

PROGRESS TOWARDS THE SYNTHESIS OF INDOLIZIDINE ALKALOID 223AB

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Master of Science

By

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THESIS DECLARATION

The experimental work described in this thesis was carried out in the School of Chemistry, University of KwaZulu-Natal, Pietermaritzburg, under the supervision of Dr. Ross S. Robinson.

These studies represent the original work of the author and have not otherwise been submitted in candidature for any other degree.

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PUBLICATION DECLARATION

The research publications declared below have been included in the text of this thesis as per faculty guidelines. The full literature reference for the publication is as follows.

Paper I: "Synthesis of various oxo- and thio- analogues of 2-oxo-2*H*-chromen-7-yl dimethylcarbamates" Submitted to the South African Journal of Chemistry

Paper II: "*Ab Initio* and NMR Investigations into the Barrier to Internal Rotation of various oxo- and thio- analogues of 2-oxo-2*H*-chromen-7-yl dimethylcarbamates" To be submitted to the Journal of Molecular Structure: THEOCHEM

The experimental work discussed in the publication as well as the writing of the publication was performed by myself and was carried out within the School of Chemistry, University of KwaZulu-Natal, Pietermaritzburg, under the supervision of Dr. Ross S. Robinson. I was the primary author for the publication and minor grammatical changes were performed at a later stage under the suggestion of my research supervisor[s].

These studies represent original work by the author and have not otherwise been submitted in candidature for any other degree.

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ABSTRACT

It has been shown that alkaloids from various sources are vital as lead compounds in medicinal research and thus also the efficient synthesis of these. With the goal of developing a general synthetic route that can potentially access pyrrolizidine, indolizidine, quinolizidine and possibly lehmizidine alkaloid skeletons, a modified route that has been shown to produce pyrrolizidines was employed towards the synthesis of indolizidine alkaloid **223AB**. Within this synthesis, a 6-endo-dig hydroamination-cyclization step was attempted for construction of the bicyclic system. For this purpose, a selection of titanium-based catalysts were synthesized in order to determine their regiochemical outcome. For the purpose of investigating *ab initio* the mechanism of regioselective hydroamination, the skills and methods involved in computational chemistry were acquired through a study into amide rotational barriers:

A range of novel 2-oxo-2*H*-chromen-7-yl dimethylcarbamates were synthesised containing either an oxygen or sulphur in the α -position to the carbonyl or thiocarbonyl group of the amide moiety. Microwave synthesis was essential for the successful synthesis of some of the sulphur containing carbamates. The barriers to internal rotation of each of these compounds were investigated as follows. Variable Temperature and Exchange Spectroscopy NMR was performed on these compounds and the barrier to free amide rotation was calculated. Each of these compounds were also modeled *ab initio* and the gas phase barrier to rotation calculated. These three sets of data were compared and the influence of the α -heteroatom on rotation for amides and thioamides evaluated.

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If you could see the future,
But could not do anything to change it...
Would you still want to know?

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1. INTRODUCTION

1.1. ALKALOIDS & THEIR BIOLOGICAL ACTIVITY

Alkaloids were among the first classes of compounds exhibiting biological activity to be isolated, their name being derived from 'alkali-oid' or 'alkali-like', defining the most important characteristic of these early alkaloids, their basicity.¹ Although we now know basicity is not a fundamental requirement for inclusion into this class of compounds, the name has endured, describing a diverse set of structures ranging from simple to extremely complex. As a result, this has necessitated further classification of this group based on the heterocyclic ring system present; each class was named after a known compound to which this ring bore similarity (even non-alkaloid and non-nitrogenous compounds).

An alkaloid is loosely defined as a naturally occurring organic compound possessing at least one nitrogen atom in a heterocyclic ring and has distinct physiological effects. These compounds are well documented for their biological activity, and are found predominantly to occur in plants, but have been documented in certain fungi and animal species. Although almost all alkaloids are dangerously toxic, at lower doses they often have medicinal applications and can be structurally altered to modify their activity.² Some of the most well known alkaloids include caffeine, nicotine, morphine, codeine, cocaine and lysergic acid diethylamide (or LSD) (Figure 1-1).

¹ 'alkaloid'. In *Encyclopedia Britannica Online*, August 04 2008.

² Hesse *Alkaloids: Nature's Curse or Blessing?*; Helvetica Chimica Acta, 2002.

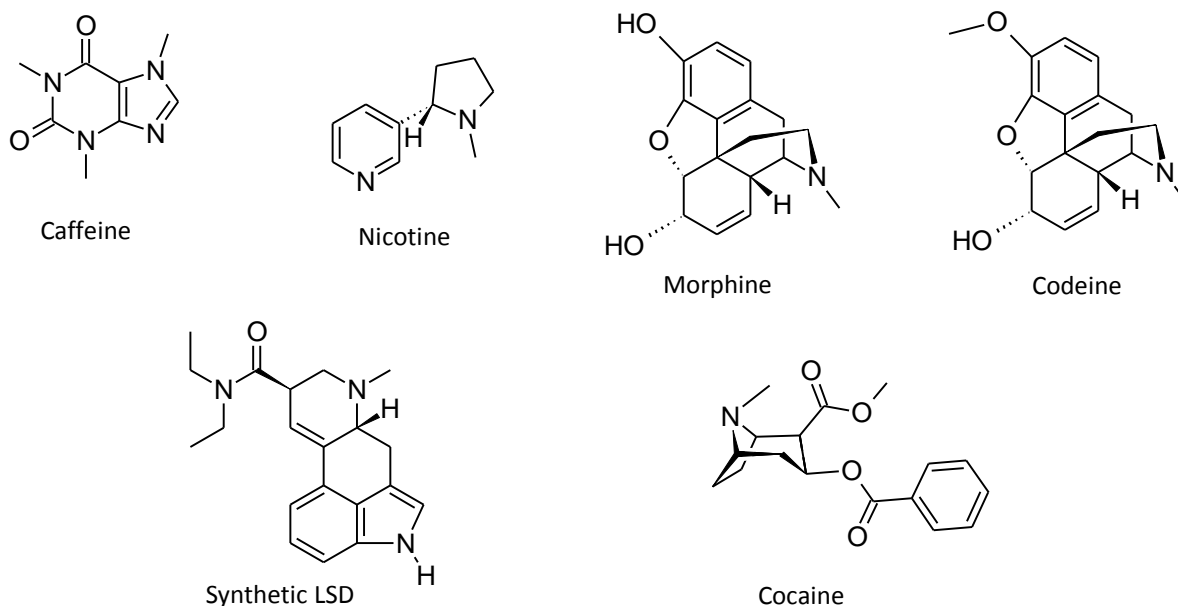


Figure 1-1 Some well known alkaloids

For over 4000 years, alkaloid containing plants have been used as medicines, poisons, in potions and in teas. Poison frogs have likewise been used since time immemorial to coat darts and hunting arrows.³ Only in the 19th century have these poison dart frog alkaloids become a particularly attractive source as prospective lead compounds for new drugs, given past success from plant derived alkaloids.^{3,4} The extraordinary structural diversity and extreme toxicity of these alkaloids reveal their biological activity and pharmacological potential. Some important discoveries from plant and frog alkaloids are outlined below.

Bisindoles, vinblastine and vincristine, isolated from the periwinkle (*Catharanthus roseus*) are used in chemotherapy treatments for leukemia and Hodgkin's disease (Figure 1-2).⁵

³ Roberts and Wink. *Alkaloids: Biochemistry, Ecology, and Medicinal Applications*; Springer, 1998.

⁴ Philippe and Angenot. *Journal of Ethnopharmacology* **2005**, 100, 85-91.

⁵ ^a Dong, Bornmann, Nakanishi and Berova. *Phytochemistry* **1995**, 40, 1821-1824.

^b Dumić, Radman, Krnić, Nola, Kušec, Begović, Labar and Rados. *Clinical Lymphoma & Myeloma* **2007**, 7, 590-593.

^c Choi, Kim, Lee, Kim, Lee and Bae. *Gynecologic Oncology* **2007**, 104, 64-69.

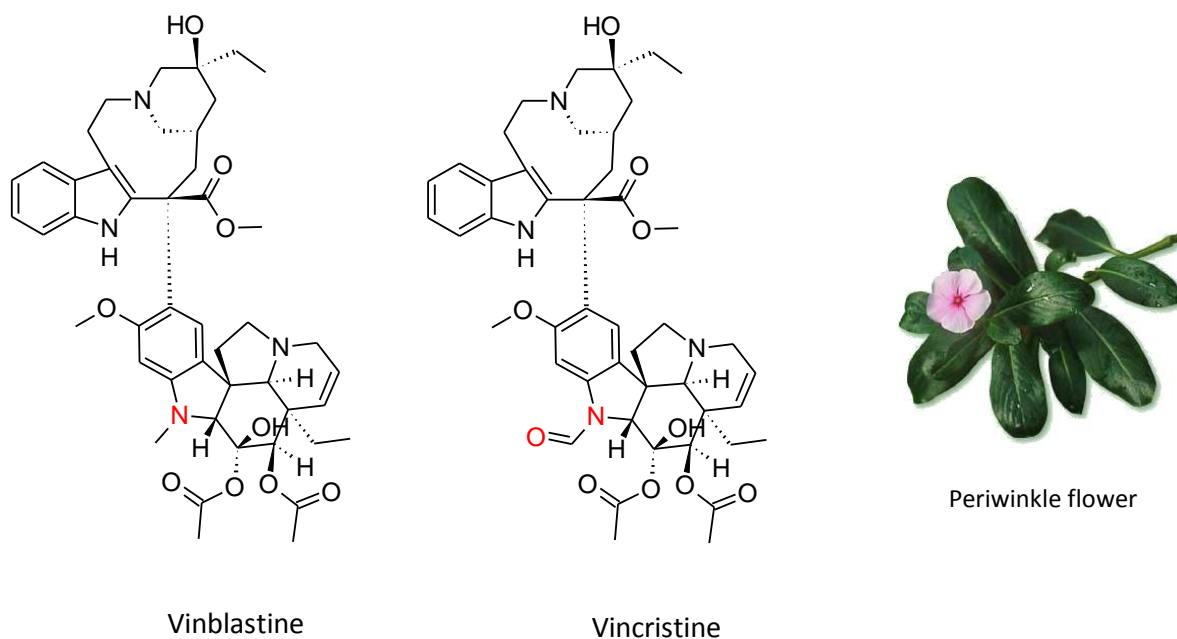


Figure 1-2 Two medicinally important alkaloids isolated from the periwinkle

A notorious set of indole alkaloids are those produced by the ergot fungus (*Claviceps purpurea*), which infects grains and grasses. During the Middle Ages, consumption of rye bread prepared with infected grain resulted in ergotism or “St. Anthony’s Fire” as it was more commonly referred to at the time. Symptoms of this ‘disease’, in reality are a result of alkaloid poisoning, and include muscle convulsions, burning sensations and gangrene of the extremities due to constriction of their blood vessels, often resulting in amputation and death. Included are hallucinations and irrational behaviour from ergine (or lysergic acid amide, natural LSD) content.^{6,7} In the past ergot extracts were used during labour to increase uterine contractions as well as to prevent haemorrhaging; this application was later abandoned due to increases in stillbirths.⁸ More recently, these alkaloids have found applications for treatment of extreme migraine attacks⁸ (ergotamine or its semi-synthetic

⁶ Madlom. In http://www.world-of-fungi.org/Mostly_Medical/Ziad_Madlom/Ergot_alkaloids.htm, August 13, 2008.

⁷ 'Ergot'. In <http://en.wikipedia.org/wiki/Ergot>, August 13, 2008.

⁸ Tfelt-Hansen and Koehler. *Cephalalgia* **2008**, 28, 877-886.

analogue methylsergide), and in the treatment of Parkinsonism with the semi-synthetic bromine derivative of ergocryptine.⁹

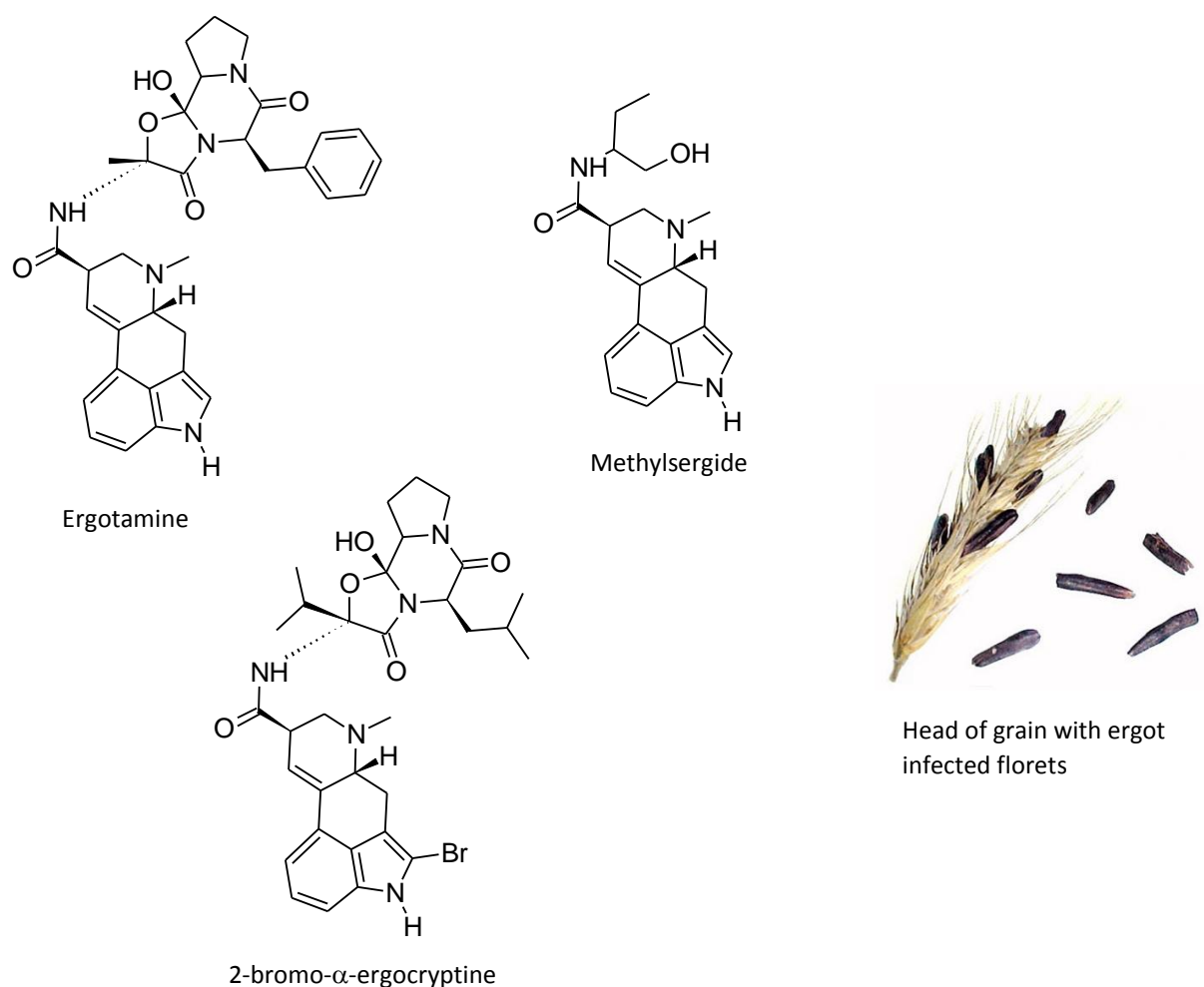


Figure 1-3 Some medicinally important Ergot alkaloids

Arguably one of the more historically significant alkaloids, and an excellent example illustrating their considerable importance, is the coca leaf's cocaine. First isolated in 1855, its local anaesthetic properties were disregarded, the potential applications eluding researchers until 1884, when a study on the therapeutic action of the drug was published.¹⁰ Up until this point, no such anaesthetic was known and cocaine soon filled the position of

⁹ Harborne, Baxter and Moss. Taylor and Francis, 1999, p200-201.

¹⁰ Pilcher. *Annals of Surgery* **1886**, 3, 51-66.

the surgeons' wonder drug. Soon into the twentieth century, the adverse narcotic and addictive effects of the drug were apparent, and research began to develop 'safer' derivatives. Analogues were synthesized with differing functional groups and in this way it was determined which moieties were required to produce the desired effects. Derivatives synthesized in this way comprise a large portion of local anaesthetics in use today and include procaine, benzocaine, lidocaine, novocaine, xylocaine and dimethocaine to name but a few.

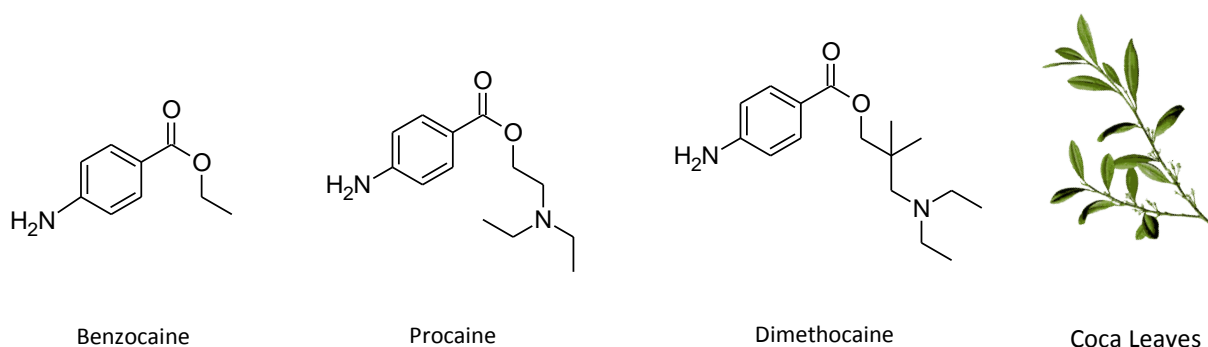


Figure 1-4 Synthetic analogues of Cocaine

Epibatidine, a nicotinic alkaloid, was isolated from the dart frog *Epipedobates tricolor* by Daly and co-workers, and was found to be a non-opioid analgesic approximately 200 times more powerful than morphine.^{11,12} Interest lies in the appealing lead this presents toward the development of new, better drugs.¹³ An interesting analogue, epiboxidine, was found to be 20 times less toxic than epibatidine while still displaying potent analgesic activity, with the added advantage that it exhibited cognitive-enhancing properties.¹⁴

¹¹ Spande, Garraffo, Edwards, Yeh, Panel and Daly. *Journal of the American Chemical Society* **1992**, 114, 3475-3478.

¹² Badio, Garraffo, Spande and Daly. *Med. Chem. Res.* **1994**, 4, 440-448.

¹³ Nishiyama, Gyermeik, Trudell and Hanaoka. *European Journal of Pharmacology* **2003**, 470, 27-31.

¹⁴ Badio, Garraffo, Plummer, Padgett and Daly. *European Journal of Pharmacology* **1997**, 321, 189-194.

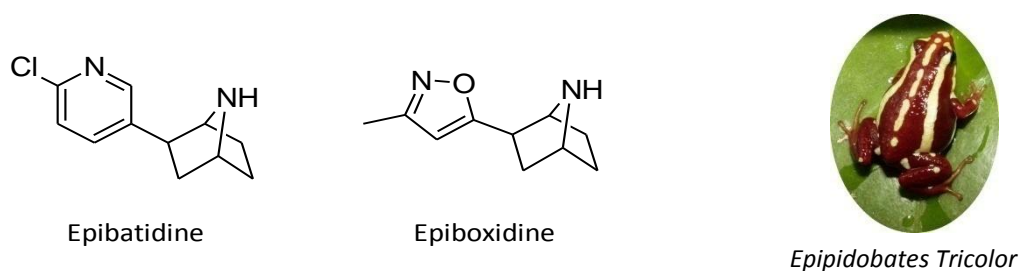


Figure 1-5 Epibatidine and synthetic Epiboxidine

More recently it has been found that frog alkaloid **235B'** exhibits non-competitive, selective inhibition of neuronal nicotinic acetylcholine receptors. This alkaloid appears to be a promising lead compound for development of drugs for treatment of autosomal dominant nocturnal frontal lobe epilepsy.^{15,16}

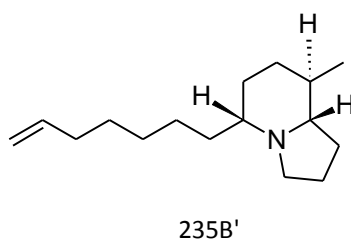


Figure 1-6 Indolizidine alkaloid 235B'

Prior to 2006, there had been over 800 identified frog alkaloids belonging to over 20 different structural classes.^{17,18} Of these, the largest group, thus containing the greatest potential for lead compounds, are the indolizidines.¹⁹ The small subclass of 3,5-disubstituted indolizidines, is found principally in the anuran family *Dendrobatidae*, or the poison dart frogs. Although it is widely accepted that these frogs acquire their alkaloids from dietary

¹⁵ Toyooka, Zhou, Nemoto, Garraffo, Spande and Daly. *Beilstein Journal of Organic Chemistry* **2007**, 3.

¹⁶ Toyooka, Tsuneki, Kobayashi, Dejun, Kawasaki, Kimura, Sasaoka and Nemoto. *Current Chemical Biology* **2007**, 1, 97-114.

¹⁷ Daly, Spande and Garraffo. *Journal of Natural Products* **2005**, 68, 1556-1575.

¹⁸ Daly, Kaneko, Wilham, Garraffo, Spande, Espinosa and Donnelly. *PNAS* **2002**, 99, 13996-14001.

¹⁹ Michael, de Koning and van der Westhuyzen. *Organic and Biomolecular Chemistry* **2005**, 3, 836-847.

sources, not all of these can accordingly be accounted for even though it has been shown that frogs raised in captivity do not possess any alkaloids.²⁰ Likewise, frogs removed from their natural habitat do not retain alkaloids in their skin for more than 7 months.

1.2. METHODS TOWARD **223AB** AND OTHER INDOLIZIDINES

Due to the limited distribution and miniscule quantities of 3,5-disubstituted indolizidines available from frog skins, these compounds have been the focus of many synthetic attempts.

Of the known indolizidines belonging to this subclass, monomorphine and **223AB** have been the most popular subjects.^{20,21} Initially, due to their scarcity in nature, syntheses were conducted to determine the absolute stereochemistry of isolated natural compounds. Thereafter, these compounds became a popular yardstick with which to measure the success of new synthetic routes toward 3,5-disubstituted indolizidines as the stereogenic orientation of substituents can be determined easily by comparison with the extensive structural data available for both natural as well as unnatural analogues.

Irrespective of the synthetic procedure followed, at some point one (or both) of the rings of the indolizidine system will need to be constructed. Because these indolizidines possess an *N*-bridgehead, the variety of methods available to construct [inevitably] one ring onto the other, are limited. Below, some recent examples outlining various methods to do this are presented.

²⁰ ^a Amat, Ilor, Hidalgo, Escolano and Bosch. *Journal of Organic Chemistry* **2003**, *68*, 1919-1928.

^b Amos, Gourlay, Molesworth, Smith and Sprod. *Tetrahedron* **2005**, *61*, 8226-8230.

^c Bernardi, Cardani, Poli and Scolastico. *Journal of Organic Chemistry* **1986**, *51*, 5043-5045.

^d Watanabe, Iida and Kibayashi. *Journal of Organic Chemistry* **1989**, *54*, 4088-4097.

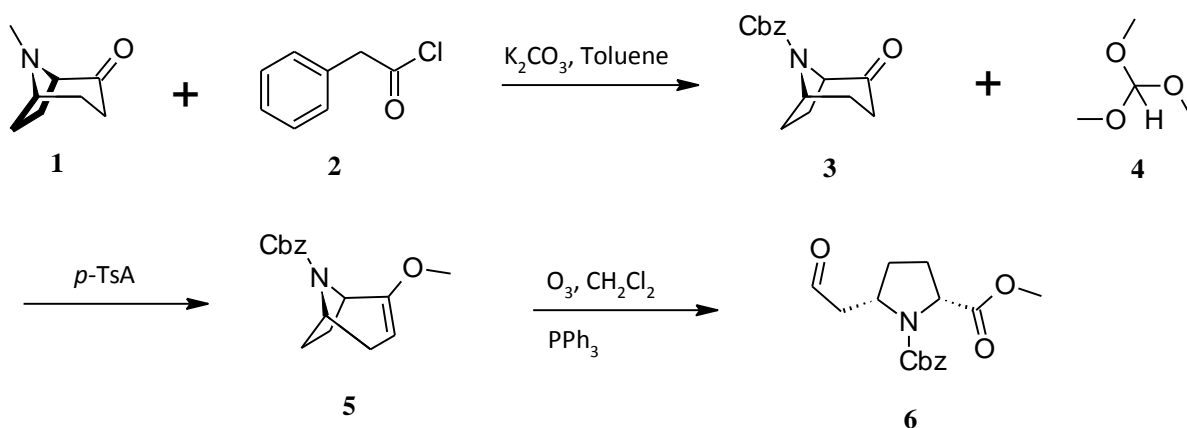
²¹ ^a Pattenden, Adams, Smith and Harrity. *Tetrahedron* **2008**, *64*, 2951-2961.

^b McGrane and Livinghouse. *Journal of Organic Chemistry* **1992**, *57*, 1323-1324.

^c Smith and Kim. *Journal of Organic Chemistry* **2006**, *71*, 2547-2557.

1.2.1. REDUCTIVE CYCLIZATION

One of the most widely used methods for construction of one or both rings of the indolizidine skeleton is reductive cyclization.²² The selected example, presented by Zhang *et al.* utilizes a single reductive step to construct the six-membered ring onto a pyrrolidine moiety to synthesise (–)-monomorine and is outlined in the following schemes 1-1 and 1-2.²³



Scheme 1-1

To obtain the desired stereochemistry of the indolizidine product, the inherent stereochemistry of cocaine was utilised. Cocaine was converted into (+)-2-tropinone **1** in 80% yield. Thereafter, (+)-2-tropinone was demethylated and protected using benzyl chloroformate **2** to produce the *N*-Cbz-2-tropanone **3** in 56% yield. Trimethyl orthoformate **4** was used to convert **3** into the methyl enol ether **5** in the presence of catalytic *p*-toluenesulphonic acid and obtained in 95% yield by distillation. Ozonolysis was performed on the enol ether, cleaving the double bond, and after treatment with triphenylphosphine,

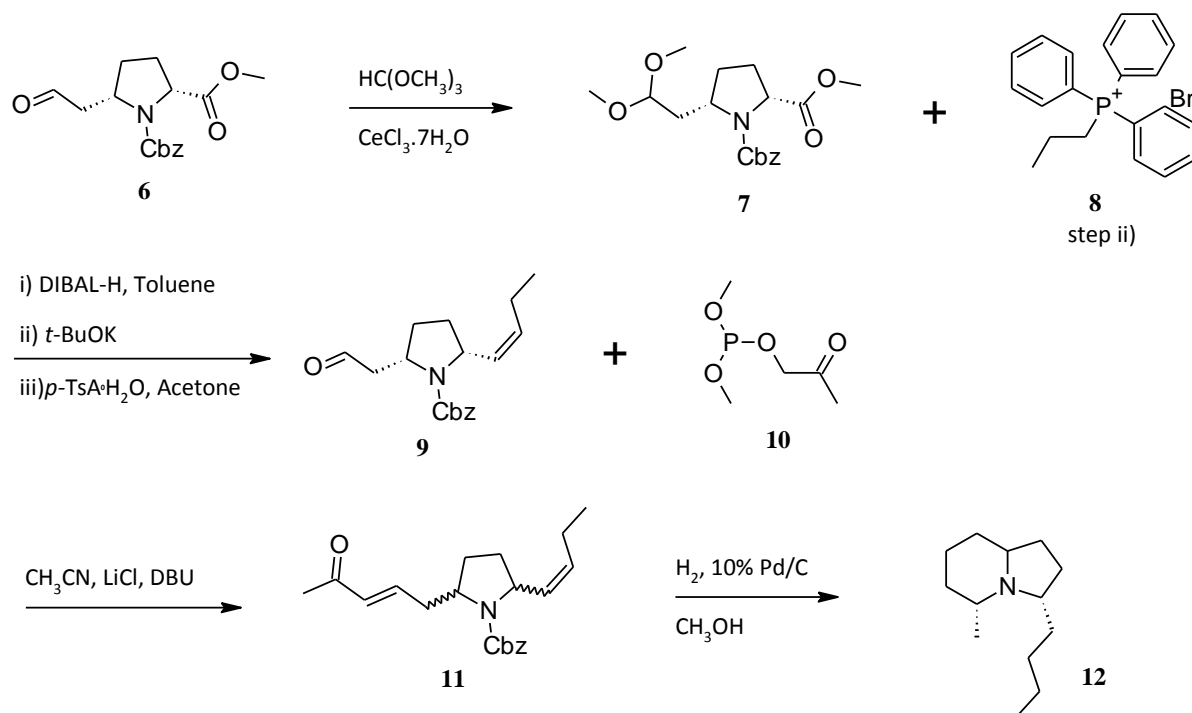
²² ^a Reinecke and Kray. *Journal of Organic Chemistry* **1964**, 29, 1736-1739.;

^b Tehrani, D'hooghe and De Kimpe. *Tetrahedron* **2003**, 59, 3099-3108.;

^c Ojima, Iula and Tzamarioudaki. *Tetrahedron Letters* **1998**, 39, 4599-4602.

²³ Zhang, Xu, Shu and Trudell. *Journal of Organic Chemistry* **2007**, 72, 3133-3136.

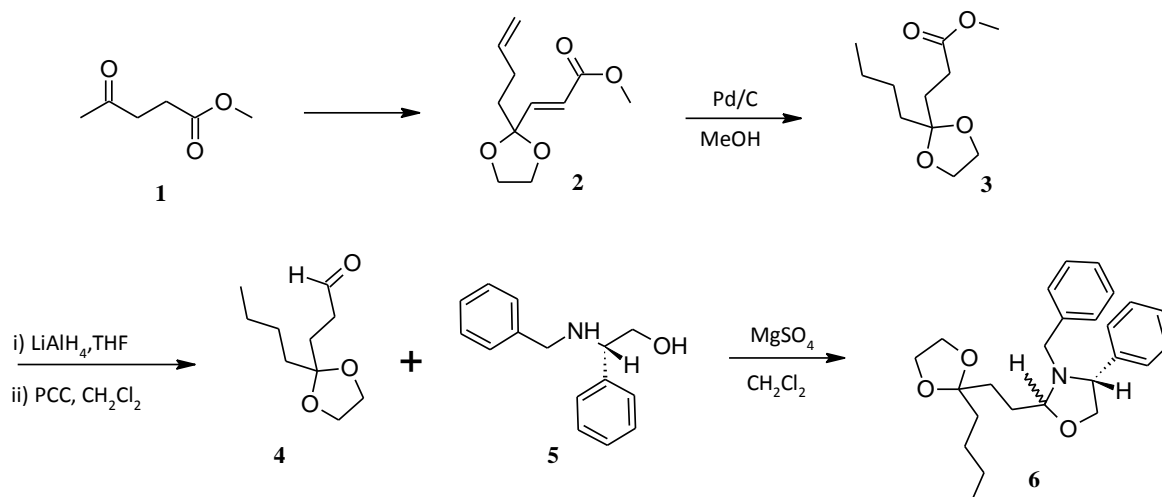
the *cis*-2,5-disubstituted pyrrolidine **6** was obtained in 74% yield as an enantiopure 3:1 mixture of two amide rotamers.



Scheme 1-2

The C2 ester of **6** was converted into the C3 chain of **12** by initial ceric chloride mediated protection of the aldehyde moiety with trimethylorthoformate to form **7** in 92% yield. The ester was then reduced to the aldehyde with DIBAL-H in toluene, followed by subsequent Wittig olefination of **7** with **8** and hydrolysis of the acetyl moiety by *p*-TsA·H₂O in acetone to form the *Z*-alkenal **9** in 55% yield. Olefination of **9** with dimethylphosphonoacetone **10** in the presence of LiCl and DBU afforded enone **11** as a mixture of rotamers and isomers in 80% yield. Hydrogenation of both olefin moieties, deprotection of the nitrogen and simultaneous reductive amination/ring closure was achieved over 10% Pd/C to provide (–) monomorphine **12** as a single isomer in 87% yield.

A second approach to reductive cyclization, proposed by Higashiyama *et al.* involves reaction of 1,3-oxazolidine with a Grignard reagent, followed by subsequent Wacker reaction and hydrogenation to form (+)-monomorine I as shown in schemes 1-2 to 1-4.²⁴

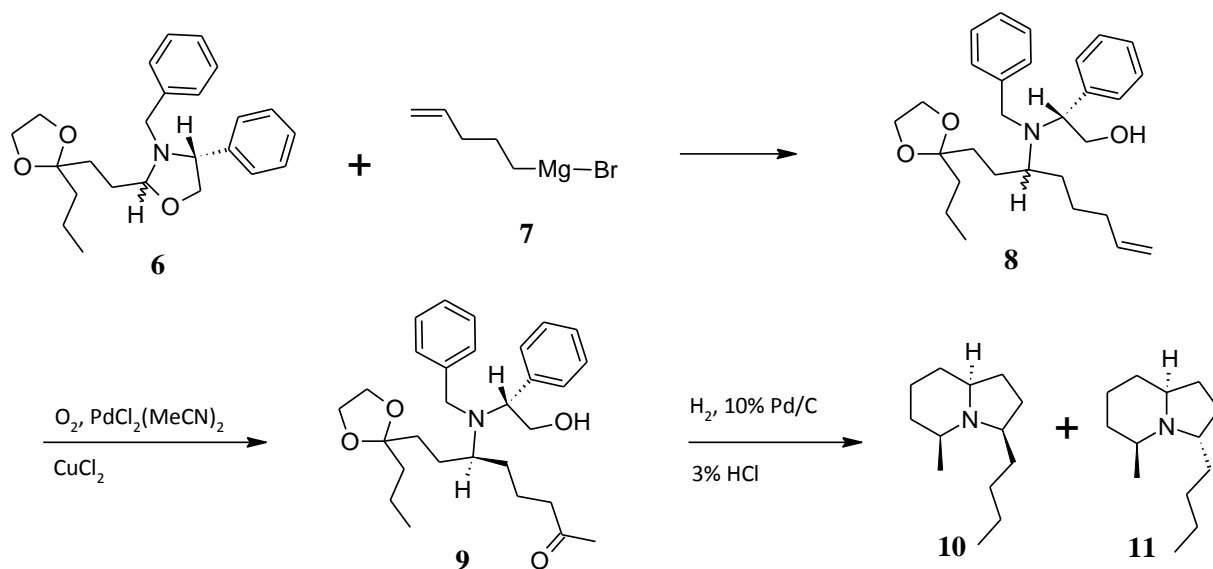


Scheme 1-3

The oxazolidine **6** was prepared from methyl levulinate **1** by a known procedure.²⁵ This was then subjected to catalytic hydrogenation over Pd/C to form **3**, followed by reduction with LiAlH₄ and oxidation with PCC to form the aldehyde **4** in 57% overall yield. This aldehyde was condensed with *N*-benzylphenylglycinol **5** in the presence of anhydrous MgSO₄ to quantitatively yield the 1,3-oxazolidine. Due to the asymmetric centre, a mixture of products were obtained; however, since the minor component was present as < 7% the authors did not see any reason for purification.

²⁴ Higashiyama, Nakahata and Takahashi. *J. Chem. Soc., Perkin Trans. 1* **1994**, 351-353.

²⁵ Hase, Ourila and Holmberg. *Journal of Organic Chemistry* **1981**, 46, 3137.

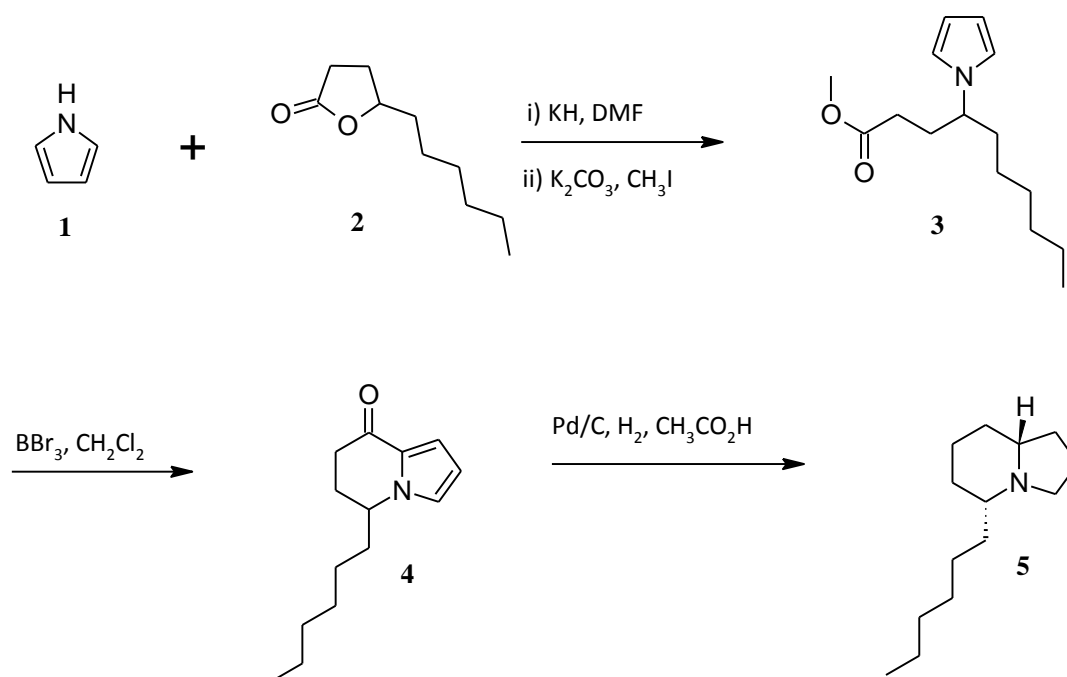


SCHEME 1-4

The oxazolidine **6**, once obtained, was reacted with pent-4-enylmagnesium bromide **7** in THF to achieve the alcohol **8** in 73% yield as an inseparable 91.5: 8.5 diastereomeric mixture. This mixture of alcohols was subjected to the Wacker reaction, affording the methyl ketone **9** in 78% yield as a 96:4 mixture. The isomers were then separated by column chromatography, and the isomer **9** was subject to catalytic hydrogenation over Pd/C to afford (+)-monomorine I **10** in 78% yield as well as 8% of its (+)-indolizidine **195B** epimer (**11**).

1.2.2. CYCLIZATION BY ANNULATION

A short synthesis of indolizidine **209D**, carried out by Amos *et al.*, employs annulation to construct the second ring of the indolizidine system onto pyrrole as shown in scheme 1-5.²⁶



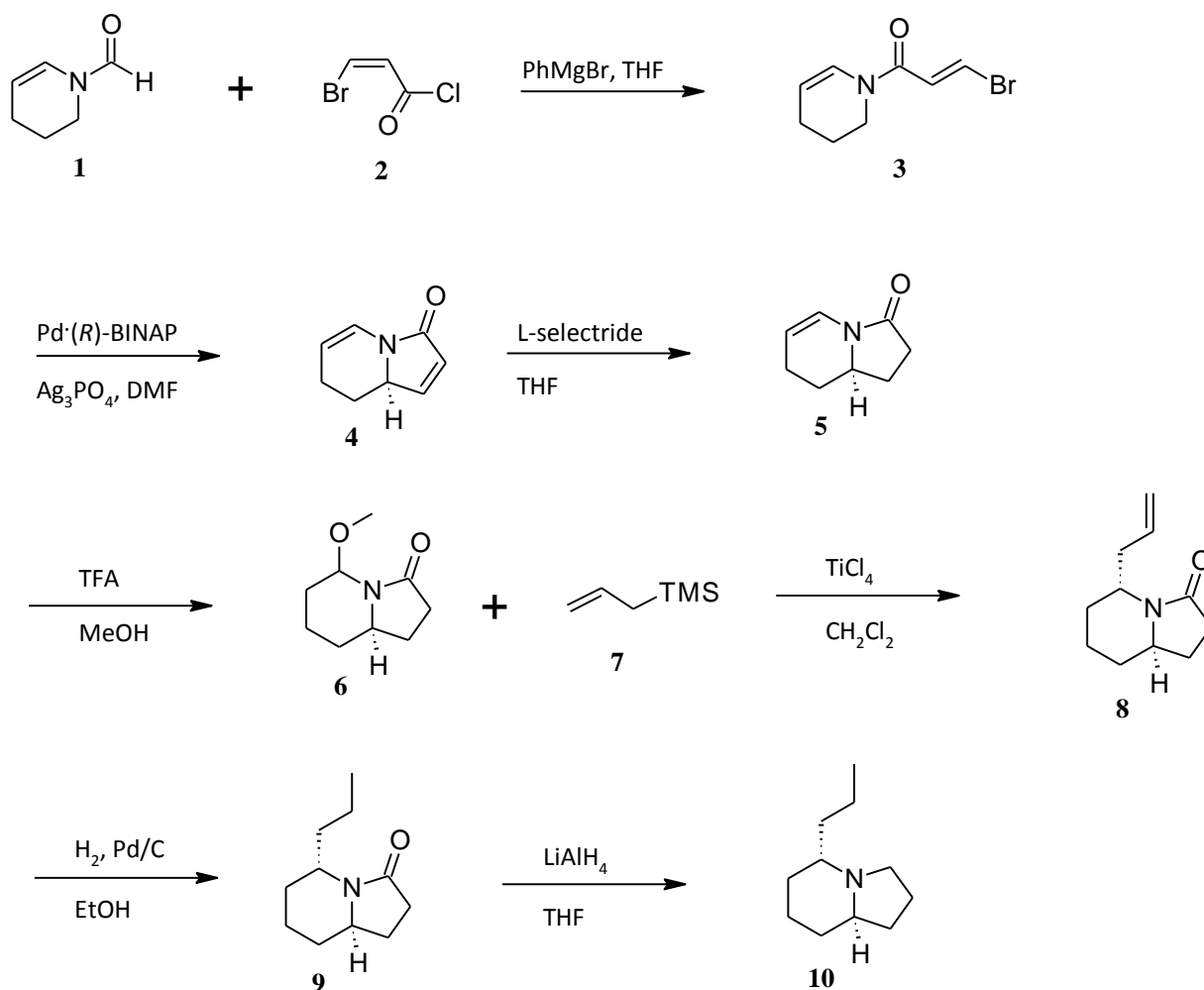
Scheme 1-5

The ester **3** was obtained in 30% yield by reaction of pyrrole **1** with γ -decanolactone over two steps *via* an intermediate acid. Cyclization by intramolecular annulation was achieved in 90% yield to produce the 5-hexyl indolizidine **4**. Hydrogenation was achieved with high diastereoselectivity and 90% yield using Pd/C to form indolizidine **5**.

²⁶ Amos, Gourlay, Molesworth, Smith and Sprod. *Tetrahedron* **2005**, 61, 8226-8230.

1.2.3. HECK CYCLIZATION

Kiewel *et al.* demonstrated the use of asymmetric Heck cyclization in a synthetic route toward (+)-5-epiindolizidine **167B**. In this case, the five-membered ring is constructed onto the six-membered ring as outlined in scheme 1-6.²⁷



Scheme 1-6

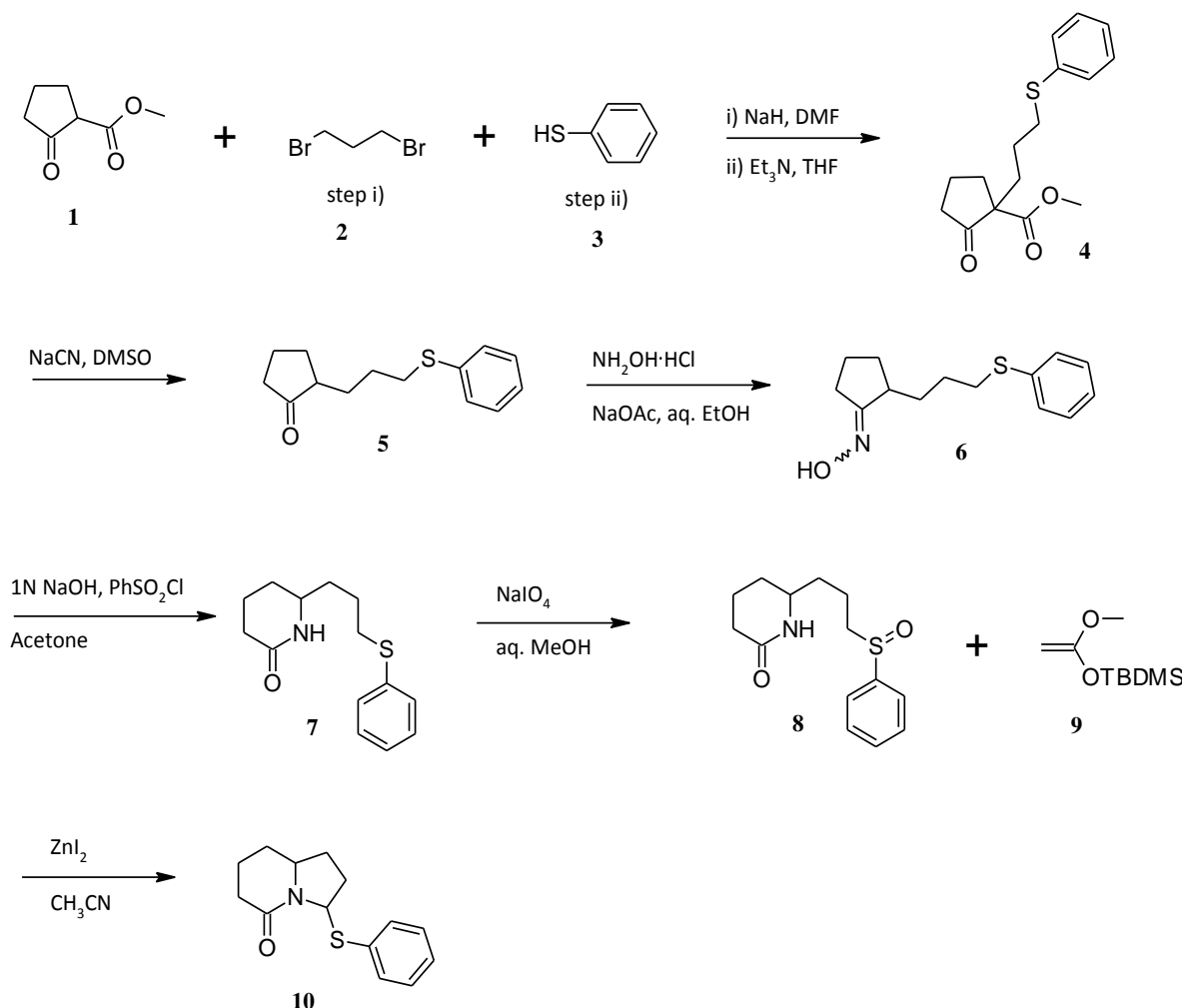
N-formyl enamide **1** was treated with phenylmagnesium bromide; followed by (Z)-3-bromopropenoyl chloride **2** to form the cyclic enamide **3** in 40-54% yields. This enamide

²⁷ Kiewel, Tallant and Sulikowski. *Tetrahedron Letters* **2001**, 42, 6621-6623.

underwent a Heck cyclization in the presence of Ag_3PO_4 as a halide scavenger in combination with $\text{Pd}\cdot(R)\text{-BINAP}$ complex to afford **4** in 64% yield and 85% enantiomeric excess. This Heck cyclization product was then reduced with L-selectride to give lactam **5** in 93% yield. To introduce the C5 propyl group, the lactam was first treated with acidic methanol to yield aminal **6** followed by allylation with **7** to afford compound **8** as the major diastereomer in 95% and 97% yields respectively. Indolizidone **9** was obtained in >98% yield by hydrogenation over Pd/C in ethanol. Reduction of indolizidone with lithium aluminiumhydride provided (+)-5-epiindolizidine **10**, in >98% yield.

1.2.4. PUMMERER CYCLIZATION

A fairly new method of cyclization based on the Pummerer reaction was recently reported by Kuhakarn *et al.* which constructs the five-member ring onto the six-member in the synthesis of (\pm)-5-butyldolizidine as detailed in the following schemes 1-7 and 1-8.²⁸

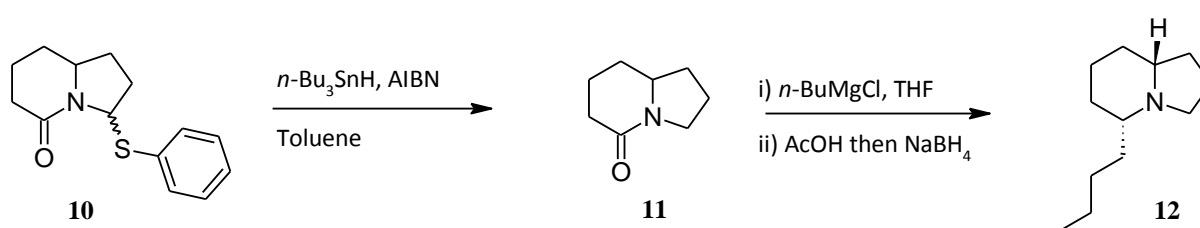


Scheme 1-7

Methyl 2-oxocyclopentanecarboxylate **1** was alkylated with 1,3-dibromopropane **2** in the presence of sodium hydride, following which thiophenol was added in the presence of triethylamine to provide the β -ketoester **4** in 57% yield. Ketosulphide **5** was obtained by

²⁸ Kuhakarn, Seehasombat, Jaipetch, Pohmakotr and Reutrakul. *Tetrahedron* **2008**, 64, 1663-1670.

Krapcho decarboxylation with sodium cyanide in 87% yield. This was subsequently transformed into oxime **6** by treatment with hydroxylamine hydrochloride and sodium acetate in quantitative yield. Lactam sulphide **7** was obtained by Beckmann rearrangement with benzenesulphonyl chloride. Reaction with NaIO_4 produced lactam sulfoxide **8** in 95% yield as a 1:1 diastereomeric mixture. The bicyclic lactam sulphide **10** was obtained in 85% yield by Pummerer reaction with *O*-silylated ketene acetal **9** in the presence of catalytic zinc iodide. This product was obtained as a 5:1 *trans-cis* mixture of diastereomers.

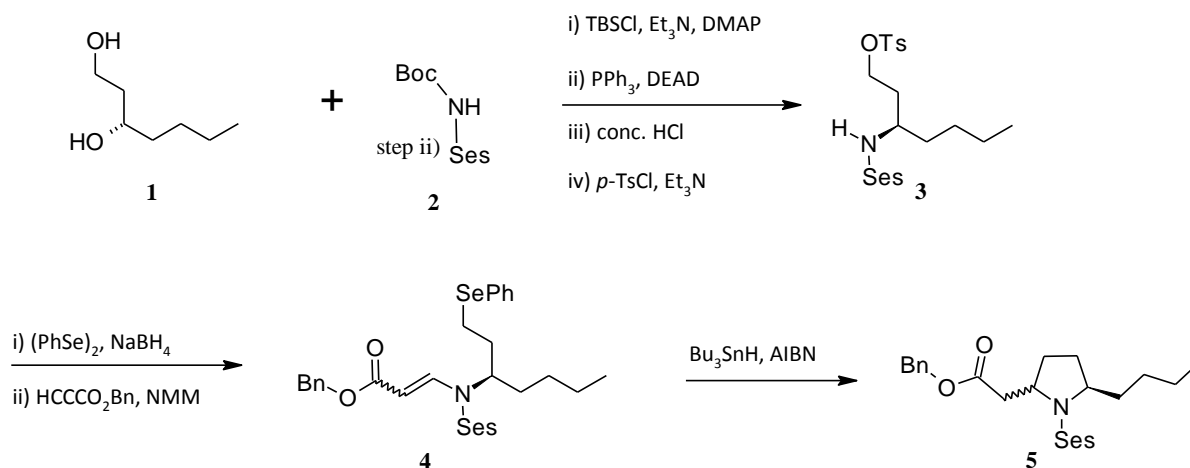


Scheme 1-8

Lactam sulphide **10** was treated with tri-*n*-butyltin hydride and AIBN to afford the bicyclic lactam **11** in 75% yield. Subsequent reaction with *n*-BuMgCl followed by sodium borohydride produced 5-butylindolizidine **12**; however no yield was reported.

1.2.5. RADICAL CYCLIZATION

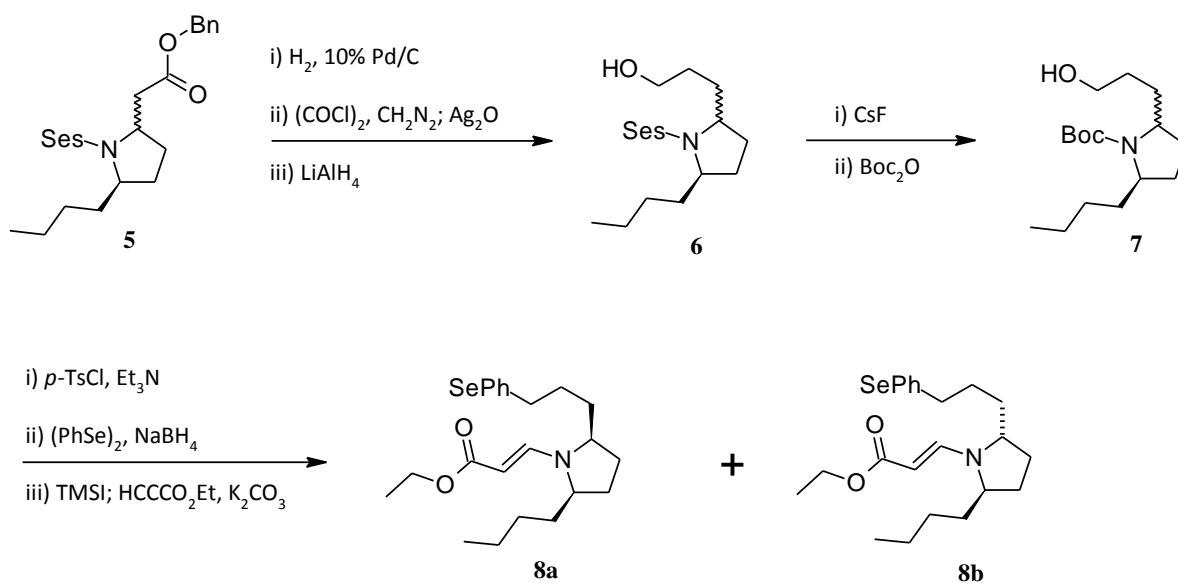
Another novel method of indolizidine construction was reported by Lee *et al.* and involves successive radical cyclizations of first the five- and then the six-member rings as outlined in schemes 1-9 to 1-11.²⁹



Scheme 1-9

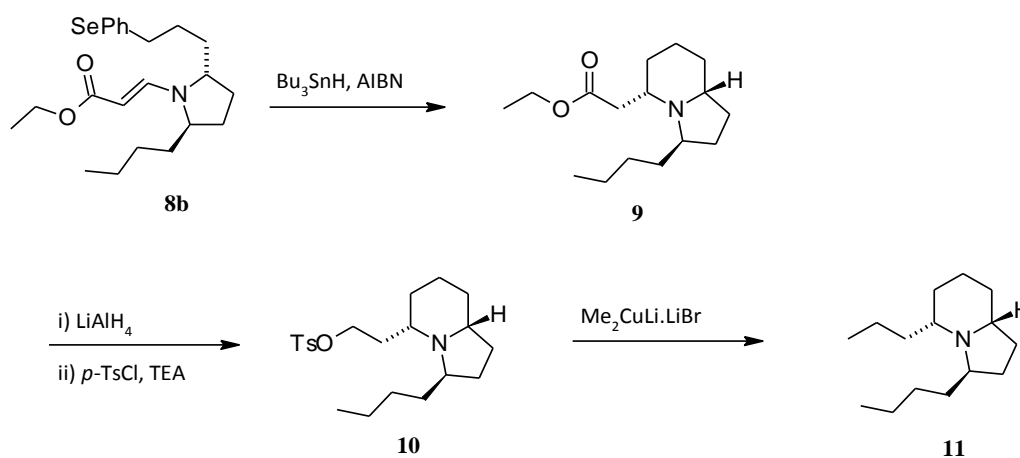
From, the diol **1**, a sequence of reactions involving TBS protection of the primary alcohol, Mitsunobu reaction with Ses-NH-Boc at the secondary alcohol, TBS deprotection and subsequent tosylation of the primary alcohol were performed to obtain the Ses amide **2** in 79% overall yield. Substitution of the tosylate with phenylselenide, and subsequent reaction with benzyl propiolate in the presence of *N*-methylmorpholine provided the β -aminoacrylate in 86% yield. This product underwent a radical cyclization in the presence of tri-*n*-butyltin hydride and AIBN to form the five-member ring product **5** as a 61:22 *trans-cis* mixture in 83% yield.

²⁹ Lee, Jeong, Min, Hong, Lim, Kim, Kim, Choi and Koo. *Organic Letters* **2000**, 2, 2169-2171.



Scheme 1-10

The compound **5** was converted to alcohol **6** by means of the Arndt-Eistert procedure and subsequent lithium aluminium hydride reduction in 70% yield. Thereafter the nitrogen was protected to form the Boc compound **7** in 51% yield. This was further reacted with $p\text{-TsCl}$ in the presence of Et_3N followed by selenide substitution. In the same pot, the nitrogen was deprotected with TMSI and reacted with ethyl propiolate to give the β -amino acrylates **8a** and **8b** in 19 and 57% yields respectively. Isomer **8b** was further used to form (–)-indolizidine **223AB**.

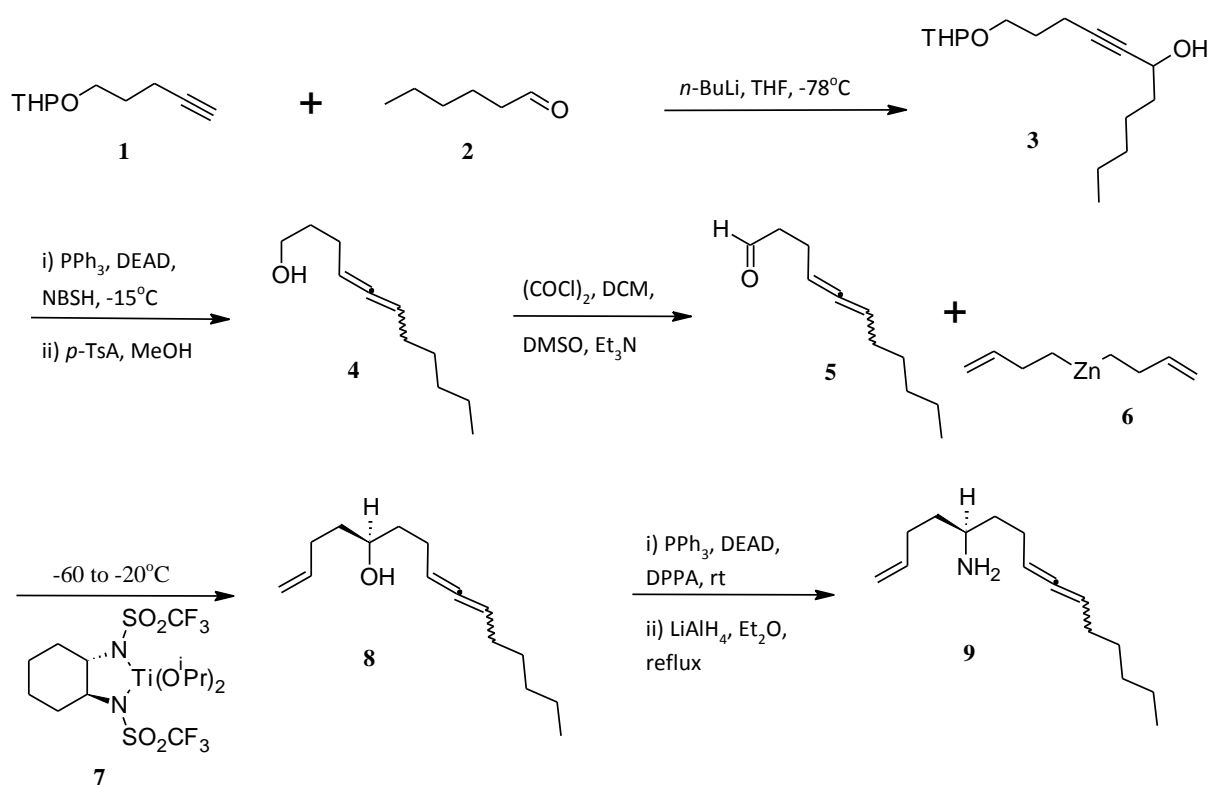


Scheme 1-11

β -Amino acrylate **8b** underwent a second radical cyclization in the presence of tri-*n*-butyltin hydride and AIBN to form the second, six-member ring of the indolizidine skeleton **9** in 58% yield. This was then tosylated by reduction with lithium aluminium hydride and reaction with *p*-TsCl in the presence of Et₃N to form **10** in 87% yield. Subsequent reaction of the tosylate with lithium dimethylcuprate afforded (–)-indolizidine **223AB** (**11**) in 88% yield.

1.2.6. CYCLIZATION BY HYDROAMINATION

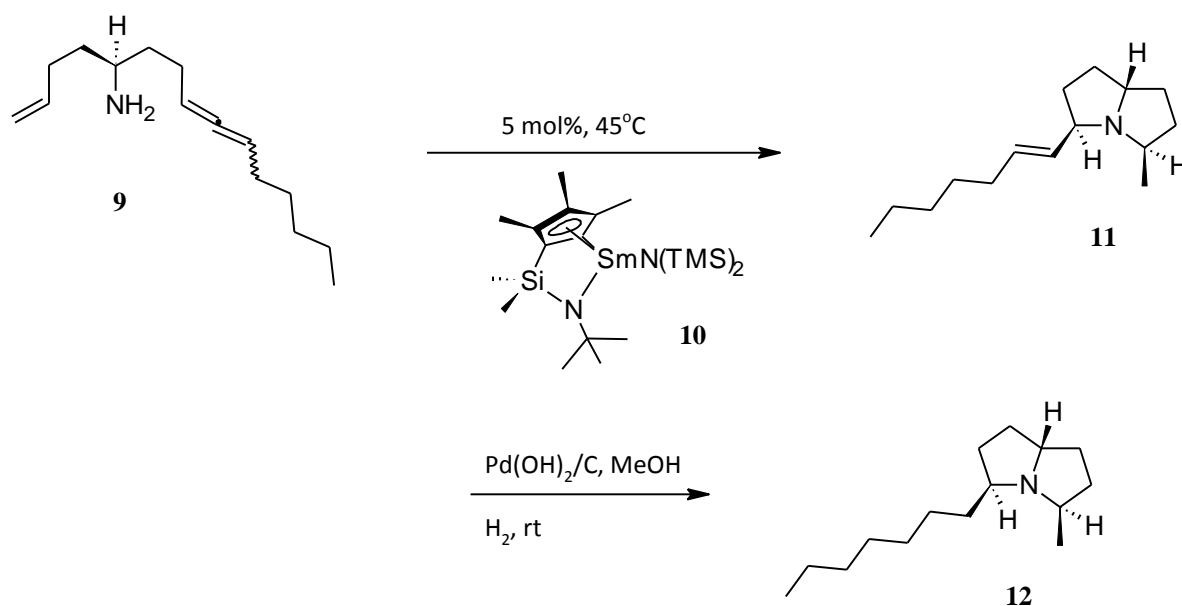
Utilizing hydroamination to construct ring[s] of *N*-bridgehead alkaloids is a method growing in significance due to the high atom-efficiency and selectivity that can be obtained. Arredondo *et al.* has reported a hydroamination/cyclization procedure for the synthesis of pyrrolizidine alkaloid (+)-xenovinine.³⁰ This is presented in schemes 1-12 and 1-13.



Scheme 1-12

³⁰ Arredondo, Tian, McDonald and Marks. *Journal of the American Chemical Society* **1999**, 121, 3633-3639.

The THP-protected alcohol **1** was treated with *n*-butyllithium followed by hexanal **2** to provide a racemic mixture of propargylic alcohol **3** in 88% yield. This was subsequently converted to the allenic alcohol **4** in 74% yield by treatment with triphenylphosphine, DEAD and NBSH followed by *p*-TsA. The aldehyde **5** was obtained by Swern oxidation in 99% yield. Further reaction with bis(3-butenyl)zinc **6** in the presence of chiral catalyst **7** afforded the (*R*)-secondary alcohol **8** in 36% yield. The –OH moiety was stereoselectively converted to the (*S*)-amine **9** in 57% yield by azide displacement under Mitsunobu conditions, followed by LiAlH₄ reduction.



Scheme 1-13

Both rings of the pyrrolizidine alkaloid were constructed by tandem hydroamination/bicyclization of **9** in the presence of organolanthanide catalyst **10** to form pyrrolizidine intermediate **11** in 80% yield. Subsequent hydrogenation over Pd(OH)₂/C afforded (+)-xenovinine **12** in 97% yield.

1.3. HYDROAMINATION

Hydroamination is the direct addition of the N-H functionality across unsaturated bonds of alkenes and alkynes to produce substituted amines. Of all methods available to construct C-N bonds, hydroamination is undoubtedly the simplest and most efficient.³¹ Despite the simplicity of these reactions, developing a general procedure for hydroamination remains elusive and a significant challenge for researchers.^{32,33}

Thermodynamically, hydroamination reactions are approximately thermoneutral³⁴ but since there is a large negative entropy, there is a high activation barrier to overcome.³⁵ Without the use of a catalyst, hydroamination may be regarded as a [2+2] cycloaddition reaction. According to the Woodward-Hoffmann rules, these are orbital-forbidden under thermal conditions, but allowed when promoted by light.³⁶ Use of a catalyst acts to open other reaction pathways, eliminating this constraint and allowing the reaction to proceed under thermal conditions, as well as lower the activation barrier.

1.3.1. REGIOSELECTIVITY

There are two possible products of a hydroamination reaction, depending on which carbon atom of the unsaturated bond the nitrogen adds to. These are termed Markovnikov and *anti*-Markovnikov products after the observations of Vladimir Vasilevich Markovnikov in 1870.³⁷ According to his rule, the nucleophile (nitrogen in this case) will preferentially add to the more substituted carbon and form the major (Markovnikov) product. The basis of his rule lies in the relative stabilities of each carbocation intermediate formed: the more

³¹ Hultzs. *Organic and Biomolecular Chemistry* **2005**, 3, 1819-1824.

³² Nobis and Driessen-Holscher. *Angewante Chemie Int. Ed. Engl.* **2001**, 40, 3983-3985.

³³ Fadini and Togni. *Chemical Communications* **2003**, 30-31.

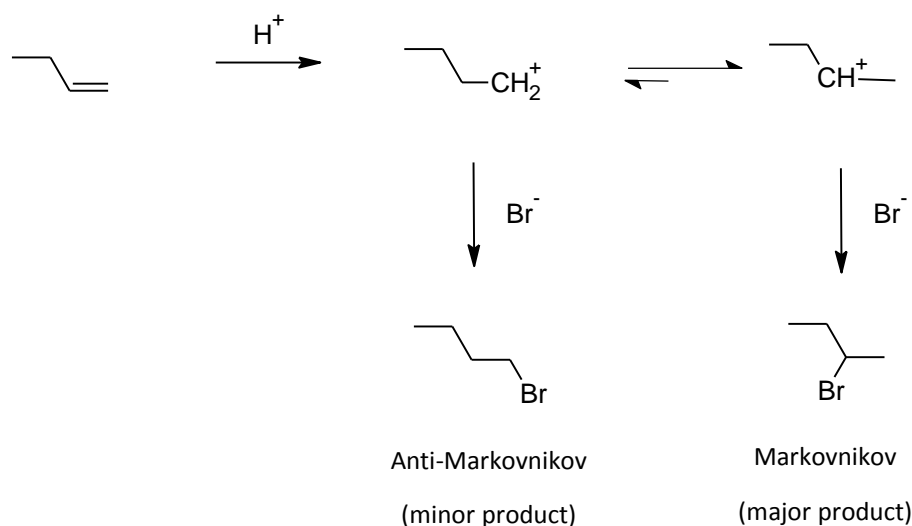
³⁴ Johns, Sakai, Ridder and Hartwig. *Journal of the American Chemical Society* **2006**, 128, 9306-9307.

³⁵ Muller, Hultzs, Yus, Foubelo and Tada. *Chemical Reviews* **2008**, 108, 3795-3892.

³⁶ Trost and Tang. *Journal of the American Chemical Society* **2002**, 124, 14542-14543.

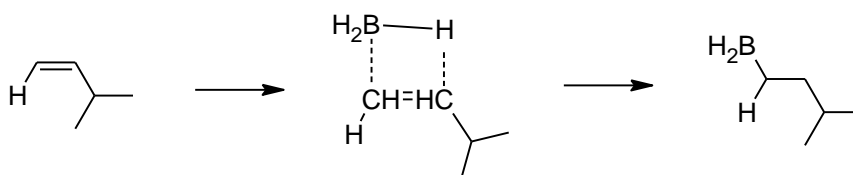
³⁷ Markovnikov. *Annalen der Pharmacie* **1870**, 153, 228-259

substituted the carbon atom is, the more stable it is, conversely the less substituted the carbon atom is the less stable it will be and the molecule will often rearrange to a certain extent to the more stable carbocation. This is shown in scheme 1-14 for the addition of HBr to 1-butene.



Scheme 1-14

It should be mentioned that in certain reactions, the *anti*-Markovnikov product is preferentially formed as is the case with hydroboration. In this instance, the hydroborane inserts in a *syn* fashion (via a concerted process rather than sequentially as shown above) with the boron preferentially adding to the least hindered carbon resulting in the *anti*-Markovnikov type product as shown in scheme 1-15 (although this reaction still follows the Markovnikov Rule, in which boron is the electropositive nucleophile).



Scheme 1-15

The earliest publication the author has found on hydroamination dates to 1968,^{38,39} and although hydroamination has existed (most likely) prior to this date, interest in these reactions has only peaked in the last 10 years, as seen from the number of publications on the subject. A graphical representation of the number of publications on the subject each year is shown in figure 1-7.

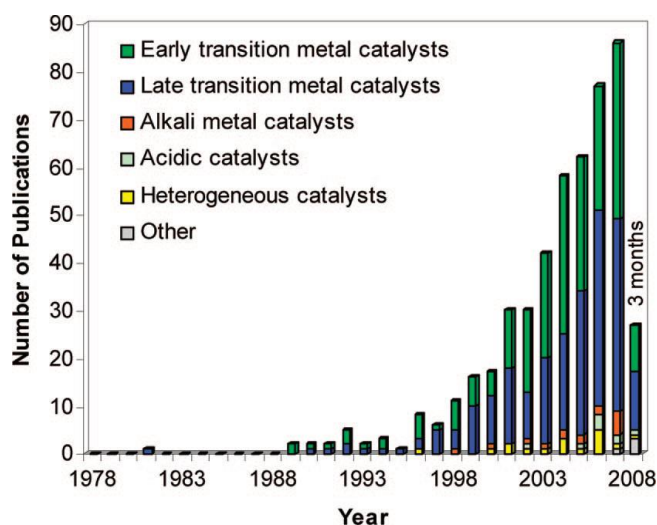


Figure 1-7 (reproduced from a review by Muller et al.⁴⁰)

When intramolecular hydroamination/cyclization reactions are performed, the Markovnikov and anti-Markovnikov products are subject to Baldwin's rules of ring closure. As such, these products are classified as shown in figure 1-8.



Figure 1-8

³⁸ Vysotskii. *Zhurnal Organicheskoi Khimii* **1968**, 4, 1494.

³⁹ Delzenne. *Industrie Chimique (Paris)* **1968**, 55, 53-57.

⁴⁰ Muller, Hultsch, Yus, Foubelo and Tada. *Chemical Reviews* **2008**, 108, 3795-3892.

Each of these ring closures, corresponding to intramolecular hydroaminations of alkynes and alkenes respectively, are orbitally allowed.^{41,42} Despite this, anti-Markovnikov addition of amines has proven extremely difficult earning it a position as one of the “ten challenges of catalysis” as put forward by Haggins *et al.*^{43,44} Accordingly there is little literature available pertaining to anti-Markovnikov hydroaminations.

One particularly interesting article by Tillack *et al.* demonstrates how changing the catalyst ligand can alter selectivity from Markovnikov to anti-Markovnikov.⁴⁵ This is discussed further under the section on catalysts.

Since the controlling factors behind anti-Markovnikov directing catalysts are not very well understood, there is little literature available on the topic.^{46,47}

1.3.2. STEREOSELECTIVITY (ASYMMETRIC HYDROAMINATION)

Control over which enantiomeric product forms is achieved *via* the ligands attached to the metal centre of the catalyst. Hultzsich *et al.* found that increased steric hindrance of the ligand resulted in an increase in the enantioselectivity. This is a result of the bulky ligand shielding the metal centre and preventing catalyst aggregation.⁴⁸ It was also discovered that

⁴¹ Baldwin. *Journal of the Chemical Society. Chemical Communications* **1967**, 734-736.

⁴² Baldwin, Thomas, Kruse and Silberman. *Journal of Organic Chemistry* **1977**, 42.

⁴³ Haggins. *J. Chem. Eng. News* **1993**, 71, 23-27.

⁴⁴ Muller, Hultzsich, Yus, Foubelo and Tada. *Chemical Reviews* **2008**, 108, 3795-3892.

⁴⁵ Tillack, Khedkar and Beller. *Tetrahedron Letters* **2004**, 45, 8875-8878.

⁴⁶ ^a Zhang and Schafer. *Organic Letters* **2003**, 5, 4733-4736.

^b Fukumoto, Asai, Shimizu and Chatani. *Journal of the American Chemical Society* **2007**, 129, 13792-13793.

⁴⁷ ^a Beller, Trauthwein, Eichberger, Breindl, Muller and Zapf. *Journal of Organometallic Chemistry* **1998**, 566, 277-285.

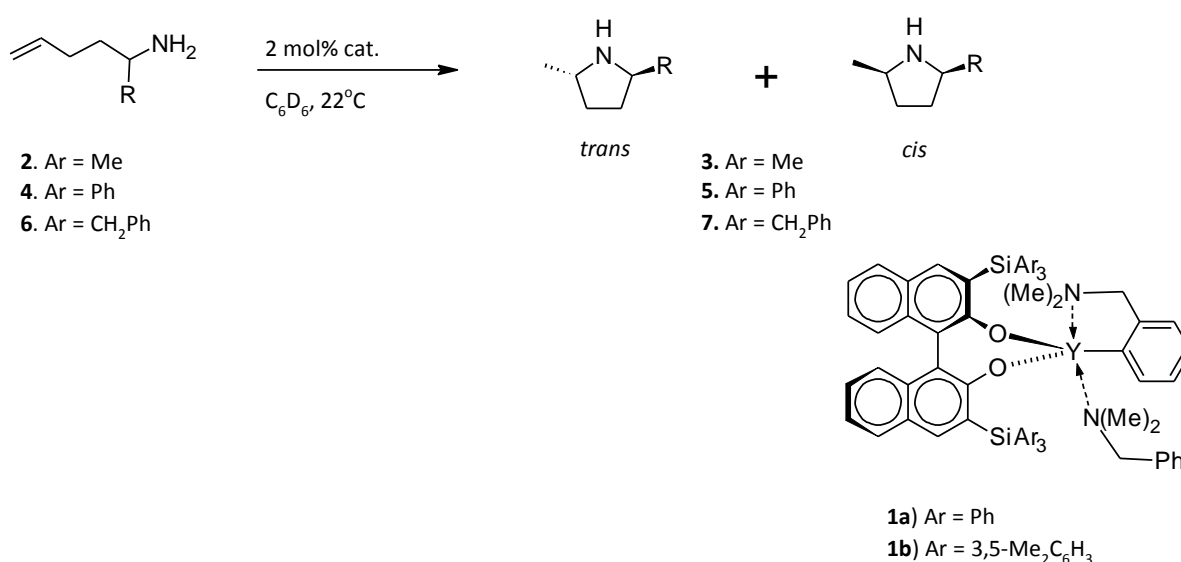
^b Joseph, Shanbhag, Sawant and Halligudi. *Journal of Molecular Catalysis A: Chemical* **2006**, 250, 210-217.

⁴⁸ Hultzsich. *Organic and Biomolecular Chemistry* **2005**, 3, 1819-1824.

co-ligands of low basicity hinder activation of the precatalyst while those with a higher basicity permit the reaction to proceed more efficiently.⁴⁹

Another important aspect of alkene hydroamination is the stereochemistry of the product, especially when using hydroamination in the synthesis of a natural product.

An article by Gribkov *et al.* outlines the use of chiral yttrium complexes of the type shown in scheme 1-16 for the intramolecular asymmetric hydroamination/cyclization of aminopentene type substrates.⁵⁰



Scheme 1-16

The results of reactions of these various substrates with catalyst 1a or 1b revealed that a bulky group at the 3- and 3'- positions of the binaphtholate ligand is an essential requirement for asymmetric control. Selectivity was obtained in $\geq 50:1$ excess of *trans* to *cis* for compound **4** above. The preference for the *trans* over the *cis* product is explained by unfavourable 1,3-diaxial interactions with the bulky R group in the *cis* chair conformation.

⁴⁹ Johns, Sakai, Ridder and Hartwig. *Journal of the American Chemical Society* **2006**, 128, 9306-9307.

⁵⁰ Gribkov and Hultzs. *Chemical Communications* **2004**, 730-731.

The further selectivity toward the (2*S*,5*S*)-*trans* diastereomer is explained using the stereochemical model shown in figure 1-9.

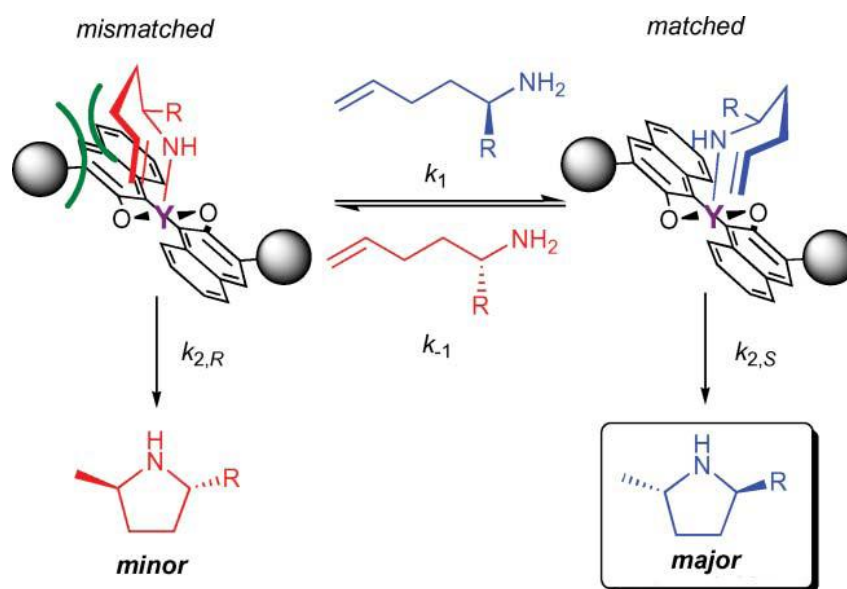


Figure 1-9 (reproduced from a review by Hultzsche *et al.*⁵¹)

Since the cyclization process takes place *via* a chair-like transition state, the diagram shows there to be an unfavourable steric interaction between the chair and the bulky tri-aryl silyl substituent of the catalyst BINOL ligand, for the (2*R*,5*R*)-*trans* diastereomer. The transition state of lower energy does not have this steric constraint, and thus forms the major (2*S*,5*S*)-*trans* diastereomer.⁵¹

1.3.3. MECHANISMS OF HYDROAMINATION

In order for hydroamination to take place, the electrostatic repulsion between the nitrogen lone pair and olefin π system needs to be overcome. Thus one of these components requires in some way to be activated, withdrawing the electron density and inducing a

⁵¹ Hultzsche. *Organic and Biomolecular Chemistry* **2005**, 3, 1819-1824.

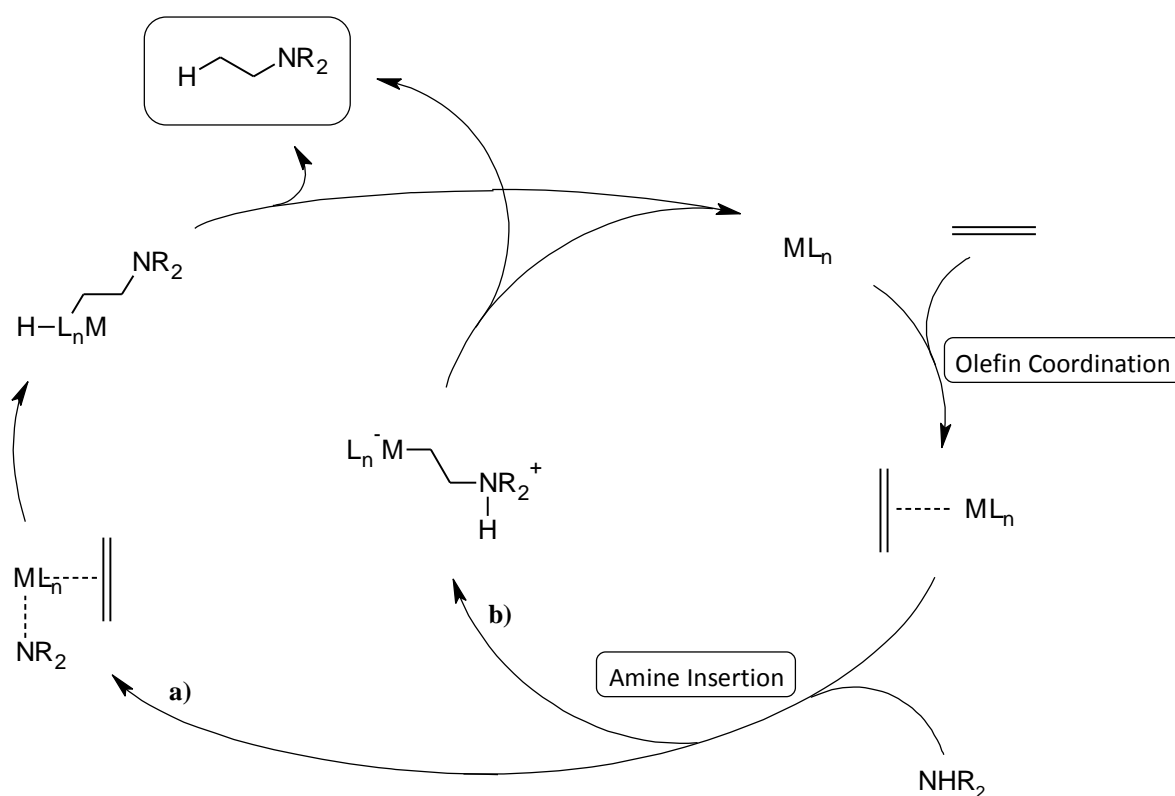
nucleophilic addition.⁵² This may occur in two possible ways; directly by metal activation of the amine or olefin, or indirectly through an activating group α to the unsaturated bond. Each of these aforementioned mechanisms will be discussed below. For activation to be successful, these mechanisms rely on the Lewis acidity of the metal centre in order to successfully coordinate either the unsaturated π -electron density of the olefin or the amine lone pair.

⁵² Muller, Hultsch, Yus, Foubelo and Tada. *Chemical Reviews* **2008**, *108*, 3795-3892.

1.3.3.1. NON-ACTIVATED OLEFINS

Olefin Activation – π -Coordination

Activation of the olefin can occur only by π coordination to the metal, and is thus characterized by initial coordination of the olefin to the metal centre, followed by nucleophilic attack of the amine.⁵³



Scheme 1-17

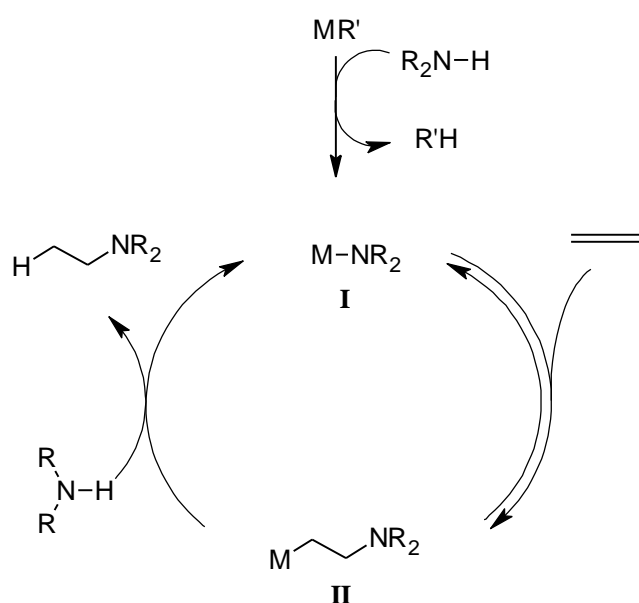
When the olefin coordinates to the metal centre, there is an umpolung of the unsaturated moiety, allowing subsequent nucleophilic attack by the amine, where normally the unactivated olefin would undergo electrophilic attack. From this point, the amine group can add to the olefin in one of two ways: a) and b) as shown in scheme 1-17. Path a) involves intramolecular attack where the amine first loses a proton and is coordinated directly to the

⁵³ Schaffrath and Keim. *Journal of Molecular Catalysis A: Chemical* **2001**, 168, 9-14.

metal, followed by addition to the olefin. In path b), the amine attacks the olefin followed by a 1, 3-hydride shift to yield the hydroamination product.

Amine Activation – Deprotonation

The first method of amine activation is shown in scheme 1-18 below, also often referred to as base catalysed hydroamination. This is characterized by deprotonation of the amine, allowing subsequent nucleophilic attack on the olefin.⁵⁴



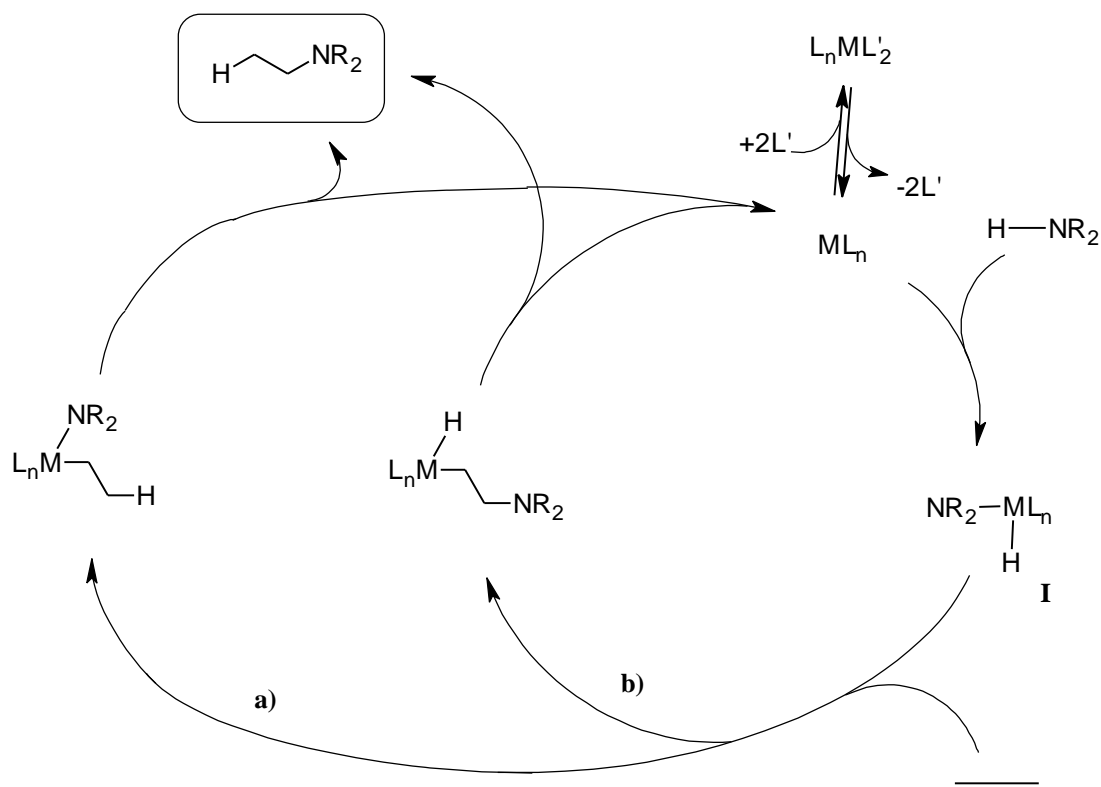
Scheme 1-18

The initial step in this mechanism is deprotonation of the amine by a strong alkali base, leading to the alkali amide salt **I**. This intermediate is extremely nucleophilic and is able to attack the olefin, forming the highly reactive organometallic species **II**. This immediately deprotonates a free amine from the reaction solution, releasing the hydroamination product and regenerating the active alkali amide **I**.

⁵⁴ Muller, Hultzs, Yus, Foubelo and Tada. *Chemical Reviews* **2008**, *108*, 3795-3892.

Amine Activation – Oxidative Addition

The second mechanism of amine activation is by oxidative addition. The catalyst in this case requires a late transition metal of low oxidation state such as Rh^1 , Ru^0 , Ir^1 , Cu^1 , Pd^0 and Pt^0 .⁵⁴

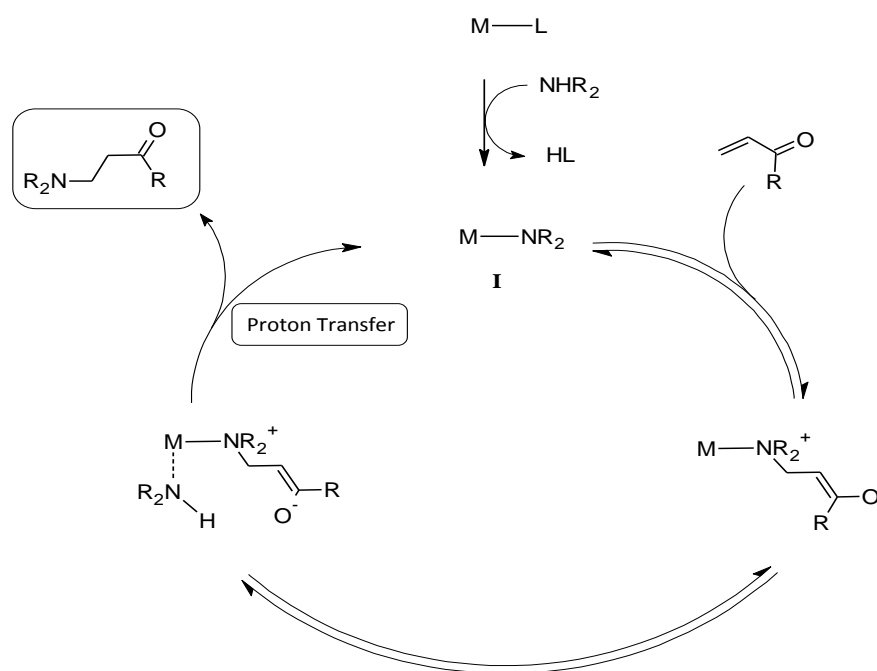


Scheme 1-19

Catalysis is initiated by reduction of the metal centre to activate the species of low valency. Subsequent formation of the amido-hydrido intermediate complex **I** is achieved by oxidative addition of the amine to the metal centre. This step requires two electrons from the metal, necessitating the low oxidation state in the metal. The olefin may then insert into either the metal-nitrogen or metal-hydride bond as depicted in scheme 1-19 as paths a) and b) respectively. The hydroamination product is obtained by reductive elimination, regenerating the low-valency active metal species.

1.3.3.2. ACTIVATED OLEFINS

Activated olefins possessing an attached electron-withdrawing group, which results in decreased electronic repulsion between the unsaturated π density and nitrogen lone pair during hydroamination. Thus, hydroamination of these substrates is as a result markedly simpler.⁵⁵ Examples of such substrates include vinylarenes, 1,3-dienes, and acrylates. These reactions are considered to be aza-Michael type additions,^{55,56} which may even occur in the absence of a catalyst.⁵⁷ As there is much speculation in the literature, the mechanisms proposed for these reactions differ from one another, a representative example is presented in scheme 1-20. However, in addition to the aza-Michael addition, these substrates also undergo catalysis by metal activation as shown by Sievers *et al.*⁵⁸



Scheme 1-20 (adapted from the mechanism proposed by Yamagiwa *et al.*)⁵⁹

⁵⁵ Hii. *Pure and Applied Chemistry* **2006**, 78, 341-349.

⁵⁶ Zhuang. *Chemical Communications* **2001**, 1240-1241.

⁵⁷ Li and Hii. *Chemical Communications* **2003**, 1132-1133.

⁵⁸ Sievers, Jimenez, Knapp, Lin, Muller, Turler, Wierczinski and Lercher. *Journal of Molecular Catalysis A: Chemical* **2008**, 279, 187-199.

⁵⁹ Yamagiwa, Qin, Matsunaga and Shibasaki. *Journal of the American Chemical Society* **2005**, 127, 13419-13427.

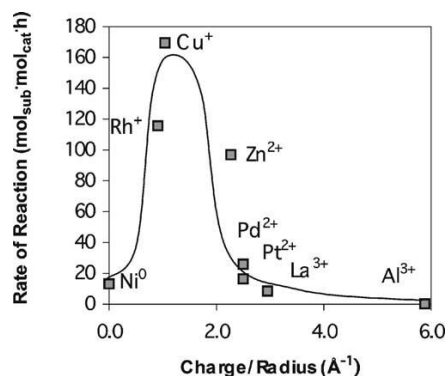
The catalyst is converted into its active form **I** by coordination of an amine and subsequent loss of a ligand. This coordinated amine may now attack the electron-poor β position of the olefin, possibly through simultaneous coordination of the carbonyl oxygen, forming the C-N bond of the product. Coordination of a second equivalent of the amine, followed by an irreversible proton transfer from the aforementioned to the product affords the hydroamination product while subsequently regenerating the active catalyst **I**.

1.3.4. CATALYSTS IN HYDROAMINATION

Due to the sheer volume of literature available on the topic of hydroamination catalysis, only a select overview of the more interesting and less exotic categories pertaining to titanium catalysts will be given (for a more complete review, please refer to the article by Muller *et al.*⁵⁴). As mentioned previously, the metal centre of the catalyst requires to act as a Lewis acid in order to coordinate the electron density of the nitrogen lone pair and unsaturated bond, thus activating them for nucleophilic attack. As the acidity increases, so the catalytic activity increases since the metal is better able to accept the electron density and successfully form a stable catalyst-substrate complex.^{60,61} If the Lewis acidity of the catalyst is too strong however, the catalyst-substrate complex formed can be sufficiently stable to preclude subsequent reaction.⁶¹ Penzien *et al.* demonstrated that there is an optimal charge/radius ratio (an approximate measure of the Lewis acidity) that will catalyse the reaction. Their results are shown graphically in figure 11. Other suitable catalysts include alkali metals, early as well as late transition metals, lanthanides and actinides.⁵⁴

⁶⁰ Odom. *Dalton Transactions* **2005**, 225-233.

⁶¹ Shanbhag and Halligudi. *Journal of Molecular Catalysis A: Chemical* **2004**, 222, 223-228.

**Figure 1-10**⁶²

It has been illustrated that the nature of the ligand or counter ion also plays a significant effect in the reactivity of the catalyst. These require to be sufficiently coordinating to form a solution stable catalyst, but not too strongly coordinating as this increase in π -donation to the metal centre douses its Lewis acidity.⁶³ The activity of late transition metal catalysts can be rationalized using the HSAB (hard soft acid base) theory as observed by Prior *et al.*⁶⁴

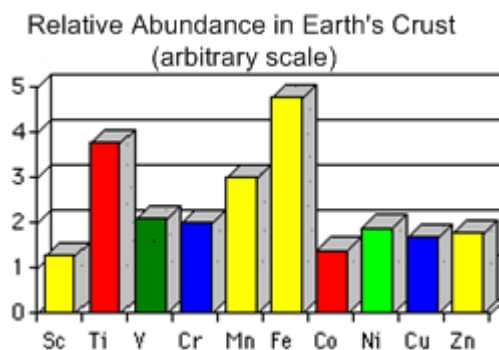
For the purposes of this study, a selection of titanium catalysts will be reviewed. Titanium is the second most abundant transition metals in the earth's crust after iron,⁶⁵ and as a result is inexpensive (as compared to other metals suitable for hydroamination catalysis). This is advantageous; not only from a financial point of view, but larger catalyst loadings may be used without concern. More importantly, titanium is environmentally benign forming TiO₂ on hydrolysis, a common additive in paints, foods and toothpaste. Titanium catalysts are also readily prepared *in situ* and can be removed from a reaction by simple filtration through a silica plug.

⁶² Penzien, Haebner, Jentys, Kohler, Muller and Lercher. *Journal of Catalysis* **2004**, 221, 302-312.

⁶³ Burling, Field, Messerle and Rumble. *Organometallics* **2007**, 26, 4335-4343.

⁶⁴ Prior and Robinson. *Tetrahedron Letters* **2008**, 49, 411-414.

⁶⁵ Murov and Stedjee *Experiments and Exercises in Basic Chemistry*, Fifth Edition ed.; Wiley: New Jersey, 2000, p34.

Figure 1-11⁶⁶

Undoubtedly the simplest of titanium catalysts are those based on $\text{Ti}(\text{NR}_2)_4$, where R is either a methyl or ethyl group. Although this complex is a catalyst in its own right, more often it is used as a precatalyst in conjunction with an additive ligand.

1.3.4.1. TITANOCENE CATALYSTS

Some of the earliest reports of titanium catalysed hydroamination, were on titanocene type systems that proved very successful in intramolecular reactions, but not for intermolecular.^{67,68} It has since been found that Cp_2TiMe_2 and $\text{Cp}^*_2\text{TiMe}_2$ (where $\text{Cp}^* = \text{C}_5\text{Me}_5$) are particularly successful for both inter- and intramolecular hydroaminations.^{69,70}

In table 1 below, the results obtained by Haak *et al.* on the asymmetric hydroamination of various alkynes with aniline.^{69b}

⁶⁶ <http://www.chemeddl.org/collections/ptl/PTL/misc/transmet.html>. Accessed 29 September 2008.

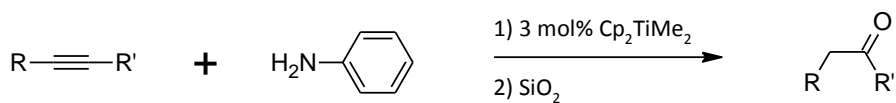
⁶⁷ McGrane and Livinghouse. *Journal of Organic Chemistry* **1992**, 57, 1323-1324.

⁶⁸ McGrane, Jensen and Livinghouse. *Journal of the American Chemical Society* **1992**, 114, 5459-5460.

⁶⁹ ^a Bytschkov and Doye. *Tetrahedron Letters* **2002**, 43, 3715-3718.

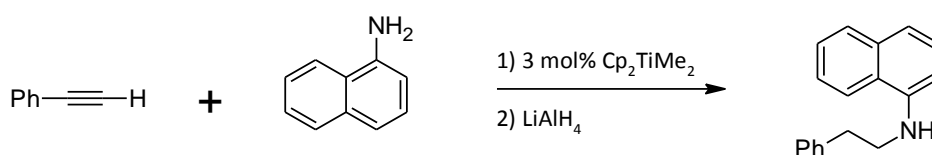
^b Haak, Bytschkov and Doye. *Angewante Chemie Int. Ed. Engl.* **1999**, 38, 3389-3391.

⁷⁰ Muller, Loos, Schulenberg and Doye. *European Journal of Organic Chemistry* **2006**, 2499-2503.

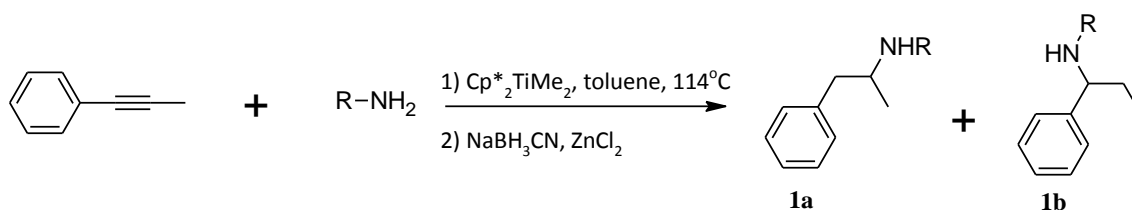
Table 1

| Entry | R | R' | Yield (%) |
|-------|---------------------------------|-------------------------------|-----------|
| 1 | Ph | Ph | 92 |
| 2 | C ₂ H ₅ | C ₂ H ₅ | 30 |
| 3 | Ph | CH ₃ | 99 |
| 4 | Ph | C ₂ H ₅ | 73 |
| 5 | Ph | C ₃ H ₇ | 35 |
| 6 | C ₁₀ H ₂₁ | H | trace |

In addition, phenylacetylene was reacted with 1-naphthylamine in the presence of 3 mol% Cp_2TiMe_2 to yield 23% of the anti-Markovnikov product and no trace of the Markovnikov regioisomer (scheme 1-21).

**Scheme 1-21**

Similar reactions were performed by Heutling *et al.* on the hydroamination/reduction of 1-phenylpropyne with various amines (scheme 1-22).⁷¹

**Scheme 1-22**

⁷¹ Heutling and Doye. *Journal of Organic Chemistry* **2002**, 67, 1961-1964.

However, in this case a distribution between the two regioisomeric products was observed. Nonetheless, the major product was of the anti-Markovnikov type isomer **1a** (where the methyl could instead be H).

Each of these are consistent with previous reports on this catalyst where the anti-Markovnikov regioisomer is the exclusive or major product.^{72,73}

A closely related group of catalysts are the titanium-indenyl complexes.⁷⁴

⁷² Haak, Siebeneicher and Doye. *Organic Letters* **2000**, 2, 1935-1937.

⁷³ Bytschkov and Doye. *European Journal of Organic Chemistry* **2001**, 4411-4418.

⁷⁴ ^a Buil, Esteruelas, Lopez, Mateo and Onate. *Organometallics* **2007**, 26, 554-565.

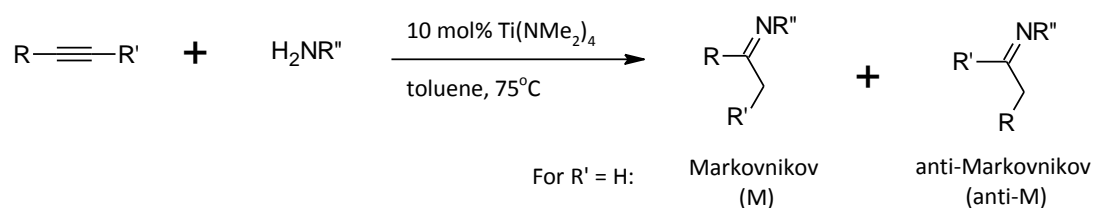
^b Muller, Saak and Doye. *European Journal of Organic Chemistry* **2008**, 2731-2739.

^c Pohlki, Bytschkov, Siebeneicher, Heutling, Konig and Doye. *European Journal of Organic Chemistry* **2004**, 1967-1972.

1.3.4.2. $\text{Ti}(\text{NMe}_2)_4$ -BASED CATALYSTS

One of the first reports of $\text{Ti}(\text{NMe}_2)_4$ being used as a catalyst was by Shi *et al.* in 2001.⁷⁵ A selection of alkynes were reacted with H_2NBu^t and H_2NPh , and the results are presented in table 2 below.

Table 2



| Entry | amine | alkyne | time (h) | yield (M:anti-M) |
|-------|---------------------------------|----------------------|----------|------------------|
| 1 | PhNH ₂ | Bu ⁿ C≡CH | 2 | 90 (3:1) |
| 2 | | EtC≡CEt | 17 | 87 |
| 3 | | PhC≡CH | 2 | 37 (>100:1) |
| 4 | | PhC≡CPh | 57 | 92 |
| 5 | Bu ^t NH ₂ | Bu ⁿ C≡CH | 48 | 0 |
| 6 | | EtC≡CEt | 48 | 0 |
| 7 | | PhC≡CH | 10 | 16 (>100:1) |
| 8 | | PhC≡CPh | 48 | 0 |

Contrasting with the popular titanocene or Cp-based catalyst systems, the Markovnikov product is the favoured or exclusive product of these hydroaminations. In some cases, such as the reaction of phenylacetylene with aniline (entry 3), oligomers and polymers of phenylacetylene were formed alongside the hydroamination product.⁷⁵ This is also the case in the reactions of *tert*-butylamine above. Attempts to minimize these side reactions were unsuccessful.

⁷⁵ Shi, Ciszewski and Odom. *Organometallics* **2001**, 20, 3967-3969.

Numerous subsequent reports include intramolecular hydroamination of alkenes^{76,77} and alkynes, co-catalysis with *N*-heterocyclic carbenes and $\text{LiN}(\text{SiMe}_3)_2$,⁷⁸ and anti-Markovnikov hydroamination⁷⁹ with little to no modification of the catalyst system.

1.3.4.3. ARYLOXOTITANIUM COMPLEXES

The work of Tillack *et al.* involved the use of sterically hindered phenols as titanium ligands that could direct the stereochemical outcome of intermolecular hydroamination of terminal alkynes. Depending on which ligand was used, either Markovnikov or anti-Markovnikov products were obtained. The tested ligands are shown in figure 1-12.⁸⁰

Of four phenol ligands tested, **1** showed 90% Markovnikov selectivity while **4** showed 94% anti-Markovnikov selectivity.

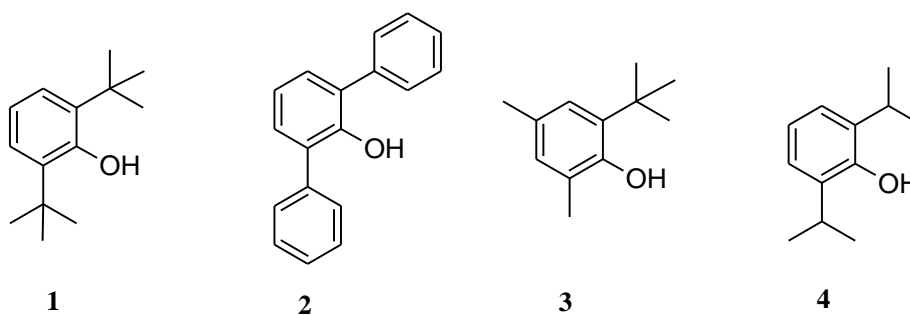


Figure 1-12

⁷⁶ Muller, Saak and Doye. *European Journal of Organic Chemistry* **2008**, 2731-2739.

⁷⁷ Bexrud, Beard, Leitch and Schafer. *Organic Letters* **2005**, 7, 1959-1962.

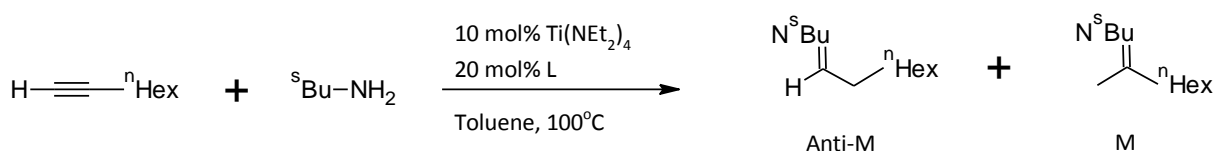
⁷⁸ Takaki, Koizumi, Yamamoto and Komeyama. *Tetrahedron Letters* **2006**, 47, 7335-7337.

⁷⁹ Ackermann and Kaspar. *Journal of Organic Chemistry* **2007**, 72, 6149-6153.

⁸⁰ Tillack, Khedkar and Beller. *Tetrahedron Letters* **2004**, 45, 8875-8878.

The results obtained for the reaction of *sec*-butylamine with 1-octyne are shown in Table 3 below.

Table 3



| Ligand | Conversion (%) | Yield (%) | Anti-M:M Ratio |
|----------|----------------|-----------|----------------|
| 1 | 100 | 98 | 10:90 |
| 2 | 100 | 97 | 49:51 |
| 3 | 100 | 88 | 72:28 |
| 4 | 100 | 97 | 94:6 |

By looking at the structures of ligands **1** and **4**, it is apparently possible to reverse the regioselectivity of the hydroamination reaction by slight modification of the ligand structure. To further test the applicability of these two ligands for catalytic hydroamination, various amines were reacted with 1-octyne and differing terminal alkynes, and these ligands were shown to consistently direct the regiochemistry. The only exceptions were *t*-butylamine (anti-M with both ligands) and aniline (M with both ligands). Due to the similarity of these ligands in steric and electronic terms, the authors were unable to afford an explanation for this complete shift in selectivity. A follow-up study concluded that the regioselectivity of the catalyst was dependant on the stability of the appropriate catalyst-substrate π complex. This stability in turn is determined by joint electrostatic attractive and steric repulsive effects present in each π complex.⁸¹

⁸¹ Tillack, Khedkar, Jiao and Beller. *European Journal of Organic Chemistry* **2005**, 5001-5012.

1.3.4.4. BIS(AMIDATE)TITANIUM-BIS(DIETHYLAMIDO) COMPLEXES

Another titanium catalyst system prepared from $\text{Ti}(\text{NEt}_2)_4$ is the bis(amidate)titanium-bis(diethylamido) complex **1** depicted in figure 1-13.

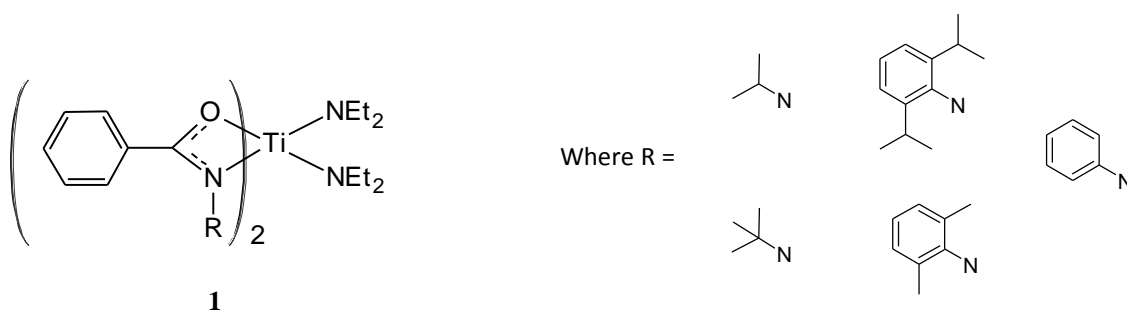
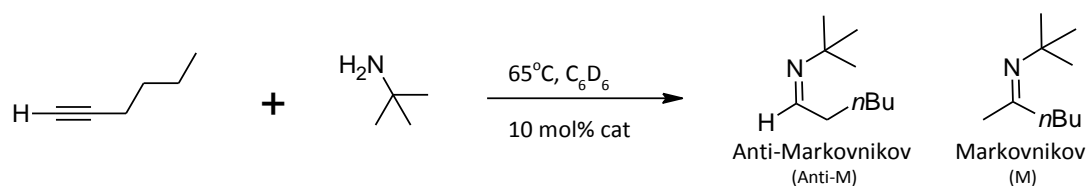


Figure 1-13

In an attempt to develop a catalyst system that is easily prepared and allows for easy modification, Zhang *et al.* selected amidates as the ligands.^{82,83} These organic amides are widely available and can be readily modified to produce complexes with diverse steric and electronic properties. The results obtained for the reaction of 1-hexyne with *tert*-butylamine are presented in table 4, and showed the regioselectivity of the ligands to be consistent.

⁸² Zhang and Schafer. *Organic Letters* **2003**, 5, 4733-4736.

⁸³ Li, Thomson, Gillon, Patrick and Schafer. *Chemical Communications* **2003**, 2462-2463.

Table 4

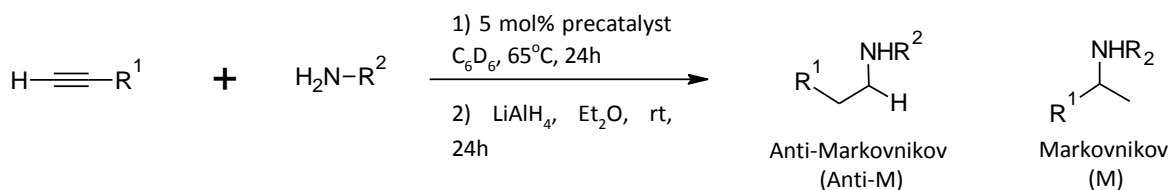
| Entry | R | t (h) | % yield (M:Anti-M) |
|-------|--------------------------------|-------|--------------------|
| 1 | <i>i</i> Pr | 24 | no reaction |
| 2 | <i>t</i> Bu | 24 | 71 (5:1) |
| 3 | Ph | 24 | 55 (99:1) |
| 4 | 2,6-dimethylphenyl | 10 | 78 (>99:1) |
| 5 | 2,6-di <i>iso</i> propylphenyl | 6 | 82 (>99:1) |

Additional intermolecular testing revealed that these catalysts show remarkable anti-Markovnikov selectivity for a wide variety of substrates and functional groups. These catalysts have also been shown to catalyze intramolecular hydroamination.⁸³

Similar catalysts have since been tested by Bexrud *et al.* by variation of both the phenyl groups of the amido ligand. Their results are as shown in table 5.⁸⁴

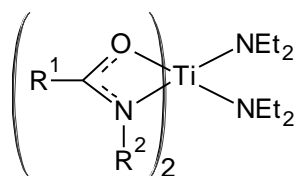
⁸⁴ Bexrud, Li and Schafer. *Organometallics* **2007**, 26, 6366-6372.

Table 5



| Entry | R 1 | R 2 | Complex 2 yield (Anti-M:M) | Complex 3 yield (Anti-M:M) |
|-------|-----------------|--------------------|----------------------------|----------------------------|
| 1 | Ph | 2,6-dimethylphenyl | 62% (>49:1) | 69% (3:1) |
| 2 | <i>p</i> -MeOPh | 2,6-dimethylphenyl | 57% (>49:1) | 65% (1.2:1) |
| 3 | <i>n</i> Bu | 2,6-dimethylphenyl | 72% (<1:49) | 84% (<1:49) |
| 4 | <i>n</i> Bu | <i>t</i> -butyl | 82% (>49:1) | >90% (>49:1) |
| 5 | <i>n</i> Bu | benzyl | 88% (>49:1) | 45% (2:1) |

Where:



Complex **2**: R¹ = Ph, R² = 2,6-diisopropylphenyl

Complex **3**: R¹ = C₆F₅, R² = 2,6-diisopropylphenyl

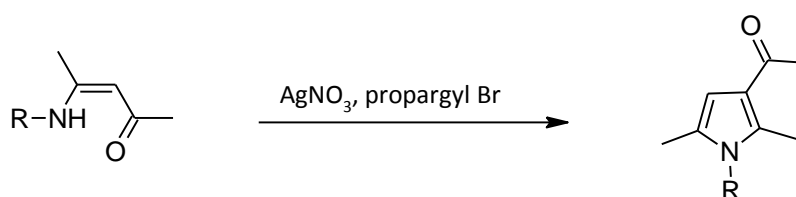
It was found that complex **3** gave comparable to higher yields than **2** at the expense of regioselectivity. The authors have suggested this result is due to the greater steric accessibility of the metal centre of **3** caused by increased ionic character of the metal-ligand bond. From these results it was also concluded that complex **2**, for the above reasons, has enhanced performance over **3** for substrates with bulky substituents.

As previously mentioned, there exists no generally applicable catalyst system in the literature to perform hydroamination reactions. Also, as has hopefully been illustrated thus far, the catalyst required depends on the desired regio- and stereochemistry, whether the substrate is activated or non-activated, whether the reaction to be performed is inter- or intramolecular, alkene, allene or alkyne. More specificity is required depending on the

nature of the substrate, such as whether it is aromatic or if the unsaturated bond is internal or terminal. The matter is made more complex still if one of the substrates is incompatible with the catalyst.

1.4. PREVIOUS WORK BY THE GROUP

Previous work within our research group involved the preparation of vinylogous amides and subsequent silver catalysed hydroamination studies for the preparation of pyrroles. This was achieved in a one-pot process as shown in scheme 1-23.⁸⁵



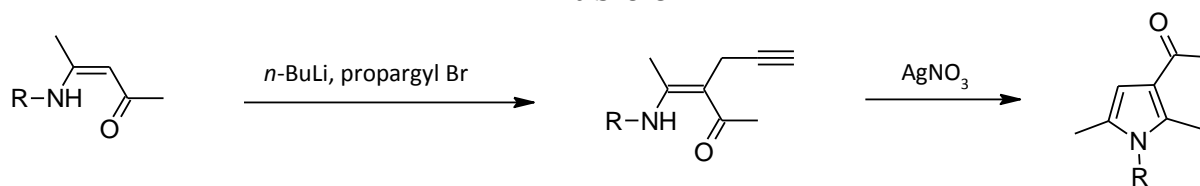
Scheme 1-23

However, due to the low yields obtained (~25%), a two-step process was pursued in which the α -proton is removed by *n*-BuLi, followed by addition of propargyl bromide. This intermediate was obtained in 51-55% yields. Subsequent addition of silver nitrate to facilitate the hydroamination afforded the corresponding pyrrole in 43-95% yields.

The results of varying the R group of the amine are presented in table 6. By utilizing microwave irradiation, reaction yields were slightly improved.

⁸⁵ Gravestock and Dovey. *Synthesis* **2003**, 4, 523-530.

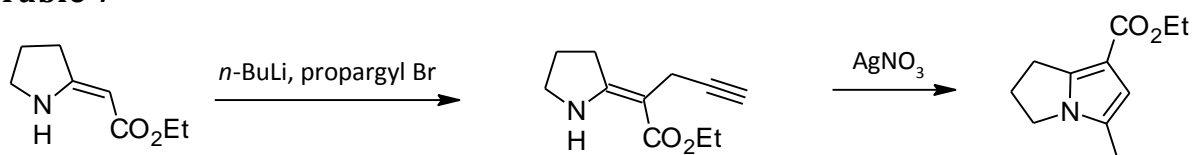
Table 6



| Entry | R | Yield 1 | Base | Yield 6 | Yield 2 | μ w Yield |
|-------|--------------|---------|----------------|---------|---------|---------------|
| a | Me | 80% | <i>n</i> -BuLi | 55% | 93% | 93% |
| b | Me | 80% | NaH | 46% | 93% | - |
| c | <i>n</i> -Bu | 76% | <i>n</i> -BuLi | 51% | 95% | 91% |
| d | Cy | 88% | <i>n</i> -BuLi | 52% | 87% | 96% |
| e | <i>t</i> -Bu | 6% | - | - | - | - |
| f | Ph | 94% | <i>n</i> -BuLi | 21% | 75% | 78% |
| g | Bn | 95% | <i>n</i> -BuLi | - | 43 | - |

This methodology was then applied to analogous secondary vinylogous carbamates to yield *N*-bridgehead pyrroles.⁸⁶

Table 7



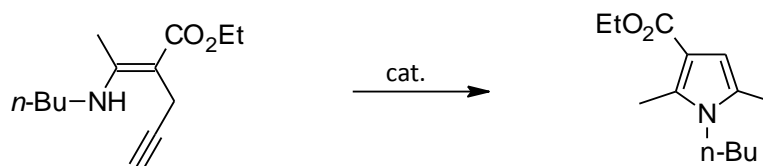
| Entry | Method | Starting Material | Yield |
|-------|----------|-------------------|-------|
| 20a | One-pot | 11a | 13% |
| 20b | One-pot | 11b | 19% |
| 20c | One-pot | 11c | 14% |
| 21a | — | 11a | 66% |
| 21b | — | 11b | 35% |
| 21c | — | 11c | 24% |
| 20a | Two-step | 21a | 75% |
| 20b | Two-step | 21b | 75% |
| 20c | Two-step | 21c | 71% |

Scheme 1-24

⁸⁶ Robinson, Dovey and Gravestock. *European Journal of Organic Chemistry* **2005**, 505-511.

Subsequent research by Prior involved use of this silver-catalyzed hydroamination process in the total synthesis of a pyrrolizidine ant alkaloid **223H**, as well as assessment of various late transition metals for this hydroamination into pyrroles. The results of which are presented in table 8.⁸⁷

Table 8



| Entry | Catalyst | Yield (%) | Entry | Catalyst | Yield |
|-------|-----------------------------------|-----------|-------|-----------------------------------|-------|
| a | - | 3 | m | ZnCl ₂ | 93 |
| b | CuO | 13 | n | CdO | 39 |
| c | CuAc ₂ | 33 | o | CdAc ₂ | 30 |
| d | Cu(NO ₃) ₂ | 53 | p | Cd(NO ₃) ₂ | 85 |
| e | CuCl ₂ | 65 | q | CdCl ₂ | 72 |
| f | Ag ₂ O | 6 | r | HgO | 24 |
| g | AgAc | 7 | s | HgAc ₂ | 68 |
| h | AgNO ₃ | 14 | t | Hg(NO ₃) ₂ | 57 |
| i | AgCl | 9 | u | HgCl ₂ | 36 |
| j | ZnO | 3 | v | ZnI ₂ | 14 |
| k | ZnAc ₂ | 96 | w | HgI ₂ | 94 |
| l | Zn(NO ₃) ₂ | 99 | | | |

These results are consistent with the activity of the metal centre corresponding to the Lewis acidity (both decreasing down a group in the periodic table), and with the observations by Burling *et al.* on the coordinating effect of the counter-ion.⁸⁸

⁸⁷ Prior and Robinson. *Tetrahedron Letters* **2008**, 49, 411-414.

⁸⁸ Burling, Field, Messerle and Rumble. *Organometallics* **2007**, 26, 4335-4343.

1.5. AIMS OF THE PROJECT

It has been shown that alkaloids from various sources are vital as lead compounds in medicinal research and thus the efficient synthesis of these is also important. With the goal of developing a general synthetic route that can potentially access pyrrolizidine, indolizidine, quinolizidine and possibly lehmizidine alkaloid skeletons, a modified route that has been shown to produce pyrrolizidines was employed to synthesize our target indolizidine alkaloid **223AB**. Within this synthesis, a 6-endo-dig hydroamination-cyclization step is to be utilised for construction of the bicyclic system. For this purpose, a selection of catalysts will be synthesized in order to determine their regiochemical outcome. As there is much speculation as to the mechanism of hydroamination and the factors involved in regioselectivity, a computational study on the topic would be ideal. To this end, the skills and methods involved in computational chemistry will be acquired through an investigation into amide rotational barriers.

2. RESULTS AND DISCUSSION

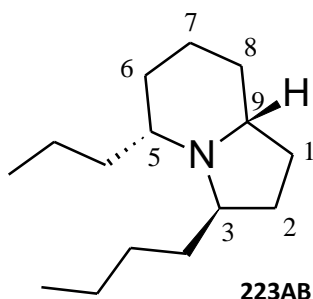


Figure 2-1

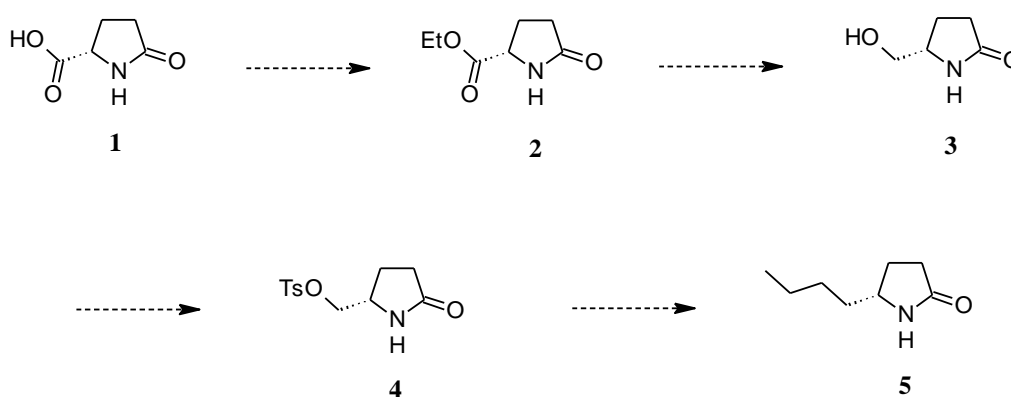
The structure of indolizidine alkaloid **223AB** with the appropriate numbering system is as shown in figure 2-1.

2.1. FOCUS OF THE PROJECT

The focus of this project will be to establish a synthetic route to produce pyrrolizidines and indolizidines through modification of key steps, one of these being an anti-Markovnikov type endo-cyclization. To explore and study the regioselectivity of various titanium-based hydroamination catalysts, a model C-propargylated enamine system is to be used. In the further interests of investigating the regioselective hydroamination mechanism, a separate study on the barrier to internal rotation in amides and thioamides is to be initiated in order gain the skills and understanding involved in such an undertaking.

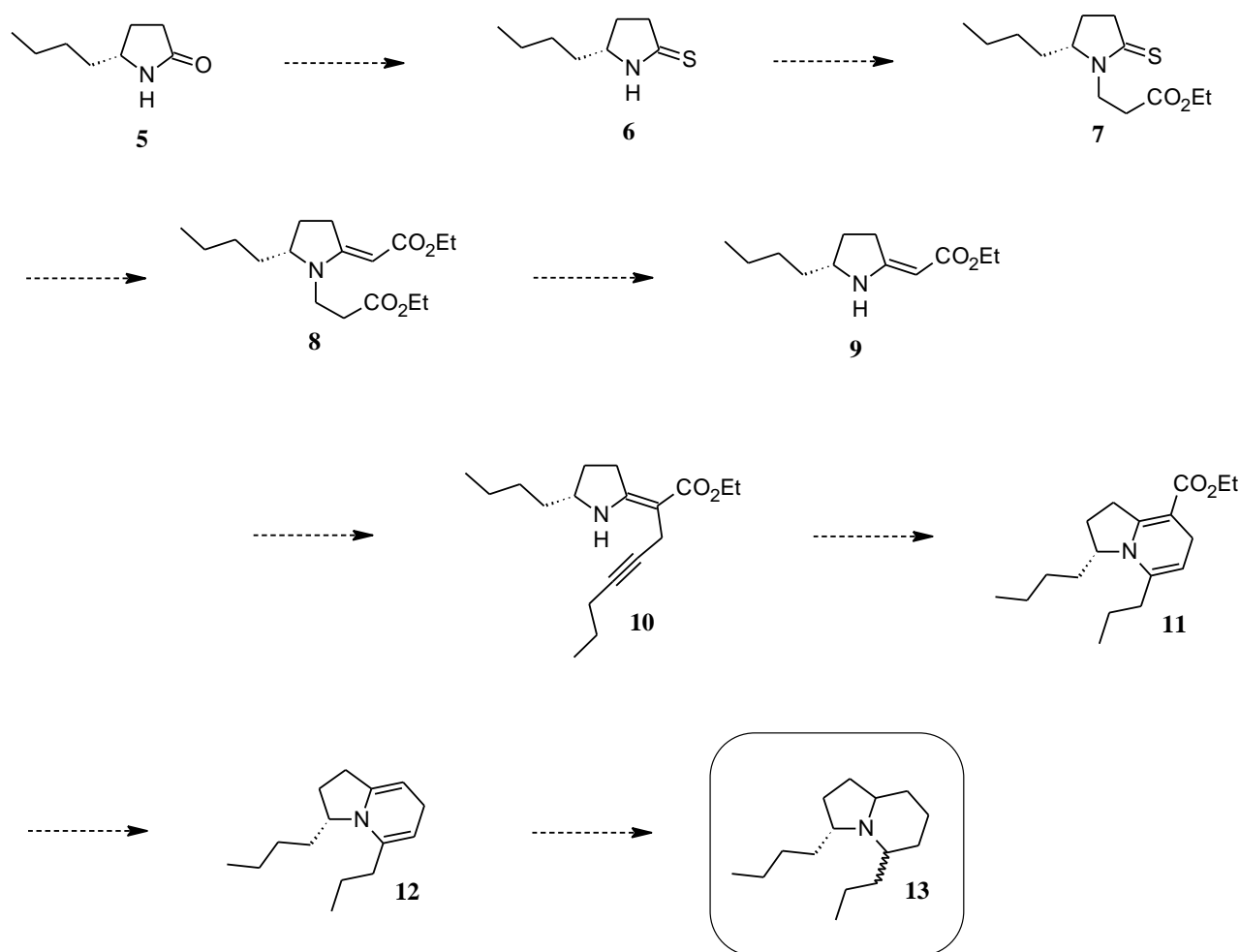
2.2. PROPOSED SYNTHETIC ROUTE

The route to be followed towards the synthesis of indolizidine frog alkaloid **223AB** (**13**) is outlined below in schemes 2-1 and 2-2. The initial section of the synthesis may be regarded as preparation of the 5-member ring with the appropriate substituent. The second section involves construction of the second 6-member ring onto the first. Only an extremely brief outline of the proposed synthetic pathway to be pursued is given here; a more detailed discourse follows within the individual discussions of each reaction and their mechanisms.



Scheme 2-1

In order to achieve the desired 3*R* stereochemistry of the butyl group, the synthesis is to be initiated with enantiopure (*S*)-pyroglutamic acid (**1**). From this point, the pyroglutamic acid could be esterified to form (**2**), reduced to (**3**), and the alcohol subsequently tosylated to obtain (**4**). An ensuing Gilman cross-coupling reaction would afford (*R*)-5-butylpyrrolidin-2-one (**5**) which may subsequently be carried forward as the starting material for the second section of this synthesis.



Scheme 2-2

Thionation of (*R*)-5-butylpyrrolidin-2-one (**5**) will afford thiolactam (**6**). The nitrogen may then be protected and an Eschenmoser sulphide contraction performed to give (**8**). Deprotection of the nitrogen is envisioned to yield (**9**) which may be propargylated and subject to hydroamination conditions. Decarboxylation and subsequent hydrogenation of the cyclized product (**11**) would be expected to afford the target indolizidine alkaloid (**13**).

As described in the introduction, syntheses of these alkaloids range from simple with few steps to long and complicated; many possess the capability to synthesise more than a single alkaloid,^{89,90} but are limited to within the 3,5-disubstituted indolizidine subclass. In general,

⁸⁹ Amos, Gourlay, Molesworth, Smith and Sprod. *Tetrahedron* **2005**, 61, 8226-8230.

many syntheses are specific to an individual alkaloid or class of alkaloids having the same skeletal structure.⁹¹

The merit of the synthesis proposed above, is that with little modification, it is theoretically possible to access a wide variety of substituted pyrrolizidine, indolizidine, quinolizidine and lehmizidine alkaloid skeletons.

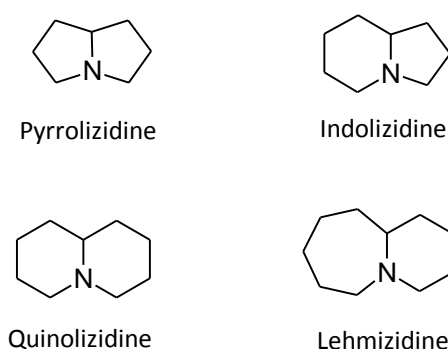


Figure 2-2

There are three essential steps that enable this modification to take place. Since the initial ring system is part of the starting reagent, either a five- or six-member ring is available from commercial sources. Firstly, the alkyl chain or substituent at position 3 of the alkaloid may be varied as required (within the limitations of the Gilman reagent). The second substituent at position 5 may also be varied by altering the alkynyl bromide reagent as required (forming **10**). Lastly, the size of the second ring may be varied by altering the regioselectivity of the hydroamination step. The CO₂Et functional group at position 8 also provides a platform for a number of transformations to take place for additional substituents.

⁹⁰ ^a Kiewel, Tallant and Sulikowski. *Tetrahedron Letters* **2001**, 42, 6621-6623.

^b Kuhakarn, Seehasombat, Jaipetch, Pohmakotr and Reutrakul. *Tetrahedron* **2008**, 64, 1663-1670.

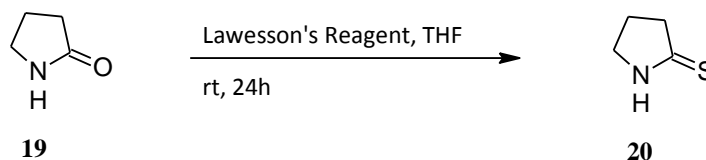
⁹¹ Celimene, Dhimane and Lhommet. *Tetrahedron* **1998**, 54, 10457-10468.

2.3. MODEL STUDIES

In order to conserve time and minimize the use of expensive reagents to optimize reaction chemistry, model studies were carried out for the core section of this synthesis (Scheme 2-3) using pyrrolidin-2-one (**19**) in place of (*R*)-5-butylpyrrolidin-2-one (**5**).

2.3.1. SYNTHESIS OF PYRROLIDINE-2-THIONE (**20**)

In order to create the scaffold for construction of the second ring by hydroamination (namely compound **10**), it is necessary to convert the carbonyl of pyrrolidin-2-one (**19**) to a thiocarbonyl. This provides the framework for the Eschenmoser sulphide contraction, an elegant means to prepare the aforementioned *exo*-cyclic enamine. Variations of the latter building block provide a versatile backbone for the synthesis of many natural products, most notably, alkaloids.⁹²



Scheme 2-3

For the thionation reaction shown in scheme 2-3 above, there are a number of reagents available to effect this transformation. Among these are hydrogen sulphide,⁹³ bis(trimethylsilyl)sulphide,⁹⁴ sodium thiosulphate,⁹⁵ thioacetoacetic esters,⁹⁵ phosphorus pentasulphide⁹⁶ (P₄S₁₀) and 2,4-bis(*p*-methoxyphenyl)-1,3-dithiadiphosphetane-2,4-

⁹² Russowsky and Neto. *Tetrahedron Letters* **2004**, 45, 1437-1440.

⁹³ Metzner and Rakotonirina. *Tetrahedron* **1985**, 41, 1289-1298.

⁹⁴ Degl'Innocenti, Capperucci, Mordini, Reginato, Ricci and Cerreta. *Tetrahedron Letters* **1993**, 34, 873-876.

⁹⁵ Campaigne. *Chemical Reviews* **1946**, 39, 1-77.

⁹⁶ Peters, Althaus and Nagy. *Organic and Biomolecular Chemistry* **2006**, 4, 498-509.

disulphide⁹⁷ (Lawesson's Reagent) (**21**). Prior to the work of Lawesson and co-workers, P_4S_{10} (**22**) was the most widely used thionating reagent, being the most successful reagent at the time and applicable over a broad range of substrates.⁹⁸ Lawesson's Reagent has since dominated thionation chemistry, producing superior yields where P_4S_{10} would often vary greatly.⁹⁹ Other advantages of Lawesson's Reagent over P_4S_{10} lie in the fact that reaction times are shorter, excess reagent is not required and high temperatures of refluxing toluene, xylene or pyridine solvent are not necessary.

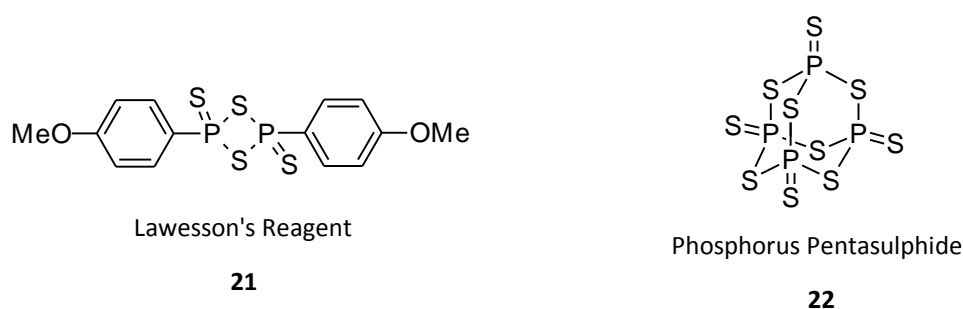


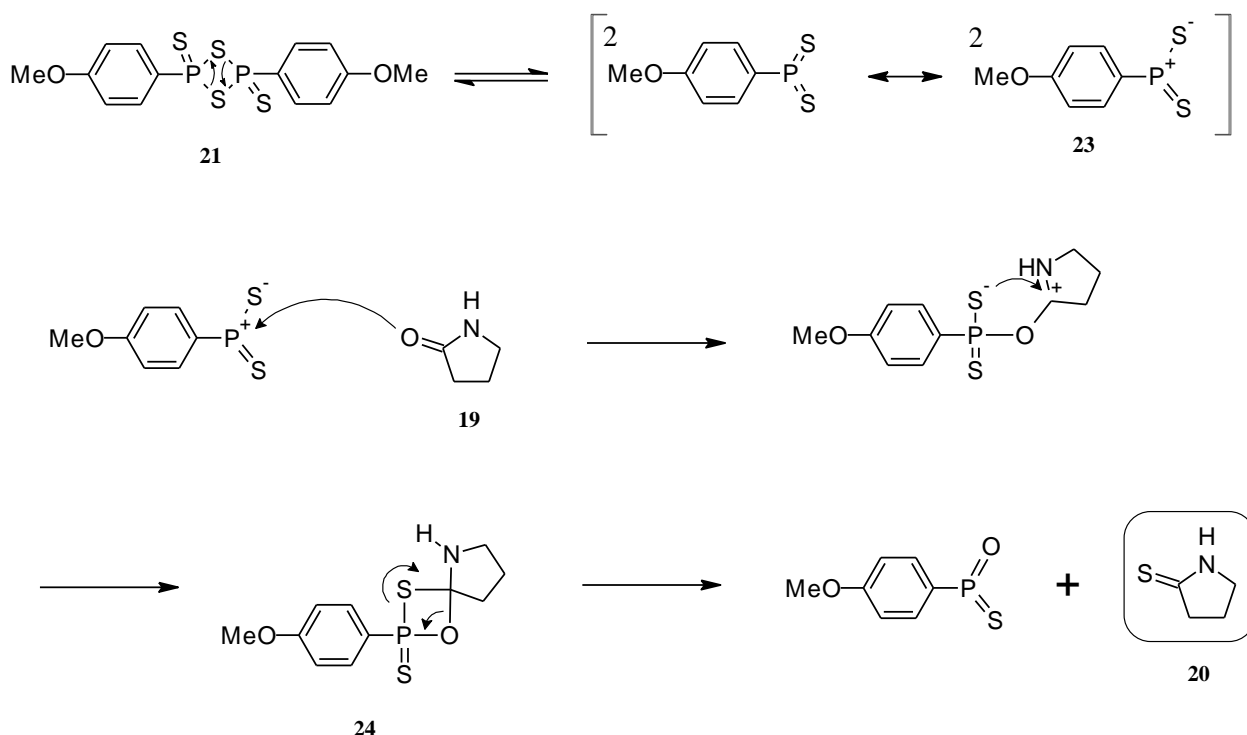
Figure 2-3

In both of these reagents, the reactive component is the dissociation product of the reagent. The mechanism of thionation is shown in scheme 2-5. In solution, Lawesson's reagent is in equilibrium with the more reactive dithiophosphine ylide (**23**). Subsequent attack of the carbonyl oxygen of **19** on the electrophilic phosphorus, followed by attack of sulphur on the carbonyl carbon produces a thiaoxaphosphetane Wittig-type intermediate (**24**). The ensuing cycloreversion step is also reminiscent of a section from the Wittig reaction. Formation of the stable $P=O$ bond is the driving force behind this step, yielding the thiocarbonyl **20**.

⁹⁷ Varma and Kumar. *Organic Letters* **1999**, *1*, 697-700.

⁹⁸ Ozturk, Ertas and Mert. *Chemical Reviews* **2007**, *107*, 5210-5278.

⁹⁹ Cava and Levinson. *Tetrahedron* **1985**, *41*, 5061-5087.



Scheme 2-4

The pyrrolidin-2-one was added slowly to a stirring solution of Lawesson's reagent (0.5 eq.) in dry THF, and the mixture allowed to stir at room temperature overnight. Thin layer chromatography of this reaction mixture revealed that no starting material remained, while two additional spots were present at $R_f = 0.25$ and 0.57 (1:1 EtOAc-hexane). Solvent was removed *in vacuo* to leave a thick yellow substance that on cooling becomes increasingly sticky and viscous forming an insoluble mass. To overcome the ensuing problems associated with purification, an aliquot of hot ethyl acetate was added to dissolve the substance before cooling could occur. This was then loaded immediately onto a pre-warmed silica column, and eluted with 100% EtOAc. Once the oil had eluted into the silica, the solvent system was altered to 1:1 EtOAc-hexane. The product was obtained as white needle-like crystals in 83% yield corresponding to the TLC spot of lower R_f . A melting point of $109\text{--}113^\circ\text{C}$ is in agreement with the literature value of $112\text{--}113^\circ\text{C}$.¹⁰⁰

The other spot on TLC corresponds to a trimeric by-product of Lawesson's reagent; 2,4,6-tris(*p*-methoxyphenyl)-1,3,5,2,4,6-thioxatriphosphinane 2,4,6-trisulphide (**25**) shown in

¹⁰⁰ Hall. *Journal of the American Chemical Society* **1985**, *80*, 6404-6409.

figure 2-4. A melting point of 154-158°C was obtained, which corresponds well with the literature value of 158-159°C.¹⁰¹

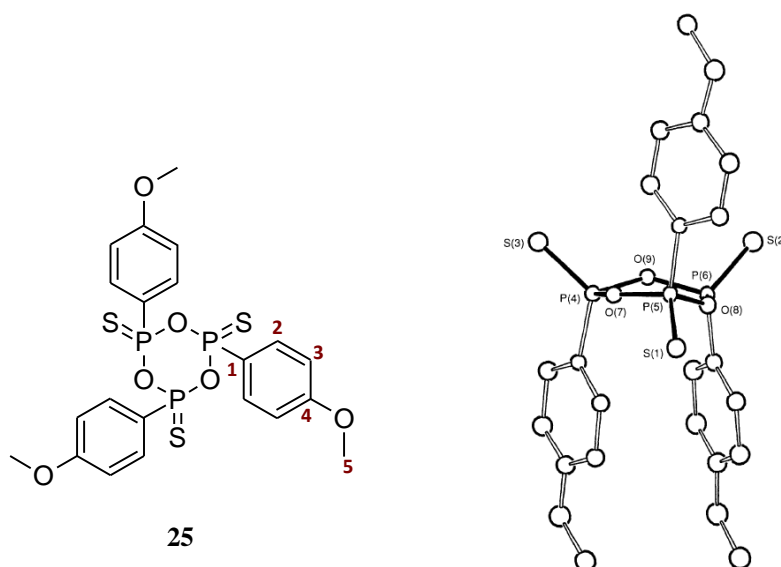


Figure 2-4 (Crystal Structure from Wen *et al.*)¹⁰¹

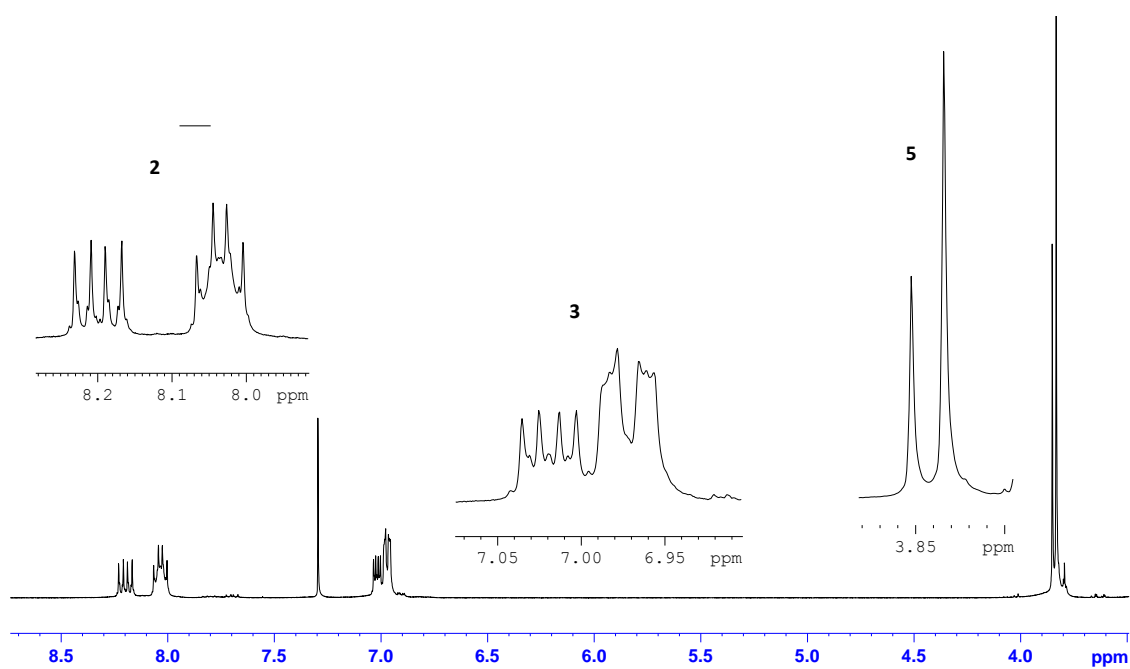


Figure 2-5.

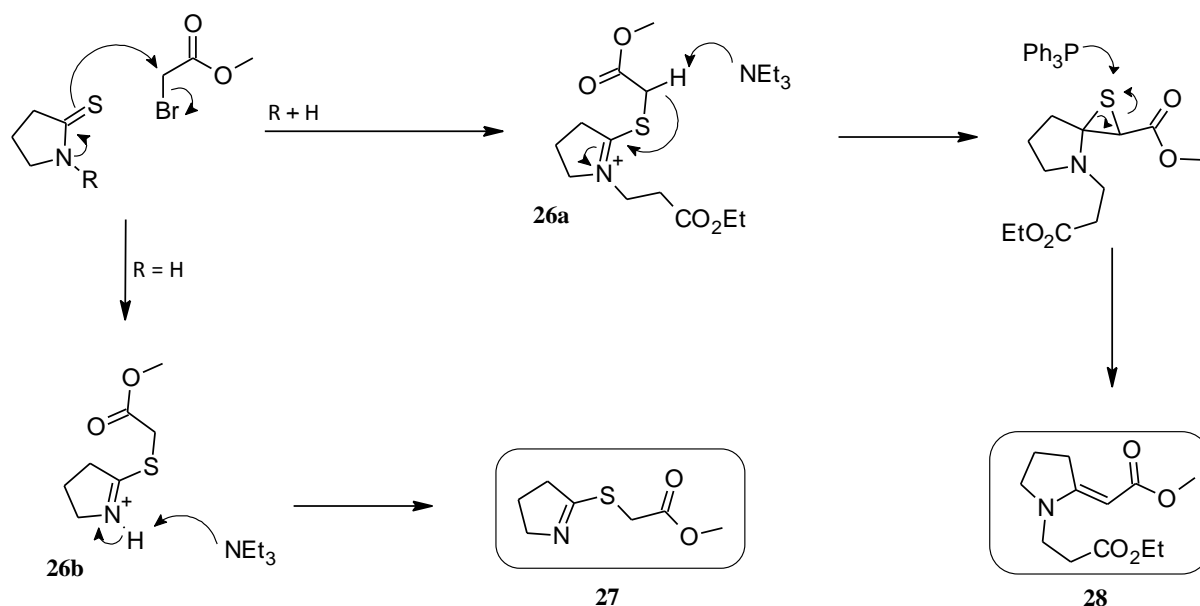
¹⁰¹ Wen, Bau and McKenna. *Journal of the Chemical Society. Chemical Communications* **1991**, 1223-1224.

The ^1H NMR spectrum (figure 2-5) of this trimeric by-product is in excellent agreement with literature, and interestingly produces separate shifts for one of the three aryl rings.^{102,103} This is a result of the three-dimensional orientation of the molecule illustrated by the X-Ray crystal structure in figure 2-4. The shifts to the left of each set correspond to the single aryl group oriented in the opposite direction to the other two.

2.3.2. SYNTHESIS OF ETHYL (PYRROLIDIN-2-YLIDENE)ETHANOATE (31)

With the thione in hand, it is possible to perform the Eschenmoser coupling, the condensation of a thioamide with an α -bromocarbonyl. However, an initial protection step of the nitrogen is essential, as thioimine side products are instead formed in high yield.

This reaction was observed by Russowsky *et al.* who have proposed a mechanism (see scheme 2-5) whereby this thioimine (**27**) forms.¹⁰⁴ This mechanism also accounts for the formation of thiozolidinones from piperidin-2-thione, although it is not included in this discussion.



Scheme 2-5

¹⁰² Lacroix, Rixhon and Marchand-Brynaert. *Synthesis* **2006**, 14, 2327-2334.

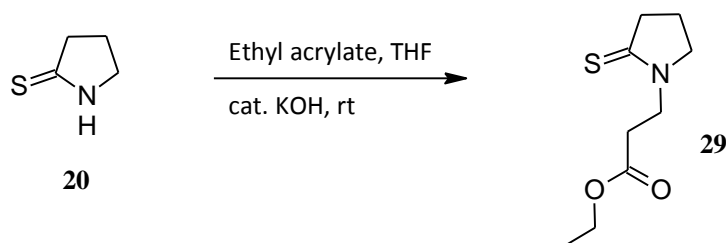
¹⁰³ Przychodzen. *European Journal of Organic Chemistry* **2007**, 2002-2014.

¹⁰⁴ Russowsky and Neto. *Tetrahedron Letters* **2004**, 45, 1437-1440.

The initial step of the Eschenmoser coupling involves nucleophilic attack, possibly *via* an S_N2 mechanism, on the bromoester by the thioamide, forming the thioiminium cation (**26**). It is at this point that the reaction pathway differs depending on whether the thioamide substrate possesses a secondary or tertiary amine moiety. Should the thioamide substrate be secondary (i.e. $R = H$), the base in this case, triethylamine, preferentially removes the more acidic thioiminium proton, resulting in the thioimine product (**27**).

If on the other hand, the thioamide substrate is tertiary (i.e. $R \neq H$), the most acidic proton present is located at the α -position of the bromoester carbonyl. Removal of this proton forms an intermediate possessing a three-member sulphur ring. The thiophile, triphenylphosphine, attacks the sulphur atom of this ring, removing it and consequently generating the β -enaminocarbonyl product (**28**).

Thus, in order to form the desired product (**28**), the amine moiety of pyrrolidin-2-thione was protected using ethyl acrylate, adducts of which have been shown to form in excellent yields and are reversible in the presence of a strong base.¹⁰⁵ The protection of the thiolactam was performed as shown in scheme 2-6.



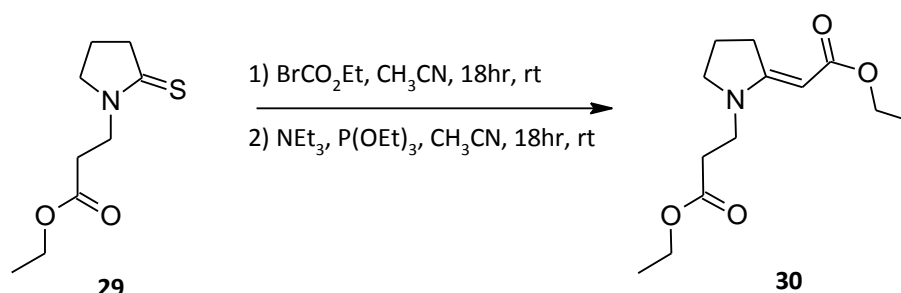
Scheme 2-6

Ethyl acrylate was added dropwise to a solution of pyrrolidin-2-thione (**20**) and a catalytic amount of base in dry THF, and allowed to stir overnight. TLC of the reaction mixture showed complete conversion of the starting material to a single spot at $R_f = 0.59$, corresponding to the protected thiolactam product (**29**). As this reaction proceeded especially cleanly, purification of the product involved simple liquid-liquid extraction in

¹⁰⁵ Robinson, Dovey and Gravestock. *European Journal of Organic Chemistry* **2005**, 505-511.

order to remove any base remaining in solution. Pure product was obtained from the organic layer in 91% yield as a pale yellow oil. NMR spectra, IR and MS data correspond well with literature.¹⁰⁶

Once the thiolactam had been protected, the Eschenmoser contraction could be performed.



Scheme 2-7

Ethyl bromoacetate was added dropwise to a solution of the protected thiolactam in dry acetonitrile and allowed to stir for 18hrs at room temperature. In order to obtain maximum conversion of the starting material, ethyl acrylate was added in 20% excess. To simplify the purification process, solvent and unreacted ethyl acrylate were removed *in vacuo*, leaving the yellow thioiminium salt (**26a**). This residue was redissolved in dry acetonitrile followed by addition of PPh₃ and NEt₃ as a solution in dry CH₃CN, and the mixture allowed to stir for a further 18hrs at room temperature. A liquid-liquid extraction was performed, and after removal of solvent from the combined extracts, a yellow oil was obtained which formed white crystals of PPh₃ on standing. Attempts to purify the oil resulted only in solidification of the material while loading onto a column or radial chromatography plate. What little product could be passed through silica could not be completely cleaned of triphenylphosphine residues. A second attempt using triethylphosphite as the thiophile was a great deal more successful as the by-products are easily removed in the aqueous phase of

¹⁰⁶ Michael, De Koning, Fat and Natrass. *ARKIVOK* **2002**, 9, 62-77.

the extraction. Subsequent radial chromatography of the remaining oil yields the β -enaminocarbonyl product in quantitative yield.

The (*E*)-geometry of the Eschenmoser product has been previously established by examining the chemical shift of the 3-methylene protons of the ring.¹⁰⁶ The proximity of the carbonyl group produces an anisotropic deshielding effect on these hydrogens, causing them to shift ~ 0.6 ppm downfield relative to the (*Z*)-isomer.¹⁰⁷ An NOE experiment on (**30**) shows clearly the NOE coupling of H-1'' to H-3' confirming the (*E*)-geometry of the double bond. Conversely, if the geometry were (*Z*), a coupling should be observed between protons H-1'' and H-3, however this is absent. The relevant NOE couplings are indicated in figure 2-7.

The fact that only the (*E*)-isomer of the product is obtained has to do with the direction of approach of the thiophile and the resulting transition intermediate. It is proposed that the steric bulk of the protecting acrylate group effectively shields approach of the bulky triphenylphosphine from this direction. Thus sulphur is removed from only one direction, producing (*E*)-(**30**). The (*E*)-isomer is in theory more stable than the (*Z*)-isomer due to formation of a six member ring (shown in blue on figure 2-x) with attractions between the 2'' carbonyl oxygen and H-3, although there is no experimental evidence of this.

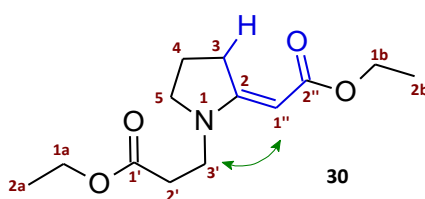


Figure 2-6

The NOE coupling observed in figure 2-7 is indicated by a green arrow.

¹⁰⁷ Roth, Dubs, Gotschi and Eschenmoser. *Helvetica Chimica Acta* **1971**, 54, 710.

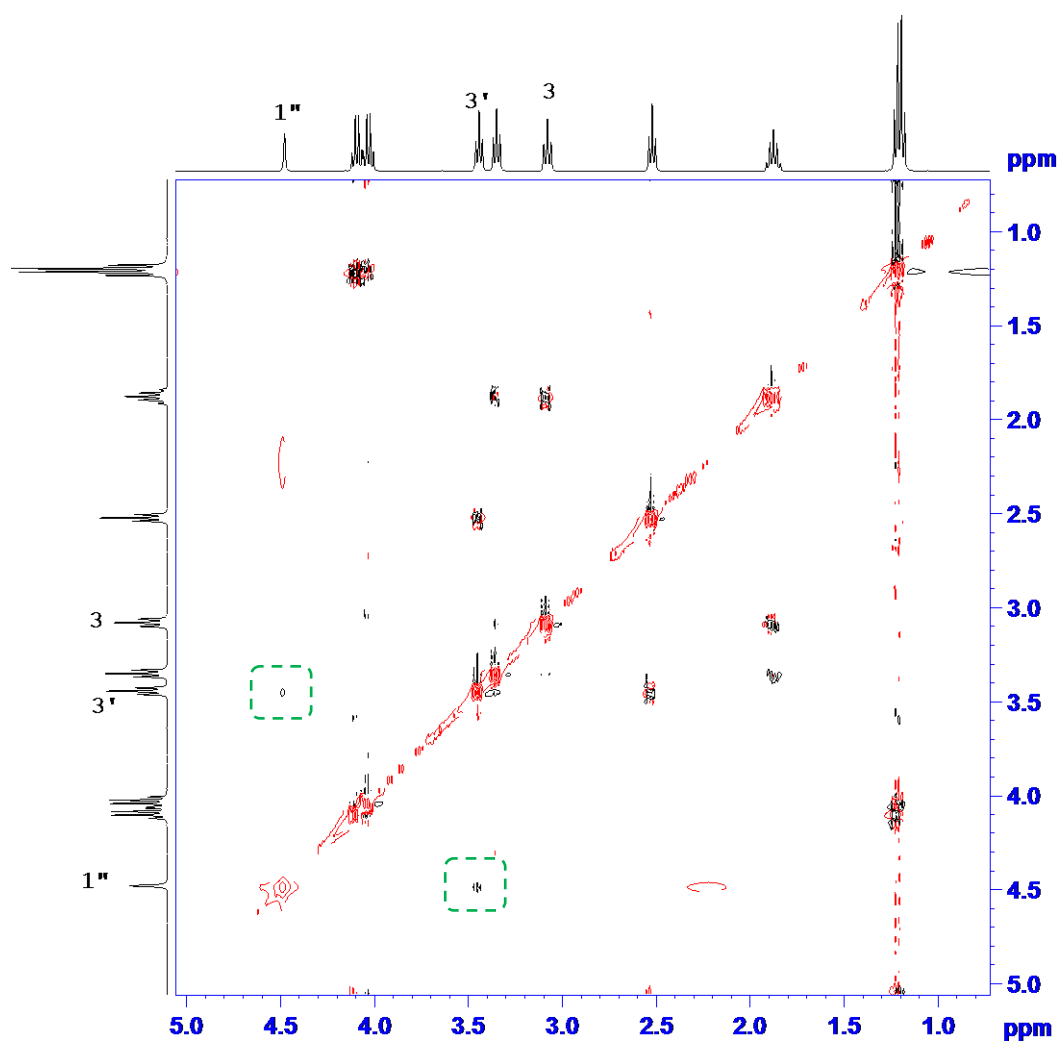
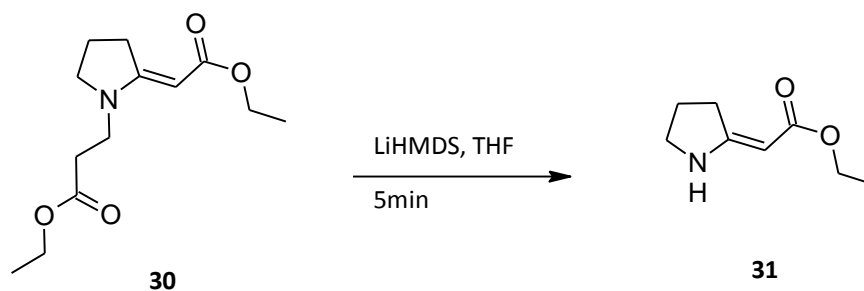


Figure 2-7 – NOESY of (30)

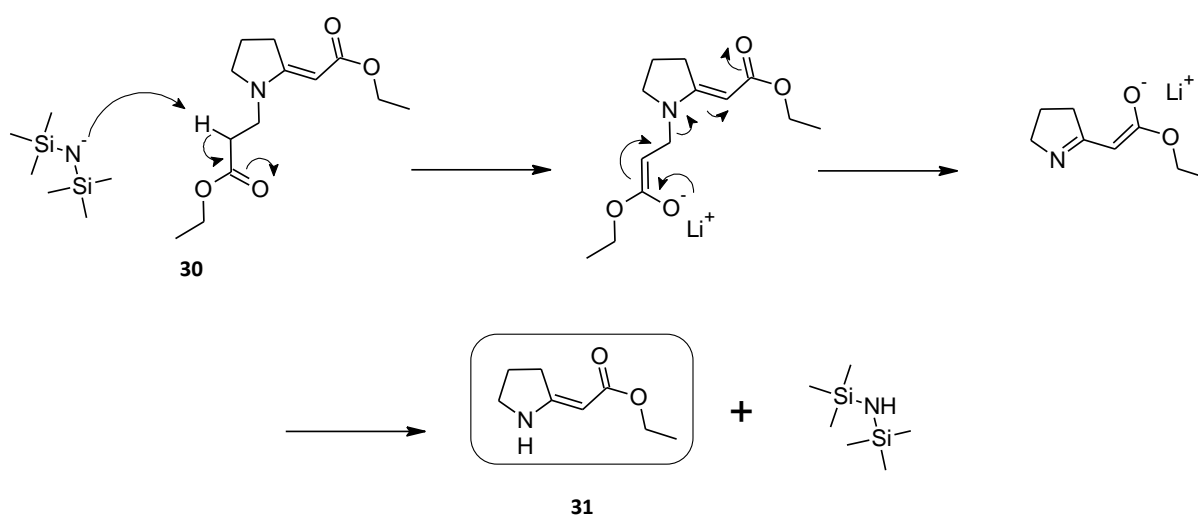
In removing the protecting acrylate, it has been reported that transesterification within the starting material can occur;¹⁰⁵ thus in the previous two steps the reagents of choice include the same ester functionality. The first reported case of such a deprotection involved removal of a similar adduct, acrylonitrile, by excess potassium *tert*-butoxide.¹⁰⁸

¹⁰⁸ Michael and Parsons. *Tetrahedron* **1996**, 52, 2199-2216.



Scheme 2-8

The acrylate group was removed by treatment with 2 equivalents of LiHMDS in dry THF (to allow for decomposition in the process of weighing). The excess of LiHMDS is needed due to the fact that the hydrogen at the α -position to the bromoester carbonyl is also acidic and will be removed in addition to those at the α -position to the acrylate carbonyl (refer to scheme 2-9).



Scheme 2-9

LiHMDS acts as a non-nucleophilic base and abstracts a hydrogen from the α -position to the “acrylate” carbonyl. The resulting enolate undergoes fission and subsequent quenching with NH_4Cl yields the product **31** in 26% yield after purification. TLC of the reaction mixture revealed complete consumption of the starting material, a major spot at $R_f = 0.62$ (1:1

EtOAc-hex) corresponding to the product, and a faint minor spot at $R_f = 0.28$. Attempts to isolate the minor spot proved to be fruitless as there was insufficient material for analysis. Initially, it seemed possible that the product was remaining in salt form, thus remaining in the aqueous phase during extraction and resulting in the low yield. So, in a subsequent reaction, the aqueous phase was acidified with HCl (2N) before extraction. This however did not yield any improved results, and it was found that the quantity of crude material extracted from the organic phase was little more than that of the purified product. This confirmed the suspicion that material was being lost to the aqueous phase. In an effort to determine what happened to the remainder of the starting material, it was found in literature that LiHMDS exists in THF as a disolvated dimer (**32**), illustrated in Figure 2-8.¹⁰⁹

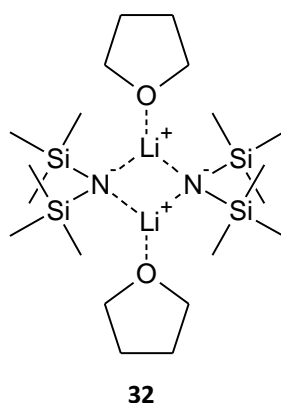


Figure 2-8

An additional research paper reported amine solvates of LiHMDS,¹¹⁰ and as a result it is not inconceivable for a similar dimer to form with complexed molecules of product (**31**). Considering the charges on this complex, it may be possible for this to be water soluble, although there is no experimental evidence to support this.

¹⁰⁹ Popenova, Mawhinney and Schreckenbach. *Inorganic Chemistry* **2007**, 46, 3856-3864.

¹¹⁰ ^a Lucht, Bernstein, Remenar and Collum. *Journal of the American Chemical Society* **1996**, 118, 10707-10718, Lucht and Collum. *Journal of the American Chemical Society* **1996**, 118, 2217-2225.

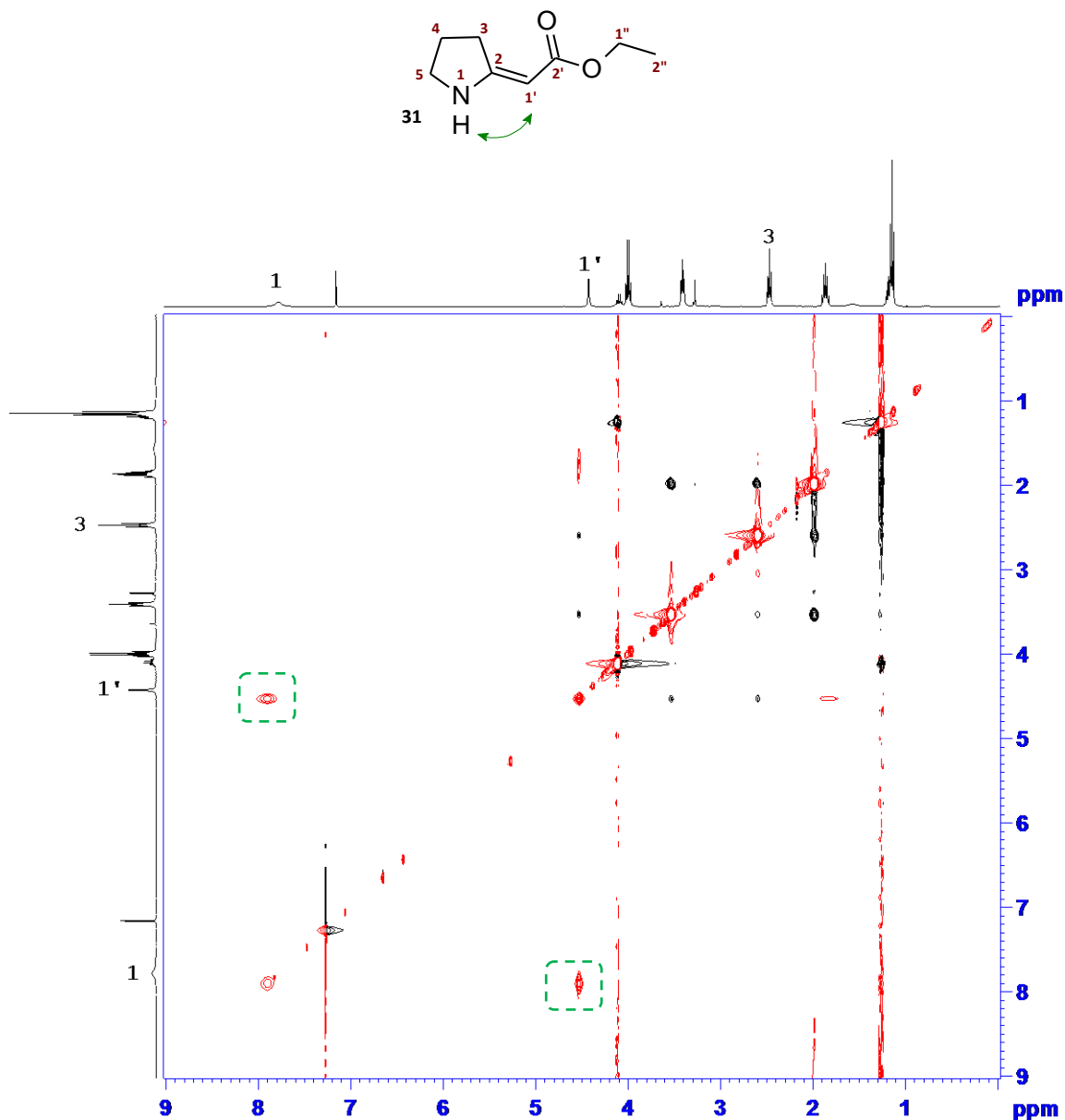


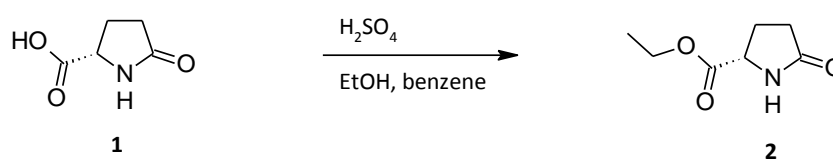
Figure 2-9 – NOESY of (**31**)

An NOE spectrum of the product (**31**) shows that the stereochemistry of the (*E*)-double bond is surprisingly retained through the deprotection step. This is observed from the coupling of the amine proton H-1 with H-1', whereas in the (*Z*)-geometry we would observe coupling between protons H-1' and H-3 (although there is a small amount of this isomer present). This isomerization of the double bond is expected if the proton at position 1'' of (**30**) were removed during the deprotection step by excess of the base.

2.4. STEPS TOWARD 223AB

2.4.1. SYNTHESIS OF (S)-5-(HYDROXYMETHYL)PYRROLIDIN-2-ONE (3)

In order to convert the carboxylic acid group of (S)-pyroglutamic acid (**1**) to the alcohol, it was first necessary to convert the carboxylic acid group to an ester (see scheme 2-10), which is able to be reduced by NaBH₄ (the choice of which is discussed in the next step), whereas the acid is not.

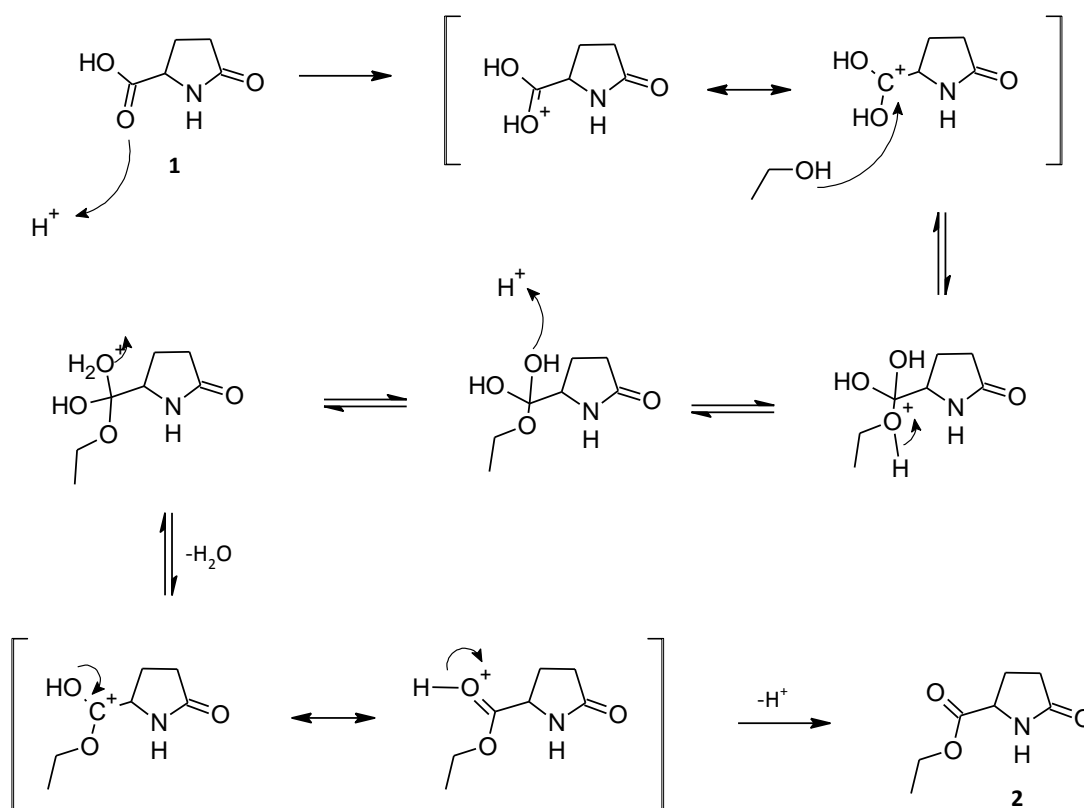


Scheme 2-10

This was achieved using the Fischer esterification as shown in scheme 2-10. Another method to achieve this is by converting the carboxylic acid to the acid chloride using SOCl₂, followed by substitution of the chloride by ethanol. This route, however, requires the use of thionyl chloride as well as dry reaction conditions and solvents. Although this method was attempted due to the lure of a one-pot reaction, simplified purification and high yields as reported in the literature, it in fact afforded extremely low yields and was not pursued further.^{111,112}

¹¹¹ Elliot and Long. *Organic and Biomolecular Chemistry* **2004**, 2, 2003-2011.

¹¹² Williams, Wade, Clarkson and Wills. *Tetrahedron: Asymmetry* **2007**, 18, 664-670.



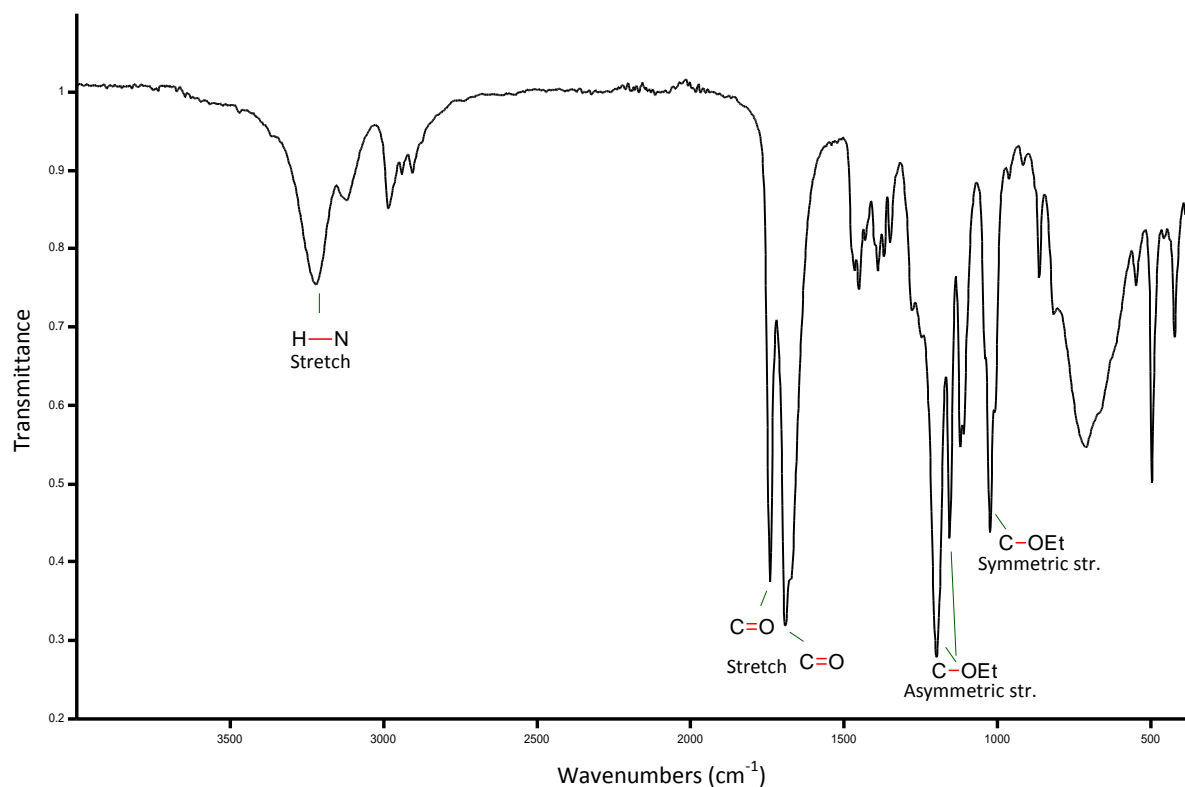
Scheme 2-11

The Fischer esterification is initiated by transfer of a proton from the acid catalyst to the carbonyl carbon of (**1**) resulting in a more reactive electrophilic carbocation. Nucleophilic attack of the alcohol oxygen on the carbonyl carbon leads to formation of the oxonium ion, a proton of which is removed by a second molecule of alcohol. Protonation of one of the hydroxyl groups yields a second oxonium ion which is lost as water. Deprotonation results in formation of the ester product (**2**) while simultaneously regenerating the acid catalyst.

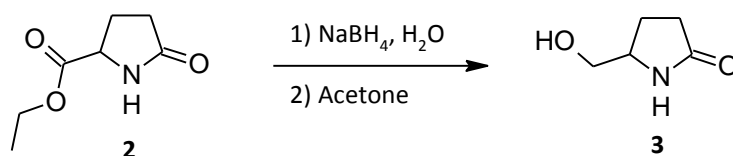
The (*S*)-pyroglutamic acid (**1**) was refluxed for 5 hours in benzene in the presence of a catalytic quantity of H_2SO_4 and an excess of ethanol. In order to remove the water produced during the course of the reaction, a Dean & Stark apparatus was used. TLC of the reaction mixture showed complete conversion of the starting material with two new spots. The higher spot of $R_f = 0.75$ (100% EtOH) corresponds to the desired product. The lower spot of $R_f = 0.44$ (100% EtOH) was very faint and corresponds to the ring opened product of ethanol addition into the ring. Due to the nature of these compounds, they are not visible under UV irradiation and an acidified $KMnO_4$ stain was used to visualize the TLC plates. Purification of

the product by column chromatography did not seem a viable option considering the high polarity of the compounds, thus after consulting literature on the relevant boiling points a distillation was performed. In this manner, the ring opened product was found to distil off first, followed by the desired ethyl glutamic acid (**2**). Initially, a short-path distillation was performed under vacuum; however the extremely high temperatures required caused complications regarding decomposition of the mixture. For this reason (as well as ease of purification), distillation using a Kugel-Röhr apparatus was preferred. However, using this approach, we were unable to isolate any of the ring opened product. The product was obtained as a clear oil which formed a white solid on cooling in 71% yield. Storage and analysis of the product proved difficult as it quickly absorbed moisture and solvent present in the air, causing it to liquefy. The IR spectrum shows the characteristic bands at 3220, 1740 and 1692 cm^{-1} corresponding to stretching of the amide N-H and two carbonyls respectively. Presence of the ester functionality is confirmed by absence of the broad carboxylic acid O-H stretch at *ca.* $\sim 3500\text{-}2500\text{ cm}^{-1}$, and presence of the dual C-O stretching bands at 1199 and 1156 cm^{-1} absent in the starting material.¹¹³

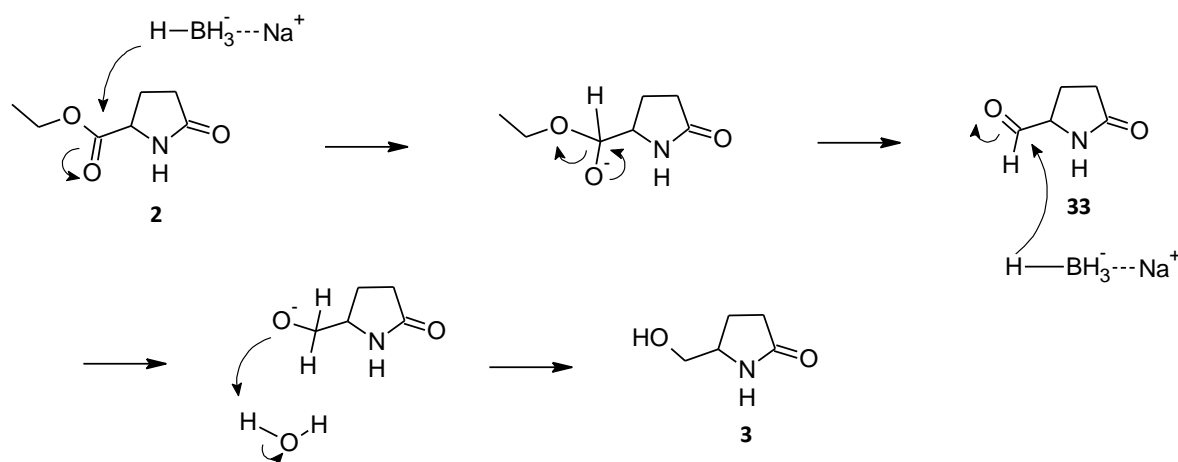
¹¹³ sigmaaldrich. In <http://www.sigmaaldrich.com/spectra/rair/RAIR014161.PDF>, October 27, 2008.

**Figure 2-10**

Once the carboxylic acid functionality has been converted into an ester, reduction to the alcohol may be carried out. The reaction was performed as shown in scheme 2-12.

**Scheme 2-12**

NaBH₄ was chosen as the reducing agent as, unlike LiAlH₄, it will selectively reduce the ester while leaving the amide moiety of the molecule intact.

**Scheme 2-13**

The reaction is initiated by hydride transfer from NaBH_4 to the electropositive carbonyl carbon of (**2**).¹¹⁴ This results in loss of the ethoxy group to form an intermediate aldehyde (**33**). A further reduction by NaBH_4 , followed by removal of a proton from an equivalent of solvent generates the fully reduced alcohol (**3**). Each subsequently removed hydride of NaBH_4 is replaced by the hydroxide ions generated from water during the course of the reaction, ultimately forming NaOH and B(OH)_3 .

For the purposes of isolation and characterization of (**3**), this reaction was carried out using ethanol as solvent, however subsequent reactions were performed in water and without further purification, used in the next step.

NaBH_4 was added in small portions to the cooled stirring solution of (**2**). After 2 hours, the reaction was quenched with acetone and filtered through a silica plug to remove residue of the boric acid derivative which was found to obstruct solvent flow through silica. A liquid-liquid extraction was not performed, since it was speculated that the product may be soluble in the aqueous layer. Although neither product nor starting material is UV-active, it was found that the solvent system used for purification caused the silica to become semi-transparent, allowing observation of the compounds as opaque white bands. The product was obtained as white crystals in 92% yield after purification. ^1H and ^{13}C NMR spectra are in

¹¹⁴ Fox and Whitesell *Organic Chemistry, Second Edition*; Jones and Bartlett: London, 1997.

accord with literature.¹¹⁵ The IR spectrum shows the O-H and N-H stretches at 3251 and 2922 cm^{-1} , as well as disappearance of the ester bands and one of the carbonyl stretching frequencies leaving only the amide carbonyl band at 1668 cm^{-1} .

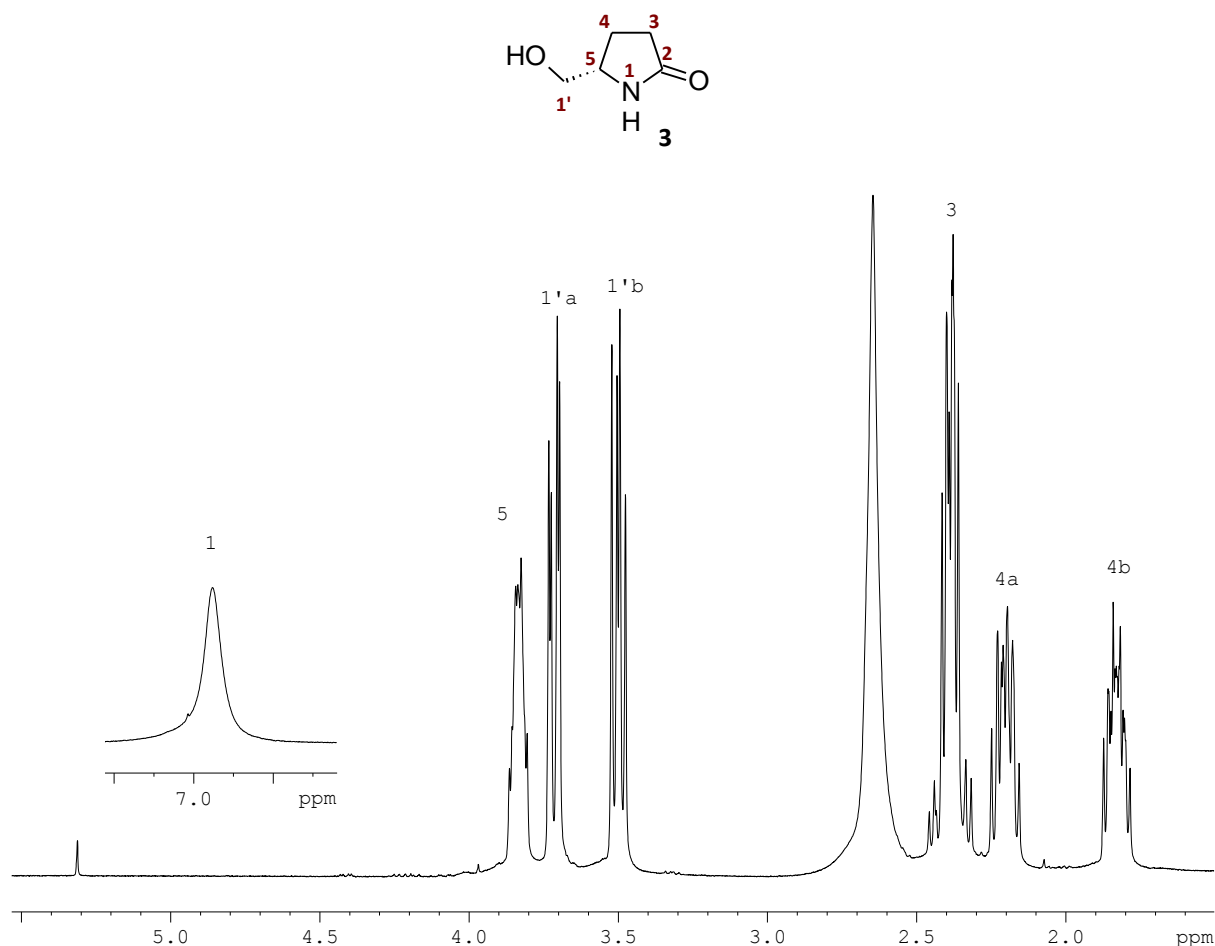


Figure 2-11

From the ^1H NMR spectrum, it can be seen that the methylene protons at positions 1' and 4 have each been split into separate signals. This effect is a result of the stereogenic centre at position 5, causing these protons to be diastereotopic. This assignment was made based on 2D NMR spectroscopy, the COSY of which is shown in figure 2-12. The OH signal is not visible due to proton exchange.

¹¹⁵ Bateman, Breeden and O'Leary. *Tetrahedron: Asymmetry* **2008**, 19, 391-396.

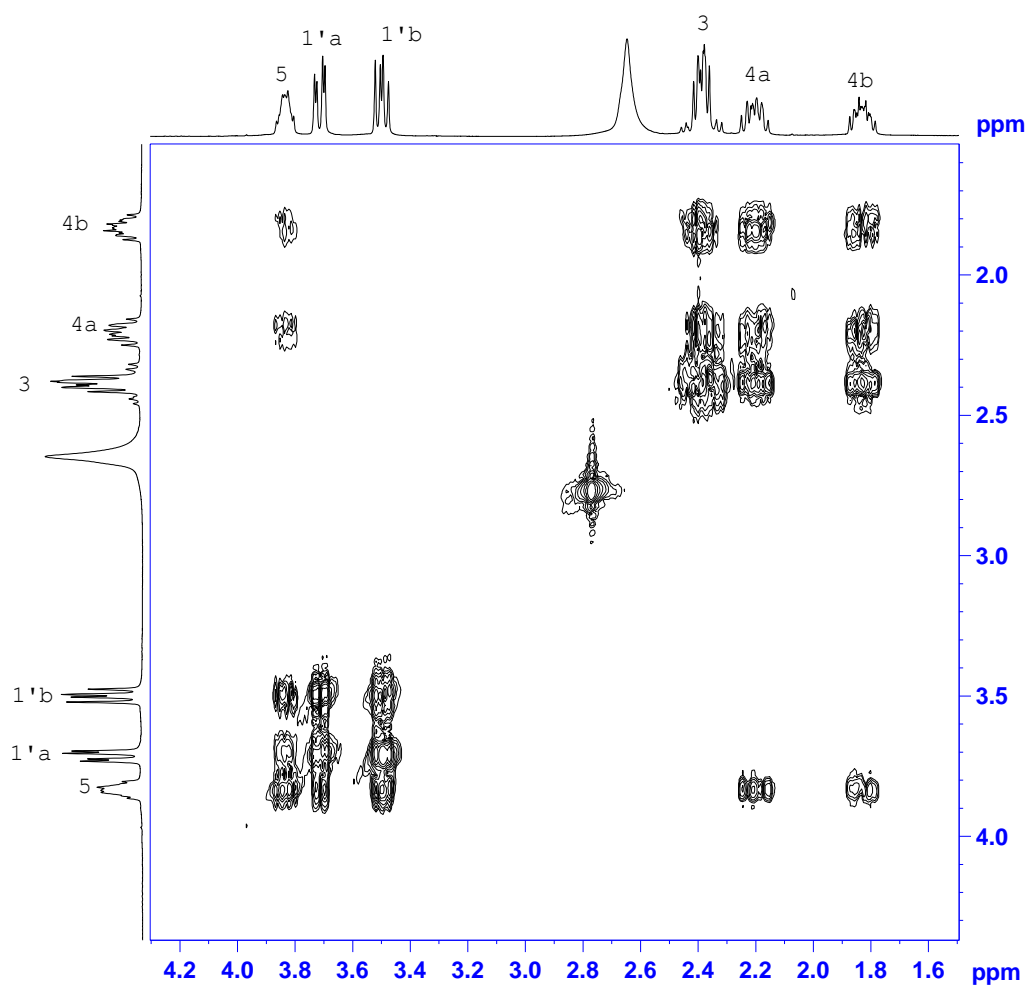


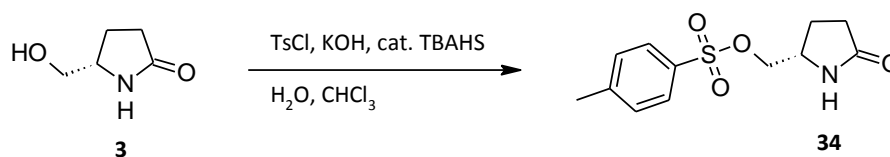
Figure 2-12

The optical rotations of compounds (**2**) and (**3**) were observed to be $+3.86^\circ$ and $+26.47^\circ$ respectively, corresponding well with literature values of $+3.5^\circ$ and $+29.2^\circ$.^{115,116} This confirms that chirality of these compounds is preserved through the esterification and reduction steps.

2.4.2. SYNTHESIS OF (*R*)-5-BUTYLPYRROLIDIN-2-ONE (**35**)

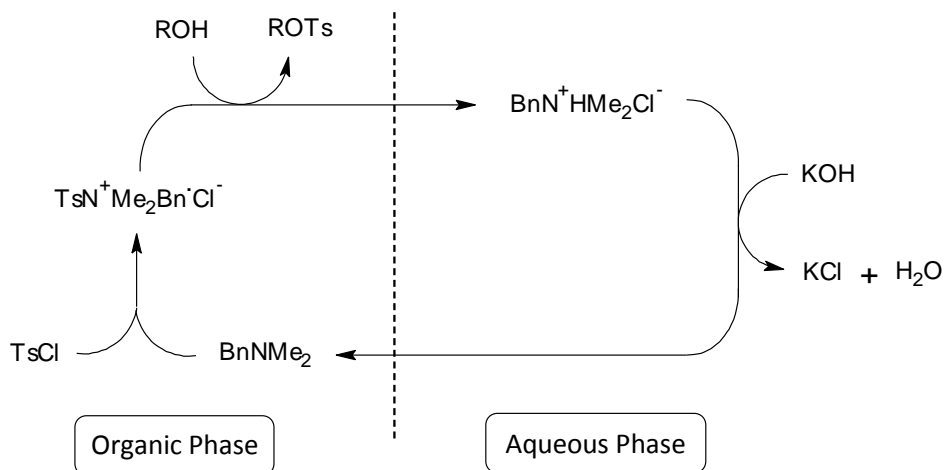
The next step in the synthetic route involves tosylation of the alcohol (**3**), forming the substrate for subsequent cross-coupling, and completing the 3-substituent of the target molecule **223AB**.

¹¹⁶ sigmaaldrich. In <http://www.sigmaaldrich.com/catalog/search/ProductDetail/FLUKA/83175>, October 21, 2008.



Scheme 2-14

The synthesis was carried out as shown in scheme 2-14. As mentioned earlier, synthesis of (**3**) was performed in water, after which the reaction mixture was used ‘as is’ for the tosylation step. Traditionally, due to the sensitivity of tosyl chloride to moisture, these reactions need to be performed under anhydrous conditions and normally in the presence of 10 eq. pyridine. Becoming increasingly popular for these reactions is the modified Schotten-Baumann-type method. The proposed catalytic cycle is shown in scheme 2-15 below.



Scheme 2-15

(graphic adapted from Morita *et al.* ¹¹⁷)

The function of potassium hydroxide is to basify the aqueous reaction solution, a study on which has shown that higher pH prevents the hydrolysis of tosyl chloride,¹¹⁸ thus removing

¹¹⁷ Morita, Nakatsuji, Misaki and Tanabe. *Green Chemistry* **2005**, 7, 711-715.

the necessity of anhydrous reaction conditions. Another side reaction that must be taken into consideration is the chlorination of the tosylated product by the acid by-product. The presence of water in the biphasic solvent system also eliminates the requirement for excess amine base to scavenge this acid as it moves from the organic (reaction) phase into the aqueous.¹¹⁹

Tosyl chloride and BnNMe_2 form the reactive sulphonylammonium salt in the organic phase which subsequently reacts with the alcohol, producing the tosylated product and $\text{BnN}^+\text{HMe}_2\text{Cl}^-$ the latter of which moves into the aqueous phase. In this phase, the catalyst, BnNMe_2 is regenerated by neutralization with potassium hydroxide to produce KCl and water. The catalyst now moves back into the organic phase and the cycle continues.

The method followed for the synthesis of (**34**) follows that of Chen *et al.*¹²⁰ To an aqueous solution of the alcohol (**3**) is added excess potassium hydroxide (to maintain a high pH environment) and a catalytic amount of tetrabutylammonium hydrogen sulphate (a phase transfer catalyst). This is diluted with an equal volume of chloroform and the resulting solution is immersed in a sonic bath equipped with an underwater stirrer. To this stirring reaction solution is added the tosyl chloride in two portions. After stirring in the sonic bath for 3 days (unoptimised), the chloroform layer was withdrawn and the aqueous layer extracted with CH_2Cl_2 . The organic extracts were combined and solvent removed *in vacuo*, leaving an off-white residue. The product was recrystallised from hot toluene to leave shiny white crystals in 71% yield over two steps. The sonic bath serves to emulsify the bilayer reaction mixture, and has been shown to improve reaction rates and yields by the phenomenon of cavitation.¹²¹

Since the tosylated alcohol (**34**) was synthesized without purification of the intermediate alcohol (**3**), it was found to be necessary to filter this aqueous reaction mixture through a

¹¹⁸ King, Rathore, Lam, Guo and Klassen. *Journal of the American Chemical Society* **1992**, 114, 3028-3033.

¹¹⁹ Deng and Mani. *Green Chemistry* **2006**, 8, 835-838.

¹²⁰ Chen, Suh and Smith. *Journal of the Chemical Society. Perkin Transactions I* **1995**, 1317-1322.

¹²¹ Mason. *Chemical Society Reviews* **1997**, 26, 443-451.

silica plug (removing boric acid residues) prior to continuing with the subsequent step. In the case where this was not done, a translucent sticky white solid formed around the walls of the reaction vessel and in the separating funnel and a minimal amount of product was obtained from the organic extracts. Analysis of this glass-like solid could not be performed as all attempts to dissolve it proved unsuccessful.

^1H and ^{13}C NMR spectra correspond to those from literature.¹²² GC-MS analysis of compound (**3**) revealed the base peak at m/z 84 corresponds to loss of the hydroxymethyl substituent forming the oxopyrrolidinide ion. This forms so easily that in fact the molecular ion is entirely absent.

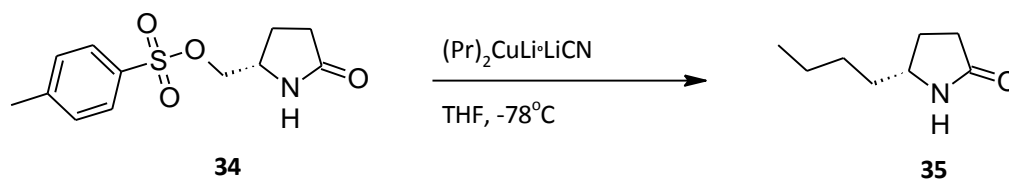
Subsequent analysis by direct injection into a TOF MS in ES^- mode provided a molecular ion of m/z 114.0574 $[\text{M}-\text{H}]^-$. Elemental analysis revealed the formula to be $\text{C}_5\text{H}_8\text{NO}_2$ with a calculated mass of 114.0555.

GC-MS analysis of tosylated (**34**) was of no use as the compound decomposed within the heating chamber. Thus, direct injection was performed as above yielding a molecular ion of m/z 268.0702 $[\text{M}-\text{H}]^-$. Elemental analysis yielded a formula of $\text{C}_{12}\text{H}_{14}\text{NO}_4\text{S}$ with a calculated mass of 268.0644.

To prepare the butyl side chain of the target molecule, a cross-coupling reaction of the tosylate with a Gilman reagent was chosen. The ease of preparation and high yields of reaction for the tosylated reagent as well as the coupling makes this reaction more feasible than other alternatives. The use of organocuprates also circumvents competing reactions such as eliminations, metal-halogen exchange, α -metallation and extraneous coupling reactions that are common in other organometallic reagents.¹²³ The Gilman reagent is a reactive lithium diorganocuprate obtained from reaction of cuprous cyanide with an alkyl lithium forming a complex of the general formula $\text{R}_2\text{CuLi}\cdot\text{LiCN}$. The reaction was carried out as depicted in scheme 2-16.

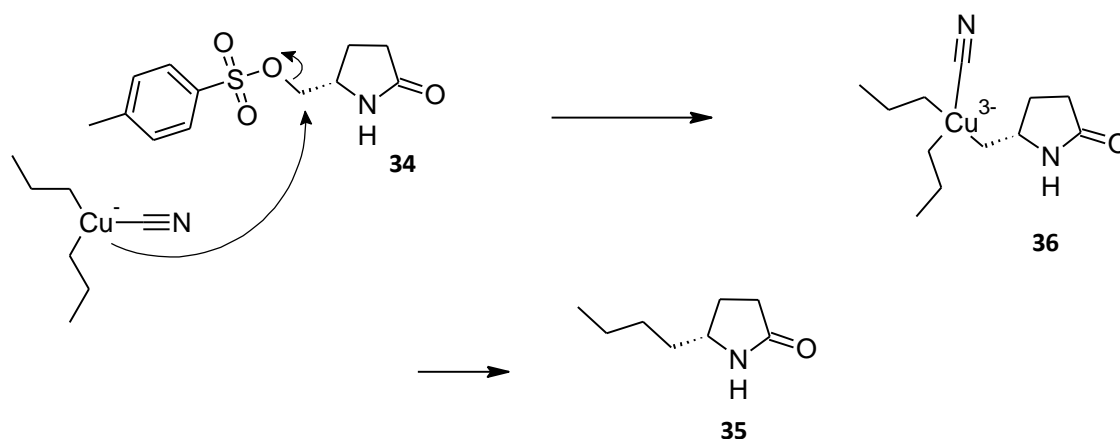
¹²² Kamimura, Nagata, Kadowaki, Uchida and Uno. *Tetrahedron* **2007**, 63, 11856-11861.

¹²³ Johnson and Dutra. *Journal of the American Chemical Society* **1973**, 95, 7777-7782.



Scheme 2-16

A mechanism for the action of these organocuprates was postulated by Johnson *et al.* in 1972¹²⁴ based on empirical deduction, and is shown in scheme 2-17.



Scheme 2-17

Organocuprates differ from other organometallic reagents such as Grignard or organolithiums in that the attacking nucleophilic centre is the copper rather than carbon atom. This accounts for the unusual nucleophilicity of these reagents. For reasons not recounted here, it was proposed that the copper intermediate must be square-planar Cu(III) . The diorganocuprate reagent attacks the electrophilic carbon of the tosylate (**34**) *via* an $\text{S}_{\text{N}}2$ -like substitution mechanism, forming a transient Cu(III) complex (**36**). The carbon-carbon bond is subsequently formed by reductive elimination from this intermediate, forming the product (**35**). Because the nucleophilic attack occurs in an $\text{S}_{\text{N}}2$ manner, should the electrophilic carbon centre of the tosylate be chiral, an inversion of stereochemistry

¹²⁴ Johnson and Dutra. *Journal of the American Chemical Society* **1973**, 95, 7783-7788.

would result. Another factor to take into account for this reaction is that for secondary tosylates, there will be a competing elimination reaction.

This mechanism has only recently been confirmed by Bertz *et al.* in a publication on the preparation and NMR spectroscopic characterisation of a sufficiently stable Cu(III) intermediate.¹²⁵ A representation of which is shown in figure 2-13.

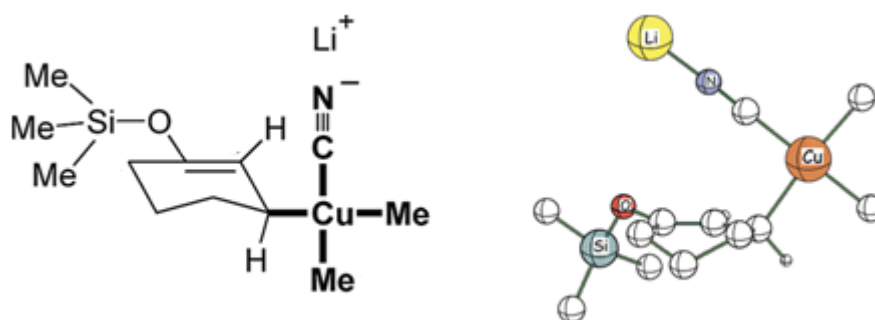


Figure 2-13.¹²⁴

This has positively confirmed that the mechanism proceeds through a triorganocuprate Cu(III) intermediate, and that it is in fact square planar as originally postulated by Johnson *et al.*¹²³

The Gilman reagent was prepared in situ, prior to addition of the tosylate reactant (**34**). Mechanistic studies have shown that for high yielding reactions, an excess of 2-5 equivalents of the reagent are necessary due to decomposition of the cuprate at higher temperatures.¹²⁶ Following the procedure of Pilli *et al.*,¹²⁶ *n*-propyllithium in hexane was added dropwise to a vigorously stirring solution of CuCN in dry THF kept at -78°C for 2 hours, after which a solution of the tosylate (**34**) in dry THF was transferred into the reaction vessel and stirred for an additional 4 hours at -78°C and subsequently overnight at room temperature. After quenching the reaction with a saturated ammonium chloride

¹²⁵ Bertz, Cope, Murphy, Ogle and Taylor. *Journal of the American Chemical Society* **2007**, 129, 7208-7209.

¹²⁶ Pilli, Dias and Maldaner. *Journal of Organic Chemistry* **1995**, 60, 717-722.

solution and dilution with water, solvent was removed *in vacuo* and a liquid-liquid extraction performed using CH_2Cl_2 . The organic extracts were combined and solvent removed *in vacuo* to leave a green oil. A ^1H NMR spectrum of this substance revealed surprisingly, not the expected product, but the brominated derivative (**37**) in 98% yield (based on NMR relative to starting material).

Figure 2-14 shows the superposition of ^1H NMR spectra of the alcohol (**3**), bromo derivative (**37**) and tosylate (**34**). As can be seen, the spectrum of the bromo derivative is distinctly different from those of the tosylate and alcohol. The most significant difference is the upfield shift of the $-\text{CH}_2-$ group attached to bromine. The ^1H NMR spectrum (of **37**) correlates faultlessly to that from literature.¹²⁷

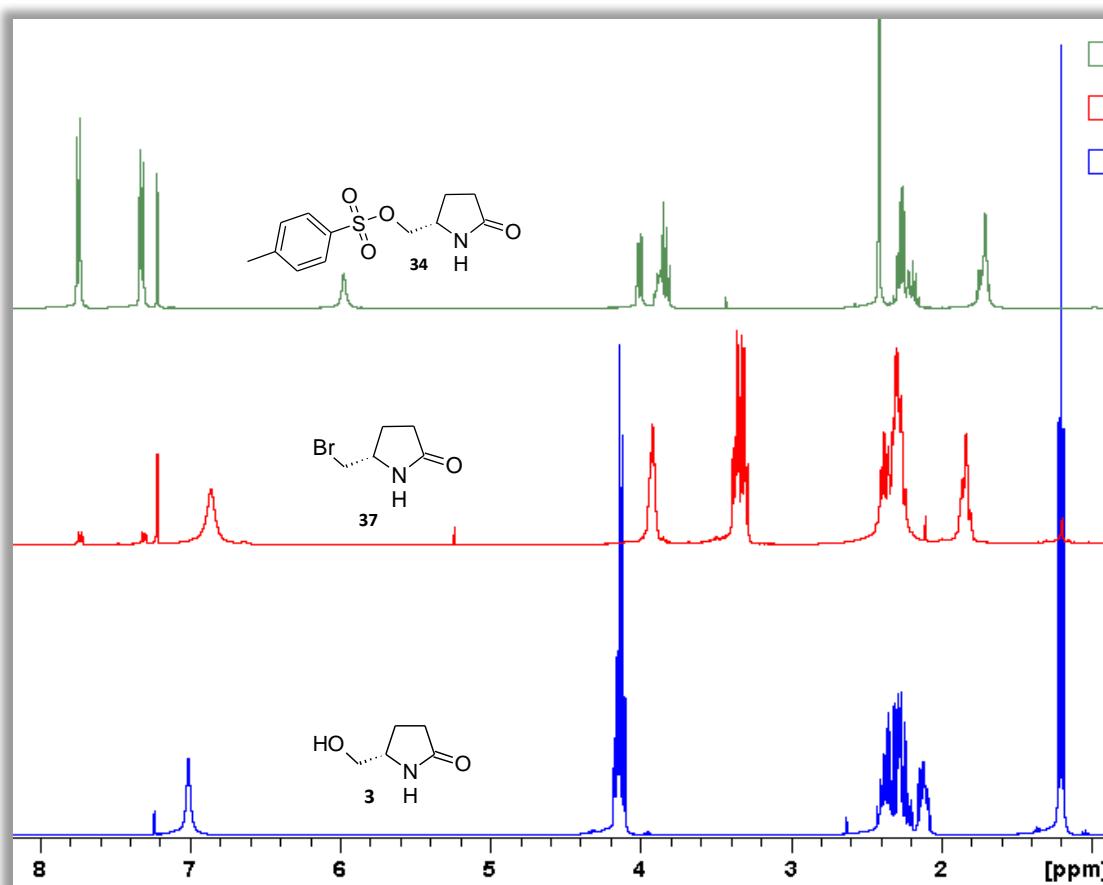


Figure 2-14

¹²⁷ Otsuka, Masuda, Haupt, Ohno, Shiraki, Sugiura and Maeda. *Journal of the American Chemical Society* **1990**, 112, 838-845.

Since the *n*-PrLi was prepared from lithium metal and propyl bromide, the bromination occurred as a result of the LiBr side-product still present in solution. To avoid this problem, an alkyl chloride should rather be used in the preparation, as the less soluble LiCl precipitates out of solution eliminating this possibility of halogenation.

In order to determine the efficacy of this reaction, the procedure was repeated using commercial *n*-butyllithium. Removal of solvent from the combined organic extracts yielded a yellow oil which was purified by radial chromatography to provide the (*R*)-5-pentylpyrrolidin-2-one product (**38**) in quantitative yield.

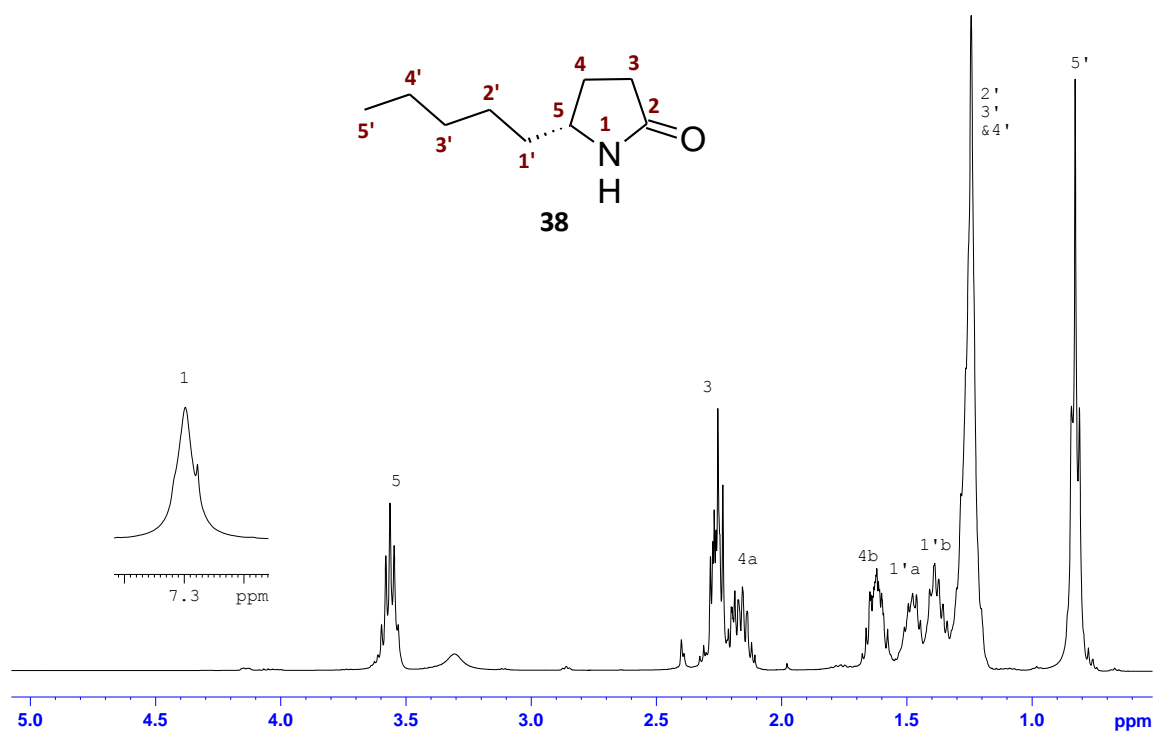


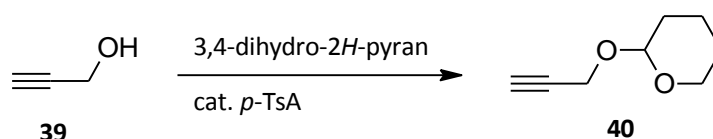
Figure 2-15

These ^1H and ^{13}C NMR spectra correspond to literature.¹²⁸

¹²⁸ Holmes, Smith, Williams and Hughes. *Journal of Organic Chemistry* **1991**, 56, 1393-1405.

2.4.3. SYNTHESIS OF HEPT-2-YN-1-OL (42)

To obtain the butyl group at position 3 of the target alkaloid, the chain length of the alkynyl bromide used to form (10) (please refer to page 49) for the hydroamination step may be varied. To do this, an alkyl chain is attached to propargyl alcohol (39) followed by subsequent bromination. The first step in this process is protection of the alcohol functionality as shown in scheme 2-18.



Scheme 2-18

It is necessary to protect the alcohol before alkylation, to prevent the undesired abstraction of the –OH proton.

To a solution of pre-distilled dihydropyran and propargyl alcohol (39) in CH₂Cl₂ (1.2:1 ratio) was added a catalytic amount of *p*-TsA and the mixture allowed to stir for 3 hours. The reaction mixture was neutralised with NaHCO₃, diluted with water and extracted with CH₂Cl₂. The organic extracts were combined and the solvent removed *in vacuo* to leave a green oil which was filtered through a silica plug to yield the crude product as a yellow oil. This was purified by column chromatography to yield the product as a pale yellow oil. It was observed that deprotection of the product occurred after purification, possibly due to the slight acidity of the silica. Thus in order to obtain the purest product possible for subsequent alkylation (hence simplifying purification of the latter), the propargyl alcohol and DHP were reacted neat in a 1:1 ratio with a single crystal of *p*-TsA. After stirring for 3 hours, the mixture turned from clear to a pale yellow generating pure product in quantitative yield.

As such an insignificant quantity of catalyst was added, no purification was necessary and this mixture could be stored for extended periods of time without any observable deprotection of 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (40) due to residual acid catalyst.

^1H and ^{13}C NMR, IR and MS spectra correspond impeccably with literature.^{129, 130} Assignments in the ^1H NMR are shown in figure 2-16.

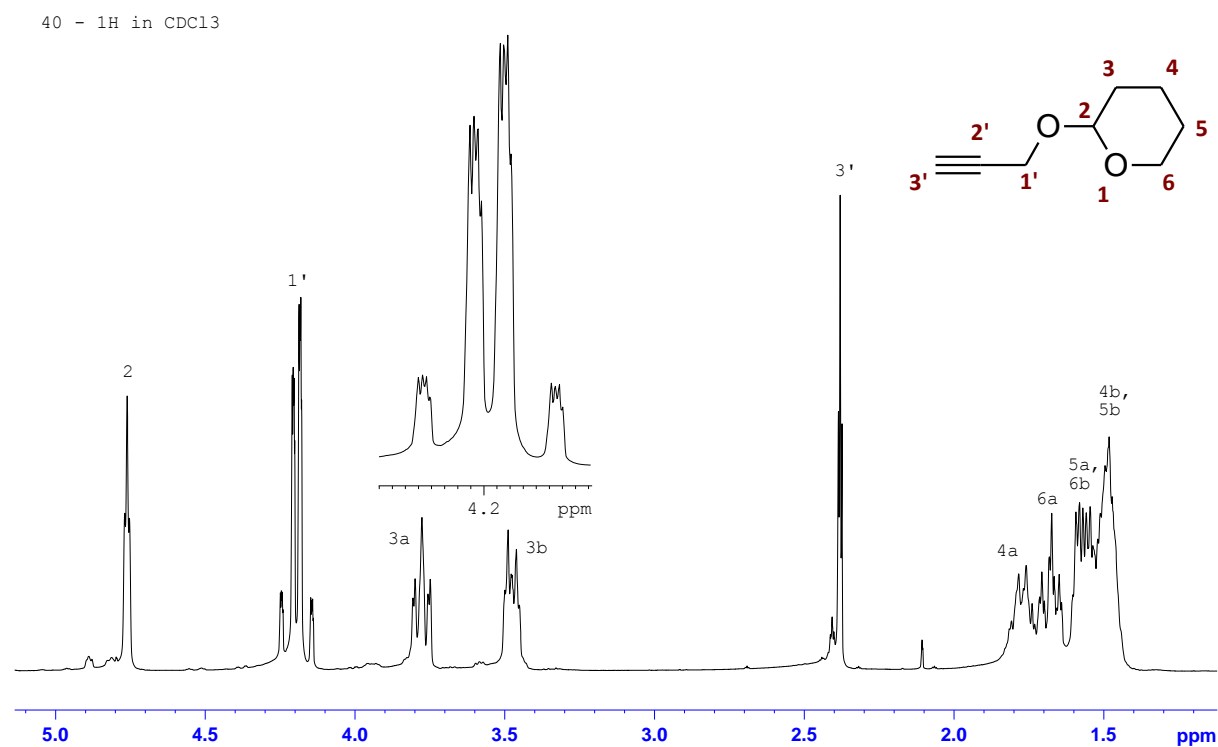
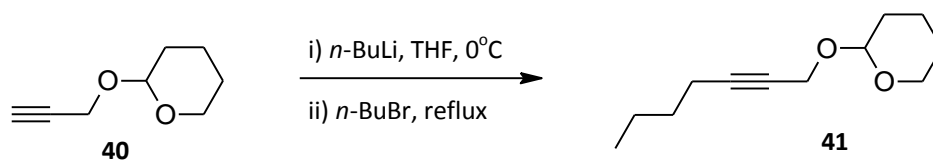


Figure 2-16

The subsequent step involves deprotonation at the terminal position of the alkyne followed by alkylation as shown in scheme 2-19.



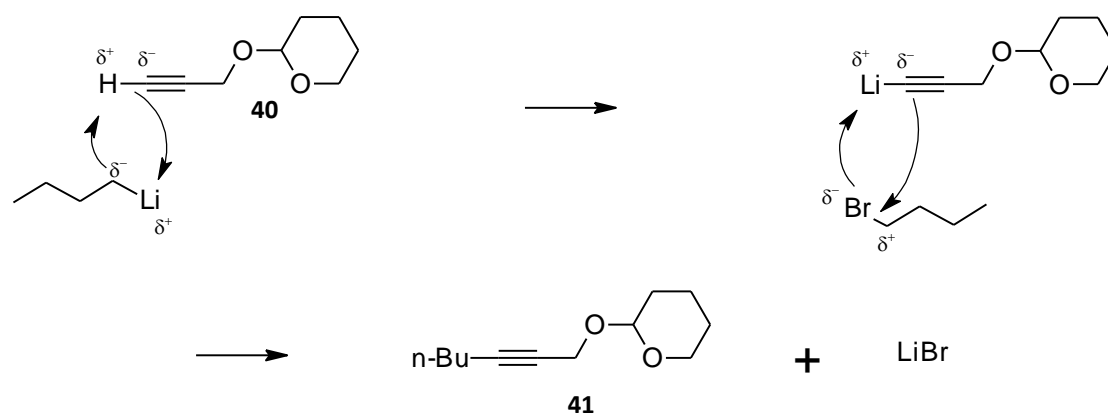
Scheme 2-19

¹²⁹ ^a Mikami and Yoshida. *Tetrahedron* **2001**, 57, 889-898.

^b Joshi, Joshi and Rawat. *ARKIVOK* **2006**, xvi, 65-74.

¹³⁰ Larock and Liu. *Journal of Organic Chemistry* **1983**, 48, 2151-2158.

To a solution of (**40**) in dry THF was added *n*-BuLi dropwise in 1.2 equivalents. This was allowed to stir for 30 minutes at 0°C, after which *n*-BuBr was added and allowed to stir for a further 30 minutes at 0°C and warmed to room temperature. Once warmed, the reaction mixture was refluxed overnight under nitrogen. TLC of the reaction mixture revealed a new spot with $R_f = 0.79$ corresponding to the product. Water was added to quench the reaction and dilute the mixture, after which solvent was removed *in vacuo*. A liquid-liquid extraction was performed using Et₂O/water, the organic extracts from which were combined and solvent removed *in vacuo*. Following a publication by Savoia *et al.*,¹³¹ the remaining residue was distilled on the Kugel-Röhr apparatus to obtain the product as a pale yellow liquid in 61% yield.

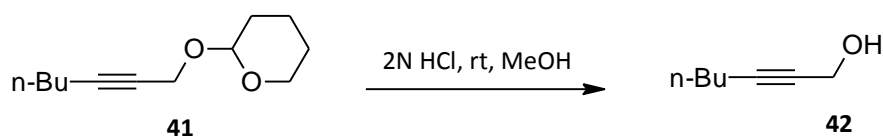


Scheme 2-20

The first step involves substitution of the terminal proton of the starting material (**40**) with lithium to form a lithiated intermediate. This is subsequently attacked by butyl bromide eliminating LiBr and generating the desired product (**41**).

Once the butyl group has been attached, the THP protecting group can be removed. This is achieved by treatment with acid as shown in scheme 2-21.

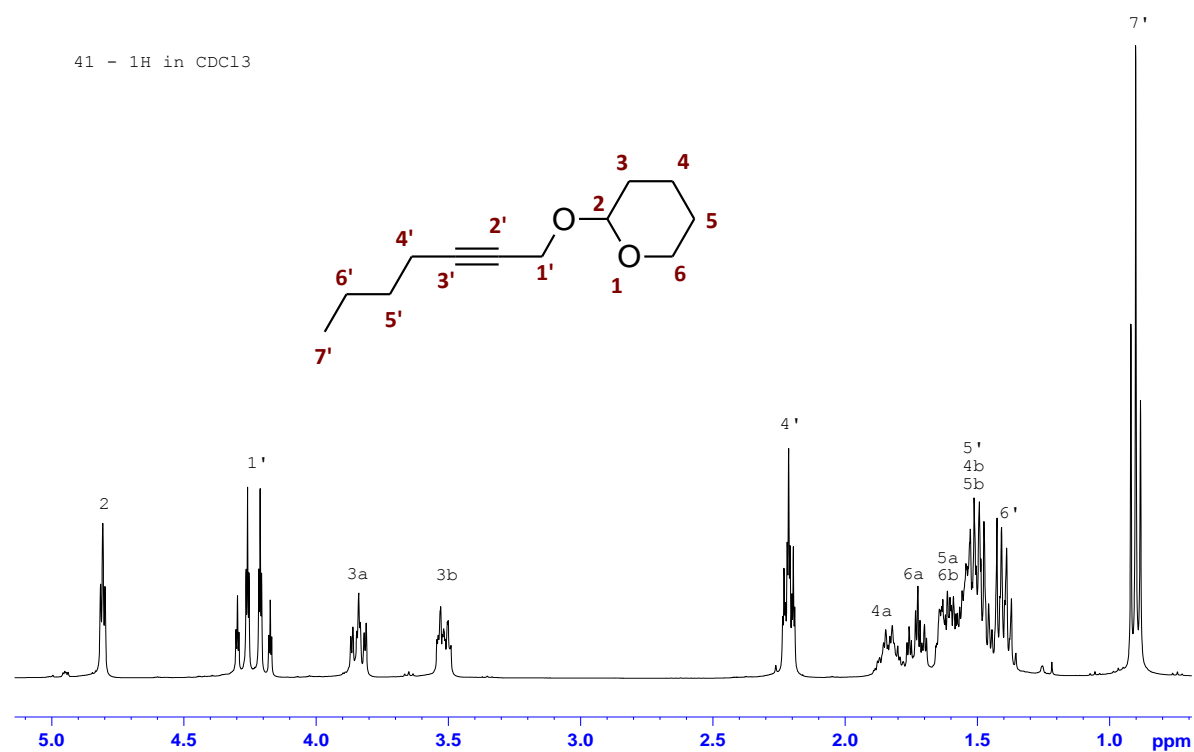
¹³¹ Savoia, Tagliavini, Trombini and Umani-Ronchi. *Journal of Organic Chemistry* **1981**, 46, 5340-5343.

**Scheme 2-21**

A small portion of pure (**41**) was dissolved in MeOH and 2N HCl added until the mixture turned blue litmus red. This was left to stir for 3 hours at room temperature after which the mixture was neutralised with aq. NaHCO₃ and a liquid-liquid extraction performed using CH₂Cl₂/water. The organic extracts were combined and solvent removed *in vacuo* to leave a pale yellow oil in quantitative yield (based on ¹H NMR of the crude extract). TLC of the reaction mixture shows disappearance of the starting material and formation of two new spots at R_f = 0.72 and 0.54. The spot of lower R_f corresponds to the removed tetrahydro-2H-pyran protecting group, while the spot of higher R_f corresponds to the expected product.

To simplify purification procedures, in all subsequent reactions the intermediate material (**41**) was not purified prior to the deprotection step.

The ¹H NMR spectra of these compounds exhibited some unexpectedly unusual peak splitting; sections of the spectrum for (**41**) are shown below with the associated splitting diagrams explaining their origin.



In the figure 2-18, the protons $1'$ are diastereotopic and thus unequivalent. Each of these are split by geminal coupling with one another ($J = 15.2$ Hz). Two further splittings occur as a result of vicinal coupling with each diastereotopic proton H-2 and with the protons of H-4' (each of these produce $J = 2.2$ Hz). Since the latter two coupling constants are the same, two peaks overlap in the centre, producing a triplet at each terminus. The result is an apparent quartet of triplets.

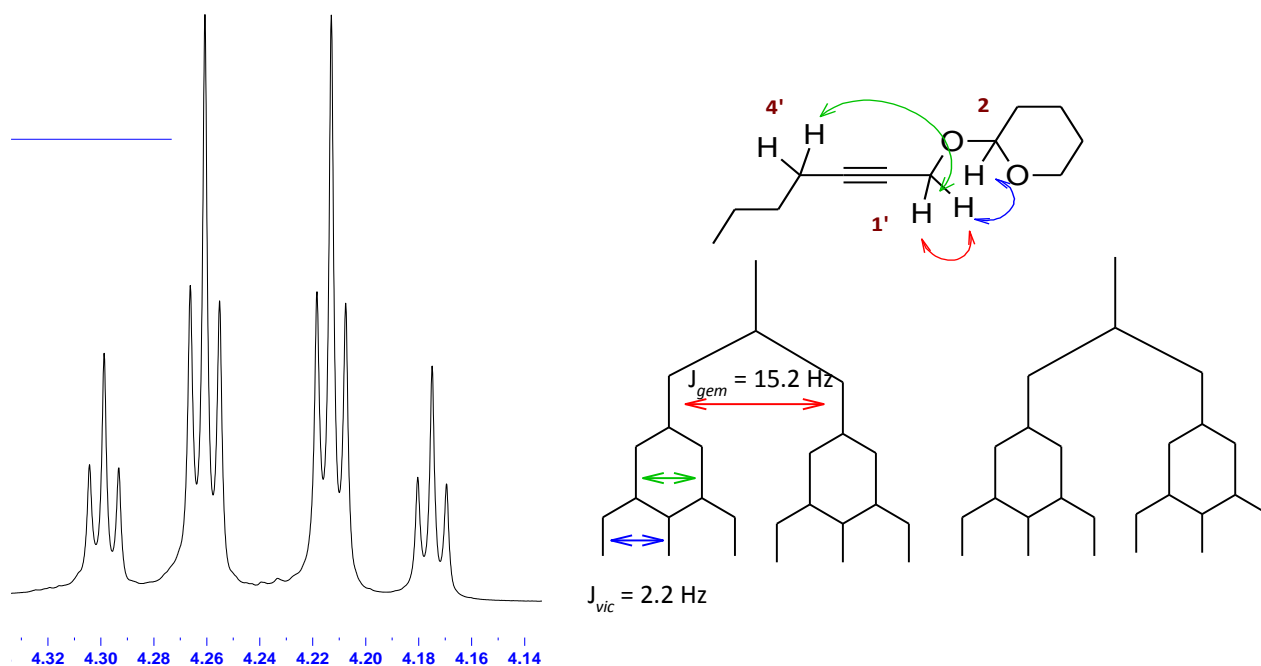
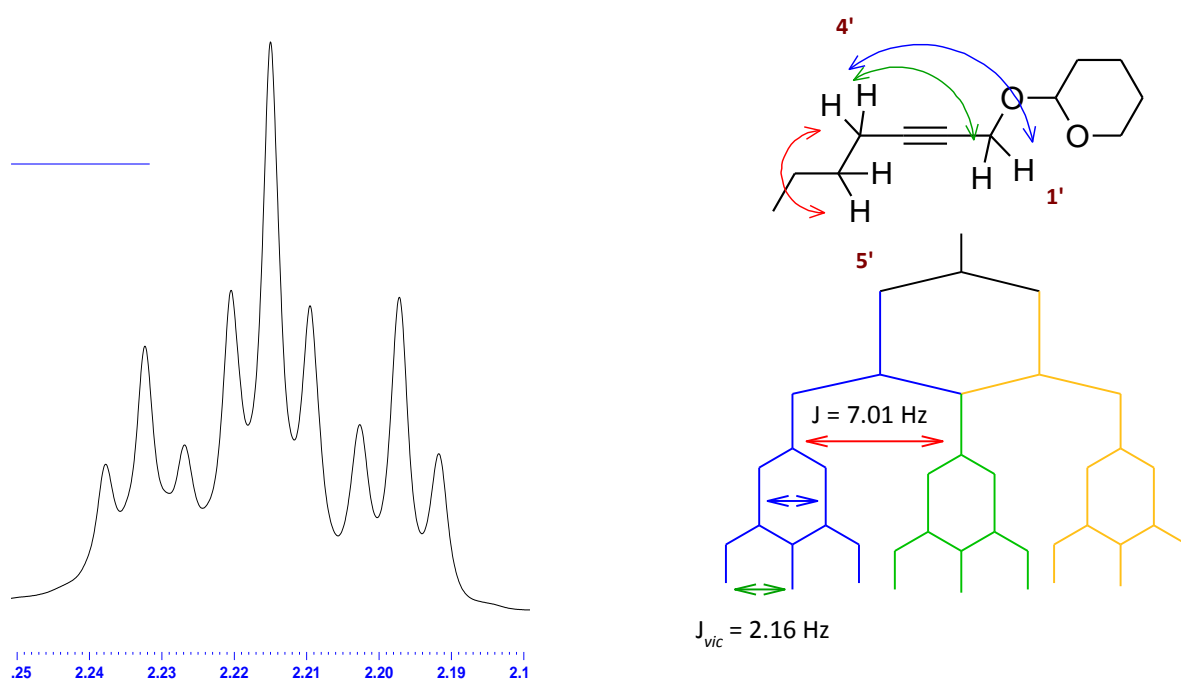
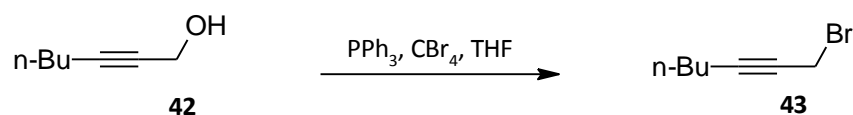
**Figure 2-18**

Figure 2-19 shows the splitting of equivalent protons $4'$. These couple with the $-\text{CH}_2-$ group of $5'$, producing a triplet ($J = 7.01 \text{ Hz}$). This is in turn split twice more by coupling to each diastereotopic proton $1'$ ($J = 2.16 \text{ Hz}$). This produces an apparent tripled triplet.

**Figure 2-19**

2.4.4. BROMINATION OF HEPT-2-YN-1-OL

The alcohol functionality must be converted to bromine in order to attach the alkyne group onto the α -carbon of (**10**) for construction of the second alkaloid ring. This is achieved as shown in scheme 2-22.

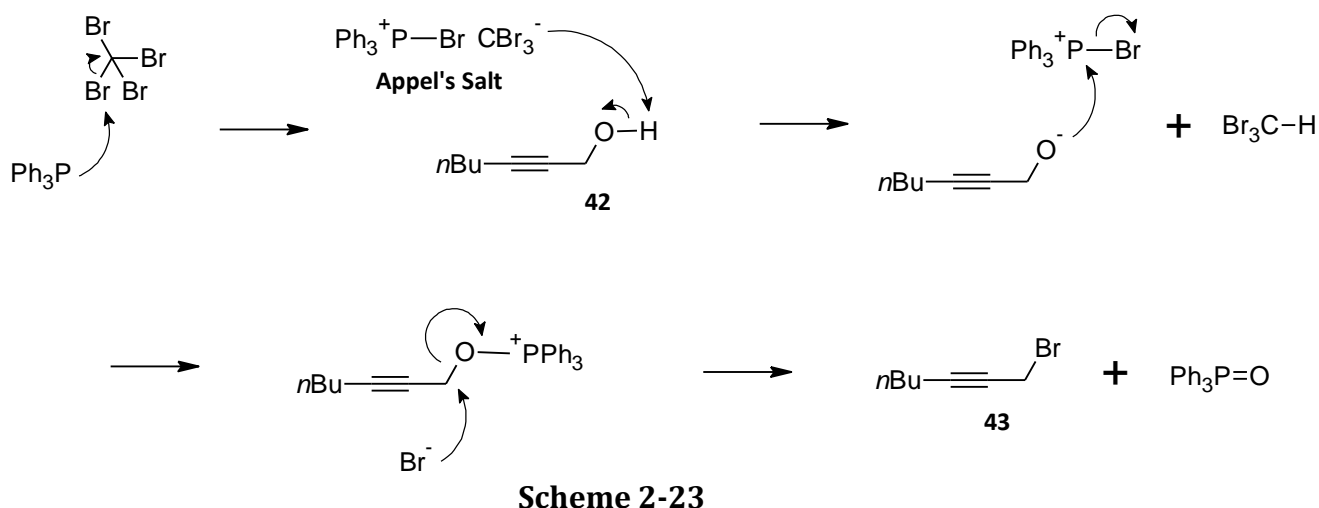


Scheme 2-22

The reactants were added to a round bottom flask and dissolved in dry THF. This reaction mixture was allowed to stir at room temperature for 24hr after which it was diluted with water and the solvent removed *in vacuo*. The remaining aqueous solution was extracted with ether and the combined organic extracts triturated to deposit any remaining PPh₃O. The liquid was decanted and concentrated *in vacuo* to leave a light yellow oil with 54% yield of product (based on crude ¹H NMR).

The halogenation of alcohols with triphenylphosphine and carbon tetrabromide is known as the Appel reaction.¹³²

¹³² Li *Name Reactions, Third Edition*; Springer: Berlin, 2007.



In the Appel reaction, triphenylphosphine is activated by reaction with carbon tetrabromide, forming the so-called Appel's salt. This removes the alcohol proton and the oxygen attacks phosphorus, forming an oxyphosphonium intermediate. The bromide then displaces triphenylphosphine oxide *via* an S_N2 mechanism, to yield the bromoalkyne (**43**). Should the alcohol carbon be asymmetric, an inversion of stereochemistry would occur due to the S_N2 mechanism of substitution.

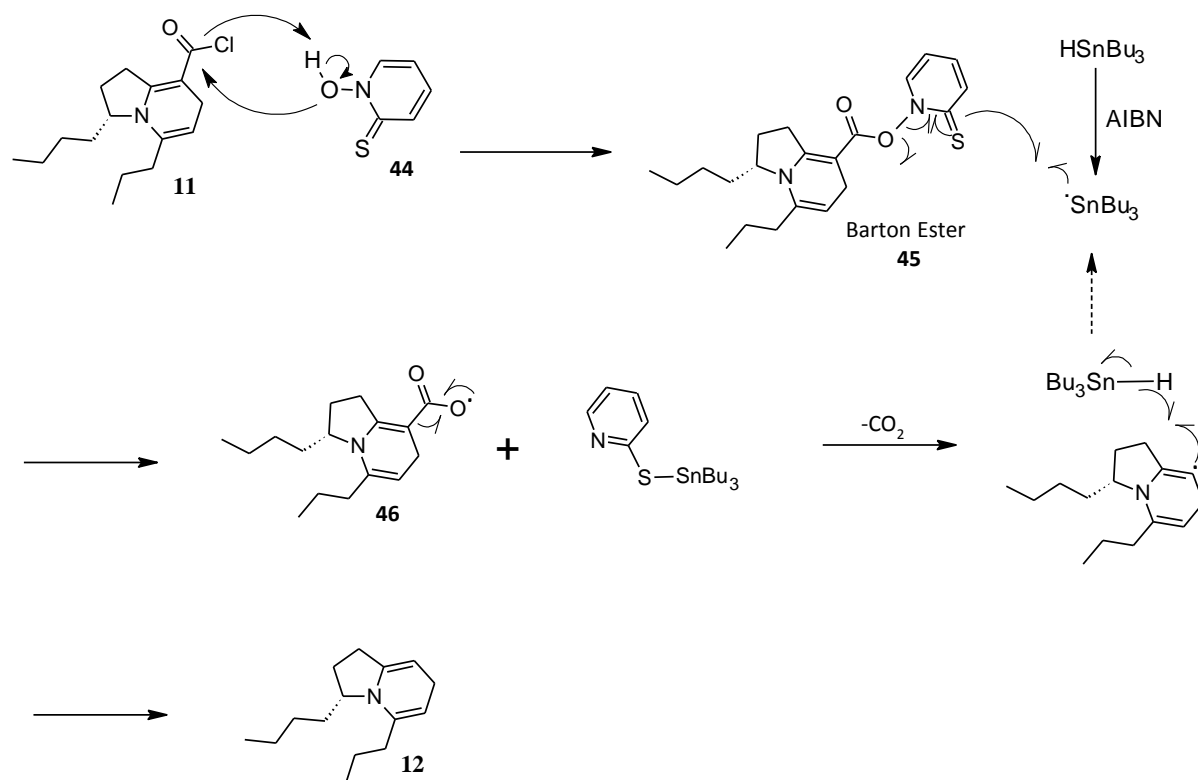
A crude ^1H NMR spectrum revealed the presence of the product, however before it could be purified, extensive decomposition was observed. All subsequent attempts to synthesize (**43**) were unsuccessful.

2.4.5. DECARBOXYLATION

Once the hydroamination step is complete, the only remaining steps involve decarboxylation of the ethylester followed by hydrogenation to furnish the target alkaloid **223AB**.

For the decarboxylation step, the Barton Decarboxylation is reviewed as it presents the simplest procedure with the possibility of introducing a substituent at this position. Before this can be done however, the ethyl ester requires to be converted to the corresponding acid chloride. This can be performed either directly by reaction with thionyl chloride or in a

two step process by initial conversion to the carboxylic acid. The mechanism is shown in scheme 2-24 below using the acyl chloride derivative as starting material.



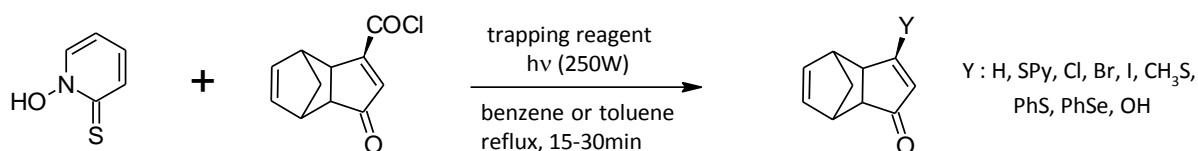
Scheme 2-24

The Barton decarboxylation involves initial formation of the purported Barton Ester by reaction of the acyl chloride starting material with 1-hydroxypyridine-2(1H)-thione (44). Decarboxylation of this ester is initiated by a tributyltin radical formed by decomposition of tributyltin hydride by AIBN. The driving force is formation of the stable S-Sn bond, and the pyridine moiety is lost. The resulting radical (46) undergoes decarboxylation and abstracts a proton from HSnBu_3 , reforming the 'SnBu_3 radical and generating the decarboxylated product (12). This mechanism is similar to that of the Barton-McCombie deoxygenation.^{133,134}

¹³³ Forbes and Zard. *Tetrahedron Letters* **1989**, 30, 4367.

¹³⁴ Zard *Radical Reactions in Organic Chemistry*; Oxford University Press, 2003.

Should a substituent be required at this position, the Barton ester may also be cleaved under thermal or photochemical conditions in the presence of a suitable radical trapping agent. An example by Zhu *et al.* is given in scheme 2-25.¹³⁵



Scheme 2-25

Reaction yields were reported to be between 60 and 90 %, with reaction times of 15-30 minutes.

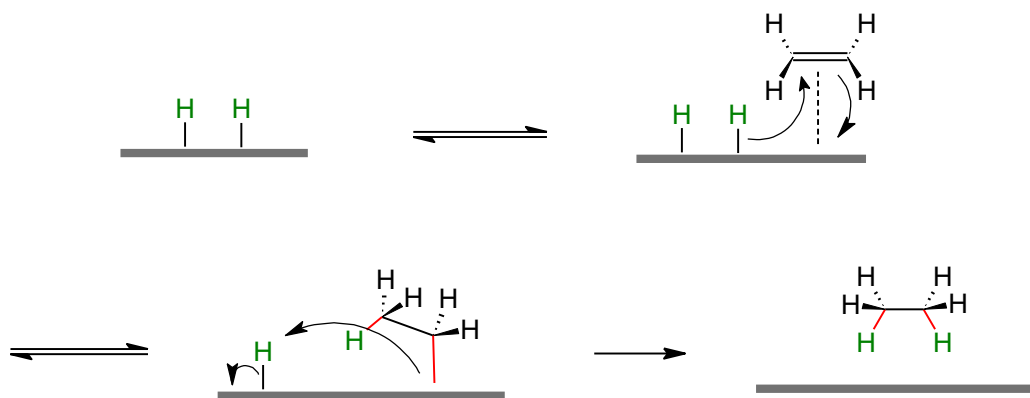
2.4.6. HYDROGENATION

It is important to mention at this time that although the (5*E*, 9*E*) stereochemistry of **223AB** is generally accepted as the 'correct' natural isomer, all four diastereomers can in fact be found in the skin of different frogs as well as their dietary ant and arthropod sources.¹³⁶

The typical hydrogenation procedure involves utilising a positive pressure of H₂ over a catalyst such as Pd/C (heterogeneous) or Wilkinson's Catalyst (homogeneous). These reactions yield exclusively the *syn* addition product, unlike alkyne hydrogenation in which it is possible to obtain either *syn* or *anti* addition products. The generally accepted Horiuti-Polanyi mechanism of alkene hydrogenation on a heterogeneous catalyst is shown in scheme 2-26.

¹³⁵ Zhu, Klunder and Zwanenburg. *Tetrahedron* **1995**, 51, 5099-5116.

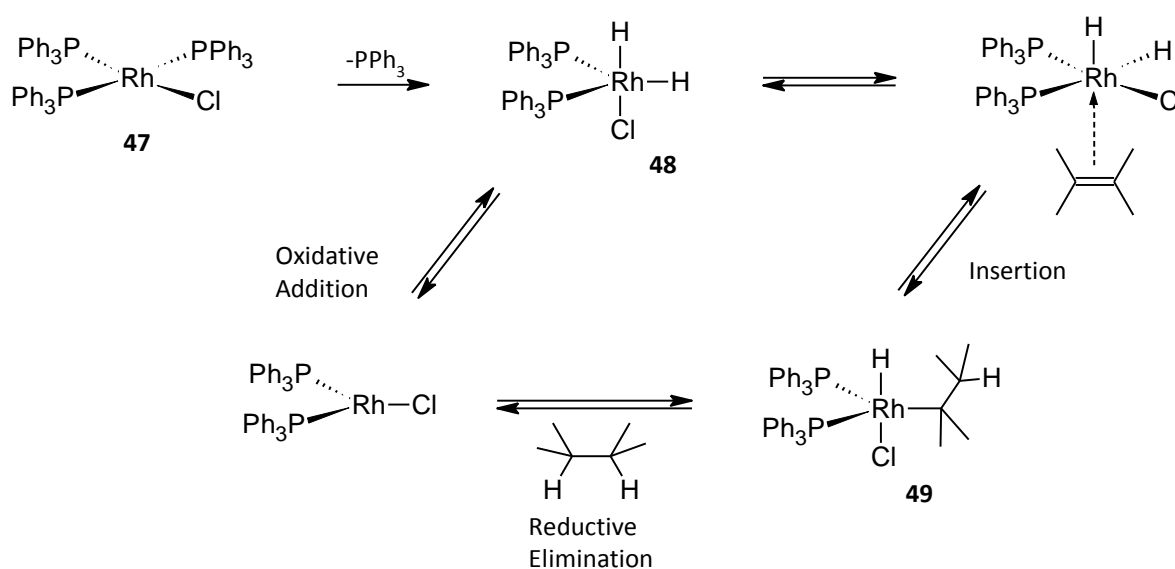
¹³⁶ Jones, Voegtler, Miras, Weatherford, Spande, Garraffo, Daly, Davidson and Snelling. *Journal of Natural Products* **2007**, 70, 160-168.



Scheme 2-26

Gaseous hydrogen as well as the alkene absorb and are bound to the surface of the catalyst. In this way, both the π bond of the alkene and the σ bond of the hydrogen are activated. Addition of the first hydrogen atom is effectively reversible; however the second addition is not. Once H_2 has been added across the olefin, it is released from the surface of the catalyst.

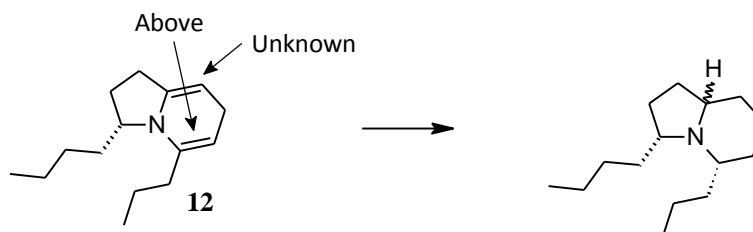
Homogeneous catalysis is somewhat dissimilar, the mechanism of which is shown in scheme 2-27.



Scheme 2-27

Wilkinson's catalyst (**47**) undergoes an oxidative addition with H_2 and loss of a PPh_3 group to form a metal-hydride complex (**48**). The alkene coordinates to this complex and a hydride insertion takes place to generate (**49**). The second hydride addition followed by reductive elimination releases the hydrogenated compound. As with heterogeneous catalysts, addition of H_2 is *syn*, however bond rotation in complex (**49**) can lead to a stereochemical mixture.¹³⁷

Since both of these mechanisms require binding to the double bond and addition occurs in a *syn* fashion, the hydrogens will add to the least sterically hindered face. In the case of (**12**), it seems most likely that the resulting stereochemistry of the 5-propyl group will orient in the same direction as that of the 3-butyl, as the hydrogenation will occur on the opposite face to that in which the 3-butyl is pointing. Without experiment, the stereochemistry of the 9 position cannot be predicted.



Scheme 2-28

Although one of the aims of the project was towards the synthesis of the frog alkaloid **223AB**, we also wished to explore the control of regioselectivity from Markovnikov (exo-cyclization) to anti-Markovnikov (endo-cyclization). For this purpose, a model study was undertaken.

¹³⁷ Smith and March *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; 6th Edition; Wiley-Interscience, 2007.

2.5. CATALYTIC HYDROAMINATION STUDY

Part of the aim of this study was to explore the role of the hydroamination catalyst and to determine their regioselectivity in order to direct towards the anti-Markovnikov isomeric product. For the purpose of testing the catalysts, the hydroamination reaction was performed on model compound (**50**) which is analogous to (**9**) and easily prepared in bulk.

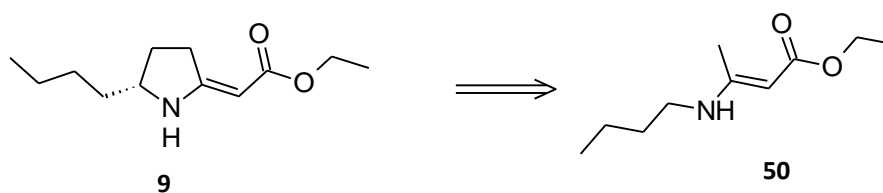
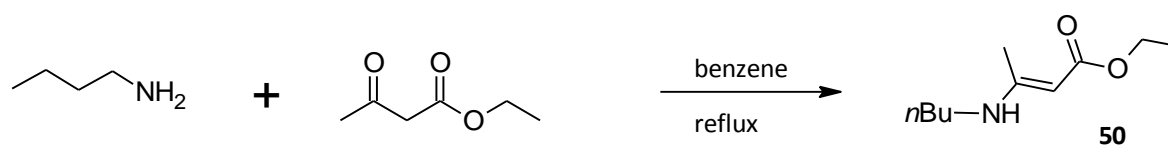


Figure 2-20

2.5.1. SYNTHESIS OF ETHYL (2*E*)-2-[1-(BUTYLAMINO)ETHYLIDENE]PENT-4-ENOATE (**51**)

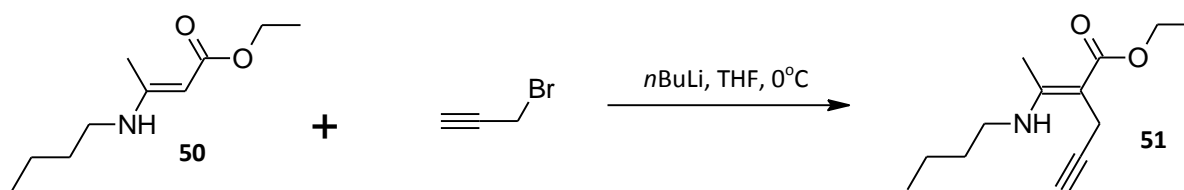
Compound (**50**) was synthesised by condensation of butylamine with ethyl acetoacetate as shown in scheme 2-29.



Scheme 2-29

Ethyl acetoacetate and an excess of butylamine were dissolved in benzene and a Dean & Stark apparatus connected for azeotropic removal of water. After refluxing for 2 hours, the solvent was removed *in vacuo* to leave the product as a brown oil in quantitative yield. There is no need for purification due to the low boiling point of butylamine (77°C); it will be removed *in vacuo* with the solvent.

Subsequent propargylation of (**50**) yields the hydroamination substrate (**51**).

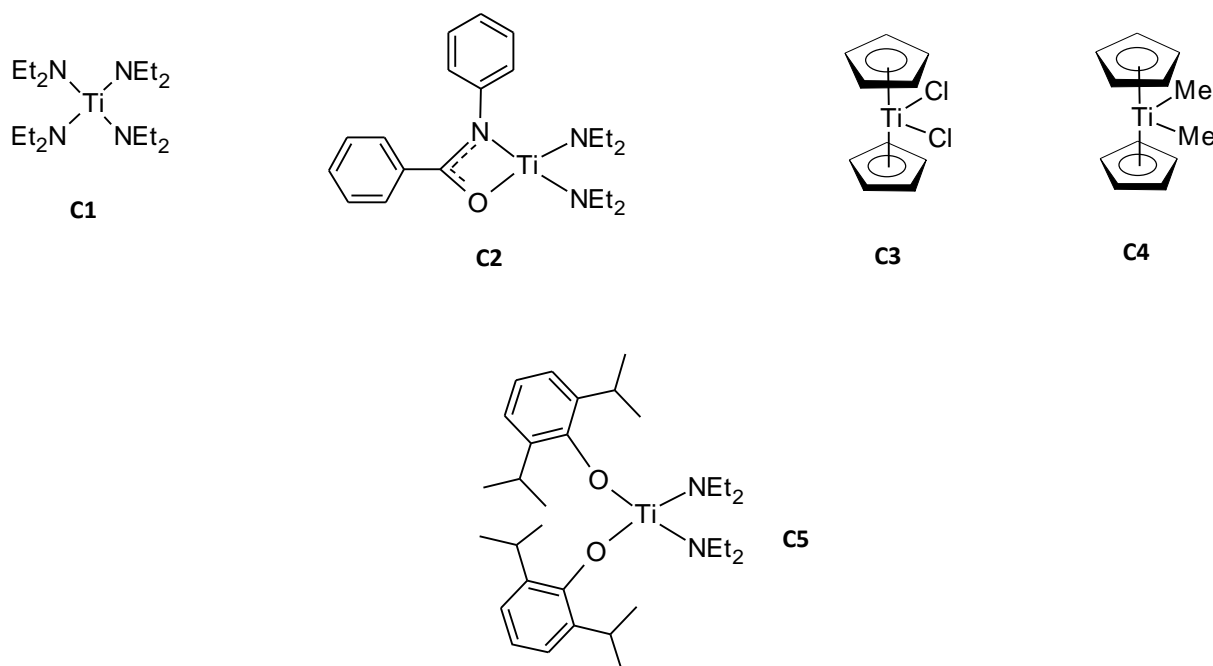


Scheme 2-30

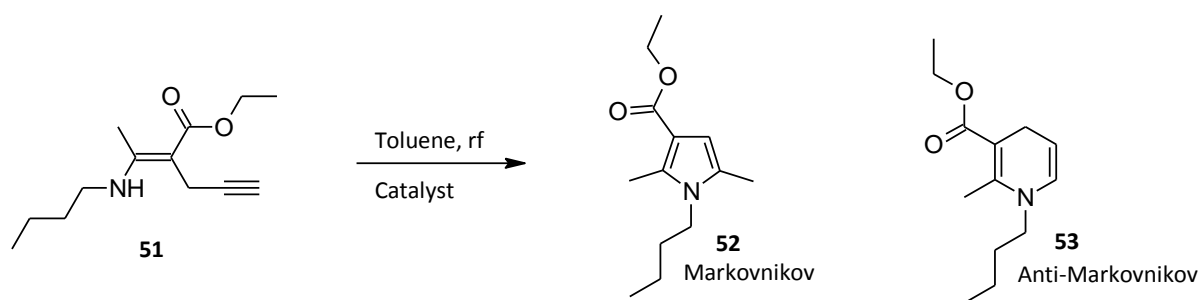
To a solution of the enamine (**50**) in dry THF, cooled to 0°C is added $n\text{-BuLi}$ dropwise and allowed to stir for 30min. Thereafter propargyl bromide is added dropwise to the mixture and allowed to stir overnight while warming to room temperature. The reaction mixture was quenched with a few drops of water and solvent removed *in vacuo*. Purification by radial chromatography (1:1 EtOAc-hex) did not prove entirely successful as the product (**51**) was found to partially decompose on silica, making it impossible to obtain an entirely pure sample for analysis. The ^1H NMR spectrum is shown in figure 2-21. For this reason, all subsequent hydroamination reactions were performed *in situ* on (**51**) without purification of this intermediate reagent.

2.5.2. CATALYSED HYDROAMINATION

To this end, a range of titanium based catalysts were selected from the literature that have been shown to direct anti-Markovnikov. The catalysts used are shown in figure 2-22, and were either available in our laboratories or readily prepared from available materials.

**Figure 2-21**

The hydroamination reactions were performed either by adding the prepared catalyst to the reaction mixture (C1, C2, C3 & C4) or by adding the precatalyst (in this case $\text{Ti}(\text{NEt}_2)_4$) and ligand (2,6-diisopropylphenol) to the reaction mixture (C5). The latter catalyst was too air sensitive to preform and thus was prepared *in situ*. The reaction mixture was diluted with dry toluene and refluxed for 24hr, after which a little water was added to quench then reaction. The reaction mixture was then filtered through a silica plug to remove the catalyst, and solvent was removed *in vacuo*. ^1H NMR spectra were run on the crude residue to determine the yield of product[s] formed from the reaction.

**Scheme 2-31**

Disappointingly, it was observed that for all catalysts, the Markovnikov isomer was the exclusive product formed. Yields are reported in table 6.

Table 9

| Catalyst | C1 | C2 | C3 | C4 | C5 ^b | AgNO ₃ ⁶⁴ |
|--------------------|-----|-----|-----|-----|-----------------|---------------------------------|
| Yield ^a | 77% | 45% | 80% | 77% | 60% | 14% |

^a Reaction time: 24hr, yields based on ¹H NMR; ^b Reaction time: 48hr

The assignment of the product as being Markovnikov was based on NMR data as shown in figure 2-23.

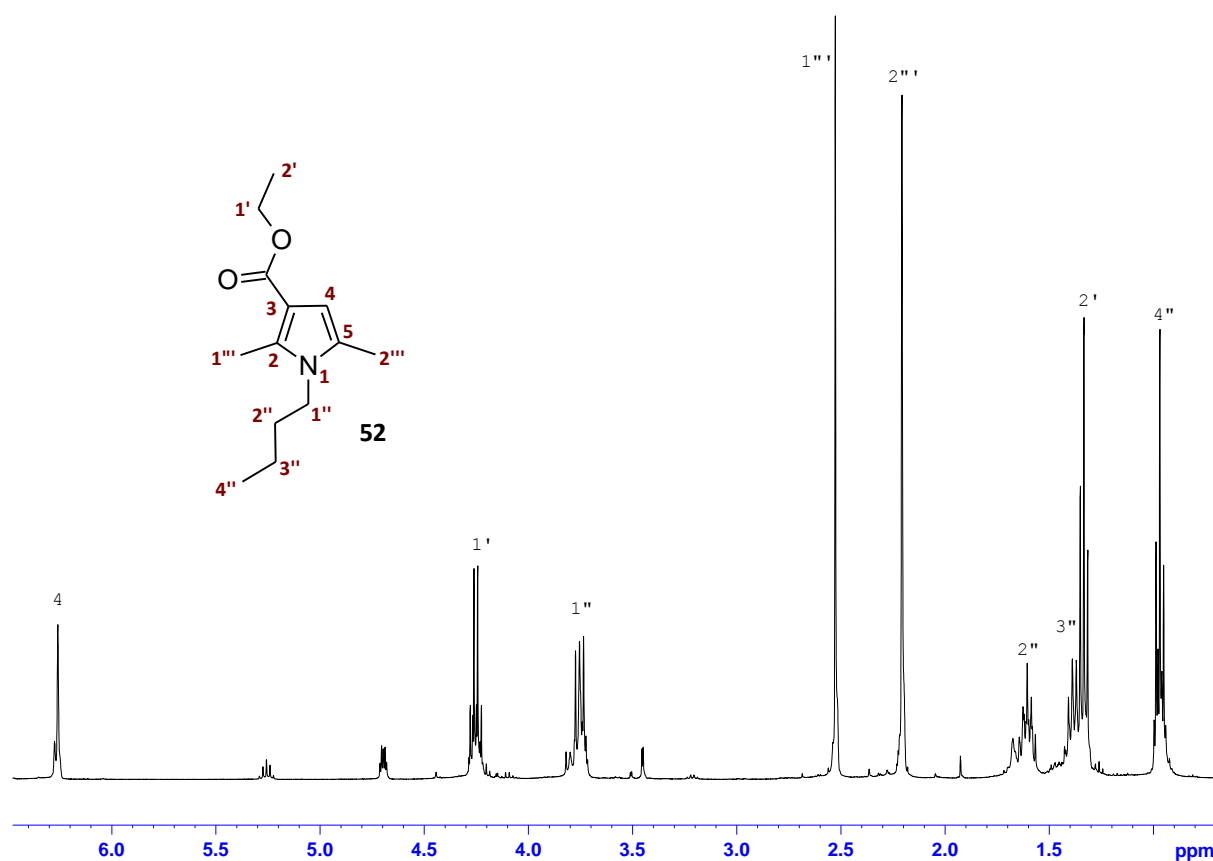


Figure 2-22

The primary indicator that this is the Markovnikov product is the presence of two singlets at $\delta = 2.44$ & 1.12 ppm integrating each for three protons. These correspond to the two methyl

groups 1''' and 2''' attached to the pyrrolidine ring. The protons of the butyl and ethoxy groups would not be expected to differ much between the Markovnikov and anti-Markovnikov products, the only other shift that would be different is the singlet -CH- (position 4), which in the anti-Markovnikov isomer would instead be a multiplet integrating for two protons rather than one. An example of a ^1H NMR spectrum used for the calculation of product yield is shown in figure 2-24.

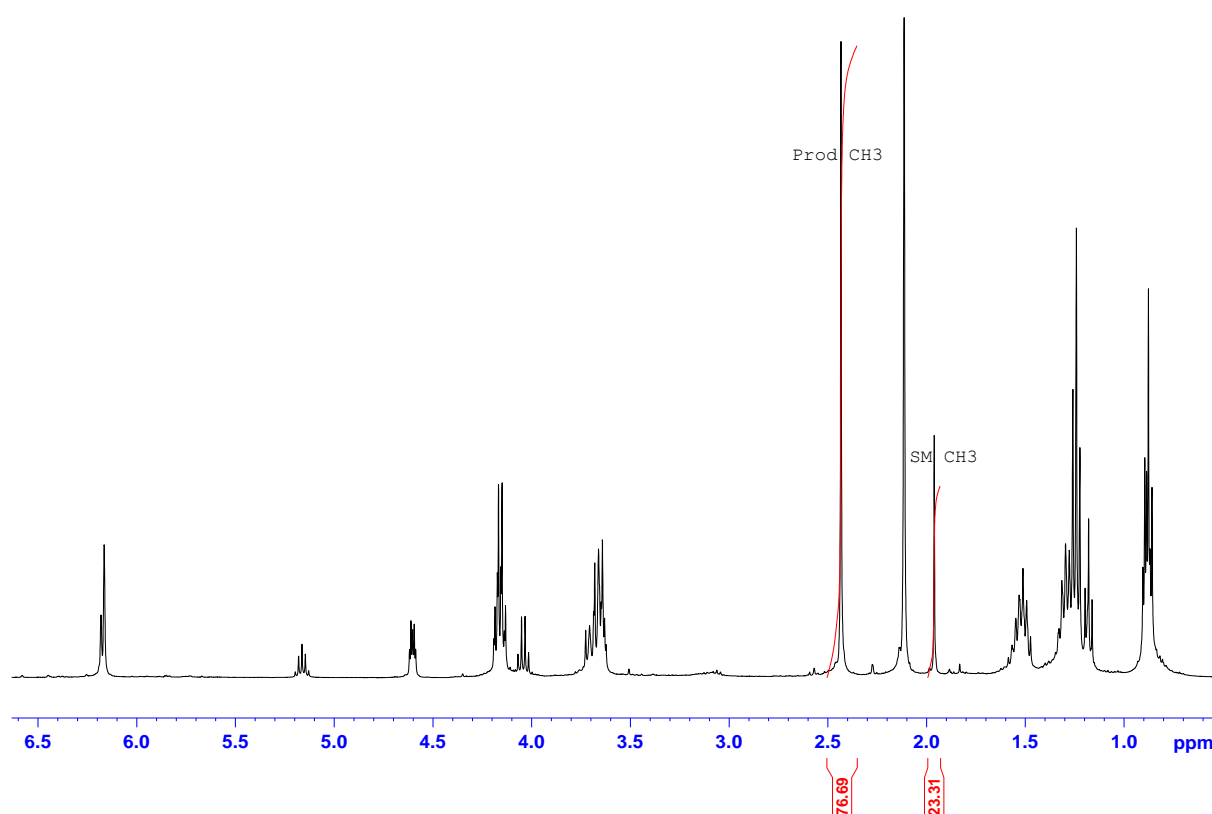


Figure 2-23

The peaks chosen to calculate the %yield are those corresponding to the enamine methyl 1''' which is present in the starting material and both possible products, being the most distinguishable from one another. These are indicated in the above spectrum as 'Prod CH₃' and 'SM CH₃'. By normalising the sum of these integrals, the percentage of the starting material and product are obtained as 23% and 77% respectively.

GC-MS provided a molecular ion of 222.97Da, expected: 223.1572Da

A closer inspection of the products according to Hückel's Rules for aromaticity revealed that although both products contains $4(n)+2 = 6$ π -electrons (where $n = 1$), are planar and are cyclic; only the Markovnikov product possesses on all atoms of the ring, overlapping p-orbitals perpendicular to the plane of the ring. This last criterion is however not met for the anti-Markovnikov product. This is illustrated in figure 2-25 by computational calculations of the HOMO of each optimized product.

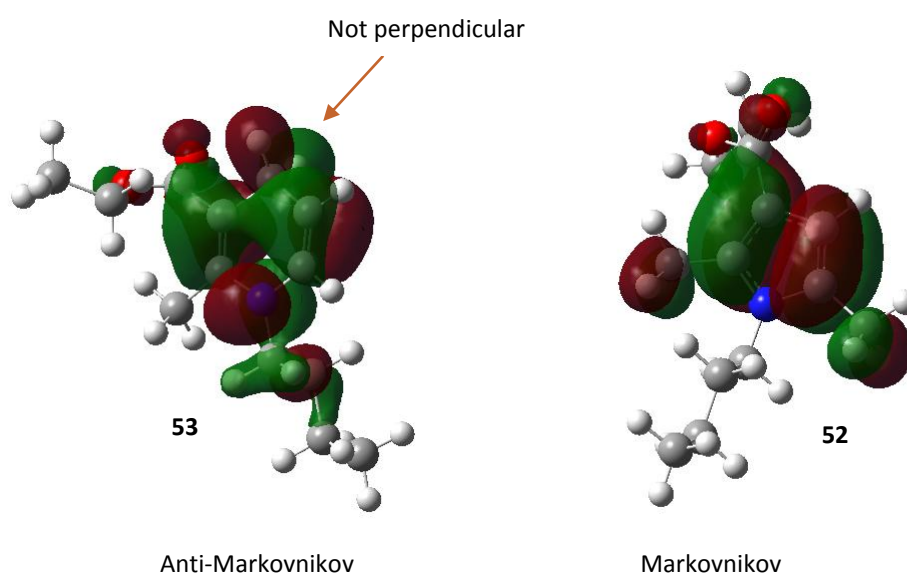


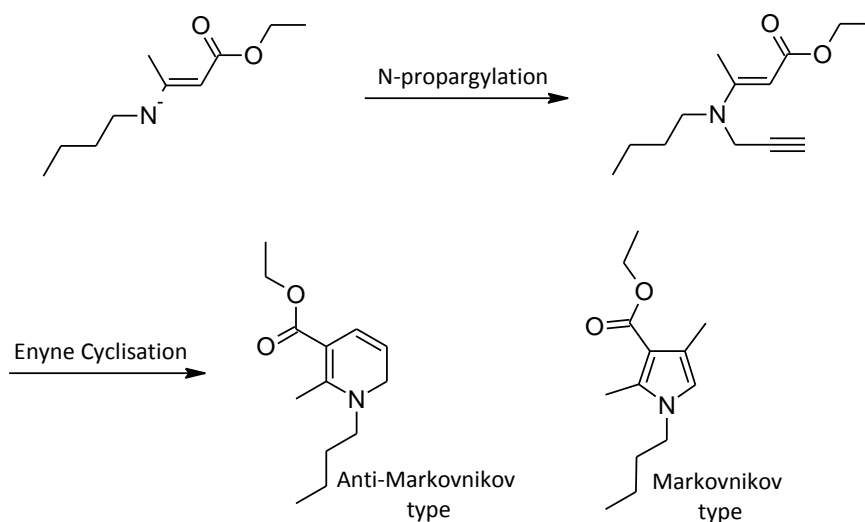
Figure 2-24

From these optimized structures, it is evident that both these ring systems are, in fact planar.

As can be seen from these HOMO orbital representations, all the p-orbitals of the Markovnikov product (**52**) are perpendicular to the plane of the ring and as a result overlap. In the anti-Markovnikov product however, the p-orbital of the apical carbon (indicated in figure 2-25 by the orange arrow) is not perpendicular, resulting in a break of the orbital overlap over the ring.

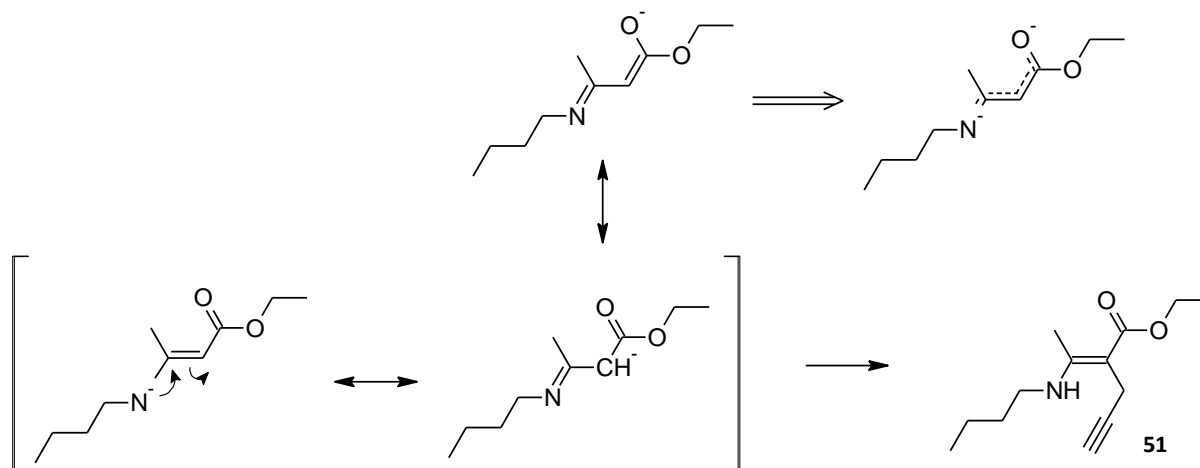
As a result, the aromatic Markovnikov product will be preferentially formed over the non-aromatic anti-Markovnikov isomer.

In order to circumvent this problem, an N-propargylation of (**51**) as opposed to C-propargylation was considered (shown in scheme 2-29), following which an enyne cyclization could be performed.

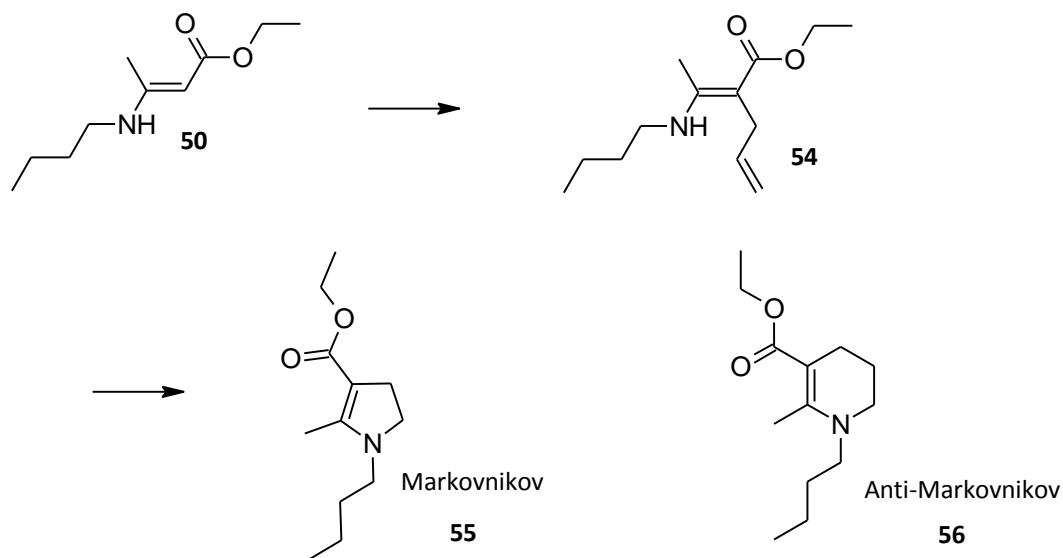


Scheme 2-32

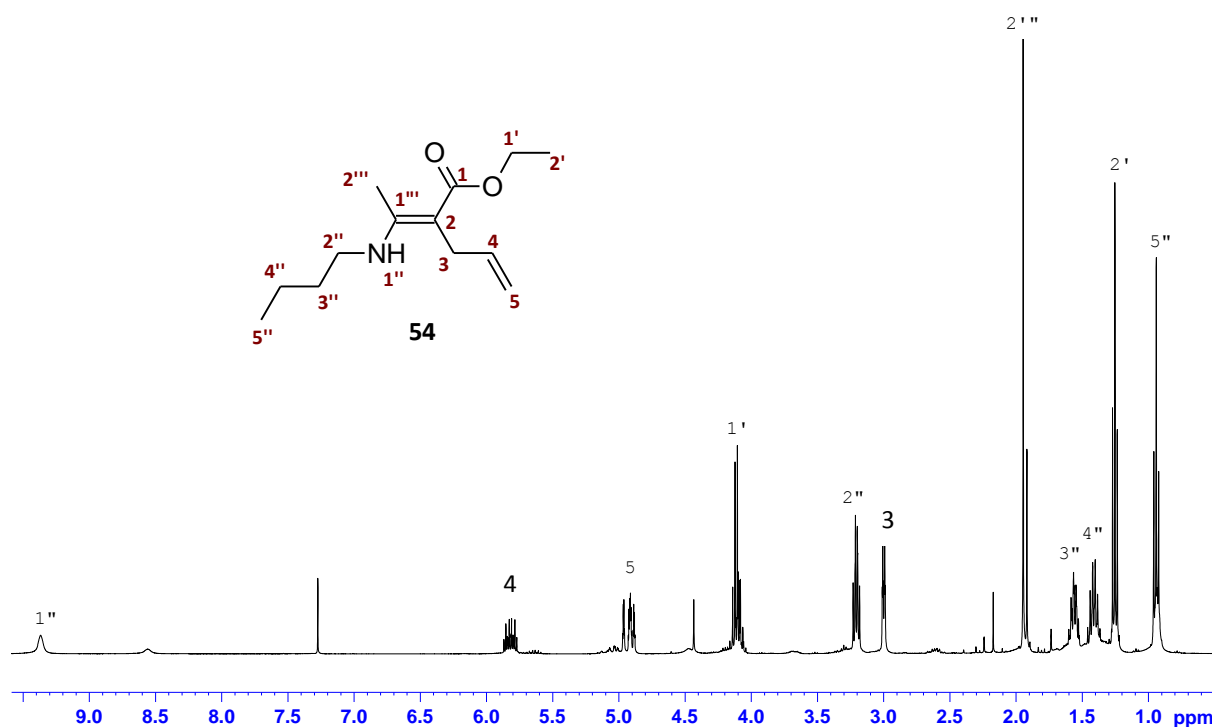
Consideration of the deprotonated intermediate however, led to the conclusion that this would isomerise to the carbanion by resonance, forming the C-propargylated product. The negative charge is less stable positioned on the nitrogen atom by virtue of the fact that it is more easily accommodated at the α -carbon position due to subsequent possibility of resonance. In doing this, a conjugated system forms and the negative charge is spread over the $-\text{CH}-\text{C}=\text{O}$ bonds.

**Scheme 2-33**

For this reason, reaction with allyl bromide was pursued in an effort to eliminate aromaticity of the products and thus preference for the Markovnikov isomer. This is shown in scheme 2-31.

**Scheme 2-34**

The identity of (54) was confirmed by 1D and 2D NMR spectroscopy as discussed below. The former spectrum is shown in figure 2-26.

**Figure 2-25**

The 2D COSY NMR shows the obvious coupling of the amine $-\text{NH}-$ with the attached $2''$ $-\text{CH}_2-$ and so forth down the butyl chain, identifying these peaks in the ^1H NMR spectrum. The peaks due to the ethoxy group were identified as the quartet and triplet that couple only to one another in the COSY. The singlet $\delta = 1.95$ ppm corresponds to the methyl group $2'''$, leaving only identification of the allyl group protons. Of the remaining peaks, the one at $\delta = 5.8$ ppm integrated for one proton whereas the other two integrated for two protons each, identifying it as proton H-4. Since no distinction could be made between the latter two from the COSY, assignment was based on 2D HSQC and HMBC NMR. The carbon at position 5 is expected to couple only with the protons at 4; likewise the carbon at position 3 is expected to couple with the protons at 4 and the protons of 3 with the tertiary carbon 2. These predictions are what were seen in the 2D spectra. Figure 2-27 shows the overlay of HSQC (red) and HMBC (blue).

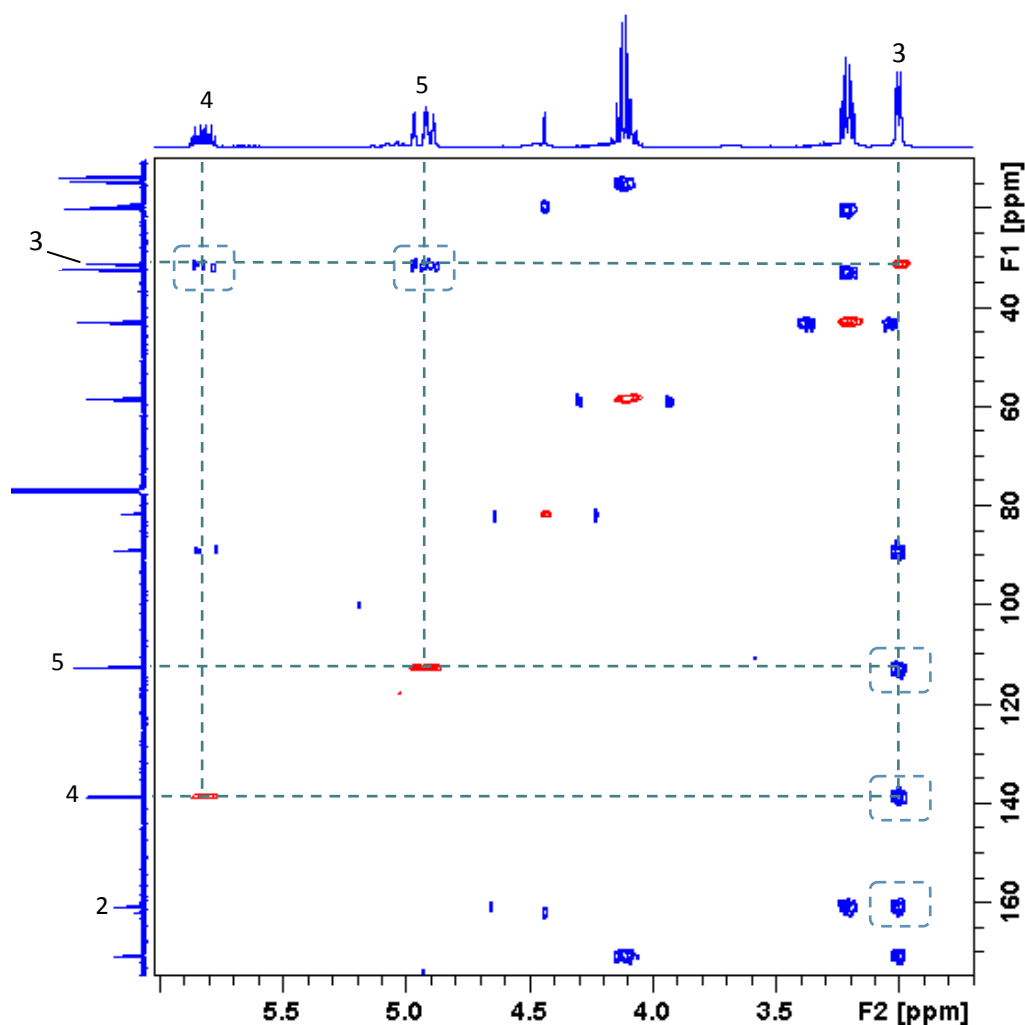


Figure 2-26

GC-MS provided a molecular ion peak at $m/z = 225.2$ (expected 225.17 Da) confirming the identity of compound (**54**) beyond reasonable doubt. Subsequent hydroamination however proved unsuccessful.

To the reaction mixture of (**54**) was added toluene and an amount the catalyst. This was refluxed for 24hr after which a sample was extracted for crude ^1H NMR. This showed only starting material with the appearance of duplicate peaks of the allyl protons. After reflux for an additional 5 days no further change was observed. This same result was obtained irrespective of the catalyst used, the catalyst loadings or reflux time.

Initially it was thought that the titanium hydroamination catalysts were instead catalysing an oligomerization process, following an article by Bianchini *et al.* reporting oligomerization catalysed by Cp_2ZrCl_2 .¹³⁸

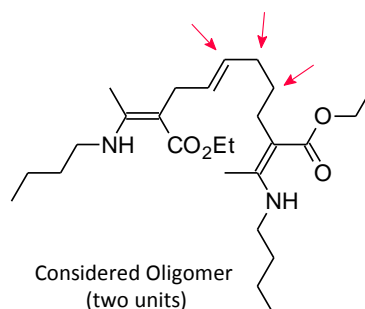


Figure 2-27

If this were the case, analysis of the ^{13}C and DEPT NMR spectra would reveal the necessary change in hybridization that occurs for this process. This, however, was not the case, as the ^{13}C peaks were exactly duplicated as those in the ^1H NMR spectra were.

The other explanation for the appearance of these peaks was verified by 2D NOE. Cross-peaks were observed between the 'original' allyl peaks and the methyl group at position 2'''. These were not present for the 'new' peaks that appear after addition of the catalyst. Thus the original peaks are due to the (Z)-isomer and addition of the catalyst has caused isomerisation to the (E)-isomer in an approximate 46:54% Z/E ratio.

¹³⁸ Bianchini, Butler, Barsan, Martens, Frost, Galland and dos Santos. *Spectrochimica Acta Part A* **2008**, 71, 45-52.

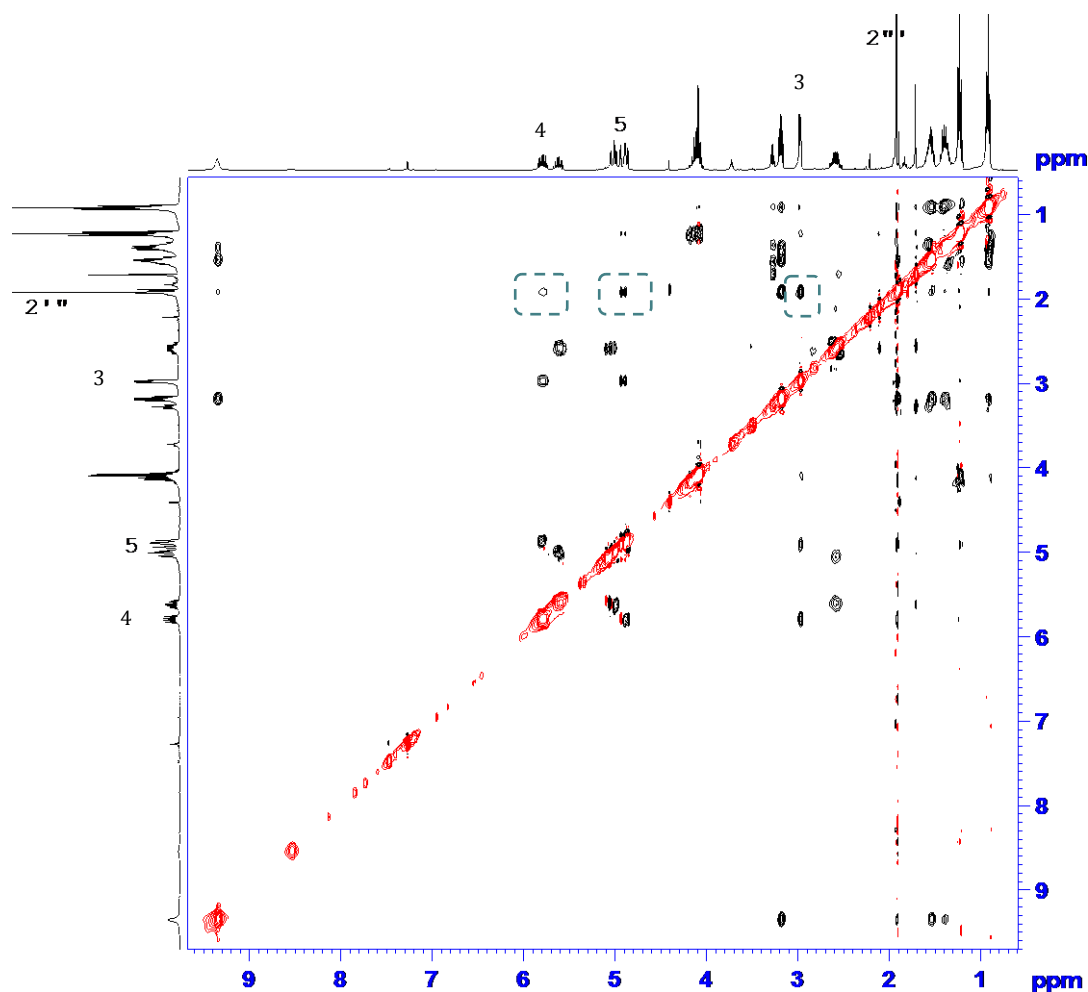


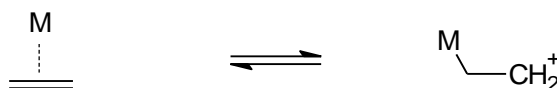
Figure 2-28

It has been established by Gravestock¹³⁹ and Prior¹⁴⁰ that the initial geometry about the double bond of these vinylogous amides is (Z) and isomerisation about the double bond must occur in order for hydroamination to take place. Prior *et al.* recognised this to be due to the metal-olefin complex existing in equilibrium with a polarized form, enabling rotation about the double bond to take place.¹⁴¹

¹³⁹ Gravestock and Dovey. *Synthesis* **2003**, 4, 523-530.

¹⁴⁰ Prior and Robinson. *Tetrahedron Letters* **2008**, 49, 411-414.

¹⁴¹ Brochmann *Organometallics 2: Complexes with Transition Metal-Carbon π -Bonds*; Oxford University Press, 2000, 20-21.

**Figure 2-29**

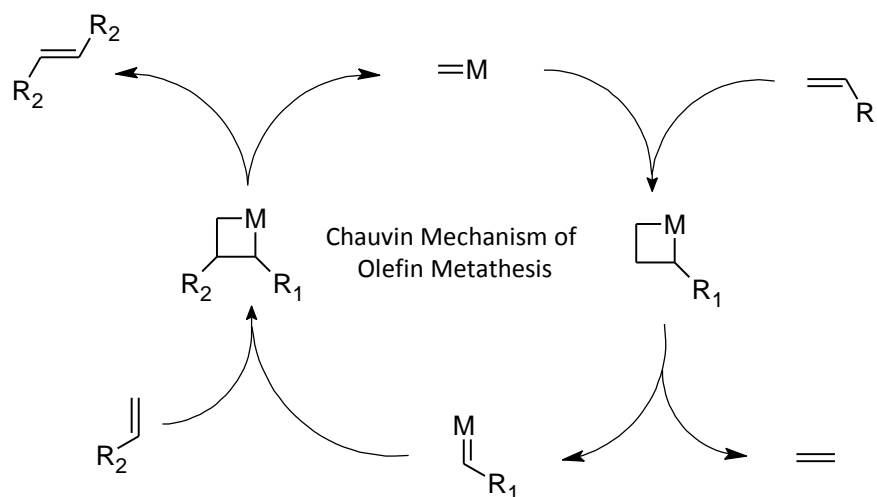
Although the work of Dovey and Prior indicates this isomerisation must take place in order for hydroamination to occur, there has until now been no experimental evidence to support this in these systems. The above NMR spectra are irrefutable evidence that upon addition of the hydroamination catalyst, their assumption was indeed correct and isomerisation about the double bond occurs before hydroamination takes place. The question however remains; why did the hydroamination reaction not occur?

2.5.3. HYDROAMINATION MECHANISM

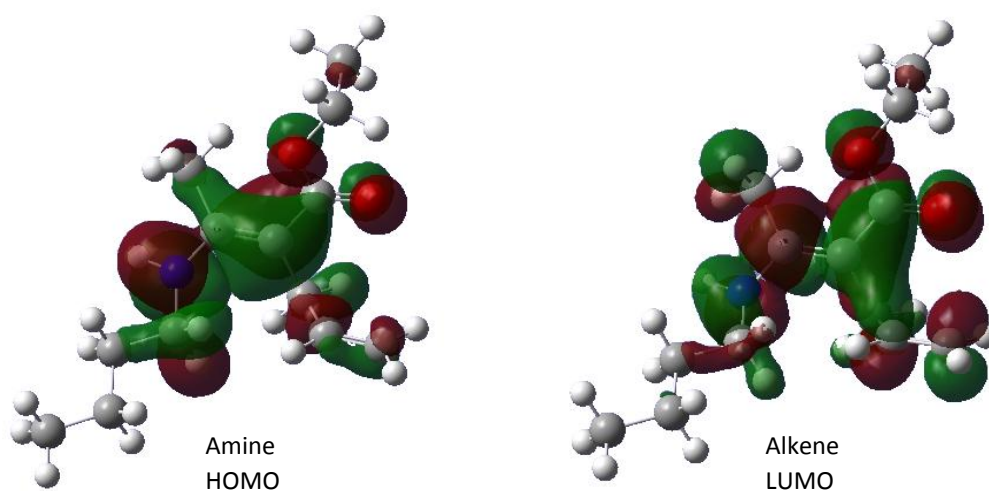
In order to understand why hydroamination of the propargyl compound was successful while that of the allyl compound was not, a deeper understanding of the mechanism behind titanium-catalysed hydroamination was required.

An extensive survey of the literature revealed that among the greatly differing mechanisms proposed, a consistent aspect was that the hydroamination proceeded through coordination of titanium to both the nitrogen and unsaturated bond forming a four-member ring resembling the Chauvin mechanism of olefin metathesis (see scheme 2-35).¹⁴²

¹⁴² Wenzel and Grubbs. *Journal of the American Chemical Society* **2006**, 128, 16048-16049.

**Scheme 2-35**

Since the process of hydroamination is essentially a [2+2] cycloaddition,¹⁴³ which is allowed only under photochemical conditions by the Woodward-Hoffman rules, it seemed appropriate to investigate the HOMO and LUMO orbitals of (**46**).

**Figure 2-30**

For a cycloaddition reaction to occur, the orbitals involved require to be of the same phase and correct orientation to overlap. As can be seen from figure 2-30, the necessary

¹⁴³ Although this has been purported in literature, there is no experimental evidence in support of this.

movement for orbital overlap cannot occur due to the rigidity of the enamine system, thus resulting in misalignment with the nitrogen orbitals and consequently no overlap. In the case of the propargyl compound (**51**), the orbitals lie in both planes of the alkyne, requiring no rotation for overlap to occur.

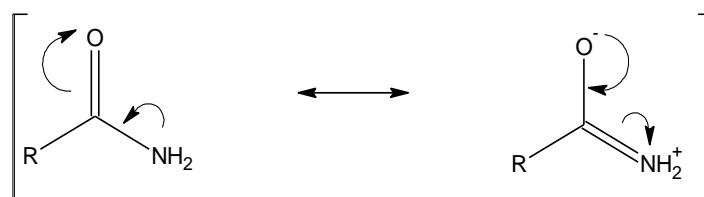
Although the target in this project was the synthesis of frog alkaloid 223AB, the focus was on exploring the applicability of the synthetic route to multiple classes of alkaloid skeletons through minor modifications. One of these was to employ hydroamination to alter the regioselectivity from Markovnikov (exo) to anti-Markovnikov (endo), producing respectively a 5-member or 6-member ring. At the onset of the project it was an intention to look closer at the mechanism of hydroamination and factors involved through computational investigation. In order to develop the skills and expertise in computational techniques, an *ab initio* study into amide rotational barriers was undertaken. Although unrelated, the skills acquired have been used in parallel with the alkaloid synthesis as a tool to gain a better understanding of certain problems faced in this synthesis.

2.6. COMPUTATIONAL STUDY

In the hopes that time would allow for a computational investigation into the mechanism of regioselective hydroamination, a study on amide rotational barriers was undertaken at the onset of the project. This study stems from previous work within our group in which it was discovered that 2-oxo-2*H*-chromen-7-yl dimethylcarbamate derivatives exhibited interestingly variable barriers to internal amide rotation. Thus a selection of similar derivatives were synthesized and their barriers to internal rotation determined both experimentally and theoretically by *ab initio* calculations. The results are presented below in two papers that have been submitted for publication detailing separately the synthesis of and rotational barrier calculations on these compounds.

It is a well known fact that *N,N*-disubstituted amides may exhibit two separate signals in the ¹H NMR spectrum for each substituent. This anomaly is attributed to resonance between the carbonyl group and the nitrogen lone pair, resulting in a partial double bond and thus

resulting in the substituents being unequivalent. The Pauling model of this is represented in scheme 2-36.



Scheme 2-36

The aim of this study was to calculate the rotational barriers of a number of *N,N*-disubstituted carbamates and thiocarbamates and determine the effect of an additional chalcogen substituent (O or S) in the position β to the nitrogen. It was envisaged that this substituent would result in a competing resonance with the carbonyl, weakening the rotational barrier. An example is shown in figure 2-31.

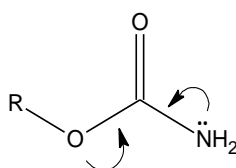


Figure 2-31

The first publication follows as per faculty guidelines, and discusses the synthesis of analogues of 2-oxo-2*H*-chromen-7-yl dimethylcarbamates and -thiocarbamates possessing an α oxygen or sulphur atom.

PAPER I

Synthesis of oxo- and thio- analogues of 2-oxo-2H-chromen-7-yl dimethylcarbamates**Caryl K. A. Janse van Rensburg and Ross S. Robinson***

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Abstract: A range of novel 2-oxo-2H-chromen-7-yl dimethylcarbamates were synthesised containing either an oxygen or sulphur in the α -position to the carbonyl or thiocarbonyl group of the amide moiety. The synthesis and spectroscopic data of these compounds are reported. Microwave synthesis was essential for the successful synthesis of some of the sulphur containing carbamates.

Introduction

Furocoumarins (psoralens) and their related coumarin derivatives, isopsoralens are well recognized for their photochemotherapeutic activity.¹⁻³ For this reason, there has been much research performed to optimise and provide new routes for their synthesis.^{2,4-7} Previous work within our group involved the development of a synthetic route toward derivatives of 7-oxo- and 7-thioisopsoralen derivatives substituted at the 5' position, as potential DNA intercalators.⁸ During this study, it was found that the 2-oxo-2H-chromen-7-yl dimethylcarbamate derivatives synthesised exhibited interesting and widely varying amide rotational barriers.

These barriers to internal rotation in amides are a result of resonance between the nitrogen lone pair and the carbonyl group. This results in a partial double bond character along the C-N bond. This model, proposed by L. Pauling has been the subject of much contention and extensive research has been conducted to examine the actual influences and reason for this rotation. The bulk of research in this area has been conducted on small molecules such as dimethylformamide (DMF), dimethylacetamide (DMA), and their thio analogues. There is

little literature however, concerning larger molecules with additional substituents on the nitrogen and/or at the α -position to the carbonyl.^{9,10}

With the intention to further study the barrier to internal rotation, a range of these compounds were synthesised to investigate the effect of an oxygen or sulphur substituent α to the amide carbonyl as illustrated in figure 1.

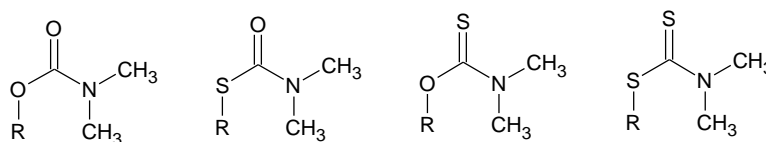
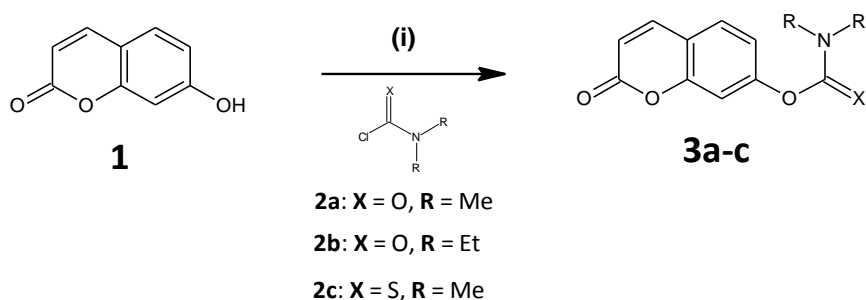


Figure 1

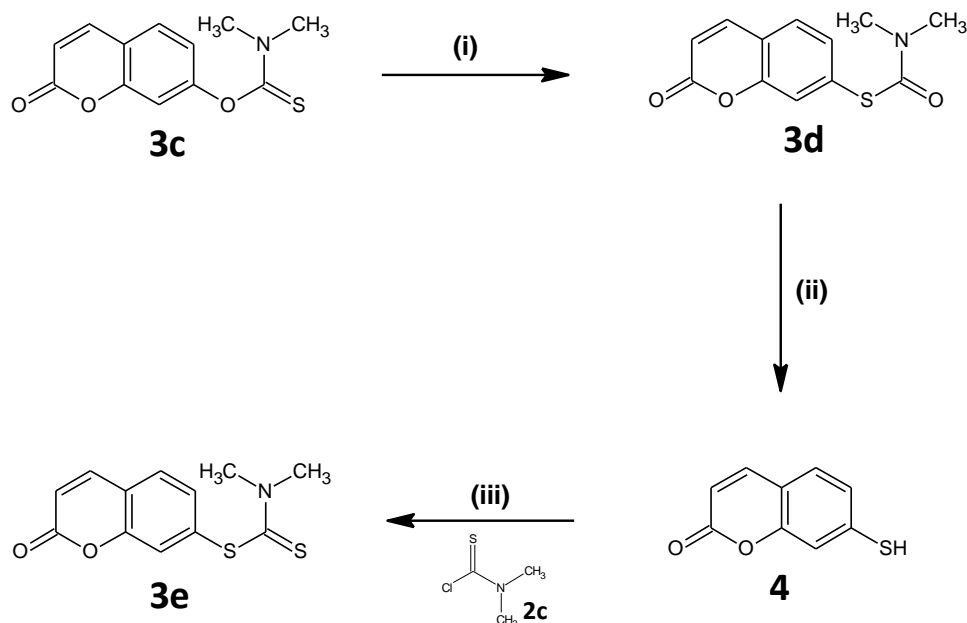
Results and Discussion

For carbamates (**3a-c**) possessing an oxygen α to the amide carbonyl, the synthetic route is shown in Scheme 1. 7-Hydroxycoumarin (**1**) was treated with NaH and subsequently reacted with the relevant carbamyl chloride (**2a-c**), to yield the 2-oxo-2*H*-chromen-7-yl dimethylcarbamates (**3a-c**) in 57-81% yields.



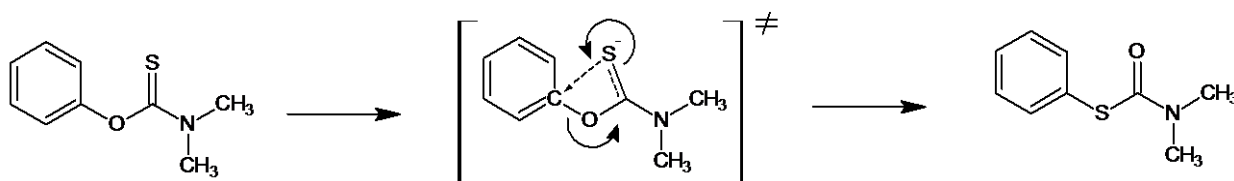
Scheme 1. (i) THF, NaH, then R_2NCXCl , 57-81%

In order to obtain analogues with sulphur at the α position, as shown in scheme 2, the prepared compound **3c** was subject to a Newman-Kwart type rearrangement to form **3d**.



Scheme 2. (i) DMA, μw , 250W, 260°C, 89%; (ii) KOH, MeOH, rf 7hr, then HCl (iii) THF, NaH, then $(\text{CH}_3)_2\text{NCSCl}$

The Newman-Kwart rearrangement has been shown computationally by Jacobsen *et al.* to occur through a four-member cyclic transition state in a concerted fashion (Scheme 3), which is consistent with earlier kinetic studies.¹¹⁻¹³ It has also been established by Jacobsen *et al.* that in order for this concerted process of C-O bond breaking and C-S bond formation in the transition state to occur, a π system connected *via* oxygen to the thiocarbonyl moiety is essential. More recently a bimolecular transition state fitting these criteria has been proposed which is also a concerted process but proceeds through an equivalent 8 member ring as shown in figure 2.¹⁴ This transition state remains as yet un-investigated.



Scheme 3. Mechanism of the Newman-Kwart rearrangement.

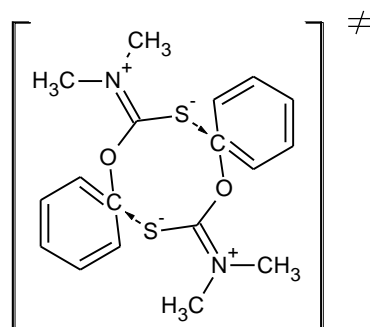


Figure 2. Proposed bimolecular transition state.¹⁴

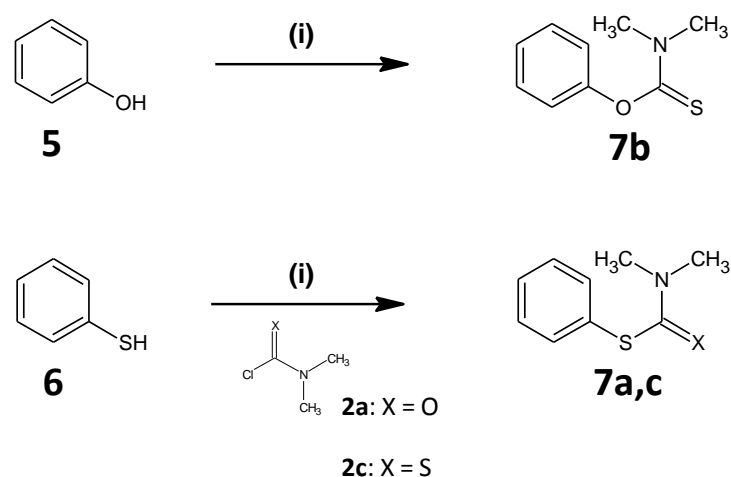
Although this reaction is well-documented,¹⁴⁻²² all attempts using conventional approaches failed to afford any product, yielding only charred remains. It has been reported that in some cases, decomposition occurs in the presence of atmospheric oxygen, before the rearrangement is able to take place.²² In our case, a nitrogen atmosphere was applied to avoid this problem; however, it did not prevent decomposition. Compound **3d** was subsequently obtained, to our delight, in 89% yield by use of microwave irradiation in the presence of a minimal volume of DMA. This result is attributed to non-thermal microwave effects. Interestingly, this result was obtained without the use of an inert atmosphere. Compound **3d** was subsequently used for both the rotational barrier investigations (which are currently under investigation) and as a starting material for **3e**.

In order to achieve the dithio analogues, it is necessary to cleave the carbamate group of compound **3d**, affording 7-mercapto-2*H*-chromen-2-one (**4**). This can subsequently be treated with NaH and further reacted with *N,N*-dimethylthiocarbamoyl chloride, forming 2-oxo-2*H*-chromen-7-yl dimethylcarbamodithioate (**3e**). Unfortunately obtaining **3e** was not possible and is explained below.

Cleavage of the carbamate group to afford **4** can be achieved in two ways, by reflux under basic conditions²³ as described below or by reaction with LiAlH₄.²⁴ Both of these methods were performed and both were found to be unsuccessful, with recovery of only the starting material. The former mentioned method was attempted using both convection heating and microwave irradiation; to our surprise, the latter did not afford any product either.

In summary, three of the four compounds required for further study were successfully synthesised (**3a-d**). Due to the inability to overcome the problem of cleaving the dimethylcarbamothioate group to yield **3e**, analogous phenolic compounds were synthesised

as described in Scheme 3. Using this approach, the calculated barriers of **7a** and **7b** will be compared to their coumarin counterparts to determine whether the coumarin ring has a similar effect on C-N rotation as the phenyl ring and consequently whether these can be considered equivalent. If so, the data obtained for **7c** may be substituted for that of **3e**.



Scheme 3. (i) THF, NaH, then $(\text{CH}_3)_2\text{NCXCl}$, 42–72%

Phenol (**5**) was used as starting material for **7b**, the equivalent for **3c**. To obtain the equivalents for **3d** and **3e**, thiophenol (**6**) was used as a precursor. Compound **7c** could be achieved either by using *N,N*-dimethylcarbamyl chloride with **6** or by Newman-Kwart rearrangement of **7b** under microwave irradiation.

The ^1H NMR spectra of these compounds show the methyl peaks of the amide resonate as two separate peaks, however, in some cases these peaks are already partially (**3d** and **7a**) or completely (**7c**) coalesced at room temperature. This indicates a lower barrier to internal rotation.

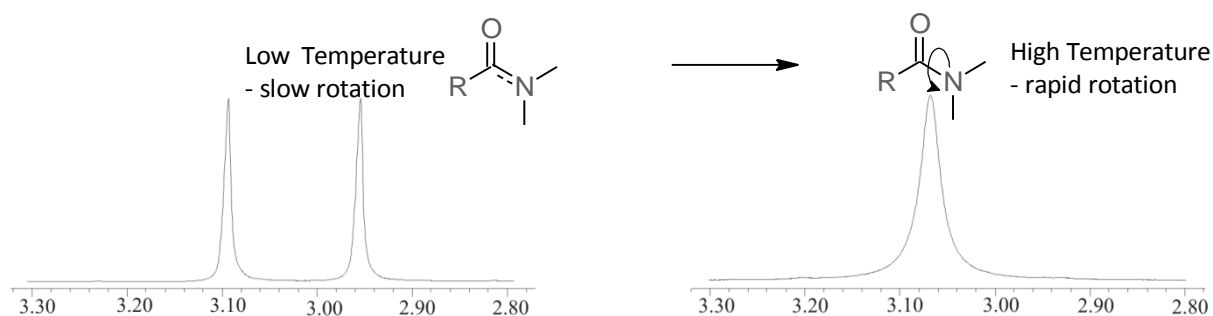


Figure 3. Coalescence of the amide ^1H NMR signals with increased temperature

A crystal structure of phenyl *N,N*-dimethylcarbamdithioate (**7c**), shows the molecules pack in a $P2_1/c$ space group and arrange perpendicular to one another.

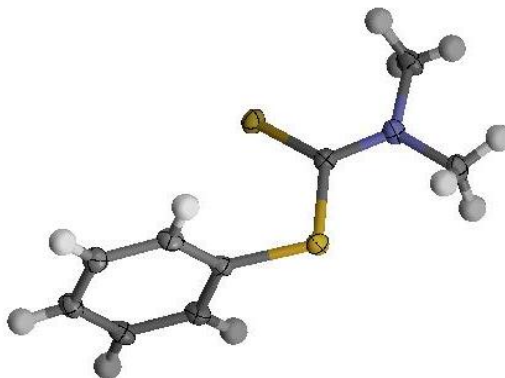


Figure 4. ORTEP model from crystal structure of compound 7c

As expected, the thioamide moiety is planar indicating the delocalisation between the amine and thiocarbonyl. It is also observed to be rotated 88.6° out of the plane of the phenyl ring. Examination of the bond lengths also support this ground state resonance; the C–N bond is found to be 1.336\AA in the crystal structure indicating it to be partial double bond, the literature value for this being 1.34\AA .²⁵ Interestingly, the C=S bond is found to be less than expected, indicating partial resonance at 1.661\AA ; comparing to literature values of 1.82\AA (C–S) and 1.56\AA (C=S).²⁵

One of the methods used to calculate the rotational barriers of these compounds is Exchange Spectroscopy (EXSY) NMR, a 2D NOESY method that makes use of the intensities of the relevant peaks to quantitate the magnetization exchange rates of the exchange equilibrium. This is achieved using the EXSYCalc program.²⁶ To do this, two spectra are required at mixing times of 0 and x (where x is large enough for the exchange process to occur). A representative example is shown in figure 5.

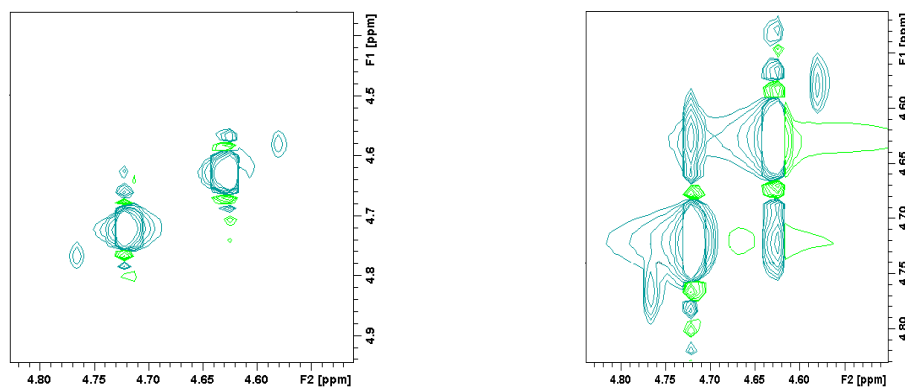


Figure 5. Partial ^1H 2D NOESY's showing the two methyl peaks of a dimethylcarbamothioate group at mixing times of a) 0 ms and b) 1147 ms

From the magnetisation exchange rates, the rotational barrier is calculated using the Eyring equation: $\Delta G_{\text{rot}} = -RT \ln(k_1 h / k_b T)$

Conclusion

Four of the five coumarin analogues (**3a-d**) were successfully synthesised, however attempts toward the dithio derivative (**3e**) proved unsuccessful. To circumvent this problem, phenyl analogues (**7a-c**) were synthesised in order to obtain suitable analogues for further investigation by NMR spectroscopy and computational techniques obtained for C-N rotation in these simpler analogues (**7c** in particular). To the best of our knowledge, very little research has been conducted, to date investigating the influence of substituents positioned *alpha* to the carbonyl on the amide rotational barrier. Consequently we believe the synthesis of these compounds is important in order to shed light upon such processes, which forms the part of an ongoing investigation.

Experimental

General

All NMR spectra, were obtained from CDCl_3 or $\text{C}_2\text{D}_2\text{Cl}_4$ reference solutions using a Bruker Avance 400 MHz Spectrometer. ^{13}C spectra were obtained at 100MHz.

Low-resolution mass spectra (electron impact) were obtained using a Thermofinnigan trace GC coupled with a Polaris Q mass spectrometer. Infrared spectra were recorded with a Perkin-Elmer Spectrum One spectrometer as thin films neat or as a nujol mix. Melting points were recorded using a Kofler Hotstage melting point apparatus and are uncorrected. Radial chromatography was performed on a Harrison Research Chromatatron model 7924T using a 2 mm layer of Merck silica gel 7749. The solvent system was delivered by gravity flow. Microwave reactions were performed in a CEM Discovers Microwave SystemTM. Tetrahydrofuran was distilled over sodium metal/benzophenone under a nitrogen atmosphere prior to use, and stored over 3Å molecular sieves. Distilled hexane was used for all chromatography.

X-Ray Crystallography

Crystallographic measurements were made using a 3 kW Spellman X-ray generator with a 3 kW ceramic X-ray tube and an Xcalibur 2 CCD diffractometer. The structure was solved using the SHELXS-97²⁷ program by direct methods. The structure was plotted using the program ORTEP.²⁸ Detailed crystallographic data for compound **7c** have been deposited at the Cambridge Crystallographic Data Centre and are available on request (CCDC No. 711835)

Crystal Data of Compound 7c. C₉H₁₁NS₂, *M*=197.31, *T*=100(2) K, λ =0.71073 Å, *a*=7.538(5), *b*=8.989(5), *c*=14.229(5) Å, α =90.000(5)°, β =90.959(5)°, γ =90.000(5)°, *V*=964.0(9) Å³, space group *P*2₁/*c*, *Z*=4, *D*_x=1.359 mg m⁻³, μ =0.495 mm⁻¹, *F*(000)=416. Crystal Size 0.6x0.55x0.25 mm; θ range for data collection 3.82–34.11°; index range –10<*h*<11, –13<*k*<13, –21<*l*<21; reflections collected 14324; independent reflections 3567 [*R*_(int)=0.0538]; refinement method full-matrix least-squares on *F*²; data/restraints/parameters 3567:0:153; goodness-of-fit on *F*² 1.071; *R*(*F*) [*I*>2σ(*I*)]=0.0568; *wR*₂=0.1461; largest diff. peak and hole 1.721 and -0.986 e Å⁻³.

Typical Synthesis of O-(2-oxo-2H-chromen-7-yl) *N,N*-dimethylcarbamothioate (3c)

NaH (0.093g of an 80% oil dispersion, 3.2mmol) was added to a 100ml round bottom flask under a dry nitrogen atmosphere. This was washed with a little THF to remove the oil. 7-hydroxy-2H-chromen-2-one (0.50g, 3.09mmol) was then dissolved in dry THF (40ml) in a round bottom flask and transferred *via* canula to the reaction vessel. This was allowed to stir

at rt for 30min until evolution of hydrogen gas had ceased. Dimethylthiocarbamoyl chloride (0.396g, 3.2mmol) was transferred *via* canula into the reaction as a solution in dry THF. The solution was then stirred at 60°C for a further 30min with a nitrogen-containing balloon to allow for increased pressure. The solution was then cooled and concentrated to 10ml *in vacuo* after which it was poured over ice-water causing precipitation. This was filtered and recrystallised from ethanol to give the product as white crystals (0.636g, 81%).

m.p. 182-183°C (lit.²⁹ 156-157°C).

¹H NMR (500 MHz, C₂D₂Cl₄) δ (ppm) = 4.64 and 4.73 [2xs, 6H, N(CH₃)₂], 7.68 (d, 1H, J = 9.52 Hz, H-3), 8.35 (dd, 1H, J = 2.22 and 8.30 Hz, H-8), 8.37 (d, 1H, J = 2.08 Hz, H-6), 8.79 (d, 1H, J = 8.32 Hz, H-5), 9.02 (d, 1H, J = 9.56 Hz, H-4).

¹³C NMR (100 MHz, C₂D₂Cl₄) δ (ppm) = 40.4 and 44.8 [N(CH₃)₂], 112.9 (C-8), 117.2 (C-2), 118.0 (C-4), 121.3 (C-6), 129.6 (C-5), 144.6 (C-3), 155.7 (C-9), 157.6 (C-1), 161.9 (C-7), 187.6 (C-10).

IR (neat): 2933, 1713, 1700, 1620, 1538, 1119, 839.

MS (EIMS): *m/z* (%) = 249 [M⁺] (5), 207 (2), 177 (6), 149 (7), 121 (9), 77 (6), 72 (100).

Attempted synthesis of S-(2-oxo-2H-chromen-7-yl) *N,N*-dimethylcarbamothioate (6c)

O-(2-oxo)-2H-chromen-7-yl) *N,N*-dimethylcarbamothioate (0.100g, 0.40mmol) was heated neat under nitrogen for 40min at 240 - 260°C. This was then cooled and an attempt to recrystallise from ethanol yielded only insoluble charred remains with 14% starting material recovered. Attempts in refluxing solvent also failed, yielding the same insoluble remains with varying recovery of starting material.

Synthesis of S-(2-oxo-2H-chromen-7-yl) *N,N*-dimethylcarbamothioate (6c)

O-(2-oxo)-2H-chromen-7-yl) *N,N*-dimethylcarbamothioate (64mg, 0.26mmol) was dissolved in 2ml DMA in a microwave pressure tube and irradiated with 260W for 40min (cooling off). The solution was then cooled and 1ml distilled water added, causing precipitation of the product as a light orange solid. This was filtered and washed with cold water (2 x 6ml aliquots) yielding 57mg of the product (89%).

m.p. 179 - 184°C (lit.²⁹ 180 - 183°C).

¹H NMR (500 MHz, C₂D₂Cl₄) δ (ppm) = 4.30 and 4.37 [2xs, 6H, N(CH₃)₂], 7.72 (d, 1H, J = 9.55 Hz, H-3), 8.71 (dd, 1H, J = 1.45 and 8.05 Hz, H-6), 8.76 – 8.79 (m, 2H, H-5 and H-8),

9.01 (d, 1H, $J = 9.45$ Hz, H-4).

^{13}C NMR (100 MHz, $\text{C}_2\text{D}_2\text{Cl}_4$) δ (ppm) = 30.8 (C-10), 117.0 (C-3), 118.8 (C-4a), 123.0 (C-8), 127.5 (C-5), 131.0 (C-6), 133.5 (C-7), 142.8 (C-4), 153.2 (C-8a), 160.1 (C-2), 165.0 (C-9).

IR (neat): 3051, 2928, 1717, 1664, 1601, 1392, 848.

MS (EIMS): m/z (%) = 249 [M^+] (6), 207 (1), 177 (7), 149 (8), 121 (10), 77 (6), 72 (100).

Synthesis of 2-oxo-2H-chromen-7-yl *N,N*-dimethylcarbamate (3a)

Method was carried out as described for **3c** above. NaH (0.093g of an 80% oil dispersion, 3.2mmol), 7-hydroxy-2H-chromen-2-one (0.50g, 3.09mmol), dimethylcarbamyl chloride (0.342g, 3.2mmol). The remaining peach solid was purified by radial chromatography (1:2 ethyl acetate-hexane) to yield the product as white crystals (0.422g, 57%).

m.p. 148 - 154°C (lit.²⁹ 149 - 150°C)

^1H NMR (500 MHz, CDCl_3) δ (ppm) = 2.96 and 3.05 [2xs, 6H, $\text{N}(\text{CH}_3)_2$], 6.30 (d, 1H, $J = 9.65$ Hz, H-3), 7.02 (dd, 1H, $J = 2.20$ and 8.44 Hz, H-6), 7.06 (d, 1H, $J = 2.12$ Hz, H-8), 7.38 (d, 1H, $J = 8.44$ Hz, H-5), 7.61 (d, 1H, $J = 9.52$ Hz, H-4).

^{13}C NMR (100 MHz, $\text{C}_2\text{D}_2\text{Cl}_4$) δ (ppm) = 36.5 and 36.8 [$\text{N}(\text{CH}_3)_2$], 110.4 (C-8), 115.6 (C-3), 116.1 (C-4a), 118.6 (C-6), 128.3 (C-5), 142.9 (C-4), 153.8 (C-7), 154.2 (C-8a), 154.7 (NCO), 160.6 (C-2).

IR (neat): 2904, 2724, 1460, 1376, 722

MS (EIMS): m/z (%) = 233 [M^+] (8), 133 (2), 105 (3), 77 (4), 72 (100), 51 (3).

Synthesis of 2-oxo-2H-chromen-7-yl *N,N*-diethylcarbamate (3b)

Method was carried out as described for **3c** above. NaH (0.093g of an 80% oil dispersion, 3.2mmol), 7-hydroxy-2H-chromen-2-one (0.50g, 3.09mmol), diethylcarbamyl chloride (0.434g, 3.2mmol). The product was obtained as a viscous mustard liquid, which could not be recrystallised or purified due to its tackiness.

^1H NMR (500 MHz, CDCl_3) δ (ppm) = 1.24 and 1.29 [2xt, 6H, $J = 7.15$ Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$], 3.42 and 3.47 [2xq, 4H, $J = 6.86$ Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$], 6.38 (d, 1H, $J = 9.54$ Hz, H-3), 7.12 (dd, 1H, $J = 2.26$ and 8.53 Hz, H-6), 7.15 (d, 1H, $J = 2.26$ Hz, H-8), 7.48 (d, 1H, $J = 8.28$ Hz, H-5), 7.70 (d, 1H, $J = 9.54$ Hz, H-4).

^{13}C NMR (100 MHz, $\text{C}_2\text{D}_2\text{Cl}_4$) δ (ppm) = 10.8 and 11.7 [$\text{N}(\text{CH}_2\text{CH}_3)_2$], 39.6 and 39.9

[N(CH₂CH₃)₂], 107.7 (C-8), 112.8 (C-3), 113.4 (C-4a), 116.2 (C-6), 125.9 (C-5), 140.8 (C-4), 115.6 (C-7), 115.9 (C-8a), 153.1 (NCO), 158.3 (C-2).

MS (EIMS): m/z (%) = 260 [M^+] (6), 134 (8), 100 (100), 72 (56), 44 (26).

Synthesis of *o*-phenol *N,N*-dimethylcarbamoithioate

Method was carried out as described for **3c** above. NaH (0.147g of an 80% oil dispersion, 4.90mmol), phenol (0.419g, 4.45mmol), dimethylthiocarbamoyl chloride (0.660g, 5.34mmol). The product was extracted with dichloromethane and purified by radial chromatography (1:2 ethyl acetate-hexane), to give 583mg (72%) as a yellow oil.

lit.²⁹ m.p. 31 - 32°C

¹H NMR (500 MHz, C₂D₂Cl₄) δ (ppm) = 3.31 an 3.43 [2xs, 6H, N(CH₃)₂], 7.08 (2xd, 2H, J = 8.40 and 8.70 Hz, -O-C=CH-CH=CH-), 7.26 (t, 1H, J = 7.42 Hz, -O-C=CH-CH=CH-), 7.40 (t, 2H, J = 7.95 Hz, -O-C=CH-CH=CH-).

¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 38.7 and 43.2 [N(CH₃)₂], 122.8 (O-C=CH-CH=CH), 125.9 (O-C=CH-CH=CH), 129.2 (O-C=CH-CH=CH), 154.1 (O-C=CH-CH=CH), 187.8 [-O-(C=S)-N].

IR (neat): 3340, 2940, 1781, 1535, 1395, 1206, 769, 691.

MS (EIMS): m/z (%) = 181 [M^+] (4), 180 (12), 88 (58), 72 (100).

Synthesis of *S*-phenyl *N,N*-dimethylcarbamoithioate: Method 1

O-phenol *N,N*-dimethylcarbamoithioate (200mg, 1.10mmol) was dissolved in 2ml DMA in a microwave pressure tube and irradiated with 260W for 40min (cooling off). The solution was then cooled and 1ml distilled water added, causing deposition of the product as a dark orange oil. The DMA/water solution was decanted, to leave the oil product. Conversion was accomplished in 50% yield by NMR.

Synthesis of *S*-phenyl *N,N*-dimethylcarbamoithioate: Method 2

Method was carried out as described for **3c** above. Thiophenol (0.656g, 5.95mmol), NaH (0.157g, 6.54mmol), dimethylcarbamyl chloride (0.735g, 5.95mmol). The product was extracted with dichloromethane and purified by radial chromatography (1:2 ethyl acetate-hexane) to give 679mg (63%) as a light yellow oil, which solidified under vacuum.

m.p. 41 - 42°C (lit.¹⁵ 43 - 44°C)

¹H NMR (500 MHz, CDCl₃) δ (ppm) = 4.32 [br. s, 6H, N(CH₃)₂], 8.65-8.72 (m, 3H), 8.76-8.82 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 38.37 (N(CH₃)₂), 130.17 (S-C=CH-CH=CH), 130.3 (S-C=CH-CH=CH), 130.5 (S-C=CH-CH=CH), 137.1 (S-C=CH-CH=CH), 168.0 [S-(C=O)-N].

IR (neat): 2974, 2885, 1455, 1380, 1090, 881.

MS (EIMS): *m/z* (%) = 180.9 [M⁺] (6), 109 (7), 72.1 (100), 65.2 (6), 39.1 (3).

Synthesis of Phenyl *N,N*-dimethylcarbamdithioate

NaH (0.128g of an 80% oil dispersion, 4.26mmol), thiophenol (0.427g, 3.87mmol), dimethylthiocarbamoyl chloride (0.574g, 4.65mmol). The product was extracted with dichloromethane and purified by radial chromatography (1:2 ethyl acetate-hexane), to give 321mg (42%) as a yellow solid.

m.p. 88 – 92°C (lit.³⁰ 93 – 94°C)

¹H NMR (500 MHz, CDCl₃) δ (ppm) = 3.52 and 3.57 [2xs, 6H, N(CH₃)₂], 7.43 – 7.53 (m, 5H).¹³C

NMR (100 MHz, CDCl₃) δ (ppm) = 42.0 and 45.6 (N(CH₃)₂), 129.1 (S-C=CH-CH=CH), 130.0 (S-C=CH-CH=CH), 131.8 (S-C=CH-CH=CH), 136.9 (S-C=CH-CH=CH), 197.6 [S-(C=S)-N].

IR (neat): 3071, 1948, 1864, 1574, 1438, 1071, 738, 688.

MS (EIMS): *m/z* (%) = 197 [M⁺] (6), 196 (42), 88 (100).

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END – PAPER I

In conclusion, a range of oxo- and thio- analogues of 2-oxo-2*H*-chromen-7-yl dimethylcarbamates were successfully synthesized with the exception of the dithio derivative. To circumvent the problem of not having this derivative for further investigation, analogous compounds were synthesized from phenol and thiophenol. The Newman-Kwart rearrangement of the *O*-thiocarbamate was unsuccessful under normal conditions and could only be performed using microwave irradiation. With these compounds in hand, calculation of their rotational barriers was undertaken by *ab initio* methods as well as variable temperature and EXSY NMR spectroscopic techniques. The details of these methods are detailed in the body of the publication below. Traditionally, amide resonance is explained by Pauling's model as shown in Scheme 2-36(p. 104), however there has been much debate as to the accuracy and applicability of this model as it does not adequately explain the higher rotational barriers of thioamides as compared to their amide analogues. In fact it predicts the opposite. Investigations into the origins of this are ideally performed by computational methodology. The second publication thus investigates both the barriers to internal rotation as described above as well as the mechanisms behind the origin of the barrier.

PAPER II:

Part II: *Ab Initio* and NMR Investigations into the Barrier to Internal Rotation of various oxo- and thio- analogues of 2-oxo-2*H*-chromen-7-yl dimethylcarbamates

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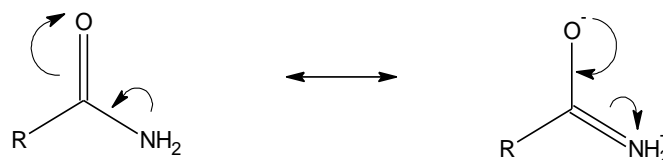
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*Abstract: The rotational barriers of a range of 2-oxo-2*H*-chromen-7-yl dimethylcarbamates, containing either an oxygen or sulphur α to the carbonyl or thiocarbonyl group of the amide moiety were investigated. Variable Temperature and Exchange Spectroscopy NMR was performed on these compounds and the barrier to free amide rotation was calculated. Each of these compounds were also modelled *ab initio* and the gas phase barrier to rotation calculated. These three sets of data were compared and the influence of the α -heteroatom on rotation for amides and thioamides evaluated.*

Introduction

The barrier to internal rotation in amides and thioamides has been the subject of much attention over past years due to the importance of the amide bond in proteins (and peptides), the secondary and tertiary structure thereof and thus their biological activity.¹⁻⁴ In the application of peptide design and elucidation of the structure-activity relationships thereof, it is crucial to understand the conformational properties of such amide bonds.⁵ Similarly carbamates have gained importance in peptide chemistry as a protecting strategy for the amine groups of amino acid moieties.⁶ They also play an important function in the pharmaceutical, agricultural, and chemical industries, reiterating the importance in understanding the methods and influences of amide resonance.⁷⁻⁹ For like reasons, thiocarbamates and selenocarbamates are of equal importance.⁹⁻¹¹

The most widely used and generally accepted explanation for the hindered rotation is the classical model of chemical resonance as proposed by L. Pauling (1977)^{12,13} shown in Scheme 1.



Scheme 1

Transfer of the nitrogen lone pair to the electron deficient carbonyl carbon results in delocalized π character along the N-C-O bonds. Accordingly, the C-N bond is stabilized by the above ionic configuration in planar amides by adopting partial double bond character.⁶ It has long been known that thioamides have a larger barrier to internal rotation than their amide analogues, however according to Pauling's model, the lesser electronegativity of sulphur compared to oxygen predicts the opposite effect (!).¹ For this reason, a new model has been put forward by Wiberg *et al.* that proposes electron transfer on rotation occurs in the direction of $C \rightarrow N$ rather than $O \rightarrow N$ as illustrated above.¹⁴⁻¹⁶ Because oxygen is more electronegative than carbon, it withdraws electron density to itself, polarizing the C=O bond in both the σ and π systems.¹⁷ This in turn allows the nitrogen lone pair to merge into a p orbital capable of interacting with the deficient carbon.¹⁷ *Ab initio* studies led by Wiberg *et al.* on formamide revealed that the oxygen is effectively a spectator to the process of rotation away from planarity. Evidence for this is seen by examining both the bond lengths and charge distributions on the carbonyl and C-N bonds. On rotation from planarity, the length of the C-N bond increases by 0.08 Å where the C-O bond decreases only 0.01 Å,¹⁴ this indicates there is partial double bond character in the planar form originating from the C-N bond and the carbonyl is reasonably unaffected. This does not however explain why thioamides have a larger rotational barrier than amides. *Ab initio* studies have shown that amide resonance, and thus the magnitude of the barrier, increases as the electronegativity of the chalcogen decreases.⁸ Further research has found that this increase is due to greater π -electron conjugation to the chalcogen.^{18,19} Since it is known the electron delocalization in amides involves the $n_N \rightarrow \pi^*_{[C-X]}$ transfer, the closer in energy these orbitals are, the greater the overlap is.^{8,20}

Extensive studies have been performed on *N,N*-dimethylacetamide (DMA), *N,N*-dimethylformamide (DMF),^{18,21,22} as well as thioformamides,¹⁸ selenamides,²³ carbamates²⁴ and others^{25,4} to determine the effects of solvent on the rotational barriers. One of the earliest reports on this topic by Drakenberg *et al.* presented an NMR line shape analysis of DMF and DMA in various solvents to determine the barrier. They have found that proton-donating solvents such as H₂O hydrogen bond to the amide oxygen, thereby increasing the rotational barrier by *ca.* 8-12 kJmol⁻¹ (2-3 kcal/mol). Solvents capable of associating with the amide oxygen increase the barrier by *ca.* 4 kJmol⁻¹ (1 kcal/mol).²² Likewise this indicates that in dilute nonpolar solutions, the natural association that would normally have existed in neat solutions between amide molecules is severed.

More recently, Wiberg *et al.* published a combined experimental and theoretical study on the effect of solvent. In accord with earlier reports, it was found that the barriers of DMA and DMF increased in polar solvents. The reason for this observation being greater stabilization of the ground state as it is more polar than the transition states. However it was also noted that the effect of solvent on DMA was appreciably larger than DMF. As DMA prefers the anti-TS which has a smaller dipole moment, the difference in stabilization between ground and transition states is thus much greater resulting in an enhanced solvent effect.¹⁸ These effects were coherent with those obtained for *N,N*-dimethylthioformamide (DMTF) and *N,N*-dimethylthioacetamide (DMTA), excepting that the solvent effects on thioamide analogues are significantly larger. The reason for this being the greater difference in dipoles between ground and transition state due to the larger ground state dipole moment of thioamides.¹⁸

Additional investigations on selenoamides have shown that substitution of H at the α -position with a more electronegative or electron withdrawing group results in a decrease in the rotational barrier, while electron donating groups have shown to increase the barrier.^{23,26} This increase is a result of increased resonance through the nitrogen lone pair. However, this is not always the case as shown by Kaur *et al.* with π -donors at the α -position such as NO₂ and CN, as they stabilize the transition states resulting in the observed decrease in the rotational barrier.²³ Also noted in a study of amide resonance in thio- and seleno- carbamates,⁸ the substitution of sulphur for selenium caused an increase in the rotational barrier. This was attributed to the larger size of selenium which in turn causes a decrease in the $n_X \rightarrow \pi^*_{[C-O]}$ transfer and thus less competition for population of the $\pi^*_{[C-O]}$ orbital.

There are various reported methods to experimentally measure the barrier to rotation, among these are; variable temperature NMR,²⁷⁻³¹ Exchange Spectroscopy NMR,³²⁻³⁵ NMR line shape analysis,³⁶⁻³⁸ pre-saturation³⁹ and computational methods.³ Stemming from previous research performed within our group on the synthesis of various thio and oxo analogues of isopsoralen as potential DNA intercalators, these exhibited varying rotational barriers worthy of further investigation.^{40,41} For this study we have chosen Variable Temperature and Exchange Spectroscopy NMR as well as a Computational approach to evaluate the influence of an oxygen or sulphur substituent at the α -position of amide and thioamide variants of 2-oxo-2*H*-chromen-7-yl *N,N*-dimethylcarbamate on the rotational barrier.

Variable Temperature NMR Spectroscopy is used to determine the coalescence temperature of an exchangeable process sufficiently slow at low temperatures to produce distinct signals. As the temperature is increased, a coalescence of these signals is seen to occur until the exchange process is sufficiently fast so as to become indistinguishable by NMR resulting in a single broad signal. Figure 1 shows a characteristic coalescence at 316K of the two methyl peaks of a dimethylcarbamoethioate group.⁴⁰

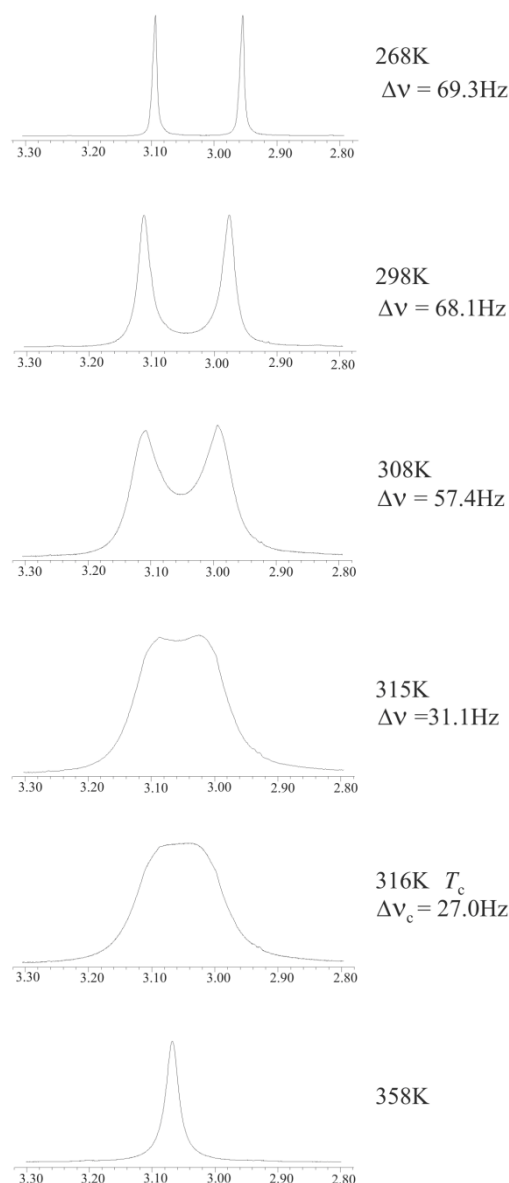


Figure 1.: Partial ^1H NMR Spectrum showing coalescence of two methyl peaks of a dimethylcarbamothioate group⁴⁰

Once the coalescence temperature, T_c , has been determined, there are two possible techniques to calculate the rotational barrier, ΔG . The first is illustrated by equation 1:

$$\Delta G = 2.303 RT_c (\log k_b T_c / h - \log 2.22 \Delta\nu) \quad \text{Eq. 1}$$

Where R = Gas Constant

T_c = Coalescence Temperature (K)

k_b = Boltzmann's Constant

h = Planck's Constant

$\Delta\nu$ = Difference in chemical shift when signals are at maximum separation (Hz)

The other method as reported by Smith *et al.*²⁸ makes use of $\Delta\nu_c$, the estimated difference in chemical shift at the coalescence point, and is calculated as follows:

$$\Delta G = RT_c [22.96 + \ln (T_c / \Delta\nu_c)] \quad \text{Eq. 2}$$

Although theoretically similar, in practice equation 1 is preferable as it becomes indeterminate where exactly the ‘correct’ coalescence occurs and additionally difficult to determine $\Delta\nu_c$ if the signals have coalesced.

Exchange spectroscopy is a 2D NOESY method, which makes use of two spectra, one taken with no mixing time and one taken with a mixing time large enough for the magnetization exchange process to take place. A typical example is shown in figure 2.

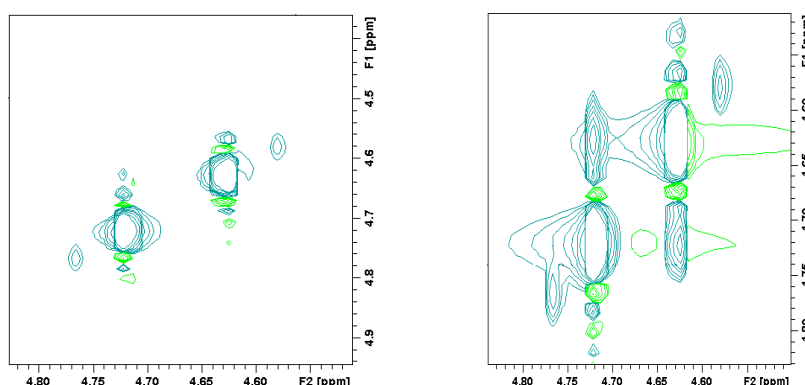


Figure 2. Partial ^1H 2D NOESY's showing the two methyl peaks of a dimethylcarbamothioate group at mixing times of a) 0 ms and b) 1147 ms

Using the intensities of the relevant peaks, it is possible to quantitatively calculate the magnetization exchange rates of the exchange equilibrium (k'), which is related to the rate constants of the reaction (k). This is achieved using the EXSYCalc program.⁴² In turn, the rate constant is used to calculate the rotational barrier from the Eyring equation:

$$\Delta G = -RT \ln(k_1h/k_bT) \quad \text{Eq. 3}$$

Where, R = Gas Constant

h = Planck's Constant

k_b = Boltzmann's Constant

T = Temperature at the spectra were recorded (K)

k_1 = Reaction Rate Constant

The purpose of the zero mixing time experiment is as a reference.

Results and Discussion

A range of carbamates were synthesized as previously described,⁴³ (see figure 3) and the three techniques were employed to investigate and contrast their amide rotational barriers.

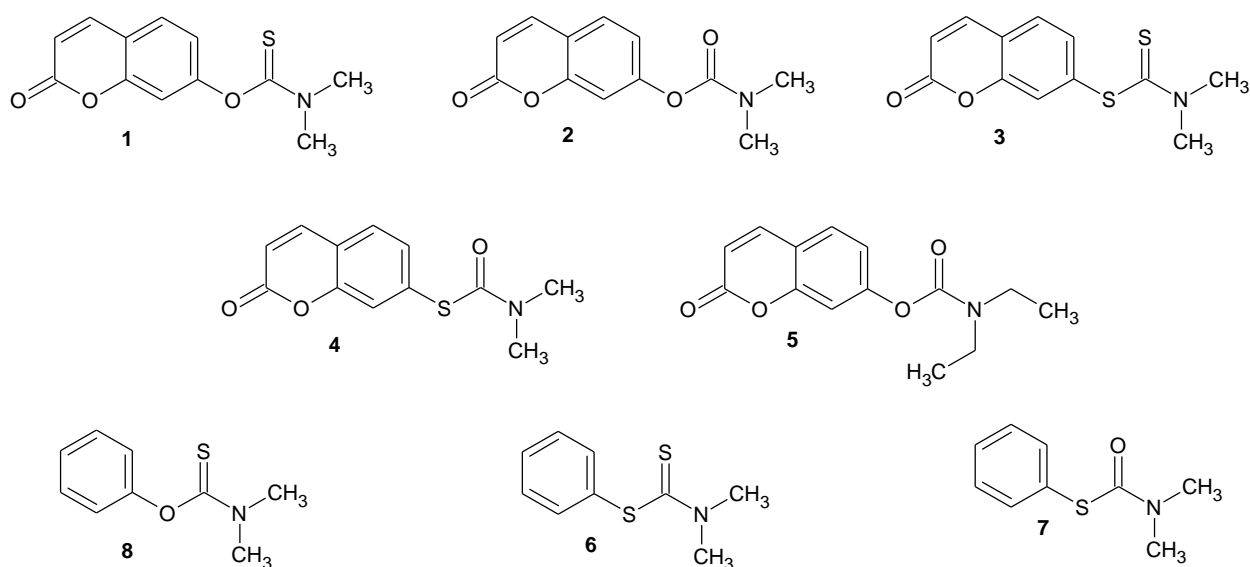


Figure 3. Carbamate compounds to be investigated

For ease of discussion, the following analysis methods are discussed only for compound **1** shown above. Raw data sets obtained for this compound from each technique are shown in table 1.

Variable Temperature NMR was carried out in deuterated 1,1,2,2-tetrachloroethane to accommodate the wide temperature range required for this study. The barrier to rotation was then calculated using equation 1.

Exchange Spectroscopy (EXSY) was chosen for comparison of results with those obtained by variable temperature, as well as to evaluate this fairly new technique as a reliable method to

calculate rotational barriers. As solvent has an effect on the rotational barrier,^{18,21,22} the same solvent was selected as for the variable temperature study, namely deuterated 1,1,2,2-tetrachloroethane, to exclude variations in the solvent effect. The absolute integrals of the amide methyl and cross peak areas were quantified and using the EXSYCalc program to yield the chemical exchange rate constants. This value was then substituted into the Eyring equation to calculate the rotational barrier, $\Delta_{\text{rot}}G^\circ$.

To evaluate ΔG from computational data, first the structure of each compound was optimized to a ground state, from which a 360° scan of the X=C-N-CH₃ dihedral was performed. Following this rotation profile, two transition states were identified: where the nitrogen lone pair and carbonyl heteroatom are respectively *syn* or *anti* to one another. To avoid unnecessary calculations, it was assumed that the most stable conformation with respect to rotation about the α -position would be where the coumarin system and amide moiety are perpendicular to one another.

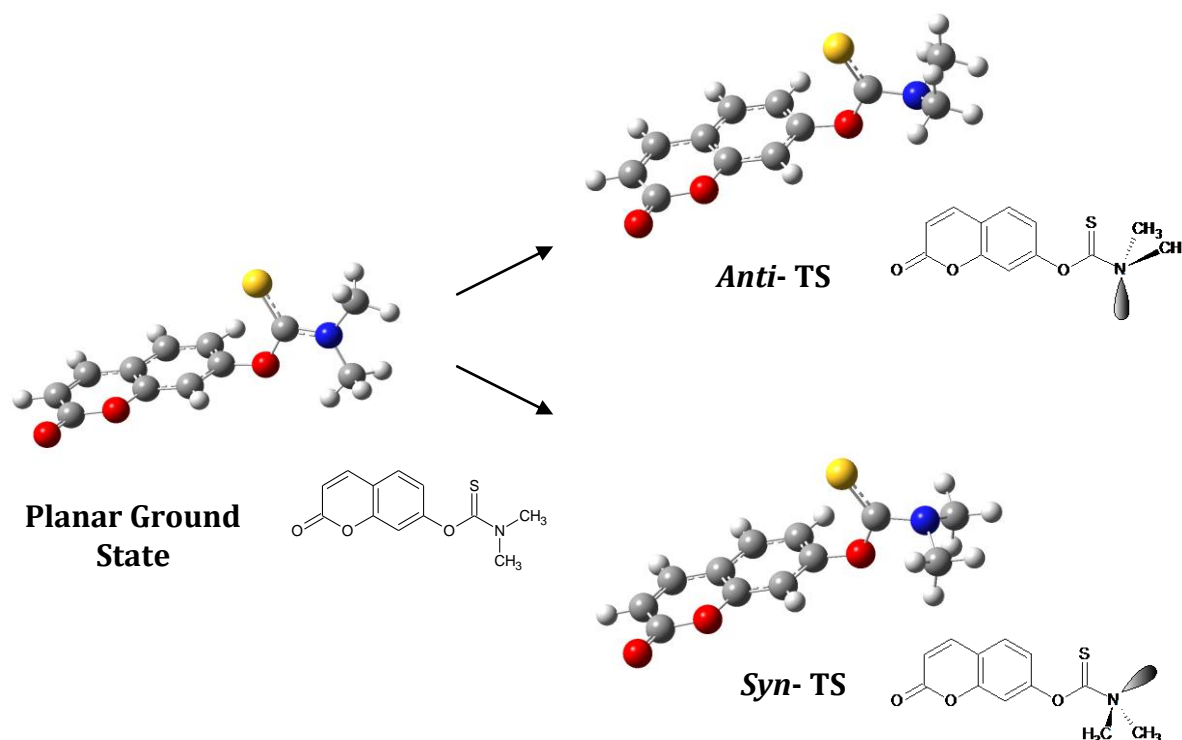


Figure 4. The *syn*- and *anti*- transition states [B3LYP/6-31+G(d)]

It was found that the higher energy transition state was that of the *syn* conformer (+ 4.22 kJmol⁻¹), correlating to electronic repulsion between the nitrogen lone pair and applicable

chalcogen. Frequency calculations performed on the geometry optimized transition states exhibited a single imaginary vibration corresponding to amine rotation away from the amide chalcogen. This verifies they are indeed true transition states of the rotation.

In order to obtain the rotational barrier for each molecule, frequency data was obtained for all optimised ground and transition states, and the following equation was used: ⁴⁴

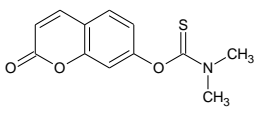
$$\Delta_{\text{rot}}G^{\circ} = \Delta G^{\circ}_{\text{ground state}}(298\text{K}) - \Delta G^{\circ}_{\text{transition state}}(298\text{K})$$

However, since the computational output only provides the sum of electronic and thermal energies, this equation transforms as follows:

$$\Delta_{\text{rot}}G^{\circ}(298\text{K}) = (\epsilon_0 + G_{\text{corr}})_{\text{ground state}} - (\epsilon_0 + G_{\text{corr}})_{\text{transition state}}$$

Where, ϵ_0 is the total electronic energy. In this way two rotational barriers are obtained, each corresponding to rotation through their respective transition states. Similarly, it is possible to calculate $\Delta_{\text{rot}}H^{\circ}$ and $\Delta_{\text{rot}}S^{\circ}$.

Table 1. Raw data used to calculate ΔG obtained from each method

| Structure | Raw Data | | | | |
|-------------------------------------------------------------------------------------|----------------|------------------------------------------------------------|--------------------------------------------|-------------------------------------------------------------|--------------------------------------------|
|  | EXSY | k_1 | $\Delta_{\text{rot}}G / \text{kJmol}^{-1}$ | k_{-1} | $\Delta_{\text{rot}}G / \text{kJmol}^{-1}$ |
| | | 1.513 | 72.00 | 0.027 | 81.98 |
| | Variable Temp. | T_c / K | $\Delta\nu / \text{Hz}$ | $\Delta_{\text{rot}}G / \text{kJmol}^{-1}$ | |
| | | 393 | 46.70 | 82.01 | |
| | Computational | $\Delta_{\text{rot}}G_{\text{syn-ts}} / \text{kJmol}^{-1}$ | | $\Delta_{\text{rot}}G_{\text{anti-ts}} / \text{kJmol}^{-1}$ | |
| | | 78.18 | | 82.41 | |

Looking at the variation in bond length with amide rotation, it is seen that the C=S bond varies very little on rotation with the key changes occurring in the C-N and C-O bonds. These changes are shown in table 2 and graphically illustrated in figure 5.

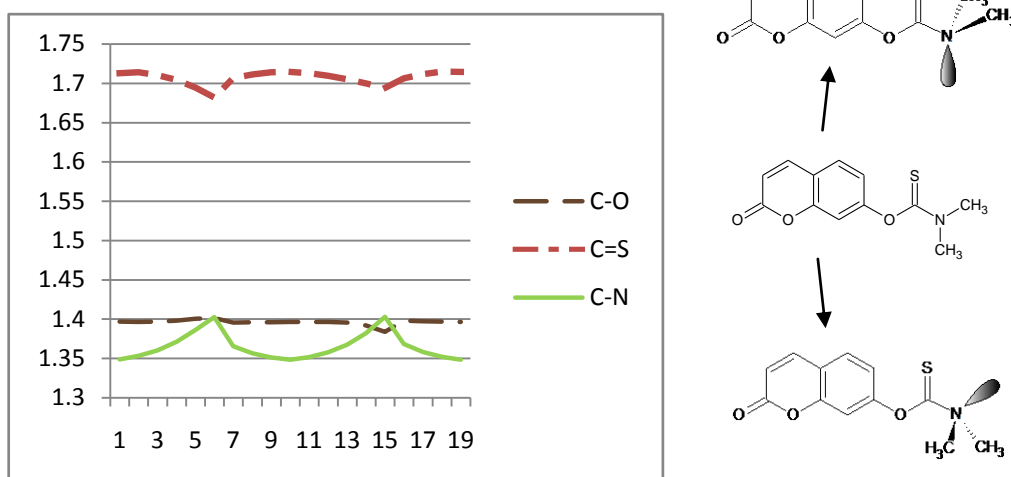
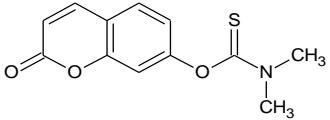


Figure 5. Typical Variation of the Calculated Bond Length with Dihedral Rotation through 360° [B3LYP/6-31+G(d)]

From figure 5 we see that the C-O bond is almost completely unaffected by rotation. The C=S bond is also essentially unaffected with only a slight decrease in bond length compared to the large increase in the length of C-N. Numerical values are shown in table 2.

Table 2. Selected bond lengths for the two calculated transition states of compound 1

| Structure | Bond Length Change ^{a,b} /Å | | |
|-----------------------------------------------------------------------------------|--------------------------------------|----------|---------|
|  | O-C | C=S | C-N |
| Syn- Transition State | -0.00342 | -0.03188 | 0.0627 |
| Anti- Transition State | -0.0182 | -0.02284 | 0.06811 |

^a Difference between ground and transition state structures.

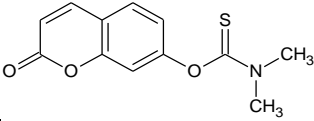
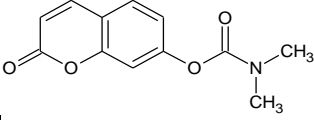
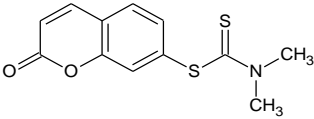
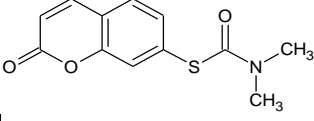
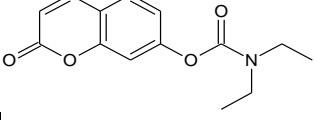
^b A negative change in bond length indicates shortening

The C=S bond decreases by 0.02-0.03 Å, where the C-N bond lengthens by a larger 0.06-0.07 Å, clearly indicating the main participants in this electron delocalization are the carbonyl carbon and nitrogen atoms. These results are consistent with those obtained by Wiberg *et al.*¹⁴ and likewise contradict Pauling's classical model of resonance. Interesting to note is that C-O bond length decreases more in the anti-TS while the C=S bond length shortens in the *syn*-TS. This suggests that there is greater $n_O \rightarrow \pi^*_{[C=S]}$ transfer in the *syn*-TS, whereas there is greater $n_N \rightarrow \pi^*_{[C=S]}$ transfer in the *anti*-TS. This same trend is observed for all the compounds investigated.

Since there is a preference for rotation through the lower energy anti-TS, these were the computationally obtained values used to be a more accurate representation of the measured quantities, although in reality, the latter is undoubtedly larger due to a statistical mixture of rotation through both transition states.

Comparative data is shown in tables 3 and 4. As can be seen, the NMR and computational methods are in excellent agreement with one another. As the molecular calculations were performed in the gas phase, the experimental values are on the whole larger due to solvent and other interactive molecular effects.

Table 3. Free energies of rotation for coumarin analogues

| Entry | Carbamate | Variable Temperature NMR ^a | Exchange Spectroscopy NMR ^b | Computational Data |
|-------|------------------------------------------------------------------------------------|---------------------------------------|----------------------------------------|--------------------------------------------------------|
| 1 |  | $\Delta G = 82.01 \text{ kJmol}^{-1}$ | $\Delta G = 81.98 \text{ kJmol}^{-1}$ | $\Delta G_{\text{anti-TS}} = 78.10 \text{ kJmol}^{-1}$ |
| 2 |  | $\Delta G = 71.35 \text{ kJmol}^{-1}$ | $\Delta G = 75.01 \text{ kJmol}^{-1}$ | $\Delta G_{\text{anti-TS}} = 74.52 \text{ kJmol}^{-1}$ |
| 3 |  | $\Delta G = 69.75 \text{ kJmol}^{-1}$ | - | $\Delta G_{\text{anti-TS}} = 59.33 \text{ kJmol}^{-1}$ |
| 4 |  | $\Delta G = 64.61 \text{ kJmol}^{-1}$ | $\Delta G = 63.52 \text{ kJmol}^{-1}$ | $\Delta G_{\text{anti-TS}} = 58.79 \text{ kJmol}^{-1}$ |
| 5 |  | - | $\Delta G = 83.99 \text{ kJmol}^{-1}$ | $\Delta G_{\text{anti-TS}} = 84.07 \text{ kJmol}^{-1}$ |

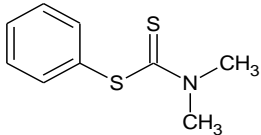
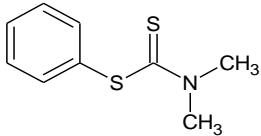
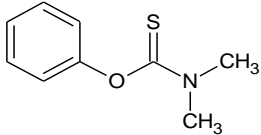
^a Variable Temperature results obtained from previous work within our group⁴⁰

^b All EXSY data collected as 30°C

Consistent with previous reports,^{1,17,45-47} thioamides **1** and **3(6)** have a substantially larger barrier to rotation than their respective amides **2** and **4**, however the presence of α -sulphur (as opposed to oxygen) decreases the magnitude of this difference to virtually zero. Significant is the decrease in barrier with replacement of oxygen at the α -position with sulphur, consistent with earlier results that the rotational barrier is due to $n_N \rightarrow \pi^*_{[C=X]}$ electron transfer.^{8,20,23} Also, substitution of the methyl groups for ethyl's (entries **2** and **5**) shows a significant increase in the rotational barrier. This increase is due to the larger inductive effect of CH_3CH_2- as compared to CH_3- , conceivably resulting in enhancement of $n_N \rightarrow \pi^*_{[C=X]}$ electron transfer. This is consistent with early reports that substituents on the nitrogen produced the opposite effect on the rotational barrier than if they were on the carbonyl.⁴⁸

Due to problems experienced in the synthesis of the dithiol derivative (entry 3), a study was carried out using analogues derived from phenol and thiophenol.⁴³ This data is presented in table 4.

Table 4. Free energies of rotation for phenol analogues

| Entry | Carbamate | Variable Temperature NMR | Exchange Spectroscopy NMR ^a | Computational Data |
|-------|-----------------------------------------------------------------------------------|--------------------------|----------------------------------------|--------------------------------------------------------|
| 6 |  | - | $\Delta G = 59.38 \text{ kJmol}^{-1}$ | $\Delta G_{\text{anti-TS}} = 56.58 \text{ kJmol}^{-1}$ |
| 7 |  | - | $\Delta G = 59.80 \text{ kJmol}^{-1}$ | $\Delta G_{\text{anti-TS}} = 59.41 \text{ kJmol}^{-1}$ |
| 8 |  | - | $\Delta G = 79.97 \text{ kJmol}^{-1}$ | $\Delta G_{\text{anti-TS}} = 76.31 \text{ kJmol}^{-1}$ |

^a All EXSY data acquired at 30°C unless otherwise indicated.

^b Data acquired at -15°C as the amide methyl signals were either completely or partially coalesced at ambient temperature

Phenol derivative **8** is in excellent agreement with its coumarin equivalent, **1**, likewise for compounds **7** and **4**. Thus, we have established that the phenol derivatives are satisfactory models for the coumarin analogues, and the value obtained for **6** may be used as an adequate approximate value for compound **3**.

Examination of the HOMO's for both the ground state and anti- transition state, shows the carbonyl (or thiocarbonyl) orbitals unchanged between ground state and rotated transition state. This applies as well to the lone pairs of the atom in the α -position. On the nitrogen however, we see a large increase in the orbital density in the transition state and in the slightly rotated form, indicating that the lone pair is 'regained' on rotation away from the planar ground state.

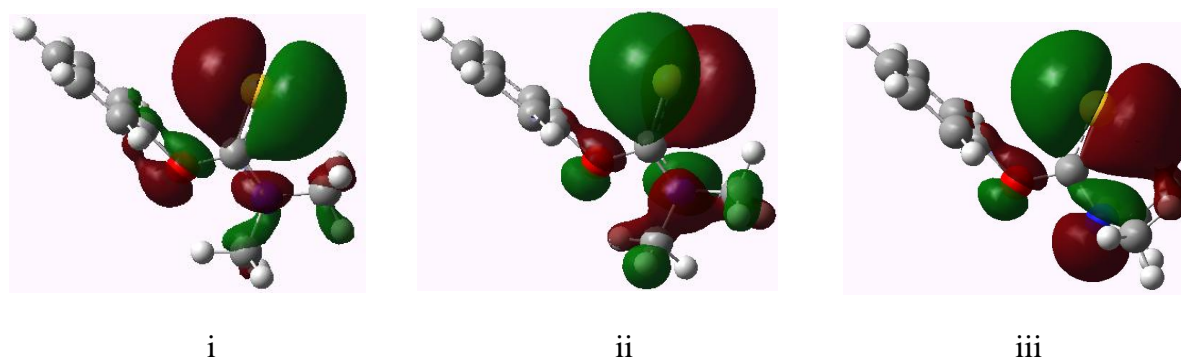


Figure 6. HOMO of i) Ground State, ii) Dihedral rotation through 40° and iii) anti- TS of O-phenyl *N,N*-dimethylcarbamothioate

These observations of the HOMO orbitals correlate with the bond length data, supporting the model by Wiberg *et al.* that the carbonyl (or thiocarbonyl), is effectively a spectator to rotation about the amide bond. X-Ray Diffraction analysis of compound **6** shows the molecules to align in a $P2_1/c$ space group. Bond angles and lengths are in excellent correlation with the computational data obtained for the ground state, reflecting the partial double bond character along the C-N bond.

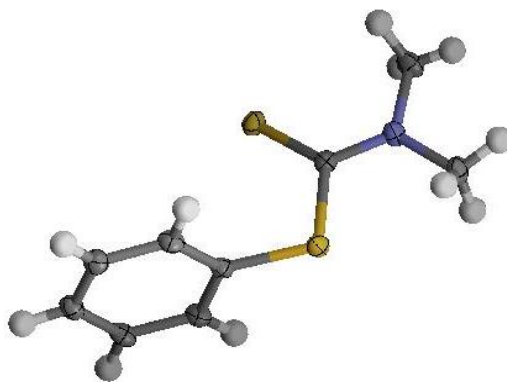


Figure 7. ORTEP model from crystal structure of compound 6

Table 5 shows the bond lengths for the ground state of compound **6** as obtained computationally and from the X-Ray structure analysis. To our delight, the two data sets correlate exceedingly well both with one another and with literature values. It should be noted that the methods of measurement of these bond lengths are essentially different and thus mention should be made. As explained in a publication by Hargittai *et al.*, the computed bond lengths represent the equilibrium distance (r_e) while those obtained experimentally often represent the distance average (r_g). The difference between these may vary considerably with temperature and especially in more flexible molecules, or molecules in which the bond length differs in different conformations.^{49,50} For this reason the latter r_g is expected to be longer than the calculated r_e . In table 5, this can in a sense be seen for the different types of bonds. The greatest difference between experimental and calculated lengths is seen for the longest, (most flexible) C-S bond. This is lessened in the C-N partial double bond and least in the C=S (least flexible) bond. Despite this fundamental difference, as computational techniques have improved, they have become increasingly comparable to experiment, although these often subtle differences should not be overlooked.

Table 5. Comparison of bond lengths (Å)

| Bond | Computational | X-Ray Diffraction | Literature ^a |
|------|---------------|-------------------|-------------------------|
| C-S | 1.822 | 1.788 | 1.82 (single) |
| C=S | 1.666 | 1.661 | 1.56 (double) |
| C-N | 1.356 | 1.336 | 1.34 (partial double) |

^a Literature values taken from ref. ⁵¹

The crystal structure reflects the ground state of the molecule where the carbamate group is *ca.* 90° to the phenyl ring and the amide grouping is planar, indicating our initial assumption that this would be the most stable position with regard to rotation about the –S–C– bond at the α -position was indeed correct.

Conclusion

The eight compounds previously synthesized were analyzed by Variable Temperature and Exchange Spectroscopy NMR to determine the barrier to internal rotation in these α -substituted amides. These barriers were also determined computationally, and all methods were found to be in excellent agreement, and we can conclude that EXSY NMR is a reliable new technique to evaluate rotational barriers, and additionally as a time saving equivalent to variable temperature NMR. The crystal structure of compound **6** is in excellent agreement with the computational data obtained, and adds significance to computational methods as applied within this study. All the results obtained verify the model proposed by Wiberg *et al.*, not to say that Pauling's model is incorrect, but merely insufficient to describe adequately the factors involved in amide resonance.

Experimental

X-Ray Crystallography

Crystallographic measurements were made using a 3 kW Spellman X-ray generator with a 3 kW ceramic X-ray tube and an Xcalibur 2 CCD diffractometer. The structure was solved using the SHELXS-97⁵² program by direct methods. The structure was plotted using the program ORTEP.⁵³ Detailed crystallographic data for compound **6** have been deposited at the Cambridge Crystallographic Data Centre and are available on request (CCDC No. 711835)

Crystal Data of Compound 6. C₉H₁₁NS₂, $M=197.31$, $T=100(2)$ K, $\lambda=0.71073$ Å, $a=7.538(5)$, $b=8.989(5)$, $c=14.229(5)$ Å, $\alpha=90.000(5)^\circ$, $\beta=90.959(5)^\circ$, $\gamma=90.000(5)^\circ$, $V=964.0(9)$ Å³, space group $P2_1/c$, $Z=4$, $D_x=1.359$ mg m⁻³, $\mu=0.495$ mm⁻¹, $F(000)=416$. Crystal Size 0.6x0.55x0.25 mm; θ range for data collection 3.82-34.11°; index range $-10 < h < 11$, $-13 < k < 13$, $-21 < l < 21$; reflections collected 14324; independent reflections 3567 [$R_{\text{int}}=0.0538$]; refinement method full-matrix least-squares on F^2 ; data/restraints/parameters 3567:0:153; goodness-of-fit on F^2 1.071; $R(F)$ [$I > 2\sigma(I)$]=0.0568; $wR_2=0.1461$; largest diff. peak and hole 1.721 and -0.986 e Å⁻³.

Computational Details

All *ab initio* gas phase calculations were performed using the Gaussian 03W package⁵⁴ at the DFT (B3LYP) level of theory with the 6-31+G(d) basis set. In this case, the diffuse functions were incorporated in order for a more accurate description of π -electron delocalization and the lone pairs associated with oxygen, sulphur and nitrogen. The ground state geometries of all amide compounds were optimized, following a scan calculation in which the amide dihedral angle was rotated. The structures associated with the two maxima on the energy profile of the scan were manually extracted and used as starting structures in a full transition state optimization (no constraints) at the same level of theory and basis set. Each of the two possible transition states had one negative eigenvalue only. Analysis of the movement of atoms associated with this eigenvalue confirmed rotation of the amide bond, as expected for these transition states. Thermochemical data was obtained from frequency calculations performed on both ground and transition states.

Cartesian coordinates of all geometry optimized structures are available as supplementary material.

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END – PAPER II

Interestingly it was found that the classical model of resonance as proposed by L. Pauling is not in fact the true origin behind the partial double bond character of the amide bond. In fact, the chalcogen is effectively a spectator to the process of this 'resonance', the explanation behind the partial double bond and thus rotational barrier is a result of $n_N \rightarrow \pi^*_{[C=X]}$ transfer. Thus the closer in energy these orbitals are, the greater the overlap and higher the barrier to free rotation, explaining the higher barrier of thioamides compared to their amide analogues. It was also found that the sulphur at the α -position (as opposed to

oxygen) decreases the barrier due to competition for population of the $\pi^*_{[C=X]}$ orbital by nitrogen and the α -chalcogen.

2.7. CONCLUSIONS

Although the target alkaloid 223AB was not synthesized (the aim being to explore the possibility of modification to access multiple alkaloid frameworks), progress was made to this end. All reactions up to the point of hydroamination, including attachment of the alkyl group of position 3 and synthesis of the heptynyl bromide, were successful showing these modifications to be viable in the synthesis of many different alkaloids. The hydroamination step proved more problematic as the model studies using the propargyl derivative showed exclusive formation of the undesired 5-membered ring (Markovnikov) product instead of the 6-member ring (Anti-Markovnikov) product with all catalysts synthesized. The reason for this selectivity was found to be that the Markovnikov isomer was aromatic where the anti-Markovnikov was not. To circumvent this problem, an allyl derivative was used (eliminating aromaticity in the products), however absolutely no hydroamination was observed to have taken place, however a mixture of (*E*)-(*Z*) isomers was obtained, indicating that isomerisation in the presence of the metal catalyst occurs prior to hydroamination taking place. The lack of hydroamination was accounted for by inspection of the HOMO and LUMO orbitals of each derivative.

The study of amide rotational barriers was completed successfully using *ab initio* and NMR techniques.

2.8. FUTURE WORK

Future work would include optimisation of the LiHMDS deprotection step and possibly an investigation into the reasons and cause for the extremely low yields obtained, continuation of the synthetic route to obtain the target alkaloid, and further modification to obtain a quinolizidine and possibly a lehmizidine. The fact that the NH protection by ethyl acrylate proceeds without a catalyst to yield the anti-Markovnikov product is also worthy of further investigation, even though it is classified as activated hydroamination.

A computational investigation into hydroamination catalysts as well as their mechanism and the factors involved in regioselectivity is necessary before performing additional work.

3. EXPERIMENTAL

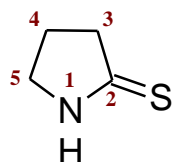
3.1. GENERAL

All NMR spectra, excluding EXSY experiments, were obtained from CDCl_3 or CD_3OD reference solutions using a Bruker Avance III 400 MHz Spectrometer. ^{13}C spectra were obtained at 100MHz. Exchange Spectroscopy experiments were performed using a Bruker Avance 500MHz spectrometer in $\text{C}_2\text{D}_2\text{Cl}_4$ reference solutions. Spectra were recorded at 30°C unless otherwise specified. All coupling constants (J) are quoted in Hz

Low-resolution mass spectra (electron impact) were obtained using a Thermofinnigan trace GC coupled with a Polaris Q mass spectrometer. High-resolution masses (electrospray) were obtained by direct injection using a Waters Micromass LCT PremierTM oa-TOF mass spectrometer. Thin film infra-red spectra were recorded with a Perkin-Elmer Spectrum One spectrometer using NaCl disks. Neat spectra were recorded using a Bruker Alpha FT-IR. Melting points were recorded using a Kofler Hotstage melting point apparatus and are uncorrected. Optical rotations were recorded using a Perkin Elmer 241 Polarimeter with a sodium lamp (D line 589nm). Radial chromatography was performed on a Harrison Research Chromatatron model 7924T using a 2 mm layer of Merck silica gel 7749. The solvent system was delivered by gravity flow. Flash chromatography was performed using Merck silica gel 60 (230 - 400 mesh; particle size 0.040 – 0.063nm). Thin layer chromatography was performed on Merck aluminium sheets with silica gel 60F₂₅₄ and visualized under UV light (254/365 nm) or by using an anisaldehyde or acidified KMnO_4 stain. Microwave reactions were performed in a CEM Discovers Microwave SystemTM. Tetrahydrofuran was distilled over sodium metal/benzophenone under a nitrogen atmosphere prior to use, and stored over 3Å molecular sieves. Dry toluene was acquired by distillation over sodium metal and used immediately. Distilled hexane was used for all chromatography.

3.2. PREPARATIVE PROCEDURES & SPECTROMETRIC DATA

Pyrrolidin-2-thione (20)



Lawesson's Reagent (1.353g, 3.34mmol) was weighed into a dry 100ml round bottom flask equipped with magnetic stirrer bar and septum. The flask was flushed with nitrogen and dry THF (40ml) added *via* canula. Pyrrolidin-2-one (0.51ml, 6.68mmol) was injected slowly into the reaction mixture and allowed to stir overnight. Solvent was removed *in vacuo* to leave a viscous yellow substance. This was immediately dissolved in hot ethyl acetate (2ml) and purified by column chromatography (100% EtOAc followed by 1:1 EtOAc-hex) to produce the title compound as white needle-like crystals (0.563g, 83%).

R_f = 0.25 (1:1 EtOAc-hex)

m.p. 109-113°C (lit.¹⁴⁴ 112-113°C)

^1H NMR (400MHz, CDCl_3) δ (ppm) = 9.02 (br. s, 1H, H-1), 3.63 (t, 2H, J = 7.24 Hz, H-3), 2.87 (t, 2H, J = 7.96 Hz, H-5), 2.17 (pent, 2H, J = 7.60 Hz, H-4)

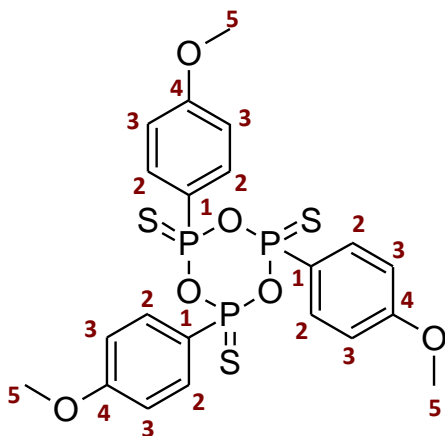
^{13}C NMR (100MHz, CDCl_3) δ (ppm) = 205.5 (C-2), 49.7 (C-3), 43.4 (C-5), 22.9 (C-4)

IR ν_{max} (neat)/ cm^{-1} = 3152, 2883, 1537, 1449, 1417, 1293, 1113, 972, 786, 483

MS (EIMS): m/z (%) = 101 [M^+ , 100%], 100 (36%), 71 (15%), 45 (8%), 41 (20%), 39 (26%)

¹⁴⁴ Hall. *Journal of the American Chemical Society* **1985**, 80, 6404-6409.

2,4,6-tris(*p*-methoxyphenyl)-1,3,5,2,4,6-thioxatriphosphinane 2,4,6-trisulphide (25)



R_f = 0.57 (1:1 EtOAc-hex)

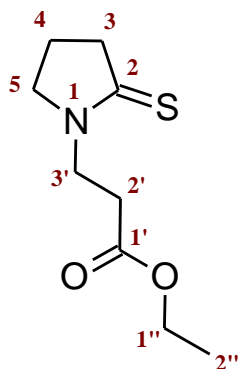
m.p. 154-158°C (lit.¹⁴⁵ 158-159°C)

¹H NMR (400MHz, CDCl₃/MeOD) δ(ppm) = 8.16 - 8.24 (m, 2H, H-2), 7.99 – 8.17 (m, 4H, H-2), 6.99 - 7.04 (m, 2H, H-3), 6.94 – 6.99 (m, 4H, H-3), 3.85 (s, 3H, H-5), 3.83 (s, 6H, H-5)

¹³C NMR (100MHz, CDCl₃) δ(ppm) = 164.3 & 164.2 (C-4), 134.5 & 135.3 (C-), 114.1 & 114.0 (C-), 55.5 (C-5)

¹⁴⁵. Wen, Bau and McKenna. *Journal of the Chemical Society. Chemical Communications* **1991**, 1223-1224.

Ethyl 3-(2-thioxo-1-pyrrolidinyl)propanoate (29)



Pyrrolidin-2-thione (5.006g, 49.5mmol) and a catalytic amount of potassium hydroxide were weighed into a dry 100ml round bottom flask equipped with a stirrer bar and septum. The flask was flushed with nitrogen and dry THF (60ml) added *via* canula. Ethyl acrylate (5.91ml, 54.5mmol) was added dropwise to the reaction mixture and allowed to stir at room temperature overnight. Solvent was removed *in vacuo* and the residue dissolved in water which was subsequently extracted with CH₂Cl₂ (4 x 10ml). The organic layers were combined and the solvent removed *in vacuo* to yield the product as a pale yellow oil (9.063g, 91%).

R_f = 0.59 (1:1 EtOAc-hex)

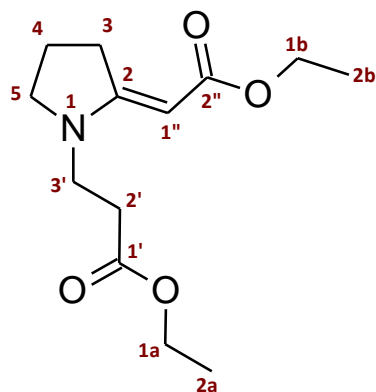
¹H NMR (400MHz, CDCl₃) δ(ppm) = 3.97 (q, 2H, J = 7.14 Hz, H-1''), 3.83 (t, 2H, J = 6.86 Hz, H-3'), 3.65 (t, 2H, J = 7.32 Hz, H-5), 2.82 (t, 2H, J = 7.94 Hz, H-3), 2.58 (t, 2H, J = 6.86 Hz, H-2'), 1.90 (pent, 2H, J = 7.63 Hz, H-4), 1.09 (t, 3H, J = 7.14 Hz, H-2'')

¹³C NMR (100MHz, CDCl₃) δ(ppm) = 201.4 (C-2), 171.2 (C-1'), 60.7 (C-1''), 55.7 (C-5), 44.8 (C-3), 43.6 (C-3'), 30.9 (C-2'), 19.8 (C-4), 14.0 (C-2'')

IR ν_{max}(neat)/cm⁻¹ = 2981, 1729, 1508, 1186

MS (EIMS): *m/z* (%) = 201 [M⁺, 100%], 172 (%), 128 (%), 85 (%)

 Ethyl 3-[(2E)-2-(2-ethoxy-2-oxoethylidene)pyrrolidinyl]propanoate (30)



Ethyl 3-(2-thioxo-1-pyrrolidinyl)propanoate (6.85g, 34mmol) was added to a 100ml round bottom flask equipped with a magnetic stirrer and septum. This was dissolved in 40ml dry CH_3CN under a nitrogen atmosphere and ethyl bromoacetate (4.54ml, 40.8mmol) added dropwise. This was allowed to stir at room temperature for 18hrs, after which all volatiles were removed *in vacuo*. The remaining residue was redissolved in 50ml dry CH_3CN , and the flask flushed with nitrogen. Triethylphosphite (6.41ml, 37.4mmol) and triethylamine (5.21ml, 37.4mmol) were injected into the reaction mixture simultaneously and this was allowed to stir for a further 18hrs at room temperature. Water (10ml) was added and solvent removed *in vacuo*, the remaining aqueous mixture was extracted repeatedly with CH_2Cl_2 (5 x 10ml). The combined organic extracts were evaporated *in vacuo* to leave a thick yellow oil which was purified by radial chromatography (1:1 EtOAc-hex) to remove any residual triethylphosphite. The product was obtained as a clear yellow oil in quantitative yield.

$R_f = 0.71$ (1:1 EtOAc-hex)

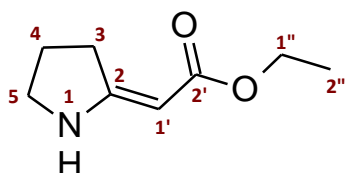
^1H NMR (400MHz, CDCl_3) δ (ppm) = 4.48 (br. s, 1H, H-1''), 4.09 (q, 2H, $J = 7.14$ Hz, H-1a), 4.03 (q, 2H, $J = 7.12$ Hz, H-1b), 3.44 (t, 2H, $J = 6.96$ Hz, H-3'), 3.35 (t, 2H, $J = 7.06$ Hz, H-5), 3.08 (t, 2H, $J = 7.76$ Hz, H-3), 2.52 (t, 2H, $J = 6.96$ Hz, H-2'), 1.88 (pent, 2H, $J = 7.43$ Hz, H-4), 1.20 (2xt, 6H, $J = 7.39$ Hz, H-2a & H-2b)

^{13}C NMR (100MHz, CDCl_3) $\delta(\text{ppm}) = 171.4$ (C-1'), 169.2 (C-2''), 164.4 (C-2), 78.3 (C-1''), 60.7 (C-1a), 58.2 (C-1b), 52.8 (C-5), 41.9 (C-3'), 32.5 (C-3), 30.9 (C-2'), 21.1 (C-4), 14.6 (C-2b), 14.1 (C-2a)

IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1} = 2979, 1732, 1683, 1590, 1129, 1018, 964, 782$

MS (EIMS): m/z (%) = 255 [M^+ , 89%], 210 (100%), 182 (93%), 168 (31%), 154 (30%), 136 (40%), 111 (58%), 94 (10%), 80 (11%), 55 (7%)

Ethyl (Pyrrolidin-2-ylidene)ethanoate (**31**)



Ethyl 3-[(2E)-2-(2-ethoxy-2-oxoethylidene)pyrrolidinyl]propanoate (202mg, 0.791mmol) was added to a dry round bottom flask equipped with stirrer bar and septum. THF (20ml) was added *via* canula. In a separate dry round bottom flask, lithium hexamethyl disilazide (529mg, 3.16mmol) was dissolved in dry THF (10ml), both flasks were flushed with nitrogen. The solution of LiHMDS was added rapidly *via* canula to the carbamate solution. This was allowed to stir for 5min at room temperature and subsequently quenched with ammonium chloride (5ml). An additional portion of water was added and the organic solvent was removed *in vacuo*. The remaining aqueous solution was extracted with CH_2Cl_2 (3x20ml), after which the extracts were combined and solvent removed in *vacuo*, to leave an orange oil. This was purified by radial chromatography (1:1 EtOAc-hex) to yield the product as an orange to white crystalline solid (32mg, 26%).

$R_f = 0.62$ (1:1 EtOAc-hex)

m.p. 60-61°C (lit.¹⁴⁶ 60-62°C)

¹⁴⁶ Robinson, Dovey and Gravestock. *European Journal of Organic Chemistry* **2005**, 505-511.

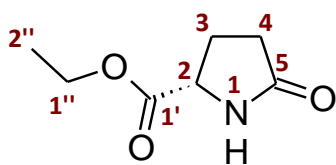
^1H NMR (400MHz, CDCl_3) $\delta(\text{ppm}) = 7.78$ (br.s, 1H, H-1), 4.42 (s, 1H, H-1'), 3.99 (q, 2H, J = 7.11 Hz, H-1''), 3.41 (t, 2H, J = 6.84 Hz, H-5), 2.47 (t, 2H, J = 7.78 Hz, H-3), 1.86 (pent, 2H, J = 7.31 Hz, H-4), 1.14 (t, 3H, J = 7.10 Hz, H-2'')

^{13}C NMR (100MHz, CDCl_3) $\delta(\text{ppm}) = 170.8$ (C-2'), 166.5 (C-2), 76.6 (C-1'), 58.4 (C-1''), 47.0 (C-5), 32.2 (C-3), 22.0 (C-4), 14.7 (C-2'')

IR $\nu_{\text{max}}(\text{NaCl})/\text{cm}^{-1} = 3361, 2939, 1597, 1240, 1144, 1059, 780$

MS (EIMS): m/z (%) = 155 [M^+ , 68%], 127 (7%), 110 (99%), 108 (20%), 83 (100%), 80 (30%), 68 (11%), 54 (10%), 39 (14%)

Ethyl (2S)-5-oxopyrrolidine-2-carboxylate (**2**)



(S)-pyroglutamic acid (7.367g, 57.1mmol) was weighed into a 250ml round bottom flask equipped with a magnetic stirrer. This was dissolved in benzene (80ml) an excess of ethanol (120ml). To this was added a catalytic amount of H_2SO_4 (70%, 0.5ml) and a reflux condenser equipped to a Dean & Stark apparatus was fitted. The reaction mixture was refluxed under atmosphere for 6hrs, after which solvent was removed *in vacuo* to leave a clear to slightly peach coloured oil. Water (20ml) was added and aq. NaHCO_3 (sat.) added slowly until all bubbling ceased. This aqueous solution was extracted with CH_2Cl_2 (3 x 20ml) and solvent removed *in vacuo* from the combined organic extracts to leave a slightly peachy oil. The product was purified by Kugel-Rohr distillation under reduced pressure to yield a clear oil which solidified forming a white solid (6.325g, 71%).

$R_f = 0.75$ (100% EtOH)

m.p. 39-42°C [lit.¹⁴⁷ 49-50°C]

$[\alpha]_D^{29} +3.86^\circ$ (c. 1.062, EtOH), [lit.¹⁴⁸ +3.5°]

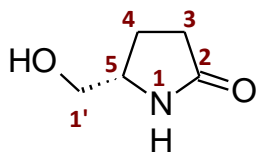
¹H NMR (400MHz, CDCl₃) δ (ppm) = 7.05 (br. s, 1H, H-1), 4.17 (q, 2H, J = 7.12 Hz, H-1''), 4.14 - 4.22 (m, 1H, H-2), 2.36 – 2.48 (m, 1H, H-3a), 2.22 – 2.36 (m, 2H, H-4), 2.08 – 2.22 (m, 1H, H-3b), 1.24 (t, 3H, J = 7.14, H-2'')

¹³C NMR (100MHz, CDCl₃) δ (ppm) = 178.3 (C-5), 172.1 (C-1'), 61.5 (C-1''), 55.5 (C-2), 29.3 (C-4), 24.7 (C-3), 14.0 (C-2'')

IR ν_{\max} (neat)/cm⁻¹ = 3220, 2985, 1740, 1692, 1199, 1156, 1024, 708, 497

MS (EIMS): m/z (%) = 158 [M^+ , 1%], 84 (100%), 56 (5%), 41 (16%), 28 (5%)

(S)-5-(hydroxymethyl)pyrrolidin-2-one (**3**)



Ethyl (2S)-5-oxopyrrolidine-2-carboxylate (1.010g, 6.96mmol) was weighed into a 50ml round bottom flask equipped with a stirrer bar and dissolved in ethanol (20ml). This solution was cooled in an ice bath and sodium borohydride (0.210g, 5.57mmol) added in small portions. This was allowed to stir for a further 2 hrs while warming to room temperature. Acetone (2ml) was added to the solution to ensure no excess of NaBH₄ was present before purification. The reaction mixture was filtered through a silica plug to remove the boric acid derivative. Solvent was removed *in vacuo* and the resulting clear oil was purified by column chromatography (1:6 MeOH-CH₂Cl₂) to yield the product as white crystals (0.735g, 92%).

¹⁴⁷ Elliot and Long. *Organic and Biomolecular Chemistry* **2004**, 2, 2003-2011.

¹⁴⁸ sigmaaldrich. In <http://www.sigmaaldrich.com/catalog/search/ProductDetail/FLUKA/83175>, October 21, 2008.

$R_f = 0.52$ (1:6 MeOH-CH₂Cl₂)

m.p. 81 - 85°C (lit.¹⁴⁹ 86 - 87°C)

$[\alpha]_D^{30} +26.47^\circ$ (c. 0.034, EtOH), [lit.¹⁵⁰ +29.2°]

¹H NMR (400MHz, CDCl₃) δ (ppm) = 6.95 (br s, 1H, H-1), 3.77 – 3.87 (m, 1H, H-5), 3.71 (dd, 1H, J = 3.20 & 11.29 Hz, H-1'a), 3.46 – 3.53 (m, 1H, H-1'b), 2.30 – 2.45 (m, 2H, H-3), 2.15 – 2.26 (m, 1H, H-4a), 1.78 – 2.88 (m, 1H, H-4b)

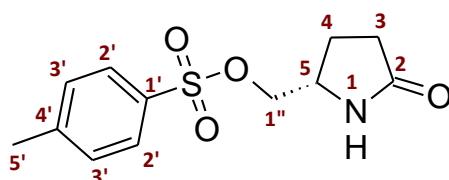
¹³C NMR (100MHz, CDCl₃) δ (ppm) = 179.1 (C-2), 65.9 (C-1'), 56.4 (C-5), 30.2 (C-3), 22.6 (C-4)

IR ν_{\max} (NaCl)/cm⁻¹ = 3251, 2922, 1668, 1422, 1286, 486

MS (EIMS): m/z (%) = 85 (12%), 84 (100%), 56 (11%), 41 (40%), 39 (13%), 28 (16%)

HRMS (ES⁻): found 114.0574 (C₅H₈NO₂), required 115.1305

(S)-(2-oxopyrrolidin-5-yl)methyl 4-methylbenzenesulfonate (**34**)



(S)-5-(hydroxymethyl)pyrrolidin-2-one was synthesized from ethyl (2S)-5-oxopyrrolidine-2-carboxylate (3.706g, 25.5mmol) as described previously, using water (50ml) as solvent in place of ethanol. This reaction mixture was filtered through a silica plug and decanted into a 250ml conical flask equipped with a stopper and magnetic stirrer. To this solution was added KOH (2.6g, 47.0mmol) and TBAHS (cat.). This solution was diluted with CHCl₃ (50ml) and *p*-toluenesulphonyl chloride (6.73g, 35.3mmol) added in two portions. The flask was stoppered submerged in a sonic bath equipped with underwater stirrer. This was allowed to

¹⁴⁹ Hashimoto, Matsumoto and Terashima. *Tetrahedron* **2003**, 59, 3019-3040.

¹⁵⁰ Bateman, Breeden and O'Leary. *Tetrahedron: Asymmetry* **2008**, 19, 391-396.

stir in the sonic bath for 3 days. The CHCl_3 layer was removed and the aqueous layer extracted with CH_2Cl_2 (2 x 20ml). Solvent was removed from the combined organic fractions to leave an off-white residue which was recrystallised from hot toluene (30ml). The product was obtained as fine shiny white crystals (5.371g, 71% over two steps).

$R_f = 0.24$ (1:1 EtOAc-hex)

m.p. 133 - 138°C (lit.¹⁵¹ 128 - 130°C)

$[\alpha]_D^{29.5} +7.89^\circ$ (c. 2.002, EtOH), [lit.¹⁵² +7.9°]

^1H NMR (400MHz, CDCl_3) $\delta(\text{ppm}) = 7.80$ (d, 2H, $J = 8.28$ Hz, H-2'), 7.38 (d, 2H, $J = 8.12$ Hz, H-3'), 6.04 (br s, 1H, H-1), 4.07 (dd, 1H, $J = 3.34$ & 9.39 Hz, H-4a), 3.92 – 3.98 (m, 1H, H-5), 3.89 (dd, 1H, $J = 7.26$ & 9.39 Hz, H-4b), 2.47 (s, 3H, H-5'), 2.29 – 2.36 (m, 2H, H-3), 2.20 – 2.39 (m, 1H, H-1''a), 1.73 – 1.81 (m, 1H, H-1''b)

^{13}C NMR (100MHz, CDCl_3) $\delta(\text{ppm}) = 177.5$ (C-2), 145.4 (C-1'), 132.5 (C-4'), 130.1 (C-3'), 127.9 (C-2'), 72.0 (C-4), 52.6 (C-5), 29.1 (C-3), 22.8 (C-1''), 21.6 (C-5')

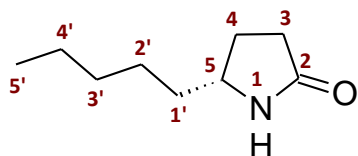
IR $\nu_{\text{max}}(\text{NaCl})/\text{cm}^{-1} = 3289, 2925, 1699, 1658, 1460, 1376$

HRMS (ES^-): found 268.0702 ($\text{C}_{12}\text{H}_{14}\text{NO}_4\text{S}$), required 269.3168

¹⁵¹ Hjelmgaard, Sotofte and Tanner. *Journal of Organic Chemistry* **2005**, 70, 5688-5697.

¹⁵² Occhiato, Prandi, Ferrali and Guarna. *Journal of Organic Chemistry* **2005**, 70, 4542-4545.

(R)-5-pentylpyrrolidin-2-one (38)



CuCN (3.24g, 37.3mmol) was weighed into a 150ml round-bottom flask and dry THF (20ml) added. This was cooled to -78°C following which *n*-BuLi (46.6ml, 74.6mmol, 1.6M) was added dropwise and allowed to stir for 1hr. In a separate round bottom flask, (*S*)-(2-oxopyrrolidin-5-yl)methyl 4-methylbenzenesulfonate (2.01g, 7.5mmol) was dissolved in dry THF (20ml) and transferred *via* canula to the solution of the prepared Gilman reagent. This was allowed to stir at -40°C for 4hrs after which it was allowed to warm to room temperature and stirred for an additional 24hrs. The reaction mixture was quenched with NH_4Cl (sat., 5ml), diluted with water (10ml) and the solvent removed in vacuo. The remaining aqueous solution was extracted with CH_2Cl_2 (3x20ml) and solvent removed from the combined organic extracts. The remaining crude material was purified by radial chromatography (1:1 EtOAc-hex) to obtain the product as a yellow oil in quantitative yield.

$R_f = 0.27$ (1:1 EtOAc-hex)

$[\alpha]_D^{30} +6.86^{\circ}$ (c. 2.231, EtOH), [lit.¹⁵³ $+8.51^{\circ}$]

^1H NMR (400MHz, CDCl_3) δ (ppm) = 7.30 (br s, 1H, H-1), 3.56 (pent, 1H, $J = 6.63$ Hz, H-5), 2.22 - 2.34 (m, 2H, H-3), 2.07 - 2.22 (m, 1H, H-4a), 1.55 - 1.70 (m, 1H, H-4b), 1.44 - 1.55 (m, 1H, 1'a), 1.33 - 1.44 (m, 1H, H-1'b), 1.16 - 1.33 (m, 6H, H-2', 3' & 4'), 0.83 (t, 3H, $J = 6.38$ Hz, H-5')

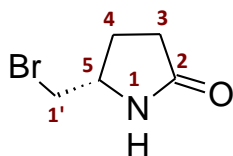
^{13}C NMR (100MHz, CDCl_3) δ (ppm) = 178.6 (C-2), 54.8 (C-5), 36.6 (C-1'), 31.6 (C-2'), 30.4 (C-3), 27.2 (C-4), 25.4 (C-3'), 22.4 (C-4'), 13.9 (C-5')

IR $\nu_{\text{max}}(\text{NaCl})/\text{cm}^{-1} = 3236, 1696, 732$

MS (EIMS): m/z (%) = 155 [M^+ , 8%], 126 (3%), 84 (100%), 41 (19%)

¹⁵³ Holmes, Smith, Williams and Hughes. *Journal of Organic Chemistry* **1991**, 56, 1393-1405.

(S)-5-(bromomethyl)pyrrolidin-2-one (37)



Li metal shavings (1.1g, 160mmol) were weighed into a 150ml round-bottom flask and dry hexane added (50ml). This was cooled to -40°C and propyl bromide (7.28ml, 80mmol) added dropwise and allowed to stir for 1hr at -40°C or until all Li metal was consumed. This prepares a solution of $\sim 1.6\text{M}$ *n*-PrLi concentration.

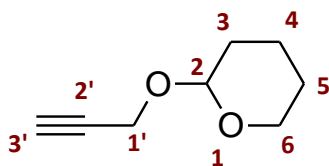
CuCN (3.24g, 37.3mmol) was weighed into a round-bottom flask and dry THF added (20ml). This was cooled to -78°C following which *n*-PrLi (46.6ml, 74.6mmol, 1.6M) was added dropwise and allowed to stir for 1hr. In a separate round bottom flask, (*S*)-(2-oxopyrrolidin-5-yl)methyl 4-methylbenzenesulfonate (2.01g, 7.5mmol) was dissolved in dry THF (20ml) and transferred *via* canula to the solution of the prepared Gilman reagent. This was allowed to stir at -40°C for 4hrs after which it was allowed to warm to room temperature and stirred for an additional 24hrs. The reaction mixture was quenched with NH_4Cl (sat., 5ml), diluted with water (10ml) and the solvent removed in vacuo. The remaining aqueous solution was extracted with CH_2Cl_2 (3x20ml) and solvent removed from the combined organic extracts. The remaining crude material was purified by radial chromatography (1:1 EtOAc-hex) to yield the product as a green-yellow oil in quantitative yield.

$R_f = 0.76$ (1:1 EtOAc-hex)

^1H NMR (400MHz, CDCl_3) $\delta(\text{ppm}) = 6.89$ (br s, 1H, H-1), 3.91 (pent, 1H, $J = 5.79$ Hz, H-5), 3.34 (dd, 1H, $J = 10.26$ & 23.19 Hz, H-1'a), 3.32 (dd, 1H, $J = 10.26$ & 24.59 Hz, H-1'b), 2.40 – 2.50 (m, 1H, H-3a), 2.28 – 2.40 (m, 2H, H-3b & 4a), 1.85 – 1.99 (m, 1H, H-4b)

^{13}C NMR (100MHz, CDCl_3) $\delta(\text{ppm}) = 177.8$ (C-2), 55.1 (C-5), 36.7 (C-1'), 30.4 (C-3), 25.7 (C-4)

 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (40)



Propargyl alcohol (1.6g, 28.5mmol) and 3,4-dihydro-2H-pyran (2.4g, 28.5mmol) were distilled before use and weighed into a 50ml flat-bottom flask equipped with a stirrer bar. To this was added a single crystal of *p*-TsA and the mixture allowed to stir at room temperature for 3hrs in the absence of solvent. Pure product was obtained from the reaction mixture as a yellow oil in quantitative yield without need of purification.

$R_f = 0.69$ (1:1 EtOAc-hex)

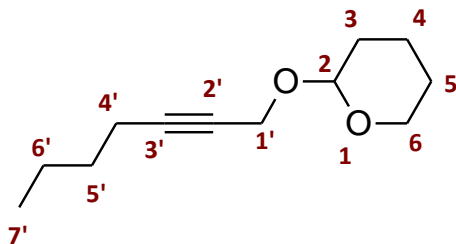
^1H NMR (400MHz, CDCl_3) $\delta(\text{ppm}) = 4.76$ (t, 1H, $J = 3.22$ Hz, H-2), 4.23 (ddd, 1H, $J = 1.18$, 2.39 & 15.72 Hz, H-1'a), 4.16 (ddd, 1H, $J = 1.07$, 2.31 & 15.70 Hz, H-1'b), 3.75 – 3.83 (m, 1H, H-3a), 3.45 – 3.52 (m, 1H, H-3b), 2.38 (t, 1H, $J = 2.40$ Hz, H-3'), 1.74 – 1.85 (m, 1H, H-4a), 1.65 – 1.74 (m, 1H, H-6a), 1.54 – 1.62 (m, 2H, H-5a & H-6b), 1.44 – 1.54 (m, 2H, H-4b & H-5b)

^{13}C NMR (100MHz, CDCl_3) $\delta(\text{ppm}) = 96.7$ (C-2), 79.7 (C-2'), 73.9 (C-3'), 61.8 (C-3), 53.9 (C-1'), 30.1 (C-6), 25.2 (C-5), 18.9 (C-4)

IR $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1} = 2943, 1118, 1021, 901$

MS (EIMS): m/z (%) = 139 (15%), 85 (100%), 67 (20%), 55 (21%), 41 (4%), 39 (34%)

 2-(hept-2-yn-1-yloxy)tetrahydro-2H-pyran (**41**)



2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran (1.01g, 7.2mmol) was weighed into a 100ml round-bottom flask and dissolved in dry THF (40ml). This was cooled to 0°C and *n*-BuLi (4.95ml, 7.9mmol) added dropwise. The solution was allowed to stir at 0°C for 1hr after which bromobutane (0.93ml, 8.6mmol) was added dropwise and stirred for a further hour at 0°C. The reaction mixture was allowed to warm to room temperature and refluxed for 24hrs. The reaction was quenched with NaHCO₃ (), diluted with water and solvent removed *in vacuo*. The remaining aqueous solution was extracted with ether (5x20ml) and solvent removed from the combined organic extracts *in vacuo*. The product was purified from the residue by Kugel-Röhr distillation as a light yellow liquid (0.855g, 61%).

R_f = 0.81 (1:1 EtOAc-hex)

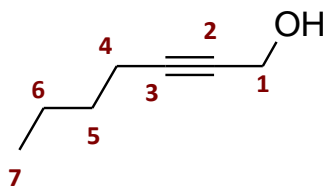
¹H NMR (400MHz, CDCl₃) δ(ppm) = 4.81 (t, 1H, J = 3.44 Hz, H-2), 4.28 (m, 1H, J = 2.21 & 15.23 Hz, H-1'a), 4.19 (m, 1H, J = 2.18 & 15.24 Hz, H-1'b), 3.80 – 3.88 (m, 1H, H-3a), 3.48 – 3.55 (m, 1H, H-3b), 2.21 (m, 2H, J = 2.19 & 7.03 Hz, H-4'), 1.79 – 1.90 (m, 1H, H-4a), 1.68 – 1.78 (m, 1H, H-6a), 1.58 – 1.67 (m, 2H, H-5a & H-6b), 1.45 – 1.57 (m, 4H, H-4b & H-5b & H-5'), 1.36 – 1.45 (m, 2H, H-6'), 0.90 (t, 3H, J = 7.26 Hz, H-7')

¹³C NMR (100MHz, CDCl₃) δ(ppm) = 96.6 (C-2), 86.6 (C-3'), 75.7 (C-2'), 61.9 (C-3), 54.6 (C-1'), 30.7 (C-5'), 30.3 (C-6), 25.4 (C-5), 21.9 (C-6'), 19.1 (C-4), 18.5 (C-4'), 13.5 (C-7')

IR ν_{max}(NaCl)/cm⁻¹ = 3390, 2935, 2871, 1456, 1023, 733

MS (EIMS): *m/z* (%) = 196 [M⁺, 2%], 153 (3%), 125 (4%), 111 (20%), 101 (24%), 93 (20%), 85 (49%), 79 (26%), 67 (100%), 55 (37%)

Hept-2-yn-1-ol (42)



2-(hept-2-yn-1-yloxy)tetrahydro-2*H*-pyran (205mg, 1.04mmol) was dissolved in CH₃OH (10ml) and HCl (2ml, 2N) added. This was allowed to stir at room temperature for 3hrs, after which the reaction was basified with NaHCO₃ () and solvent removed in vacuo. The remaining aqueous solution was extracted with CH₂Cl₂ (3x10ml) and solvent removed from the combined organic fractions to leave the product as a clear oil obtained in quantitative yield.

R_f = 0.61 (1:1 EtOAc-hex)

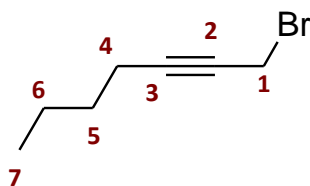
¹H NMR (400MHz, CDCl₃) δ(ppm) = 4.19 (t, 2H, J = 2.18 Hz, H-1), 2.71 (br s, 1H, -OH), 2.18 (m, 2H, J = 2.16 & 7.01 Hz, H-4), 1.39 – 1.48 (m, 2H, H-5), 1.30 – 1.38 (m, 2H, H-6), 0.87 (t, 3H, J = 7.24 Hz, H-7)

¹³C NMR (100MHz, CDCl₃) δ(ppm) = 86.1 (C-3), 78.4 (C-2), 51.0 (C-1), 30.6 (C-5), 21.9 (C-6), 18.3 (C-4), 13.5 (C-7)

IR ν_{max}(NaCl)/cm⁻¹ = 2941, 2872, 1740, 1035, 733

MS (EIMS): *m/z* (%) = 111 [M⁺, 5%], 101 (23%), 85 (56%), 67 (100%), 55 (41%), 41 (38%)

1-Bromohept-2-yn (43)

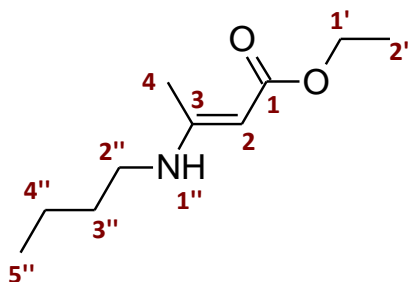


Hept-2-yn-1-ol (53mg, 0.47mmol) was weighed into a 50ml round-bottom flask and dissolved in dry THF (10ml). Triphenylphosphine (0.12g, 0.47mmol) and carbon tetrabromide (0.17g, 0.5mmol) were added as a solution in dry THF (20ml) and the mixture was allowed to stir for 24 hrs at room temperature. Water was added and solvent removed *in vacuo*, after which the aqueous solution was extracted with ether (3x15ml). The combined organic extracts were triturated, the solution filtered off and solvent removed *in vacuo*. The residue was purified by radial chromatography (100% ether) to yield crude product. Based on the crude ^1H NMR spectrum, the product was obtained in 54% yield.

$R_f = 0.83$ (1:1 EtOAc-hex)

^1H NMR (400MHz, CDCl_3) $\delta(\text{ppm}) = 4.08$ (d, 2H, $J = 7.88$ Hz, H-1), 2.51 (t, 2H, $J = 7.36$ Hz, H-4), 1.52 – 1.64 (m, 2H, H-5), 1.30 – 1.38 (m, 2H, H-6), 0.93 (t, 3H, $J = 7.34$ Hz, H-7)

Ethyl (2*E*)-3-(butylamino)but-2-enoate (50)



To a 100ml round-bottom flask was added ethylacetoacetate (6.0g, 46mmol) and butylamine (9.9ml, 100mmol) in benzene (50ml). This was refluxed for 2hrs with a Dean & Stark apparatus. Solvent was removed *in vacuo* to leave the product as a brown oil in quantitative yield.

R_f = 0.83 (1:1 EtOAc-hex)

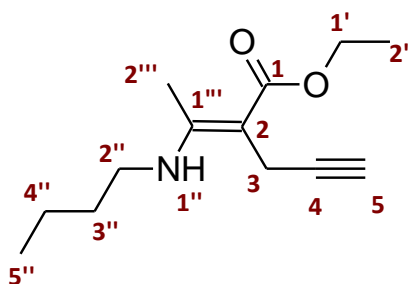
^1H NMR (400MHz, CDCl_3) δ (ppm) = 8.52 (br s, 1H, H-1''), 4.39 (s, 1H, H-2), 4.04 (q, 2H, J = 7.11 Hz, H-1'), 3.16 (q, 2H, J = 6.56 Hz, H-2''), 1.87 (s, 3H, H-4), 1.46 – 1.56 (m, 2H, H-3''), 1.31 – 1.42 (m, 2H, H-4''), 1.20 (t, 3H, J = 7.12 Hz, H-2'), 0.90 (t, 3H, J = 7.28 Hz, H-5'')

^{13}C NMR (100MHz, CDCl_3) δ (ppm) = 170.6 (C-1), 161.8 (C-3), 81.7 (C-2), 58.1 (C-1'), 42.6 (C-2''), 32.4 (C-3''), 19.9 (C-4''), 19.2 (C-4), 14.6 (C-2'), 13.6 (C-5'')

IR ν_{max} (NaCl)/ cm^{-1} = 2957, 2931, 2873, 1649, 1601, 1268, 1169, 1140, 1056, 782

MS (EIMS): m/z (%) = 185 [M^+ , 89%], 170 (48%), 140 (58%), 122 (38%), 110 (38%), 96 (100%), 84 (25%), 71 (57%), 55 (33%), 42 (34%)

Ethyl (2E)-2-[1-(butylamino)ethylidene]pent-4-ynoate (51)



A solution of ethyl (2E)-3-(butylamino)but-2-enoate (1.01g, 5.5mmol) in dry THF (50ml) was cooled to 0°C and *n*-BuLi (3.75ml, 6.0mmol) added dropwise. This was allowed to stir for 30min after which propargyl bromide (0.75ml, 6.73mmol) was added dropwise and allowed to stir for a further 1hr while warming to room temperature, and then for 24hrs at rt. The reaction mixture was quenched with water (2ml) and solvent removed *in vacuo*. The residue was purified by radial chromatography (1:1 EtOAc-hex) to yield the product as a brown oil in 75% purity (by ^1H NMR).

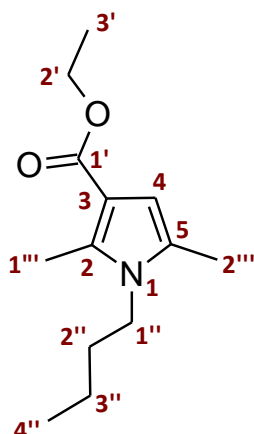
R_f = 0.86 (1:1 EtOAc-hex)

^1H NMR (400MHz, CDCl_3) δ (ppm) = 9.30 (br s, 1H, H-1''), 4.04 (q, 2H, J = 7.10 Hz, H-1'), 3.13 (q, 2H, J = 7.00 Hz, H-2''), 3.08 (d, 2H, J = 2.64 Hz, H-3), 1.98 (s, 3H, H-2'''), 1.83 (t, 1H, J = 2.62 Hz, H-5), 1.42 – 1.52 (m, 2H, H-3''), 1.27 – 1.38 (m, 2H, H-4''), 1.19 (t, 3H, J = 7.08 Hz, H-2'), 0.85 (t, 3H, J = 7.30 Hz, H-5'')

^{13}C NMR (100MHz, CDCl_3) δ (ppm) = 169.7 (C-1), 161.1 (C-1'''), 87.1 (C-2), 84.7 (C-4), 66.4 (C-5), 58.7 (C-1'), 43.0 (C-2''), 32.3 (C-3''), 19.9 (C-4''), 16.6 (C-3), 14.9 (C-2'''), 14.5 (C-2'), 13.6 (C-5'')

IR ν_{max} (NaCl)/ cm^{-1} = 3289, 2958, 2931, 2872, 1643, 1595, 1261, 1206, 1172, 1064, 785, 683, 624

MS (EIMS): m/z (%) = 223 [M^+ , 77%], 206 (15%), 194 (94%), 178 (35%), 166 (19%), 150 (86%), 138 (47%), 108 (58%), 94 (48%), 79 (21%), 42 (31%), 27 (100%)

Ethyl (2*E*)-2-[1-(butylamino)ethylidene]pent-4-ynoate (52)

Ethyl (2*E*)-3-(butylamino)but-2-enoate (1.01g, 5.5 mmol) was weighed into a 100 ml round-bottom flask and dissolved in dry THF (40 ml). This solution was cooled to 0°C and *n*-BuLi added dropwise (3.75 ml, 6.0 mmol) after which the mixture was allowed to stir for 30 min. Allyl bromide (0.61 ml, 7.1 mmol) was added dropwise and allowed to stir for a further 30 min at 0°C and subsequently for 18 hr at room temperature. $\text{Ti}(\text{NEt}_2)_4$ catalyst and dry toluene (20 ml) was added and allowed to reflux for a further 18 hr. Thereafter the reaction mixture was quenched with water (2 ml) and filtered through a silica plug to remove the catalyst. The solvent was removed *in vacuo* and the residue purified by radial chromatography (1:1 EtOAc-hex) to yield the product as a yellow oil (77% by ^1H NMR of the crude residue).

$R_f = 0.79$ (1:1 EtOAc-hex)

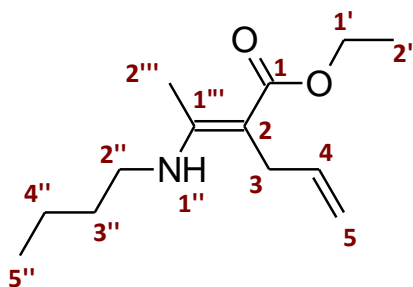
^1H NMR (400 MHz, CDCl_3) δ (ppm) = 6.17 (s, 1H, H-4), 4.16 (q, 2H, $J = 7.11$ Hz, H-2'), 3.66 (t, 2H, $J = 7.76$ Hz, H-1''), 2.43 (s, 3H, H-1'''), 2.11 (s, 3H, H-2'''), 1.51 (pent, 2H, $J = 7.61$ Hz, H-2''), 1.26 – 1.34 (m, 2H, H-3''), 1.24 (t, 3H, $J = 7.10$ Hz, H-3'), 0.88 (t, 3H, $J = 7.32$ Hz, H-4'')

^{13}C NMR (100 MHz, CDCl_3) δ (ppm) = 165.7 (C-1'), 134.9 (C-2), 127.2 (C-5), 110.7 (C-3), 107.5 (C-4), 59.0 (C-2'), 43.4 (C-1''), 32.7 (C-2''), 20.0 (C-3''), 14.5 (C-3'), 13.7 (C-4''), 12.2 (C-2'''), 11.3 (C-1''')

IR $\nu_{\text{max}}(\text{NaCl})/\text{cm}^{-1}$ = 2960, 2933, 1720, 1229, 1217, 1066, 773

MS (EIMS): m/z (%) = 223 [M^+ , 100%], 194 (60%), 178 (46%), 152 (59%), 122 (26%), 108 (87%)

Ethyl (2E)-2-[1-(butylamino)ethylidene]pent-4-enoate (54)



A solution of ethyl (2E)-3-(butylamino)but-2-enoate (1.01g, 5.5mmol) in dry THF (50ml) was cooled to 0°C and *n*-BuLi (3.75ml, 6.0mmol) added dropwise. This was allowed to stir for 30min after which allyl bromide (0.61ml, 7.08mmol) was added dropwise and allowed to stir for a further 1hr while warming to room temperature, and then for 24hrs at rt. The reaction mixture was quenched with water (2ml) and solvent removed *in vacuo*. The residue was purified by radial chromatography (1:1 EtOAc-hex) to yield the product as a yellow oil in 100% purity (by ¹H NMR).

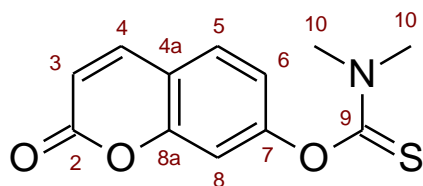
R_f = 0.81 (1:1 EtOAc-hex)

¹H NMR (400MHz, CDCl₃) δ(ppm) = 9.37 (br s, 1H, H-1''), 5.76 – 5.88 (m, 1H, H-4), 4.87 – 4.98 (m, 2H, H-5), 4.11 (q, 2H, J = 7.10 Hz, H-1'), 3.21 (q, 2H, J = 6.50 Hz, H-2''), 3.00 (m, 2H, J = 1.61 & 5.82 Hz, H-3), 1.95 (s, 3H, H-2'''), 1.52 – 1.61 (m, 2H, H-3''), 1.36 – 1.47 (m, 2H, H-4''), 1.25 (t, 3H, J = 7.10 Hz, H-2'), 0.94 (t, 3H, J = 7.30 Hz, H-5'')

¹³C NMR (100MHz, CDCl₃) δ(ppm) = 170.8 (C-1), 160.8 (C-2), 138.7 (C-4), 112.7 (C-5), 89.0 (C-1'''), 58.6 (C-1'), 43.1 (C-2''), 32.5 (C-3''), 31.3 (C-3), 20.1 (C-4''), 14.8 (C-2'''), 14.6 (C-2'), 13.7 (C-5'')

IR ν_{max}(neat)/cm⁻¹ = 3391, 2959, 2933, 2873, 1643, 1599, 1267, 1214

MS (EIMS): *m/z* (%) = 225 [M⁺, 52%], 224 (68%), 210 (19%), 192 (72%), 182 (100%), 178 (32%), 150 (57%), 136 (30%), 122 (20%), 108 (28%), 94 (21%), 79 (20%), 67 (9%), 42 (35%)

TYPICAL SYNTHESIS OF O-(2-OXO-2H-CHROMEN-7-YL) *N,N*-DIMETHYLCARBAMOTHIOATE

NaH (0.093g of an 80% oil dispersion, 3.2mmol) was added to a 100ml round bottom flask under a dry nitrogen atmosphere. This was washed with a little THF to remove the oil. 7-hydroxy-2H-chromen-2-one (0.50g, 3.09mmol) was then dissolved in dry THF (40ml) in a round bottom flask and transferred *via* canula to the reaction vessel. This was allowed to stir at rt for 30min until evolution of hydrogen gas had ceased. Dimethylthiocarbamoyl chloride (0.396g, 3.2mmol) was transferred *via* canula into the reaction as a solution in dry THF. The solution was then stirred at 60°C for a further 30min with a nitrogen-containing balloon to allow for increased pressure. The solution was then cooled and concentrated to 10ml *in vacuo* after which it was poured over ice-water causing precipitation. This was filtered and recrystallised from ethanol to give the product as white crystals (0.636g, 81%).

m.p. 182-183°C (lit.¹⁵⁴ 156-157°C).

¹H NMR (500 MHz, C₂D₂Cl₄) δ (ppm) = 4.64 and 4.73 [2xs, 6H, N(CH₃)₂], 7.68 (d, 1H, J = 9.52 Hz, H-3), 8.35 (dd, 1H, J = 2.22 and 8.30 Hz, H-8), 8.37 (d, 1H, J = 2.08 Hz, H-6), 8.79 (d, 1H, J = 8.32 Hz, H-5), 9.02 (d, 1H, J = 9.56 Hz, H-4).

¹³C NMR (100 MHz, C₂D₂Cl₄) δ (ppm) = 40.4 and 44.8 [N(CH₃)₂], 112.9 (C-8), 117.2 (C-2), 118.0 (C-4), 121.3 (C-6), 129.6 (C-5), 144.6 (C-3), 155.7 (C-9), 157.6 (C-1), 161.9 (C-7), 187.6 (C-10).

IR (neat): 2933, 1713, 1700, 1620, 1538, 1119, 839.

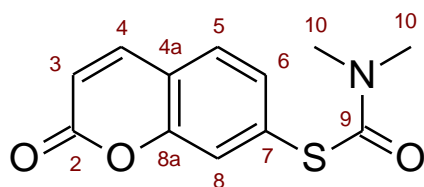
MS (EIMS): *m/z* (%) = 249 [M⁺] (5), 207 (2), 177 (6), 149 (7), 121 (9), 77 (6), 72 (100).

¹⁵⁴ Clarke, University of Natal, 2001.

 ATTEMPTED SYNTHESIS OF S-(2-OXO-2H-CHROMEN-7-YL) *N,N*-DIMETHYLCARBAMOTHIOATE

O-(2-oxo)-2H-chromen-7-yl) *N,N*-dimethylcarbamothioate (0.100g, 0.40mmol) was heated neat under nitrogen for 40min at 240 - 260°C. This was then cooled and an attempt to recrystallise from ethanol yielded only insoluble charred remains with 14% starting material recovered. Attempts in refluxing solvent also failed, yielding the same insoluble remains with varying recovery of starting material.

 SYNTHESIS OF S-(2-OXO-2H-CHROMEN-7-YL) *N,N*-DIMETHYLCARBAMOTHIOATE



O-(2-oxo)-2H-chromen-7-yl) *N,N*-dimethylcarbamothioate (64mg, 0.26mmol) was dissolved in 2ml DMA in a microwave pressure tube and irradiated with 260W for 40min (cooling off). The solution was then cooled and 1ml distilled water added, causing precipitation of the product as a light orange solid. This was filtered and washed with cold water (2 x 6ml aliquots) yielding 57mg of the product (89%).

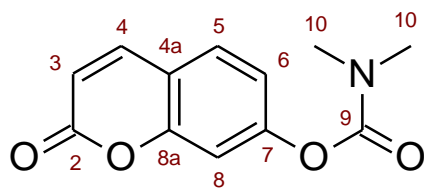
m.p. 179 - 184°C (lit.¹³⁹ 180 - 183°C).

¹H NMR (500 MHz, C₂D₂Cl₄) δ (ppm) = 4.30 and 4.37 [2xs, 6H, N(CH₃)₂], 7.72 (d, 1H, J = 9.55 Hz, H-3), 8.71 (dd, 1H, J = 1.45 and 8.05 Hz, H-6), 8.76 – 8.79 (m, 2H, H-5 and H-8), 9.01 (d, 1H, J = 9.45 Hz, H-4).

¹³C NMR (100 MHz, C₂D₂Cl₄) δ (ppm) = 30.8 (C-10), 117.0 (C-3), 118.8 (C-4a), 123.0 (C-8), 127.5 (C-5), 131.0 (C-6), 133.5 (C-7), 142.8 (C-4), 153.2 (C-8a), 160.1 (C-2), 165.0 (C-9).

IR (neat): 3051, 2928, 1717, 1664, 1601, 1392, 848.

MS (EIMS): *m/z* (%) = 249 [M⁺] (6), 207 (1), 177 (7), 149 (8), 121 (10), 77 (6), 72 (100).

SYNTHESIS OF 2-OXO-2H-CHROMEN-7-YL *N,N*-DIMETHYL CARBAMATE

Method was carried out as described for **3c** above. NaH (0.093g of an 80% oil dispersion, 3.2mmol), 7-hydroxy-2H-chromen-2-one (0.50g, 3.09mmol), dimethylcarbamyl chloride (0.342g, 3.2mmol). The remaining peach solid was purified by radial chromatography (1:2 ethyl acetate-hexane) to yield the product as white crystals (0.422g, 57%).

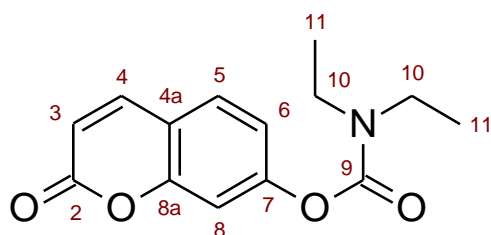
m.p. 148 - 154°C (lit.¹³⁹ 149 - 150°C)

¹H NMR (500 MHz, CDCl₃) δ (ppm) = 2.96 and 3.05 [2xs, 6H, N(CH₃)₂], 6.30 (d, 1H, J = 9.65 Hz, H-3), 7.02 (dd, 1H, J = 2.20 and 8.44 Hz, H-6), 7.06 (d, 1H, J = 2.12 Hz, H-8), 7.38 (d, 1H, J = 8.44 Hz, H-5), 7.61 (d, 1H, J = 9.52 Hz, H-4).

¹³C NMR (100 MHz, C₂D₂Cl₄) δ (ppm) = 36.5 and 36.8 [N(CH₃)₂], 110.4 (C-8), 115.6 (C-3), 116.1 (C-4a), 118.6 (C-6), 128.3 (C-5), 142.9 (C-4), 153.8 (C-7), 154.2 (C-8a), 154.7 (NCO), 160.6 (C-2).

IR (neat): 2904, 2724, 1460, 1376, 722

MS (EIMS): *m/z* (%) = 233 [M⁺] (8), 133 (2), 105 (3), 77 (4), 72 (100), 51 (3).

SYNTHESIS OF 2-OXO-2H-CHROMEN-7-YL *N,N*-DIETHYLCARBAMATE

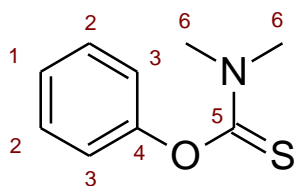
Method was carried out as described for **3c** above. NaH (0.093g of an 80% oil dispersion, 3.2mmol), 7-hydroxy-2H-chromen-2-one (0.50g, 3.09mmol), diethylcarbamyl chloride (0.434g, 3.2mmol). The product was obtained as a viscous mustard liquid, which could not be recrystallised or purified due to its tackiness.

^1H NMR (500 MHz, CDCl_3) δ (ppm) = 1.24 and 1.29 [2xt, 6H, $J = 7.15$ Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$], 3.42 and 3.47 [2xq, 4H, $J = 6.86$ Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$], 6.38 (d, 1H, $J = 9.54$ Hz, H-3), 7.12 (dd, 1H, $J = 2.26$ and 8.53 Hz, H-6), 7.15 (d, 1H, $J = 2.26$ Hz, H-8), 7.48 (d, 1H, $J = 8.28$ Hz, H-5), 7.70 (d, 1H, $J = 9.54$ Hz, H-4).

^{13}C NMR (100 MHz, $\text{C}_2\text{D}_2\text{Cl}_4$) δ (ppm) = 10.8 and 11.7 [$\text{N}(\text{CH}_2\text{CH}_3)_2$], 39.6 and 39.9 [$\text{N}(\text{CH}_2\text{CH}_3)_2$], 107.7 (C-8), 112.8 (C-3), 113.4 (C-4a), 116.2 (C-6), 125.9 (C-5), 140.8 (C-4), 115.6 (C-7), 115.9 (C-8a), 153.1 (NCO), 158.3 (C-2).

MS (EIMS): m/z (%) = 260 [M^+] (6), 134 (8), 100 (100), 72 (56), 44 (26).

 SYNTHESIS OF *O*-PHENOL *N,N*-DIMETHYLCARBAMOTHIOATE



Method was carried out as described for **3c** above. NaH (0.147g of an 80% oil dispersion, 4.90mmol), phenol (0.419g, 4.45mmol), dimethylthiocarbamoyl chloride (0.660g, 5.34mmol). The product was extracted with dichloromethane and purified by radial chromatography (1:2 ethyl acetate-hexane), to give 583mg (72%) as a yellow oil.

^1H NMR (500 MHz, $\text{C}_2\text{D}_2\text{Cl}_4$) δ (ppm) = 3.31 and 3.43 [2xs, 6H, $\text{N}(\underline{\text{H}}_3)_2$], 7.08 (2xd, 2H, $\text{J} = 8.40$ and 8.70 Hz, $-\text{O}-\text{C}=\underline{\text{H}}-\text{CH}=\text{CH}-$), 7.26 (t, 1H, $\text{J} = 7.42$ Hz, $-\text{O}-\text{C}=\text{CH}-\text{CH}=\underline{\text{H}}-$), 7.40 (t, 2H, $\text{J} = 7.95$ Hz, $-\text{O}-\text{C}=\text{CH}-\underline{\text{H}}=\text{CH}-$).

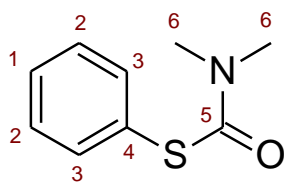
^{13}C NMR (100 MHz, CDCl_3) δ (ppm) = 38.7 and 43.2 [$\text{N}(\underline{\text{C}}\text{H}_3)_2$], 122.8 ($\text{O}-\text{C}=\underline{\text{C}}\text{H}-\text{CH}=\text{CH}$), 125.9 ($\text{O}-\text{C}=\text{CH}-\text{CH}=\underline{\text{C}}\text{H}$), 129.2 ($\text{O}-\text{C}=\text{CH}-\underline{\text{C}}\text{H}=\text{CH}$), 154.1 ($\text{O}-\underline{\text{C}}=\text{CH}-\text{CH}=\text{CH}$), 187.8 [$-\text{O}-\underline{\text{C}}(\text{S})-\text{N}$].

IR (neat): 3340, 2940, 1781, 1535, 1395, 1206, 769, 691.

MS (EIMS): m/z (%) = 181 [M^+] (4), 180 (12), 88 (58), 72 (100).

 SYNTHESIS OF *S*-PHENYL *N,N*-DIMETHYLCARBAMOTHIOATE: METHOD 1

O-phenol *N,N*-dimethylcarbamothioate (200mg, 1.10mmol) was dissolved in 2ml DMA in a microwave pressure tube and irradiated with 260W for 40min (cooling off). The solution was then cooled and 1ml distilled water added, causing deposition of the product as a dark orange oil. The DMA/water solution was decanted, to leave the oil product. Conversion was accomplished in 50% yield by NMR.

SYNTHESIS OF S-PHENYL *N,N*-DIMETHYLCARBAMOTHIOATE: METHOD 2

Method was carried out as described for **3c** above. Thiophenol (0.656g, 5.95mmol), NaH (0.157g, 6.54mmol), dimethylcarbamyl chloride (0.735g, 5.95mmol). The product was extracted with dichloromethane and purified by radial chromatography (1:2 ethyl acetate-hexane) to give 679mg (63%) as a light yellow oil, which solidified under vacuum.

m.p. 41 - 42°C (lit.¹⁵⁵ 43 - 44°C)

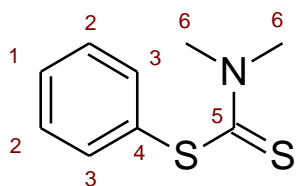
¹H NMR (500 MHz, CDCl₃) δ (ppm) = 4.32 [br. s, 6H, N(CH₃)₂], 8.65-8.72 (m, 3H), 8.76-8.82 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 38.37 (N(CH₃)₂), 130.17 (S-C=CH-CH=CH), 130.3 (S-C=CH-CH=CH), 130.5 (S-C=CH-CH=CH), 137.1 (S-C=CH-CH=CH), 168.0 [S-(C=O)-N].

IR (neat): 2974, 2885, 1455, 1380, 1090, 881.

MS (EIMS): *m/z* (%) = 180.9 [M⁺] (6), 109 (7), 72.1 (100), 65.2 (6), 39.1 (3).

¹⁵⁵ Moseley, Sankey, Tang and Gilday. *Tetrahedron* **2006**, 62, 4685-4689.

SYNTHESIS OF PHENYL *N,N*-DIMETHYLCARBAMODITHIOATE

NaH (0.128g of an 80% oil dispersion, 4.26mmol), thiophenol (0.427g, 3.87mmol), dimethylthiocarbamoyl chloride (0.574g, 4.65mmol). The product was extracted with dichloromethane and purified by radial chromatography (1:2 ethyl acetate-hexane), to give 321mg (42%) as a yellow solid.

m.p. 88 – 92°C (lit.¹⁵⁶ 93 – 94°C)

¹H NMR (500 MHz, CDCl₃) δ (ppm) = 3.52 and 3.57 [2xs, 6H, N(CH₃)₂], 7.43 – 7.53 (m, 5H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm) = 42.0 and 45.6 (N(CH₃)₂), 129.1 (S-C=CH-CH=CH), 130.0 (S-C=CH-CH=CH), 131.8 (S-C=CH-CH=CH), 136.9 (S-C=CH-CH=CH), 197.6 [S-(C=S)-N].

IR (neat): 3071, 1948, 1864, 1574, 1438, 1071, 738, 688.

MS (EIMS): *m/z* (%) = 197 [M⁺] (6), 196 (42), 88 (100).

3.3. COMPUTATIONAL DETAIL

All *ab initio* gas phase calculations were performed using the Gaussian 03W package¹⁵⁷ at the DFT (B3LYP) level of theory with the 6-31+G(d) basis set. In this case, the diffuse functions were incorporated in order for a more accurate description of π -electron delocalization and the lone pairs associated with oxygen, sulphur and nitrogen. The ground state geometries of all amide compounds were optimized, following a scan calculation in which the amide dihedral angle was rotated. The structures associated with the two

¹⁵⁶ Chen, Jin and Stang. *Journal of Organic Chemistry* **1987**, 52, 4117-4118.

¹⁵⁷ Gaussian 03. 2004.

maxima on the energy profile of the scan were manually extracted and used as starting structures in a full transition state optimization (no constraints) at the same level of theory and basis set. Each of the two possible transition states had one negative eigenvalue only. Analysis of the movement of atoms associated with this eigenvalue confirmed rotation of the amide bond, as expected for these transition states. Thermochemical data was obtained from frequency calculations performed on both ground and transition states.

3.4. X-RAY CRYSTALLOGRAPHY

Crystallographic measurements were made using a 3 kW Spellman X-ray generator with a 3 kW ceramic X-ray tube and an Xcalibur 2 CCD diffractometer. The structure was solved using the SHELXS-97⁵² program by direct methods. The structure was plotted using the program ORTEP.⁵³ Detailed crystallographic data for Phenyl *N,N*-dimethylcarbamodithioate have been deposited at the Cambridge Crystallographic Data Centre and are available on request (CCDC No. 711835)

Crystal Data of Phenyl N,N-dimethylcarbamodithioate. $C_9H_{11}NS_2$, $M=197.31$, $T=100(2)$ K, $\lambda=0.71073$ Å, $a=7.538(5)$, $b=8.989(5)$, $c=14.229(5)$ Å, $\alpha=90.000(5)^\circ$, $\beta=90.959(5)^\circ$, $\gamma=90.000(5)^\circ$, $V=964.0(9)$ Å³, space group $P2_1/c$, $Z=4$, $D_x=1.359$ mg m⁻³, $\mu=0.495$ mm⁻¹, $F(000)=416$. Crystal Size 0.6x0.55x0.25 mm; θ range for data collection 3.82-34.11°; index range $-10 < h < 11$, $-13 < k < 13$, $-21 < l < 21$; reflections collected 14324; independent reflections 3567 [$R_{\text{int}}=0.0538$]; refinement method full-matrix least-squares on F^2 ; data/restraints/parameters 3567:0:153; goodness-of-fit on F^2 1.071; $R(F)$ [$I > 2\sigma(I)$]=0.0568; $wR_2=0.1461$; largest diff. peak and hole 1.721 and -0.986 e Å⁻³.

4. REFERENCES

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5. APPENDIX

All original NMR fid files as well as GC-MS traces and IR data for compounds synthesised are available on the accompanying CD. Also available are pdf files for each compound containing processed NMR spectra, all Gaussian input and output files, a copy of the free programs Spekwin (to view the IR spectra) & Mercury (to view crystal structures), and a pdf copy of this thesis.

