C-12), 154.1/153.9 (C-6), 145.4/145.1 (C-14), 140.0/139.9/139.8/139.7 (C-8,26), 136.7/136.6 (C-4), 134.7/134.5/134.4 (C-10,24), 130.2/130.1/130.1 (C-9,25), 128.7/128.7/128.3/128.3 (C-1,2,3), 128.2 (C-13),

124.2/124.1/124.0/123.9 (C-11,23), 67.0 (C-5), 57.9/57.3 (C-17), 55.2/54.7 (C-20), 47.2/45.7 (C-21), 32.2/31.0 (C-16), 29.5/29.4 (C-15), 28.4/27.5 (C-19), 27.4/26.6 (C-18), 21.5 (C-7,27) ppm; **IR (ATR)**: $\nu_{max}$ 2923, 1692, 1631, 1598, 1494, 1453, 1404, 1354, 1330, 1305, 1211, 1182, 1103, 1061, 1017, 989, 807, 771, 734, 698, 604, 534, 474 $cm^{-1}$; **HRMS (ESI)** 596.1915 ($M + Na^+$. $C_{33}H_{35}NNaO_4S_2$ requires 596.1900); **$[\alpha]_D^{20}$** -17.3 (c 0.99, $CHCl_3$)

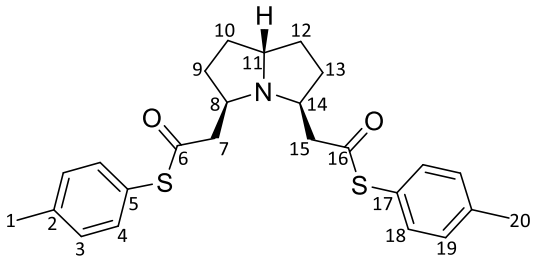



**(2*S*,5*R*)-*tert*-butyl 2-(2-oxo-2-(*p*-tolylthio)ethyl)-5-((*E*)-5-oxo-5-(*p*-tolylthio)pent-3-en-1-yl)pyrrolidine-1-carboxylate** (**115**)

For the racemic cyclisation, amino-thioester **107** (50.0 mg, 0.093 mmol) dissolved in 1,2-DCE (10 ml) was added to racemic CSA (65.0 mg, 0.28 mmol) under $N_2$. The reaction mixture was the heated to 50 °C for 24 h. The reaction was cooled to room temperature, quenched with $Et_3N$ (0.5 ml), diluted with DCM (10 ml) and then washed with saturated $NaHCO_3$. The organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 10% EtOAc/hexane) to afford Boc-pyrrolidine **115** as a yellow oil (24.2 mg, 0.045 mmol, 48% yield).

For the asymmetric cyclisation, amino-thioester **107** (56.0 mg, 0.104 mmol) dissolved in cyclohexane (5 ml) was added to (R)-TRIP (15.8 mg, 0.021 mmol) under $N_2$. The reaction mixture was the heated to 80 °C for 24 h. The reaction was cooled to room temperature, quenched with $Et_3N$ (0.5 ml) and then concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 5%-10% EtOAc/hexane) to afford Boc-pyrrolidine **115** as a yellow oil (52.9 mg, 0.098 mmol, 94% yield (44.5 mg, 0.082 mmol, 79% yield, 84% ee, major diastereomer)) as a 1:1 mixture of rotamers. **TLC ($SiO_2$)** $R_f$ = 0.30 (20% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.33 – 7.26 (4H, m, H-9,23), 7.25 – 7.19 (4H, m, H-8,24), 7.01 – 6.89 (1H, m, H-13), 6.21 (1H, d, *J* = 15.8 Hz, H-12, *rotamer 1*), 6.17 (1H, d, *J* = 15.8 Hz, H-12, *rotamer 2*), 4.31 – 4.23 (1H, m, H-19, *rotamer 1*), 4.21 – 4.14 (1H, m, H-19, *rotamer 2*), 3.84 – 3.77 (1H, m, H-16, *rotamer 1*), 3.75 – 3.68 (1H, m, H-

16, *rotamer 2*), 3.33 (1H, dd, , *J* = 14.7, 3.2 Hz, H-20, *rotamer 1*), 3.11 (1H, dd, , *J* = 14.7, 3.2 Hz, H-20, *rotamer 2*), 2.66 (1H, dd, , *J* = 14.6, 9.6 Hz, H-20, *rotamer 1*), 2.62 (1H, dd, , *J* = 14.6, 9.6 Hz, H-20, *rotamer 2*), 2.37 (6H, s, H-6,26), 2.30 – 1.80 (6H, m, $CH_2$), 1.70 – 1.63 (1H, m, $CH_2$), 1.51 (9H, s, H-1,2,3, *rotamer 1*), 1.48 (9H, s, H-1,2,3, *rotamer 2*), 1.46 – 1.35 (1H, m, $CH_2$) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 196.1/196.0 (C-21), 188.6/188.5 (C-11), 153.6/153.5 (C-5), 145.6/145.4 (C-13), 140.0/139.9/139.8/139.7 (C-7,25), 134.8/134.7/134.5/134.4 (C-9,23), 130.2/130.2/130.2/130.1 (C-8,24), 128.4/128.2 (C-12), 124.3/124.2/124.0/123.9 (C-10,22), 80.2/79.9 (C-4), 57.5/57.1 (C-16), 54.9/54.8 (C-19), 47.4/45.9 (C-20), 32.3/31.2 (C-15), 29.9/29.7 (C-14), 28.7 (C-1,2,3), 28.2/27.4 (C-18), 27.4/26.6 (C-17), 21.5 (C-6,26) ppm; **IR (ATR)**: $\nu_{max}$ 2971, 2926, 1685, 1632, 1598, 1494, 1477, 1454, 1386, 1365, 1305, 1277, 1256, 1167, 1119, 1104, 1016, 991, 887, 807, 774, 732, 647, 608, 575, 534, 474 $cm^{-1}$; **HRMS (ESI)** 562.2061 ($M + Na^+$. $C_{30}H_{37}NNaO_4S_2$ requires 562.2056); **$[\alpha]_D^{20}$** -16.2 (c 0.95, $CHCl_3$)

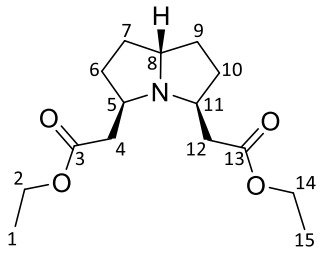



***S*,*S*'-di-*p*-tolyl 2,2'-((3*R*,5*S*,7a*s*)-hexahydro-1*H*-pyrrolizine-3,5-diyl)diethanethioate** (**116**)

Cbz-pyrrolidine **104** (37.0 mg, 0.064 mmol) was dissolved in DCM (4 ml), 1M solution of boron trichloride in DCM (0.322 ml, 0.322 mmol) was then added at 0 °C and the reaction stirred at room temperature for 24 h. The reaction mixture was diluted with DCM (5 ml) and quenched with a saturated aqueous solution of $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 1:1 $Et_2O$/hexane, column deadened with 1% $Et_3N$) to afford pyrrolizidine **116** as a colourless oil (10.5 mg, 0.024 mmol, 38% yield).

Boc-pyrrolidine **115** (50.0 mg, 0.093 mmol) was dissolved in a 4M solution of HCl in dioxane (1 ml) and then stirred at room temperature for 24 h. The reaction mixture was diluted with DCM (2 ml) and quenched with solid $K_2CO_3$. The reaction was then washed with brine and extracted with DCM (3 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

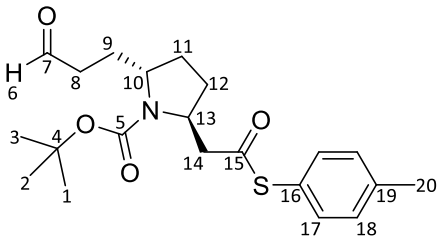
The crude product was purified by flash column chromatography ($SiO_2$, 1:1 $Et_2O$/hexane, column deadened with 1% $Et_3N$) to afford pyrrolizidine **116** as a colourless oil (14.5 mg, 0.033 mmol, 35% yield). **TLC ($SiO_2$)** $R_f$ = 0.32 (1:1 $Et_2O$/hexane, plates deadened with 1% $Et_3N$). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.31 – 7.27 (4H, m, H-4,18), 7.21 (4H, d, *J* = 8.1 Hz, H-3,19), 3.62 (1H, quintet, *J* = 6.7 Hz, H-11), 3.31 – 3.23 (2H, m, H-8,14), 2.90 (2H, dd, *J* = 14.9, 6.0 Hz, H-7,15), 2.60 (2H, dd, *J* = 14.7, 7.9 Hz, H-7,15), 2.37 (6H, s, H-1,21), 2.06 – 1.91 (4H, m, $CH_2$), 1.60 – 1.49 (2H, m, $CH_2$), 1.49 – 1.38 (2H, m, $CH_2$) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 196.8 (C-6,16), 139.7 (C-2,20), 134.6 (C-4,18), 130.2 (C-3,19), 124.5 (C-5,17), 64.5 (C-11), 63.5 (C-8,14), 50.5 (C-7,15), 31.4 (C-$CH_2$), 31.2 (C-$CH_2$), 30.5 (C-$CH_2$), 21.48 (C-1,21) ppm; **IR (ATR)**: $\nu_{max}$ 2954, 1700, 1598, 1494, 1400, 1354, 1182, 1088, 985, 807, 751, 534, 473 $cm^{-1}$; **HRMS (ESI)** 462.1535 (M + $Na^+$. $C_{25}H_{29}NNaO_2S_2$ requires 462.1532)




**Diethyl 2,2'-((3*R*,5*S*,7as)-hexahydro-1H-pyrrolizine-3,5-diyl)diacetate** (**55**)

Boc-pyrrolidine **115** (83.6 mg, 0.155 mmol) was dissolved in a 4M solution of HCl in dioxane (1 ml) and then stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo,* dissolved in EtOH (1 ml), and then treated with 1M solution of NaOEt (3 equiv) for 24 h. The reaction was filtered and concentrated *in* vacuo. The crude residue was then dissolved in EtOAc, washed with a saturated aqueous solution of $K_2CO_3$ and the aqueous layer extracted with EtOAc (3 x 10 ml). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($Al_2O_3$, 20% EtOAc/hexane) to afford pyrrolizidine **55** as a yellow oil (23.6 mg, 0.083 mmol, 54% yield). *Data was consistent with those reported in the literature*.[24] **TLC ($Al_2O_3$)** $R_f$ = 0.35 (20% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 4.11 (4H, q, *J* = 7.3 Hz, H-2,14), 3.58 (1H, quintet, *J* = 6.5 Hz, H-8), 3.23 – 3.14 (2H, m, H-5,11), 2.54 (2H, dd, *J* = 15.0, 6.0 Hz, H-4,12), 2.24 (2H, dd, *J* = 15.0, 8.2 Hz, H-4,12), 2.05 – 1.89 (4H, m, $CH_2$), 1.53 – 1.37 (4H, m, $CH_2$), 1.25 (6H, t, *J* = 7.3 Hz, H-1,15) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 172.5 (C-3,13), 64.5 (C-8), 63.0 (C-5,11), 60.3 (C-2,14), 41.7 (C-4,12), 31.5 (C-6,10), 31.2 (C-7,9), 14.4 (C-1,15) ppm; **IR**

**(ATR)**: $\nu_{max}$ 2919, 2850, 1731, 1464, 1448, 1417, 1370, 1296, 1268, 1250, 1170, 1141, 1105, 1086, 1032, 952, 920, 852, 805, 732, 642, 570, 503 $cm^{-1}$; **HRMS (ESI)** 284.1853 ($M + H^+$. $C_{15}H_{26}NO_4$ requires 284.1856).

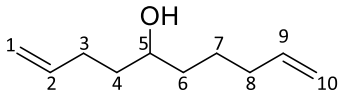



**(2*S*,5*S*)-*tert*-butyl 2-(2-oxo-2-(*p*-tolylthio)ethyl)-5-(3-oxopropyl)pyrrolidine-1-carboxylate** (**126**)

Boc-pyrrolidine **115** (20.0 mg, 0.037 mmol), osmium tetroxide (0.05 mg, 0.00019 mmol) and benzyl triethyl ammonium chloride (0.27 mg, 0.0012 mmol) were dissolved in THF and $H_2O$ (1.5 ml, 2:1). Sodium metaperiodate (16.0 mg, 0.074 mmol) was added and the resulting mixture stirred vigorously at room temperature for 1 h. The reaction was then diluted with $H_2O$ (5 ml) and extracted with DCM (3 x 5 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 30% EtOAc/hexane) to afford aldehyde **126** as a yellow oil (3.96 mg, 0.010 mmol, 27% yield).

Boc-pyrrolidine **115** (120 mg, 0.22 mmol) was added to a stirred solution of potassium osmate (8.1 mg, 0.022 mmol) and NMO (51.5 mg, 0.44 mmol) in THF and $H_2O$ (10 ml, 4:1). The reaction was stirred vigorously for 72 h, after which Sodium metaperiodate (94.1 mg, 0.44 mmol) was added and the resulting mixture stirred vigorously at room temperature for further 72 h. The reaction was then quenched with sodium metabisulfite solution (10 ml, 10% w/w aq) and extracted with EtOAc (3 x 10 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 30% EtOAc/hexane) to afford aldehyde **126** as a yellow oil (20.2 mg, 0.052 mmol, 23% yield) as a 1:1 mixture of rotamers. **TLC ($SiO_2$)** $R_f$ = 0.36 (40% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 9.76 (1H, s, H-6), 7.29 – 7.19 (4H, m, H-17,18), 4.30 – 4.23 (1H, m, H-13, *rotamer 1*), 4.20 – 4.13 (1H, m, H-13, *rotamer 2*), 3.84 – 3.77 (1H, m, H-10, *rotamer 1*), 3.75 – 3.68 (1H, m, H-10, *rotamer 2*), 3.33 (1H, dd, , *J* = 14.7, 3.2 Hz, H-14, *rotamer 1*), 3.11 (1H, dd, , *J* = 14.7, 3.2 Hz, H-14, *rotamer 2*), 2.66

(1H, dd, , *J* = 14.8, 9.6 Hz, H-14, *rotamer 1*), 2.58 (1H, dd, , *J* = 14.8, 9.6 Hz, H-14, *rotamer 2*), 2.53 – 2.38 (2H, m, H-$CH_2$), 2.37 (3H, s, H-20), 2.20 – 1.82 (4H, m, $CH_2$), 1.71 – 1.60 (2H, m, $CH_2$), 1.50 (9H, s, H-1,2,3, *rotamer 1*), 1.48 (9H, s, H-1,2,3, *rotamer 2*), ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 202.1/201.6 (C-7), 196.1/196.0 (C-15), 153.6 (C-5), 140.0/139.8 (C-19), 134.6/134.5 (C-17), 130.3/130.2 (C-18), 124.0 (C-16), 80.3/80.1 (C-4), 57.2 (C-10), 55.0/54.9 (C-13), 47.3/45.9 (C-14), 41.4/41.2 (C-9), 29.9 (C-8), 28.7 (C-1,2,3), 28.2/27.5 (C-12), 27.5/26.8 (C-11), 21.5 (C-20) ppm; **IR (ATR)**: $\nu_{max}$ 2933, 1691, 1494, 1455, 1389, 1367, 1256, 1171, 1122, 1103, 996, 889, 808, 775, 721, 577, 534, 476 $cm^{-1}$; **HRMS (ESI)** 414.1717 ($M + Na^+$. $C_{21}H_{29}NNaO_4S$ requires 414.1710)

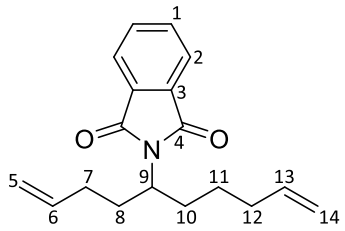



**Deca-1,9-dien-5-ol** (**131**)

Oxalyl chloride (2.90 ml, 34.3 mmol) was dissolved in DCM (50 ml), DMSO (4.70 ml, 66.2 mmol) was then added dropwise within 5 min at -78 °C. The reaction mixture was stirred at -78 °C for 10 min before 5-hexen-1-ol (2.50 ml, 20.8 mmol) in DCM (7.5 ml) was added dropwise over 10 min. The resulting reaction mixture was stirred at -78 °C for 1 h. Triethylamine (9.20 ml, 66.0 mmol) was added over 10 min and the reaction mixture allowed to warm to 0 °C, after which $H_2O$ (60 ml) and DCM (60 ml) were added and the phases separated. The aqueous phase was then extracted with DCM (3 x 60ml). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo* (up to 500 mbar). The crude product was purified by flash column chromatography ($SiO_2$, pentane/$Et_2O$ 9/1) to afford aldehyde **130** as a pale-yellow solution (1.80 g, 18.0 mmol, 88% yield) (aldehyde kept in a solution of pentane/$Et_2O$ due to volatility. Yield calculated from NMR).

Magnesium turnings (446 mg, 18.3 mmol) and iodine (1 crystal) were added to a flame dried flask under $N_2$, which was warmed until the iodine sublimed. The flask was allowed to cool to room temperature before the addition of dry THF (50 ml). To this mixture, 4-bromo-1-butene (1.86 ml, 18.3 mmol) was added slowly at room temperature (the flask was placed in a water bath to control the temperature). The resulting reaction mixture was then stirred at room temperature for 1 h to form the Grignard reagent. The reaction was then cooled to 0 °C before the dropwise addition of aldehyde **130** (900 mg, 9.17 mmol) over 10 min. The reaction was stirred at room temperature overnight. The reaction mixture was then cooled to 0 °C and quenched with saturated aqueous

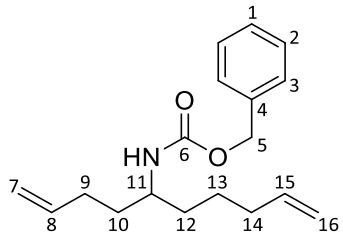
solution of $NH_4Cl$ (50 ml). The aqueous phase was extracted with $Et_2O$ (3 x 50ml) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 10% EtOAc/hexane) to afford secondary alcohol **131** as a yellow oil (746.1 mg, 4.84 mmol, 53% yield). *Data was consistent with those reported in the literature*.[26] **TLC ($SiO_2$)** $R_f$ = 0.16 (10% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 5.83 (2H, ddt, *J* = 16.9, 10.4, 6.6 Hz, H-2,9), 5.80 (2H, ddt, *J* = 16.9, 10.1, 6.6 Hz, H-2,9), 5.08 – 4.92 (2H, m, H-1,10), 3.67 – 3.58 (1H, m, H-5), 2.26 – 2.00 (4H, m, $CH_2$), 1.62 – 1.38 (7H, m, $CH_2$ and OH) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$); δ 138.8/138.7 (C-2,9), 114.9/114.8 (C-1,10), 71.5 (C-5), 37.0/36.6 (C-4,6), 33.8/30.2 (C-3,8), 25.0 (C-7) ppm; **IR (ATR)**: $\nu_{max}$ 3343, 3078, 2978, 2931, 2860, 1641, 1441, 1416, 1262, 993, 908, 827, 636, 554 $cm^{-1}$; **HRMS (APCI)** 155.1436 ($M + H^+$. $C_{10}H_{19}O$ requires 155.1430).




**2-(deca-1,9-dien-5-yl)isoindoline-1,3-dione** (**132**)

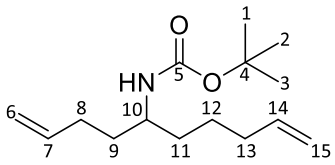
Phthalimide (596 mg, 4.05 mmol) and triphenylphosphine (1.06 g, 4.05 mmol) were dissolved in THF (25 ml). Secondary alcohol **131** (500 mg, 3.24 mmol) was then added followed by DEAD (2.06 ml, 4.54 mmol) at room temperature over 20 min. The reaction mixture was stirred at room temperature for 24 h. The solvent was then removed under reduced pressure and the resulting crude oil triturated with hexane/$Et_2O$ (2:1 mixture) until complete removal of the solids. The combined organic layers were concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 5% EtOAc/hexane) to afford *N*-alkyl phthalimide **132** as a yellow oil (525 mg, 1.85 mmol, 57% yield). **TLC ($SiO_2$)** $R_f$ = 0.33 (10% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.81 (2H, dd, *J* = 5.5, 3.2 Hz, H-2), 7.71 (2H, dd, *J* = 5.5, 3.2 Hz, H-1), 5.75 (1H, ddt, *J* = 17.0, 10.2, 6.5 Hz, H-6,13), 5.72 (1H, ddt, *J* = 17.0, 10.2, 6.5 Hz, H-6,13) 5.00 – 4.87 (4H, m, H-5,14), 4.22 (1H, m, H-9), 2.28 – 1.97 (6H, m, $CH_2$), 1.84 – 1.66 (2H, m, $CH_2$), 1.42 – 1.26 (2H, m, $CH_2$) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$); δ 168.9 (C-4), 138.4/137.6 (C-6,13), 134.0 (C-1), 131.9 (C-3), 123.3 (C-2), 115.3/114.9 (C-5,14), 51.8 (C-9), 33.4/31.9 (C-8,10), 31.7/31.0 (C-7,12), 26.0 (C-11) ppm; **IR (ATR)**: $\nu_{max}$ 3077, 2928, 2860, 1772, 1704, 1641, 1613, 1468, 1456, 1393, 1369, 1332, 1261, 1172, 1068,

995, 911, 871, 794, 719, 698, 642, 531, 510 $cm^{-1}$; **HRMS (ESI)** 284.1642 ($M + H^+$. $C_{18}H_{22}NO_2$ requires 284.1645).



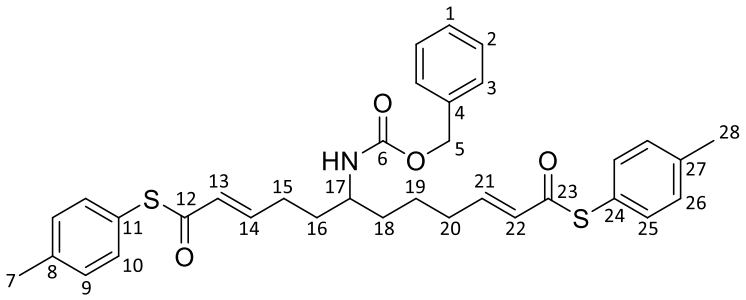

**Benzyl deca-1,9-dien-5-ylcarbamate** (**134a**)

Phthalimide **132** (362 mg, 1.28 mmol) was dissolved in EtOH (20 ml). Hydrazine hydrate (0.12 ml, 2.56 mmol) was then added and the reaction mixture was refluxed overnight, during this time a white solid precipitated. The reaction was cooled to room temperature and quenched with concentrated HCl (37% w/w, 5ml). The solvent was removed under reduced pressure and the residual aqueous solution was diluted with $H_2O$ (30 ml) and then washed with $Et_2O$ (3 x 30ml). The aqueous layer was treated with NaOH until pH 12 and then extracted with $Et_2O$ (3 x 30ml). The combined organic layers were washed with 2M HCl (aq, 5 x 30 ml). The aqueous layer was concentrated *in vacuo* to give the amine HCl salt **133** (230 g, 1.21 mmol, 94% yield). To the amine HCl salt **133** (50.8 mg, 0.268 mmol) was added $K_2CO_3$ (50% w/w, aq, 0.127 ml, 0.670 mmol) and 1,4-dioxane (2 ml) and the resulting mixture was stirred for 15 min to generate the free amine. Benzyl chloroformate (0.050 ml, 0.32 mmol) was then added. The reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with $H_2O$ (5 ml) and extracted with DCM (3 x 5 ml). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 10% EtOAc/hexane) to afford Cbz-Amine **134a** as a white solid (26.2 mg, 0.0911 mmol, 34% yield). **TLC ($SiO_2$)** $R_f$ = 0.25 (10% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.38 – 7.28 (5H, m, H-1,2,3), 5.86 – 5.70 (2H, m, H-8,15), 5.09 (2H, s, H-5) 5.05 – 4.91 (4H, m, H-7,16), 4.49 (1H, bd, *J* = 9.6 Hz, H-NH), 3.72 – 3.59 (1H, m, H-11), 2.16 – 1.97 (4H, m, $CH_2$), 1.62 – 1.30 (6H, m, $CH_2$) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$); δ 156.2 (C-6), 138.6/138.2 (C-8,15), 136.8 (C-4), 128.7/128.2 (C-1,2,3), 115.0/114.9 (C-7,16), 66.7 (C-5), 51.0 (C-11), 34.9/34.8 (C-10,12), 33.6/30.25 (C-9,14), 25.16 (C-13) ppm; **IR (ATR)**: $\nu_{max}$ 3323, 3074, 2935, 2857, 1693, 1641, 1532, 1455, 1415, 1243, 1053, 1028, 995, 910, 774, 736, 697, 642 $cm^{-1}$; **HRMS (ESI)** 310.1778 ($M + Na^+$. $C_{18}H_{25}NNaO_2$ requires 310.1777)



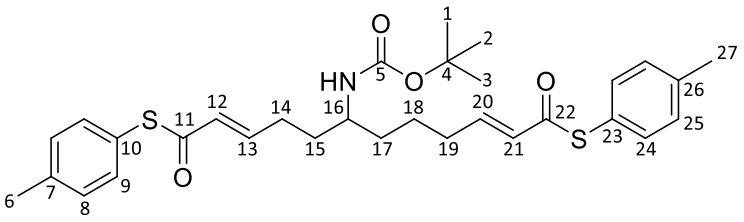

***tert*-butyl deca-1,9-dien-5-ylcarbamate** (**134b**)

Phthalimide **132** (362 mg, 1.28 mmol) was dissolved in EtOH (20 ml). Hydrazine hydrate (0.12 ml, 2.56 mmol) was then added and the reaction mixture was refluxed overnight, during this time a white solid precipitated. The reaction was cooled to room temperature and quenched with concentrated HCl (37% w/w, 5ml). The solvent was removed under reduced pressure and the residual aqueous solution was diluted with $H_2O$ (30 ml) and then washed with $Et_2O$ (3 x 30ml). The aqueous layer was treated with NaOH until pH 12 and then extracted with $Et_2O$ (3 x 30ml). The combined organic layers were washed with 2M HCl (aq, 5 x 30 ml). The aqueous layer was concentrated *in vacuo* to give the amine HCl salt **133** (230 g, 1.21 mmol, 94% yield). Amine HCl salt **133** (230 mg, 1.21 mmol) and $Et_3N$ were added to DCM (10 ml) and stirred for 15 min to generate free amine. The reaction was then cooled to 0 °C before the addition of Di-*tert*-butyl dicarbonate (528 mg, 2.42 mmol). The reaction was stirred at room temperature for 24 h. The reaction was quenched with citric acid (0.1M aq. 15 ml) and extracted with DCM (3 x 30 ml). The combined organic layers were washed with a saturated solution $NaHCO_3$ (aq) and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 5% $Et_2O$/hexane) to afford Boc-Amine **134b** as a yellow oil (152 mg, 0.60 mmol, 49% yield). *Data was consistent with those reported in the literature*.[26] **TLC ($SiO_2$)** $R_f$ = 0.25 (10% $Et_2O$/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 5.87 – 5.73 (2H, m, H-7,14), 5.05 – 4.91 (4H, m, H-6,15), 4.27 (1H, bd, *J* = 9.6 Hz, H-NH), 3.66 – 3.49 (1H, m, H-10), 2.19 – 1.96 (4H, m, $CH_2$), 1.60 – 1.27 (6H, m, $CH_2$), 1.44 (9H, s, H-1,2,3) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$); δ 155.8 (C-5), 138.8/138.4 (C-7,14), 114.9/114.8 (C-6,15), 79.1 (C-4), 50.2 (C-10), 35.1/35.0 (C-9,11), 33.7/30.4 (C-8,13), 28.6 (C-1,2,3), 25.2 (C-12) ppm; **IR (ATR)**: $\nu_{max}$ 3342, 3078, 2978, 2932, 2858, 1687, 1641, 1519, 1453, 1391, 1365, 1247, 1171, 1050, 995, 909, 864, 777, 641 $cm^{-1}$; **HRMS (ESI)** 276.1934 ($M + Na^+$. $C_{15}H_{27}NNaO_2$ requires 276.1934)



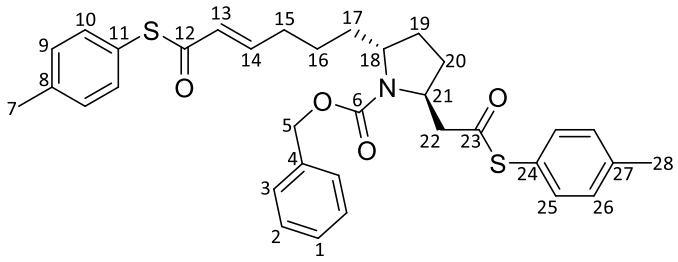
**(2*E*,10*E*)-*S*,*S*-di-*p*-tolyl 6-(((benzyloxy)carbonyl)amino)dodeca-2,10-dienebis(thioate)** (**135a**)

Thioester **108** (93.0 mg, 0.522 mmol) was dissolved in 1,2-DCE (2.5 ml) and placed under $N_2$. Cbz-Amine **134a** (25.0 mg, 0.087 mmol) was dissolved in 1,2-DCE (2.5 ml) and placed under $N_2$. To a flame dried flask under $N_2$ were added Hoveyda-Grubbs Catalyst™ 2nd generation (5 mg, 0.009 mmol) and copper iodide (16 mg, 0.087 mmol), followed by the solutions of thioester and Cbz-Amine. The flask was then degassed and backfilled with $N_2$ (x3). The reaction mixture was then heated to 50 °C for 24 h. The reaction was then cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 10%-50% EtOAc/hexane) to afford amino-thioester **135a** as a brown oil (33 mg, 0.056 mmol, 64% yield). **TLC ($SiO_2$)** $R_f$ = 0.15 (20% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.39 – 7.28 (9H, m, H-1,2,3,10,25), 7.22 (4H, dd, *J* = 8.1, 2.4 Hz, H-9,26), 7.00 – 6.86 (2H, m, H-14,21), 6.18 (2H, bd, *J* = 14.4 Hz, H-13,22), 5.20 – 5.03 (2H, m, H-5), 4.47 (1H, d, *J* = 9.5 Hz, H-N-H), 3.75 – 3.62 (1H, m, H-17), 2.38 (6H, s, H-7,28), 2.35 – 2.14 (4H, m, $CH_2$), 1.75 – 1.35 (6H, m, $CH_2$) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 188.7/188.6 (C-12,23), 156.2 (C-6), 145.8/145.3 (C-14,21), 139.8 (C-8,27), 134.7 (C-10,25), 130.1 (C-9,26), 128.7 (C-1,2,3), 128.3/128.3 (C-13/22), 124.1 (C-11,24), 67.0 (C-5), 51.0 (C-17), 35.3 (C-16/18), 34.2 (C-16,18), 32.1/29.1 (C-15,20), 24.5 (C-19), 21.5 (C-7,28) ppm; **IR (ATR)**: $\nu_{max}$ 3346, 3030, 2925, 2859, 1683, 1630, 1524, 1494, 1452, 1399, 1237, 1055, 1017, 807, 738, 698, 649, 535, 475 $cm^{-1}$; **HRMS (ESI)** 610.2056 (M + $Na^+$. $C_{34}H_{37}NNaO_4S_2$ requires 610.2056).



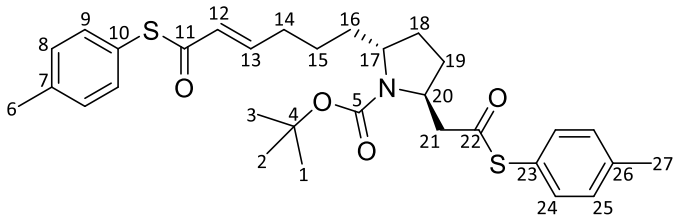
**(2*E*,10*E*)-*S*,*S*-di-*p*-tolyl 6-((*tert*-butoxycarbonyl)amino)dodeca-2,10-dienebis(thioate)** (**135b**)

Thioester **108** (422 mg, 2.37 mmol) was dissolved in 1,2-DCE (9 ml) and placed under $N_2$. Boc-amine **134b** (100 mg, 0.395 mmol) was dissolved in 1,2-DCE (9 ml) and placed under $N_2$. To a flame dried flask under $N_2$ were added Hoveyda-Grubbs Catalyst™ 2nd generation (25.0 mg, 0.0395 mmol) and copper iodide (75.0 mg, 0.395 mmol), followed by the solutions of thioester and Boc-amine. The flask was then degassed and backfilled with $N_2$ (x3). The reaction mixture was heated to 50 °C for 24 h. The reaction was then cooled to room temperature and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 10%-30% EtOAc/hexane) to afford amino-thioester **135b** as a brown oil (131.8 mg, 0.238 mmol, 60% yield). **TLC ($SiO_2$)** $R_f$ = 0.19 (20% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.31 (4H, dd, *J* = 8.2, 1.6 Hz, H-9,24), 7.22 (4H, d, *J* = 8.2 Hz, H-8,25), 7.00 – 6.89 (2H, m, H-13,20), 6.19 (2H, dd, *J* = 15.5, 2.5 Hz, H-12,21), 4.26 (1H, d, *J* = 9.6 Hz, H-NH), 3.68 – 3.54 (1H, m, H-16), 2.38 (6H, s, H-6,27), 2.35 – 2.18 (4H, m, H-14,19), 1.73 – 1.48 (6H, m, H-15,17,18), 1.46 (9H, s, H-1,2,3) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 188.7/188.6 (C-11,22), 155.8 (C-5), 145.9/145.6 (C-13,20), 139.8 (C-7,26), 134.7 (C-9,24), 130.1 (C-8,25), 128.3/128.2 (C-12,21), 124.1 (C-10,23), 79.5 (C-4), 50.2 (C-16), 35.4/34.3 (C-15,17), 32.1,29.1 (C-14,19), 28.5 (C-1,2,3), 24.5 (C-18), 21.5 (C-6,26) ppm; **IR (ATR)**: $\nu_{max}$ 3368, 2975, 2928, 2863, 1681, 1630, 1598, 1511, 1494, 1450, 1391, 1365, 1303, 1245, 1167, 1105, 1092, 1053, 1017, 982, 807, 733, 705, 684, 617, 535, 475 $cm^{-1}$; **HRMS (ESI)** 576.2225 ($M + Na^+$. $C_{31}H_{39}NNaO_4S_2$ requires 576.2213).



**(2*S*,5*R*)-benzyl 2-(2-oxo-2-(*p*-tolylthio)ethyl)-5-((*E*)-6-oxo-6-(*p*-tolylthio)hex-4-en-1-yl)pyrrolidine-1-carboxylate** (**136**)

For the racemic cyclisation, amino-thioester **135a** (30.0 mg, 0.051 mmol) dissolved in 1,2-DCE (2.5 ml) was added to racemic CSA (36.0 mg, 0.153 mmol) under $N_2$. The reaction mixture was the heated to 50 °C for 24 h. The reaction was cooled to room temperature, quenched with $Et_3N$ (0.3 ml), diluted with DCM (10 ml) and then washed with saturated aqueous solution of $NaHCO_3$. The organic layer was dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 10%-20% EtOAc/hexane) to afford Cbz-pyrrolidine **136** as a colourless oil (17.3 mg, 0.029 mmol, 57% yield) for the major diastereomer with as a 1:1 mixture of rotamers. **TLC ($SiO_2$)** $R_f$ = 0.21 (20% EtOAc/hexane).**$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.44 – 7.19 (13H, m, H-1,2,3,9,10,25,26), 6.94 (1H, dt, *J* = 15.6, 6.5 Hz, H-14, *rotamer 1*), 6.91 (1H, dt, *J* = 15.6, 6.5 Hz, H-14, *rotamer 2*), 6.17 (1H, d, *J* = 15.6 Hz, H-13, *rotamer 1*), 6.11 (1H, d, *J* = 15.6 Hz, H-13, *rotamer 2*), 5.24 – 5.08 (2H, m, H-5), 4.35 – 4.25 (1H, m, H-21), 3.88 – 3.76 (1H, m, H-18), 3.37 (1H, dd, *J* = 14.8, 3.2 Hz, H-22, *rotamer 1*), 3.07 (1H, dd, *J* = 14.8, 3.2 Hz, H-22, *rotamer 2*), 2.67 (1H, dd, *J* = 14.9, 9.8 Hz, H-22, *rotamer 1*), 2.59 (1H, dd, *J* = 14.9, 9.8 Hz, H-22, *rotamer 2*), 2.37 (6H, s, H-7,28), 2.35 – 1.81 (6H, m, $CH_2$), 1.73 – 1.62 (1H, m, $CH_2$), 1.53 – 1.27 (3H, m, $CH_2$) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 196.1/195.9 (C-23), 188.7/188.5 (C-12), 154.2/153.9 (C-6), 146.1/145.8 (C-14), 140.0/139.8/139.8/139.7 (C-8,27), 136.8/136.7 (C-4), 134.7/134.7/134.5/134.5 (C-10,25), 130.2/130.1 (C-9,26), 128.7/128.7/128.2/128.2 (C-1,2,3), 128.1 (C-13), 124.1/124.0/123.9 (C-11,24), 66.7 (C-5), 58.2/57.7 (C-18), 55.1/54.6 (C-21), 47.2/45.8 (C-22), 33.8 (C-15) 32.5/32.3/32.1 (C-16), 28.4/27.6 (C-20), 27.5/26.5 (C-19), 25.2/25.1 (C-17), 21.5 (C-7,28) ppm; **IR (ATR)**: $\nu_{max}$ 2923, 1689, 1631, 1494, 1454, 1404, 1353, 1330, 1305, 1281, 1211, 1181, 1103, 1017, 985, 806, 771, 733, 698, 648, 603, 534, 474 $cm^{-1}$; **HRMS (ESI)** 610.2064 ($M + Na^+$. $C_{34}H_{37}NNaO_4S_2$ requires 610.2056).



**(2*S*,5*R*)-*tert*-butyl 2-(2-oxo-2-(*p*-tolylthio)ethyl)-5-((*E*)-6-oxo-6-(*p*-tolylthio)hex-4-en-1-yl)pyrrolidine-1-carboxylate** (**137**)

For the racemic cyclisation, amino-thioester **135b** (53.0 mg, 0.096 mmol) dissolved in 1,2-DCE (5 ml) was added to racemic CSA (67.0 mg, 0.288 mmol) under $N_2$. The reaction mixture was the heated to 50 °C for 24 h. The reaction was cooled to room temperature, quenched with $Et_3N$ (0.5 ml), diluted with DCM (10 ml) and then washed with saturated aqueous solution of $NaHCO_3$. The organic layer was dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography ($SiO_2$, 10% EtOAc/hexane) to afford Boc-pyrrolidine **137** as a yellow oil (20.6 mg, 0.036 mmol, 38% yield) for the major diastereomer with as a 1:1 mixture of rotamers. **TLC ($SiO_2$)** $R_f$ = 0.29 (20% EtOAc/hexane). **$^1$H NMR** (400 MHz, $CDCl_3$); δ 7.33 – 7.26 (4H, m, H-9,24), 7.25 – 7.18 (4H, m, H-8,25), 6.94 (1H, dt, *J* = 14.6, 9.6 Hz, H-13), 6.19 (1H, d, *J* = 15.5 Hz, H-12, *rotamer 1*), 6.16 (1H, d, *J* = 15.5 Hz, H-12, *rotamer 2*), 4.30 – 4.21 (1H, m, H-20, *rotamer 1*), 4.20 – 4.12 (1H, m, H-20, *rotamer 2*), 3.81 – 3.73 (1H, m, H-17, *rotamer 1*), 3.72 – 3.64 (1H, m, H-17, *rotamer 2*), 3.33 (1H, dd, *J* = 14.7, 3.2 Hz, H-21, *rotamer 1*), 3.11 (1H, dd, *J* = 14.7, 3.2 Hz, H-21, *rotamer 2*), 2.65 (1H, dd, *J* = 14.8, 9.7 Hz, H-21, *rotamer 1*), 2.58 (1H, dd, *J* = 14.8, 9.7 Hz, H-21, *rotamer 2*), 2.37 (6H, s, H-6,27), 2.34 – 1.80 (6H, m, $CH_2$), 1.69 – 1.60 (2H, m, $CH_2$), 1.51 (9H, s, H-1,2,3, *rotamer 1*), 1.48 (9H, s, H-1,2,3, *rotamer 2*), 1.46 – 1.36 (2H, m, $CH_2$) ppm; **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 196.2/196.1 (C-22), 188.7/188.5 (C-11), 153.7/153.5 (C-5), 146.3/145.9 (C-13), 140.0/139.8/139.8/139.7 (C-7,26), 134.7/134.5/134.5 (C-9,24), 130.2/130.1 (C-8,25), 128.3/128.2/128.0/127.9 (C-12), 124.3/124.2/124.0 (C-10,23), 80.0/79.7 (C-4), 57.7/57.6 (C-17), 54.8/54.7 (C-20), 47.4/47.3/46.0/45.9 (C-21), 33.8 (C-14), 32.6/32.3 (C-15), 28.7 (C-1,2,3), 28.2/27.5 (C-19), 27.5/26.5 (C-18), 25.3/25.2 (C-16), 21.5 (C-6,27) ppm; **IR (ATR)**: $\nu_{max}$ 2972, 2924, 1685, 1632, 1598, 1494, 1454, 1387, 1365, 1257, 1168, 1117, 1017, 987, 911, 889, 806, 773, 731, 647, 608, 573, 534, 474 $cm^{-1}$; **HRMS (ESI)** 576.2213 ($M + Na^+$. $C_{31}H_{39}NNaO_4S_2$ requires 576.2213).

# 11. Abbreviations

| | |
|---|---|
| **(R)-anth-cat** | (R)-3,3'-Bis(9-anthracenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate |
| **(R)-phen-cat** | (11bR)-2,6-Di-9-phenanthrenyl-4-hydroxy-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-oxide |
| **(R)-TiPSY** | (R)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate |
| **(R)-TRIP** | (R)-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate |
| **1,2-DCE** | 1,2-dichloroethane |
| **1,2-DME** | 1,2-dimethoxyethane |
| **4 Å M S** | 4 Ångström molecular sieves |
| **aq** | aqueous |
| **APCI** | atmospheric pressure chemical ionization |
| **BHT** | butylated hydroxy toluene (2,6-di-t-butyl-4-methylphenol) |
| **Boc** | tert-butyloxycarbonyl |
| **BTEAC** | benzyl triethyl ammonium chloride |
| **cat.** | catalyst |
| **Cbz** | carboxybenzyl |
| **COSY** | correlated spectroscopy |
| **CPA** | chiral phosphoric acid |
| **CSA** | camphorsulfonic acid |
| **CuTC** | copper(I)-thiophene-2-carboxylate |
| **DEAD** | diethyl azodicarboxylate |
| **DIBAL** | diisobutylaluminium hydride |
| **DMF** | *N*,*N*-dimethylformamide |
| **DMSO** | dimethylsulfoxide |
| **dr** | diastereomic ratio |
| **ee** | enantiomeric excess |

| | |
|---|---|
| **eq.** | equivalents |
| **ESI** | electrospray ionization |
| **FDA** | U.S. Food and Drug Administration |
| **HMBC** | heteronuclear multiple bond coherence |
| **HPLC** | High Performance Liquid Chromatography |
| **IR** | infra-red |
| ***J*** | coupling constant (Hz) |
| **LDA** | lithium diisopropylamide |
| **NMO** | *N*-methylmorpholine *N*-oxide |
| **NMR** | nuclear magnetic resonance |
| **NOESY** | nuclear overhauser effect |
| **OTf** | trifluoromethanesulfonate |
| **Py** | pyridine |
| **rt** | room temperature |
| ***t*-Bu** | *tert*-butyl |
| **TFA** | trifluoroacetic acid |
| **THF** | tetrahydrofuran |
| **TLC** | thin layer chromatography |
| **TMS** | trimethylsilyl |
| **Ts** | *p*-toluenesulfonyl |

# 12. References


1. B. Shen, *Cell*, 2015, **163**, 1297-1300.
2. E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257-10274.
3. G. Z. Dai, W. B. Han, Y. N. Mei, K. Xu, R. H. Jiao, H. M. Ge and R. X. Tan, *Proc. Natl. Acad. Sci. U.S.A.,* 2020, **117**, 1174-1180.
4. (a) J. Robertson and K. Stevens, *Nat. Prod. Rep*., 2014, **31**, 1721-1788; (b) J. P. Michael, *Nat. Prod. Rep*., 2001, **18**, 520-542.
5. (a) J. Robertson and K. Stevens, *Nat. Prod. Rep*., 2017, **34**, 62-89; (b) J. Zhang, S. L. Morris-Natschke, D. Ma, Xiao-Fei Shang, Chen-Jie Yang, Ying-Qian Liu and Kuo-Hsiung Lee, *Med. Res. Rev*., 2021, **41**, 928-960.
6. (a) W. T. Bradner, *Cancer Treat. Rev*., 2001, **27**, 35-50; (b) M. Tomasz, *Chem. Biol*., 1995, **2**, 575-579.
7. K. Whitby, T. C. Pierson, B. Geiss, K. Lane, M. Engle, Y. Zhou, R. W. Doms and M. S. Diamond, *J. Virol*., 2005, **79**, 8698-8706.
8. D. Durantel, *Curr. Opin. Investig. Drugs.,* 2009, **10**, 860-870.
9. N. K. Ratmanova, I. A. Andreev, A. V. Leontiev, D. Momotova, A. M. Novoselov, O. A. Ivanova and I. V. Trushkov, *Tetrahedron*., 2020, **76**, 131031.
10. (a) V. Sharma, R. Kamal, D. Kumar and V. Kumar, *Current Traditional Medicine*., 2021, **7**, 45-56; (b) A. Belal and Bahaa El-Dien M. El-Gendy, *Bioorg. Med. Chem*., 2014, **22**, 46-53.
11. P. Wyatt and S. Warren, *Organic Synthesis, Strategy and Control, Oxford, Wiley*., 2007, 465-503.
12. C. Bhat and S. G. Tilve, *RSC Adv*., 2014, **4**, 5405–5452.
13. G. Lhommet, H. Dhimane and C. C´elim´ene, *Tetrahedron*, 1998, **54**, 10457-10468.
14. H. Takahata, H. Bandoh and T. Momose, *J. Org. Chem*., 1992, **57**, 4401-4404.
15. J. R. Parikh and W. v. E. Doering, *J. Am. Chem. Soc*., 1967, **89**, 5505-5507.
16. M. Juhl and D. Tanner, *Chem. Soc. Rev*., 2009, **38**, 2983-2992.
17. Y. Watanabe, H. Iida, and C. Kibayashi, *J. Org. Chem*., 1989, **54**, 4088-4097.
18. N. Ortega, D. D. Tang, S. Urban, D. Zhao, and F. Glorius, *Angew. Chem. Int. Ed*., 2013, **52**, 9500-9503.
19. T. Jiang and T. Livinghouse, *Org. Lett*., 2010, **12**, 4271-4273.

20. M. Asai, Y. Takemoto, A. Deguchi, Y. Hattori and H. Makabe, *Tetrahedron: Asymmetry*., 2017, **28**, 1582-1586.
21. A. Minatti and K. Muñiz, *Chem. Soc. Rev.*, 2007, **36**, 1142-1152.
22. S. R. Magnuson, *Tetrahedron.*, 1995, **51**, 2167-2213.
23. A. F. Newton, S. J. Roe, J. C. Legeay, P. Aggarwal, C. Gignoux, N. J. Birch, R. Nixon, Marie-Lyne Alcarazc and R. A. Stockman, *Org. Biomol. Chem*., 2009, **7**, 2274–2277.
24. J. C. Legeay, W. Lewis and R. A. Stockman, *Chem. Commun*., 2009, 2207-2209.
25. A. Barthelme, D. Richards, I. R. Mellorb and R. A. Stockman, *Chem. Commun*., 2013, **49**, 10507-10509.
26. M. D. Galvilan, W. R. J. D. Galloway, K. M. G. O'Connell, J. T. Hodkingson and D. R. Spring, *Chem. Commun*., 2010, **46**, 776-778.
27. M. Guerola, M. Sánchez-Roselló, C. Mulet, C. del Pozo and S. Fustero, *Org. Lett*., 2015, **17**, 960–963.
28. Z. Sun, G. A. Winschel, P. M. Zimmerman and P. Nagorny, *Angew. Chemie - Int. Ed.*, 2014, **53**, 11194-11198.
29. C. J. Maddocks, K. Ermanis and P. A. Clarke, *Org. Lett*., 2020, **22**, 8116–8121.
30. C. J. Maddocks, *PhD Thesis*, University of York, 2020.
31. C. J. Maddocks and P. A. Clarke, *Tetrahedron*., 2021, **78**, 131789.
32. S. Hanessian, A. Tehim and P. Chen, *J. Org. Chem.*, 1993, **58**, 7768-7781.
33. A. M. Fournier, R. A. Brown, W. Farnaby, H. Miyatake-Ondozabal and J. Clayden, *Org. Lett.*, 2010, **12**, 2222-2225.
34. C. J. Maddocks, Unpublished results.
35. K. Voigtritter, S. Ghorai and B. H. Lipshutz, *J. Org. Chem*., 2011, **76**, 4697–4702.
36. K. Ermanis, Y.T. Hsiao, U. Kaya, A. Jeuken and P. A. Clarke, *Chem. Sci*., 2017, **8**, 482-490.
37. A. Agora, *MSc(Research) Thesis*, University of York, 2020.
38. A. Farwick and G. Helmchen, *Adv. Synth. Catal*., 2010, **352**, 1023 – 1032.
39. H. Fuwa, N. Ichinokawa, K. Noto and M. Sasaki, *J. Org. Chem*., 2011, **77**, 2588–2607.
40. S. Nicolai and J. Waser, *Org. Lett*., 2011, **13**, 6324-6327.
41. O. Mitsunobu, *Synthesis*., 1981, 1-28.
42. H. R. Ing and R. H. F. Manske, *J. Chem. Soc*., 1926, 2348-2351.

43. P. Kiviranta, T. Suuronen, E. Walleen, J. Leppanen, J. Tervonen, S. Kyrylenko, A. Salminen, A. Poso and E. Jarho, *J. Med. Chem.*, 2009, **52**, 2153–2156.
44. C. Dong, Q. Zhou, J. Xiang, F. Liu, Z. Zhou and Y. Shen, *Journal of Controlled Release*., 2020, **321**, 529-539.
45. D. R. Williams, D. L. Brown and J. W. Benbow, *J. Am. Chem. Soc*., 1989, **111**, 1923-1925.
46. G. A. Rolla, *PhD Thesis*, University of York, 2008.
47. K. Yahata, M. Minami, K. Watanabe, and H. Fujioka, *Org. Lett*., 2014, **16**, 3680-3683.
48. L. S. Liebeskind and J. Srogl, *J. Am. Chem. Soc*., 2000, **122**, 11260-11261.
49. Yin-Ting Hsiao, *PhD Thesis*, University of York, 2017.
50. H. Fuwa, K. Noto and M. Sasaki, *Org. Lett*., 2011, **13**, 1820-1823.
51. R. Pappo, D. S. Allen, R. U. Lemieux and W. S. Johnson, *J. Org. Chem*., 1956, **21**, 478-479.
52. Bayer Healthcare AG, US2010/35902, 2010, A1.
53. V. Vanrheenen, R. C. Kelly and D. Y. Cha, *Tetrahedron Lett*., 1976, **17**, 1973-1976.
54. S. P. Kasturi, S. Surarapu, S. Uppalanchi, S. Dwivedi, P. Yogeeswari, D. K. Sigalapalli, N. B. Bathini, K. S. Ethiraj and J. S. Anireddy, *Eur. J. Med. Chem*., 2018, **150**, 39-52.
55. J. M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal*., 2001, **343**, No. 1.
56. J. E. Baldwin, *J. Chem. Soc. Chem. Commun*., 1976, **18**, 734-736.
57. M. Liniger, C. Neuhaus, T. Hofmann, L. Fransioli-Ignazio, M. Jordi, P. Drueckes, J. Trappe, D. Fabbro and K. Altmann, *ACS Med. Chem. Lett*., 2011, **2**, 22-27.