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SYNTHESIS OF HETEROCYCLES
USING
METAL AND BASE CATALYSIS

BY

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A Thesis Submitted to the

Nanyang Technological University

in Partial Fulfillment of the Requirement for the

Degree of

Doctor of Philosophy

2010

Acknowledgements.

Many people have helped and supported me during my education and I shall not be able to acknowledge all of them in this small space. First and foremost, I must express my whole-hearted thanks and appreciation to Dr Roderick W. Bates, for giving me the opportunity to move out to Singapore and for allowing me work in his group. Under his guidance I have learnt so much! His never ending enthusiasm, unfaltering grasp of the literature and dedication to the cause have been nothing less than amazing. Rod's guidance all started at the University of Exeter, where I was an undergraduate student in his lab, the main topic of discussion was chemistry and school work, but now as a friend he has also proven to be an excellent source of tourist information. He has enlightened me with the wonders of Thailand, and this has allowed me to have fabulous extra-curricular experiences whilst studying for my Ph.D.

Whilst studying in Singapore, I have been lucky enough to share my lab life with a whole host of people, form many different nations, Song Ping my fellow batch mate has been a continuous source of encouragement and amusement. I remember our first year in N4.1 fondly, where we had the whole of B1 to ourselves. The next additions to the Bates group were Attapol and subsequently Bank (Krisada), who have been great fun to work and socialise with. I must also thank Kalpana, whose been doing some of my lab duties while I have been immersed in my thesis writing, thank you so much. Sridhar, Yongna and Pat have also provided me with great assistance over the last few years, of which I shall be forever thankful. I also must express my thanks to Joyce, Pei Juan and Ana for all the coffee/tea sessions and the words of encouragement they have offered me, you are all great friends.

I have also been lucky enough to have a wonderful project student Filza, she has been amazing to work with, thanks for putting up with my rants, working round my exceptionally well organized fumehood and generally cheering me up.

I would also like to thank all the people I have lived with over the past four years, for providing me with a peaceful relaxed environment away from the lab.

Ee Ling, Hendra, Ramesh, Siew Ping, Wen Wei and Shu Qi have all done a wonderful job of maintaining the facilities, that have been invaluable to me during my Ph.D. I am exceptionally grateful to them, as I am to Dr Yongxin, for obtaining my crystal structure.

On a more serious note I must express great thanks to Professor Stephen Hashmi for the generous gift of his catalyst and useful discussions on the gold chemistry. I must also express my thanks to Professor Louis Hegedus and Dr Christopher Hyland for the useful discussions.

Finally I must thank my parents and family, who I've only seen once in over four years, without their support and love none of this would have been possible.

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Summary.

Brevetoxin B was isolated from the organism *Gymnodium breve*, its structure was determined as containing 11 *trans*-fused oxygen heterocycles, of which eight are fused pyrans, two are fused polyoxepanes and one alone was a *trans*-fused eight membered ring. It has become a formidable challenge for synthetic organic chemists. We have made progress toward the formation of the fused pyran segment, initially investigating the formations of pyran rings via the metal catalysed cyclisations of allene diols. This however posed a great challenge, as the allene proved unwilling to undergo the desired 6-*exo*-cyclisation, instead favoring the undesired 5-*endo*-cyclisation, to form an undesired furan. Subsequently we have revised our synthetic route to investigate the cyclisation of a range of Michael accepters by Michael addition of a pendant oxygen nucleophile. As a result of these studies we have obtained a route to a functionalised pyran by tandem deprotection and cyclisation under basic conditions. We are currently in the progress of demonstrating the iterative nature of this synthetic route and the mild cyclisation conditions.

(-)-Swainsonine, a (1*S*, 2*R*, 8*R*, 8*aR*)-1,2,8-trihydroxyindolizidine, first isolated from the fungus *Rhizoctonia leguminicola,* demonstrates potentially great anticancer capabilities. It has attracted our attention due to its molecular architecture, containing a fused 6,5-heterocyclic rings with four contiguous stereocenters. We have successfully produced two formal sysnthesis of (-)-swainsonine, the first an enantioselective formal synthesis via the metal catalysed cyclisation of an allene amide, using gold catalysis. This key cyclisation proceeded stereoselectively proving exclusive access to the *trans* functionalised piperidine, in quantitative yield. The *trans* piperidine was subsequently functionalised to provide a diene piperidine, which underwent ring closing metathesis to form a known indolizidine core.

The second formal synthesis of swainsonine was racemic and used a palladium catalysed Tsuji-Trost cyclisation, of an allylic acetate. The cyclisation proceeded with the formation of a *trans* functionalised piperidine core as a 10:1 mixture of diastereomers in high yield. Functionalisation of the secondary alcohol allowed for isolation of the desired *trans* product that could then be functionalised to provide a diene that also underwent ring closing metathesis to provide a second known indolizine core.

Abbreviations.

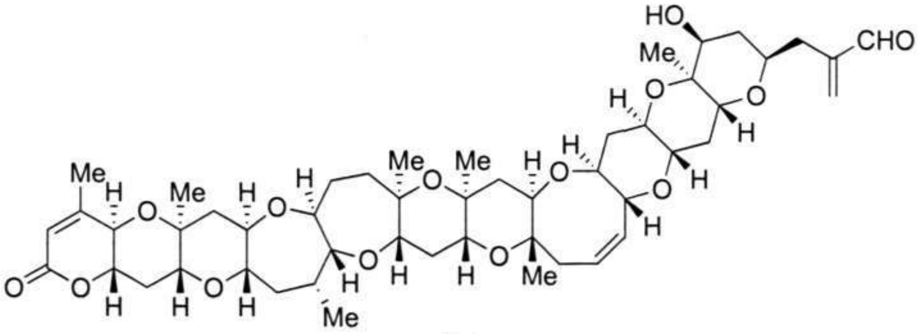
δ	Chemical shift
Å	Angstrom units
Ac	Acetyl
Alloc	Allyloxycarbonyl
Ar	Aromatic
App	Apparent
aq	Aqueous
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
Bz	Benzoyl
Bu	Butyl
cat.	Catalyst
Cbz	Carbobenzyloxy
CSA	Camphorsulfonic acid
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undecane
DCE	1,2-Dichloroethane
DIBAL	Diisobutylaluminium hydride
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-*N,N*-Dimethylamino pyridine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
Et	Ethyl

h.	Hour(s)
HMDS	Hexamethyldisiazide
HRMS	High Resolution Mass Spectrometry
IBX	2-Iodoxybenzoic acid
J	Coupling constant (Hz)
LCMS	Liquid Chromatography Mass Spectrometry
m	multiplet
*m*CPBA	3-chloroperoxybenzoic acid
Me	Methyl
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
o-Ns/Nosyl	*ortho*-nitrobenzenesulfonyl
Nu	Unspecified nucleophile
p	para
PDC	Pyridinium dichromate
PCC	Pyridinium chlorochromate
Ph	Phenyl
PMB	*para*-Methoxybenzyl
ppm	Parts per million
PPTs	Pyridinium *p*-toluenesulfonate
Pr	Propyl
q	Quartet
R	Undefined alkyl or aryl group
RCM	Ring closing metathesis
Red-Al	Sodium bis(2-methoxyethoxy)aluminium hydride

s	singlet
sat.	Saturated
t	triplet
t	tertiary
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMG	Tetramethyl guanidine
TMS	Trimethylsilyl
TPAP	Tetra-n-propylammonium perruthenate

Chapter 1: Access towards *trans,syn,trans*-fused pyran rings of Brevetoxin B.

Introduction to Brevetoxin B.



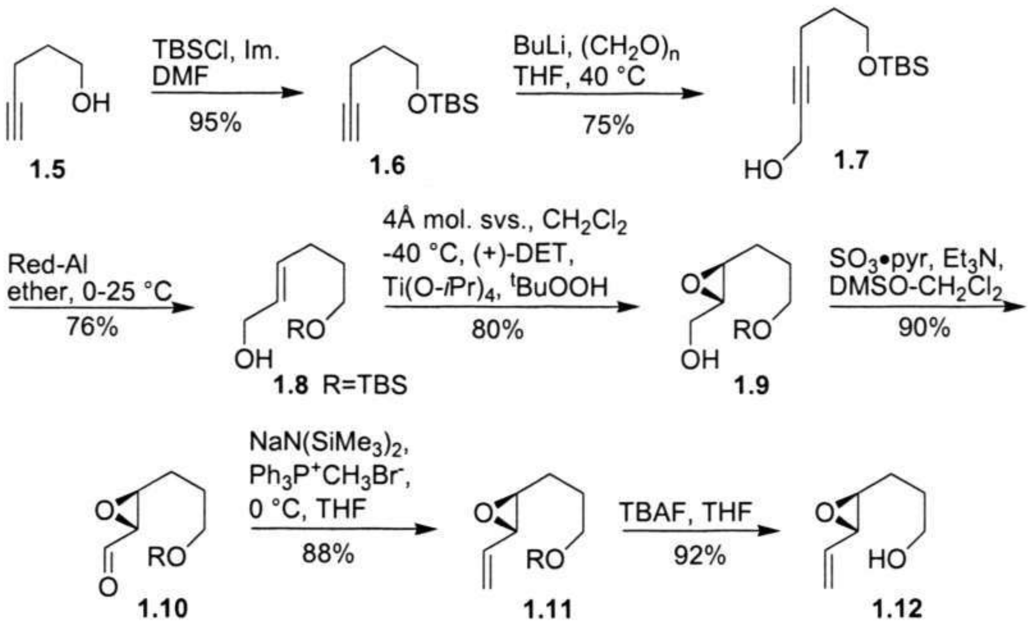
1.1

Figure 1. Brevetoxin B

Lin, Clardy and Nakanishi in 1981 reported the isolation and structure of Brevetoxin B **(1.1)** from the "Red Tide" Dinoflagellate *Ptychodiscus brevis (Gymnodinium breve)*.[1] The complex structural architecture of Brevetoxin B **(1.1)** was unprecedented at the time and it became a formidable challenge for many synthetic chemists. Brevetoxin B **(1.1)** contains 11 *trans*-fused oxygen containing rings, which are divided by C-C bonds. The substituents on either side of the oxygen atom are all *cis* to each other, whilst being *trans* across the dividing C-C bonds. Out of the 11 *trans*-fused rings eight are fused pyrans, two are fused polyoxepanes and one alone is a *trans*-fused eight membered ring. It is this beautiful molecular complexity and the challenge of construction that it poses attracted us to this molecule. Whilst the intention was to tackle the whole molecule in due course initially we set out to obtain a synthetic route towards the elegantly constructed *trans*-fused pyran rings. The intention was to establish a procedure that was iterative and could by simple elongation of the carbon chain be applied to the formation of larger heterocycles. During this chapter we will discuss our attempts to obtain this goal. Firstly reviewed here after are some of the more interesting procedures that have already been published, we are however intent on obtaining the *trans*-fused pyran systems and this will be the focus of the introduction, not the complete total synthesis of Brevetoxin B **(1.1)**.

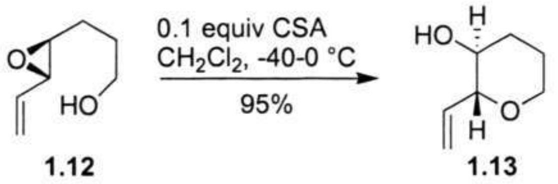
Scheme 1. Nicolaou's synthesis.

Nicolaou was the first to achieve the total synthesis of Brevetoxin **(1.1)**,[2] he proposed the formation of the *trans*-fused pyran system by the ring opening of epoxides (Scheme 1).[3] Nicolaou's concept was built on the assumption that if a π-system were placed adjacent to an epoxide unit, it would activate the nearest C-O bond. It would then be this side of the epoxide unit that would cleave selectively when attacked by a nucleophile and as seen in scheme 1 this would result in formation of the 6-*endo* product **(1.3)**, which is *anti* to Baldwin's rules.[4] The transition state involved would require the carbon at the center of the nucleophilic attack to become electron deficient, this would then be stabilized by electron donation from the neighboring π-system. The 5-*exo* product **(1.4)** would require a transition state where there is no neighboring π-system to the carbon that became electron deficient, therefore this transition state would be less stabilized and disfavored as a result. To test this theory, Nicolaou created the hydroxy epoxide **(1.12)** from 5-pentyn-1-ol **(1.5)**. Protection of the hydroxyl group, followed by alkylation of the alkyne with paraformaldehyde gave the propagalyic alcohol **(1.7)**. Reduction of the alkyne to the alkene with the use of Red-Al was then achieved in 76%. A Sharpless asymmetric epoxidation with (+)-diethyl tartarate then gave the epoxide **(1.9)** stereoselectively. Oxidation of the alcohol followed by a Wittig reaction introduced the alkene π-system, α to the epoxide **(1.11)**. The silyl protecting group was then removed to give the hydroxy epoxide precursor to cyclisation **(1.12)**.



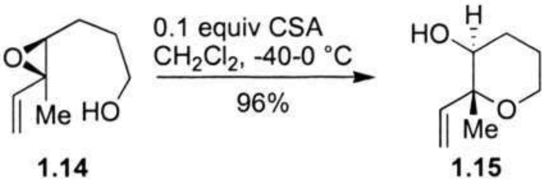
Scheme 2. Nicolaou's epoxide opening route to THP formation.

Nicolaou then proceeded with his ring-forming step under acidic conditions. As expected, Nicolaou observed the selective 6-*endo* cyclisation of the hydroxy epoxide (**1.12**) with 0.1 equivalent of camphorsulfonic acid (CSA) in the high yield of 95% (Scheme 3).



Scheme 3. Nicolaou's *anti*-Baldwin ring closing cyclisation.

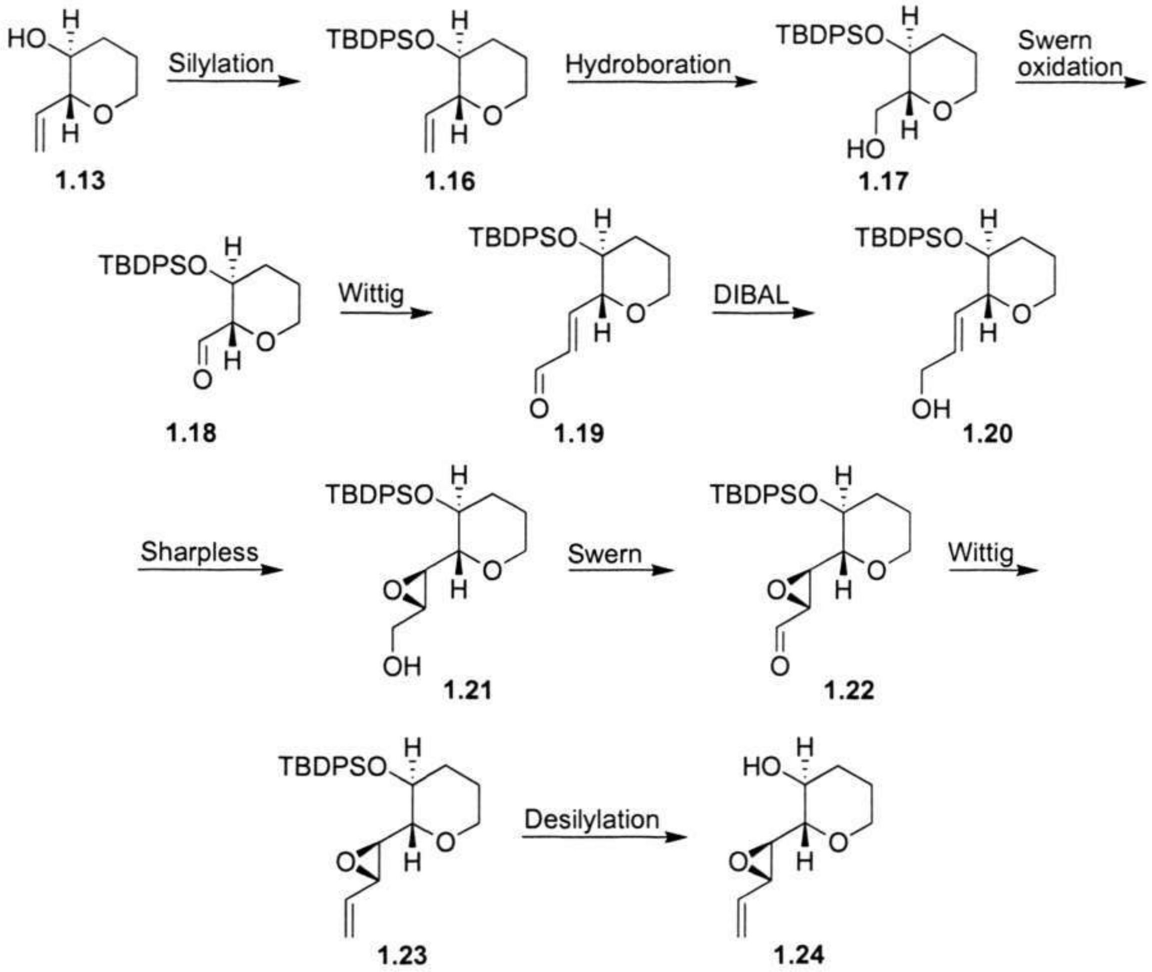
Nicolaou then elaborated on his original synthetic route, so as to install the methyl group at the position of the new ring junction on cyclisation (**1.14**).



Scheme 4. Nicolaou's ring closing reaction with the extra steric bulk at the created ring junction.

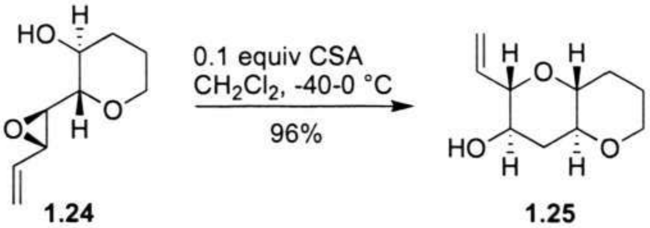
This extra steric bulk did not prove to be a problem and the reaction proceeded as expected and gave the desired 6-*endo* product (**1.15**) in 96% yield (scheme 4).

To install the second ring of the bicyclic product that was required for the construction of Brevetoxin B, Nicolaou further functionalised the product of the trial system (Scheme 5).



Scheme 5. Nicolaou's continued synthesis towards the second ring.

The hydroxyl group of (**1.13**) was protected as the *tert*-butyldiphenylsilyl ether under standard conditions, this was followed by hydroboration of the terminal alkene providing the terminal alcohol (**1.17**). Oxidation of this alcohol by Swern chemistry then gave the aldehyde (**1.18**) that was used in the Wittig reaction to install the alkene and aldehyde of (**1.19**). The aldehyde was then reduced to the alcohol (**1.20**) by DIBAL to give a product that was reminiscent of the product of the Red-Al reduction in Scheme 2. Now by repetition of the original sequence of asymmetric Sharpless epoxidation to give the desired epoxide (**1.21**), Swern oxidation of the alcohol, Wittig reaction to install the alkene (**1.23**) and then finally desilylation gave the hydroxy epoxide **(1.24)** as the precursor to the second cyclisation.



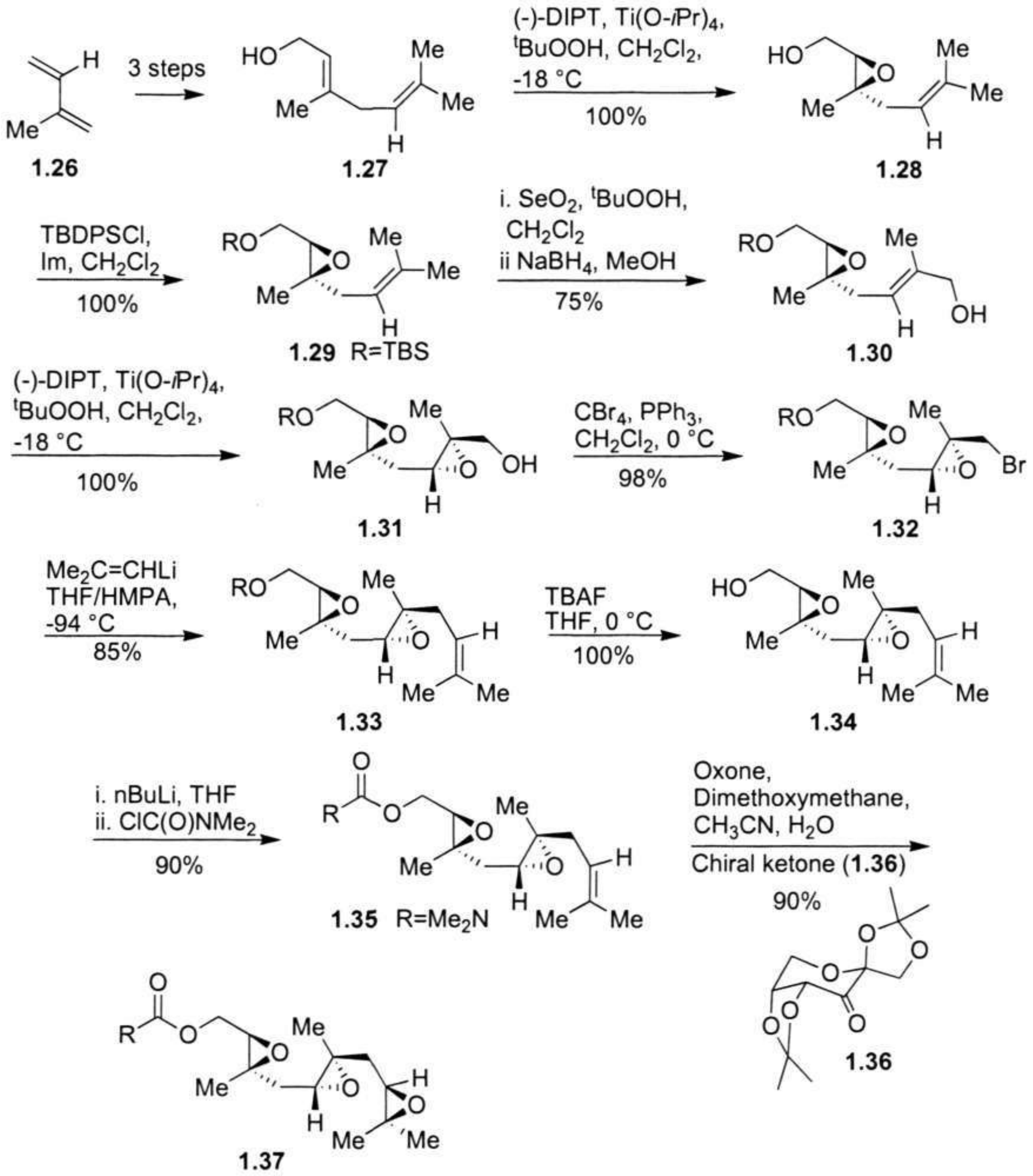
1.24

1.25

Scheme 6. Nicolaou's formation of the fused pyran.

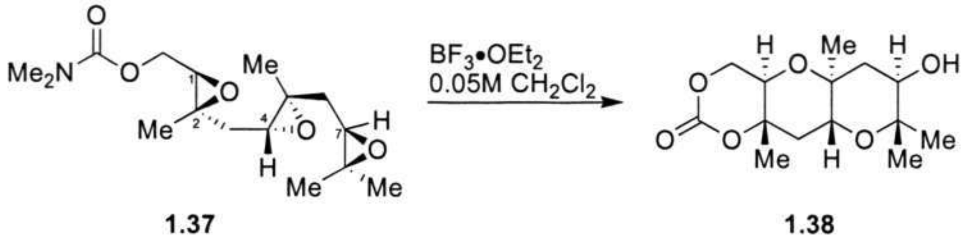
Once again, treatment of the hydroxy expoxide (**1.24**) with CSA resulted in the desired 6-*endo* cyclisation creating the desired *trans*-fused pyran (**1.25**) in quantitative yield. The high level of selectivity was attributed as already mentioned to the favorable ring opening of the epoxide.

McDonald has also made progress towards the formation of Brevetoxin B (**1.1**), they have proposed a biomimetic synthetic route towards fused pyrans.[5,6] The route involves a cascade of 5-*endo*-regioselective oxacyclisations to create the fused polycyclic ether skeleton in a single step (Scheme 8).



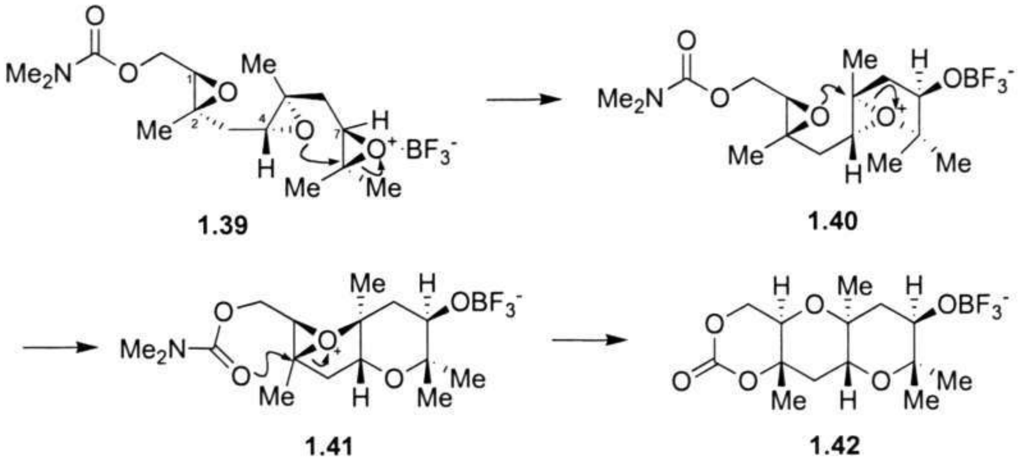
Scheme 7. McDonald's synthesis of the polycyclic ether **(1.37)**, the precursor to cyclisation.

McDonald's route to the precursor for cyclisation (Scheme 7) started from isoprene (**1.26**), which was converted in three steps to the known dienyl alcohol (**1.27**).[7] The first epoxide was then introduced by a hydroxyl-directed Sharpless asymmetric epoxidation. Protection of the alcohol as the silyl ether and subsequent regioselective allylic oxidation gave the second hydroxyl group of (**1.30**) that would again be used in a hydroxyl-directed Sharpless asymmetric epoxidation to install the second epoxide (**1.31**). The alcohol was then converted into the bromide, nucleophilic substitution of this bromide with lithiated 2-methyl-1-propene then introduced the third alkene (**1.33**). The silyl protecting group was then removed and the alcohol (**1.34**) was functionalised as the carbamate (**1.35**), so as to act as a terminator in the cascade sequence. The choice of carbamate proved to be vital, as only a strong nucleophile had been proven to give the correct 6-membered ring product. The final isolated alkene was then converted into the epoxide by the method of Shi,[8] this provided the polycyclic ether (**1.37**) that would be used in the cascade.



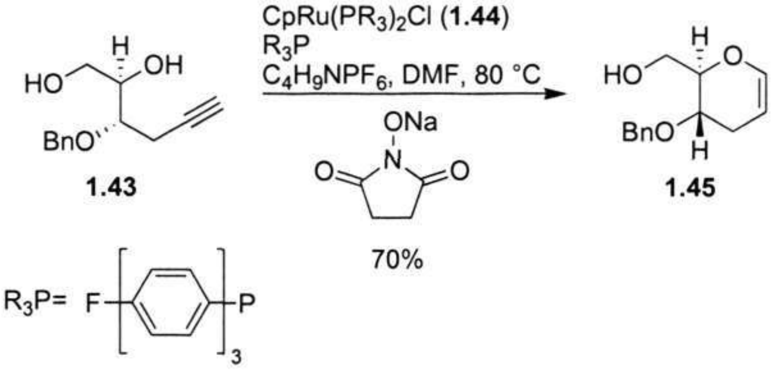
Scheme 8. McDonald's cascade cyclisation.

By exposing their polycyclic compound (**1.37**) to boron trifluoride diethyl etherate, in dichloromethane at -40 °C, they were able to achieve their cyclisation (Scheme 8). It was thought that the Lewis acid activates the epoxide at position 7-8 (**1.39**). This activation would be followed by the nucleophilic addition of the epoxide at position 4-5, creating an epoxonium ion and also cleaves the initially activated epoxide ring. This new epoxonium ion (**1.40**) was then attacked by the 1-2 epoxide, creating another epoxonium ion (**1.41**) and cleaving the first. Termination of the propagating reaction was achieved by attack of the carbamate, which eliminates in the basic work up to give the desired product (**1.42**) (Scheme 9).



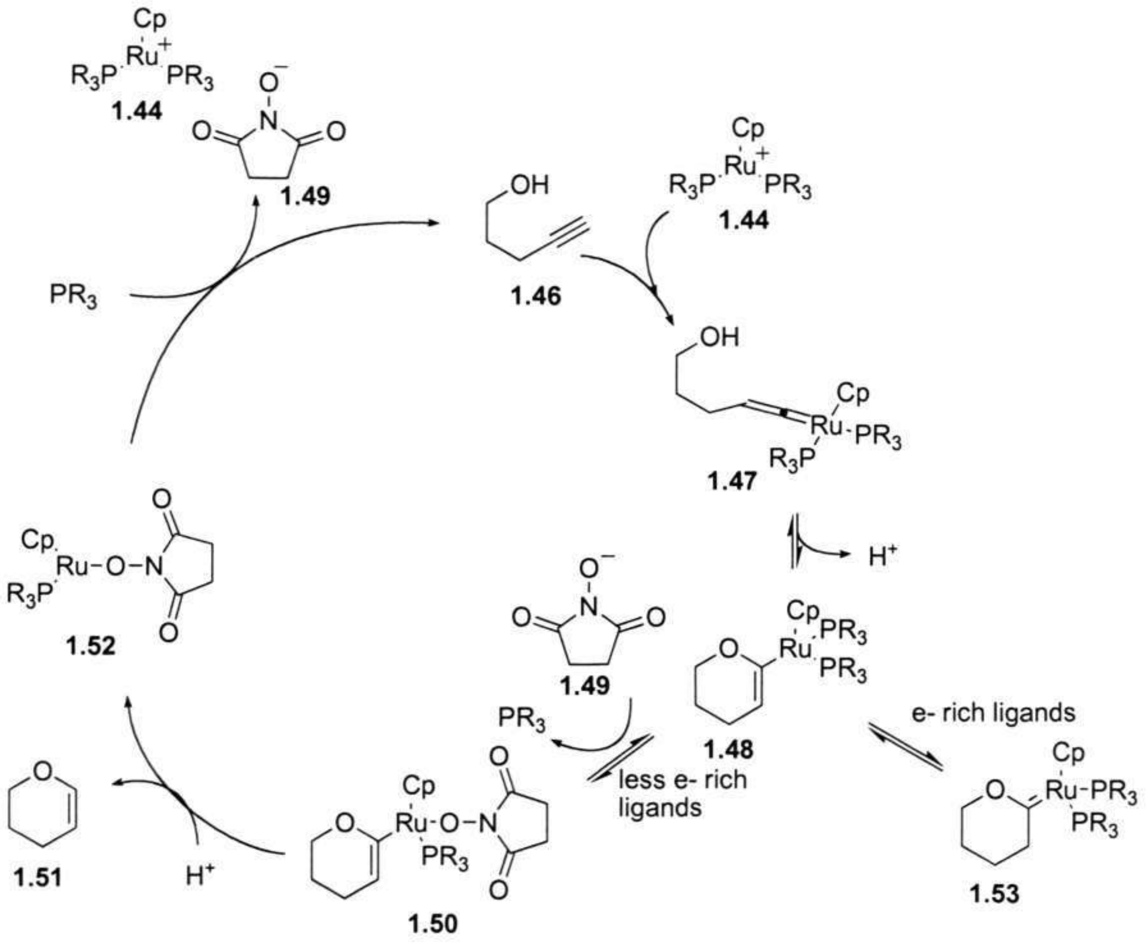
Scheme 9. McDonald's cascade mechanism.

Trost has also made progress towards *trans*-fused pyrans, but his target were fragments of Yessotoxin and Prymnesin.[9] Trost and co-workers intended on forming the pyran rings by a ruthenium catalysed cycloisomerization and oxidative cyclisation of a bis-homopropargylic alcohol (Scheme 10).



Scheme 10. Trost's Ruthenium cyclisation.

Their synthesis starts from the chiral ynediol (**1.43**) that was available as an intermediate from one of Nicoloau's synthetic routes to Brevetoxin B, but prepared by the method of Wu.[10] Scheme 11 demonstrates the mechanism, when yne-ol (**1.46**) was subjected to the ruthenium catalyst (**1.44**) its forms a vinylidene (**1.47**), which was then attacked by the hydroxy nucleophile to give the dihydropyran (**1.48**) under the conditions stated in Scheme 10. They note that by altering ligands on the catalyst they could choose the course of the reaction to favour either formation of a lactone (not shown) or the desired dihydropyran, here they found electron poor ligand favours formation of the dihydropyran.

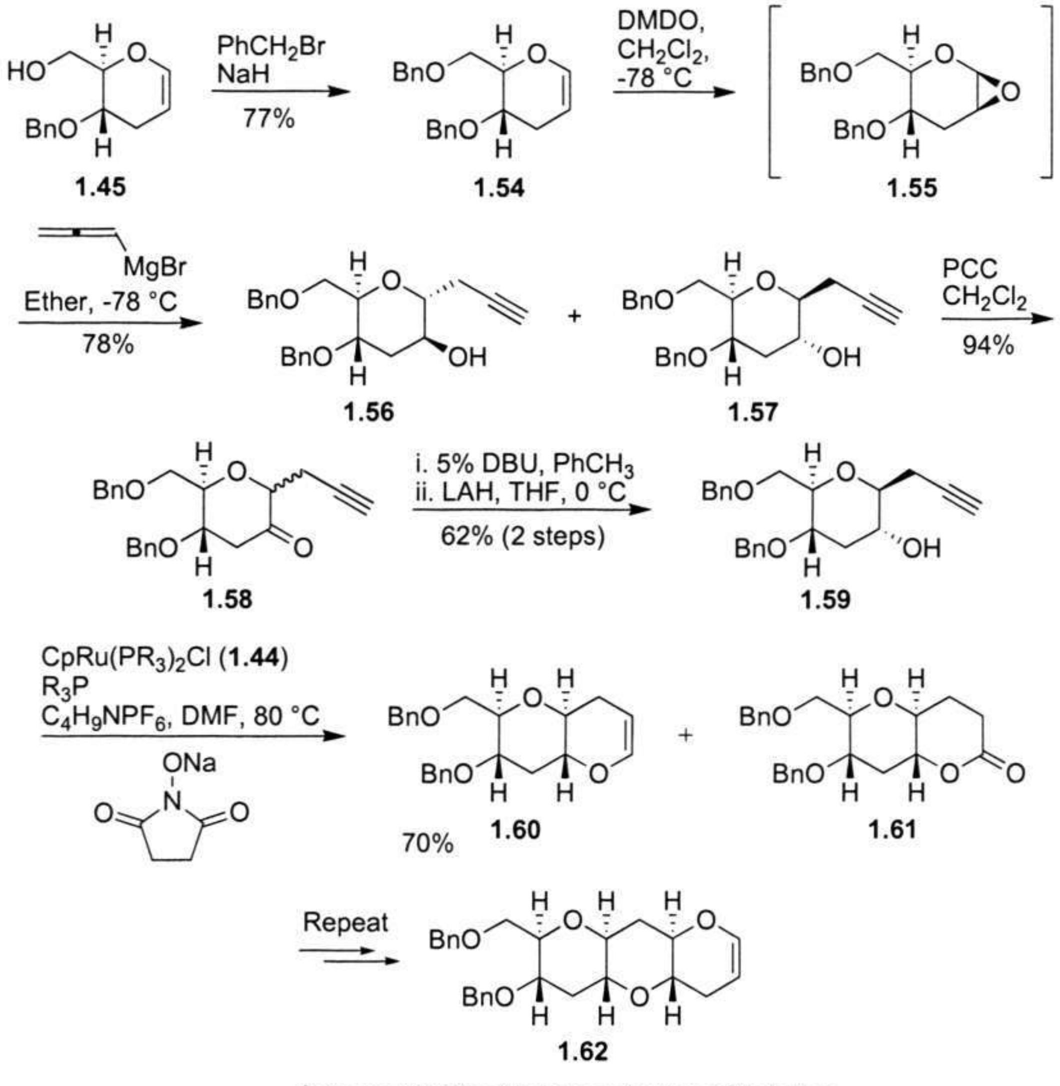


Scheme 11. Trost's Ruthenium cycloisomerization and cyclisation mechanism.

Trost gave this mechanistic rational for his observation,[11] formation of the vinylidene (**1.47**) was followed by attack of the hydroxyl group to give the intermediate (**1.48**). If the catalyst contains less electron rich ligands they are displaced by the *N*-hydroxysuccinimide (**1.49**) to give the intermediate (**1.50**), which then by simple protonation liberates the dihydropyran (**1.51**). However, if the phosphorous ligands are electron rich the reaction proceeds with protonation of intermediate (**1.48**) at the carbon (C3) position to produce a oxacarbene complex (**1.53**). The complex **(1.53)** would then lead to the formation of a lactone (not shown).

Scheme 12 demonstrates the iterative nature of the reaction forming the second ring, the free alcohol of (**1.45**) was protected as the benzyl ether and the alkene was then converted into the chiral epoxide (**1.55**). This expoxide was then subjected to allenyl magnesium bromide, which resulted in the formation of a pair of diastereomers (**1.56**) and (**1.57**).

After oxidation of the alcohol to the ketone (**1.58**) the racemic mixture was base equilibriated, subsequent reduction of the ketone then gave the desired *trans*-*syn*-diastereomer (**1.59**) as a 9:1 mixture.

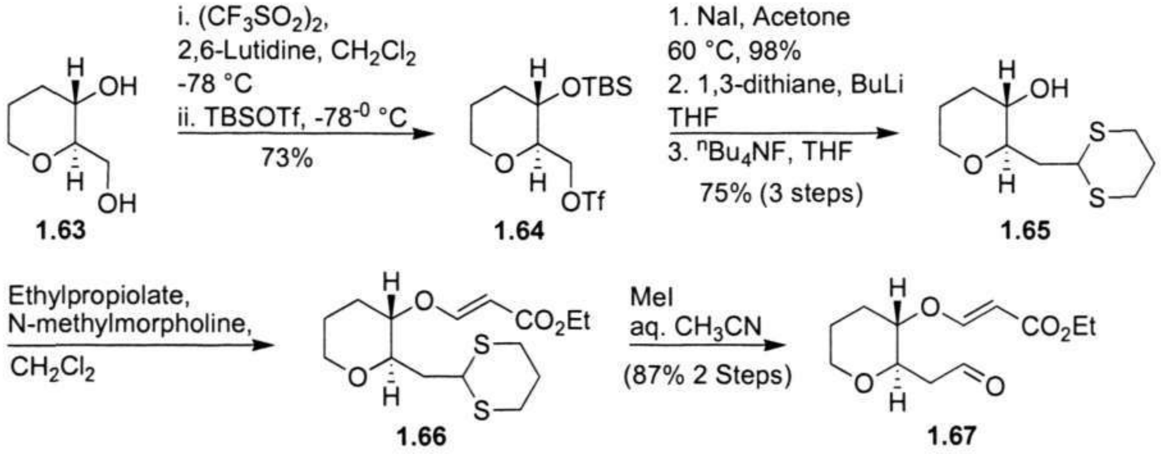


Scheme 12. Trost's demonstration of iteration

Submitting Ynediol **(1.59)** to the established cyclisation conditions resulted in the formation of the desired fused dihydropyran (**1.60**) in 70% yield and a trace amount of the lactone. A third ring could then be introduced in an identical manner to give the *trans*-*syn*-fused tetrahydropyran **(1.62)**.

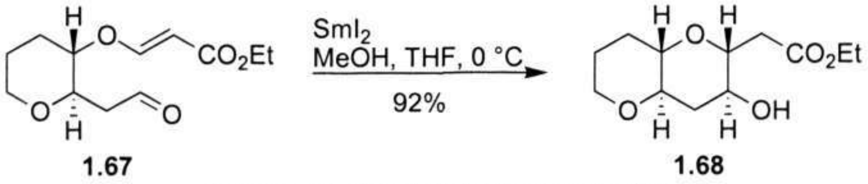
Another noteworthy route to fused tetrahydropyrans was contributed by Nakata,[12] their route was based on a samarium(II) iodide induced reductive intramolecular cyclisation

(Scheme 14). This synthesis also starts from the established tetrahydropyran ring (**1.63**) that they obtained by the method of Nicoloaou (Scheme 13).[13]



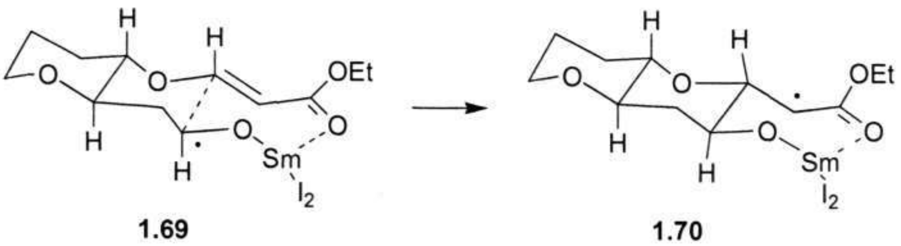
Scheme 13. Nakata's approach to fused tetrahydropyrans.

The two hydroxyl groups were selectively activated and functionalised in one pot as the triflate and the silyl ether (**1.64**) by the method of Mori.[14] The triflate was then displaced by the iodide, which was then displaced by the dithiane to effectively give a protected aldehyde. The silyl protecting group was then removed to give the alcohol (**1.65**) that acted as the nucleophile in the subsequent Michael addition to ethylpropiolate in the presence of base. The dithiane was then removed to give the β-alkoxyacrylate aldehyde (**1.67**) as the precursor to their key transformation.



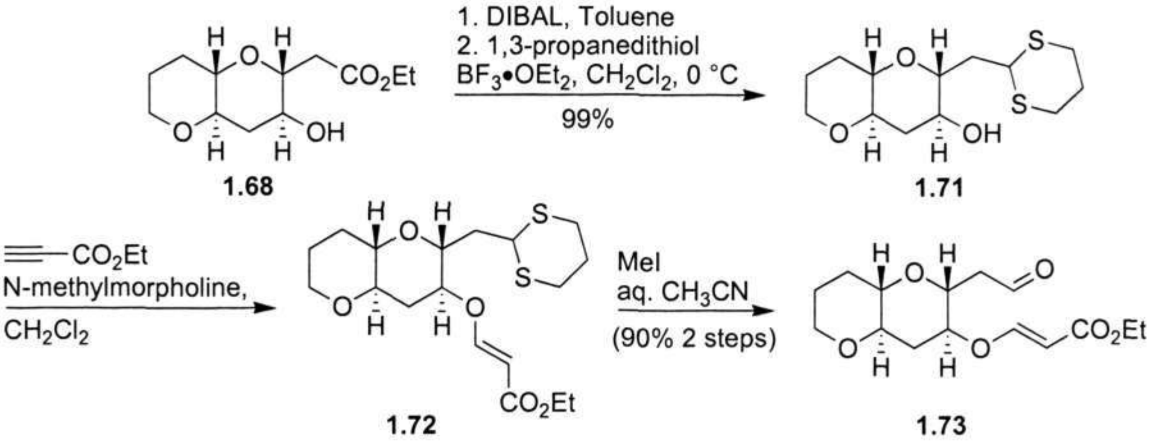
Scheme 14. Nakata's radical cyclisation.

Treatment of the β-alkoxyacrylate aldehyde (**1.67**) with samarium(II) iodide resulted in the formation of a radical that would add to the unsaturated double bond and form the *trans*-tetrahydropyran (**1.68**). The virtually complete stereoselectivity they proposed as the result of a more favorable transition state in which chelation of the samarium(III) to the carbonyl of the ester exists (Scheme 15).



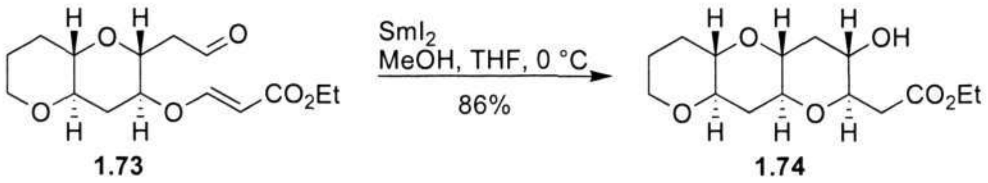
Scheme 15. Nakata's transition states for the complete stereoselectivity of cyclisation.

The radical (**1.69**) created by single electron reduction of the aldehyde then attacks the β-position of the alkoxyacrylate to give a second intermediate the ketyl radical (**1.70**). Reduction of the Ketyl radical (**1.70**) by a second samarium iodide and protonation would then give the desired *trans-syn-trans*-fused tetrahydropyran (**1.68**). Demonstration of the iterative nature of the reaction sequence was then provided (Scheme 16).



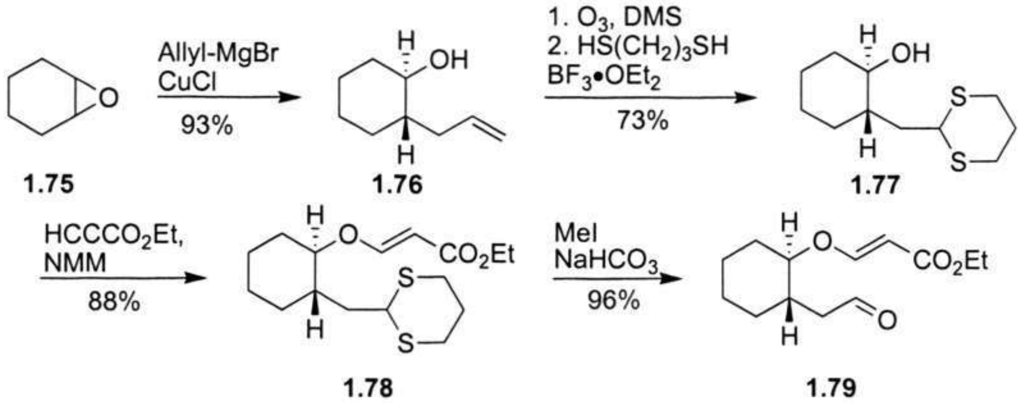
Scheme 16. Nakata's demonstration of iteration.

The ester was reduced using DIBAL to the aldehyde, which was then protected as the dithiane (**1.71**). Repetition of the heteroatom Michael addition gave the second β-alkoxyacrylate (**1.72**) and removal of the dithiane then gave the aldehyde (**1.73**), which was subjected to the same cyclisation system as before (Scheme 17). This time the reaction provided the *trans-syn-trans*-fused tetrahydropyran (**1.74**) exclusively in 86% yield.



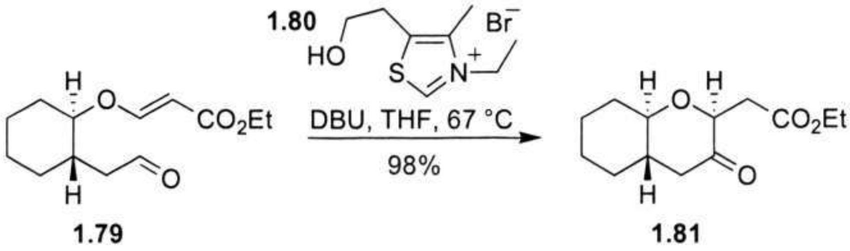
Scheme 17. Nakata's 2nd radical cyclisation.

Very recently, McErlean published a different approach to *trans-syn-trans*-fused tetrahydropyrans,[15] his synthesis used an intramolecular Stetter reaction as the key transformation. The synthesis began from a model system using a cyclohexane ring as the building block instead of an established chiral tetrahydropyran (Scheme 18).



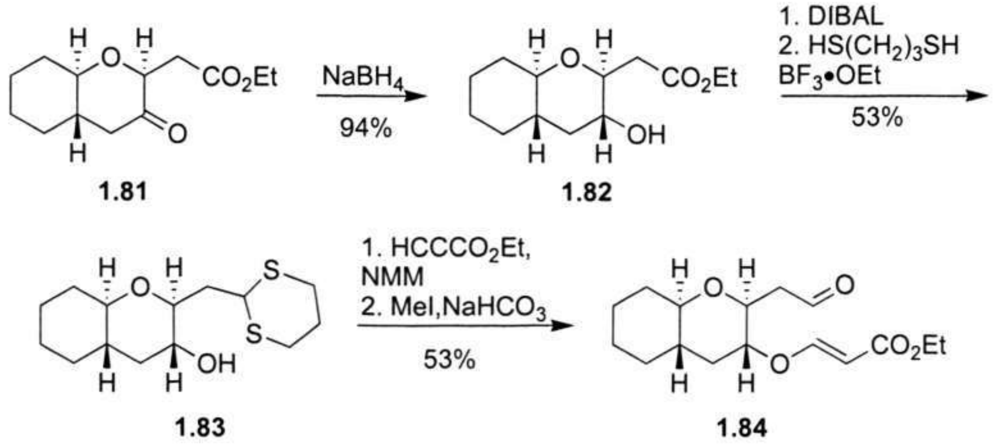
Scheme 18. McErlean's syntheitc route.

Firstly, ring opening of cyclohexene oxide with allyl magnesium bromide gave the *trans*-allylic alcohol (**1.76**). The alkene was then converted into the aldehyde by ozonolysis, which was then protected as the dithiane (**1.77**). Michael addition to the alcohol with ethyl propiolate gave access to the *E*-alkene (**1.78**) and subsequent removal of the dithiane provided the aldehyde (**1.79**) as the precursor to cyclisation.



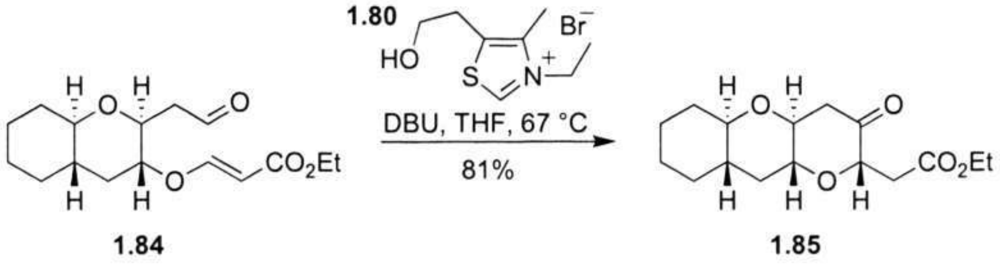
Scheme 19. McErlean's intramolecular Stetters reaction.

McErlean then proceeded with his key reaction. Attempts at using the optimized reaction conditions of Rovis (triazolium salts and KHMDS) proved unsatisfactory as it was thought that the strongly basic conditions caused decomposition of the starting material. It was not until they switched to a thiazolium salt (**1.80**) that they observed a marked improvement. However, they still observed byproducts as a result of interference of the basic catalyst with the acrylate. Only by using the less nucleophilic base, DBU, they were able to obtain the desired pyran (**1.81**) as a single diastereomer. They attempted to rationalize this outcome as being due to the formation of the more thermodynamically stable *syn*-pyranone, but they also suggested that, as there is DBU and the basic thaiazolium carbene in the reaction mixture, either epimerization or an elimination addition sequence could convert any initial mixture into the more stable isomer. They also have no proof that the observed product was not just the kinetic outcome of the Stetter addition to an *E*-alkene.



Scheme 20. McErlean's demonstration of iteration.

McErlean then went on to prove the iterative nature of the reaction sequence. Sodium borohydride reduction to the alcohol at low temperature gave the *trans*-product (**1.82**) selectively. DIBAL reduction of the ester and protection as the dithiane was followed by Michael addition and deprotection to give the aldehyde (**1.84**) as precursor to second cyclisation (Scheme 20). When submitted to the cyclisation conditions of scheme 19, they obtained the desired *trans-syn-trans*-fused tetrahydropyran ring (**1.85**) in high yield and stereoselectively (Scheme 21).

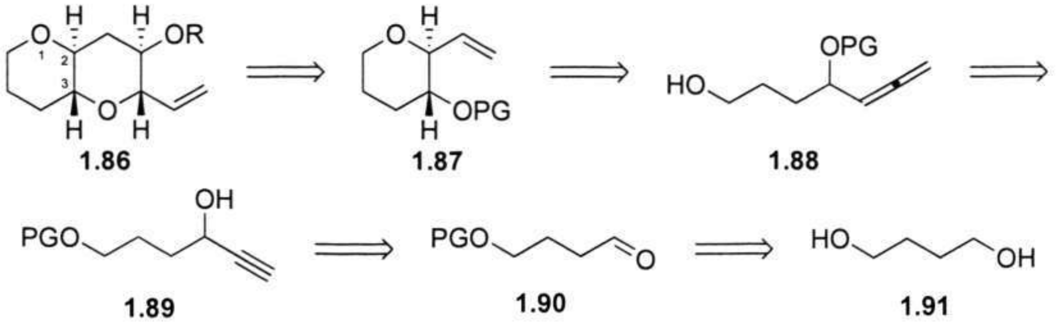


Scheme 21. McErlean's demonstration of the iterative cyclisation.

Chapter 1: Access towards *trans,syn,trans*-fused pyran rings of Brevetoxin B.

Retrosynthetic Analysis.

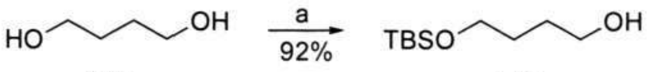
Outlined below is our initial retrosynthetic analysis we had anticipated that the *trans,syn,trans*-fused pyrans **(1.86)** would be a valid model system to test our key step. Pyran **(1.86)** is a simplified system compared to the actual *trans,syn,trans*-fused pyrans of Brevetoxin B (**1.1**) which have a methyl substituent at the C(2) position. We believed that the extra steric bulk on this carbon in the real **(1.1)** system would not cause any significant problem on application of our novel transformation to the real system. The product of the model system contains a protruding alkene substituent and alcohol moiety that potentially allows for an iterative route to be established. Retrospectively this iterative route would take us to the single pyran (**1.87**) as the product of the first cyclisation prior to any iteration to for the fused system.



Scheme 22. Retrosynthetic analysis of the fused pyrans.

The plan was to introduce the *trans* stereochemistry of this pyran **(1.87)** by the cyclisation of an allene diol (**1.88**). Many complex issues would arise from this cyclisation, such as ring size and the level if any of stereoselectivity. We anticipated that allene moiety of allene diol (**1.88**) would be installed by homologation of a suitable alkyne (**1.89**), whilst the alkyne could be obtained by standard transformations from a readily available, cheap source such as 1,4-butanediol (**1.91**). The formation of a synthetic intermediate such as allene diol (**1.88**) allows access to a large range of compounds by protecting group manipulation allowing us to effectively evaluate the potential of our cyclisation.

Results and Discussion.

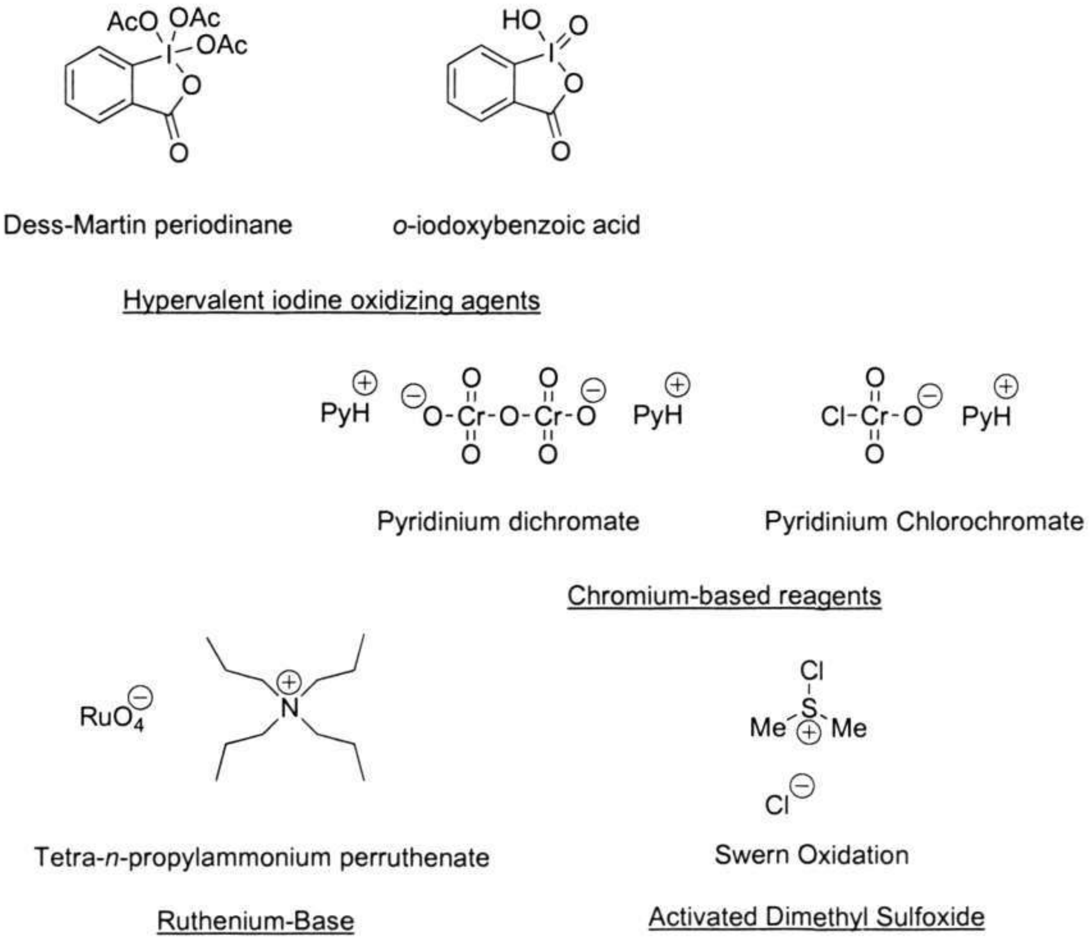


1.91 **1.92**

Reagents and conditions: (a). TBSCl, Imidazole, DMAP, THF.

Scheme 23. Mono-protection of diols.

Preparation of the requisite aldehyde (**1.90**) was achieved by the mono-protection of 1,4-butanediol (**1.91**) by the method of Nicolaou.[16] The use of 1 equivalent of TBSCl and a 5-fold excess of 1,4-butanediol gave the desired product in near quantitative yield. The polarity of the diol allows for simple purification as the excess is removed by simple washing with water to give the clean product. The mono protected diol was identified by its ^1H NMR spectrum with the TBS group being observed as two singlets at 0.06 and 0.87 ppm. While the free hydroxyl group was observed at 2.50 ppm and also seen at 3368 cm^{-1} in the IR spectrum. The aldehyde was then to be installed by simple oxidation.



Dess-Martin periodinane

o-iodoxybenzoic acid

Hypervalent iodine oxidizing agents

Pyridinium dichromate

Pyridinium Chlorochromate

Chromium-based reagents

Tetra-*n*-propylammonium perruthenate

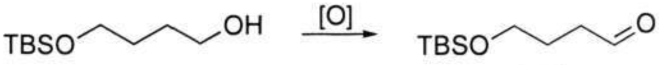
Ruthenium-Base

Swern Oxidation

Activated Dimethyl Sulfoxide

Figure 2. Common Oxidizing agents of alcohols.

Many methods for the oxidation of alcohols exist,[17] hypervalent iodine compounds behave as strong oxidants and one commonly used in synthesis is the Dess-Martin periodinane (DMP). This reagent is a very effective oxidizing agent that is exceptionably soluble in most organic solvents and is obtainable from 2-iodoxybenzoic acid (IBX). Its formation is sometimes challenging,[18] and the DMP obtained is often of questionable quality and ability. However, IBX itself was shown to oxidize alcohols very effectively,[19] This hypervalent iodine compound is an extremely effective oxidizing agent and shows great tolerance of functional groups, and can be easily produced on a multi gram scale by addition of 2-iodobenzic acid to a solution of oxone® in water, with warming to 73 °C for three hours before cooling and simple filtration.[20] This procedure is far superior to the original $KBrO_3$ procedure, which generates noxious gasses and requires hot sulfuric acid.[21] This oxidizing agent does have some drawbacks such as its limited solubility, being only readily soluble in DMSO. Reports in the literature also suggest that it is explosive under excessive heating (>200 °C) or on impact. However, with access to IBX being far more convenient than DMP, we chose to utilize this reagent first.

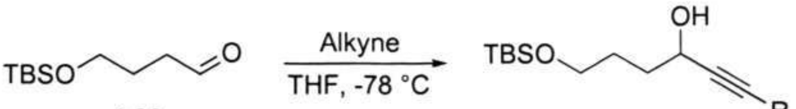


1.92 **1.90**

Oxidizing Agent	Reagents and Conditions	% Yield
IBX	DMSO, 20 °C	60
PDC	CH_2Cl_2, 10 °C	46
Swern	$(COCl_2)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C	60
TPAP	NMO, CH_2Cl_2, CH_3CN, 4Å mol. sieves, 20 °C	62

Table 1. Oxidation of the silyl alcohol.

Oxidation of alcohol (**1.92**) with IBX gave the desired aldehyde product in 60% yield. The ^1H NMR spectrum showed the characteristic aldehyde proton as a triplet at 9.78 ppm, the silyl protecting group was still present and observed as a 9 proton singlet at 0.87 ppm and a 6 proton singlet at 0.03 ppm. The aldehyde was also observed as a sharp absorbance in the IR spectrum at 1729 cm^{-1}. Due to the moderate nature of the obtained yield optimization was attempted (summarised in Table 1). Chromium-based oxidizing agents such as Jones reagent,[22] Sarett and Collins reagents,[23] pyridinium dichromate (PDC),[24] and pyridinium chlorochromate[25] (PCC) are all common oxidizing agents. The latter two are often more efficient and can be prepared and stored for long periods of time without loss of activity. We chose to prepare and use PDC, which was prepared on a large scale by addition of pyridine to a concentrated aqueous solution of CrO_3 to give bright orange crystals. Addition of alcohol (**1.92**) to PDC as a solution in CH_2Cl_2 resulted in the formation of a black tar like solution, standard diethyl ether work up led to a black precipitate that was removed by filtration through celite this however only led to the desired product in 46% yield, much lower than desired. Activated dimethyl sulfoxide reagents have also achieved great popularity in the oxidation of alcohols the most common protocol being the Swern oxidation a method requiring the activation of DMSO with oxalyl chloride.[26] The alcohol when added to the activated DMSO forms a alkoxydimethylsulfonium chloride, subsequent addition of triethylamine then forms a ylide which undergoes a 1,3-sigmatropic shift to give the aldehyde and dimethyl sulfide. However, on addition of alcohol (**1.92**) to the activated DMSO and stirring for 15 minutes led to the formation of a cloudy solution, which is uncommon. After completing the reaction procedure the desired aldehyde was obtained in the same yield as that of the more simple IBX protocol (60%). Another routinely used oxidant is tetra-*n*-propylammonium perruthenate (TPAP), which was developed by Griffith and Ley.[27] They showed that the perruthenate ion RuO_4^- could be made soluble in apolar solvents such as CH_2Cl_2 and was capable of oxidizing alcohols to aldehydes catalytically, using *N*-methyl morpholine *N*-oxide (NMO) as a secondary oxidant. We used 5 mol% of TPAP in CH_2Cl_2 with 1.5 equivalent of NMO the reaction however, failed to proceed to completion and the desired aldehyde was only obtained in 62% yield. Reports suggest that the addition of acetonitrile in such cases can be beneficial as it can prevent deactivation of the metal by other ligands.[28,29] Acceleration of oxidation can also be achieved with the use of ultrasound,[30] yet here no further improvement was attempted as the expensive cost of the catalyst would outweigh any improvement in yield. As such we concluded that IBX oxidation was by far the most efficient and convenient route to 1-(*t*-butyldimethylsilyloxy)-4-butanal (**1.90**). With the aldehyde (**1.90**) in hand the alkyne was now to be installed, attempts to form the terminal α-hydroxy acetylene directly by addition of acetylene proved inadequate.



1.90

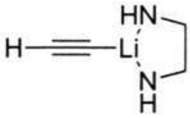
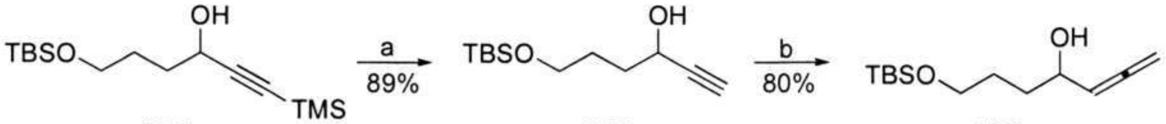
Reactive intermediate	R	% Yield
$H{-}{\equiv}{-}Li$	H **1.93**	67
	H **1.93**	47
$TMS{-}{\equiv}{-}Li$	TMS **1.94**	77

Table 2. Alkyne addition.

Treatment of acetylene with *n*-BuLi followed by addition of the aldehyde gave α-hydroxy acetylene (**1.93**), but only in a 67 % yield we attribute this poor yield to the instability of the lithioalkyne. We thought that the use of lithium ethylene diamine in place of the Li-acetylene would create a more stable intermediate however, treatment of this lithioalkyne with our aldehyde (**1.90**) proceeded only in 47 % yield. Our attention then turned to the use of a non-terminal alkene such as TMS-acetylene, which proved to be highly beneficial. Treatment of TMS-acetylene with *n*-BuLi and subsequent addition of the aldehyde gave access to the TMS-alkyne (**1.94**) in 77 % yield. The ^1H NMR spectrum of TMS-alkyne (**1.94**) shows a 9 proton singlet at -0.01 ppm, a 6 proton singlet at 0.05 ppm and a 9 proton singlet at 0.90 ppm, which can be assigned to the TMS and TBS groups respectively. The IR spectrum showed the alkyne at 2171, and the OH at 3382 cm^{-1}. Removal of the TMS group was then achieved by addition of K_2CO_3 in methanol in a quantitative yield. In the ^1H NMR spectrum the TMS group was no longer present at 0.07 ppm but a new peak was observed at 2.42 ppm as a sharp doublet that coupled to an apparent doublet of triplets at 4.43 ppm, these two peaks were assigned as the terminal alkyne proton and the proton α to the alkyne respectively. The IR spectrum still showed the alkyne at 2110 cm^{-1} and the OH at 3312 cm^{-1}.

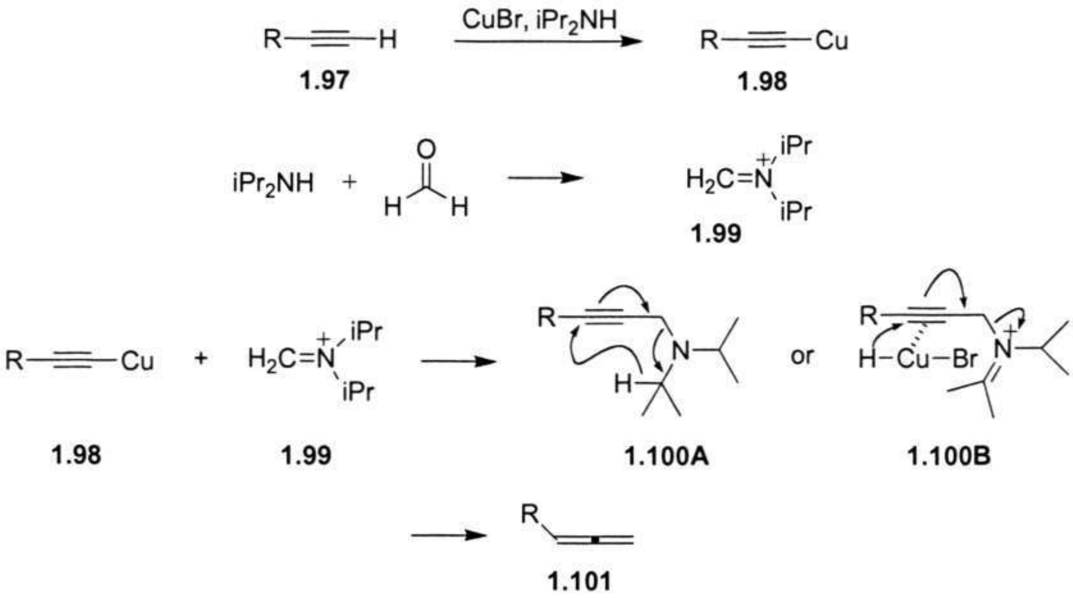


1.94 **1.95** **1.96**

Reagents and conditions: (a). K_2CO_3, MeOH (b). CuBr, *i*-Pr_2NH, $(CH_2O)_n$, Dioxane, 100 °C.

Scheme 24. Deprotection and homolgation of the alkyne.

Allenes are accessible *via* a great number of procedures,[31, 32, 33] we intended to form allene **(1.96)** from alkyne **(1.95)** directly. Many powerful methods have been developed to transform an appropriately functionalised alkyne into an allene such as, S_N2 addition of a nucleophile, sigmatropic rearrangements and carbon homologation. We were attracted to the Searles Crabbé procedure, which was developed in 1979.[34,35] This homologation reaction gives access to monosubstituted allenes from terminal acetylenes the reaction is effectively a Cu based variation of the Mannich reaction as seen in Scheme 25.



Scheme 25. Mechanism for formation of the allene moiety.

While the mechanism still remains a subject of conjecture it is believed the reaction proceeds with the formation of a copper acetylide (**1.98**), which reacts with the iminum ion (**1.99**) that was formed *in situ* from the diisopropylamine and paraformaldehyde to form the complex (**1.100A**). Hydrogen transfer which has been demonstrated by isotopic labeling,[96] possibly but not necessarily via a hydridocopper(I) complex (**1.100B**) in an S_N2 fashion then yields the allene (**1.101**). The reaction was simple in itself, requiring only a few hours to reach completion and being tolerant of moisture. However, care must be taken to ensure an inert atmosphere as the presence of oxygen allows for the formation of symmetric bisacetylenes via the Glaser coupling reaction.[36] The reaction work up was simple, after cooling to room temperature air was bubbled through the reaction mixture oxidizing the Cu(I) to Cu(II), the latter being insoluble in dioxane precipitates out of solution allowing for removal by simple filtration. Product isolation was then possible via standard acidic aqueous work up giving the desired allenes generally as colourless oils with no need for further purification. In our synthesis the alkyne (**1.95**) was transformed into the allene (**1.96**) in 78 % yield. The ^{1}H NMR spectrum showed a one proton apparent quartet at 5.25 ppm with a coupling constant of 6.3 Hz and two, one proton apparent doublets at 4.84 and 4.83 ppm, which couple to each other with a coupling constant of 6.3

Hz. These three protons are all characteristic of the allene moiety. The broad multiplet at 4.21 ppm was the proton α to the allene. Confirmation of the ^1H NMR assignment was achieved using a COSY NMR spectrum in which cross peaks are observed between the proton at the proximal allene position and both the distal allene protons. Coupling was also observed between all three of the allene protons and the proton α to the allene. This coupling across the 4 carbons centers accounts for the complex nature of the two doublets at 4.84 and 4.83 ppm. The ^{13}C NMR spectrum was also conclusive proof of the allene moiety with peaks at 207.1 and 94.8 ppm, which are consistent with the internal carbon and the proximal carbon of the allene moiety. The distal carbon was not clearly observable as its signal was underneath the internal reference at 77 ppm. The allene was also observed at 1956 cm^{-1} in the IR spectrum. With allene (**1.96**) in hand we were now ready to explore the key cyclisation reaction, as shown in Figure 3 cyclisation could potentially provide a number of products as a mixture of *regio* and *stereo* chemical isomers.

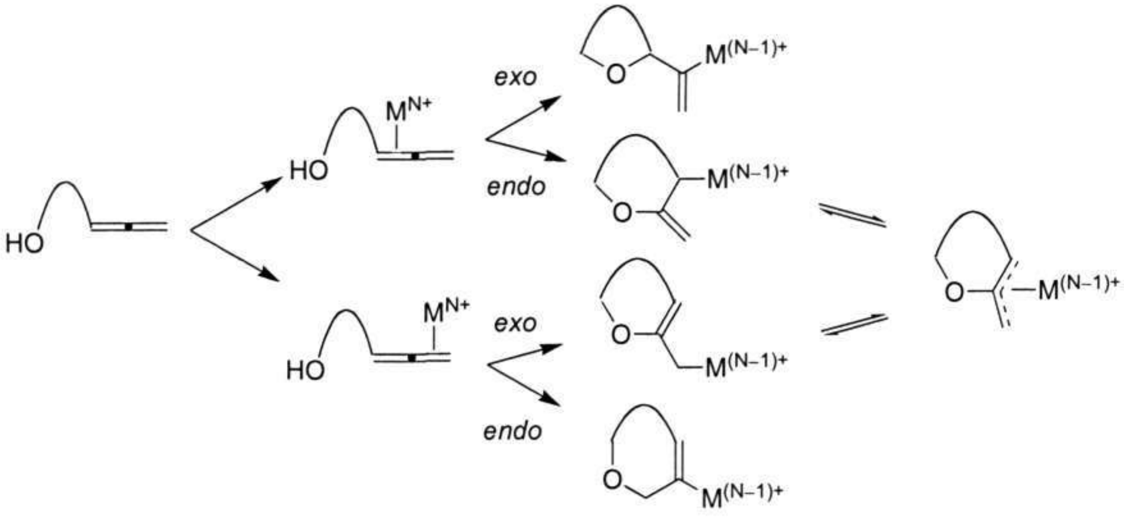
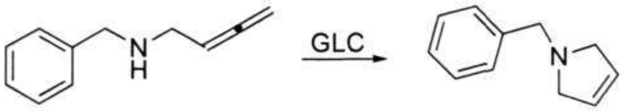


Figure 5. Cyclisation issues.

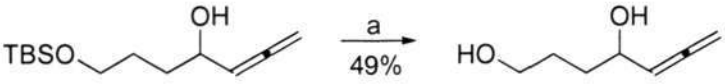
The cyclisations of allenes has been demonstrated with a whole host of nucleophiles,[37] progress in this field all began with the seminal paper of Claesson.[38] What Claesson observed was the decomposition of an allenic amine (**1.97**) on injection into a GLC instrument.



1.102 **1.103**

Scheme 26. The 1st Allene cyclisation from Claesson's seminal publication.

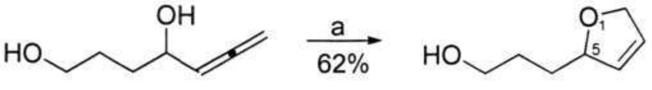
Claesson postulated a metal catalysed cyclisation subsequently proven by treatment of allenic amide (**1.102**) with silver tetrafluoroborate. Later on in that very same year Claesson also demonstrated the silver-catalysed cyclization of allenic alcohols to dihydrofurans and dihydropyrans.[39] Since then, Walkup has demonstrated the cyclisations of allene alcohols via an organopalladium halide,[40] Marshall has explored the cyclisations of allenyl ketones and aldehydes by silver catalysis as well as numerous allene amides, [41] which are not the subject of discussion here. McDonald and Marks have also demonstrated the cyclisation of allene amines with organolanthanides.[42,43] We were attracted to the original paper and its use of silver salts, as such reaction conditions are convenient as the salts are air stable and cheap. Claesson showed that both α-allenic alcohols and β-allenic alcohols could cyclise in the presence of a silver salt such as silver nitrate, both occurred in an *endo* manner. Bäckvall demonstrated that palladium(II)/ halide ion systems could cyclise allenic alcohols to give the *exo*-products.[44] The advantage of the *exo* cyclisation is that an external functional group will be available for further manipulation. Similarly Snider showed that a palladium(II) carbonylation method of cyclisation could also provide access to the *exo* products.[45] Gallagher has also demonstrated the formation of *exo* products from the cyclisation of an oxime with silver.[46] We envisaged that the cyclisation of our allene alcohol with a silver salt would be capable of providing us with the desired *exo*-product, yet the selectivity could give rise to diastereomers.



1.96 **1.104**

Reagents and Conditions: (a). PPTs, MeOH.
Scheme 27. Deptoection of the primary alcohol.

In the initial attempt at cyclisation we had to investigate cyclisation of the simplest system to determine the intrinsic selectivity, here that would require the unprotected diol (**1.104**). The TBS group was easily removed with the use of potassium fluoride or pyridinium *p*-toluensulfonate (PPTs) to give the free diol (**1.104**) (Scheme 27). Then with the use of the established procedure by Claesson, where silver nitrate and calcium carbonate were used in a mixed solvent system of water/dioxane resulted in the formation of dihydrofuran (**1.105**) as the sole isolable product in 62% yield (Scheme 28).

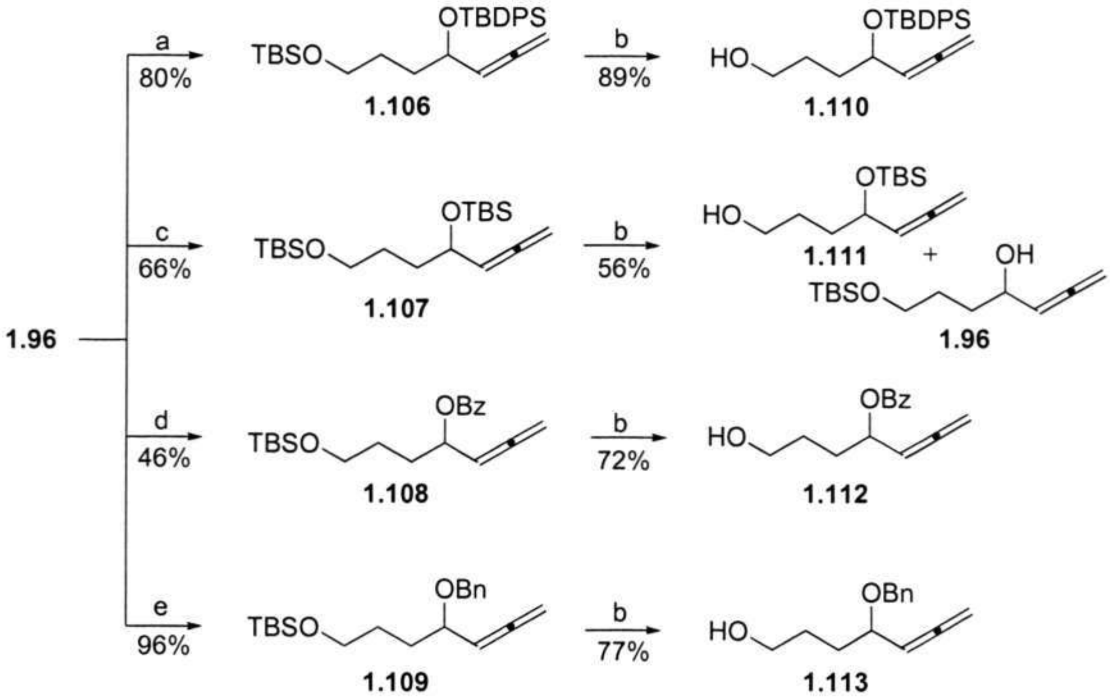


1.104 **1.105**

Reagents and Conditions: (a). $AgNO_3$, $CaCO_3$, H_2O:Dioxane.

Scheme 28. Claesson conditions for cyclisation.

The dihydrofuran was not rigorously characterized, but from the ^{1}H NMR spectrum the proton observed as a broad singlet at 4.86 ppm could be assigned as the proton of C(5). While the two proton multiplet observed at 4.64 ppm was consistent with the two protons of C(2), and the pair of multiplets at 5.89 and 5.75 ppm were characteristic of the C(3) and C(4) protons. The spectrum lacked the typical terminal alkene splitting pattern that one would expect of the desired 6-*exo*-product. We concluded that to obtain the tetrahydropyran this facile 5-*endo* cyclisation must be prevented, which could most simply be achieved by protection of the secondary alcohol of the allene (**1.96**). Therefore we now intended to produce a range of protected α-hydroxy allene diols and attempt their cyclisation.

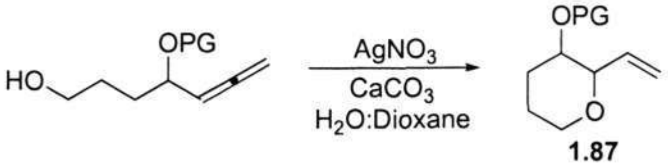


Reagents and Conditions: (a). TBDPSCl, Im, DMAP, THF. (b). PPTs, MeOH, 45 °C. (c). TBSCl, Im, DMAP, DMF. (d). BzCl, Et_3N, DMAP, CH_2Cl_2. (e). Bn-OPT, MgO, DCE, 83 °C.

Scheme 29. Preparation of secondary protected, primary dihydroxy allenes.

Allene alcohol **(1.96)** was taken and treated with *t*-butyldiphenylsilyl chloride, *t*-butyldimethylsilyl chloride, benzoyl chloride and benzyl triflate to give the di-protected allenes **(1.106)**, **(1.107)**, **(1.108)** and **(1.109)**, then the primary silyl ether was to be selectively removed in each case. Treatment of the primary TBS, secondary TBDMS allene **(1.106)** with pyridinium *p*-toluensulfonate (PPTs) in methanol at 40 °C, successfully allowed for the removal of the TBS group solely in 89 % yield within 3 hours. The ^{1}H and ^{13}C NMR spectra were consistent with the proposed structure **(1.110)**, the TBDPS group was clearly observed as two mulitplets at 7.67 and 7.38 ppm characteristic of the di-phenyls. The *t*-butyl group was observed as a singlet at 1.04 ppm. The allene moiety was also observed as an apparent quartet at 5.10 ppm (coupling constant of 6.9 Hz) for the proximal allene proton and now two resolvable doublet of doublet of doublets at 4.49 and 4.56 ppm, which are the two distal allene protons. The di-TBS ether allene **(1.107)** was treated under the same deprotection conditions as it was thought that the primary alcohol would deprotect at a faster rate than that of the more hindered secondary. However, complete loss of the diprotected starting material was observed after 6 hours and upon work up the PPTs proved to have been indiscriminate giving a 1:1 mixture of the mono protected primary and secondary allene diols (**1.111**) and (**1.96**), fortunately no global deprotection was observed. Separation by flash chromatography gave a 38% yield of the desired secondary protected TBS ether allene (**1.111**). The TBS benzoyl ether allene (**1.108**) was selectively deprotected at the silyl ether with PPTs, the ^{1}H NMR showed only the benzoyl ether of (**1.112**) with the aromatic peaks at 8.06, 7.56 and 7.44 ppm, the C=O carbon was clearly observed in the ^{13}C NMR spectrum at 165.0 ppm, as was the characteristic allene carbon at 208.1 ppm. the allene could also be observed in the IR spectrum by the weak peak at 1957 cm^{-1}. The benzyl secondary alcohol allene (**1.113**), was also available by acid removal of the silyl group, the benzyl alcohol was observed by the as a multiplet at 7.35 ppm and the two proton AB system for CH_2 of the benzyl at 4.67 and 4.41 ppm. The allene moiety was still present as an apparent quartet at 5.08 ppm (J = 6.6) for the proximal allene proton and a doublet of doublet of doublets at 4.80 ppm for the two protons on the distal allene carbon.

With these four alcohols in hand, we were now able to return to our pivotal step the cyclisation of the allenic alcohol.



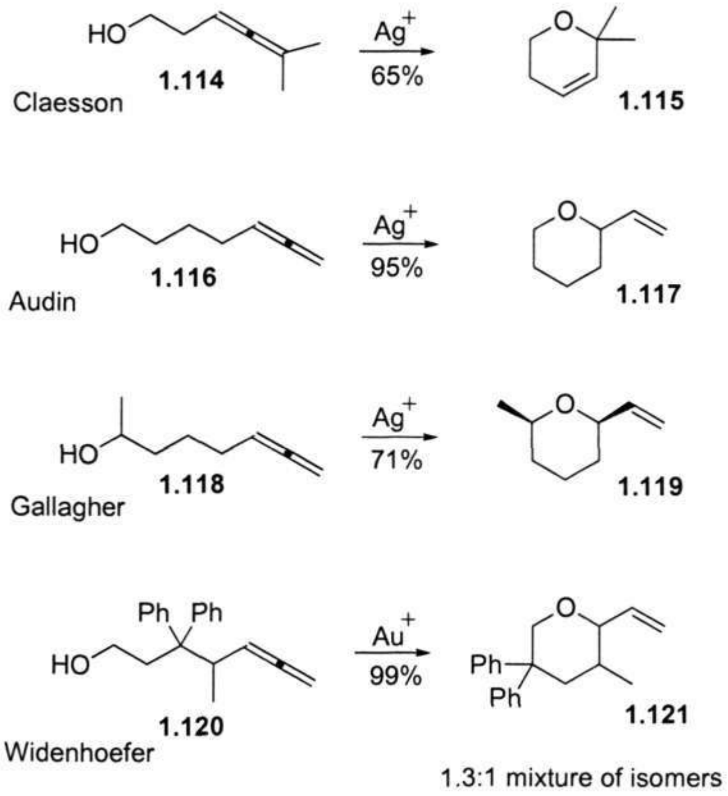
1.87

Entry	Starting material	PG	Temperature	Product
1	**1.110**	TBDPS	RT	NR
2	**1.110**	TBDPS	50	NR
3	**1.110**	TBDPS	80	NR
4	**1.111**	TBS	RT	NR
5	**1.111**	TBS	50	NR
6	**1.111**	TBS	80	NR
7	**1.112**	Bz	RT	NR
8	**1.112**	Bz	50	NR
9	**1.112**	Bz	80	NR
10	**1.113**	Bn	RT	NR
11	**1.113**	Bn	50	NR
12	**1.113**	Bn	80	NR

NR= no reaction observed

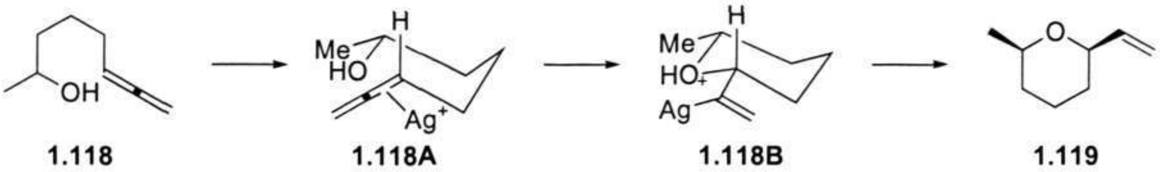
Table 3. Attempted silver catalysed cyclisations.

The use of the standard cyclisation conditions at room temperature with all four of the alcohols were unsuccessful, increasing the reaction temperature to 50 °C also failed to bring about cyclisation as did further increasing the reaction temperature to 80 °C. This was somewhat surprising and disappointing considering the results of Claesson,[38] Audin,[47] Gallagher [48] and Widenhoefer.[49]



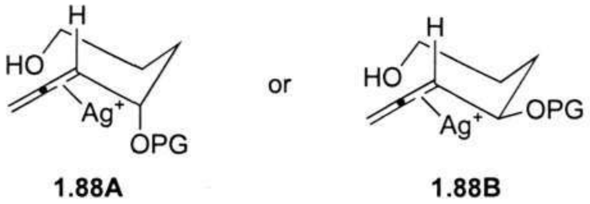
Scheme 30. Known allene cyclisations.

As seen in scheme 30 above, Audin and Gallagher were both able to cyclise their hydroxy allenes (**1.116**) and (**1.118**) using silver salts. Based on these results we thought that our cyclisation would be equally as possible this however proved not to be the case. Gallagher proposed a chair like transition state for his cyclisation as shown (Scheme 31).



Scheme 31. Gallagher's reaction mechanism, and proposed chair conformation.

We thought that such a transition state as (**1.118A**) could be possible for our allene, which would be very similar (**1.88A** or **1.88B**) and we do not suppose that there would have been any steric interaction that would prevent cyclisation (Scheme 32).



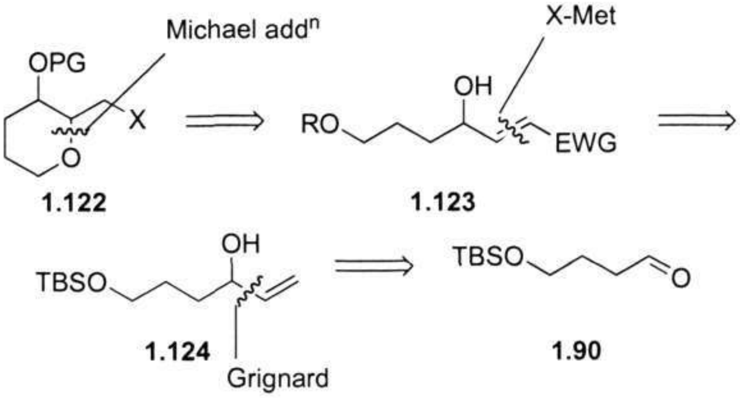
Scheme 32. Our proposed transition state

Therefore we propose that the electron withdrawing OPG group must cause electronic deactivation of the allene moiety thereby preventing cyclisation.

Widenhoefer has demonstrated the cyclisation of allene (**1.120**) that has a pendent alcohol group and also a methyl substituent α to the allene, his procedure called for the use of a gold catalyst. Gold demonstrates a higher affinity for alkenes and is superior to silver in terms of reactivity and further investigations into our cyclisation of allene's (**1.110-1.113**) with gold catalysis are to be pursued.

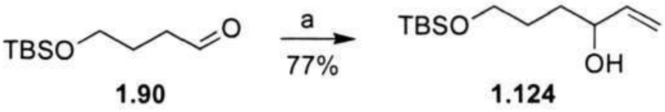
Rethinking the Strategy

With the allene cyclisation proving to be unsuccessful, we required a different route to the tetrahydropyran ring system that by simple elaboration/iteration would allow us to form the second fused tetrahydropyran. Within our group, we are interested in the use of functional groups that can act as Michael accepters and by intramoleculer cyclisation form heterocycles. This has been successfully applied to the total synthesis of Diospongin A by a fellow group member.[50]



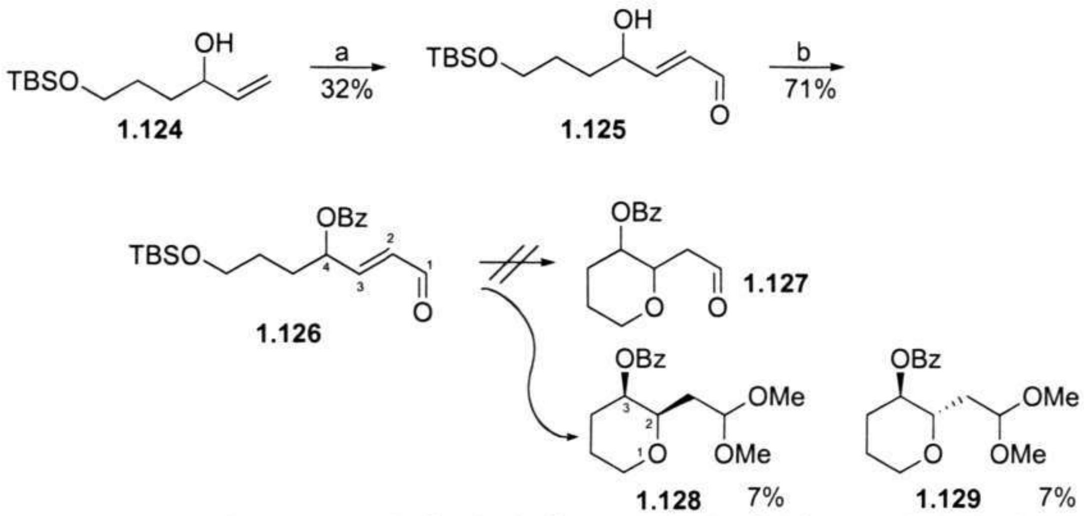
Scheme 33. Revised retrosynthesis of the tetrahydropyran.

The intention now was synthesis the tetrahydropyran core **(1.122)** via Michael cyclisation of a Michael acceptor. The Michael accepter **(1.123)**, we thought would be installed via a Grubbs cross metathesis with the allylic alcohol **(1.124)**. The allylic alcohol **(1.124)** could be obtained via a simple Grignard addition to 4-(*t*-butyldimethylsilyloxy)-butanal **(1.90)**, which was already available to us from our primary strategy in 55% overall yield from 1,4-butanediol **(1.91)**.



Reagents and conditions: (a) $CH_2CHMgCl$, Ether, -78 °C
Scheme 34. Preparation of Allylic alcohol.

4-(*t*-Butyldimethylsilyloxy)-butanal **(1.90)** was treated with vinyl magnesium chloride in ether to cleanly give the desired allylic alcohol **(1.124)** in 77 % yield (Scheme 34). The ^{1}H NMR spectrum showed a doublet of doublet of doublets at 5.87 ppm with coupling constants of 17.0, 10.7 and 6.0 Hz for the CH of the alkene. The doublet of doublets at 5.17 ppm had coupling constants of 17.0 and 10.7 Hz and was characteristic of the two terminal protons of the alkene. The proton α to the alkene was observed as a triplet at 3.66 ppm with a coupling constant of 6.0 Hz. The alkene and TBS protecting group were also clearly observed in the ^{13}C NMR spectrum, confirming the structure. Installation of an electron withdrawing group that would be able to function as a Michael accepter was then necessary. Our attention was first drawn to acrolein, but as this cannot be shipped to Singapore we were forced to use crotonaldehyde. There are two advantages of using crotonaldehyde as the Michael accepter. Firstly, after cyclisation the external aldehyde would allow for easy manipulation and then secondly, the low boiling point would allow for an advantageous work up. To form the Michael accepter we used a Grubbs cross metathesis reaction. The use of Grubbs 2nd generation catalyst with electron withdrawing alkenes is well established in the literature.[51,52] The use of a 2-fold excess of the electron deficient alkene is generally advisable as it provide access to the cross metathesis product in higher yields, this is because electron deficient alkenes demonstrate a slower rate of homo-dimerization. A slower rate of homo-dimerization is advantageous when the cross metathesis reaction is viewed as three separate competing reactions; the desired cross metathesis, and the homo-dimerization of either of the two starting materials. The slower rate of homo-dimerization of one partner makes the other two pathways more favorable, therefore the use of an excess of this less reactive (toward homodimerization) partner makes the desired cross metathesis even more favorable. The result should be an extremely efficient cross metathesis reaction.[53,54]



Reagents and Condiditons: (a). Grubbs II, Crotonaldehyde, CH_2Cl_2, 40 °C. (b). BzCl, NaOH, Toluene. (c). Amberlyst 15, MeOH.

Scheme 35. Synthesis of the Michael accepter and its cyclisation.

As seen in Scheme 35 the desired reaction between vinyl alcohol (**1.124**) and 3 equivalents of crotonaldehyde proceeded in a poor 26% yield, by increasing to 6 equivalents of crotonaldehyde the yield was improved marginally to 32%. Characterisation by ^{1}H NMR showed a doublet at 9.59 ppm with a coupling constant of 8.0 Hz for the aldehyde proton. A doublet of doublets observed at 6.82 ppm with the coupling constants of 15.6 and 4.3 Hz was observed for the proton of C(3). The observed doublet of doublet of doublets at 6.36 ppm with the coupling constants of 15.6, 8.0 and 1.7 Hz was assigned at the proton of C(2). The proton of C(4) was observed as a multiplet at 4.46 ppm, while the OH was observed as a doublet at 3.91 ppm with a coupling of 4.3 Hz.

The aldehyde and alkene protons were also observed in the ^{13}C NMR spectrum clearly at 193.7, 159.5 and 130.8 ppm, confirming the cross metathesis product (**1.125**). Benzoylation of the secondary alcohol was then achieved under standard conditions using benzoyl chloride and triethylamine in 71% yield. Loss of the hydroxyl group and appearance of the carbonyl group of the ester was observed in the IR spectrum. Change in the proton and carbon spectra was also observed with appearance of the additional characteristic aromatic peaks.

Michael cyclisation of enal (**1.126**) could now be attempted, Michael additions are generally controlled by the thermodynamics of the reaction. At this stage it was not clear if the cyclised product would be more thermodynamically favored over the open chain, or whether a base would be required. Treatment of our enal (**1.126**) with amberlyst 15 exchange resin resulted in the removal of the silyl protecting group and cyclisation. Purification gave two products (**1.128**) and (**1.129**) in a 1:1 ratio. Neither spectra was consistent with our desired product (**1.127**) as both lacked the distinctive aldehyde proton, but did display a two singlets at 3.35 and 3.31 ppm each integrating to three protons. Therefore we deduced that the methoxy group from the methanol had attacked the aldehyde resulting in the formation of the acetals (**1.128**) and **1.129**).

With the use of a COSY NMR spectrum we were able to assign the protons of C(2) and C(3). For acetal (**1.129**) the C(3) proton was observed as a doublet of triplet at 4.75 ppm, whilst the C(2) proton was observed as a doublet of doublets at 4.63 ppm. The C(2) proton displayed coupling constants of 8.5 and 2.9 Hz, while C(3) protons had two 10.4 Hz couplings and a single 4.6 Hz coupling constant. We have assigned the two 10.4 Hz coupling constants as the axial axial couplings of this proton with the protons of C(2) and C(4), and thus assigned (**1.129**) as the *trans* diastereoisomer (Figure 4). Therefore, we would expect acetal (**1.128**) to be the *cis* diastereoisomer by analogy and display small coupling constants of the magnitude associated with an axial equatorial coupling to the proton of C(3). Again a COSY NMR spectrum allowed for assignment of the C(2) proton as the doublet of doublets at 4.57 ppm and the C(3) proton as the broad singlet at 5.06 ppm. The doublet of doublets had coupling constants of the magnitude of 7.9 and 3.8 Hz. The broad singlet observed for the proton of C(3) is a result to the small coupling constants associated with axial-equatorial protons. The small coupling constant would give rise to only a small amount of splitting and as such the (C)3 proton is observed as a unresolved singlet. Therefore, we conclude that (**1.128**) product is the *cis* diastereoisomer (Figure 4).

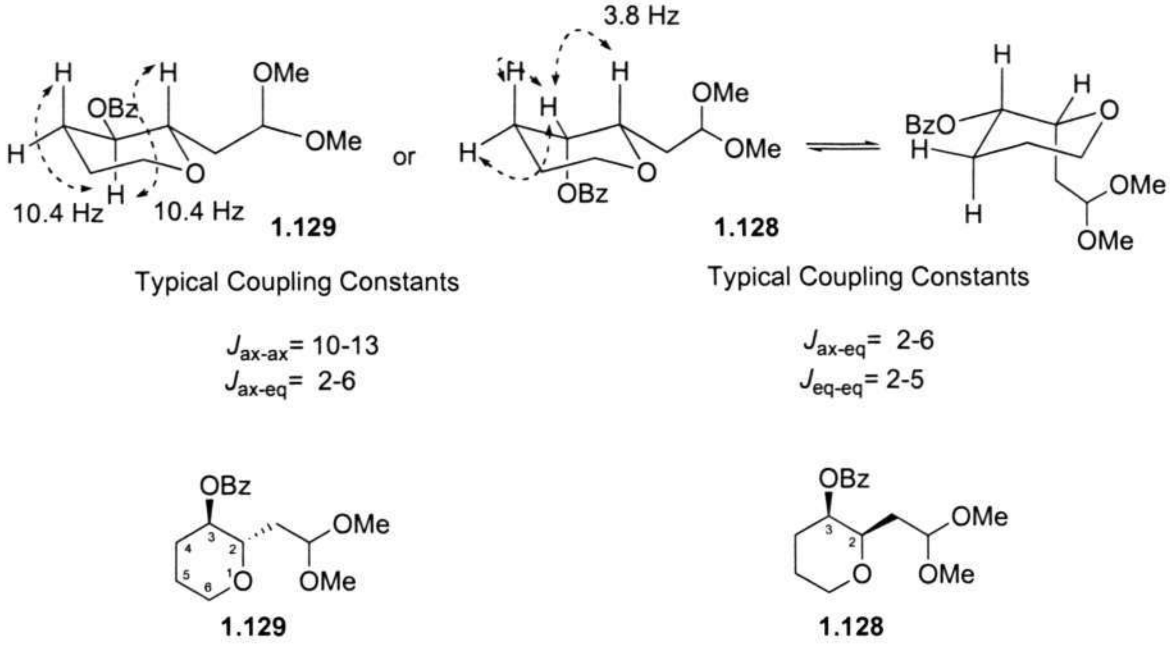
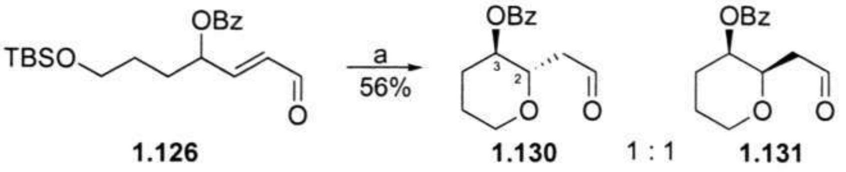


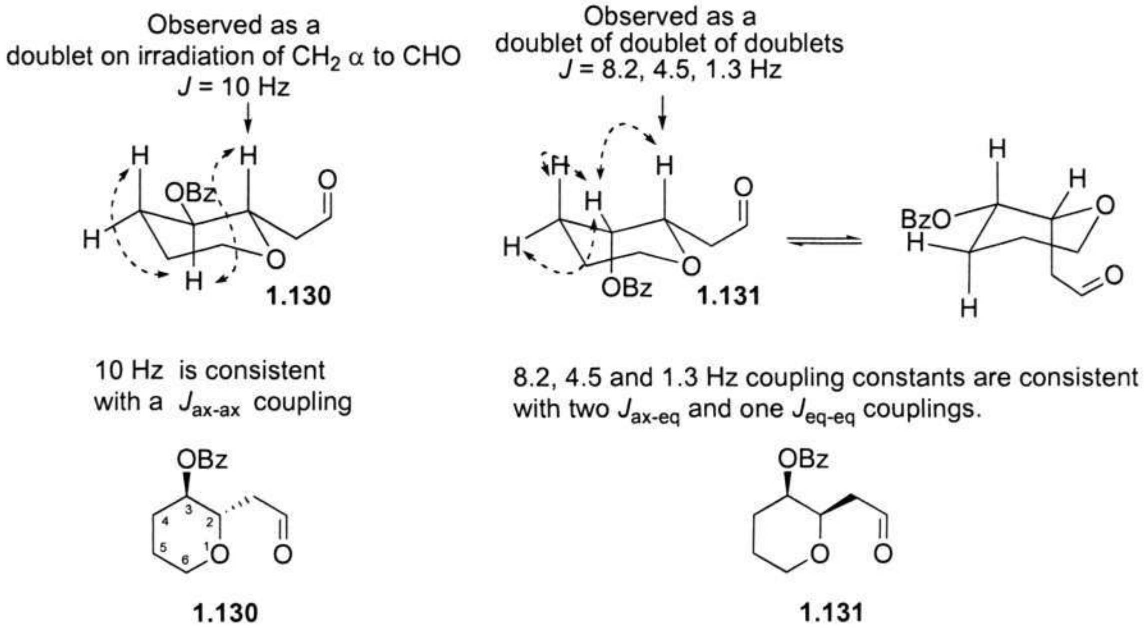
Figure 4. Stereochemical assignment based on coupling constants.

We assume that the desired aldehyde (**1.127**) was converted to the acetals (**1.128/1.129**) after cyclisation as we know from the Diospongin A synthesis that ketones cyclise rapidly. Also, acetals are not good electron withdrawing groups, so formation of the acetal moiety first would make then have made cyclisation difficult.



Reagents and Condiditons: (a). Amberlyst 15, wet THF.
Scheme 36. Alteration of the cyclisation conditions to obtain the aldyhyde.

The reaction was repeated with the intention of obtaining the desired aldehyde product and observing any selectivity (Scheme 36). The solvent system for cyclisation was altered to wet THF in place of the methanol, this resulted in formation of a 1:1 mixture of diastereomers (**1.130**) and (**1.131**) in 56 % combined yield. The first aldehyde product (**1.130**) has been assigned as the *trans* diastereomer and the second product (**1.131**) has been assigned as the *cis* diastereomer. The aldehyde (**1.130**) ^{1}H NMR spectrum displayed a triplet at 9.8 ppm for the aldehyde with the coupling constants of 2.1 Hz. The doublet of triplets observed at 4.82 ppm with couplings constants of 14.7 and 4.7 Hz was assigned as the proton of C(3). The proton of C(2) overlapped with a proton of C(6) and appeared as a multiplet at 3.97 ppm. The other proton of C(6) was observed as a doublet of triplets at 3.48 ppm with coupling constants of 14.7 and 3.1 Hz. The CH_2 group α to the aldehyde was observed as a doublet of doublet of doublets at 2.69 ppm. The C(3) proton's coupling constants suggest a *trans* relationship between the protons of C(3) and C(2) and confirmation of this assignment was obtained with use of a homonuclear decoupling experiment. Irradiation of the protons α to the aldehyde simplified the coupling on the C(2) proton, which was now observed as two doublets at 4.01 and 3.98 ppm, for the C(2) proton and the C(6) proton, respectively. The coupling constant of the C(2) proton was now 10 Hz, which fully supports the *trans* assignment (**1.130**). Using a COSY NMR spectrum in conjunction with the proton spectrum for aldehyde (**1.131**) allowed for its assignment as the *cis* product. Observed was a triplet at 9.77 ppm which was assigned as the aldehyde proton, a singlet at 5.13 ppm assigned as the C(3) proton and a doublet of doublet doublets at 4.14 ppm with coupling constants of 8.2, 4.5 and 1.3 Hz for the C(2) proton. A doublet of doublet of triplets at 4.08 ppm with coupling constants of 11.8, 4.5 and 2.3 Hz, was assigned as one of the protons of C(6). The other C(6) proton was observed at 3.61 ppm with the coupling constants of 11.8 and 2.3 Hz. The smaller coupling constants of the proton at C(2) suggested a *cis* relationship. The *cis* assignment was supported by the observation of a singlet for the proton of C(3), which has only small coupling constants associate with axial-equatorial or equatorial-equatorial interactions (Figure 5).


Observed as a doublet on irradiation of CH_2 α to CHO J = 10 Hz

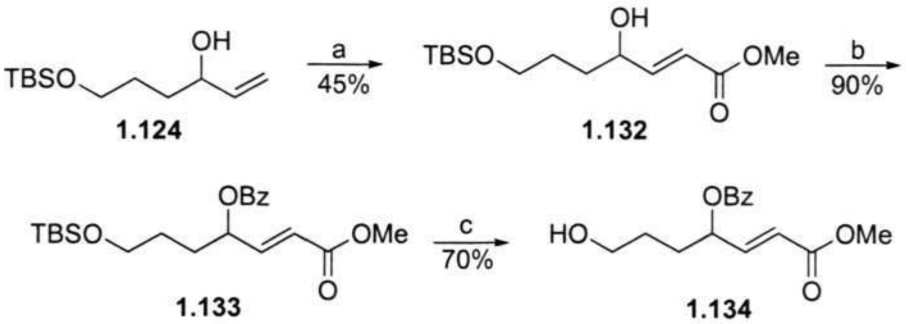
Observed as a doublet of doublet of doublets J = 8.2, 4.5, 1.3 Hz

10 Hz is consistent with a $J_{ax\text{-}ax}$ coupling

8.2, 4.5 and 1.3 Hz coupling constants are consistent with two $J_{ax\text{-}eq}$ and one $J_{eq\text{-}eq}$ couplings.

Figure 5. Stereochemical assignment based on coupling constants.

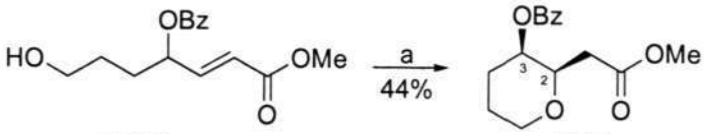
As a mixture of diastereomers was obtained we chose to alter the electron withdrawing substituent hoping to improve the diastereoselectivity. We believe that it was only logical to move from an aldehyde moiety to an ester. Such a change could be achieved simply by exchanging the cross metathesis partner and use either methyl acrylate or ethyl acrylate in place of crotonaldehyde (Scheme 37).



Reagents and Condiditons: (a). Grubbs II, Methyl Acrylate, CH_2Cl_2, 40 °C. (b). BzCl, NaOH, Toluene. (c). Amberlyst 15, MeOH.

Scheme 37. Revised Michael accepting group.

Most accessible to us was methyl acrylate, standard Grubbs cross metathesis conditions gave the desired allylic ester (**1.132**) in 28% yield, this was improved to 45% by slow addition of the catalyst and using 10 equivalent of methyl acrylate, no further optimization was not attempted at this stage. The alkene protons were observed as a doublet of doublets at 6.95 ppm (15.6 and 4.4 Hz), and as a doublet at 6.09 ppm with a coupling constant of 15.6 Hz. The methoxy group was observed as a singlet at 3.74 ppm. A small amount of homodimer of allylic alcohol (**1.124**) was also obtained but not rigorously characterized. The free hydroxyl group of (**1.132**) was then protected as the benzoyl ester in 90% yield. Loss of the OH was observed in the IR, and ^{1}H NMR spectrum displayed additional aromatic peaks confirming the benzoyl protecting groups installation. For cyclisation we employed the same conditions as used for allylic aldehyde (**1.126**) (Scheme 35), amberlyst 15 exchange resin in methanol, however, this time cyclisation did not occur and we isolated the desilylated product (**1.134**). In the aldehyde version the acidic reaction system protonates the aldehyde and create a more efficient electron with drawing group making cyclisation more favorable. However this is not the case for the ester. The ester appears to be a weaker electron withdrawing group and so to promote cyclisation a base was required, thereby creating a better nucleophile by deprotonating the alcohol (Scheme 38).

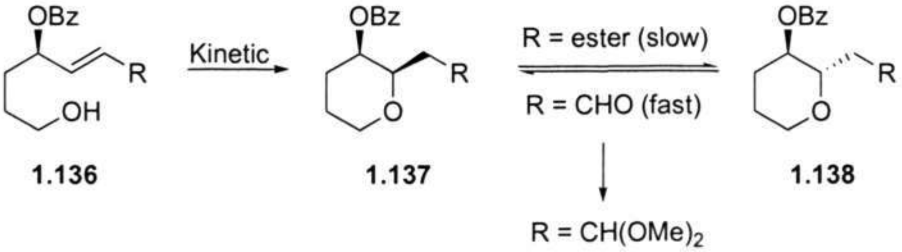


1.134 **1.135**

Reagents and Condiditons: (a). TMG, CH_2Cl_2

Scheme 38. Cyclisation under basic conditions.

The allylic ester (**1.134**) was taken into CH_2Cl_2 and a trace amount of tetramethyl guanidine was added. After three days of stirring at room temperature all of the starting material had been consumed and a single diastereomer (**1.135**) was obtained on purification. Assignment of the *cis* stereochemistry was achieved by NMR coupling constant analysis. From the ^1H and COSY NMR spectra we assigned the broad singlet at 5.13 ppm as proton of C(3). The 2 proton multiplet observed at 4.06 ppm was assign as the proton of C(2) and one of the protons of C(6). The singlet observed at 3.67 ppm was quite clearly the methoxy group, while the doublet of triplets at 3.60 ppm was the other C(6) proton. Assignment of the broad singlet as the proton of C(3) was consistent with our previous observations for the *cis* conformation of the two cyclised products (**1.128**) and (**1.129**). The *cis* conformation displays only small amounts of splitting and so the C(3) proton is observed as a broad singlet (an unresolved doublet), all three *cis* assignments are therefore in agreement. Our observations were also consistent with the findings of Martin, however his cyclisations required the use of strong bases such as NaH, $LiN(TMS)_2$, $NaN(TMS)_2$ $LiN(TMS)_2$, $NaN(TMS)_2$ or $KN(TMS)_2$.[55]



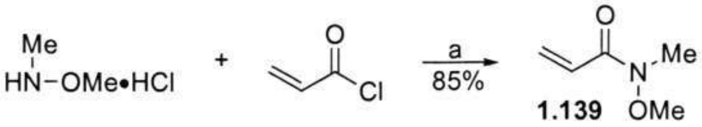
1.136 **1.137** **1.138**

Scheme 39. Explaination of the selectivity observed.

As an explanation for such a high level of selectivity in the ester system (Scheme 38), compared to the aldehyde cyclisation (Scheme 36), we propose that from the work of Martín, where, when R is an ester, and the *E* alkene (**1.136**) cyclises to give the *cis* product

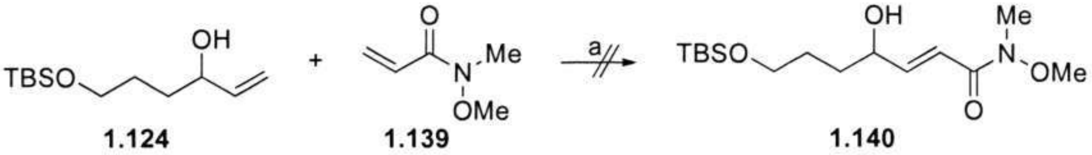
(**1.137**), and the *Z* alkene cyclises to give the *trans* product, means that the *cis*-tetrahydropyran is the kinetic product, therefore explaining why this is the only product from our cyclisation, as the equilibrium is so slow. We already knew this from the Diospongin A synthesis, but when R is an aldehyde (**1.136**), the equilibrium is fast and we therefore obtain a 1:1 mixture of the *cis/trans* tetrahydropyrans (**1.137**/**1.138**), which is subsequently, in the methanol solvent system, attacked to give the acetals (Scheme 39).

Weinreb amides are also very good electron withdrawing groups and we thought to explore their use as a Michael accepter in our cyclisation. Once again we decided to proceed by performing a cross metathesis reaction of our vinyl alcohol (**1.124**), this time with a prepared Weinreb amide (**1.139**).



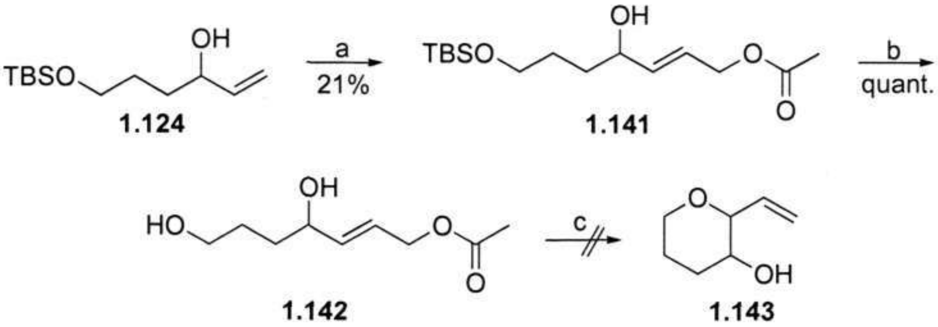
Reagents and Condiditons: (a). Et_3N, CH_2Cl_2.
Scheme 40. Weinreb amide synthesis.

The Weinreb amide (**1.134**) was prepared by addition of N,O-dimethylhydroxy amine hydrochloride to acryloyl chloride, then this reagent was used in a standard cross metathesis reaction with Grubbs second generation catalyst.



Reagents and Condiditons: (a).Grubbs II, CH_2Cl_2
Scheme 41. Attempted Weinreb amide synthesis.

However the reaction was unsuccessful allowing only for recovery of the starting material and this route was therefore not pursued any further. In our final attempt at cyclisation we were able to draw on the results from Chapter 3, where we successfully demonstrated the formation of a piperidine ring via a Tsuji-Trost cyclisation of an allylic acetate. We thought that a similar route, this time employing a terminal hydroxyl group would provide access to tetrahydropyrans hopefully with a similar level of selectivity as observed for the piperidines of Chapter 3.

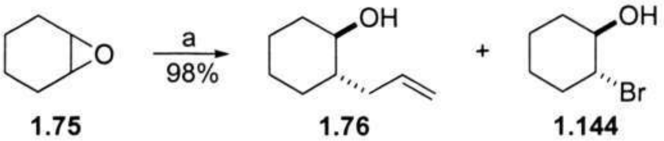


Reagents and Condiditons: (a). Grubbs II, *cis*-butene-1,4-diacetate, CH_2Cl_2. (b). Amberlyst 15, MeOH. (c). $Pd(PPh_3)_4$, TMG, THF.

Scheme 42. Attempted Tsuji-Trost reaction.

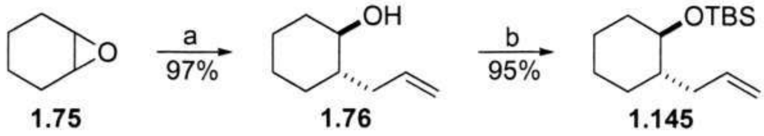
The allylic acetate (**1.141**) was prepared by a Grubb's cross metathesis reaction of sallylic alcohol (**1.124**) with a non-terminal alkene, *cis*-butene-1,4-diacetate. The advantages of using a non-terminal alkene are discussed further on page 186. The cross metathesis proceeded in a low 21 % yield, unoptimized (Scheme 42). The ^{1}H NMR spectrum displayed a broad singlet at 5.80 ppm which was assigned as the two protons of the alkene, the two protons next to the acetate unit were observed as a broad singlet at 4.56 ppm and the acetate was observed as a 3 proton singlet at 2.06 ppm. The alkene was also observed at 137.5 and 124 ppm in the ^{13}C NMR spectrum, a change was seen in the pendant ^{13}C NMR spectrum as both were now sp^2 hybridised. From the amine equivalent we already knew that protection of the secondary alcohol would serve as an obstacle and prevent cyclisation. As protection was not needed for palladium chemistry we proceeded directly to the cyclisation, however, the silyl protecting group must first be removed (Scheme 42). The most convenient procedure uses amberlyst 15 exchange resin, which can be removed easily by simple filtration to give the desired alcohol (**1.142**). This was accomplished in quantitative yield, loss of the silyl protecting group was most observable in the ^{1}H NMR spectrum with the loss of the 6 and 9 proton singlets at 0.07 and 0.09 ppm. The Tsuji-Trost reaction with the established procedure from Chapter 3 was then attempted, here however the reaction failed and neither starting material nor product was obtainable from the reaction mixture.

We conclude that the formation of tetrahydropyrans by Michael cyclisations was exceptionally problematic, the yields for the cross metathesis reactions and the yields of the cyclisations that we achieved were all low and required major optimization. The use of techniques such as slow addition of the catalyst, blowing of nitrogen over the reaction to drive off the ethylene, increasing the boiling point by either switching to dichloroethane or toluene have all been shown to greatly improve the yields of cross metathesis reactions. If these techniques failed we would also have the option of changing the catalyst and trying the Hoveyda-Grubbs catalyst. The diastereoselectivity of cyclisation was also an issue, providing no selectivity in the first two examples (Scheme 36 and Scheme 38). While the tetrahydropyran (**1.135**) was obtained as a single diastereoisomer it was the undesired *cis* conformation, we therefore thought that the cyclisations maybe more efficient if a more robust/rigid starting material was used. We therefore turned our attention to a functionalised cyclohexane ring system, as this should provide a more rigid structure 'back bone' to attempt cyclisation from.



Reagents and conditions: (a). CH_2CHCH_2Br, Mg, CuI, Et_2O, -78 °C
Scheme 43. Cyclohexene oxide ring opening.

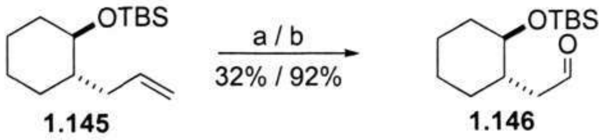
The new route started from cyclohexene oxide (**1.75**), with ring opening of the epoxide. Initially we intended to use the Grignard reagent allyl magnesium bromide that was prepared prior to reaction from allyl bromide and magnesium. However, the Grignard reagent proved to be insoluble in THF producing a think grey precipitate. On changing the solvent to ether this initial problem was solved. But on addition of the now soluble Grignard reagent to the epoxide in the presence of copper iodide, two products were obtained. The first product was the desired allylic alcohol (**1.76**), the second product was that of bromide opening the epoxide to give the halogenated alcohol (**1.144**) as a 1:1 mixture. To overcome this problem the allyl bromide was exchanged for allyl chloride. As the chloride is less nucleophilic than the bromide it should no longer be able to open the epoxide (Scheme 44).



Reagents and conditions: (a). CH_2CHCH_2Cl, Mg, CuI, THF, -78 °C (b). TBSCl, Im., DMAP, THF.

Scheme 44. Epoxide ring opening and protection og the hydroxyl group.

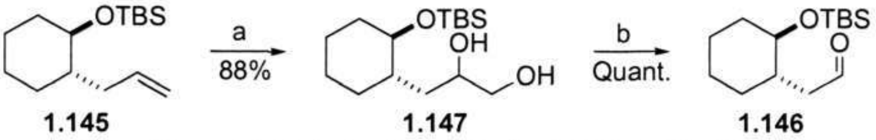
This time the Grignard reagent was prepared in ether and was found to be only partially soluble. Fortunately addition of THF to the reaction mixture gave a free stirring solution and on addition of epoxide (**1.75**), this time without any copper iodide the known *bis* homo allylic alcohol (**1.76**) was obtained in 97% yield. The intention was then to convert the alkene into the aldehyde, but first the alcohol was protected as the TBS ether (**1.145**) under standard conditions in 95% yield. For preparation of the desired aldehyde two procedures were available, but both reported the product as extremely unstable.



Reagents and conditions: (a). O_3, CH_2Cl_2, Me_2S, -78 °C. (b). K_2OsO_4, $NaIO_4$, Dioxane:H_2O

Scheme 45. Known aldehyde preparation procedures.

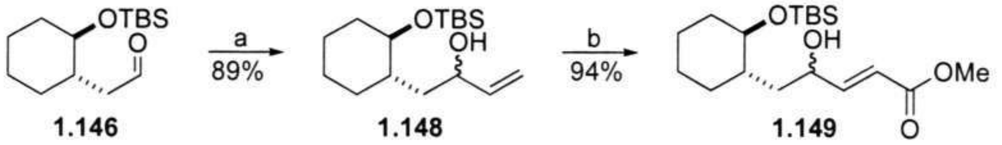
The first procedure used ozonolysis (Scheme 45), while we believe we were able to cleanly create the ozonide (spot to spot on TLC), after the addition of the dimethylsulfide, we observed a large amount of decomposition and obtained only a small portion of the desired aldehyde (**1.146**). The second procedure used the Lemieux-Johnson osmium tetroxide-catalyzed periodate oxidation.[56] Using the standard reaction protocol, we were able to efficiently oxidise the alkene to the desired aldehyde (**1.146**) in 92% yield. The aldehyde (**1.146**) was found to be stable enough for characterization, but the product was heavily contaminated with osmium residue and was dark brown in colour. This contamination proved to be detrimental in the subsequent Grignard addition reaction and we were in desperate need of an alternative route to purer aldehyde (**1.146**). We thought that if we separated the two steps involved in the Lemieux-Johnson reaction and obtained the diol, it would be much easier to remove the osmium residue and then oxidative cleavage should efficiently provide the desired pure aldehyde.



Reagents and conditions: (a). K_2OsO_4, K_3FeCN_6, $^tBuOH:H_2O$. (b). SiO_2-$NaIO_4$, CH_2Cl_2

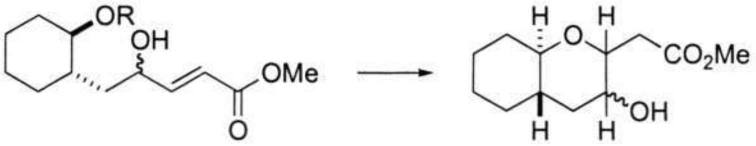
Scheme 46. Improved access to the aldehyde.

We are happy to report that this proved to be the case, dihydroxylation of the alkene was achieved under the osmium tetroxide, potassium hexacyanoferrate and potassium carbonate conditions of Tsuji in 88% yield giving diol (**1.147**) as a colourless viscous oil.[57] The diol (**1.147**) was then efficiently oxidatively cleaved under the conditions of Shing.[58] This very efficient procedure required the use and preparation of silica gel-supported sodium *meta*-periodate reagent. This was achieved by pouring a fully dissolved aqueous solution of sodium *meta*-periodate on to silica gel, and shaking vigorously. The silica gel coated in sodium *meta*-periodate was then set stirring in CH_2Cl_2, and the diol (**1.147**) dissolved in CH_2Cl_2 was added. After 15 minutes the reaction had proceeded to completion, simple filtration then gave the desired aldehyde (**1.146**) in a quantitative yield as a colourless oil (Scheme 46), we therefore conclude that it was impurities causing the instabilities reported previously. The distinctive aldehyde proton was clearly observed at 9.72 ppm as a singlet in the ^1H NMR spectrum. The subsequent Grignard reagent addition to aldehyde (**1.146**) then gave the allylic alcohol (**1.148**) in 89% yield. The peak that was observed at 9.72 ppm disappeared signifying the loss of the aldehyde. The spectrum now displayed a multiplet at 5.84 ppm, a doublet at 5.23 ppm and a doublet of doublets at 5.07 ppm, which are all consistent with the desired alkene. Installation of the electron withdrawing group was achieved by a Grubb's cross metathesis reaction (Scheme 47), using 5 equivalent of methyl acrylate we obtained the desired Michael acceptor product (**1.149**) in 55% yield. This was then improved to 94% yield by of slow addition of Grubb's II catalyst.



Reagents and conditions: (a).$CH_2CHMgBr$, THF, -78 °C. (b). Grubbs II, methyl acrylate, CH_2Cl_2, 40 °C

Scheme 47. Formation of the precursor to cyclisation.



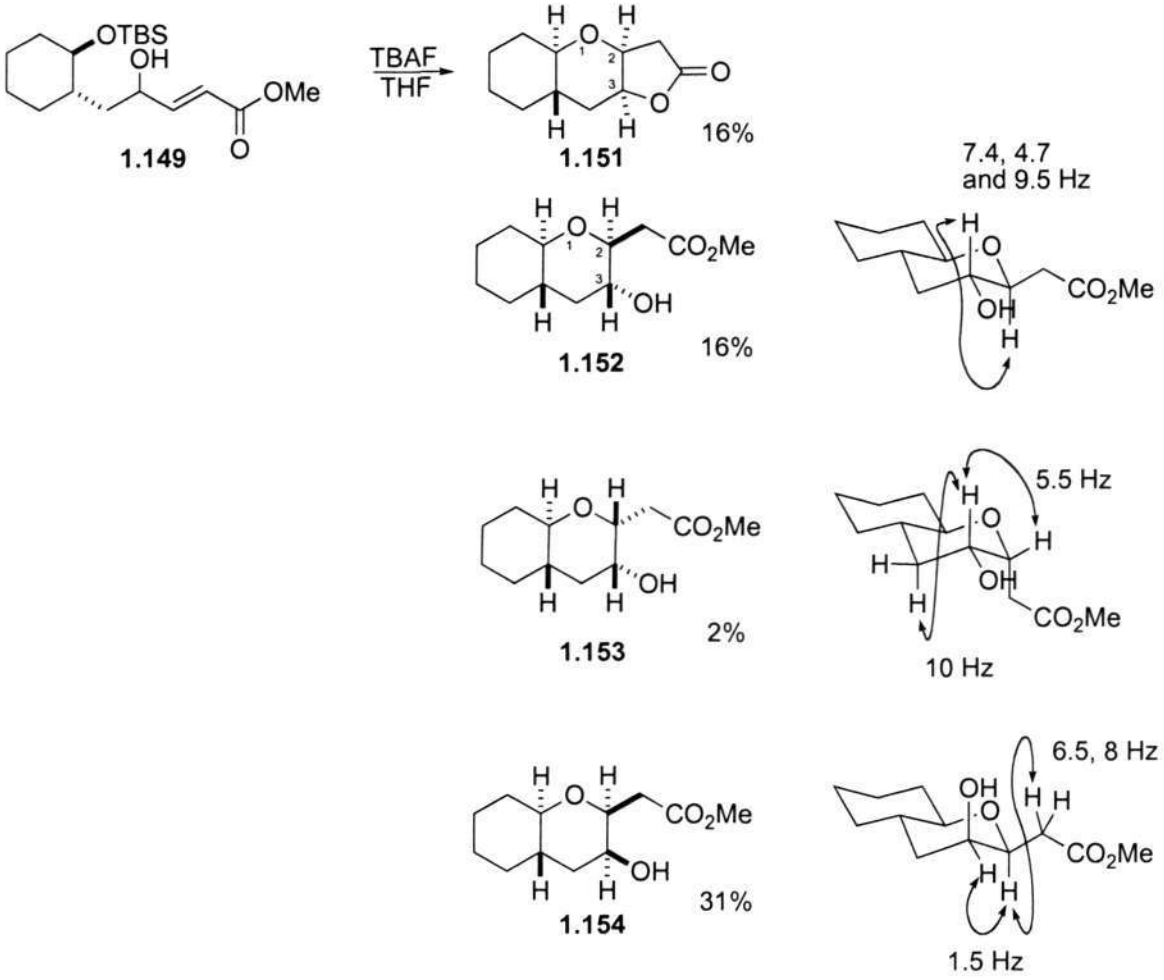
SM	R	Conditions	Solvent	Temp. °C	% Yield.
1.149	TBS	NaOMe	MeOH	0-25	-[a]
1.149	TBS	●–SO_3H	MeOH	0-25	-[b]
1.150	OH	●–Base	MeOH	0-25	-[c]
1.150	OH	K_2CO_3	MeOH	0-25	~8
1.149	TBS	KF, Bu_4N^+	CH_3CN	0-25	-[a]
1.149	TBS	●–SO_3H, + ●–Base	MeOH	50	-[b]
1.149	TBS	TBAF	THF	0-25	49
1.149	TBS	TBAF	THF	-3	-[b]

[a] Decomposition occured. [b] Deprotection occured giving **1.150**. [c] Trace by NMR

●–SO_3H = Amberlyst-15 ●–Base = Amberlyst A-21

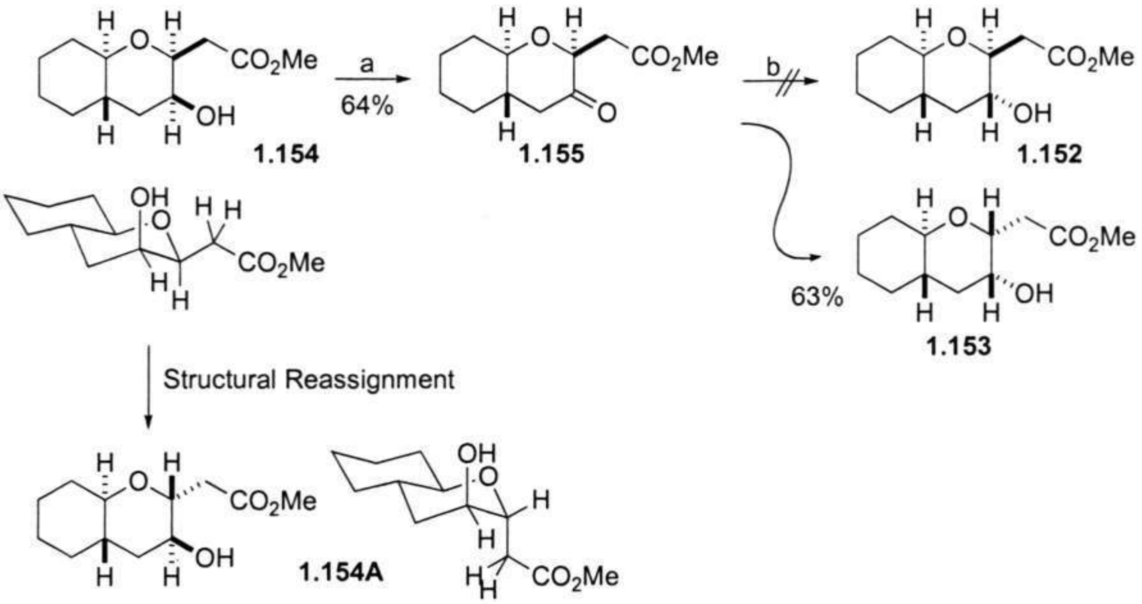
Table 4. Attempted cyclisation conditions.

The Michael addition was then to be attempted (Table 4), initially we thought that the silyl protecting group could be easily removed and that cyclisation would occur in a tandem fashion. However attempts to achieve the above result using amberlyst 15 exchange resin were unsuccessful as deprotection occurred only (**1.150**). It was thought that addition of a base to the deprotected mixture (**1.150**) would be sufficient to cause cyclisation. Initially we used amberlyst 21 exchange resin, a polymer supported triethylamine. However this base was insufficient giving only a trace amount of cyclisation product as observed from NMR spectrum of the crude reaction product. The use of a stronger base such as potassium carbonate also proved to be insufficient giving only a trace amount of cyclisation. We then returned our attention to strongly basic conditions first using sodium methoxide in methanol, this led to the decomposition of our starting material (**1.149**), the use of potassium fluoride in acetonitrile also proved to be insufficient, providing mainly recovered starting material. The use of TBAF in THF was beneficial as after 36 hours of reaction time we were able to isolate 4 products, which were assigned initially as shown in Scheme 48.



Scheme 48. Cyclisation and assignment of diastereoisomers.

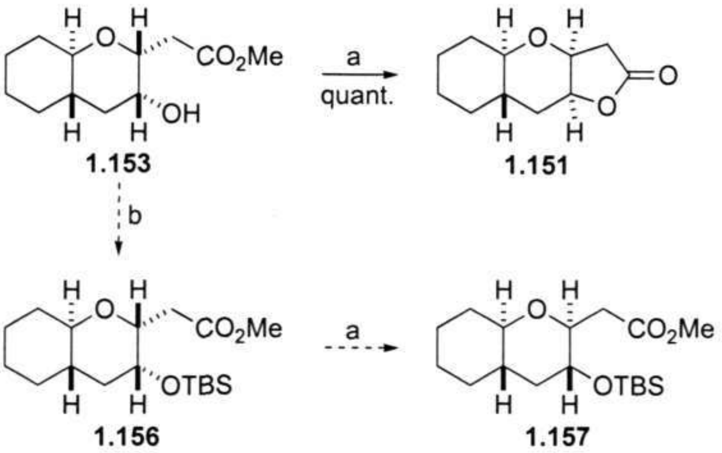
The assignments established here were from NMR studies and coupling constant correlations, we have assigned (**1.151**) as the lactone. This assignment was obvious from the ^{1}H NMR spectrum, which showed two doublet of triplets at 4.70 and 4.59 ppm, that are assigned as the protons of C(2) and C(3). The CH_2 group α to the lactone was apparent as an AB pair system at 2.83 and 2.52 ppm. In the IR spectrum we observed a sharp peak at 1774 cm^{-1}, which is characteristic for a five membered cyclic lactone. The tetrahydropyran (**1.152**) we assigned from the COSY spectrum. The doublet of doublet of doublets observed at 3.55 ppm was assigned as the proton of C(2), with the coupling constants of 9.4, 7.5 and 4.7 Hz. The 9.4 Hz coupling constant represents the *trans* coupling to the proton of C(3), which was observed as a doublet of doublet of doublets at 3.41 ppm. The ^1H NMR spectrum was also is good agreement with the work of McErlean and his *trans* assignment of the ethoxy equivalent to our tetrahydropyran.[15] For tetrahydropyran (**1.153**), we assigned the proton of C(2) as the apparent quartet observed at 4.49 ppm with a 6.4 Hz coupling constant, the proton at C(3) was observed at 4.05 ppm as a doublet of triplet with 10.5 and 5.5 Hz coupling constants. The 10.5 Hz coupling constant we assigned as the axial axial coupling between the protons of C(3) and C(4). The 5.5 Hz coupling constant was assigned as an axial equatorial coupling between the protons of C(3) and C(2). For tetrahydropyran (**1.154**) the proton at C(2) was observed as a doublet of doublet of triplets at 4.31 ppm, with the coupling constants of 8.0, 6.6 and approximately 1.5 Hz. The proton of C(3) was obscured by the CH_3 of the methoxy group, but the coupling constants strongly supports an equatorial proton at C(2) and an axial proton at C(3).



Reagents and conditions: (a). DMP, CH_2Cl_2, 0 °C. (b). $NaBH_4$, MeOH, -78 °C

Scheme 49. Attempted structural convergence and subsequent structural reassignment.

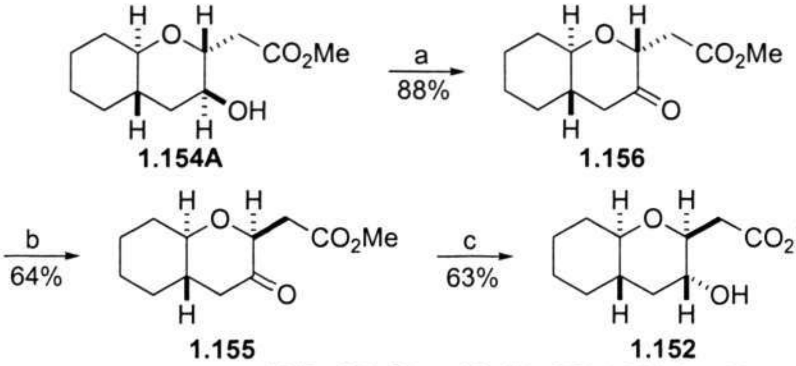
After assigning the diastereomers, attempted were made to converge the wrong diastereomers in to the desired one. First we started by taking the incorrect stereoisomer at the C(3) position, that is tetrahydropyran (**1.154**) which had the hydroxyl group in the axial position and a proton in the equatorial position. The stereochemistry was corrected by oxidizing the alcohol with DMP to ketone (**1.155**) that was then reduced at -78 °C using $NaBH_4$. As $NaBH_4$ is known to demonstrate a preference for axial attack, it should have provided us with an equatorial alcohol and an axial proton thereby correcting the stereochemistry at C(3). However the ^{1}H NMR spectrum was not consistent with the desired diastereoisomer (**1.152**), the spectrum instead showed that it had been converted into the *cis*-terahydropyran (**1.153**). As such we then had to reassign the starting material as being the incorrect diastereomer at both the C(2) and C(3) and called it (**1.154A**). Therefore the 1.5 Hz coupling constant was infact an equatorial equatorial coupling between the two protons of C(3) and C(2).



Reagents and conditions: (a). KO^{t}Bu, THF. (b). TBSCl, Im., DMAP, THF.

Scheme 50. Structural convergence of the *cis*-THP (**1.153**).

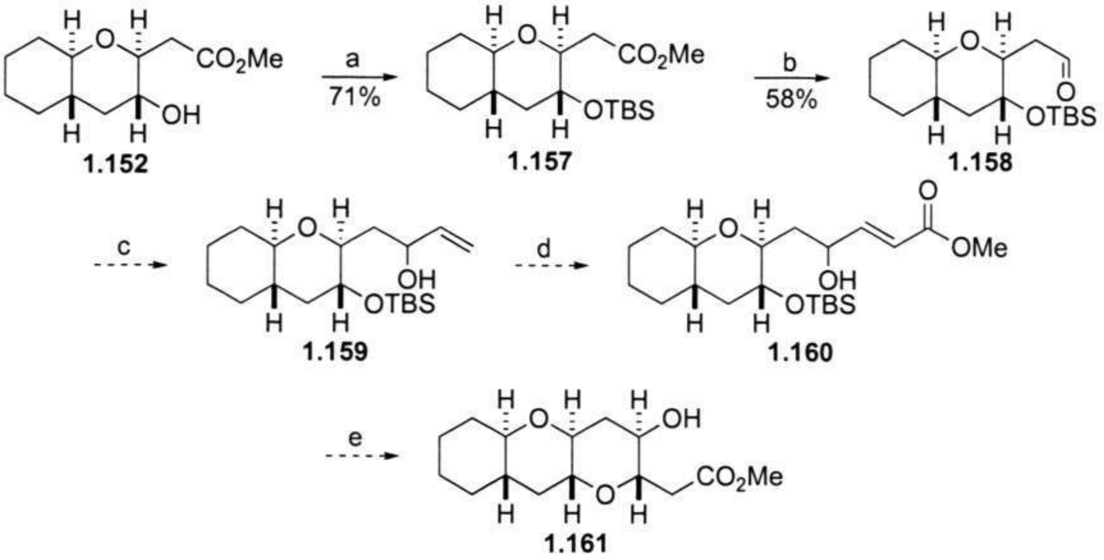
By miss assigning tetrahydropyran (**1.154A**) and obtaining the *cis*-tetrahydropyran (**1.153**) as the product of reduction (Scheme 49), we were now convinced of (**1.153**) stereochemistry, and thought that by simple base equilibriation tetrahydropyran (**1.153**) could be converted into the desired *trans*-tetrahydropyran (**1.152**). We therefore exposed tetrahydropyran (**1.153**) to potassium *t*-butoxide, but on work up we had not altered the stereochemistry at C(2), we had instead formed the lactone (**1.151**), thereby confirming its stereochemistry. We now knew that the alcohol must be protected before we attempt basic equilibriation (Scheme 50).



Reagents and conditions: (a). DMP, CH_2Cl_2, 0 °C. (b). DBU, CH_2Cl_2. (c). NaBH$_4$, MeOH

Scheme 51. Structural convergence.

To correct the stereochemistry of tetrahydropyran (**1.154A**), we oxidized the alcohol to the ketone (**1.156**) and used the base equilibriation conditions of McErlean,[15] correcting the chiral centre at C(2). Reduction of the ketone (**1.155**) with NaBH$_4$ in methanol then gave the desired *trans*-tetrahydropyran (**1.152**) (Scheme 51).



Reagents and conditions: (a). TBSCl, Im., DMAP, THF. (b). DIBAL, CH_2Cl_2. (c). $CH_2CHMgBr$, THF, -78 °C. (d). methyl acrylate, Grubbs II, CH_2Cl_2, 40 °C. (e). TBAF, THF.

Scheme 52. Demonstration of the iterative nature of our procedure.

With the desired diastereoisomer now available to us we intend to continue our synthesis and demonstrate the iterative nature of the synthetic route (Scheme 52). Firstly the alcohol needed to be protected, this was achieved under standard TBS protection conditions (as used for the TBS ether (**1.157**)), and now also available from the *cis*-tetrahydropyran (**1.153**) (Scheme 50). We then reduced the ester with DIBAL to give the aldehyde (**1.158**), which we have obtained as a crude product. The aldehyde group was observed as a singlet at 9.3 ppm in the proton spectrum. Our future work will aim to install the second tetrahydropyran ring, we also intend to further explore this mild cyclisation in the formation of the 7 membered rings of Brevetoxin B (**1.1**), whilst also exploring the effect of the extra steric bulk at the newly formed ring junction by installing a methyl substituent.

In summary, our initial synthetic route using an allene cyclisation to form the desired tetrahydropyran rings under mild silver catalysis reaction conditions failed. We have attributed this to the ineffectiveness of the silver in activating the allene double bonds, and due to the deactivation of the allene double bonds by the α-alcohol. We then revised our synthetic route to use a Michael cyclisation as the key step. However, we found that the lack of steric constraint, and the rapid rate of equilibriation did not lead to the formation of the desired diastereoisomer with any selectivity. By introducing a cyclohexene group as a 'back bone', we have successfully managed to obtain a route that under mild cyclisation conditions and with a simple convergence sequence gave us access to a desired *trans*-tetrahydropyran ring, that by simple iteration should yield the desired *trans, syn, trans* fused pyran ring system of Brevetoxin. We are now in the process of demonstrating the iterative nature of this synthetic route.

Chapter 1: Access towards *trans,syn,trans*-fused pyran rings of Brevetoxin B.

Experimental Section.

General Methods.

When required, reactions were carried out under an inert atmosphere of nitrogen in oven dried glassware. Tetrahydrofuran was distilled from sodium-benzophenone, dichloromethane and acetonitrile were dried by distillation from CaH_2 immediately prior to use. Methanol was distilled from activated magnesium. All other solvents and reagents were used as received, or purified if required, using standard methods.[59] ^{1}H NMR and ^{13}C NMR (500 and 125 MHz respectively) were recorded in $CDCl_3$ solutions using a Bruker AV500. ^{1}H-NMR and ^{13}C-NMR (400 and 100 MHz respectively) were recorded in $CDCl_3$ solutions using a Jeol ECA 400, or on a Jeol ECA 400SL, or on a Bruker AV400. ^{1}H-NMR and ^{13}C-NMR (300 and 75 MHz respectively) were recorded in $CDCl_3$ solutions using a Bruker AV300. Chemical shifts are reported in δ units using $CDCl_3$ as an internal standard (δ 7.26 ppm ^{1}H, δ 77.00 ppm ^{13}C). Coupling constants J were recorded in Hz. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), br (broad), m (multiplet) and app (apparent). Infrared spectra were recored on a Bruker Alpha-E FT-IR, either neat or as nujol mulls. Melting points were obtained using a OptiMelt MPA100. Mass spectra were obtained on a Finnigan LCQ DECA XP MAX with ESI mode. High resolution mass spectra were obtained using a Waters Q-Tof premier also with ESI mode. Specific roatation, $[\alpha]_D$, were recorded on a Jasco P-1030 polarimeter. Enantionmeric excess were determined with chiral HPLC analysis, performed on a Shimadzu HPLC and Daicel chemical industries Chiralcel OD-H column, eluting with IPA/hexane.

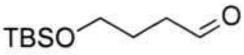
4-(*t*-Butyldimethylsilyloxy)butanol (1.92)

A solution of TBSCl (10 g, 66 mmol) in THF (50 mL) was added dropwise to a solution of 1,4-butane diol (30.30 mL, 332 mmol) and imidazole (4.94g, 72.6 mmol) in THF (150 mL) at 0 °C. The reaction mixture was allowed to stir for 3 h, before being quenched by addition of sat. aq. NH_4Cl (50 mL). The organic layer was then separated and the aqueous layer was further extracted with ether (2x50 mL), The combined organics layers were then washed with water (100 mL), brine (50 mL), and then dried over $MgSO_4$. The excess solvent was then removed *in vacuo* to give the title compound as a colourless oil (12.48 g, 92%).

δ_H (300 MHz, $CDCl_3$), 3.70-3.60 (m, 4H, CH_2O), 2.50 (br s, 1H, OH), 1.67-1.60 (m, 4H, CH_2CH_2), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$).

IR (ν/cm^{-1}), 3368, 2858, 2885, 1472, 1256.

All data was consistent with that of the literature.[60]



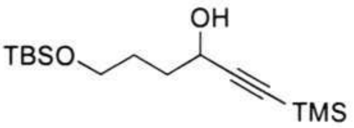
4-(*t*-Butyldimethylsilyloxy)butanal (1.90).

4-(*t*-Butyldimethylsilyloxy)-butanol (**1.92**) (1 g, 4.9 mmol) was added to a clear solution of IBX (1.64 g, 5.88 mmol) in reagent grade DMSO (12 mL) with external cooling. On complete consumption of starting material by TLC (3 h), the mixture was diluted with water (15 mL) and filtered through a thick pad of celite, washing thoroughly with EtOAc. The aqueous layer was separated, saturated with NaCl and extracted with EtOAc (3x 15 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (10 mL), sat. aq. Na_2CO_3 (10 mL), water (10 mL) and brine (10 mL) before being dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a colourless oil (0.6 g, 60%), which could be purified by distillation under reduced pressure when required.

δ_H (300 MHz, $CDCl_3$), 9.78 (t, *J* = 3.0, 1H, CHO), 3.64 (t, *J* = 6.0, 2H, CH_2OTBS), 2.49 (dt, *J* = 6.0, 3.0, 2H, CH_2CHO), 1.87 (qn, *J* = 6.0, 2H, CH_2), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_2$).

IR (ν/cm^{-1}), 2950, 2953, 2860, 1729, 1470, 1253, 1101.

All data was consistent with that of the literature.[58]



6-(*t*-Butyldimethylsilyloxy)-1-(trimethylsilyl)hex-1-yn-3-ol (1.94).

Butyl lithium (16.75 mL, 1.6 M) was added to a solution of trimethylsilylacetylene (4.07 mL, 28.83 mmol) in THF (55 mL) at -78 °C over a period of 1 h. 4-(*t*-Butyldimethylsilyloxy)-butanal **(1.90)** (3.88 g, 19.21 mmol) in THF (5 mL) was added via cannula. The reaction mixture was stirred at this temperature for 3 h. at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was quenched by addition of sat. aq. NH_4Cl at -78 °C, then allowed to warm to RT. The volatiles were removed *in vacuo*, and the mixture was extracted with EtOAc (3x25 mL). The combined organic layers were washed with water (10 mL), brine (10 mL) before being dried over $MgSO_4$. The solvent was removed *in vacuo* to give the title compound as a pale yellow oil (4.44 g, 77%), without need for purification.

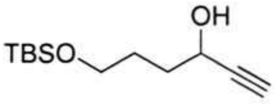
δ_H (300 MHz, $CDCl_3$), 4.43 (t, *J* = 6.0, 1H, CH(OH)), 3.71-3.62 (m, 2H, CH_2OTBS), 3.31 (br s, 1H, OH), 1.86-1.77 (m, 4H, CH_2CH_2), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 6H, $Si(CH_3)_2$), -0.01 (s, 9H, $Si(CH_3)_3$).

δ_C (75 MHz, $CDCl_3$), 106.9, 89.0, 63.3, 62.5, 35.4, 28.6, 26.0 (3C), 25.7 (3C), 18.4, 0.0 (2C).

IR (ν/cm^{-1}) 3382, 2955, 2929, 2857, 2172, 1471, 1251.

MS (ESI +) *m/z* 300.83 ($[M]^+$).

HRESIMS found 323.1831, calc. for $C_{15}H_{32}O_2Si_2Na$ 323.1839 ($[M+Na]^+$).



6-(*t*-Butyldimethylsilyloxy)hex-1-yn-3-ol (1.95).

Potassium carbonate (1.85 g, 13.37 mmol) was added to a solution of TMS alkyne (**1.94**) (4.01 g, 13.37 mmol) in MeOH (5 mL) with exclusion of moisture. The reaction mixture was stirred vigorously for 1 h. At which point TLC showed complete consumption of the starting material. The reaction mixture was quenched by addition of sat. aq. NH_4Cl and the volatiles were removed *in vacuo*. The residue was extracted with ether (3x 5 mL), the combined organics were washed with water (5 mL), brine (5 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a colourless oil (2.72 g, 89%), without need for further purification.

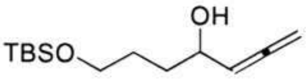
δ_H (300 MHz, $CDCl_3$), 4.43 (dt, $J = 6.0, 2.2$, 1H, CH(OH)), 3.72-3.65 (m, 2H, CH_2OTBS), 2.42 (d, $J = 2.2$, 1H, CCH), 1.88-1.81 (m, 4H, CH_2CH_2), 0.9 (s, 9H, $SiC(CH_3)_3$), 0.08 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 85.0, 72.5, 63.2, 61.9, 35.3, 28.4, 25.9 (3C), 18.3, -5.4 (2C).

IR (ν/cm^{-1}) 3311, 2954, 2929, 2857, 2110, 1725, 1471, 1256.

MS (ESI +) *m/z* 228.90 ($[M]^+$).

HRESIMS found 251.1446, calc. for $C_{14}H_{24}O_2SiNa$ 251.1443 ($[M+Na]^+$).



7-(*t*-Butyldimethylsilyloxy)-4-hydroxyhept-1,2-diene (1.96)

A mixture of alkyne (**1.95**) (468 mg, 2.32 mmol), CuBr (169 mg, 1.16 mmol), diisopropylamine (716 μL, 4.87 mmol) and paraformaldehyde (168 mg, 5.80 mmol) in dioxane (10 mL) was heated at reflux for 3 h. at which point TLC showed complete consumption of the starting material. The reaction mixture was allowed to cool to RT then air was bubbled through the reaction mixture for 1 h. The mixture was then diluted with EtOAc (10 mL) and sat. aq. NH_4Cl (10 mL), and filtered through a pad of celite washing with EtOAc (5 mL), The organic layer was separated and the aqueous layer was extracted with EtOAc (3x 10 mL). The combined organic layers were washed with HCl (10 mL, 2M), water (10 mL) and brine (10 mL) before being dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a pale yellow oil (413 mg, 80%), without need for further purification.

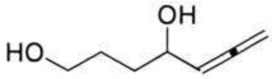
δ_H (300 MHz, $CDCl_3$), 5.25 (app. q, *J* = 6.3, 1H, $CHCCH_2$), 4.84 (app d, *J* = 6.3, 1H, $CHCCH_2$), 4.83 (app d, *J* = 6.3, 1H, $CHCCH_2$), 4.22-4.19 (m, 1H, CH(OH)), 3.66 (t, *J* = 5.7, 2H, CH_2OTBS), 1.74-1.61 (m, 4H, CH_2CH_2), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$).

δ_C (75 MHz, $CDCl_3$), 207.1, 94.8, 77.4, 69.4, 63.4, 34.8, 25.9 (3C), 18.1, -0.10 (2C).

IR (ν/cm^{-1}), 3364, 2953, 2929, 2857, 1956, 1471, 1463, 1255.

MS (ESI +) *m/z* 242.75 ($[M]^+$), 243.99 ($[M+H]^+$).

HRESIMS found 265.1602, calc. for $C_{13}H_{26}O_2SiNa$ 265.1600 ($[M+Na]^+$).



7,4-Dihydroxyhept-1,2-diene (1.104)

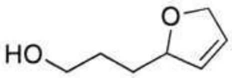
To a solution of allene (**1.96**) (200 mg, 0.82 mmol) in methanol (5 mL) was added PPTs[61] (200 mg, 0.08 mmol), with the exclusion of moisture. The reaction mixture was stirred overnight, at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was quenched by addition of sat. aq. $NaHCO_3$ (5 mL), and the volatilities were removed *in vacuo*. The aqueous layer was then extracted with EtOAc (3x 5 mL), the combined organics layers were then washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to give the title compound as a colourless oil (68 mg, 49%).

δ_H (300 MHz, $CDCl_3$), 5.26 (app q, J = 6.4, 1H, $CHCCH_2$), 4.85 (d, J = 6.4, 1H, $CHCCH_2$), 4.84 (d, J = 6.4, 1H, $CHCCH_2$), 4.25-4.22 (m, 1H, CH(OH)), 3.7-3.67 (m, 2H, CH_2OH), 2.23 (br s, 2H, OH), 1.78-1.67 (m, 4H, CH_2CH_2).

δ_C (75 MHz, $CDCl_3$), 206.9, 94.7, 77.6, 69.5, 62.7, 34,4, 29.9, 28.8.

IR (ν/cm^{-1}) 3301, 2927, 2869, 1956, 1666, 1434

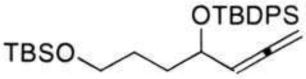
MS (ESI +) *m/z* 128.91 ($[M]^+$).



3-(2,5-Dihydrofuran-2yl)propan-1-ol (1.105)

A solution of allenic diol (**1.104**) (78 mg, 0.61 mmol) in dioxane (1 mL) was added to a solution of silver nitrate (62 mg, 20 mol%) and $CaCO_3$ (61 mg, 0.61 mmol) in dioxane (1 mL) and water (1 mL). The reaction mixture was stirred in the absence of light and followed by TLC, after 24 h the reaction failed to proceed to completion and was warmed to 50 °C. Subsequently the reaction proceeded to completion in 6 h, the reaction was quenched by addition of brine and filtered through a pad of celite. The filtrate was then extracted with EtOAc (3x5 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo* to give the title compound as a pale yellow oil (33 mg, 47%).

δ_H (300 MHz, $CDCl_3$), 5.89 (m, 1H, CH), 5.75 (m, 1H, CH), 4.86 (br s, 1H, CH-O), 4.69-4.60 (m, 2H, CH_2-O), 3.36 (m, 2H, CH_2OH), 1.83-1.56 (m, 4H, CH_2CH_2).



7-(*t*-Butyldimethylsilyloxy)-4-(*t*-butyldiphenylsilyloxy)hept-1,2-diene (1.106).

A solution of allenic alcohol **(1.96)** (413 mg, 1.81 mmol) in DMF (1 mL) was added to a soloution of TBDPSCl (531 μL, 1.81 mmol), imidazole (136 mg, 1.99 mmol) and DMAP (2.2 mg, 10 mol%) in DMF (2 mL). The reaction mixture was left to stir overnight before being quenched by addition of sat. aq. NH_4Cl (5 mL), the DMF was then removed at the pump. The aqueous layer was extracted into ether (3x5 mL), the combined organic layers were washed with brine (5 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a brown oil (632 mg, 80%).

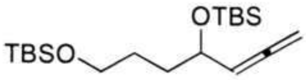
δ_H (400 MHz, $CDCl_3$), 7.66 (m, 4H, ArH), 7.40 (m, 6H, ArH), 5.08 (app. q, J = 6.4, 1H, $CHCCH_2$), 4.55 (ddd, J = 10.5, 6.4, 1.4, 1H, $CHCCH_2$), 4.47 (ddd, J = 10.5, 6.4, 1.4, 1H, $CHCCH_2$), 3.51 (m, 2H, CH_2OTBS), 1.66-1.48 (m, 4H, CH_2CH_2), 1.05 (s, 6H, $Si(CH_3)_2$), 0.87 (s, 6H, $Si(CH_3)_2$), 0.10 (s, 9H, $SiC(CH_3)_3$).

δ_C (100 MHz, $CDCl_3$), 207.6, 136, 135.9, 134.3, 134.2, 129.5 (2C), 129.4 (2C), 127.5 (2C), 127.3 (2C), 94.1, 75.8, 72.1, 63.1, 34.6, 28.2, 27.0 (3C), 26.0 (3C), 19.3, 18.3, -5.3 (2C).

IR (ν/cm^{-1}) 3071, 2930, 2857, 1956, 1471, 1427, 1112

MS (ESI +) *m/z* 480.61 ($[M]^+$), 503.21 ($[M+Na]^+$).

HRESIMS found 503.2781, calc. for $C_{29}H_{44}O_2NaSi_2$ 503.2778 ($[M+Na]^+$).



7-(*t*-Butyldimethylsilyloxy)-4-(*t*-butyldimethylsilyloxy)hept-1,2-diene (1.107).

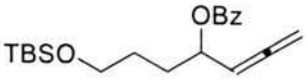
A solution of allenic diol **(1.96)** (400 mg, 1.65 mmol) in DMF (1 mL) was added to a solution of TBSCl (249 mg, 1.65 mmol), imidazole (124 mg, 1.81 mmol) and DMAP (2 mg, 10 mol%) in DMF (2 mL). The reaction mixture was stirred for 12 h at reflux, at which point the TLC showed complete consumption of the starting material. The reaction mixture was diluted by addition of ether (5 mL) and quenched by addition of sat. aq. NH_4Cl (5 mL). The organic layer was separated and the solvent was removed *in vacuo*. The residue was then taken into hexane (5 mL), washed with water (5 mL), then brine (5 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a yellow oil (386 mg, 66 %).

δ_H (400 MHz, $CDCl_3$), 5.10 (app. q, J = 6.6, 1H, $CHCCH_2$), 4.73 (app. dddd, J = 17.0, 10.5, 6.6, 1.4, 2H, $CHCCH_2$), 4.17 (m, 1H, CH(OTBS)), 3.61 (t, J = 6.6, 2H, CH_2OTBS), 0.88 (s, 18H, $SiC(CH_3)_3$), 0.07 (s, 6H, $Si(CH_3)_2$), 0.04 (s, 6H, $Si(CH_3)_2$).

δ_C (100MHz, $CDCl_3$), 207.4, 95.1, 75.8, 71.2, 63.1, 34.9, 28.8, 26 (3C), 25.9 (3C), 18.3, 18.2, -4.3, -4.9, -5.3 (2C).

IR (ν/cm^{-1}) 2955, 2930, 2887, 2858, 1457, 1721, 1472, 1255

MS (ESI +) *m/z* 356.64 ($[M]^+$), 357.16 ($[M+H]^+$), 379.76 ($[M+Na]^+$).



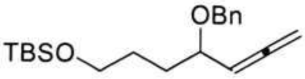
7-(*t*-Butyldimethylsilyloxy)-4-(benzoyloxy)hept-1,2-diene (1.108).

Benzoyl chloride (300 µL, 1.77 mmol) was added dropwise to a solution of allene **(1.96)** (356 mg, 1.47 mmol), Et_3N (162 µL, 2.02 mmol) and DMAP (catalytic) in CH_2Cl_2 (1.5 mL) with external cooling. The reaction mixture was stirred vigorously for 1 h at which point TLC showed complete consumption of the starting material. The reaction mixture was quenched by addition of sat. aq. NH_4Cl (5 mL), and diluted with CH_2Cl_2 (5 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were then washed with brine (5 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a yellow oil (234 mg, 46%)

δ_H (300 MHz, $CDCl_3$), 8.07-8.04 (m, 2H, ArH), 7.56 (m, 1H, ArH), 7.44 (m, 2H, ArH), 5.54 (m, 1H, CH(OBz)), 5.34 (app. q, $J = 6.6$, 1H, $CHCCH_2$), 4.90 (ddd, $J = 11.2, 6.6, 2.2$, 1H, $CHCCH_2$), 4.85 (ddd, $J = 11.2, 6.6, 2.2$, 1H, $CHCCH_2$), 3.66 (t, $J = 6.4$, 2H, CH_2OTBS), 1.87 (m, 2H, CH_2), 1.72-1.63 (m, 2H, CH_2), 0.9 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 208.5, 165.9, 132, 130.3, 129.6 (2C), 128.3 (2C), 90.6, 72.0, 64.5, 62.5, 30.6, 28.5, 25.9 (3C), 18.3, -3.6, -5.3

IR (ν/cm^{-1}) 2953, 2927, 2885, 2857, 1958, 1790, 1714.



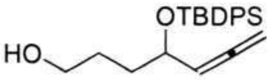
7-(*t*-Butyldimethylsilyloxy)-4-(benzyloxy)hept-1,2-diene (1.109).

A solution of allene alcohol (**1.96**) (100 mg, 0.41 mmol) in DCE (1 mL) was added to a solution of 2-benzyloxy-1-methylpyridinium triflate (276 mg, 0.83 mmol) and MgO (30 mg, 0.83 mmol) in DCE (2 mL). The reaction mixture was heated at reflux for 24 h. at which point TLC showed complete consumption of the starting material. The reaction mixture was then allowed to cool to room temperature, before being filtered through a plug of celite washing with EtOAc (15 mL). The solvent was then removed *in vacuo* to give the crude product, purification by flash chromatography on silica gel eluting with 10 % EtOAc/hexane, gave the title compound as a pale yellow oil (132 mg, 96%).

δ_H (300 MHz, $CDCl_3$), 7.37-7.27 (m, 5H, Bn), 5.25 (app q, $J = 6.5$, 1H, $CHCCH_2$), 4.82-4.76 (m, 2H, $CHCCH_2$), 4.66 (d, $J = 15.7$, 1H, AB pair CH_2Ar), 4.41 (d, $J = 15.7$, 1H, AB pair CH_2Ar), 3.88 (m, 1H, CH(OBn)), 3.60 (t, J = 7.8, 2H, CH_2OTBS), 1.66-1.55 (m, 4H, CH_2CH_2), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 6H, $SiC(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 208.8, 138.0, 128.4 (2C), 127.6 (3C), 91.5, 75.5, 72.8, 71.6, 70.1, 32.6, 30.9, 29.7, 25.8 (3C), 18.8, -0.04 (2C).

IR (ν/cm^{-1}) 2936, 2857, 1955.



7-Hydroxy-4-(*t*-butyldiphenylsilyloxy)hept-1,2-diene (1.110).

To a solution of allene (**1.106**) (100 mg, 0.21 mmol) in methanol (2 mL) was added PPTs (5 mg, 0.02 mmol), with the exclusion of moisture. The reaction mixture was warmed to 45 °C and stirred for 3 h. at which point TLC showed complete consumption of the starting material. The reaction mixture was allowed to cool to RT and the volatilities were removed *in vacuo*. The residue was then diluted by addition of EtOAc (5 mL) and quenched by addition of sat. aq. $NaHCO_3$ (2 mL). The aqueous layer was then separated and extracted with EtOAc (2x5 mL). The combined organic layers were then washed with brine (5 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a yellow oil (68 mg, 89%).

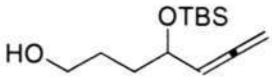
δ_H (300 MHz, $CDCl_3$), 7.69 (m, 4H, ArH), 7.38 (m, 6H, ArH), 5.10 (app q, J = 6.9, 1H, $CHCCH_2$), 4.56 (ddd, J = 11.0, 6.9, 1.8, 1H, $CHCCH_2$), 4.49 (ddd, J = 11.0, 6.9, 1.8, 1H, $CHCCH_2$), 4.28 (m, 1H, CH(OTBDPS)), 3.54 (br t, J = 6.4, 2H, CH_2OH), 2.17 (s, 1H, OH), 1.63-1.56 (m, 4H, CH_2CH_2), 1.04 (s, 9H, $SiC(CH_3)_3$).

δ_C (100 MHz, $CDCl_3$), 207.4, 136.0, 135.9, 134.8, 134.0, 129.6 (2C), 129.5 (2C), 127.5 (2C), 127.4 (2C), 93.8, 75.9, 71.9, 62.8, 34.4, 28.1, 26.5 (3C), 19.3.

IR (ν/cm^{-1}) 2257, 2930, 2857, 1957, 1722, 1427.

MS (ESI +) *m/z* 366.94 ($[M]^+$), 389.13 ($[M+Na]^+$).

HRESIMS found 367.2093, calc. for $C_{23}H_{31}O_2Si$ 367.2093 ($[M+H]^+$).



7-Hydroxy-4-(*t*-butyldimethylsilyloxy)hept-1,2-diene (1.111)

The title compound (37 mg, 56%) was obtained from allene (**1.107**), by the method described for (**1.110**), giving the product as a pale yellow oil after flash chromatography.

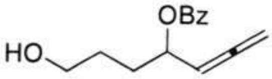
δ_H (300 MHz, $CDCl_3$), 5.13 (app q, *J* = 6.7, 1H, $CHCCH_2$), 4.78 (ddd, *J* = 10.7, 6.7, 1.8, 1H, $CHCCH_2$), 4.72 (ddd, *J* = 10.7, 6.7, 1.8, 1H, $CHCCH_2$), 4.25 (m, 1H, CH(OTBS)), 3.65 (br s, 2H, CH_2O), 1.79 (br s, 1H, OH), 1.71-1.65 (m, 4H, CH_2CH_2), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.08 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 207.4, 94.5, 76.1, 62.9, 35.1. 28.5, 25.9 (3C), 18.2, -4.3, -4.9

IR (ν/cm^{-1}), 3332, 2930, 2857, 1957, 1472, 1361

MS (ESI +) *m/z* 242.77 ($[M+H]^+$).

HRESIMS found 243.1787, calc. for $C_{13}H_{27}O_2Si$ 243.1780.



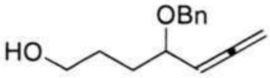
7-Hydroxy-4-(benzoyloxy)hept-1,2-diene (1.112).

The title compound (112 mg, 72%) was obtained from allene (**1.108**), by the method described for (**1.110**), giving the crude product as a pale yellow oil.

δ_H (300 MHz, $CDCl_3$), 8.1-8.03 (m, 2H, ArH), 7.6-7.54 (m, 1H, ArH), 7.46-7.41 (m, 2H, ArH), 5.58 (ddt, *J* = 12.0, 6.4, 2.2, 1H, CH(OBz)), 5.35 (app. q, *J* = 6.4, $CHCCH_2$), 4.88 (app. dddd, *J* = 18.0, 12.0, 6.4, 2.2, 2H, $CHCCH_2$), 4.37 (t, *J* = 6.5, 2H, CH_2OH) 2.3-1.8 (m, 4H, CH_2CH_2).

δ_C (100 MHz, $CDCl_3$), 208.1, 165.0, 132.9, 130.3, 129.6 (2C), 128.3 (2C), 90.3, 71.8, 64.5, 30.8, 29.7, 24.7

IR (ν/cm^{-1}) 3412, 2949, 2872, 1957, 1714, 1450, 1271

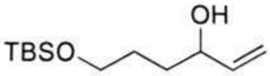


7-Hydroxy-4-(benzyloxy)hept-1,2-diene (1.113).

The title compound (25 mg, 42%) was obtained from allene (**1.109**), by the method described for (**1.110**), giving the crude product. Purification by flash chromatography on silica gel, eluting with 10% EtOAc/hexane gave the title compound as a colourless oil.

δ_H (300 MHz, $CDCl_3$), 7.35 (m, 5h, ArH), 5.08 (app q, *J* = 6.6, 1H, $C\underline{H}CCH_2$), 4.80 (app. ddd, *J* = 17.8, 10.9, 6.6, 2H, $CHCC\underline{H_2}$), 4.67 (d, *J* = 11.7, 1H, AB pair CH_2Ar), 4.41 (d, *J* = 11.7, 1H, AB pair CH_2Ar), 3.96-3.86 (m, 1H, CH(OBn)), 3.62 (t, *J* = 6, 2H, CH_2OH), 1.8-1.7 (m, 4H, CH_2CH_2).

δ_C (100 MHz, $CDCl_3$), 208.8, 138.0, 128.4 (2C), 128.0 (2C), 127.6, 91.3, 77.5, 75.8, 70.3, 62.8, 32.7, 28.8.



6-(*t*-Butyldimethylsilyloxy)-hex-1-en-3-ol (1.124).

Vinyl magnesium chloride (6.34 mL, 10.15 mmol) was added dropwise to a solution of aldehyde (**1.90**) (1.48 g, 7.81 mmol) in THF (20 mL) at -78 °C. The reaction mixture was stirred at room temperature for 3 h. at which point TLC showed complete consumption of the starting material. The reaction mixture was quenched by addition of sat. aq. NH_4Cl (10 mL) and allowed to warm to RT. The aqueous layer was separated and extracted with ether (3x10 mL), the combined organic layers were then washed with brine and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a colourless oil (1.30 g, 77 %).

δ_H (400 MHz, $CDCl_3$), 5.87 (ddd, *J* = 17.0, 10.7, 6.0, 1H, $CHCH_2$), 5.17 (dd, *J* = 17.0, 10.7, 2H, $CHCH_2$), 4.13 (m, 1H, CH(OH)), 3.66 (t, *J* = 6.0, 2H, $TBSOCH_2$), 2.68 (d, *J* =

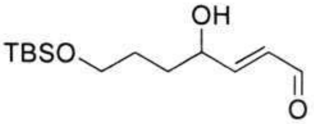
4.12, 1H, OH), 1.71-1.56 (m, 4H, CH_2CH_2), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.07 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 141.2, 114.3, 72.7, 63.4, 34.5, 28.8, 28.8, 25.9 (3C), 18.3, -5.4 (2C).

IR (ν/cm^{-1}) 3371, 2953, 2929, 2858, 1471, 1255.

MS (ESI +) *m/z* 230.87 ([M]$^+$), 253.52 ([M+Na]$^+$).

HRESIMS found 231.1780, calc. for $C_{12}H_{27}O_2Si$ 231.1780 ([M+H]$^+$).



7-*t*-Butyldimethylsilyloxy)-4-hydroxyhept-2-enal (1.125).

Allylic alcohol (**1.124**) (130 mg, 0.56 mmol) and crotonaldehyde (281 µL, 3.45 mmol) were heated at refluxed in CH_2Cl_2 (3 mL). A solution of Grubb's II catalyst (24 mg, 5 mol%) in CH_2Cl_2 (1 mL) was then added portionwise over a period of 3 h. The reaction mixture was then allowed to reflux for 12 h, before being allowed to cool to RT. Silica gel (500 mg) was then added to the reaction mixture, and the volatilities were removed *in vacuo*. The silica gel and absorbed crude product were transferred to the top of a silica gel column and purified by flash chromatography elution with 5 % EtOAc/hexane gave the title compound as a pale yellow oil (47 mg, 32%).

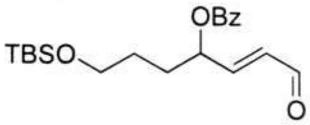
δ_H (500 MHz, $CDCl_3$), 9.59 (d, J = 8.0, 1H, CHO), 6.82 (dd, J = 15.6, 4.3, 1H, CHCHCHO), 6.36 (ddd, J = 15.6, 8.0, 1.7, 1H, CHCHCHO), 4.47-4.44 (m, 1H, CH(OH)), 3.91 (d, J = 4.3, 1H, OH), 3.77-3.59 (m, 1H, CH_2OTBS), 1.78-1.65 (m, 4H, CH_2CH_2), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.09 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 193.7, 159.5, 130.8, 70.6, 63.4, 34.5, 28.7, 25.8 (3C), 18.3, -5.5 (2C).

IR (ν/cm^{-1}), 3402, 2954, 2930, 2885, 1799, 1694, 1255.

MS (ESI +) *m/z* 258.95 ($[M]^+$), 259.92 ($[M+H]^+$), 281.06 ($[M+Na]^+$).

HRESIMS found 259.1745, calc. for $C_{13}H_{27}O_3Si$ 259.1729 ($[M+H]^+$).



7-*t*-Butyldimethylsilyloxy)-4-(benzoyloxy)hept-2-enal (1.126)

Benzoyl chloride (110 µL, 0.92 mmol) was added to a -10 °C solution of allylic aldehyde (**1.125**) (175 mg, 0.71 mmol), Et_3N (300 µL, 2.13 mmol) and DMAP (8 mg, 1 mol%) in CH_2Cl_2 (2 mL). After complete addition the reaction mixture was allowed to warm to RT and was stirred until TLC analysis showed complete consumption of the starting material. The reaction was then quenched by addition of sat. aq. NH_4Cl (5 mL) and diluted by the addition of ether (5 mL). The aqueous layer was separated and extracted into ether (3x5 mL), the combined organic layers were then washed with HCl (2M), water and then brine and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as yellow oil (176 mg, 71%).

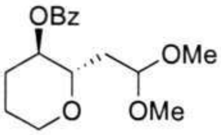
δ_H (300 MHz, $CDCl_3$), 9.59 (d, *J* = 7.7, 1H, CHO), 8.18-8.05 (m, 1H, ArH), 7.71-7.44 (m, 4H, ArH), 6.86 (dd, *J* = 15.8, 4.6, 1H, CHCHCHO), 6.29 (ddd, *J* = 15.8, 7.7, 1.6, 1H, CHCHCHO), 5.85-5.78 (m, 1H, CH(OBz)), 3.67 (t, *J* = 6.1, 2H, $TBSOCH_2$), 1.98-1.91 (m, 2H, CH_2), 1.70-1.64 (m, 2H, CH_2), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 6H, $Si(CH_3)_2$).

δ_C (75 MHz, $CDCl_3$), 193.0, 153.9, 134.5, 133.4, 131.6, 130.6 (2C), 129.7, 128.9 (2C), 72.5, 62.3, 30.3, 28.2, 25.6 (3C), 18.3, -5.4 (2C).

IR (ν/cm^{-1}) 2929, 2856, 1787, 1693, 1599, 1451.

MS (ESI +) *m/z* 249.02 ($[M+H-TBS]^+$), 362.33 ($[M]^+$), 363.0 ($[M+H]^+$).

HRESIMS found 363.1983, calc. for $C_{20}H_{31}O_4Si$ 363.1992 ($[M+H]^+$).

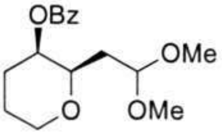


trans-2-(2,2-Dimethoxyethyl)tetrahydro-_2H_-pyran-3-yl benzoate (1.129)

Amberlyst 15 exchange resin (400 mg), was added to a solution of allyic aldehyde (**1.126**) (175 mg, 0.59 mmol) in methanol (2 mL). The reaction mixture was left to stir for 2 h, at which point TLC showed complete consumption of the starting material. The reaction was filtered through a plug of celite and concentrated *in vacuo*. The residue was then purified by flash chromatography on silica gel eluting with 10 % EtOAc/hexane a mixture of two compounds each weighing 10 mg as colourless oils.

(10 mg, 7%).

δ_H (500 MHz, $CDCl_3$), 8.01 (m, 2H, ArH), 7.56 (m, 1H, ArH), 7.44 (m, 2H, ArH), 4.75 (dt, J = 10.4, 4.6, 1H, CH(OBz)), 4.63 (dd, J = 8.5, 2.9, 1H, CH(OBz)CHO), 3.95 (m, 1H, CH_2O), 3.54 (dt, J = 9.7, 2.4, 1H, CH_2O), 3.43 (m, 1H, $CH(OMe)_2$), 3.35 (s, 3H, OMe), 3.31 (s, 3H, OMe), 2.7-2.63 (m, 1H, CH_2CH_2O), 2.33-2.3 (m, 1H, $CH_2CH(OBz)$), 2.0 (ddd, J= 14.4, 8.5, 2.9, 1H, $CHCH_2CH(OMe)_2$), 1.83-1.78 (m, 1H, CH_2CH_2O), 1.75-1.67 (m, 1H, $CH_2CH(OBz)$), 1.61-1.57 (m, 1H, $CH_2CH(OBz)$).



cis-2-(2,2-Dimethoxyethyl)tetrahydro-_2H_-pyran-3-yl benzoate (1.128).

(10 mg, 7%)

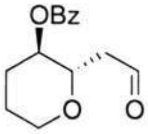
δ_H (400 MHz, $CDCl_3$), 8.12-8.1 (m, 2H, ArH), 7.77-7.56 (m, 1H, ArH), 7.47-7.44 (m, 2H, ArH), 5.06 (br s, 1H, CH(OBz)), 4.57 (dd, J = 7.9, 3.8, 1H, CHO), 4.06 (m, 1H, CH_2O), 3.66 (ddd, J = 7.9, 2.9, 1, 1H, $CH(OMe)_2$), 3.55 (dt, J = 11.9, 2.9, 1H, CH_2O), 3.32 (s, 3H, OMe), 3.30 (s, 3H, OMe), 2.15 (br d, J = 14.2, 1H, $CH_2CH(OBz)$), 1.9-1.75 (m, 4H, , $CH_2CH(OBz)$, $CH_2CH(OMe)_2$, CH_2CH_2O), 1.46 (m, br d, J = 11.4, CH_2CH_2O).

δ_C (75 MHz, $CDCl_3$), 165.7, 133.1, 130.2, 129.6 (2C), 128.4 (2C), 101.8, 76.8, 72.5, 67.6, 53.6, 52.9, 35.6, 28.1, 25.2.

IR (ν/cm^{-1}) 2950, 2853, 1715, 1451, 1270.

MS (ESI +) *m/z* 295.01 ([M+H]+), 317.12 ($[M+Na]^+$).

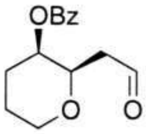
HRESIMS found 295.1545, calc. for $C_{16}H_{23}O_5$ 295.1545 ($[M+H]^+$).



trans 2-(2-Oxoethyl)tetrahydro-2*H*-pyran-3-yl benzoate (1.130).

Amberlyst 15 exchange resin (400 mg), was added to a solution of allyic aldehyde (**1.126**) (163 mg, 0.45 mmol) in THF (2 mL) with 1 drop of water. The reaction mixture was left to stir for 2 h, at which point TLC analysis showed complete consumption of the starting material. The reaction was filtered through a plug of celite and concentrated *in vacuo*. The residue was then purified by flash chromatography on silica gel, eluting with 10% EtOAc/hexane gave two compounds both as colourless oils (combined yield 62 mg, 56% as a 1:1 mixture).

δ_H (300 MHz, $CDCl_3$), 9.8 (t, *J* = 2.1, 1H, CHO), 8.17-7.42 (m, 5H, ArH), 4.82 (dt, *J* = 14.7, 4.7, 1H, CH(OBz)), 4.02-3.94 (m, 2H, CH(CH_2CHO), -CH_2O-), 3.48 (dt, *J* = 14.7, 3.1, 1H, CH_2O), 2.69 (ddd, *J* = 16.4, 4.3, 1.8, 2H, CH_2O), 2.39-2.31 (m, 1H, CH_2CH(OBz)), 1.89-1.56 (m, 3H, CH_2).



cis 2-(2-Oxoethyl)tetrahydro-2H-pyran-3-yl benzoate (1.131).

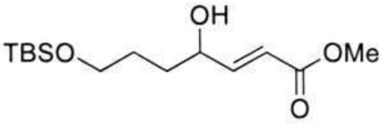
δ_H (500 MHz, $CDCl_3$), 9.77 (t, J = 2.2, 1H, CHO), 8.14 (m, 2H, ArH), 7.60 (m, 1H, ArH), 7.49 (m, 2H, ArH), 5.13 (br s, 1H, CH(OBz), 4.14 (ddd, J = 8.3, 4.5, 1.3, 1H, $CH(CH_2CHO)$), 4.08 (ddt, J = 11.8, 4.5, 2.3, 1H, CH_2O), 3.61 (dt, J = 11.8, 2.3, 1H, CH_2O), 2.74 (ddd, J = 17.2, 8.3, 2.3, 1H, CH_2CHO), 2.54 (ddd, J = 17.2, 4.5, 1.3, 1H, CH_2CHO), 2.21-2.16 (m, 1H, CH_2), 2.01 (app tq, J = 13.4, 13.4, 4.3, 1H, CH_2CH_2O), 1.93-1.86 (m, 1H, CH_2CH_2O), 1.54-1.51 (m, 1H, $CH_2CH(OBz)$).

δ_C (75 MHz, $CDCl_3$), 200, 166, 133.2, 130, 129.7 (2C), 128.5 (2C), 73.4, 69.3, 68.3, 46, 27.9, 19.6.

IR (ν/cm^{-1}) 2948, 2856, 1715, 1602, 1451, 1270.

MS (ESI +) m/z 232.64 ($[M]^+$), 254.65 ($[M+Na]^+$).

HRESIMS found 249.1135, calc. for $C_{14}H_{17}O_4$ 249.1127 ($[M+H]^+$).



Methyl-7-(_t_-butyldimethylsilyloxy)-4-hydroxyhept-2-enoate (1.132).

Allylic alcohol (**1.124**) (500 mg, 2.17 mmol) and methyl acrylate (1.96 mL, 21.74 mmol) were heated at reflux in CH_2Cl_2 (10 mL). A solution of Grubb's II catalyst (92 mg, 5 mol%) in CH_2Cl_2 (2 mL) was then added portionwise over a period of 6 h. The reaction mixture was then allowed to reflux for 12 h, before being allowed to cool to RT. Silica gel (500 mg) was then added to the reaction mixture, and the volatiles were removed *in vacuo*. The silica gel and absorbed crude product were transferred to the top of a silica gel column and purified by flash chromatography elution with 5 % EtOAc/hexane gave the title compound as a pale yellow oil (47 mg, 45%).

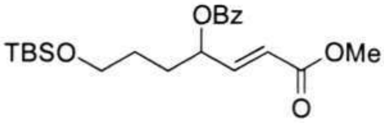
δ_H (400 MHz, $CDCl_3$), 6.95 (dd, *J* = 15.6, 4.4, 1H, $CHCHCO_2Me$), 6.09 (d, *J* = 15.6, 1H, $CHCO_2Me$), 4.34 (br s, 1H, CH(OH)), 3.74 (s, 3H, CO_2Me), 3.68 (t, *J* = 4.7, 2H, $TBSOCH_2$), 3.57 (d, *J* = 4.4, 1H, OH), 1.83-1.64 (m, 4H, CH_2CH_2), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.08 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 167.2, 150.7, 119.6, 70.5, 63.4, 51.5, 34.4, 28.6, 25.9 (3C), 18.3, -5.5 (2C).

IR (ν/cm^{-1}) 3542, 2954, 2929, 2857, 1715, 1439, 1307

MS (ESI +) *m/z* 288.90 ($[M]^+$).

HRESIMS found 289.1823, calc. for $C_{14}H_{29}O_4Si$ 289.1835 ($[M+H]^+$).



7-(*t*-Butyldimethylsilyloxy)-1-methoxy-1-oxohept-2-en-4-yl benzoate (1.128).

The title compound (202 mg, 90%) was obtained from allylic ester (**1.132**), by the method described for (**1.126**), as a yellow oil.

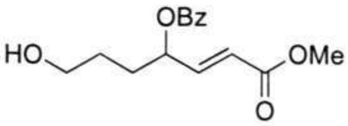
δ_H (400 MHz, $CDCl_3$), 8.06 (d, *J* = 7.6, 2H, ArH), 7.59 (m, 1H, ArH), 7.46 (m, 2H, ArH), 6.98 (dd, *J* = 15.7, 5.0, 1H, $CHCHCO_2Me$), 6.04 (d, *J* = 15.7, 1H, $CHCO_2Me$), 5.71 (dt, *J* = 5.0, 1.0, CH(OBz)), 3.74 (s, 3H, CO_2Me), 3.65 (t, *J* = 6.2, 2H, $TBSOCH_2$), 1.9-1.83 (m, CH_2), 1.65-1.6 (m, 2H, CH_2), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.04 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 166.4, 165.5, 145.8, 133.2, 129.7 (2C), 128.5 (2C), 121.2, 72.7, 62.4, 51.7, 30.4, 28.1, 25.9 (3C), 18.3, -5.4 (2C).

IR (ν/cm^{-1}) 2953, 1716, 1665, 1602, 1451, 1436

MS (ESI +) *m/z* 392.85 ($[M]^+$).

HRESIMS found 393.2092, calc. for $C_{21}H_{33}O_5Si$ 393.2097 ($[M+H]^+$).



7-Hydroxy-1-methoxy-1-oxohept-2-en-4yl benzoate (1.134).

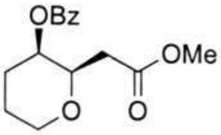
A solution of allylic ester (**1.133**) (202 mg, 0.52 mmol) in methanol (1 mL) was added to a solution of amberlyst 15 exchange resin (300 mg) in methanol (1 mL). The reaction mixture was stirred vigorously for 2 h at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was filtered through a pad of celite and the solvent was removed *in vacuo* giving the title compound as a yellow oil (100 mg, 70%).

δ_H (500 MHz, $CDCl_3$), 8.08-8.06 (m, 2H, ArH), 7.6-7.58 (m, 1H, ArH), 7.48-7.45 (m, 2H, ArH), 6.98 (dd, J = 15.8, 5.1, 1H, $CHCHCO_2Me$), 6.06 (d, J = 15.8, 1H, $CHCO_2Me$), 5.75-5.71 (m, 1H, CH(OBz)), 3.74 (s, 3H, CO_2Me), 3.71 (t, J = 6.4, 2H, $HOCH_2$), 2.17 (s, 1H, OH), 1.95-1.91 (m, 2H, CH_2), 1.74-1.68 (m, 2H, CH_2).

IR (ν/cm^{-1}) 3401, 2952, 2875, 1715, 1664, 1602, 1451

MS (ESI +) *m/z* 278.79 ([M]$^+$), 301.85 ([M+Na]$^+$).

HRESIMS found 301.1062, calc. for $C_{15}H_{18}O_5Na$ 301.1052 ([M+Na]$^+$).

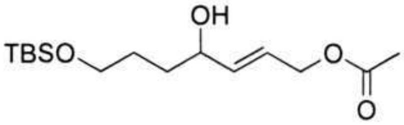


***cis*-2-(2-Methoxy-2-oxoethyl)tetrahydro-2*H*-pyran-3-yl benzoate (1.135).**

Tetramethyl guanidiene (2 drops) was added to a solution of allylic ester (**1.134**) (50 mg, 0.19 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred vigorously for 3 d, the solvent was then removed *in vacuo* and the residue was purified by flash chromatography on silica gel, eluting with 5 % EtOAc/hexane. This gave the title compound as a colourless oil (22 mg, 44%).

δ_H (500 MHz, $CDCl_3$), 8.12-8.09 (m, 2H, ArH), 7.60-7.56 (m, 1H, ArH), 7.48-7.44 (m, 2H, ArH), 5.13 (br s, 1H, CH(OBz)), 4.08-4.04 (m, 2H, $CH(CH_2CO_2Me)$, CH_2O), 3.67 (s, 3H, CO_2Me), 3.6 (dt, J = 12.0, 2.3, 1H, CH_2O), 2.64 (dd, J = 15.8, 8.6, 1H, ABX $CHCH_2CO_2Me$), 2.48 (dd, J = 15.8, 4.8, 1H, ABX, $CHCH_2CO_2Me$), 2.2-2.13 (m, 1H, $CH_2CH(OBz)$), 1.98 (ddt, J = 13.1, 13.1, 4.3, 1H, CH_2CH_2O), 1.89-1.82 (m, 1H, $CH_2CH(OBz)$), 1.49-1.45 (m, 1H, CH_2CH_2O).

All other data were in good accordance of the literature.[53]



7-(*t*-Butyldimethylsilyloxy)-4-hydroxyhept-2-enyl acetate (1.141).

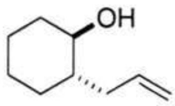
Allylic alcohol (**1.124**) (300 mg, 1.31 mmol) and *cis*-butene-1,4-diacetate (450 mg, 2.61 mmol) were heated at reflux in CH_2Cl_2 (5 mL). A solution of Grubb's II catalyst (5 mg, 3 mol%) in CH_2Cl_2 (1 mL) was then added and the reaction mixture was heated at reflux for 5 h, at which point TLC analysis showed complete consumption of the starting material. The solvent was then removed *in vacuo* and the residue was purified by flash chromatography on silica gel, eluting with 10% EtOAc/hexane. This gave the title compound as a colourless oil (83 mg, 21%).

δ_H (400 MHz, $CDCl_3$), 5.80 (br s, 2H, CHCH), 4.57 (br d, J = 3.8, CH_2OAc), 4.17 (br s, 1H, OH), 3.68-3.63 (m, 2H, CH_2OTBS), 2.17 (s, 1H, OH), 2.07 (s, 3H, C(O)Me), 1.68-1.58 (m, 6H, CH_2), 0.9 (s, 9H, $SiC(CH_3)_3$), 0.07 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 137.5, 124.0, 71.7, 64.5, 63.5, 34.7, 31.0, 28.8, 25.9 (3C), 21.0, 18.4, -5.3 (2C).

IR (ν/cm^{-1}) 3340, 2951, 2885, 1738.

MS (ESI +) *m/z* 188.67 ($[M-TBS]^+$).



trans-2-Allylcyclohexanol (1.76).

Allyl chloride (3.32 mL, 40.7 mmol) was added portion wise to a suspension of magnesium tunings (1.3 g, 53 mmol) in THF (5 mL). At the point of initiation the reaction mixture was diluted by addition of THF (10 mL) and the remainder of the allyl chloride was added at a rate to maintain a mild reflux. After the complete addition the reaction mixture was stirred for a further 1 h, before being cooled in an ice salt bath (-10 °C). Cyclohexene oxide (2 g, 20.3 mmol) was then added to the reaction mixture portionwise and stirred for 10 minutes at which point TLC analysis showed complete consumption of the starting material. The reaction was quenched by addition of sat. aq. NH_4Cl (20 mL), The organic layer was then separated and the aqueous was extracted with ether (3x10 mL). The combined organic layers were then washed with water (10 mL) and brine (15 mL). Before being dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a colourless oil (2.77 g, 97%).

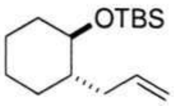
δ_H (500 MHz, $CDCl_3$), 5.85 (ddt, J = 17.1, 10.1, 7.4, 1H, CH_2CHCH_2), 5.06 (ddd, J = 17.1, 2.8, 1.2, 1H, $CHCH_2$), 5.01 (dd, J = 10.1, 2.1, 1H, $CHCH_2$), 3.75-3.73 (m, 1H, CH(OH)), 2.47-2.42 (m, 1H, $CH(CH_2CHCH_2)$, 2-1.95 (m, 2H, CH_2CHCH_2), 1.75 (m, 2H, CH_2), 1.6 (m, 2H, CH_2), 1.2-1.5 (m, 3H, CH_2CH_2), 0.96 (m, 1H, CH_2).

δ_C (100 MHz, $CDCl_3$), 137.5, 116.0, 74.7, 44.9, 37.5, 33.6, 30.4, 25.5, 24.9

IR (ν/cm^{-1}) 3336, 2924, 2856, 1640, 1448

MS (ESI +) *m/z* 141 ($[M+H]^+$), 140 ($[M]^+$), 123 ($[M-OH]^+$).

HRESIMS found 141.1277, calc. for $C_9H_{17}O$, 141.1279.



trans-(t-Butyldimethylsilyloxy)-2-allylcyclohexyl (1.145).

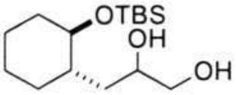
A solution of allylic alcohol (**1.76**) (2.39g, 17.06 mmol) in THF (5 mL) was added to a stirring solution of imidazole (1.63g, 23.88 mmol), TBSCl (3.34g, 22.17 mmol) and DMAP (21 mg, 0.17 mmol) in THF (15 mL). The reaction mixture was stirred vigorously overnight at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was quenched by addition of sat. aq. NH_4Cl (15 mL) and diluted by the addition of ether (20 mL) and water (5 mL). The organic layer was then separated and the aqueous layer was extracted with ether (2x20 mL). The combined organic layers were then washed with brine (20 mL), and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a colourless oil (4.47 g, 95%).

δ_H (400 MHz, $CDCl_3$), 5.75 (ddt, J = 16.7, 8.7, 3.7, 1H, $CHCH_2$), 4.98 (d, J = 16.7, 1H, $CHCH_2$), 4.96 (d, J = 8.7, 1H, $CHCH_2$), 3.75 (t, J = 6.4, 1H, CH(OTBS)), 3.21 (dt, J = 8.7, 3.7, 1H, $CH(CH_2CHCH_2)$, 2.54 (app dt, J = 8.7, 4.8, 1H, CH_2), 1.87-0.87 (m, 9H, CH_2), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 137.8, 115.6, 75.1, 68.0, 45.0, 37.0, 36.0, 29.9, 26.0, 18.1, -4.7.

IR (ν/cm^{-1}) 2929, 2857, 1253, 1070.

MS (ESI +) *m/z* 245.96 ($[M]^+$).



3-(trans-2-(t-Butyldimethylsilyloxy)cyclohexyl)propane-1,2-diol (1.147).

In one portion $K_2OsO_4 \cdot 2H_20$ (50 mg) was added to a vigorously stirring solution of allyl silyl alcohol (**1.145**) (5 g, 18.12 mmol), $K_3Fe(CN)_6$ (17.9 g, 54.35 mmol), and K_2CO_3 (7.5 g, 54.35 mmol) in ^{t}BuOH (65 mL) and water (65 mL). The reaction mixture was stirred for 48 h at which point a colour change from orange to green was observed and TLC analysis showed complete consumption of the starting material. The reaction was quenched by addition of Na_2SO_3 and stirred for 3 h to give a blue solution. The precipitate was dissolved by addition of water and the volatilities were removed *in vacuo*. The residue was then diluted by addition of ether (30 mL). The organic layer was separated and the aqueous layer was extracted with ether (3x30 mL). The combined organic layer was then washed with brine (50 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a viscous colourless oil (4.59 g, 88%).

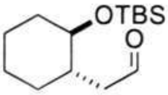
δ_H (400 MHz, $CDCl_3$), 3.86 (ddd, *J* = 14.2, 6.4, 3.2, 1/2H, CH(OTBS)), 3.72 (ddd, *J* = 10.1, 6.4, 3.2, 1/2H, CH(OTBS)), 3.62 (t, *J* = 3.2, 1/2H, CH_2OH), 3.59 (t, *J* = 3.2, 1/2H, CH_2OH) 3.42 (dd, *J* = 11.4, 7.8, 1/2H, CH_2OH), 3.39 (dd, *J* = 11.4, 6.4, 1/2H, CH_2OH), 3.23 (m, 1H, CHOH), 1.91-0.99 (m, 9H, CH_2), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.08 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 70.8, 67.6, 66.9, 60.5, 42.5, 41.9, 37.2, 36.1, 32.7, 32.4, 26.0 (3C), 25.7, 25.6, 24.9, 18.2, -3.8, -4.1.

IR (cm-1) 3370, 2928, 2856, 1462

MS (ESI +) *m/z* 288.93 ($[M]^+$), 290.01 $[M+H]^+$), 311.11 ($[M+Na]^+$).

HRESIMS found 289.2200, calc. for $C_{15}H_{33}O_3Si$ 289.2199 ($[M+H]^+$).



2-*trans*-(*trans*-(*t*-Butyldimethylsilyloxy)cyclohexyl)acetaldehyde (1.146).

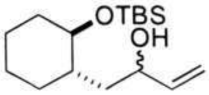
Diol (**1.147**) (4.59 g, 15.9 mmol) was added to a vigorously stirring suspension of SiO_2-$NaIO_4$ (30 g) in CH_2Cl_2 (160 mL) with external cooling. The reaction mixture was stirred for 10 minutes at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was filtered through a pad of celite washing with chloroform (100 mL). The solvent was then removed *in vacuo* to give the title compound as a colourless oil (4 g, quant.).

δ_H (500 MHz, $CDCl_3$), 9.72 (m, 1H, CHO), 3.24 (dt, *J* = 9.7, 3.9, 1H, CH(OTBS)), 2.69 (ddd, *J* = 16.2, 5.3, 2.3, 1H, CH_2CHO), 2.09 (ddd, *J* = 16.2, 7.8, 2.3, 1H, CH_2CHO), 1.90 (m, 2H, CH_2), 1.74 (m, 2H, CH_2), 1.61 (m, 1H, $CH(CH_2CHO)$), 1.29 (m, 1H, CH_2), 1.23 (m, 2H, CH_2), 1.03 (m, 1H, CH_2), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.03 (s, 6H, $Si(CH_3)_3$).

δ_C (100 MHz, $CDCl_3$), 203.4, 75.3, 47.9, 40.9, 35.9, 31.4, 25.9 (3C), 25.4, 24.9, 18, -4, -4.7.

IR (cm-1) 2929, 2857, 1705, 1448.

MS (ESI +) *m/z* 256.13 ($[M]^+$).



1-(*trans*)-2-(*t*-Butyldimethylsilyloxy)cyclohexyl)but-3-en-2-ol (1.148).

Vinylmagnesium bromide (10.7 mL, 18.33 mmol) was added dropwise to a solution of aldehyde (**1.146**) (3.61 g, 14.1 mmol) in THF (30 mL) at -78 °C. The reaction mixture was allowed to stir for 3 h at which point the reaction was quenched by addition of sat. aq. NH_4Cl (10 mL). The reaction mixture was then allowed to warm to RT. The organic layer was separated and the aqueous layer was extracted into EtOAc (3x15 mL). The combined organic layers were then washed with water (10 mL), then brine (10 mL), before being dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the crude product. Purification by flash chromatography, eluting with 10% EtOAc/hexane gave the title compound as a pale yellow oil (3.08 g, 89%).

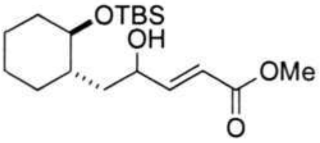
δ_H (400 MHz, $CDCl_3$), 5.89-5.79 (m, 1H, $CHCH_2$), 5.23 (d, *J* = 17.6, 1H, $CHCH_2$), 5.07 (dd, *J* = 18.0, 10.4, 1H, $CHCH_2$), 4.23 (app q, *J* = 6.3, 1/2H, CH(OTBS)), 4.11 (m, 1/2H, CH(OTBS)), 3.25-3.17 (m, 1H, CH(OH)), 1.89-0.93 (m, 9H, CH_2), 0.9 (s, 9H, $SiC(CH_3)_3$), 0.07 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 142.0, 141.2, 114.6, 113.7, 71.6, 71.4, 42.3, 41.3, 40.5, 35.9, 32.1, 25.9, 25.6, 25.4, 24.8, 18.1, -4.0, -4.1, -4.3.

IR (cm-1) 3397, 2928, 2856, 1727, 1645.

MS (ESI +) *m/z* 284.92 ([M]+), 285.9 ([M+H]+).

HRESIMS found 285.2251, calc. for $C_{16}H_{33}O_2Si$ 285.1688 ($[M+H]^+$).



methyl 5-*trans*-2-(*t*-Butyldimethylsilyloxy)cyclohexyl-4-hydroxypent-2-enoate (1.149)

A solution of Grubbs II catalyst (149 mg, 5 mol%) in CH_2Cl_2 (2 mL) was added over a period of 2 h to a solution of allyl alcohol (**1.148**) (1 g, 3.52 mmol) and methyl acrylate (2 mL, 17.6 mmol) in CH_2Cl_2 (20 mL) at reflux. The reaction mixture was then stirred for 5 h at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was allowed to cool to RT and then SiO_2 (1 g) was added and the solvent was removed *in vacuo*. The crude product absorbed onto silica gel was then purified by flash chromatography, eluting with 5% EtOAc/hexane gave the product as a yellow oil (1.13 g, 94%).

(1:1 Mixture of isomers).

δ_H (500 MHz, $CDCl_3$), 6.94-6.89 (m, 1H, $CHCO_2Me$), 6.1 (d, *J* = 15.6, 1H, CHCH), 4.46 (t, *J* = 4.7, 1/2H, CH(OTBS)), 4.27 (br d, *J* = 8.2, 1/2H, CH(OTBS)), 3.74 (s, 3H, OMe), 3.44 (d, *J* = 3.6, 1/2H, OH), 3.26-3.18 (m, 1H,CH(OH)), 3.03 (d, *J* = 4.7, 1/2H, OH), 1.93-0.98 (m, 11H, CH_2), 0.9 (s, 9H, $SiC(CH_3)_3$), 0.09 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 167.4, 167.2, 151.4, 151.0, 120.0, 119.2, 70.1, 69.4, 51.6, 41.1, 40.7, 40.2, 36.1, 33.2, 33.0, 25.7 (3C), 25.5, 24.9, 18.3, -3.9, -4.1.

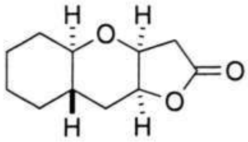
IR (cm-1) 3448, 2929, 2857, 1726, 1657.

MS (ESI +) *m/z* 342.91 ($[M]^+$), 343.97 ($[M+H]^+$).

HRESIMS found 343.2306, calc. for $C_{18}H_{35}O_4Si$ 343.2305 ($[M+H]^+$).

Cyclisation Procedure

A solution of silyl alcohol (**1.149**) (1.13 g, 3.3 mmol) in THF (1.5 mL) was added to a solution of TBAF (949 mg, 3.36 mmol) in THF (1.5 mL) with external cooling. The reaction mixture was then allowed to warm to RT and stirred for 3 d. The reaction mixture was quenched by addition of sat. aq. NH_4Cl (5 mL) and then diluted by addition of ether (5 mL). The organic layer was then separated and the aqueous layer was extracted with ether (3x 5 mL). The combined organic layers were washed with brine and dried over $MgSO_4$ to give the four compounds shown after flash chromatography, eluting with 5% EtOAc/hexane.



3,4-*trans*-8,9-*syn*-decahydro-*2H*-furo[3,2-*b*]chromen-2-one (1.151).

(98 mg, 16%)

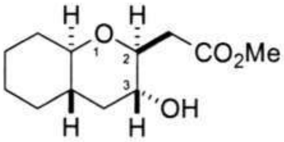
δ_H (400 MHz, $CDCl_3$), 4.70 (dt, *J* = 10.1, 7.3, 1H, CHOC(CO)C), 4.59 (dt, *J* = 9.6, 7.3, 1H, C$\underline{H}$OCCH$_2$), 3.17 (dt, *J* = 9.6, 4.1, 1H, C$\underline{H}$OCH), 2.83 (dd, *J* = 17.2, 10.1, 1H, ABX CH_2CO_2C), 2.5 (dd, *J* = 17.2 7.3, 1H, ABX CH_2CO_2C), 2.18 (m, 1H,$CH_2C\underline{H}CH_2$), 1.86-1.79 (m, 2H, CH_2), 1.66 (br d, *J* = 11.4, 2H, CH_2), 1.35-1.16 (m, 5H, CH_2), 1.07-0.98 (m, 1H, CH_2).

δ_C (100 MHz, $CDCl_3$), 174, 74.9, 74.2, 70.5, 37.3, 33.5, 31.8, 31.4, 29.5, 25.3, 24.7

IR (cm^{-1}) 2928, 2858, (sharp) 1774, 1450

MS (ESI +) *m/z* 196.87 ($[M]^+$).

HRESIMS found 219.0991, calc. for $C_{11}H_{16}O_3Na$ 219.0997 ($[M+H]^+$).



methyl 2-(2,3-*trans*-4,8-*trans*)octahydro-3hydroxy-2H-chromen-2-yl)acetate (1.152).

(122 mg, 16%)

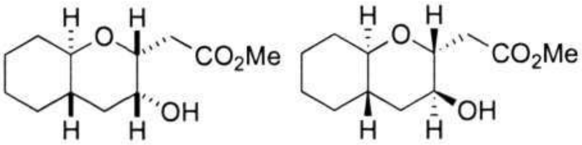
δ_H (500 MHz, $CDCl_3$), 3.7 (s, 3H, OMe), 3.55 (ddd, *J* = 9.4, 7.5, 4.7, 1H, OC<u>H</u>CH_2CO_2Me), 3.41 (ddd, *J* = 14.2, 9.4, 4.3, 1H, CH(OH)), 2.92 (dt, *J*= 11.0, 4.3, 1H, C<u>H</u>OCH), 2.83 (dd, *J*= 15.4, 4.7, 1H, ABX pair, CH_2CO_2Me), 2.53 (dd, *J*= 15.4, 7.5, 1H, ABX pair CH_2CO_2Me), 2.02 (dt, *J* = 11.0, 3.7, 1H, CH_2C<u>H</u>CH_2), 1.91-1.88 (m, 1H, CH_2), 1.87-1.75 (m, 2H, CH_2), 1.64-1.61 (m, 2H, CH_2), 1.17-1.01 (m, 3H, CH_2).

δ_C (125 MHz, $CDCl_3$),171.2, 81.6, 78.9, 70.9, 51.8, 41.2, 40.3, 38.4, 31.8, 31.3, 25.4, 24.8

IR (cm^{-1}) (br) 3411, 2927, 2857, 1738,1439

MS (ESI +) *m/z* 228.94 ($[M]^+$), 250.82 ($[M+Na]^+$).

HRMS found 229.1436, calc. for $C_{12}H_{21}O_4$ 229.1440 ($[M+H]^+$).



methyl 2-(2,3-*trans*-4,8-*trans*)octahydro-3hydroxy-2H-chromen-2-yl)acetate (1.153).

(17 mg, 2%).

δ_H (400 MHz, $CDCl_3$), 4.49 (app. q, *J* = 6.4, 1H,$CHOC\underline{H}CH_2CO_2Me$), 4.05 (dt, *J* = 10.5, 5.5, 1H, CH(OH)), 3.69 (s, 3H, OMe), 3.05 (dt, *J* = 9.6, 3.2, 1H, $C\underline{H}OCH$), 2.78 (dd, *J* = 15.3, 6.4, 1H, ABX pair CH_2CO_2Me), 2.69 (dd, *J* = 15.3, 8.2, 1H, CH_2CO_2Me), 1.79-1.65 (m, 3H, CH_2), 1.65-1.59 (m, 2H, CH_2), 1.33-1.03 (m, 3H CH_2), 1.02-0.92 (m, 1H, CH_2),

δ_C (100 MHz, $CDCl_3$), 173.3, 73.7, 73.6, 68.0, 52.0, 41.1, 34.2, 32.1, 31.7, 31.4, 25.5, 25.0.

IR (cm^{-1}) 3449, 2928, 2856, 1736, 1438.

MS (ESI +) *m/z* 228.98 ($[M]^+$), 251.06 ($[M+Na]^+$).

HRMS found 229.1435, calc. for $C_{12}H_{21}O_4$ 229.1440 ($[M+H]^+$).

methyl 2-(2,3-*trans*-4,8-*trans*)octahydro-3hydroxy-2H-chromen-2-yl)acetate (1.154A) (232 mg, 31%).

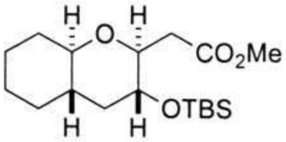
δ_H (500 MHz, $CDCl_3$), 4.31 (ddt, *J* = 8.0, 6.6, 1.5, 1H, $CHOC\underline{H}CH_2CO_2Me$), 3.70 (s, 4H, OMe, CH(OH)), 3.21 (dt, *J* = 10.1, 3.8, 1H, $C\underline{H}OCH$), 2.82 (dd, *J* = 14.9, 8.0, 1H, ABX CH_2CO_2Me), 2.54 (dd, *J* = 14.9, 6.6, 1H, ABX CH_2CO_2Me), 2.17 (br s, 1H, CH_2CHCH_2), 1.79-1.72 (m, 2H, CH_2), 1.69-1.56 (m, 3H, CH_2), 1.5-1.41 (m, 1H, CH_2), 1.32-1.2 (m, 2H, CH_2), 1.04-0.95 (m, 1H, CH_2).

δ_C (125 MHz, $CDCl_3$), 171.2, 75.7, 74.4, 67.8, 52.0, 35.7, 35.5, 32.9, 32.3, 31.4, 25.7, 25.0.

IR (cm^{-1}) 3449, 2928, 2856, 1736, 1438

MS (ESI +) *m/z* 228.9 ($[M]^+$).

HRMS found 229.1432, calc. for $C_{12}H_{21}O_4$ 229.1440 ($[M+H]^+$).



Methyl-2-((*trans,cis,trans*)-3-(*t*-butyldimethylsilyloxy)octahydro -*2H*-chromen-2-yl)acetate (1.157).

A solution of the THP **1.152** (122 mg, 0.53 mmol) in THF (1 mL) was added to a solution of TBSCl (105 mg, 0.69 mmol) and imidazole (51 mg, 0.75 mmol) in THF (1 mL). The reaction mixture was warmed to 50 °C and stirred overnight, before being quenched by addition of sat. aq. NH_4Cl (5 mL) and diluted by addition of EtOAc (5 mL). The organic layer was separated and the aqueous was extracted into EtOAc (3x5 mL). The combined organic layers were then washed with brine and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the crude product. Purification by flash chromatography eluting with 5% EtOAc/hexane, gave the title compound as a colourless oil (130 mg, 71%).

(mixture of isomers)

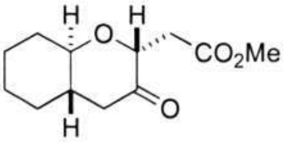
δ_H (400 MHz, $CDCl_3$), 3.69 (s, 3H, OMe), 3.56-3.51 (m, 1H, C<u>H</u>CH_2CO_2Me), 3.39 (app ddd, *J* = 11.0, 11.0, 5.0, 1H, CH(OTBS)), 2.93 (dt, *J* = 10.1, 4, 1H, C<u>H</u>OCH), 2.83 (dd, *J* = 15.8, 4.6, 1H, ABX CH_2CO_2Me), 2.52 (dd, *J* = 15.8, 7.8, 1H, ABX CH_2CO_2Me), 2.01 (dt, *J* = 11.0, 4.6, 1H, CH), 1.89-1.74 (s, 2H, CH_2)1.65-1.60 (m, 2H, CH_2), 1.31-1.02 (m, 6H, CH_2), 0.09 (s, 9H, $SiC(CH_3)_3$), 0.08 (s, 6H, $Si(CH_3)_2$).

δ_C (125 MHz, $CDCl_3$), 172.8, 134.9, 121.9, 81.6, 78.9, 72.9, 70.8, 51.8, 50.8, 41.2, 40.2, 38.9, 38.3, 31.8, 31.3, 17.9, 3.6.

IR (cm^{-1}) 2928, 2853, 1736.

MS (ESI +) *m/z* 342.88 ($[M]^+$).

HRMS found 365.2112, calc. for $C_{18}H_{34}O_4SiNa$ 365.2124 ($[M+Na]^+$).



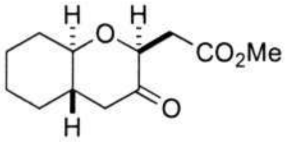
Methyl-2-(*trans,trans*)-3-oxoocathydro-*2H*-chromen-2-yl)acetate (1.156).

A solution of alcohol **(1.154A)** (225 mg, 0.98 mmol) in CH_2Cl_2 (1 mL) was added to a solution of DMP (500 mg, 1.18 mmol) in CH_2Cl_2 (2 mL) with external cooling. The reaction mixture was stirred for 1 h at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was filtered through a pad of celite and silica gel, washing with ether. The solvent was then removed *in vacuo* to give the crude product. Purification by flash chromatography, eluting with 5% EtOAc/hexane gave the title compound as a colourless oil (198 mg, 88%).

δ_H (400 MHz, $CDCl_3$), 4.55 (dd, J = 8.7, 5.0, 1H, $CHCH_2CO_2Me$), 3.70 (s, 3H, OMe), 3.48 (m, 1H, CHOCH), 2.87 (dd, J = 15.1, 8.7, 1H, ABX CH_2CO_2Me), 2.64 (dd, J = 15.1, 4.6, 1H, ABX CH_2CO_2Me), 2.18 (dd, J = 17.4, 12.4, 1H, $CH_2C{=}O$), 1.98-1.94 (m, 1H, CH_2), 1.85-1.67 (m, 3H, CH_2), 1.37-1.07 (m, 5H, CH_2).

δ_C (100 MHz, $CDCl_3$), 209.1, 170.8, 77.8, 75.3, 52.3, 43.4, 40.4, 36.5, 32.3, 32.2, 25.1, 24.8

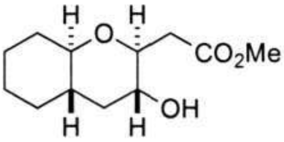
IR (cm^{-1})2933, 2858, 1722, 1437, 1498



(1.155)

To a solution of the ketone **(1.151)** (198 mg, 0.87 mmol) in toluene (2 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (37µL, 0.38 mmol) and the reaction mixture was stirred at RT for 2 d. At which point TLC analysis showed complete consumption of the starting matrial. The reaction mixture was diluted by addition of EtOAc (5 mL) and quenched by addition of sat. aq. NH_4Cl. The organic layer was separated and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a yellow oil (126 mg, 64%).

(Not isolated as the crude product was used directly.)



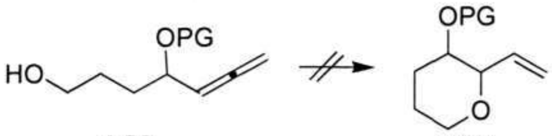
Methyl 2-(2,3-*trans*-4,8-*trans*)octahydro-3-hydroxy-2H-chromen-2-yl)acetate (1.152)

$NaBH_4$ (10 mg, 0.17 mmol) was added to a solution of ketone (**1.155**) (126 mg, 0.59 mmol) in methanol (3 mL) at -63 °C. The reaction mixture was stirred for 3 d at which point TLC showed complete consumption of the starting material. The reaction mixture was quenched by addition of water (5 mL) and the volatiles were removed *in vacuo*. The residue was then extracred with EtOAc (3x5 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound (80 mg, 63%).

NMR Spectra were identical to that of (**1.157**).

Chapter 2

A Formal Synthesis of (-)-Swainsonine by Gold Catalysed Allene Cyclisation

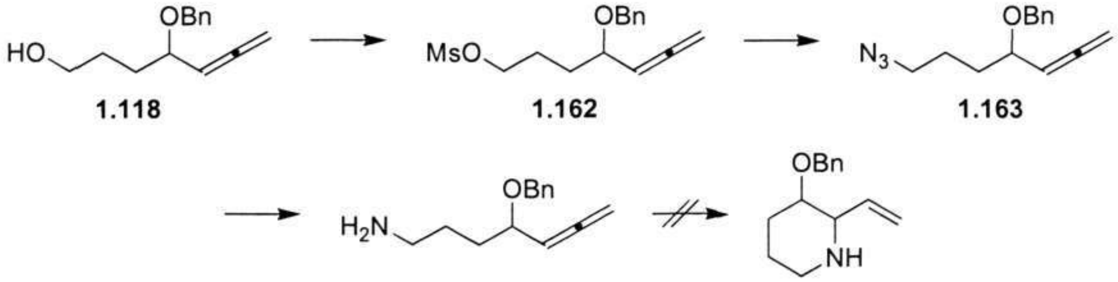


1.88 **1.87**

Scheme 53. Failure of allene alcohol cyclisation from chapter 1.

The failure of the allenic alcohols that we surveyed in Table 3 to cyclise and form the tetrahydropyran ring system was most probably due to the poor nucleophilicity of the alcohol lone pair. We felt it was only logical for us to next to examine whether substitution of the hydroxyl group for an amine would be sufficient to bring about cyclisation and form a piperidine ring system. It was hoped that the stronger nucleophilicity of the amine lone pair would be sufficient to attack a suitably activated allene moiety.

To explore this possibility a model study was performed in which the allenic alcohol (**1.113**) was converted into an allenic amine (**1.164**).



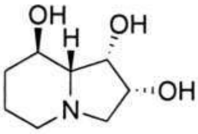
1.118 **1.162** **1.163** **1.164** **1.165**

Scheme 54. Model study of the prospects of allene amines.

The primary alcohol (**1.118**) was readily activated by conversion to the mesylate (**1.162**) under standard conditions in 91 % yield and was clearly identifiable by the loss of the hydroxyl absorbance in the IR spectrum. The mesylate was then displaced by nucleophilic attack of sodium azide to give the allene azide (**1.163**), identifiable most evidently by the characteristic azide absorbance peak in the IR spectrum at 2090 cm^{-1}. Reduction of the azide using the standard conditions of zinc and acetic acid gave the free amine (**1.164**).

The free amine was then exposed to silver nitrate in aqueous acetone the reaction was followed by TLC. Loss of starting material was observed but from the crude reaction mixtures NMR spectrum we were unable to ascertain what had taken place and little evidence of the desired piperidine (**1.165**) was seen. Nevertheless we felt the loss of the starting material was extremely promising and as a result we decided to focus our attention on the formation of a piperidine ring with the intention of utilizing the reaction in the formation of the natural product (-)-swainsonine (**2.1**).

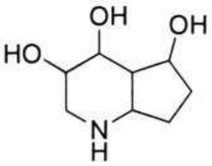
Introduction to Swainsonine



2.1

Figure 6. (-)-Swainsonine.

(-)-Swainsonine (**2.1**), a (1S, 2R, 8R, 8aR)-1,2,8-trihydroxyindolizidine was first isolated from the fungus *Rhizoctonia leguminicola* in 1973 but was incorrectly characterized as a (3,4,5-trihydroxyoctahydro-1-pyridine (**2.2**).[62] In 1981 further studies by Schneider identified inconsistencies with the first assignment and the chemical and spectroscopic observations, this led them to reassign the structure as (**2.1**).[63] After the reassignment their literature search found that an identical alkaloid swainsonine had already been isolated from the Australian plant *Swainsona Canesens* in 1979.[64] The absolute configuration had also been established, from a crystal X-ray structure obtained in 1980.[65]

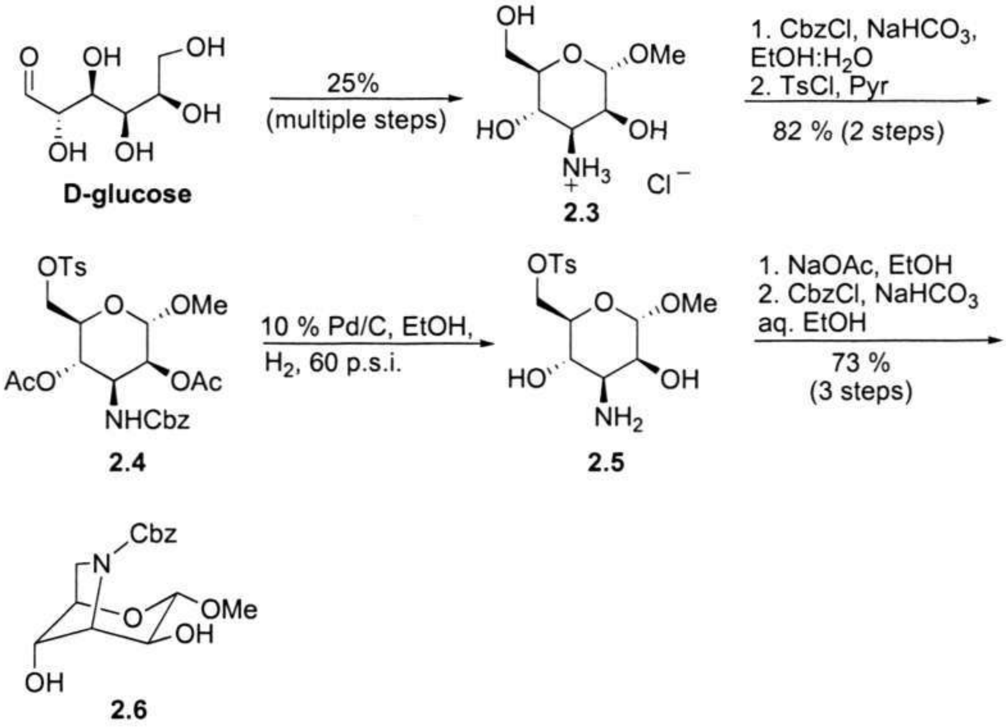


2.2

Figure 7. Original structural assignment.

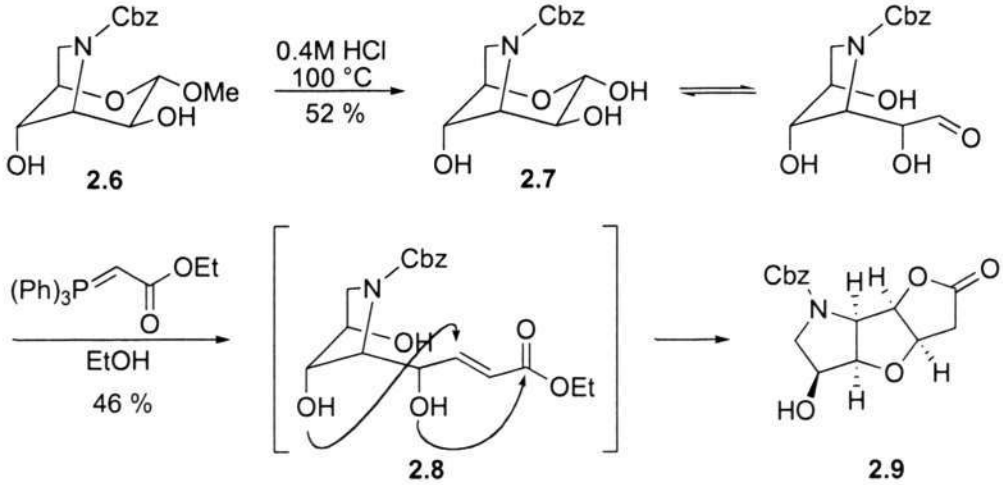
Since then swainsonine (**2.1**) has been isolated in the North American spotted locoweed plant *Astragalous lentiginosus*[66] and the fungus *Metarhizium anisopline* F-3622.[67] It was found to be an effective inhibitor of α-mannosidase and mannosidase II, the glycoprotein-processing enzyme. It shows antimestastic, antitumor-proliferative, anticancer, and immunoregulating activity. (-)-Swainsonine was the first glycoprotein processing inhibitor to be selected for clinical testing (Phase I), and has also been the subject of numerous other biological investigations. Many total synthesis of (-)-swainsonine have been published, this can be attributed to the current need for effective anticancer agents, but it has also been the trihydroxyindolizidine structural complexity that appears to have driven many chemists to develop and utilize novel synthetic processes to furnish either of the fused 6,5-hetrocyclic rings, or to establish any of the stereogenic hydroxyl functionalities. The reviews by Nemr and Pyne extensively report the synthetic routes to (-)-swainsonine and its analogues.[68,69] Here after discussed are a selection, so as to highlight the importance of (-)-swainsonine in synthetic chemistry development.

The first total synthesis of swainsonine was completed by Richardson in 1984.[70,71] Their original synthesis was very attractive due to the minimal protections and deprotections required, was however, dogged with problems, as functional groups began to interfere with there intended transformations. As such, multiple protections and deprotections became inevitable. Their total synthesis started from methyl 3-amino-3-deoxy-α-D-mannopyranoside hydrochloride (**2.3**), which was readily available from D-glucose. Sequential *N*-benzyloxycarbonylation (Cbz) and selective tosylation of the primary alcohol gave a crystalline product (**2.4**) in 82% yield. Removal of the Cbz protecting group, followed by cyclisation under basic conditions (sodium acetate in ethanol) gave the 3,6-imine, which was reprotected as the benzyloxycarbonyl (**2.6**) for isolation.



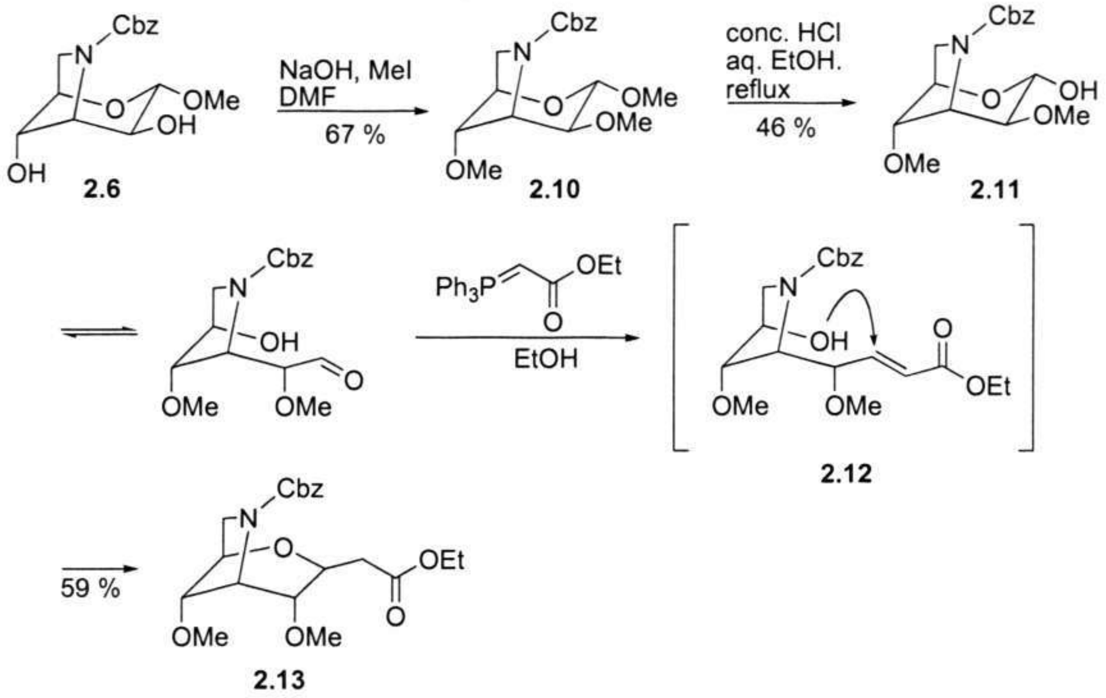
Scheme 55. The first total synthesis of swainsonine by Richardson.

Hydrolysis of the iminomannoside (**2.6**) (Cbz protected 3,6-imine) with mineral acid gave the sugar 3,6-dideoxy-3,6-iminohexofuranose (**2.7**). Here a Wittig addition of ethyl(oxycarbonyl) methylene triphenylphosphorane to the sugar was required, but this did not provide the desired product. The Wittig product (**2.8**) formed and underwent a Michael addition with HO-4, followed by lactonisation of the HO-2 onto the ester to form a tricyclic lactone (**2.9**).



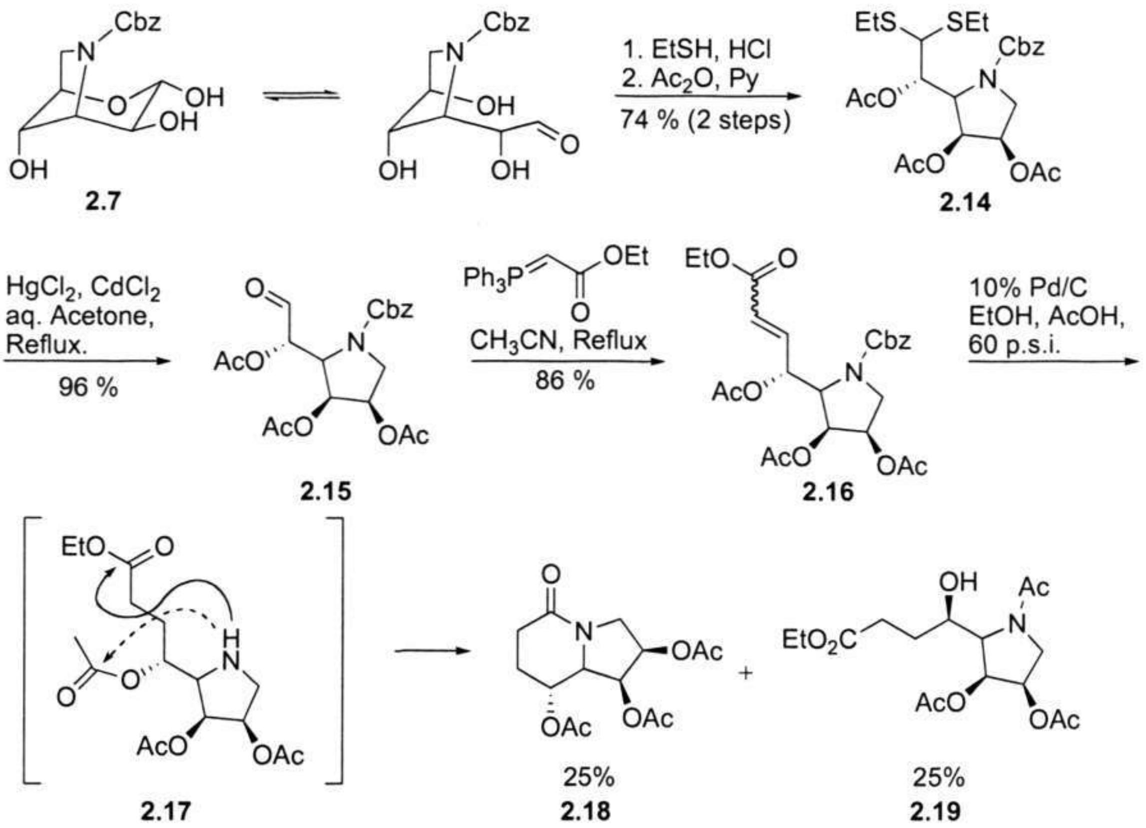
Scheme 56. Undesired Michael addition.

Thus protection of both of these alcohols was performed (**2.10**) (Scheme 57), then hydrolysis gave the hexose (**2.11**), which was resubmitted to the Wittig reaction. However, this also failed to provide access to the desired product.



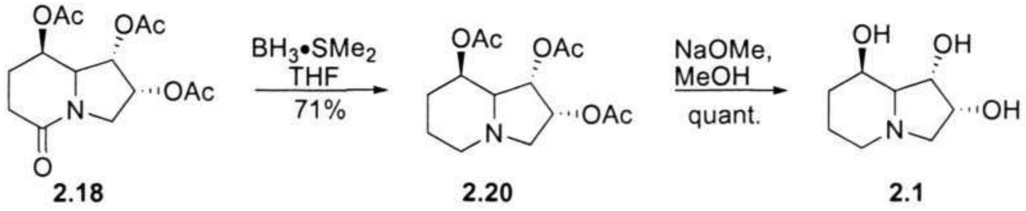
Scheme 57. Richardsons second, undesired Michael addition.

Instead a bicyclic derivative (**2.13**) formed this was a result of the desired Wittig product (**2.12**) undergoing a Michael addition reaction of HO-5. This meant that the desired Wittig product would only be available if all the hydroxyl groups were protected. Alteration of the synthetic strategy was then required. They chose to form an aldehyde before performing the Wittig reaction, causing further elongation of their synthetic route (Scheme 58).



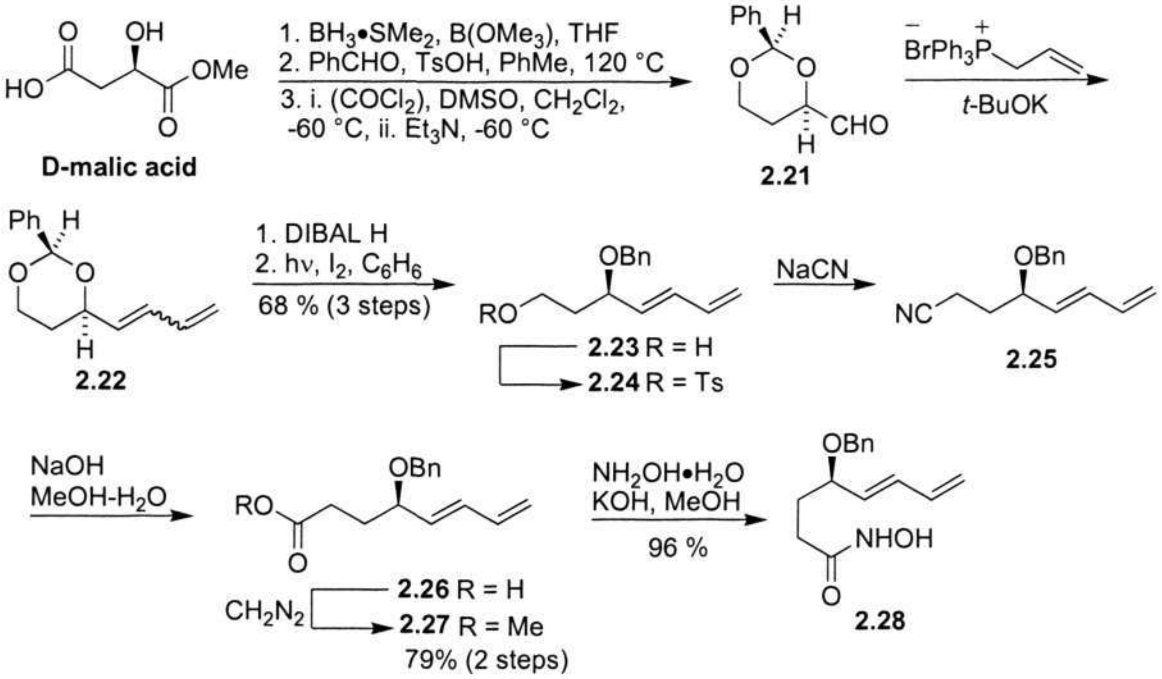
Scheme 58. Richardsons tri-protection route.

The 3,6-imine (**2.7**) was converted into a dithio-tri-*O*-acetate (**2.14**), which was de-thioacylated to give a triacetate *aldehydo*-hexose (**2.15**). Which then underwent the Wittig reaction to give the desired Wittig product (**2.16**). Hydrogenolysis of the double bond and the benzyloxycarbonyl group with palladium black gave the free amine (**2.17**), which then attacked the ester in an intramolecular fashion, in tandem. Two products were obtained, one containing the desired indolizidine core (**2.18**), the other the product of *O* to *N* acetyl migration (**2.19**). Reduction of the lactam present on the indolizidine core (**2.18**) with borane dimethyl sulfide gave the tri-*O*-acetly-swainsonine (**2.20**), which was deacetylated using sodium methoxide in quantitative yield, to give (-)-swainsonine (**2.1**) (Scheme 59).



Scheme 59. Richardsons completion of the synthesis.

The first total synthesis of (-)-swainsonine from a non-carbohydrate source was reported by Sharpless in 1985, in 21 steps with a 6% overall yield.[72] Currently there are many published routes from a wide variety of starting materials. Kibayashi has published a synthesis starting from D-malic acid using a hetero Diels-Alder reaction.[73] By starting with D-malic acid the stereochemistry of the hydroxyl group of the piperidine ring C(8) will have already been set. Conversion of this acid into the dioxane (**2.21**) was achieved in 3 steps by the procedure of Herradon (Scheme 60).[74]



Scheme 60. Kibayashi's synthetic route.

The dioxane (**2.21**) was then transformed into a diene (**2.22**) via a standard Wittig reaction with allyltriphenylphosphonium bromide. The benzylidene acetal was ring opened with the use of DIBAL-H, and photoisomerization of the diene mixture gave the *E*-diene (**2.23**) in 68% yield from the Wittig product. The primary alcohol was activated as the tosylate and displaced by an S_N2 reaction with sodium cyanide. Hydrolysis of the cyanide (**2.25**) using sodium hydroxide in wet methanol gave the carboxylic acid derivative (**2.26**), which was cleanly converted into the methyl ester (**2.27**) with the use of diazomethane with an overall yield of 79%. The ester was then converted into the hydroxamic acid (**2.28**), using hydroxylamine in 96% yield under standard conditions, this gave the penultimate precursor for the intramolecular hetero Diels-Alder reaction.

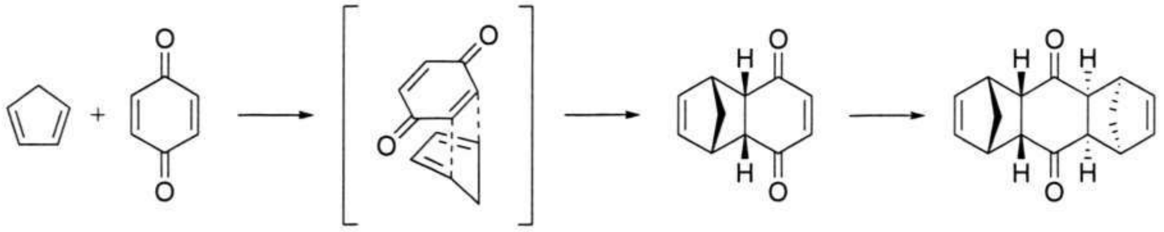
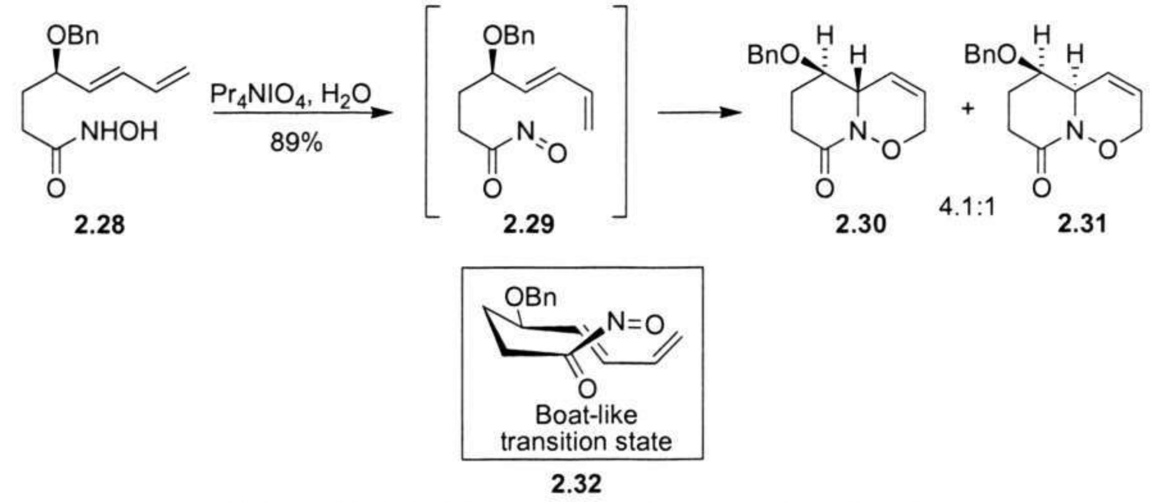


Figure 8. The Diels alder reaction.

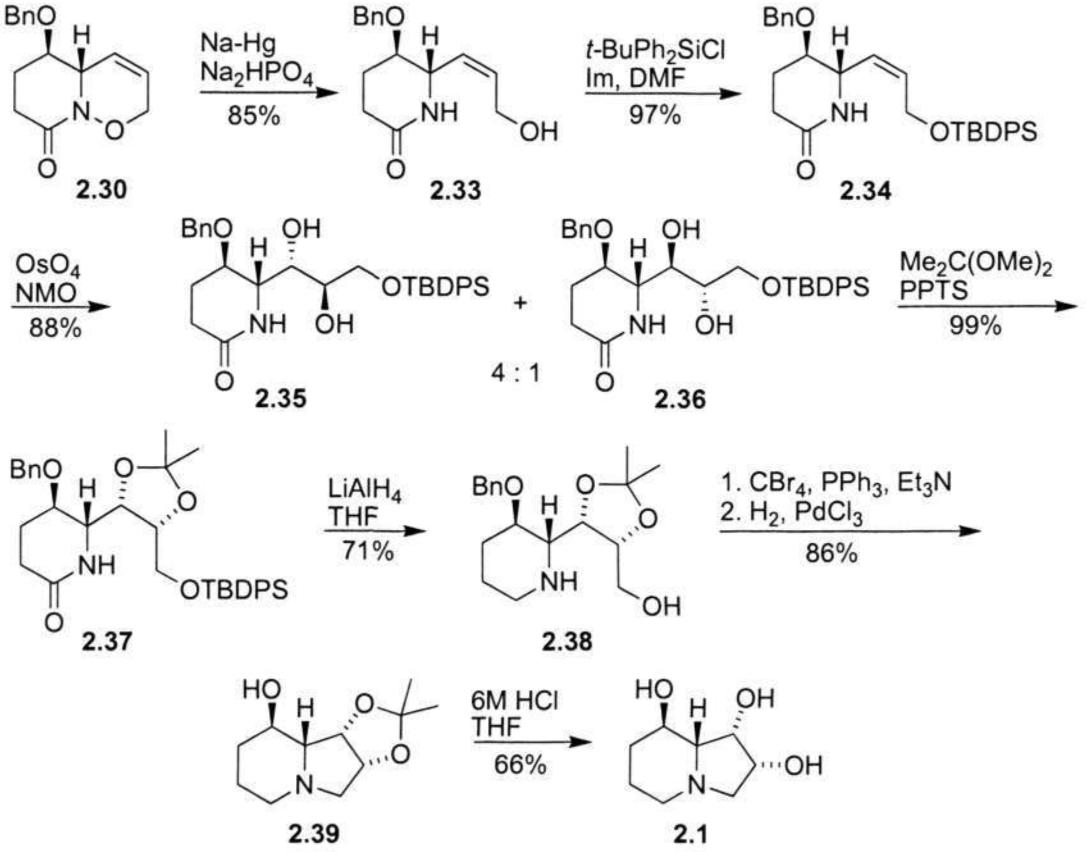
The Diels Alder reaction which bears the name of its two founders, Otto Diels and Kurt Alder, discovered from the reaction of cyclopentadiene with quinone has been known for 7 decades since 1928 (Figure 8).[75] Its mechanism has been heavily studied and identified as a [4+2]-cycloaddition of a conjugated diene with a dieneophile. The hetero Diels Alder is just a variation in which either the diene or dieneophile contains a hetero atom. In this instance the dieneophile was a pendant of the diene and contains the hetero atoms nitrogen and oxygen joined by a double bond. The Diels Alder reaction shows extensive flexibility and copes with a large range of functional groups, it is also possible to achieve stereo and regio selectivity.[76,77]



Scheme 61. Diels-Alder reaction and proposed transition state.

In Kibayashi synthesis the [4+2]-cycloaddition occurs after formation of the intermediate acylnitroso (**2.29**), by oxidation of the hydroxamic acid (**2.28**) with tetrapropylammonium periodate, demonstrating a *trans*-stereoselectivity (**2.30**):(**2.31**) of 4.1:1 in a yield of 89%.

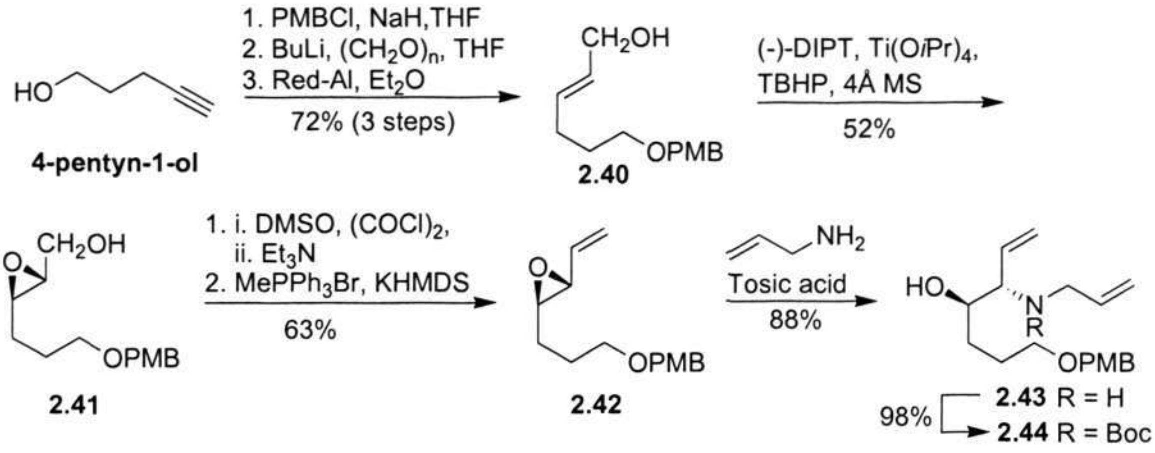
The favorability of the *trans* conformation was rationalized as due to the formation of a boatlike *endo* transition state (**2.32**), in which the O-benzoyl functional group was in a 'quasiequatorial' position (Scheme 61). Fortunately the major isomer was chromatographically separable.



Scheme 62. Completion of the Kibayashi (-)-swainsonine synthesis.

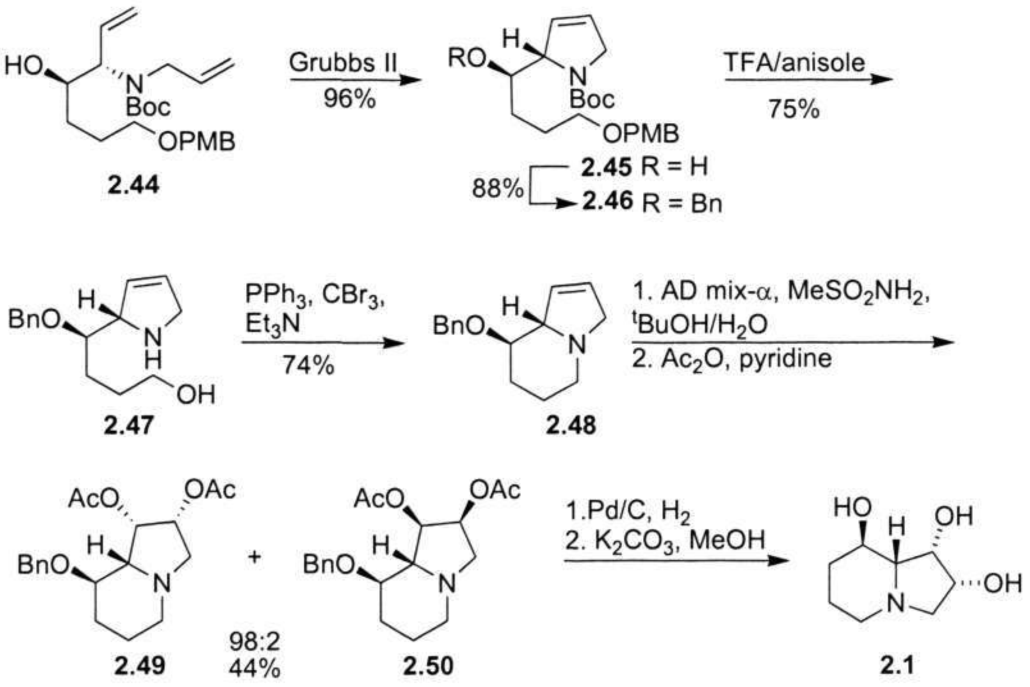
Direct dihydroxylation of (**2.30**) with osmium tetraoxide and *N*-methylmorpholine oxide gave a single diastereomer, but with the wrong stereochemistry, 3*S*,4*R* configuration. Therefore cleavage of the N-O bond from the Diels Alder product (**2.30**) gave the free alcohol (**2.33**) in 85% yield. Protection of the alcohol with *t*-butyldiphenylsilyl chloride and subsequent catalytic osmylation gave a separable mixture of the desired 7*S*,8*R* (**2.35**) and the 7*R*,8*S* (**2.36**) diols in a ratio of 4:1. The desired alcohol 7*S*,8*R* (**2.35**) was protected as the acetonide (**2.37**) in 74%, before the ketone was reduced with lithium aluminium hydride. Reduction was also accompanied by the removal of the silyl protecting group to give the free amino alcohol (**2.38**) in 59% yield. Activation of the alcohol was achieved using carbon tetrachloride and triphenylphosphine, the presence of the base, triethylamine, promoted intramolecular *N*-alkylation giving the indolizidine core (**2.39**). Removal of the benzyloxy protecting group by hydrogenolysis, using palladium black and subsequent acid hydrolysis of the acetonide gave (-)-swainsonine (**2.1**) in 66% yield.

Pyne has contributed two synthetic routes to (-)-swainsonine and also a review of some of the more recent routes published. The first total synthesis by Pyne from 2002 requires the installation of all the hydroxyl groups and the setting of the four contiguous stereocentres.[78] The hydroxyl substituent of C(8) and the proton of C(8a) were set by a stereoselective aminolysis reaction of a chiral vinyl epoxide. The Pyne synthesis can therefore be derived from the non chiral source 4-pentyn-1-ol, which is commercially available (Scheme 63).



Scheme 63. Pyne's total synthesis.

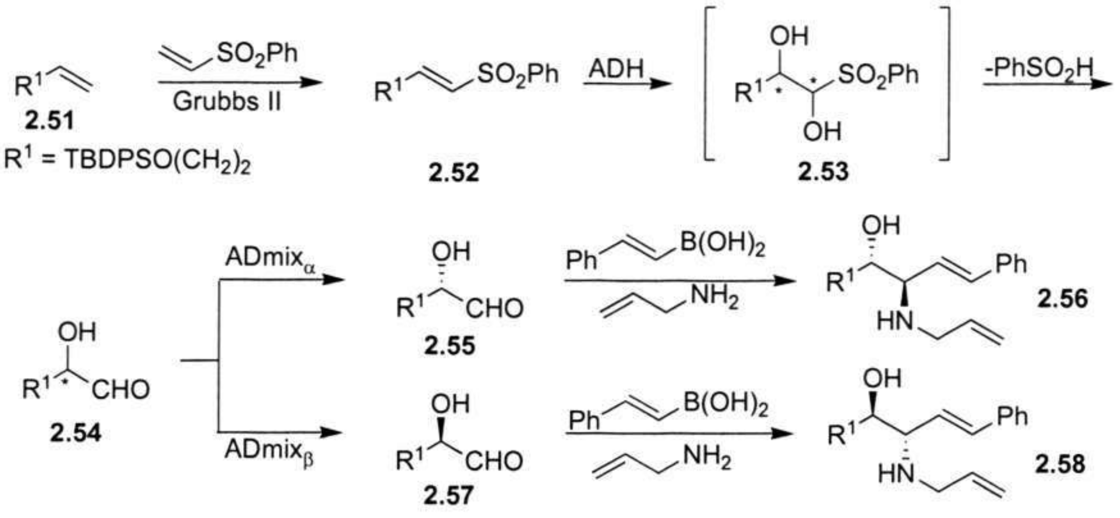
This was converted to the known *trans*-allylic alcohol (**2.40**) after protection as the PMB ether, then addition of the lithiated alkyne to *para*formaldehyde. Alkylation was then followed by Red-Al reduction of the propargylic alcohol in 72% over the three steps giving the alkene (**2.40**). Sharpless catalytic asymmetric epoxidation of the double bond using the (-)-diisopropyl tartrate gave the *(R,R)*-epoxy alcohol (**2.41**) in 52% yield, 92% ee. The free alcohol was then oxidized using either Swern or TPAP chemistry before a standard Wittig alkenation reaction gave the vinyl epoxide (**2.42**). Pyne then proceeded with the aminolysis of the vinyl epoxide (**2.42**). It has already been established that vinyl epoxides have the tendency to undergo regio- and stereoselective charge controlled ring opening at C(3) to give amino alcohols, this is a result of the alkene's π system to stabilize the charged transition state. Here the *trans* vinyl epoxide (**2.42**) underwent a nucleophilic opening at C(3) (allylic carbon) to give the *anti* amino alcohol (**2.43**). The conditions used were a variation on those of Somfai, where the vinyl expoxide in the presence of 10 equivalent of allylamine and a catalytic amount of tosic acid is heated in a sealed tube for 3 days at 105 °C.[79] These seemingly harsh conditions provided the *anti*-amino alcohol (**2.43**) as a single diastereoisomer in 88% yield. Protection of the amino functionality with Boc_2O, created a carbamate (**2.40**), which would not interfere in the subsequent metathesis reaction (Scheme 64).



Scheme 64. Pyne's 2002 total synthesis of (-)-swainsonine.

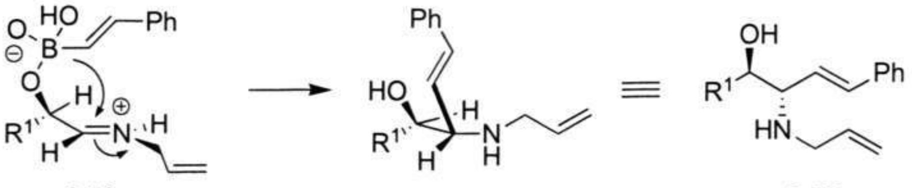
The ring closing metathesis reaction using Grubbs II catalyst at high dilution allowed for the formation of the 2,5-dihydropyrrole derivative (**2.45**), with an excellent yield of 94%. The secondary alcohol created from the aminolysis reaction was then protected as the benzyl ether (**2.46**). Reaction of the dihydropyrrole derivative with trifluoroacetic acid in the presence of a carbocation scavenger, anisole, gave the free amino alcohol (**2.47**) in high yield. The terminal alcohol was then turned into an excellent leaving group with the use of triphinylphosphine and carbon tetrabromide under basic conditions, prompting intermolecular *N*-alkylation to give the indolizidine core (**2.48**) in 74% yield. It was also noted that under these conditions a small amount, 5-10% of the pyrrole derivative of (**2.47**) appears as a minor byproduct. The indolizidine (**2.48**) was then transformed into the dihydroxy indolizidine, standard conditions of osmium tetraoxide and NMO gave poor selectivity. However Pyne reports that a twist of the classical Sharpless asymmetric dihydroxylation reaction using methanesulfonamide with AD-mix-α followed by functionalization of the dihydroxy groups as the acetates gave the triacetyloxy-swainsonine (**2.49**) in a very highly diastereoselective fashion (98:2), although it did require 7 days. Removal of the protecting group via catalytic hydrogenation and then base-catalysed methanolysis gave (-)-swainsonine (**2.1**), which was reported as particularly tricky to purify.

Pyne's second synthesis towards (-)-swainsonine created a similar *anti*-1,2-amino alcohol (**2.58**) but this time *via* the borono-Mannich reaction.[80] The synthesis this time starts with the formation of a vinyl sulfone (**2.52**) which was available from either a cross metathesis between a terminal alkene (**2.51**) and phenyl vinyl sulfone, or by iodosulfonation followed by elimination of HI (not shown). Sharpless asymmetric dihydroxylation of the vinyl sulfone (**2.52**) with either AD-mix-α or AD-mix-β could be achieved using a procedure devised by Evans.[81] In the Evans procedure an α-hydroxyl carbonyl (**2.54**) was created via the 1,2-elimination of a α-hydroxyl sulfone intermediate (**2.53**) appropriate choice of the AD-mix would then give you either the *R* or *S* α-hydroxyl aldehyde (Scheme 65).



Scheme 65. Pyne's borono-Mannich reaction.

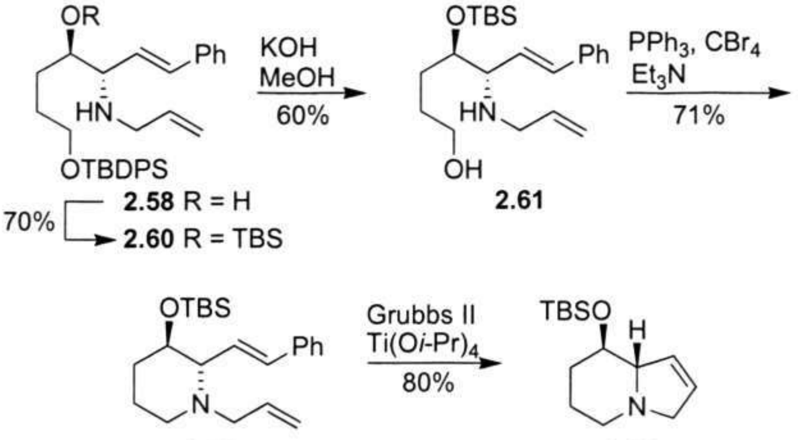
Then comes the key step the borono-Mannich reaction,[82] this one-step, three component reaction of an organoboronic acid, an amine and an α-hydroxy aldehyde. The method was said to be advantageous over the more common synthetic routes to amino alcohols such as the functional group interconversion in which amino acids and amino ketones are reduced, the hydroboration of enamines, the aminohydroxylation of olefins and the nucleophilic substitutions of epoxides, like the one used in Pyne's first (-)-swainsonine synthesis (Scheme 63). These routes often give poor stereoselectivity, require multiple steps and or require/only tolerate specific substituents. Yet the borono-Mannich procedure gives excellent diastereocontrol, with only *anti* products produced often with a d.e. greater than 99%. It was also noted by Petasis that when optically pure aldehydes are used the product is a single enantiomer with 99% ee or greater, the reaction is simple to implement requiring only mixing and stirring of the reagents which no special precautions such as an inert, water free atmosphere. Pyne uses the Petasis reaction with his α-hydroxy aldehyde (**2.57**), β-styrenyl boronic acid and allyl amine in CH_2Cl_2. The reaction takes place at room temperature over a period of 40 hours to give the *anti*-amino alcohol alkene (**2.58**) as a single diastereoisomer with a yield of 51% from the vinyl sulfone (**2.52**) and with enantiomeric purities greater than 90%. Pyne proceeded to further examine this reaction with a variety of amines and differently protected vinyl sulfones and noted that while the yields were only modest the conciseness of this procedure in providing the 1,2-amino alcohols in three steps greatly outweighs its deficiencies. The mechanism for this reaction is still of some contention, Pyne speculates a boronate intermediate in which the iminium ion (**2.59**) adopts a conformation which would minimize the 1,3-allylic strain (Scheme 66).



2.59 **2.58**

Scheme 66. Pyne's iminium ion minimises allylic strain.

The 1,2-amino alcohol diene (**2.58**) was then protected using TBS-OTf in the presence of the base 2,6-lutidine, selective removal of the primary TBDPS ether protecting group using potassium hydroxide in methanol under reflux was achieved in 60% yield to give the free primary amino alcohol (**2.61**). The free hydroxyl group of amino alcohol (**2.61**) was activated with triphenylphosphine and carbon tetrabromide in the presence of a base (Scheme 67).



2.58 R = H

2.60 R = TBS

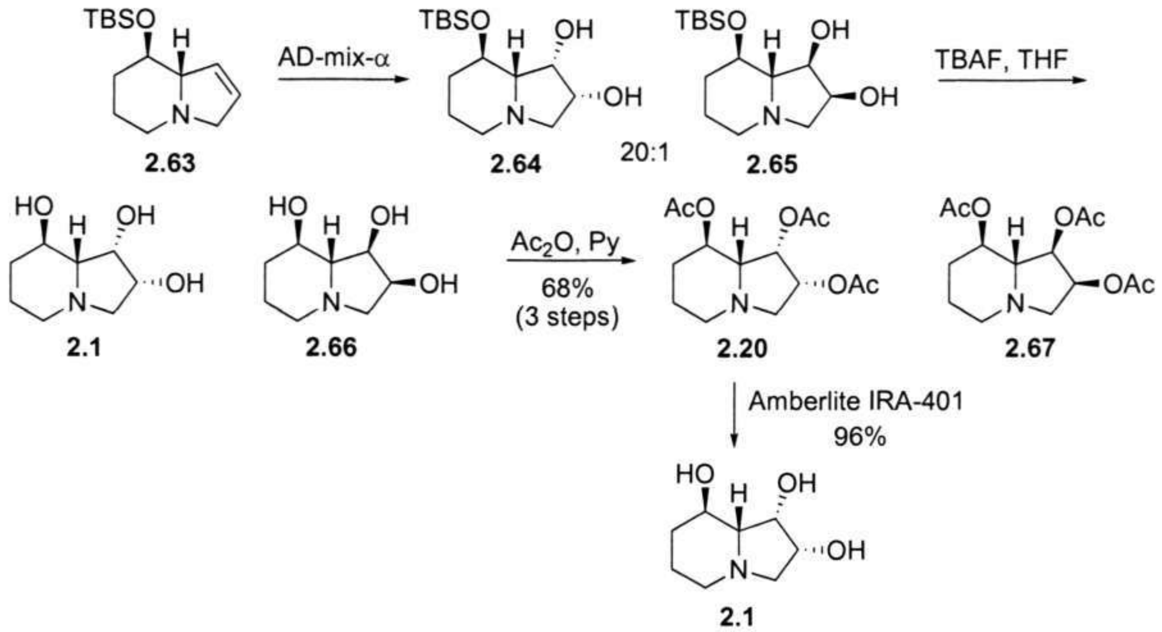
2.61

2.62

2.63

Scheme 67. Pyne completes the formal synthesis of (-)-swainsonine.

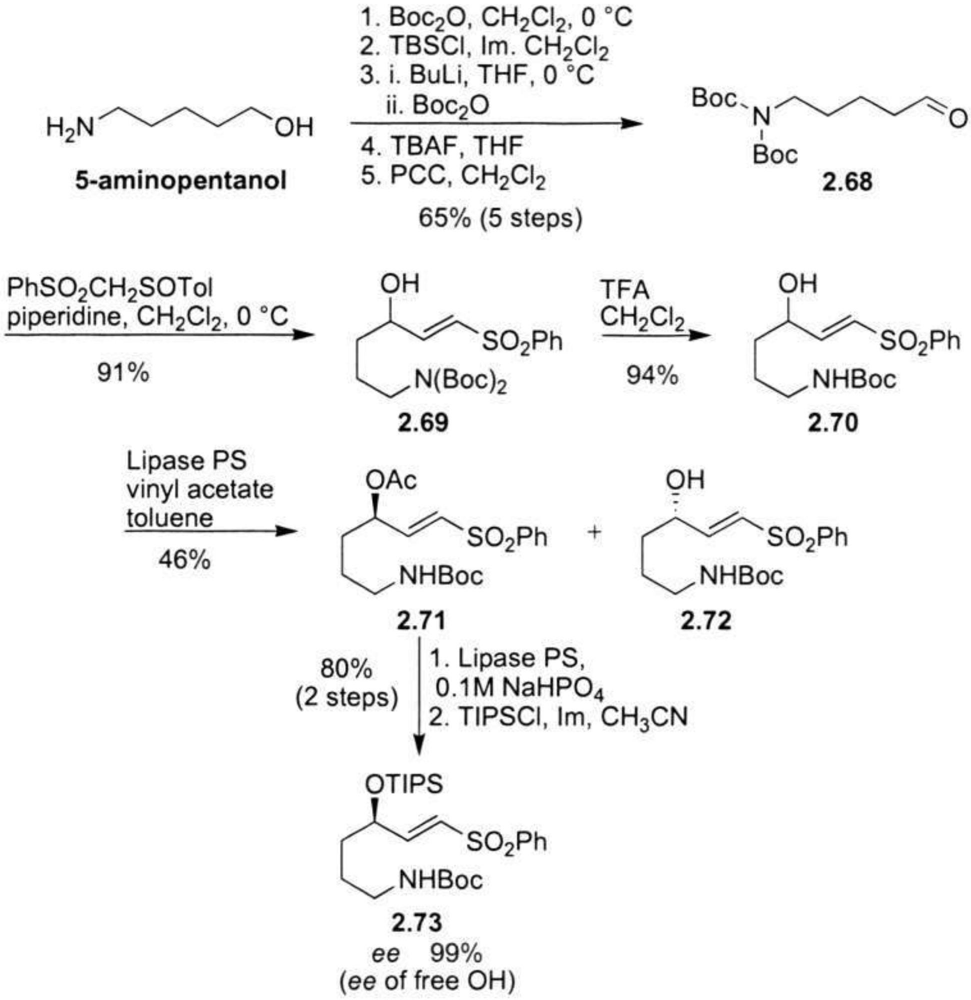
Under these conditions the intramolecular *N*-alkylation occurred to give the piperidine ring (**2.62**) in 71% yield. Ring-closing metathesis using Grubbs II catalyst in the presence of titanium tetraisoproporoxide, used as a Lewis acid to complex with the amino group gave the (8*R*,8a*S*)-8-(*t*-Butyldimethylsilanyloxy)-3,5,6,7,8,8a-hexahydro-indolizine (**2.63**), losing the superfluous phenyl group and creating a known intermediate from the synthesis of (-)-swainsonine by Blechert (Scheme 68).[83]



Scheme 68. From Pyne's intermediate to (-)-swainsonine.

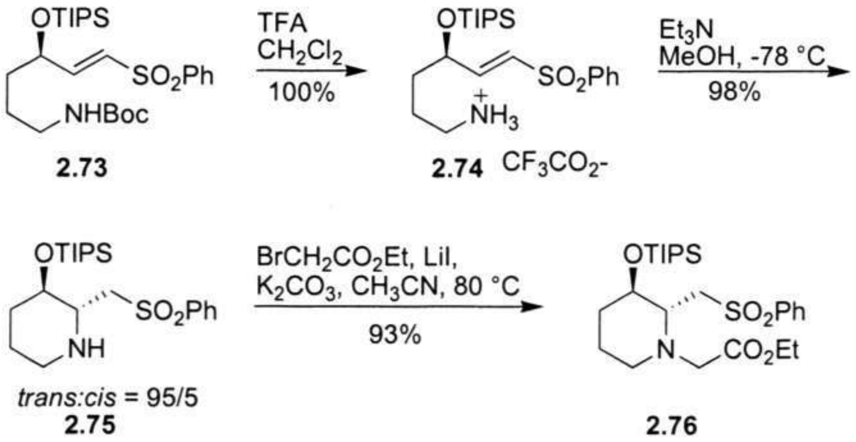
Blechert found that standard dihydroxylation with osmium tetroxide was also woefully inadequate, and so formed the *syn*-diols (**2.64**) by Sharpless asymmetric dihydroxylation with AD-mix-α as a 20:1 mixture of diastereomers. Isolation of the desired diastereomer (**2.1**) was only possible after removal of the silyl protecting group with TBAF and global acetylation under classical conditions. After separation, global de-acetylation was achieved very efficiently with amberlite IRA-401 resin in methanol to give (-)-swainsonine (**2.1**).

Carretero in 2000 published a stereodivergent route, which also started from a non-chiral source, 5-aminopentanal.[84] His synthesis introduced the stereocenter of C(8) with a Lipase PS (from *Pseudomonas cepacia)* enzymatic resolution of a vinyl sulfone (**2.71**). This vinyl sulfone was obtained from a di-Boc protected derivative (**2.68**) of 5-aminopentanal (Scheme 69).



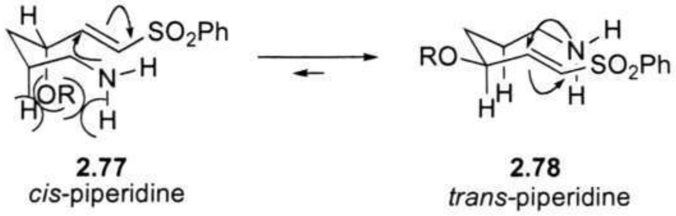
Scheme 69. Carretero's synthetic route.

Separation by column chromatography gave the desired sulfone (**2.71**), the acetate was then hydrolysed using the lipase enzyme and sodium phosphate. Protection of the free alcohol as the TIPS silyl ether was then required (**2.73**). This was necessary so as to provide a high level of selectivity in the subsequent cyclisation, where the stereochemistry of C(8a) was to be established (Scheme 70). The Boc protecting group was removed and under acidic conditions, this was followed by an intramolecular conjugate addition under basic conditions to give the piperidine (**2.75**) in 98 % yield as a 95:5 *trans:cis* mixture.



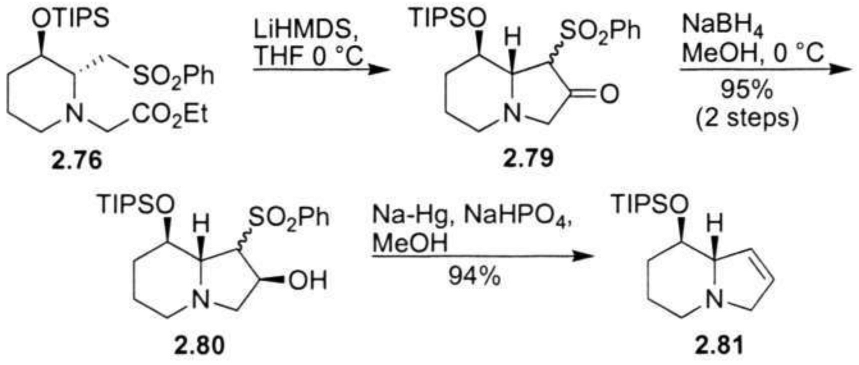
Scheme 70. Carretero's piperidine formation.

The mixture (**2.75**) was inseparable, however after *N*-alkylation the desired diastereomer (**2.76**) was separable and obtained in 93% yield. The high diastereoselectivity was attributed to the formation of the more favorable transition state (**2.78**) in which they postulate a possible NH sulfone interaction (Scheme 71).



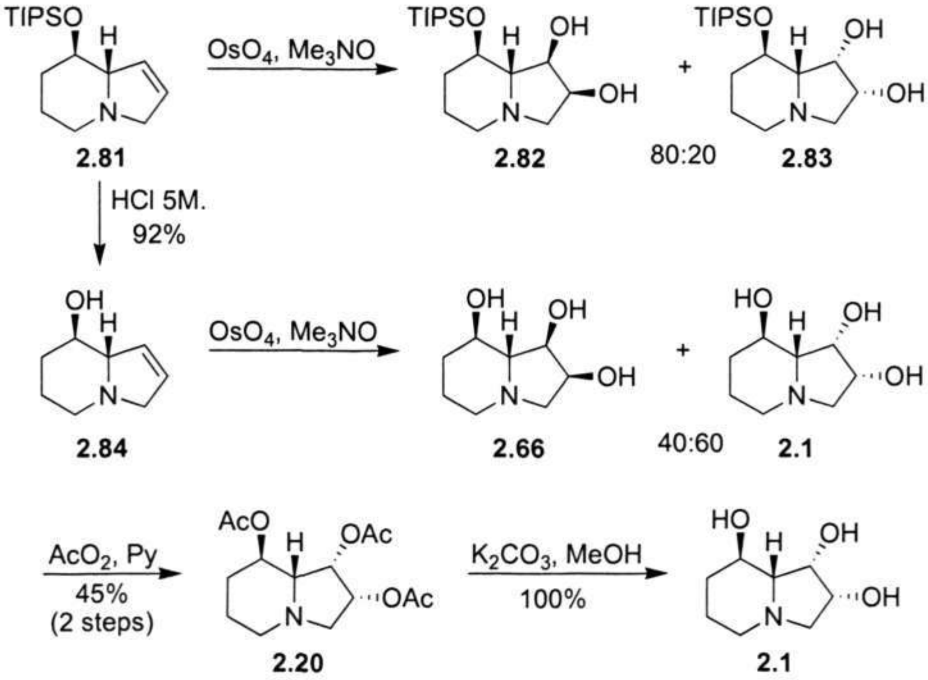
Scheme 71. Carretero's cyclisation mechanism.

The TIPS piperidine (**2.76**) was then converted into the indolizidine (**2.81**) in 3 steps (89% yield). The steps were intramolecular acylation to give a ketone (**2.79**) achieved by deprotonation α to the sulfone with LiHMDS. The ketone (**2.79**) was then reduced using $NaBH_4$ and the product (**2.80**) was desulfonylated with NaHg to give the unsaturated indolizidine core (**2.81**).



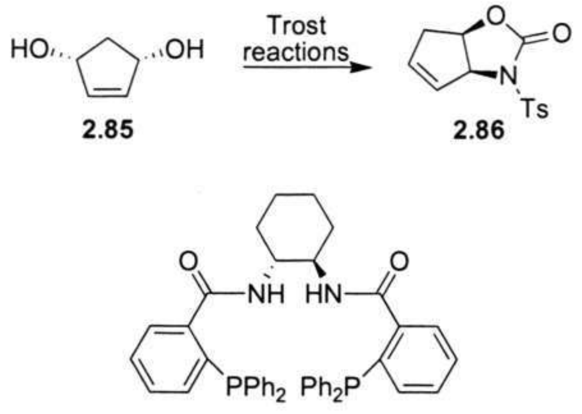
Scheme 72. Carretero's formation of the indolizidine core.

Syn-dihydroxylation of the indolizidine (**2.81**) was achieved using osmium *t*aoxide and Me_3NO directly giving an 80:20 mixture favoring the undesired *cis* product (**2.82**). However, deprotection followed by osmylation gave a 40:60 mixture favoring the *trans* product (**2.1**). Separation was only possible after global acetylation to give the triacetylated (-)-swainsonine (**2.20**), subsequent global deacetylation by basic hydrolysis then gave (-)-swainsonine (**2.1**) (Scheme 73).



Scheme 73. Carretero's completion of the total synthesis of (-)-swainsonine.

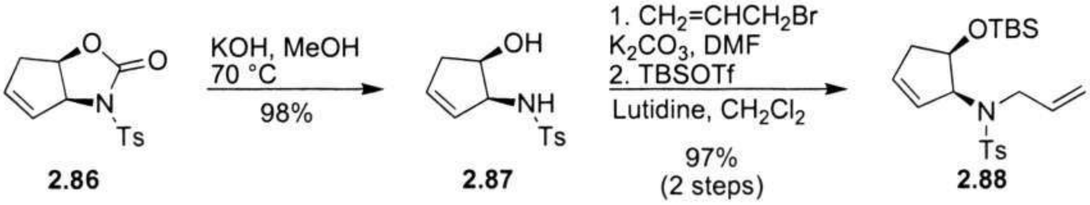
Blechert's synthesis of (-)-swainsonine utilized a ruthenium-catalysed ring rearrangement as the key transformation in which the C(8a) chiral centre is set.[85] His synthesis starts from the *meso*-diol (**2.85**) (Scheme 74).



Trost's Ligand.

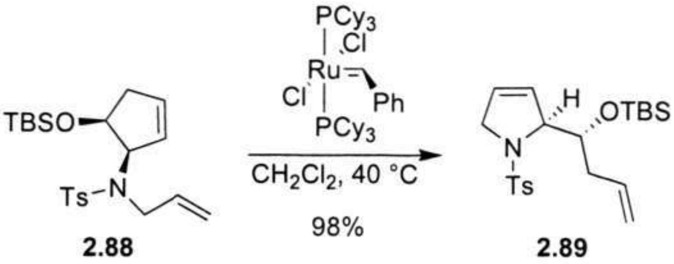
Scheme 74. Trost's reactions to give the oxazolidinone.

This *meso*-diol (**2.85**) was efficiently converted into the *meso*-biscarbamate (**2.86**) by the method of Trost,[86] which comprises of a difunctionalisation with a 2 fold excess of tosyl-isocyanate. The mixture was then treated with triethylamine and a solution of *tris*(dibenzylidineacetone)dipalladium(0)chloroform and Trost's ligand *N,N'*-(1R, 2R)-1,2-cyclohexanediylbis[2-(diphenylphosphino)benzamide], to form a π-allyl complex by loss of one of the carbamates. Lactonisation then occurs enantiodiscriminantly giving the oxazolidinone (**2.86**) in 97% ee, which was then increased to 99% ee by recrystalisation. The carbamate of the oxazolidinone (**2.86**) was then hydrolysed with a base, the free amine (**2.87**) was then *N*-alkylated and the hydroxyl group was protected as a TBS-ether (**2.88**).



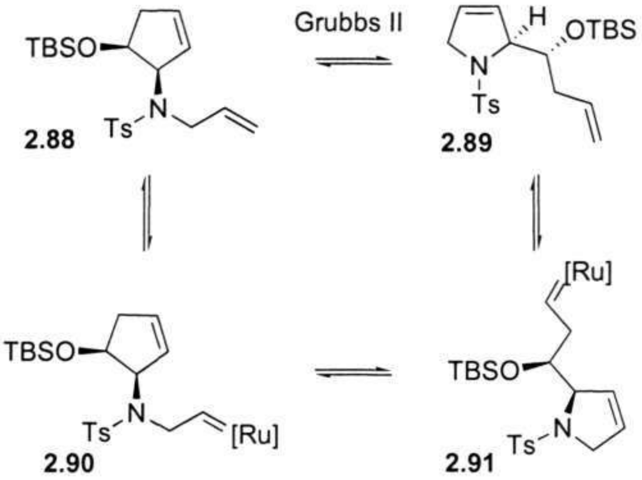
Scheme 75. Blechert's synthetic route to (-)-swainsonine.

Now the key reaction could take place (Scheme 76), the ruthenium catalysed metathesis rearrangement converted the cyclopentene (**2.88**) into the dihydropyrrole (**2.89**).



Scheme 76. Blechert's key cyclisation step.

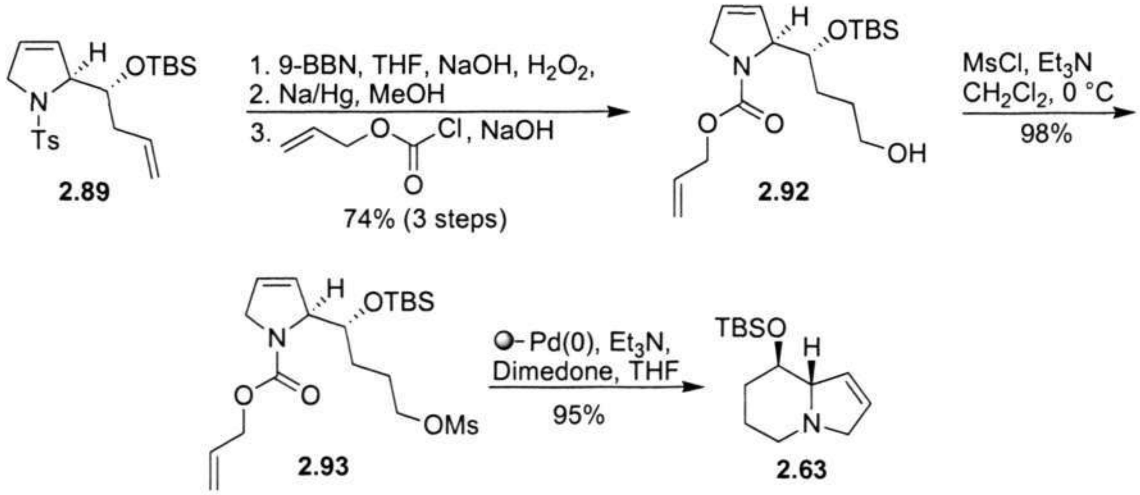
The reaction mechanism can be explained by reaction of the cyclopentene (**2.88**) with Grubbs II catalyst. The ruthenium attacks the terminal alkene creating a ruthenium carbene complex (**2.90**). Intramolecular formation of a metallacyclobutane with the *endo*cyclic double bond was followed by a [2+2] cycloreversion and this out competed the rate of dimerization (reaction with another **2.88** unit), to give complex (**2.91**). The reaction then finishes with reaction of (**2.91**) with another (**2.88**) unit, depending on the regioselectivity this can either give the desired dihydropyrole (**2.89**), by methylene transfer, or an undesired product formed due to cross metathesis (Scheme 77). Which has been found to be dependent on the size of the protecting group on the hydroxyl group.[87]



Scheme 77. Blechert's ruthenium catalysed metathesis rearrangement mechanism.

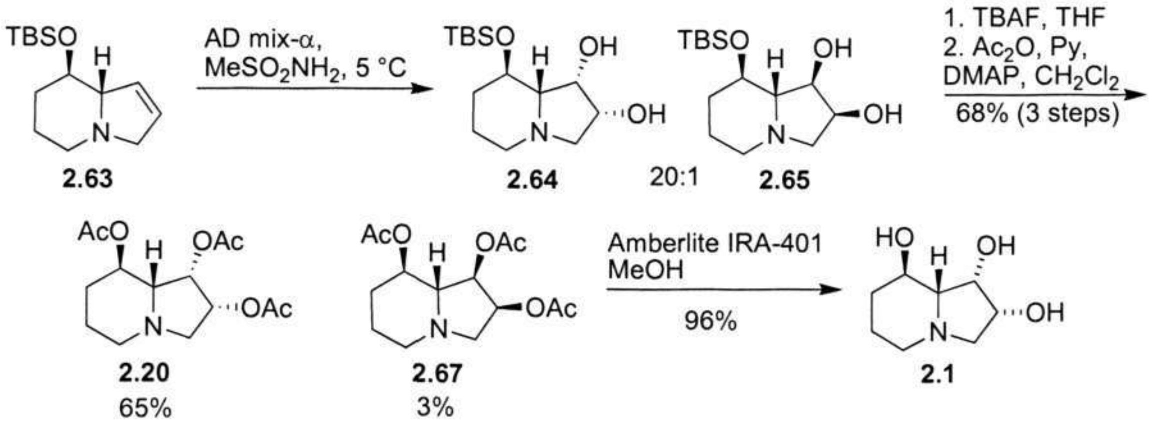
For instance, when the smaller benzylether derivative of (**2.88**) was used the equilibrium did not favor the product (benzyl ether derivative of **2.89**) and the ratio of starting material to product was 18:1. Unlike standard metathesis reactions here the driving force is not the liberation of ethylene, but the difference in enthalpy of the product and the starting material. Which in the TBS example (**2.88** to **2.89**) was mainly due to the loss of ring strain as a result of steric interaction between the *cis* TBS and the tosyl protected N-allyl groups in (**2.88**). The benzyl ether derivative of (**2.88**) does not have a large amount of ring strain, as the benzyl group is much smaller, therefore the reaction is not driven towards the benzyl ether derivative of the product.

The 6-membered ring was then to be installed, hydroboration of the alkene (**2.89**) gave the free alcohol, but only after all of the ruthenium residue had been removed. This was accomplished by treatment with lead tetraacetate. Standard chromatography was insufficient in removing the ruthenium and led to decomposition during hydroboration.



Scheme 78. Blechert's indolizidine synthesis.

Deprotection of the amine and subsequent attempts to activate the alcohol *in situ* were ineffective. Instead the free amine was functionalised as the allyloxycarbamate (**2.92**), the alcohol was then activated as the mesylate (**2.93**). Treatment then with polymer supported palladium(0) catalyst allowed for deprotection of the amine and subsequent displacement of the mesylate to give the indolizidine (**2.63**) in 95%.



Scheme 79. Blechert completes the total synthesis of (-)-swainsonine.

Now all that remained was the dihydroxylation (Scheme 79), however, they found this to be rather tricky. Treatment with osmium tetraoxide and NMO was not as efficient as expected giving no selectivity. Instead, they turned their attention to a Sharpless asymmetric oxidation using AD-mix-α. This gave access to the desired *syn*-diol (**2.64**) as a 20:1 mixture of diastereomers. Isolation of the desired diastereomer was only possible after desilylation and global acetylation (**2.20**). Subsequent removal of the acetyl groups was again achieved with amberlite IRA-401 resin giving (-)-swainsonine (**2.1**).

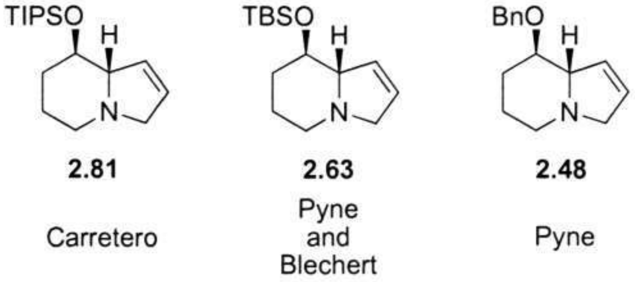
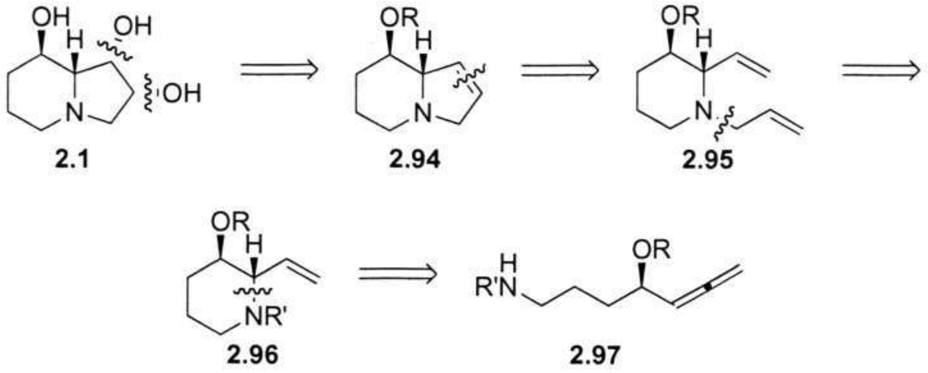


Figure 9. Unsaturated indolizidine structures as targets for the Formal synthesis of (-)-swainsonine.

Within this introduction we have reported the three unstaturated indolizidine cores (**2.81**, **2.63**, **2.48**), that differed only by the hydroxyl protecting group. While all three have been successfully converted into (-)-swainsonine (**2.1**), most efficiently by Pyne (Scheme 64), all three authors noted that the *syn*-dihydroxylation was particularly tricky. Mukai *et. al*. reported the formation of the desired polyhydoxylated indolizidine with a diastereoselective ratio of 88:22,[88] using classical osmium tetraoxide-NMO conditions, however, Blechert only obtained a 58:42 ratio of diastereomers favouring the desired compound (**2.64**) under the same conditions. Carretero reported that his TIPS protected indolizidine (**2.81**) favoured the undesired *syn*-polyhydroxyindolizidine (**2.82**) with an 80:20 ratio, while Pyne's Bn protected indolizidine (**2.48**) only gave a 2:1 mixture favouring the desired diastereoisomer, under the standard conditions. Pyne did overcome this using the Sharpless asymmetric dihydroxylation with methanesulfonamide and AD mix-α, giving the triacylated (-)-swainsonine (**2.49**) in a 98:2 fashion, the reaction did require a long reaction time, but elegantly solved the issue of dihydroxylation. As such we see these three indolizidine cores as very attractive formal synthesis targets (Figure 9).

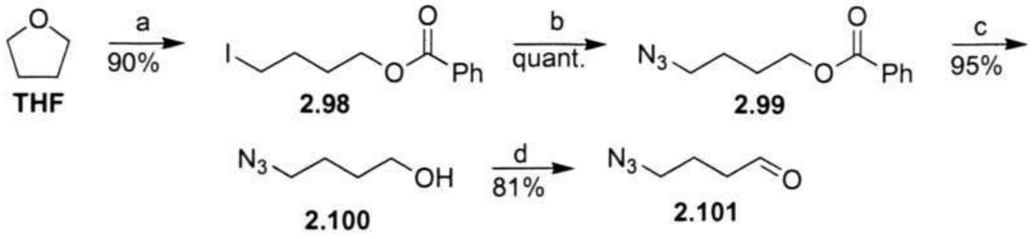
Chapter 2: A Formal synthesis of (-)-Swainsonine

Retrosynthetic Analysis



Scheme 80. Retrosynthetic analysis.

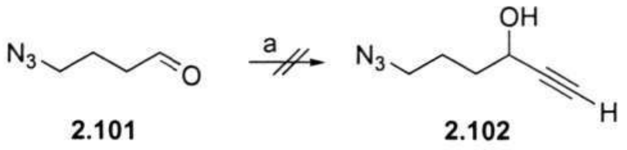
Our retrosynthesis for (-)-swainsonine (**2.1**) would use the known diastereoselective *cis*-dihydroxylation reaction with AD-mix-α to install the *cis*-dihydroxyalcohols from the (8*R*,8a*S*)-8-(protected-hydroxy)-2,3-dehydroindolizine (**2.94**). This has already been demonstrated by Pyne and therefore his TBS-indolizidine (**2.63**) would be used as a target for a formal synthesis. This indolizine core (**2.94**) could be prepared by a ring-closing metathesis reaction of the piperidine diene (**2.95**). The piperidine would then be prepared from the as yet unexplored cyclisation of the pendant amine on to an allene moiety (**2.97**). The main challenge in the synthesis is the cyclisation, as it can occur on either of the allene double bonds. The metal catalyst used to activate the alkene can also co-ordinate to either side of the double bond. As such the allene cyclisation could give rise to a mixture of products of various ring sizes, and as a mixture of diastereoisomers.



Reagents and conditions: (a) BzCl, NaI, CH_3CN. (b) NaN_3, DMF. (c) LiOH, $THF{:}H_2O{:}MeOH$. (d) IBX, DMSO.

Scheme 81. Preparation of 4-azidobutanal.

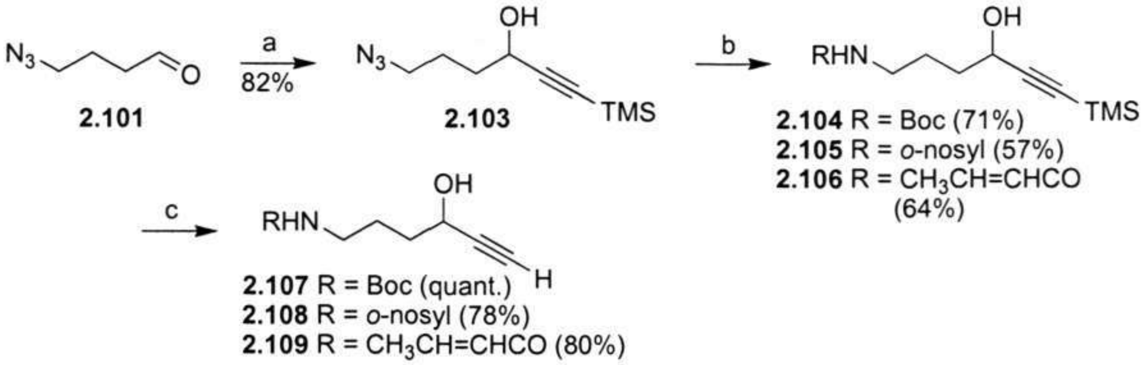
To furnish the allene alcohol (**2.97**) the first step in our synthesis was the ring opening of THF, this is an unusual starting material that we find to be heavily underutilized as it is a valuable source of 1,4-difunctionalisable material. Under the prescribed conditions of Oku, using benzoylchloride, it is thought that the iodide nucleophile attacks the O-C bond after protonation by a trace amount of HCl formed *in situ.*[89] This occurs to provide us with a 4-iodobutyl benzoate (**2.98**) in a high 90% yield with no need for further purification, the product can then be easily manipulated. The iodide was displaced with sodium azide in a nucleophilic manner providing the 4-azidobutyl benzoate (**2.99**), once again with a high yield of 98% and without need for purification. The azide was clearly observable in IR spectrum, with a distinctive peak at 2095 cm^{-1}. The benzoyl ester was then saponified under standard conditions to give the alcohol (**2.100**) as a colourless oil in near quantitative yield, again without need for any further purification. The hydroxyl functionality was clearly observable in IR spectrum at 3340 cm^{-1} and as a singlet at 1.88 ppm in the ^1H NMR spectrum. We had now rapidly gained access to multigram quantities of the alcohol (**2.100**), and after simple oxidation our synthesis would show a great level of possibilities for divergence. A variety protocols exist for oxidation of primary alcohols as discussed in Chapter 1, the first method of oxidation used the easily prepared reagent 2-iodoxybenzoic acid (IBX). Oxidation of the alcohol (**2.100**) occurred in 3.5 hours in the moderate yield of 70%, under the procedure of Santagostino (Scheme 81).[90] Looking to improve the yield we examined other common oxidizing agents such as pyridinium dichromate (PDC). This is a milder oxidizing agent and on oxidizing alcohol (**2.100**), we found that the work up procedure for this oxidizing agent was much more tedious than that of IBX, giving a black tar like compound, whilst also failing to provide the aldehyde (**2.101**) in a higher yield. Another method of oxidation used the Ley-Griffith reagent *tetra*-n-propylammonium perruthenate (TPAP).[91] Here a catalytic amount (20 mol%) of TPAP and NMO gave a mixture of starting material and desired aldehyde, purification by distillation gave the desired aldehyde (**2.101**) in a low yield of 53%, but did allow for recovery of the starting material alcohol. No oxidant is universally acceptable and it appears that the desired compound is only available in moderate yields, therefore it is comes down to the reagent of choice for the researcher. Taking into consideration the ease of reaction and work up, highest obtainable yield and partially the cost effectiveness of performing the reaction, the reagent of choice here was IBX. This gave the desired aldehyde (**2.101**) in 70% yield after a simple aqueous workup and purification by distillation, when required. The aldehyde (**2.101**) was obtained as a colourless oil and stored at -78 °C until required, this was as a precaution as azides are notoriously unstable and also as aldehydes are susceptible to oxidation.



Reagents and conditions: (a) *t*-BuOK, acetylene, THF

Scheme 82. Initial attempt at preparing the α-hydroxyacetylene.

The next step in our synthesis was the preparation of the α-hydroxyacetylene (**2.102**), many laboratory methods exist for preparing such compounds,[31] two methods attracted our attention mainly due to the readily availability of the reagents to us. The first method involved addition of excess acetylene into a solution of *t*-BuOK in THF at 10 °C (Scheme 82), and subsequent addition of aldehyde (**2.101**).[92] The active intermediate being a potassium acetylide, yet under the prescribed conditions no reaction with aldehyde (**2.101**) was observed.



2.101

2.103

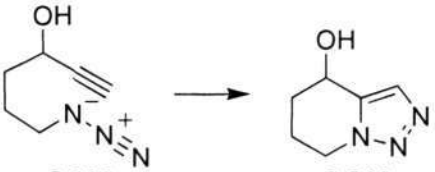
2.104 R = Boc (71%)
2.105 R = *o*-nosyl (57%)
2.106 R = $CH_3CH=CHCO$ (64%)

2.107 R = Boc (quant.)
2.108 R = *o*-nosyl (78%)
2.109 R = $CH_3CH=CHCO$ (80%)

Reagents and conditions: (a) *n*-BuLi, TMS acetylene, THF. (b) (i) Zn, AcOH, THF. (ii) Boc_2O/nsCl/crotonylCl, Na_2CO_3, CH_2Cl_2 (c) K_2CO_3, MeOH.

Scheme 83: Revised preparation of α-hydroxyacetylene.

The second procedure was the formation of a lithium acetylide, as demonstrated in the diol series previously. This could be performed using acetylene dissolved in THF and subsequent addition of *n*-BuLi, but due to our poor yield obtained from the diol series, most probably due to the instability of the complex, we chose to forgo this for the more stable lithium TMS-acetylene complex (Scheme 83). Prepared by addition of *n*-BuLi to a -78 °C solution of trimethylsilylacetylene in THF, followed by subsequent addition of the precooled aldehyde (**2.101**). The reaction proceeded cleanly in a few hours giving only the α-hydroxyacetylene (**2.103**) in 82% yield. The alkyne was not clearly observable from the IR spectrum as it has a similar wavenumber as that of the azide and it is thought they both occupy the same frequency at 2096 cm^{-1}, but it was clearly apparent in the ^{13}C spectrum at 105 and 90 ppm.



2.102

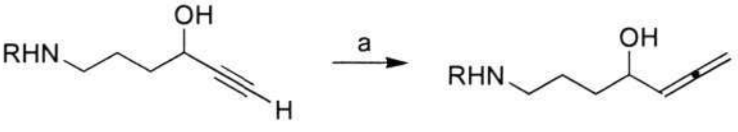
2.210

Scheme 84. Formation of 1,2,3-triazoles.

α-Hydroxyacetylene compounds such as (**2.102**) with the pendant azide show a propensity to undergo a 1,3-dipolar cycloaddtion reaction with terminal alkynes (Scheme 84), this reaction when carried out in the presence of Cu(I) is known as click chemistry,[93] but more formally as the azide-alkyne Huisgen cycloaddition to give 1,2,3-triazoles (**2.210**). [94] To prevent such decomposition of our α-hydroxyacetylene (**2.103**), the compound was stored at -78 °C until required and as such we have never encountered any of the 1,2,3-triazole.

With the versatile α-hydroxyacetylene (**2.103**) in hand the azide reduction could now be explored. Reduction to give the free amine could have been performed, but due to the polarity and with regards to the questionable purity of the compound after the subsequent reactions this would have been unwise. Therefore reduction and protection would be the most advantageous. One of the simplest procedures to do such is the one-pot, sequential, zinc and acetic acid reduction, then basic protection.[95] These reaction conditions tolerate a range of protecting groups giving easy access to a number of protected amines. The most common methods for the protection of amines are as *N*-sulfonyl derivatives, *N*-alkyl derivatives and *N*-acyl derivatives of which the carbamates were of most interest. Hence we chose an example of each depending on the availability of reagents. Initial studies looked at the use of *t*-butyloxycarbonyl (Boc) (**2.104**), *ortho*-nitrobenzenesulfonyl (nosyl) (**2.105**) and crotonyl (crotyl) (**2.106**) derivatives, they were prepared in 88, 64 and 77% yields, respectively, after silica gel purification. The advantage of nosyl protection over the more common tosyl was that whilst being stable to both strongly basic and acid conditions it can be removed easily with thiols. The desired compounds were clearly identifiable from their proton and carbon NMR spectra with the nosyl (**2.105**) observed as three multiplets at 8.14, 7.86 and 7.73 ppm, the crotyl (**2.106**) by the doublet of triplets at 6.83 ppm and the doublet at 5.77 ppm corresponding to the double bond and the Boc (**2.104**) due to the singlet at 1.44 ppm. All three showed a notable change in their IR spectra with the loss of the strong azide band of the α-hydroxyacetylene (**2.103**) at 2096 cm^{-1}. In its place was a significantly reduced in % transmittance weak band at 2171 cm^{-1}, which is consistent with that of an internal alkyne. The carbonyl of the Boc (**2.104**) and crotyl (**2.106**) compounds were also observed in the IR speactra at 1701 and 1672 cm^{-1} respectively. The subsequent reaction was the removal of the TMS functionality (Scheme 83). Hurst and McInnes championed the methanolysis of trialkyloxisilanes,[96] there method of cleavage was applied to the TMS alkynes (**2.104**, **2.105** and **2.106**), giving the terminal α-hydroxyacetylene (**2.107**, **2.108** and **2.109**) in 80% to quantitative yields, with incredible simplicity and without the need to use a toxic reagent like KCN, or an expensive silver reagent that had often been used previously.[97,98]

The next step in the synthesis required the conversion of the alkyne moiety into the allene. Allenes have become exceptionally interesting compounds as they allow access to structurally challenging and biologically active molecules, this has been possible due to the development of efficient methods of preparation, since the initial notion that the 1,2-diene moiety would be unstable.[30] An upto date review of preparation methods is available,[29] but within the group the particular method of Searles and Crabbé has stood the test of time and always proved to be efficient (Scheme 85).[99]

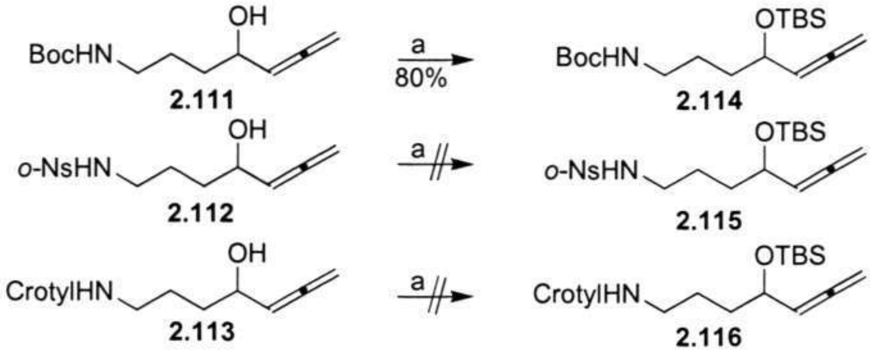


2.111 R = Boc (99%)
2.112 R = *o*-nosyl (74%)
2.113 R = $CH_3CH=CHCO$ (76%)

Reagents and conditions: (a) CuBr, *i*-Pr_2NH, $(CH_2O)_n$, Dioxane.

Scheme 85. Searles Crabbé procedure.

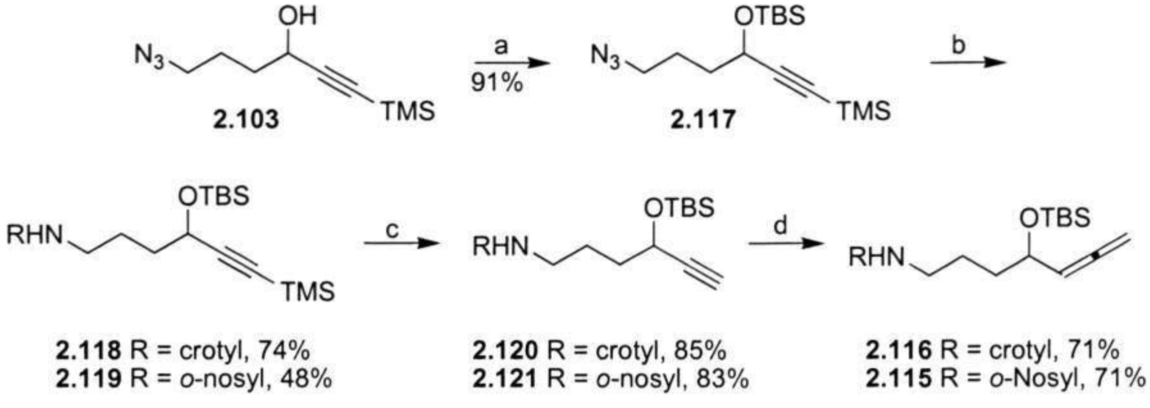
Their method, which was developed in 1979 has been applied many times in the formation of monosubstituted allenes from terminal alkynes, and is effectively a copper based variation of the Mannich reaction (see page 28). Here the Boc protected allene (**2.111**) was most efficiently produced in 90% yield. Whilst the nosyl (**2.111**) and crotyl protected allenes (**2.113**) were produced only in moderate yields. The allene moiety was distinctive in its appearance under standard spectroscopic methods, with an IR wavenumber of around 1950 cm^{-1} and with characteristic ^{13}C NMR peaks at 206.9 and 156.3 ppm for the central and terminal carbons of the allene, respectively.



Reagents and conditions: (a) TBSCl, Imidazole, DMAP, THF

Scheme 86. Protection of the secondary alcohols.

Protection of the secondary alcohol as the TBS ether was then attempted (Scheme 87). Many methods for this protection exist, the most standard being the use of TBSCl and imidazole in THF. Under these conditions the secondary alcohol of the Boc allene (**2.111**) was cleanly protected in 80 % yield after silica gel purification, the secondary alcohols of nosyl (**2.112**) and crotyl (**2.113**) allenes, however failed to protect under these conditions.



Scheme 87. Revised route for the formation of the silylhydroxy allenes.

With this problem a brief review of our synthesis suggest that the most efficient method would be protection prior to the reduction of the azide (**2.103**), from where the synthesis diverges (Scheme 87). The α-hydroxyacetlyene (**2.103**) was conveniently protected in

91% yield, and subsequently reduced in the same manner as before to prepare the silylated nosyl (**2.119**) and crotyl (**2.118**) amides. The TMS protecting group was then removed and homologation of the alkyne proceeded smoothly providing the TBS ether protected allenes (**2.115**) and (**2.116**).

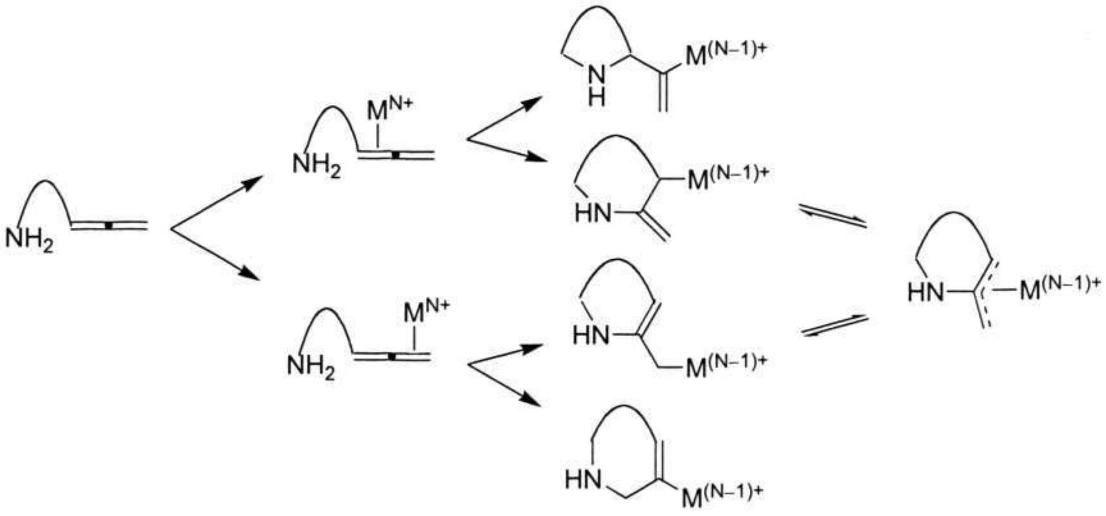
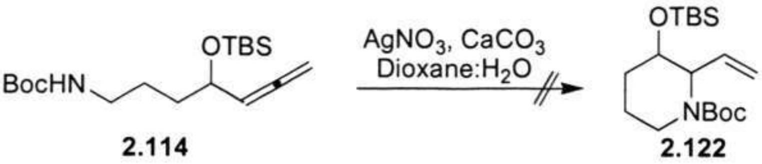


Figure 10. Allene amide cyclisation issues.

The cyclisation of allenes with pendant nucleophiles can be achieved under a variety of conditions, utilizing a large range of transition metals (Figure 10).[37] Lee and co-workers demonstrated the cyclisation of 4-(1-methylallenyl)-2-azetidinone derivatives with gold(III) chloride in pure CH_2Cl_2 to give bicyclic β-lactams,[100] Ibuka and co-workers have demonstrated the formation of 2-alkenylaziridines from amino allenes.[101] Dieter showed the formation of pyrrolines from amino allenes using both palladium and silver,[102] while Gallagher has used a range of catalysts to trigger allenic amide cyclisation,[103,104,105] including Hegedus carbomethoxylation conditions. Bates has also reported the cyclisation of allenes on treatment with acetyltetracarbonylcobalt.[106]

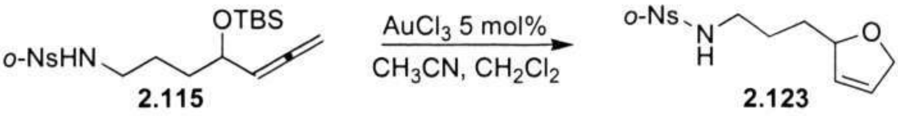
When examining the possible catalysts it is logical to examine those that are most easily available and trivial to use, many cyclisation examples exist using silver salts, the first reported example used silver nitrate, its electrophilic nature means it has a good affinity for unsaturated C=C double bonds, thus enabling cycloadditions. This was our first choice of reagent.



Scheme 88. Silver cyclisation.

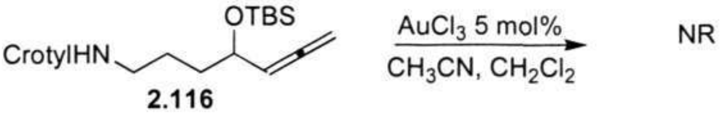
Reaction of the Boc allene (**2.114**), with silver nitrate and calcium carbonate in aqueous dioxane, and in the absence of light, standard conditions reported for such cyclisations failed to provide us with any cyclised piperidine (**2.122**). Instead we recovered starting material even after warming the reaction mixture. This is an identical result to that of the previously described alcohol equivalent (Table 3), it appears that silver(I) is not sufficient in activating the double bonds of our allenes to allow the pendant nucleophile to attack, this could be due to the α protected alcohol being too bulky, or due to the unfavorability of the 6-*exo* cyclisation, or maybe it was just insufficiently activation of the double bond. We should also note that it could also have been the low nucleophilicity of the *N*-Boc group. The bulky hydroxyl blocking access to the alkene and ring size arguments seem unlikely as the unprotected α-hydroxyl allene readily cyclises and the 6-*exo*-cyclisation would be favored under Baldwins rules. We now believe that a stronger electrophile is required, once again our attention was caught by another noble metal, this time gold.

Hashmi, a noted authority in gold catalysis, reports that by far the most common reactivity pattern in gold-catalysed organic reactions is that of nucleophilic additions to C=C multiple bonds, which are efficiently activated, the majority of examples exist with alkynes but allenes are no exception.[107] The only gold species immediately available was gold(III) chloride.



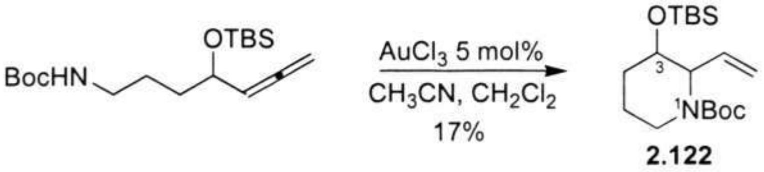
Scheme 89. Allene cyclisation

Reactions with $AuCl_3$ are often carried out in the presence of acetonitrile so as to allow for solvation of the gold. Our initial reaction conditions therefore used 1 equivalent of CH_3CN in CH_2Cl_2 (0.5M), and the reactions were carried out under an inert atmosphere of nitrogen with 5 mol% of $AuCl_3$. The nosyl allene (**2.115**) reaction proceeded with extensive decomposition yielding only a trace of compound that bore no comparison to that of the desired piperidene and with little recovery of starting material. Elucidation of the structure of the unknown product was trivial, as from the analogous diol series we knew that the cyclisation of the free secondary alcohol occurs readily giving the dihydrofuran. The ^1H NMR clearly shows the presence of the nosyl protecting group, absence of the allene, and the presence of four peaks, a one proton multiplet at 5.87, a two proton multiplet at 5.68, a one proton broad singlet at 4.80 and a two proton multiplet at 4.59 ppm. These peaks can be convincingly attributed to the formation of a similar dihydrofuran (**2.123**) as that of the analogous diol series.



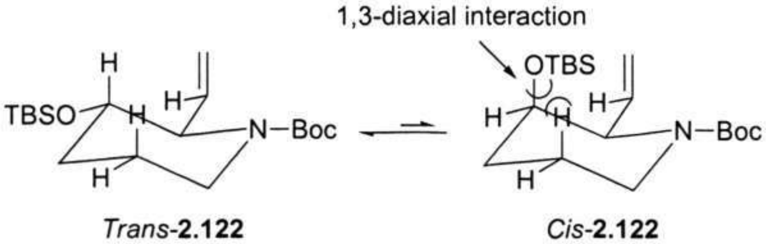
Scheme 90. Allene cyclisation

The crotyl allene (**2.116**) showed no reaction under the prescribed conditions providing recovery of severely decomposed starting material. The Boc allene (**2.114**) however showed great prospects. The reaction yielded two products, recovered starting material in 14% and a compound that resembled what we expected to be the desired piperidene in 17% yield.



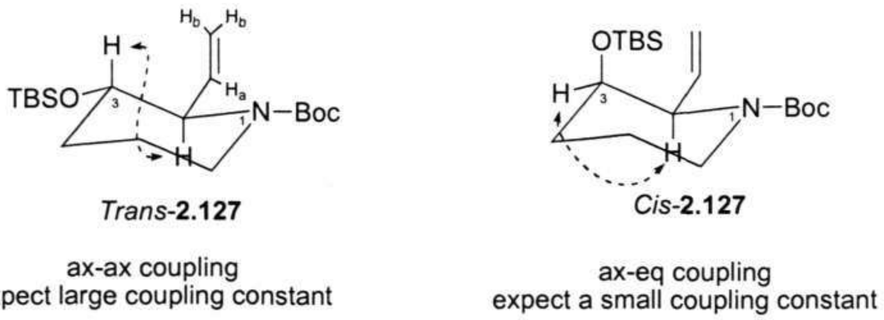
Scheme 91. Allene cyclisation.

The desired piperidine (**2.122**) was identifiable from the doublet of doublet of doublets at 5.72 ppm and the two doublets of triplets at 5.18 and 5.09 ppm. These two peaks were characteristic of the external double bond formed by cyclisation onto the internal double bond of the allene. The product was observed as a single diasteroisomer, elucidation of the stereochemistry and confirmation of our assignment was possible from the COSY and NOE NMR spectra. First we considered the most probable chair conformations, which are shown (Scheme 92). We assumed that the *trans* conformation of the piperidine **(2.122)** would be the most stable, as it would have minimal steric interactions. We also assumed the silyl protecting group would prefer to be in an equatorial position, both of these together mean a minimal 1,3-diaxial interaction. We then used the COSY spectrum to assign and support our initial assumption of the *trans* product.



Scheme 92. Proposed most stable chair conformation.

From the COSY NMR spectrum we were able to fully assign our ^{1}H NMR spectrum, the allylic protons were the most obvious to assign as the doublet of doublet of doublets at 5.72 ppm and two doublet of triplets at 5.18 and 5.09 ppm. We observe allylic coupling with the broad singlet at 4.64 ppm, which must therefore be the proton at C(2). The proton of C(2) couples as expected to the proton of C(3), which was observed as a quartet at 3.85 ppm. This proton of C(3) couples to one of the C(4) protons at 1.58 ppm. From the proton of C(4) we were able to assign one of the C(5) protons as the multiplet at 1.92 ppm, this then coupled to the broad doublet at 4.02 ppm and the double triplet at 2.81 ppm which are the protons of C(6). The proton now at 1.48 ppm would be the other proton on 5, and therefore couples as expected to the proton of C(6) at 2.81 and the other proton of C(5) at 1.92 ppm.



Trans-**2.127**

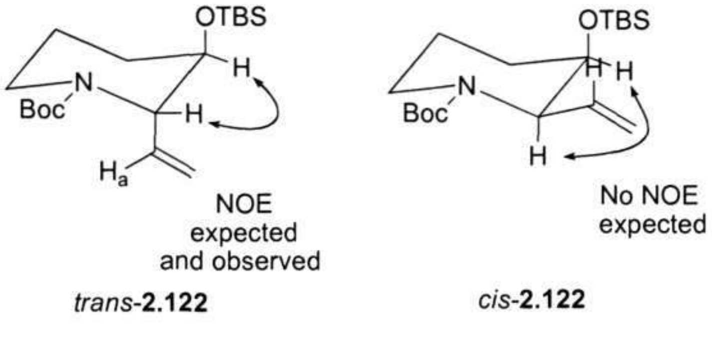
ax-ax coupling
expect large coupling constant

Cis-**2.127**

ax-eq coupling
expect a small coupling constant

Scheme 93. Coupling constant assignment.

On examination of the coupling constants (Scheme 93), if the silyl ether and alkene of (**2.127**) were *cis* to each other a small coupling constant should be observed between the protons of C(2) and C(3). While if they were *trans* a large coupling constant with a magnitude of 10 Hz was expected. However both these protons were observed as broad singlets and as such no NMR coupling constants were available. We then examined the coupling observed between the protons of C(2) and the alkene. From the COSY NMR spectrum we observed a cross peak between the proton of C(2) and the proton of C(3). The proton of C(2) coupled with the alkene proton H_a, but H_a does not couple to the proton of C(3). We explain this missing coupling by assuming a dihedral angle of 90° exists, which would suggest the vinyl and silyl group are *trans* as shown (Scheme 94).

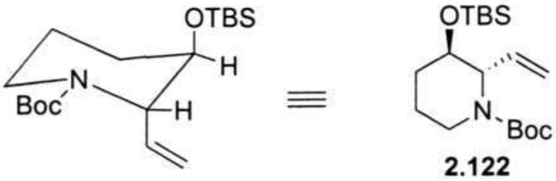


trans-**2.122**

cis-**2.122**

Scheme 94. Structural assignment *via* NOE.

NOE studies support the *trans* arrangement, as irradiation of the proton of C(2) resulted in an enhancement of the signal for the proton of C(3). Indicating that these protons are likely to be *cis* di-equatorial (Scheme 94). This would indicate that both the vinyl and silyloxy groups would be axial. Although this is at first counter intuitive, this axial effect, due to A-strain with the N-substituent has been reported and explored by Martin.[108] Irradiation of the proton on C(3) has minimal effect on the proton of C(2)

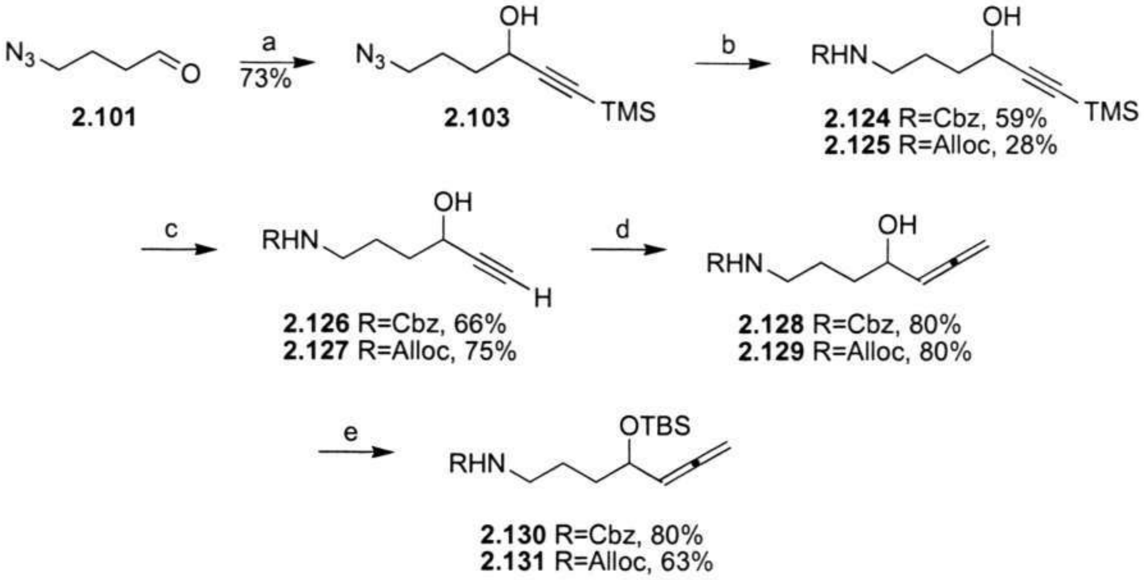


2.122

Scheme 95. Reassignment of the chair conformation as diaxial.

The *trans* stereochemistry was subsequently confirmed by the synthesis of the indolizidine (**2.63**) which correlated directly to that of Pyne's. It could also be inferred by the distinctive similarity of the NMR spectrum obtained here and the NMR spectrum of nosyl piperidine (**3.22**) obtained in Chapter 3, for which we were able to obtain an X-ray crystallographic structure.

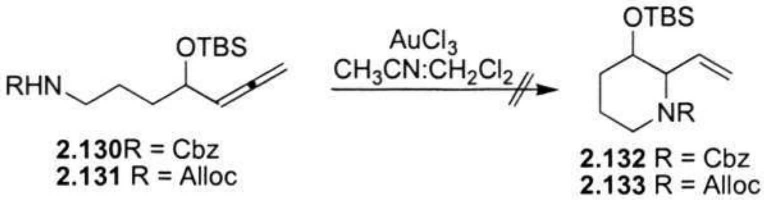
With the total failure of the crotyl allene (**2.116**) to cyclise and with the nosyl allene (**2.115**) showing no formation of the desired product our attention was concentrated on the carbamates. The other two most common carbamates used to protect amines are the benzyloxycarbonyl (Cbz) and the allyloxycarbonyls (Alloc), each was prepared in an identical procedure to that of the Boc allene (**2.114**) giving the Cbz allene (**2.130**) and Alloc allene (**2.131**). We note that the synthesis of these two other derivatives was not as high yielding across many of the transformations as the Boc allene.



Reagents and conditions: (a) *n*-BuLi, TMS acetylene, THF. (b) (i) Zn, AcOH, THF. (ii) AllocCl/CbzCl, Na_2CO_3, CH_2Cl_2 (c) K_2CO_3, MeOH. (d) CuBr, *i*-Pr_2NH, $(CH_2O)_n$, Dioxane. (e) TBSCl, Im., DMAP, THF.

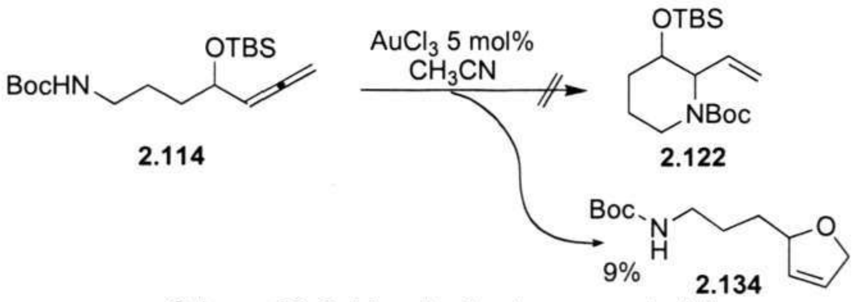
Scheme 96. Preperation of the Alloc and Cbz allenes

With the allenes in hand our attention returned to the cyclisation step. By repeating the initial reaction (Scheme 91) on the newly obtained carbamate allenes, was of limited success. While the Boc allene **(2.114)** consistently gave some of the desired piperidine (**2.122**) it was never high yielding. The other two derivatives never provided any desired piperidines, but occasionally provided some of the respective dihydrofurans, fortunatly all reactions consistently allowed for recovery of the stating material.



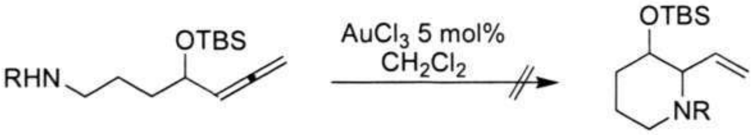
Scheme 97. Gold cyclisation of the carbamates.

We concluded that $AuCl_3$ was sufficiently electrophilic enough to activate the double bond, but that the conditions prevented the full conversion or resulted in the decomposition/deactivation of the catalyst, therefore the reaction conditions were reviewed.



Scheme 98. Gold cyclisation in pure acetonitrile.

The use of pure acetonitrile was also well established in the literature,[25] however, attempts at cyclisation of the Boc allene (**2.114**) in pure acetonitile was fruitless and proceeded with recovery of a significant amount of starting material and with the formation of a trace amount of dihydrofuran, on occasion. Discussions with Prof Hashmi revealed that such reaction conditions are considered harsh by gold chemists and as starting material is lost by decomposition with 1 equivalents worth of CH_3CN we should explore milder conditions.



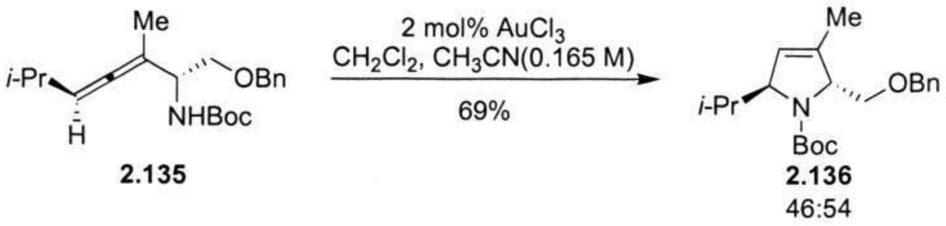
2.114 R = Boc
2.130 R = Cbz
2.131 R = Alloc

2.122 R = Boc
2.132 R = Cbz
2.133 R = Alloc

Scheme 99. Gold cyclisations in pure CH_2Cl_2.

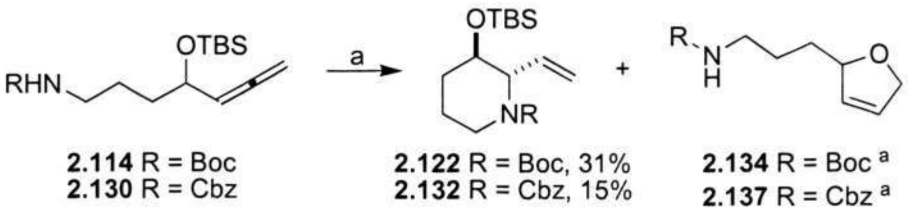
Examples of gold catalysis in pure CH_2Cl_2 exist, and so we attempted reactions in 0.5M CH_2Cl_2, and noted that the solution was very different in appearance. Instead of being bright yellow and homogeneous the catalyst appeared to coat the side of the flask, all attempts at cyclisation failed, and we attribute this to the insolubility of the gold(III). From these reactions we concluded that a trace of CH_3CN would be required.

Publications by Krause have shown that the most efficient solvent system for the formation of 3-pyrrolines and 2,5-dihydrofurans from α-aminoallenes and α-hydroxyallenes respectively was a mixture consisting mainly of CH_2Cl_2, but with only a trace (0.165M) of CH_3CN (Scheme 100).[109,110]



Scheme 100. Krause's cyclisation.

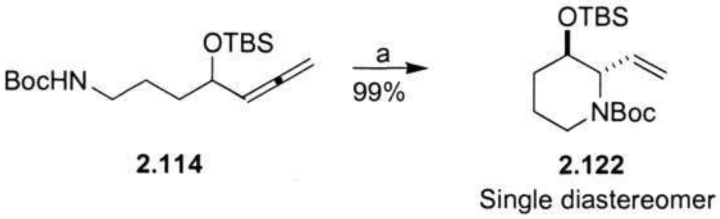
We chose to apply these reaction conditions to our Cbz and Boc allenes (**2.130**), (**2.114**), which we had in hand. The results proved to be capricious, giving a mixture of up to three compounds, consisting of recovered starting material, desired piperidines and the undesired product formed by deprotection and subsequent 5-*endo* cyclisation of the secondary alcohol (Scheme 101). We assumed desilylation occurred as a result of adventitious moisture entering the reaction system, this led to the formation of traces of HCl which desilylated the alcohol.



Reagents and conditions: (a). $AuCl_3$ 5 mol%, CH_2Cl_2, CH_3CN (0.165 M)
[a]Trace by NMR.

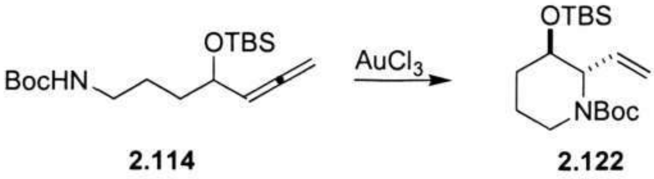
Scheme 101. Gold cyclisation under Krause's conditions.

These reactions failed to go to completion even when an additional 2 mol% of $AuCl_3$ was introduced to the reaction mixture after 24 hours. The continued formation of the dihydrofuran in these reactions was causing concern and therefore suppression was thought to be the best method for dealing with any HCl formed *in situ.* It was thought that the addition of one equivalent of calcium carbonate would be the most simple solution, this base was also used in Claesson cyclisations with silver nitrate.[36]



Reagents and conditions: (a). $AuCl_3$ 5 mol%, $CaCO_3$, CH_2Cl_2, CH_3CN (0.165 M)
Scheme 102. Gold cyclisation with supression of any HCl formed *in situ*.

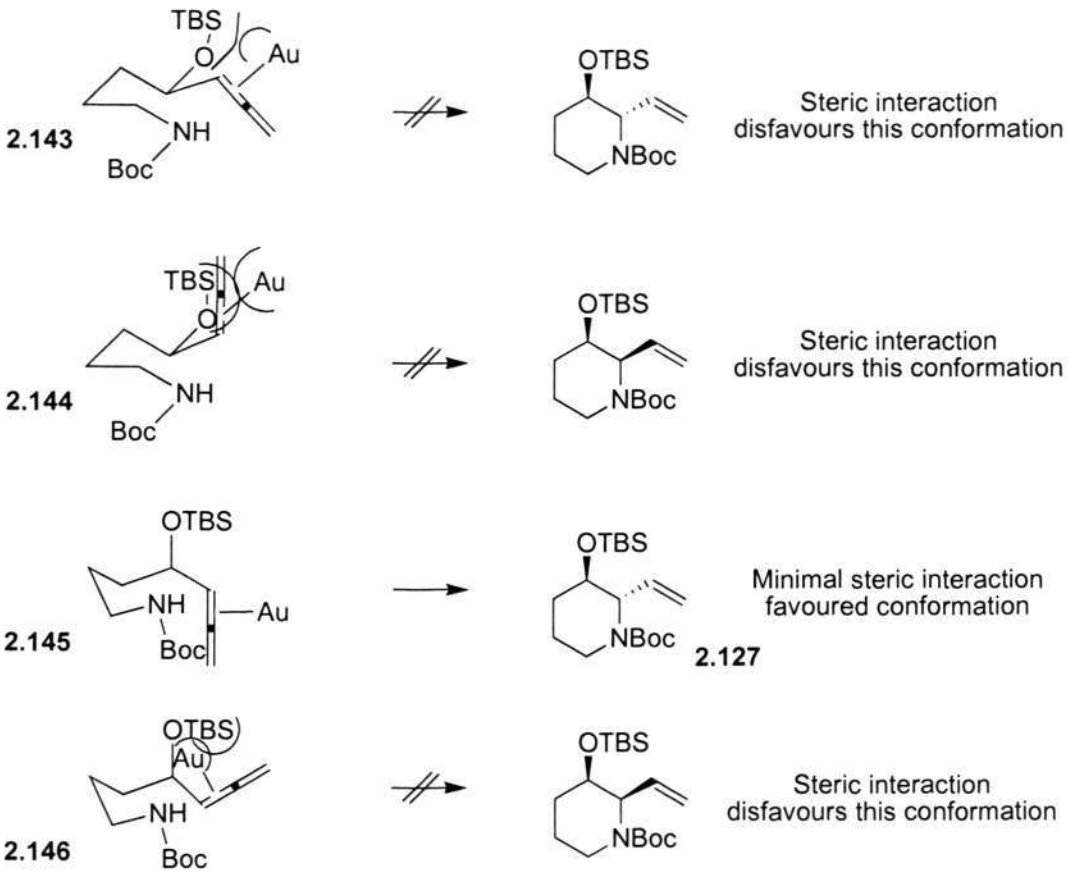
We were delighted to find that the primary reaction carried out under these conditions with the Boc allene (**2.114**) resulted in quantitative formation of the desired *trans*-piperidine (**2.122**) in less than 24 hours. Subsequent repeats were still capricious ranging from 50% to quantative yields. It was thought that the gold could be of questionable purity as an old bottle was being used. At this point more gold(III) chloride was ordered. When the new gold(III) chloride arrived we found a marked improvement but the reaction still lacked a consistency in the results obtained. The discussion was taken to move away from using a solvent purifying system (SPS). The SPS employed alumina columns for drying, we chose to return to traditional methods, distilling the dichloromethane and acetonitrile from calcium hydride directly. Only then did we have consistent quantitative conversion of the Boc allene (**2.114**) to the piperidine (**2.122**) as a single diastereomer in a matter of hours. We assume that this is due to the removal of small traces of moisture, but this could also be due to the removal of impurities in the solvent. Such as some of the stabilizers used, these may not have been successfully removed by the alumina columns. The Alloc and Cbz allenes (**2.130**), (**2.131**) also cyclised under these optimized conditions giving the respective piperidines as single diasteromers but the yields were not as high, the Alloc piperidine (**2.133**) was obtained only in 25% with another 36% of recovered starting material. We postulate that the golds affinity for C=C double bonds means that it coordinates to the Alloc alkene instead of the allene moiety, effectively trapping the gold and preventing further reaction. The use of the old catalyst also improved remarkably with the distilled CH_2Cl_2 and in conjunction with holding the $AuCl_3$ *in vacuo* over P_2O_5 for an hour before use.



	Products		
Solvent	Piperidine	Dihydrofuran	Recovered sm
CH_2Cl_2	-	-	≈90
CH_3CN	-	-	≈80
CH_2Cl_2:CH_3CN 1:1	17	20	14
CH_2Cl_2, $CaCO_3$ CH_3CN (0.165 M)	99	-	-

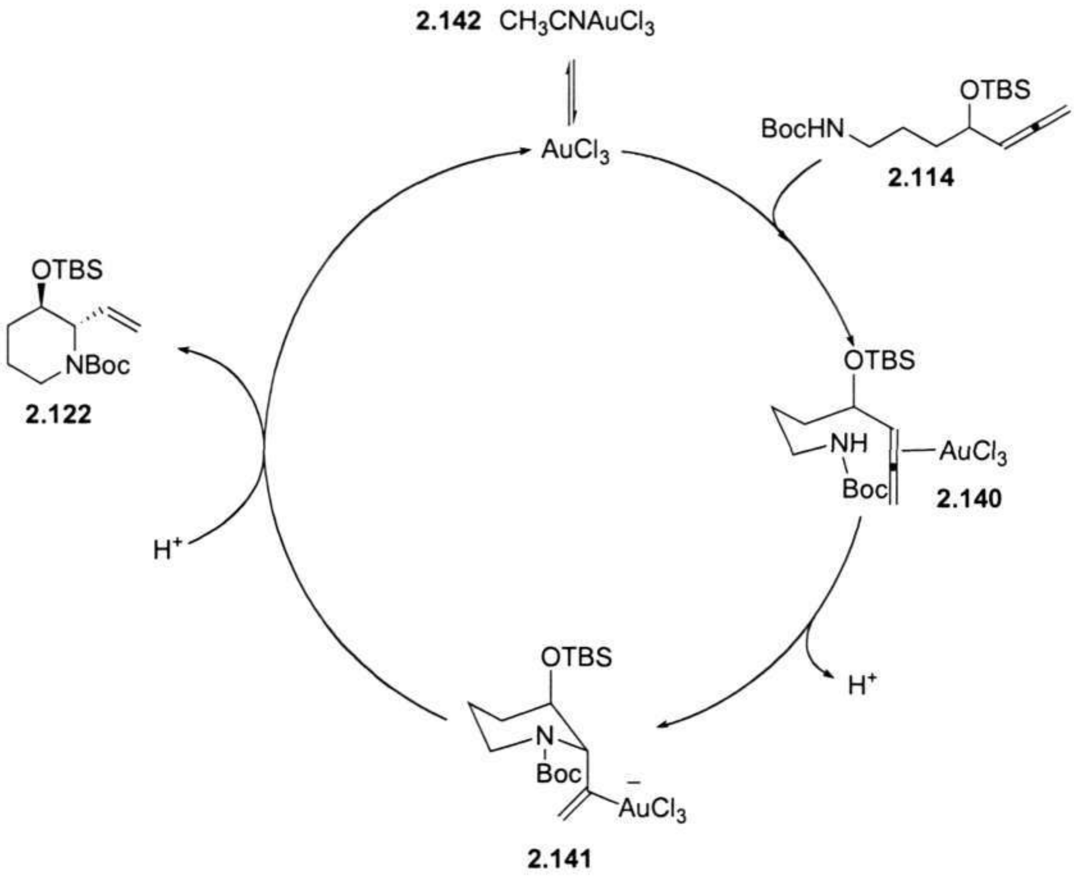
Table 5. Allene cyclisation condition's.

By drawing on the observations we have seen with respect to the effect of solvent we can postulate about the reaction mechanism. Table 5 summarizes the allene cyclisation conditions attempted thus far, as the gold was insoluble in pure CH_2Cl_2 and no reaction was observed. Acetonitrile was therefore required, this will coordinate to the gold and solvate it. Only then could the reaction proceed, as observed when the 1:1 mixture of solvents was used. However, if the reaction was carried out in pure acetonitrile, again no reaction was observed, we assume here that only completely solvated gold(III) exists, the completely solvated gold(III) can not catalyse the reaction. We therefore draw the conclusion that the gold(III) chloride catalyses the reaction and the acetonitrile must then coordinate to the gold after catalyzing the reaction and returning it to the catalytic cycle. If this was not the case we would have expected to observe reactions in both of the pure solvent reaction systems. This observation is reminiscent of Sharpless's observation for the requirement of acetonitrile in ruthenium catalysed alkene cleavage.[111]



Scheme 104. Possible conformation of transition states.

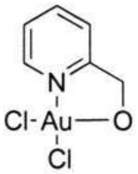
Having established the *trans* stereochemistry of piperidine (**2.122**) and by assigning both the hydroxyl and alkene substituent's as being in the axial positions, we now had to reassess our proposed transition state from Scheme 92. By returning to our chair diagrams and using the argument of steric interaction and attack of the carbamate nitrogen onto the opposite side to that of the gold complex, we now propose that the chair conformation (**2.140)** as the most probable, the being due to the minimal steric interactions (Scheme 103).



Scheme 104. Our proposed reaction mechanism.

Based on the two observations (favourable chair conformation and solvation effect) we now postulate a reaction mechanism (Scheme 104). We believe the gold sits at rest as a complex with the acetonitrile (**2.142**), which is in equilibrium with the active $AuCl_3$. This active catalyst co-ordinates in an η^2 fashion to the internal allene carbon double bond, with a conformation such as our chair (**2.140**). Subsequent nucleophilic attack of the carbamate nitrogen *anti* to the gold creates the *trans* intermediate (**2.141**). Protonation of the Au-C bond regenerates the active intermediate and releases the product (**2.122**). We do not believe that the steric interaction argument alone can create such a high level of selectivity and would propose some sort of O-Au interaction as a contributing factor as well, but we are well aware of the speculative nature of this proposition and have no supporting information for such an interaction at this time.

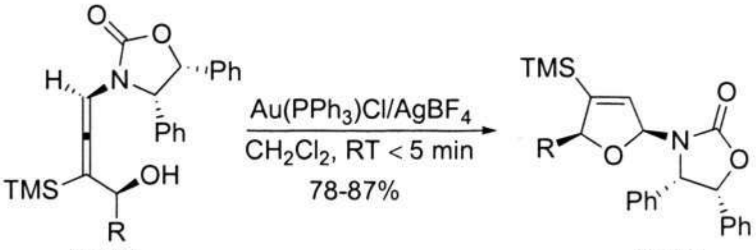
The use of other gold(III) catalysts have also been shown to afford catalytic cyclisations, a more stable source of gold(III) is available from the pyridine complex with the chelating oxygen functionality (**2.143**) (Figure 11).



2.143

Figure 11. Pre-catalytic source of gold(I).

This complex is a pre-catylitic source of gold(III), it is known to be less reactive than that of $AuCl_3$, but as mentioned by Prof Hashmi this can be overcome by using a pure CH_2Cl_2 solution of the catalyst instead of CH_2Cl_2/CH_3CN mixture.[112] The gold(III) complex was formed by reaction of $AuCl_3$ with pyridine-2-methanol, to give bright pink crystals. The complex has been used by Toste to catalyze a [4 + 3]-cycloaddition in a higher yield and a shorter period of time than $AuCl_3$.[113] The catalyst was easily prepared, and an attempt at cyclising the Boc allene (**2.114**) with 2 mol% of pre-catalyst (**2.143**) was unsuccessful, only resulting in the recovery of the starting material. As already mentioned this catalyst is less reactive than $AuCl_3$, the reactive intermediate is unknown and we therefore cannot assume that the complex would co-ordinate to the same double bond/face of the allene as $AuCl_3$. Therefore the failure to realize cyclisation was not surprising, but is unfortunate.

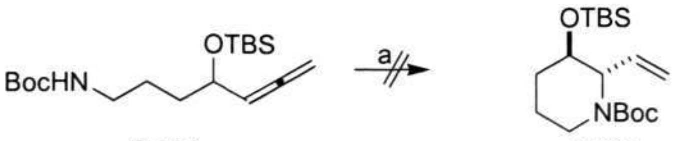


2.144 **2.145**

Scheme 105. Hegedus' example of a Au(I) cyclisation.

Another gold source that has been used in the cyclisations of allenes was gold(I) triphenylphosphene chloride. Gold(I) triphenylphosphene chloride reagent has commonly been employed in conjunction with a co-catalytic halide abstraction agent to activate π-systems.

Hegedus,[114] Widenhoefer,[115,116] and Liao[117] have successfully demonstrated the use of gold(I) triphenylphosphene chloride in very different circumstances. Hegedus reports the O-nucleophile cyclisation of alleneamides (**2.144**), using a 5 mol% mixture of $Au(PPh_3)Cl/AgBF_4$ in less than 5 mins (Scheme 105). Hegedus's example is a 5-*endo* cyclisation and is similar to the trivial cyclisation that occurs when our secondary alcohol is unprotected. Liao reports the $Au(PPh_3)Cl/AgOTf$ catalyzed hydrative carbocyclization of 1,5- and 1,7-allenynes, using a 5 mol% solution in wet solvents demonstrating the stability of the catalyst to a variety of conditions. However, no reaction was observed between the Boc allene (**2.114**) and a 5 mol% catalytic loading of $Au(PPh_3)Cl$ and AgOTf (Scheme 106).



2.114 **2.122**

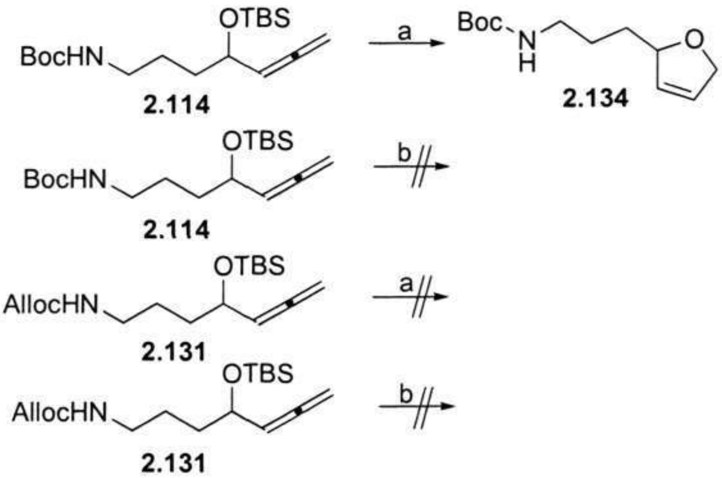
Reagents and conditions: (a). $Au(PPh_3)Cl$ 5 mol%, AgOTf, CH_2Cl_2

Scheme 106. Attempted Au(I) cyclisation.

Our system was very different to that of Hegedus and the failure was not surprising, as we already knew that the catalyst was less reactive than the $AuCl_3$. We were also attempting to form a larger ring size, which is more challenging. The Au(I) was probably insufficiently activating the allene π-system which therefore prevented cyclisation.

We discussed our results with Prof Hashmi at a conference in Australia, and he generously offered to send us a mild gold(I) catalyst that he has developed in his laboratories at Heidelberg. While the full compound structure was not disclosed it should suffice to say that it was a $AuNTf_2$ salt with a phosphorous-gold ligand. The advantages of this Au(I) complex were that it was not necessary to use any silver co-catalysts, whilst also being readily soluble in CH_2Cl_2. Reactions with the catalyst and our Boc (**2.114**) and

Alloc (**2.131**) allenes (Scheme 107), were unsuccessful. We encountered deprotection of our silyl ether and observed the 5-*endo*-cyclisation with the newly generated hydroxyl group in the case of our Boc allene (**2.114**) but no reaction with our Alloc allene (**2.131**).



Reagents and conditions: (a). Hashmi catalyst, CH_2Cl_2 (b). Hashmi catalyst, $CaCO_3$, CH_2Cl_2

Scheme 107. Cyclisation's using a $AuNTf_2$ complex.

Once again we attempted to suppress any acid formation by the addition of a base, again employing $CaCO_3$. However, no reaction was observed and significant amounts of starting material were recovered.

Having established that using our optimised $AuCl_3$, $CaCO_3$ conditions were the most reliable source of the *trans* piperidine (**2.122**), we now returned our focus to the formal synthesis of (-)-swainsonine (**2.1**).

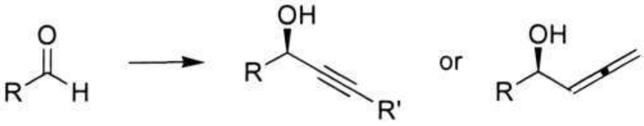
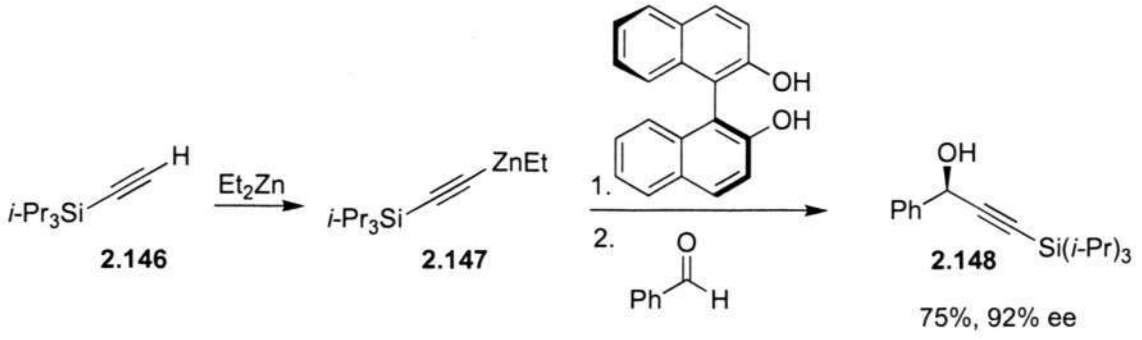


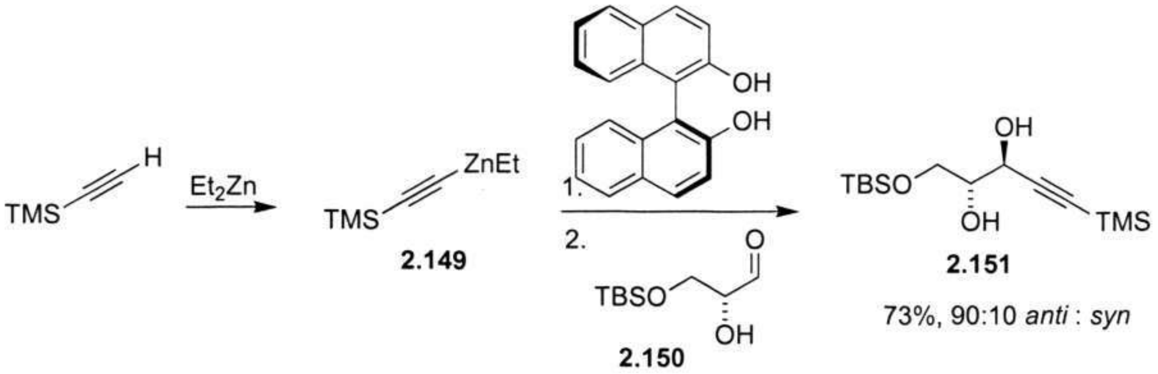
Figure 12. Desired chiral compounds.

With the intention of formally synthesising (-)-swainsonine (**2.1**), we required methodology to access enantiopure allenes or propargylic alcohols as illustrated in Figure 12. Recently a number of highly promising methods for enantioselective additions of alkynes to achiral aldehydes have appeared in the literature, and it was to these that our attention first turned. The research group of Pu has shown that BINOL in combination with Ti(O-*i*Pr)$_4$ could affect the highly enantioselective alkynylzinc additions to aldehydes.[118]



Scheme 108. Pu's conditions for the preparation of chiral propargylic alcohols.

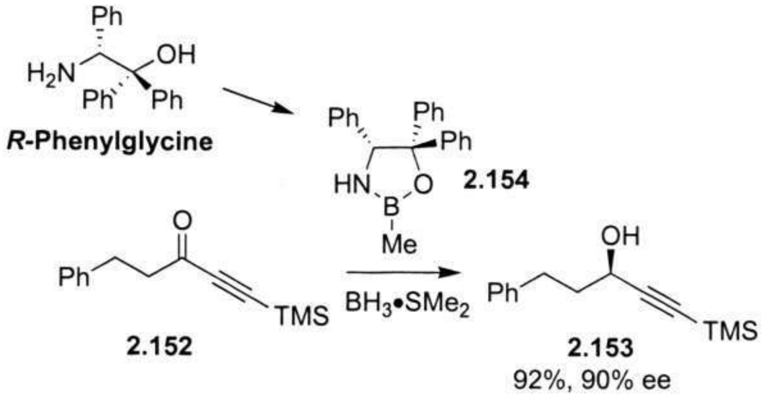
In Pu's experiments the first step involved heating a solution of triisopropylsilylacetylene (**2.146**) (2.2 equiv.) and Et$_2$Zn (2 equiv.) at reflux under nitrogen for 5 hours (Scheme 109). The mixture was then cooled to room temperature and combined with (*S*)-BINOL (20 mol%), CH$_2$Cl$_2$, Ti(O^{i}Pr)$_4$ (50 mol%) and then benzaldehyde giving the desired chiral alcohol (**2.148**) in 75 % yield and 92% ee. However, when these conditions were applied to our aldehyde (**2.101**) and TMS acetylene the reaction only proceeded in 40% yield and 60% ee, which was significantly less than desirable. Use of other 'optimised' conditions available in the literature, such as using a 1.1:1 ratio of alkyne to dialkyl zinc and heating under reflux for 5 hours, followed by addition of (*S*)-BINOL (10 mol%) in CH$_2$Cl$_2$ with vigorous stirring for 15 minutes, and then subsequent addition of Ti(O^{i}Pr)$_4$ (25 mol%) and stirring for 1 hour before addition of the aldehyde gave little improvement. Marshall explored the applicability of Pu's methodology using TMS acetylene with a slight variation.[119]



Scheme 109. Marshall's chiral adidtion conditions.

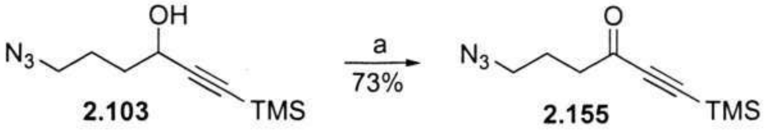
In Marshall's procedure, TMS acetylene (2.7 equiv.) and Et_2Zn (2 equiv.) were heated at reflux in toluene for 1 hour, cooled to room temperature before addition of (*S*)-BINOL (20 mol%), ether and $Ti(O^iPr)_4$. After 1 hour, the aldehyde (**2.150**) (0.5 equiv.) was added giving the desired alcohol (**2.151**) in 73% yield and as a 90:10 mixture of the *anti* and *syn* propargylic alcohols. On applying these reaction conditions to our aldehyde (**2.101**), the alcohol (**2.103**) was obtained in a 56% yield, but again in 60% ee. The absence of any steric bulk on the aldehyde (**2.101**) is believed to be the limitation in this procedure. As the methyl group α to the aldehyde in Marshall's example and the aromatics aldehydes of Pu's are much greater in size compared to our aliphatic chain.

Another very useful asymmetric reaction is the reduction of a prochiral ketone to an optically active alcohol, but proper selection of the asymmetric reducing agent is critical. We were influenced by the availability of the reagent, its ability to reduce acetylenic ketones in high yields and high enantiomeric purity. Whilst also employing reagents that are easy to handle, inexpensive and tolerant of other functional groups. The trialkylboranes appeared to embody many of these features that we desired. The group of Garcia have reported the reduction of an acetylenic ketones (**2.152**) with (*R*)- and (*S*)-B-methyl-4,5,5-triphenyl-1,3,2-oxazaborolidine (**2.154**), derived from phenylglycine (Scheme 110).[120]



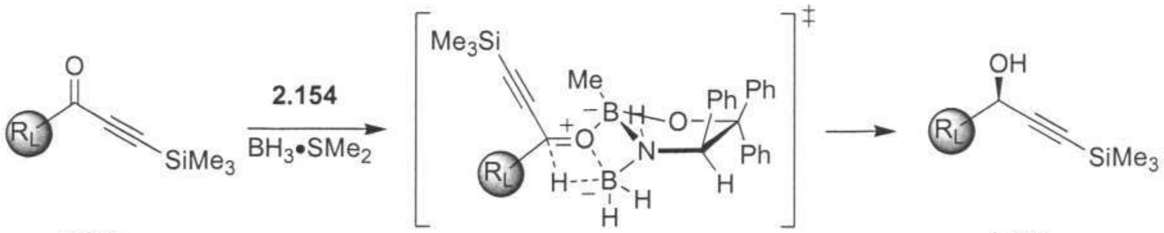
Scheme 110. Garcia's ynone reduction.

First, the alcohol (**2.103**) was oxidized to the ynone (**2.155**) in 73% yield (after flash chromatography). The ynone proved to be unstable and was held at -78 °C until required for the subsequent reduction (Scheme 111).



Reagents and conditions: (a). DMP, CH_2Cl_2, 0 °C.
Scheme 111. Formation of the ynone.

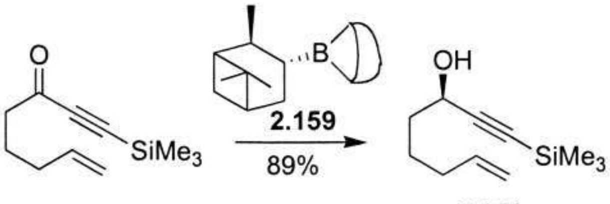
The oxazaborolidine (**2.154**) was prepared prior to use from methyl (*R*)-phenylglycinate hydrochloride and phenylmagnesium bromide. A soloution of the ynone (**2.155**) (1 equiv.) was then taken in THF and added slowly (1 mmol/h) to a solution of (*R*)-oxazaborolidine (**2.154**) (1 equiv.) and BH_3•SMe_2 (1.1 equiv.) in THF at 0 °C. The reaction proceeded to give the alcohol ((***R***)**-2.103**) in 14% yield but with an appalling 53% ee. Repetition, but with formation of the catalyst immediately before use, gave the propargylic alcohol ((***R***)**-2.103**) in 38% yield and 73% ee. By varying the procedure and adding the catalyst to a solution of ynone (**2.155**) pre cooled to -25 °C, we found that the reaction required 17 hours to proceed to completion. Standard workup then gave the alcohol in 83% yield but only with a 3 % ee, this was then improved to 27% ee on repetition. Addition of the catalyst to a 0 °C solution of ynone (**2.155**) gave the alcohol ((***R***)**-2.103**) in 63% ee, while addition of ynone to a pre-cooled catalytic mixture gave a 53% ee of the desired ((***R***)**-2.103**). The use of *i*PrOH as an additive as in the Shi procedure was also attempted.[121] Addition of the catalyst to a pre cooled and aged solution of the ynone (**2.155**), *i*PrOH and borane dimethyl sulfide at -10 °C gave the alcohol (**(*R*)-2.103**) in 68% ee and 50% yield. Again here we assume the acetylene moiety and the aliphatic chain are of an insignificant size, thereby neither taking the place of a large group in the intermediate (**2.157**) and giving a low level of enantioselectively (Scheme 112).[39]



2.156 **2.157** **2.158**

Scheme 112. Mechanism with a Large substituent.

Another excellent reagent for the reduction of acetylenic ketones to propargylic alcohols is Midland's reagent *B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane, sold by Aldrich as Alpine-Borane (**2.159**),[122] this was one of the most selective reducing agents available in the early 1990's. Brown's recent synthesis of (-)-galanthamine utilized this chemistry,[123] here ynone (**2.160**) (1 equiv.) was cooled to 0 °C before treatment with *R*-Alpine borane (**2.159**) (2 equiv., of a 0.5 M soln. in THF). Followed by immediate concentration *in vacuo*, the neat mixture then stirred for 18 hours before an appropriate work up.

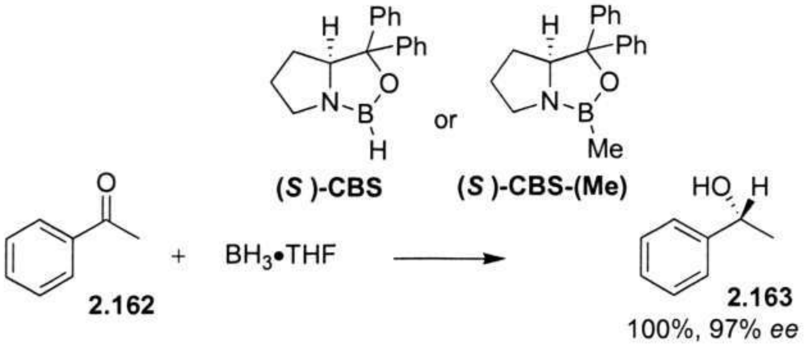


2.160 **2.161**

92% ee

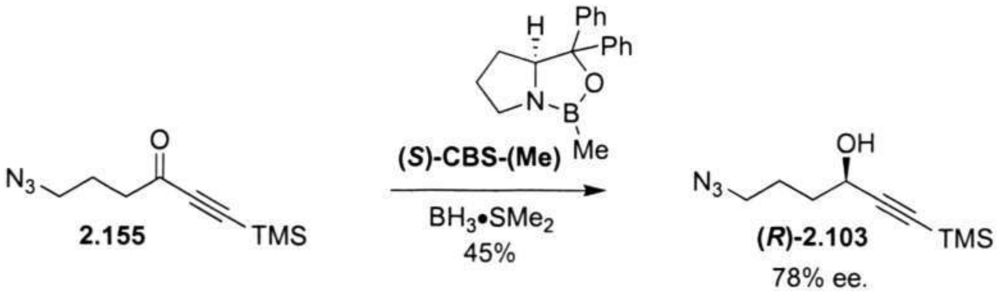
Scheme 113. Brown's Alpine Borane example.

Brown's experiment proceeded to provide the propargylic alcohol (**2.161**) in 89% yield and with a 92% ee, it was believe that our ynone (**2.155**) which also contains an aliphatic chain with no moiety for four carbons could be comparable, but unfortunately the procedure failed to provide any clean product. We assume that this was most probably due to competitive reduction of the azide. With another poor result our attention now turned to probably the most well know enatioselective reducing agents the, oxazaborolidines, namely the Corey-Bakshi-Shibata *(CBS)*-oxazaborolidine.[124]



Scheme 114. Coreys CBS reduction.

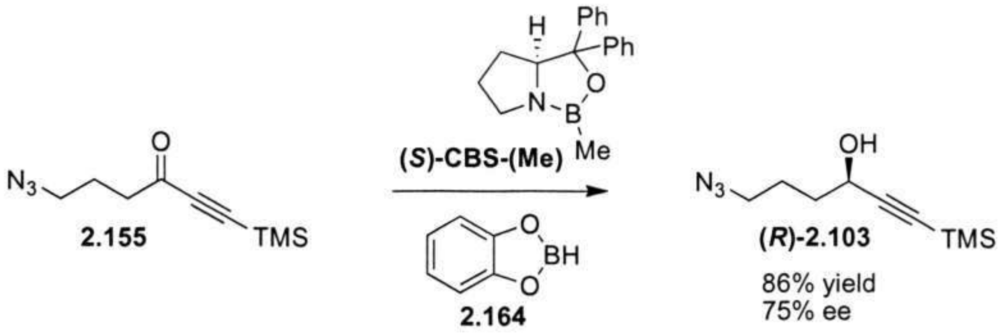
The original catalyst developed by Corey was (*S*)-CBS-(H) version with a boron hydrogen bond, this has generally been superseded by the CBS-(Me) version with the boron methyl substituent. The CBS-(Me) reagent was found to be superior as an enantioselective reduction catalyst compared to the CBS catalyst, this superiority can been seen when acetophenone (**2.162**) is reduced to (*R*)-1-phenylethanol (**2.163**). With the CBS-(Me) (0.1 equiv.) and $BH_3 \cdot THF$, the acetophenone is reduced in 97% ee and quantitative yield at 25 °C. While the CBS-(H) catalyst only provided (*R*)-1-phenylethanol (**2.163**) in 94.7 % ee.[44] Other advantages of the CBS-(Me) catalyst was it ease of preparation and handling, as it is less sensitive to air. These reagents have been applied many times to produce a wide variety of chiral alcohols and as such a large range of protocols are available,[125,126] our initial experimentation used the standard Corey procedure.[43]



Scheme 115. CBS reduction of the ynone.

A reaction on a 100 mg scale gave the desired *R*-alcohol (**(*R*)-2.103**) in low yield, but with a 78% ee. On scaling the reaction up to a 400 mg scale, the chiral alcohol (**(*R*)-2.103**) was obtained only in 45% yield but still with moderate enantioselectivity, 73% ee. Subsequent reactions gave only moderate yields of 33-44%. As the yield was so low, we chose to explore other experimental procedures, such as the protocol developed by Merck.[127] In their protocol the ketone (**2.155**) was predried over activated molecular sieves and taken into THF. The CBS catalyst (10 mol%) was then added and the mixture was cooled to -15 °C. Borane•dimethylsulfide (0.7 equiv.) in THF (0.6 M) was then added at a rate so as to maintain the -15 °C temperature. The reaction, however, failed to proceed to completion after 24 hours and was subsequently allowed to warm to 0 °C. Isolation of the alcohol (**(*R*)-2.103**) in 33% yield was also not satisfactory. Another procedure was that of Jones,[128] here, the CBS catalyst was taken into THF, and borane•dimethylsulfide was added to the reaction mixture with stirring for 30 minutes at RT, before being cooled to -10 °C. The ketone (**2.155**) was then added slowly and TLC analysis showed complete consumption of the starting material. After workup the *R*-alcohol (**(*R*)-2.103**) was obtained in 67% yield and with a 99% ee. On subsequent repeats the ee value and yield varied greatly and on one occasion a trace amount of alkene was observed, most obviously from the reduction of the alkyne by the borane•dimethylsulfide solution. We found that by reversing the addition protocol and cooling the ketone (**2.155**) to -10 °C followed by addition of the aged CBS catalyst and borane•dimethylsulfide solution in THF also gave the (*R*)-alcohol with the same kind of unreliability.

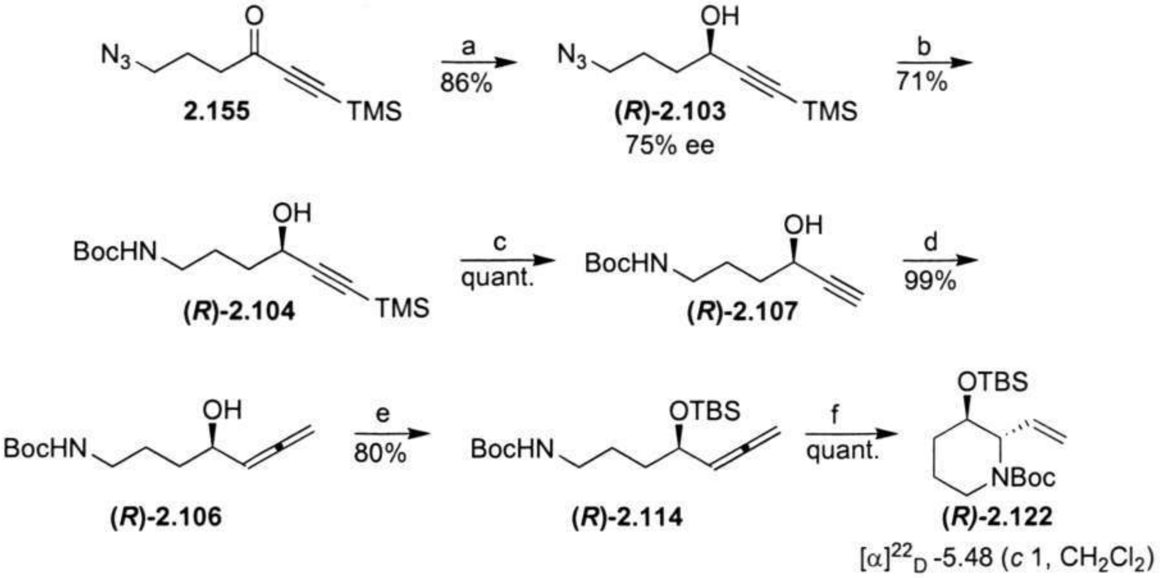
With the moderate yields obtained, due to continued decomposition of the starting material and the formation of the alkene, we chose to change the hydride source, thereby reducing the loss of any product as a result of alkyne reduction. A brief review of the literature showed that the use of catecholborane (**2.169**) as stoichiometrical reductant, was quite common and in some cases more efficient.



Scheme 116. Improved CBS reduction with catecholborane.

Gratifyingly we found that reduction of our ketone (**2.155**) at -10 °C, by slow addition of a preformed catalytic mixture of catecholborane (**2.164**) and the (*S*)-CBS-Me catalyst in THF proceeded in 86 % yield and 75 % ee, even when performed on a large scale. While the ee value was not as high as could be desired, we decided that it was sufficient. We are aware of two other noteworthy enantioselective approaches to chiral propargylic alcohols, the first a Corey procedure that reports a marked enhancement of the enantioselectivity of the reduction when either or both, the size of the distal group attached to the alkyne increases and the size of the alkyl group attached to the boron atom of the catalyst increases.[129] The second is that of the conversion of the alkyne to a π-$Co_2(CO)_6$ protected derivative in which the alkyne becomes the effective large group.[130] However, in our synthesis both methods would have been indirect and required the insertion of further steps into our synthesis and neither were examined.

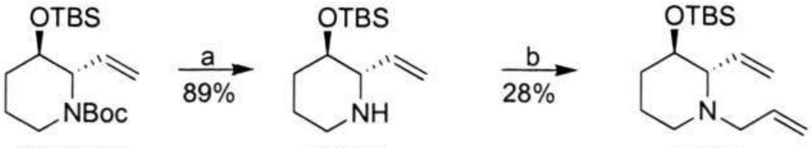
With the enantioenriched propargylic alcohol (**(*R*)-2.103**) in hand we continued with our formal synthesis, repeating our reactions to provide the (*R*)-piperidine (**(*R*)-2.122**) obtaining the optical rotations along the route with ease.



Reagents and conditions: (a). *(S)*-Me CBS, catecholborane, CH_2Cl_2, -10 °C, (b). (i) Zn, AcOH, THF. (ii). Na_2CO_3, Boc_2O, CH_2Cl_2, (c). K_2CO_3, MeOH, (d). CuBr, (*i*-Pr)$_2$NH, $(CH_2O)_n$, dioxane, (e). TBSCl, Im, THF, (f). $AuCl_3$, $CaCO_3$, CH_3CN, CH_2Cl_2.

Scheme 117. Enantioselective preparation of the piperidine.

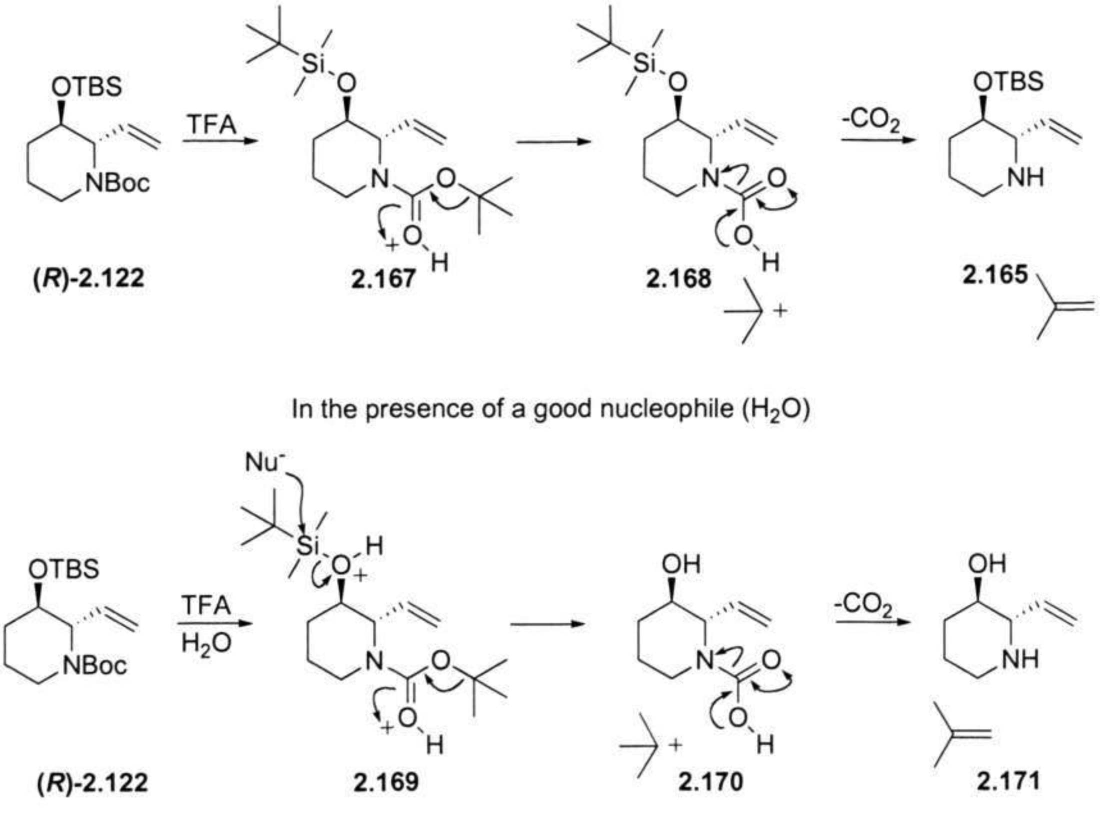
With the (*R*)-piperidine (**(*R*)-2.122**) in hand we now had to construct the five membered ring, in order to do this we had to achieve selective deprotection of the Boc group in the presence of an acid labile TBS ether. The cleavage of Boc protected amines in the presence of TBS and TBDPS ethers are scattered through the literature, and few show any selectivity with indiscriminate removal of both groups. However, one literature procedure does show 94% yield of a selectivity removed Boc group in the presence of a TBS ether, with 2% of the yield being double deprotected product.[131,132] The procedure required a saturated solution of HCl in ethyl acetate, calculated to be 7.5M at room temperature and stirring for 8 hours. However, in our hands this procedure for failed to show any selectivity for the Boc amine, cleaving the TBS group selectively.



(*R*)-2.122 **2.165** **2.166**

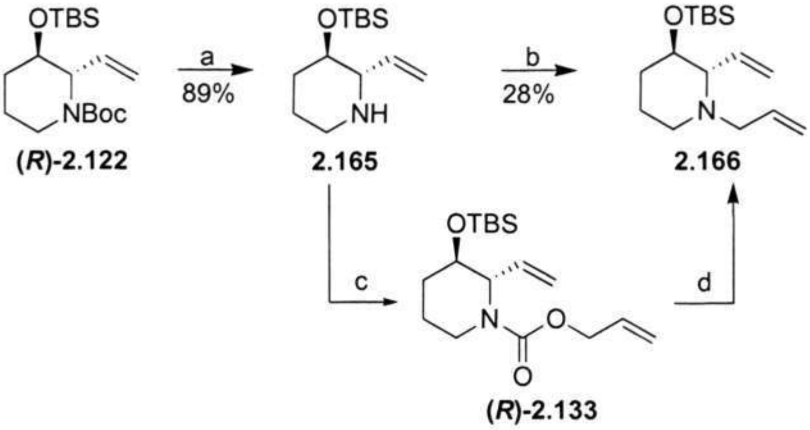
Reagents and conditions: (a). TFA, CH_2Cl_2, (b). NaOH allylBr, Toluene.
Scheme 118. Selective cleavage of the Boc group and allylation.

Deprotection using 10 equivalents of trifluroacetic acid in anhydrous CH_2Cl_2 resulted in the isolation of a single product in 89% yield (Scheme 118). Gratifyingly, we found this to be the product of selective removal of the Boc protecting group with our TBS ether still intact (**2.166**). This selectivity can be attributed to the absence of any nucleophile in the reaction mixture capable of nucleophilic attack on the silicon atom, a reaction with reagent grade CH_2Cl_2 from the bench resulted in the isolation of a mixture of mono and di deprotected piperidine, with water presumably acting as the nucleophile attacking the silicon atom of the piperidine (**2.169**) (Scheme 119).



Scheme 119. Mechanism for the removal Boc and silyl groups and their dependance on moisture.

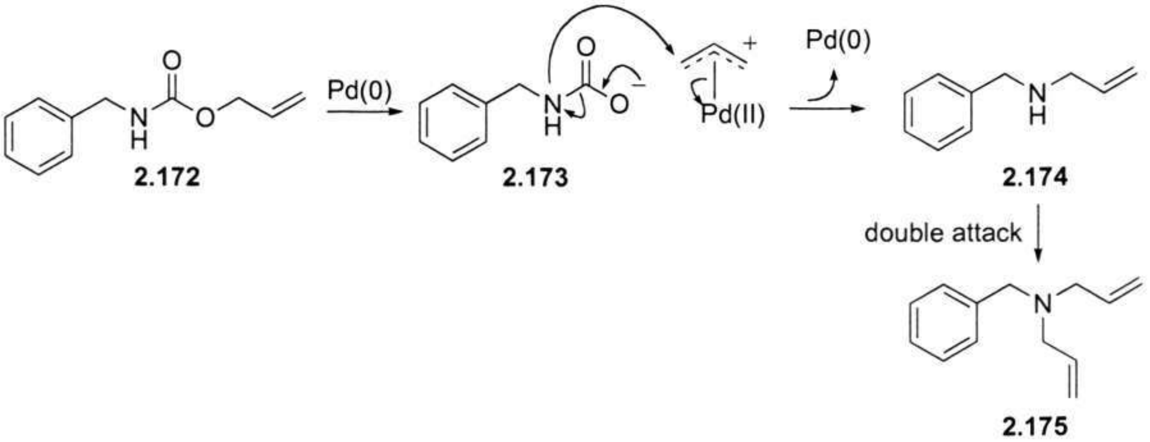
We now intended to perform allylation of the free amine under standard conditions using sodium hydroxide and allyl bromide in toluene. To our surprise this reaction proceeded with limited success, giving only a 28% yield of the desired piperidine (**2.166**) (Scheme 120). This was clearly identifiable from it ^{1}H NMR spectrum, with the doublet of doublet of doublet of doublets at 5.83 ppm for the CH of the allyl moiety. The vinyl CH was observed as a doublet of doublet of doublets at 5.58 ppm, the allyl CH_2 next to nitrogen was clearly observed at 3.46 ppm as a doublet of doublet of triplets. The allyl group was also clearly observable in the ^{13}C NMR spectrum at 138, 117 and 58 ppm. We now know that this low yield is a result of steric hindrance caused by the large silyl protecting group. This was assumed because as seen in Chapter 3, the smaller protected hydroxyl group of the benzyloxy piperidine (**3.36**) readily allylates. However, with the unsatisfactory yield here, we chose to install the allyl moiety from the allyloxycarbamate ((***R***)-**2.133**) by performing what we term an 'Alloc contraction'.



Reagents and conditions: (a). TFA, CH_2Cl_2, (b). NaOH allylBr, Toluene, (c). Allylchloroformate, Na_2CO_3, CH_2Cl_2. (d). $Pd(PPh_3)_4$, THF

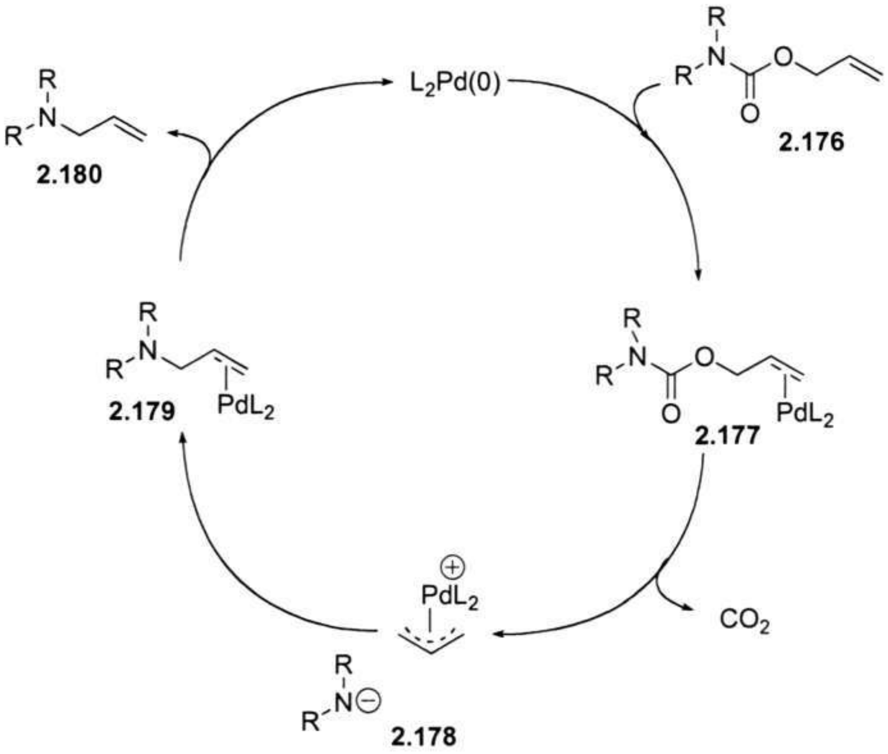
Scheme 120. Improved access to the allylated piperidine.

Functionalisation of the piperidine (**2.165**) as the allyloxycarbamate ((***R***)-**2.133**) proceeded as expected in high yield (92%) under the mild Schotten-Baumann conditions. This compound was spectroscopically identical to the material obtained from the gold(III) cyclisation of allene (**2.131**). We then turned our attention to the Alloc contraction. The deprotection of allyloxycarbamates is well established in the literature and is extremely gentle, requiring a catalytic amount of tetrakis(triphenylphosphene)palladium(0) with a scavenger, often dimedone (5,5-dimethyl-1,3-cyclohexanedione). When standard deprotection is desired the scavenger is necessary, otherwise, the π-allylpalladium complex formed will be attacked by the liberated amino group of (**2.173**) (Scheme 120). This is generally considered as undesirable as Guibé found (Scheme 121),[133,134] but in our case, we desired such an *N*-alkylation.



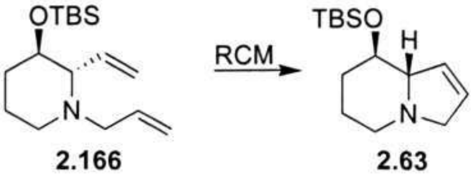
Scheme 121. Guibé N-allylated biproducts.

We decided that in the absence of any scavenger, we should be able to isolate the *N*-allylated piperidine (**2.180**) formed *via* an allylic alkylation mechanism (Scheme 122). Reaction of our allyloxycarbamate protected piperidine ((***R***)-**2.133**) with 10 mol% tetrakis(triphenylphosphene)palladium(0) in THF resulted in the formation of the desired allylated piperidine (**2.166**) in 85% yield. This material was spectroscopically identical to the 28% of piperidine (**2.166**) isolated from the standard allylation (Scheme 118).



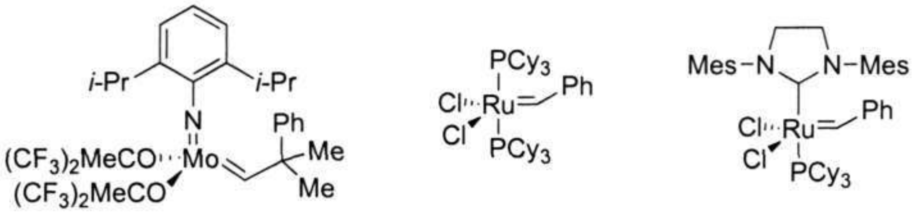
Scheme 122. Palladium(0) allylic alkylation mechanism.

To complete our formal synthesis, a ring closing metathesis reaction was then required (Scheme 123). This type of reaction has received a great deal of attention, mainly due to the development of well defined catalytic systems that are extremely tolerant of different functional groups.



Scheme 123. Formation of the indolizidine

Ring closing diene metathesis started with the Philips tri-olefin process,[135] but it was Schrock and Grubbs proof of a carbene's involvement that really started the field, using metathesis in fine molecule synthesis. Schrock's developed the molybdenum imido alkylidene complexes (**2.181**),[136] which Grubbs demonstrated to be extremely effective in the formation of O and N heterocycles *via* ring-closing metathesis in 1992.[137,138] This catalyst has generally been superseded by Grubbs ruthenium complexes which are more easily accessible, much less air sensitive and showed great tolerance of other functional groups. Grubbs I (**2.182**) and Grubbs II catalysts (**2.183**) are both capable of achieving ring closeing metathesis. Although Grubbs less reactive 1st generation catalyst (**2.182**) is generally more often used in ring closing metathesis (RCM) reactions, as the more reactive catalyst (**2.183**) favors dimerization.



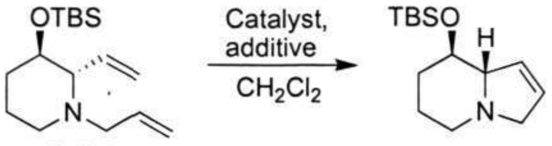
2.181
Schrock's Mo complex

2.182
Grubbs I

2.183
Grubbs II

Figure 13. Metathesis catalysts

Ring closing metathesis has emerged as a very effective method for the formation of heterocycles. The driving force of the reactions is the release of the highly volatile ethylene unit and the increase in entropy. Although Grubbs ruthenium catalysts (**2.182/2.183**) have a greater tolerance of functional groups, the construction of nitrogen heterocycles is still somewhat problematic. As the amines and amides have a tendency to form complexes with the ruthenium. However, this is not necessarily the case, as examples of Grubbs ruthenium ring closing metathesis in the presence of free amides do exist. Yet, these results appear to be very dependent on steric factors around the amides. Where there is little steric demand ring-closing metathesis is significantly reduced, this however, can be overcome by complexation, prior to addition of the Grubbs catalyst.



2.166 **2.63**

Cat.	amount	Additive	Temp. °C	Yield %
Grubbs I	5 mol%	-	25	-[a]
Grubbs I	5 mol%	-	40	-[a]
Grubbs II	5 mol%	-	25	-[a]
Grubbs II	5 mol%	-	40	-[a]
Grubbs I	5 mol%	TsOH	25	-[a]
Grubbs I	5 mol%	TsOH	40	-[a]
Grubbs II	5 mol%	TsOH	25	-[a]
Grubbs II	5 mol%	TsOH	40	73
Grubbs II	5 mol%	Ti(O-*i*Pr)$_4$	40	36[b]

[a] Significant amounts of starting material were recovered. [b] product was significantly contaminated with Ti residue after purification

Table 6. Ring closing metathesis conditions.

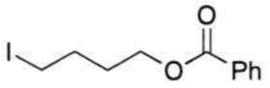
With the capricious literature evidence, we attempted the Grubbs ring closing metathesis of piperidine (**2.166**) with just Grubbs I generation catalyst. However, treatment with 5 mol% catalyst at RT and at reflux failed to provide any cyclised product (**2.63**). On exchanging the catalyst for the more reactive Grubbs II and repeating the experiments at both RT and reflux we also failed to bring about any RCM. As mentioned before, we assume the nitrogen complexes to the ruthenium, thereby inhibiting the reaction. We now turned our attention to the formation of a complex. We were then inspired by a Grubbs' publication that showed unreactive amino dienes could be made to react with Grubbs I by converting them to the corresponding hydrochloride salts.[139] So we decided to convert our piperidine (**2.171**) to the *p*-toluenesulfonic salt, by treatment with 1 equivalent of tosic acid and subsequent stirring for 30 minutes before addition of Grubbs catalyst. We chose to use tosic acid, as it was considerably simpler to handle than HCl that Grubbs used. Reactions of the piperidine salt with Grubbs I catalyst were unsuccessful after basic work-up, with starting material recovered. We believe that this was due to the large bulk of the TBS group interfering and preventing cyclisation. When using the more reactive Grubbs II catalyst in CH_2Cl_2 under reflux, we were able to effect cyclisation in 2 hours to give the indolizidine (**2.63**) with a yield of 73%. Conformation of the indolizidine (**2.63**) structure was possible as the spectroscopic data for the indolizidine was in agreement with Pyne's work, confirming the *trans*-assignment of the piperidine obtained from cyclisation of the allene (**2.114**). The more reactive catalyst was able to out compete the steric bulk of the TBS group and co-ordinate to the alkene, which allowed cyclisation to take place.

Soon after our first racemic attempts at ring closing metathesis Pyne published his 2006 synthesis of (-)-swainsonine, here a similar piperidine (**2.166**) was ring-closed using Grubbs II catalyst, but they opted to employ the method of Xiao,[140] using Ti(O-*i*Pr)$_4$ as a Lewis acid to protect the amino group *in situ* by complexation giving the indolizindine in 80% yield. Our attempt at this reaction was less successful, as it was exceptionally more difficult to remove the titanium residue compared to the acid.

In summary, the synthetic route described in this chapter is a formal synthesis of (-)-swainsonine (**2.1**). We have explored and demonstrated the use of α-hydroxy allenes as exceptionally versatile compounds that can efficiently be cyclised under the correct conditions to give *N*-heterocycles as single diastereomers. We have noted that strong electrophilic catalysts, such as gold(III) chloride are vital in this cyclisation reaction to activate the internal allene double bond. Our synthetic route employed the chiral reduction of a ynone to set the chiral centre C(8) of (-)-swainsonine (**2.1**). As such both enantiomers of this chiral center are equally accessible, giving easy access to any of swainsonine's analogues. Other noteworthy reaction procedures were the successful contraction of the allyloxycarbamate (**(*R*)-2.133**), to give the *N*-allylated species (**2.166**) as the desired product, and the ring closing metathesis to complete the indolizidine core (**2.63**) from the *p*-toluene sulfonic piperidine salt.

Chapter 2: The Formal synthesis of (-)-Swainsonine

Experimental Section.



4-Iodobutyl benzoate (2.98).

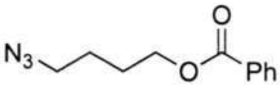
To a solution of sodium iodide (55.31 g, 369 mmol) in reagent grade THF (30 mL, 369 mmol) and reagent grade acetonitrile (15 mL), with external cooling, benzoyl chloride (42.8 mL, 369 mmol) was added in one portion. The reaction mixture was stirred in the absence of light overnight. The reaction mixture was then diluted with water (approx. 100 mL) and ether (approx. 100 mL), the organic layers were separated and the aqueous layer was extracted with ether (3x 30 mL). The combined organic layers were washed with sat. aq. $NaHSO_3$ (50 mL), sat. aq. Na_2CO_3 (50 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a colourless oil (113 g, 90%).

δ_H (400 MHz, $CDCl_3$), 8.01 (m, 2H, ArH), 7.53 (t, *J* = 7.3, 1H, Ar), 7.43 (t, *J* = 7.8, 2H, ArH), 4.34 (t, *J* = 6.4, 2H, CH_2-O), 3.24 (t, *J* = 6.8, 2H, -CH_2-I), 1.88-1.99 (m, 4H, -CH_2-CH_2-).

δ_C (100 MHz, $CDCl_3$), 166.5, 132.9, 130.1, 129.5 (2C), 128.3 (2C), 63.7, 30.0, 29.6, 5.9.

IR (ν/cm^{-1}) 2956, 1714, 1450, 1271.

All data was consistent with that of the literature.[141]



4-Azidobutyl benzoate (2.99).

Sodium azide (29.43 g, 452 mmol) was added portionwise to a solution of 4-iodobutyl benzoate (**2.98**) (91.82 g, 301 mmol), in reagent grade DMF (450 mL) with external cooling and in the absence of light. The reaction mixture was allowed to stir overnight, then diluted with ether (200 mL) and water (200 mL). The organic layer was separated and the aqueous layer was further extracted with ether (3x 100 mL), the combined organic layers were concentrated *in vacuo*. The concentrate was then taken into hexane (100 mL), washed with water (50 mL), brine (30 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a colourless oil (67.48 g, quantitative).

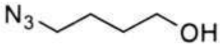
δ_H (400 MHz, $CDCl_3$), 8.03 (dd, J = 8.2, 0.9, 2H, ArH), 7.55 (dt, J = 8.2, 0.9, 1H, ArH), 7.46 (t, J = 7.8, 2H, ArH), 4.35 (t, J = 6.0, 2H, CH_2-O), 3.36 (t, J = 6.4, 2H, CH_2-N_3), 1.72-1.90 (m, 4H, -CH_2CH_2-),

δ_C (100 MHz, $CDCl_3$), 166.4, 132.9, 130.1, 129.5 (2C), 128.3 (2C), 64.2, 51.0, 26.0, 25.6.

IR (cm^{-1}) 2955, 2096, 1717, 1272, 711.

MS (ESI +) *m/z* 220.1 ($[M+H]^+$), 241.2 ($[M+Na]^+$).

HRMS found 220.1086, calc. for $C_{11}H_{14}N_3O_2$ 220.1087 ($[M+H]^+$).



4-Azidobutanol (2.100).

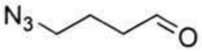
Lithium hydroxide (15.52 g, 370 mmol) was added to a solution of 4-azidobutyl benzoate (**2.99**) (67.48 g, 308 mmol) in reagent grade THF (200 mL), water (81 mL) and methanol (22 mL). The reaction mixture was left to stir overnight. The reaction was then diluted with water (50 mL) and ether (50 mL). The layers were then separated and the aqueous layer was further extracted with ether (3x 50 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a pale yellow oil (33.66 g, 95%).

δ_H (400 MHz, $CDCl_3$), 3.65 (t, J = 6, 2H, CH_2OH), 3.31 (t, J = 6.4, 2H, CH_2N_3), 1.88 (s, 1H, OH), 1.72-1.56 (m, 4H, -CH_2CH_2-).

δ_C (100 MHz, $CDCl_3$), 62.1, 51.3, 29.7, 25.3

IR (cm^{-1}), 3340, 2942, 2874, 2091.

All data was consistent with that of the Literature.[142]



4-Azidobutanal (2.101).

4-Azidobutanol **(2.100)** (2.72 g, 23.69 mmol) was added to a clear solution of IBX (7.96 g, 28.43 mmol) in reagent grade DMSO (30 mL) with external cooling. On complete consumption of starting material by TLC analysis, 6 h, the mixture was diluted with water (90 mL) and filtered through a thick pad of celite, washing thoroughly with EtOAc. The aqueous layer was separated, saturated with NaCl and extracted with EtOAc (3x 50 mL).

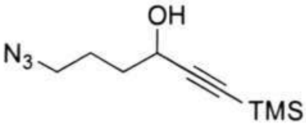
The combined organic layers were washed with sat. aq. $NaHCO_3$ (50 mL), sat. aq. Na_2CO_3 (50 mL), water (50 mL) and brine (50 mL) before being dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a colourless oil (2.16g, 81%), which could be purified by distillation under reduced pressure when required (0.1 torr, ~60 °C).

δ_H (400 MHz, $CDCl_3$), 9.80 (s, 1H, -CHO), 3.35 (t, J = 6.7, 2H, CH_2N_3), 2.58 (q, J = 6.8, 2H, CH_2CHO), 1.91 (dt, J = 13.8, 6.8, 2H, $C\underline{H_2}CH_2N_3$),

δ_C (100 MHz, $CDCl_3$), 200.9, 50.5, 40.8, 21.4.

IR (cm^{-1}), 2936, 2836, 2087, 1710.

All data was consistent with that of the literature.[143]



Rac- 6-Azido-1-(trimethylsilyl)hex-1-yn-3-ol (2.103).

n-Butyl lithium (27 mL, 1.6 M) was added to a solution of trimethylsilylacetylene (6.17 mL, 43.72 mmol) in THF (55 mL) at -78 °C over a period of one hour. 4-Azidobutanal **(2.101)** (3.8 g, 33.63 mmol) in THF (5 mL) was added via cannula. The reaction mixture was stirred at this temperature for 3 h at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was quenched by addition of sat. aq. NH_4Cl at -78 °C, then allowed to warm to RT. The volatiles were removed *in vacuo*, and the mixture was extracted with EtOAc (3x25 mL). The combined organic layers were washed with water (10 mL), brine (10 mL) before being dried over $MgSO_4$.

The solvent was removed *in vacuo* to give the title compound as a pale yellow oil (3.17 g, 82%), without need for purification.

(*R*)-6-Azido-1-(trimethylsilyl)hex-1-yn-3-ol ((*R*)-2.103).

Catecholborane (1.22 mL, 11.48 mmol) was added to a solution of (*S*)-methyl oxazaborolidine [(*S*)-Me CBS] (957 μL, 0.96 mmol, 1 M soln. in toluene) in CH_2Cl_2 (2.5 mL). The catalyst mixture was stirred for 30 min at RT. A solution of ynone **(2.155)** (2 g, 9.57 mmol) in CH_2Cl_2 (2 mL) was briefly held over activated 4 Å mol. sieves, before being transferred by cannula into a fresh reaction vessel, further diluted with CH_2Cl_2 (13 mL) and cooled to -10 °C. The borane solution was then added to the reaction flask dropwise over the period of 1.5 h. Upon complete addition TLC analysis showed complete consumption of the starting material. The reaction mixture was then quenched by addition of excess methanol and allowed to warm to RT slowly. The reaction mixture was concentrated *in vacuo* and transferred directly to a silica gel chromatography column eluting with 2 % EtOAc/hexane to give the title compound as a colourless oil (1.63 g, 81%). The enantiomeric excess was estimated to be 75% *ee* from chiral HPLC analysis (OD-H chiral column, *i*PrOH/hexane).

$[\alpha]^{24}_{D}$ +20.4 (*c* 1, CH_2Cl_2).

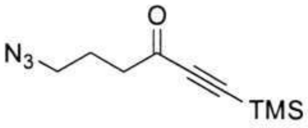
δ_H (400 MHz, $CDCl_3$), 4.41 (br q, *J* = 5.0, 1H, CH(OH)), 3.34 (m, 2H, CH_2N_3), 1.89 (d, *J* = 5.0, 1H, OH), 1.74-1.80 (m, 4H, CH_2CH_2), 0.16 (s, 9H, TMS).

δ_C (100 MHz, $CDCl_3$), 105.9, 90.1, 62.2, 51.1, 34.6, 24.6, -0.0 (3C).

IR (cm^{-1}), 3265, 2096, 1248, 839.

MS (ESI +), *m/z* 212.1 ($[M+H]^+$).

HRESIMS found 212.1222, calc. for $C_9H_{18}N_3OSi$ 212.1219 ($[M+H]^+$).



6-Azido-1-(trimethylsilyl)hex-1-yn-3-one (2.155).

Dess-Martin periodate (7 g, 16.50 mmol) was added to a solution of alcohol **((*rac*)-2.103)** (2.94 g, 13.93 mmol) in CH_2Cl_2 (20 mL) with the exclusion of moisture at -10 °C (ice/salt bath). After 1 h at this temperature, TLC showed complete consumption of the starting material. The white precipitate was removed by filtration through silica gel on celite. Silica gel was then added to the solution and the volatiles were removed *in vacuo* without external heating. The silica gel powder was then transferred to the top of a silica gel column which was eluted with 5 % EtOAc/Hexane to give the title compound after concentration *in vacuo* again without external heating as a colourless oil (2.12g, 73%). The compound was stored at -78°C until required.

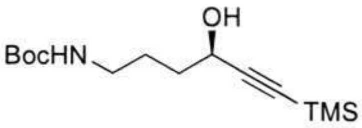
δ_H (400 MHz, $CDCl_3$), 3.33 (t, J = 6.9, 2H, CH_2N_3), 2.68 (t, J = 7.3, 2H, $CH_2C{=}OC$), 1.93 (app. qn, J = 6.9, 2H, CH_2), 0.24 (s, 9H, TMS).

δ_C (100 MHz, $CDCl_3$), 186.1, 101.6, 98.3, 50.5, 42.1, 23.2, -0.7 (3C).

IR (cm^{-1}), 2961, 2099, 1678, 1252.

MS (ESI +), *m/z* 209.1 ($[M]^+$), 137.0 ($[MH\text{-}SiMe_3]^+$).

HRESIMS found 209.0971, calc. for $C_9H_{15}N_3OSi$ 209.0979 ($[M]^+$).



(*R*)-*t*-Butyl 4-hydroxy-6-(trimethylsilyl)hex-5-ynylcarbamate ((*R*)-2.104).

A solution of azide (***R***)-**2.103** (1.54 g, 7.30 mmol) in THF (20 mL) was cooled with an ice water bath. Freshly activated zinc (2.38 g, 36.39 mmol) was added to the reaction mixture cautiously (portionwise), followed by portionwise addition of acetic acid (1.66 mL, 29.11 mmol), the reaction mixture was stirred for 4 h and allowed to warm to RT. TLC analysis showed complete consumption of the starting material. The reaction mixture was quenched by addition of Na_2CO_3 (3.09 g, 29.11 mmol) with vigorous stirring. The mixture was filtered through a pad of celite washing with CH_2Cl_2 (20 mL). The reaction mixture was then placed back into the cold water bath and Na_2CO_3 (3.09 g, 29.11 mmol) was added followed by di-*t*-butyl dicarbonate, (2.06 g, 9.46 mmol). The reaction mixture was allowed to warm to RT and left to stir overnight. The reaction mixture was filtered through a pad of celite washing thoroughly with EtOAc. The solvent was then removed *in vacuo* to give the crude product. Purification by flash chromatography on silica gel eluting with 20 % EtOAc/hexane, gave the title compound as a colourless solid (1.48 g, 71%).

$[\alpha]^{22}_D$ +2.08 (*c* 1, CH_2Cl_2).

δ_H (400 MHz, $CDCl_3$), 4.59 (br s, 1H, NH), 4.39 (q, *J* = 5.9, 1H, -CH(OH)C), 3.18 (br q, *J* = 6.4, 2H, $-CH_2NHC$), 2.00 (br s, 1H, OH), 1.62-1.76 (m, 4H, CH_2CH_2), 1.44 (s, 9H, $C(CH_3)_3$), 0.17 (s, 9H, TMS).

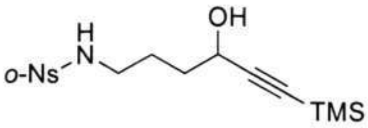
δ_C (100 MHz, $CDCl_3$), 156.1, 106.4, 89.7, 62.5, 40.1, 34.6, 28.4 (3C), 28.2, 25.8, -0.1 (3C).

IR (cm^{-1}), 3350, 2934, 2171, 1691.

MS (ESI +), *m/z* 308.2 ([M+Na]$^+$), 285.2 ([M]$^+$), 212 ([M-TMS]$^+$), 185.1 ([MH-Boc]$^+$)

HRESIMS found 286.1840, calc. for $C_{14}H_{28}NO_3Si$ 286.1838 ([M+H]$^+$).

mp 72-74 °C



ortho-nitrobenzene 4-hydroxy-6-(trimethylsilyl)hex-5-ynylsulfonamide (2.105).

The title compound (1.08 g, 57%) was obtained from azide **2.103**, by the method described for **(*R*)-2.104**, using *ortho*-nitrobenzenesulfonyl chloride, giving the product as a pale yellow oil.

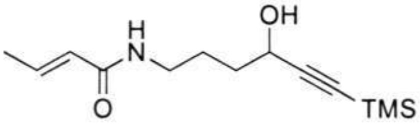
δ_H (400MHz, CDCl$_3$), 8.14 (m, 1H, ArH), 7.86 (m, 1H, Ar), 7.73 (m, 2H, ArH), 5.46 (t, *J*= 5.92, 1H, N$\underline{H}$), 4.38 (br s, 1H, C$\underline{H}$OH), 3.17 (m, 2H, CH$_2$NH), 1.88 (s, 0.5H, OH), 1.74 (q, *J*= 3.2, 4H, CH$_2$CH$_2$CH$_2$), 1.59 (s, 0.5H, OH), 0.16 (s, 9H, TMS).

δ_C (100MHz, CDCl$_3$), 148.1, 133.8, 133.5, 132.8, 131.1, 125.4, 105.7, 90.2, 62.1, 43.5, 34.2, 25.4, -0.19 (3C).

IR 3533, 3345, 2171, 2098, 1539.

MS (ESI +) *m/z* 370.93 ([M]$^+$), 393.06 ([M+Na]$^+$).

HRMS found 393.0918, calc. for $C_{15}H_{22}N_2O_5NaSiS$ 393.0916 ([M+Na]$^+$).



Rac-N-4-Hydroxy-6-(trimethylsilyl)hex-5-ynyl-but-2-enamide (2.106).

The title compound (771 mg, 64%) was obtained from azide (**2.103**), by the method described for **(*R*)-2.104**, using crotonoyl chloride, giving the product as a colourless oil.

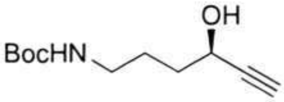
δ_H (400 MHz, CDCl$_3$), 6.83 (dq, *J* = 15.2, 6.2, 1H, CH$_3$CH), 5.77 (dd, *J* = 15.2, 1.4, 1H, COC<u>H</u>CH), 5.60 (br s, 1H, NH), 4.42 (app q, *J* = 5.5, 1H, C<u>H</u>OH), 3.38 (q, *J* = 6.0, 2H, CH$_2$N), 2.27, (br s, 1H, OH), 1.84 (d, *J* = 6.2, 3H, CH$_3$), 1.58-1.75 (m, 4H, CH$_2$CH$_2$), 0.16 (S, 9H, TMS).

δ_C (100 MHz, CDCl$_3$), 166.1, 139.9, 125, 106.4, 89.5, 62.4, 38.9, 34.5, 25.4, 17.7, -0.2 (3C).

IR (cm^{-1}), 3293, 3087, 2171, 1671, 1629, 1551.

MS (ESI +) *m/z* 253.92 ([M]$^+$), 276.03 ([M+Na]$^+$).

HRESIMS found 254.1583, calc. for C$_{13}$H$_{24}$NO$_2$Si 254.1576 ([M+H]$^+$).



(*R*)-*t*-Butyl 4-hydroxyhex-5-ynylcarbamate ((*R*)-2.107).

Potassium carbonate (660 mg, 4.76 mmol) was added to a solution of TMS alkyne **(*R*)-2.104** (1.24 g, 4.33 mmol) in MeOH (10 mL) with exclusion of moisture. The reaction mixture was stirred vigorously for 1 h. At which point TLC analysis showed complete consumption of the starting material. The reaction mixture was quenched by addition of sat. aq. NH_4Cl and the volatiles were removed *in vacuo*. The residue was extracted with ether (3x5 mL), the combined organics were washed with water (5 mL), brine (5 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a colourless oil (0.97 g, quantitative), without need for further purification.

$[\alpha]^{23}_{D}$ +2.5 (*c* 1, CH_2Cl_2)

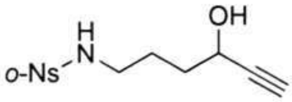
δ_H (400 MHz, $CDCl_3$), 4.60 (s, 1H, NH), 4.41 (dq, *J* = 6.0, 2.3, 1H, -CH(OH)-), 3.18 (br q, *J* = 6.4, 2H, $NHCH_2$), 2.46 (d, *J* = 2.3, 1H, -CCH), 2.27 (s, 1H, OH), 1.60-1.78 (m, 4H, -CH_2CH_2-), 1.44 (s, 9H, $C(CH_3)_3$).

δ_C (100 MHz, $CDCl_3$), 156.1, 84.7, 80.9, 73.2, 62.0, 40.2, 34.6, 28.5 (3C), 25.9.

IR (cm^{-1}), 3357, 3308, 2933, 2114 (weak), 1687.

MS (ESI +) *m/z* 236.0 ($[M+Na]^+$), 428.3 ($[2M+2H]^+$).

HRESIMS found 214.1448, calc. for $C_{11}H_{20}NO_3$ 214.1443 ($[M+H]^+$).



***Rac-ortho*-Nitrobenzene 4-hydroxyhex-5-ynylsulfonamide (2.108)**.

The title compound (325 mg, 78%) was obtained from alkyne (**2.105**), by the method described for **(*R*)-2.107**, giving the product as a colourless oil.

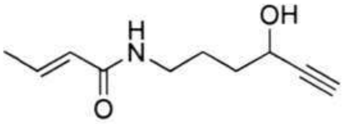
δ_H (400 MHz, $CDCl_3$), 8.14 (m, 1H, ArH), 7.86 (m, 1H, Ar$\underline{H}$), 7.75 (m, 2H, Ar$\underline{H}$), 5.47 (m, 1H, NH), 4.41 (m, 1H, CH(OH)), 3.17 (m, 2H, CH_2NH-), 2.47 (d, J = 2.3, 1H, CCH), 1.95 (m, 1H, OH), 1.76 (m, 4H, CH_2CH_2).

δ_C (100 MHz, $CDCl_3$), 148.0, 133.8, 133.5, 132.8, 131.1, 125.4, 84.0, 73.6, 61.6, 43.4, 34.1, 25.2.

IR (cm-1) 3511, 3099, 2936, 2116, 1537, 1161.

MS (ESI +) *m/z* 298.73 ($[M]^+$), 320.96 ($[M+Na]^+$).

HRESIMS found 299.0690, calc. for $C_{12}H_{15}N_2O_5S$ 299.0702 ($[M+H]^+$).



Rac-N-4-Hydroxyhex-5-ynyl-but-2-enamide (2.109).

The title compound (229 mg, 80%) was obtained from alkyne (**2.106**), by the method described for **(*R*)-2.107**, giving the product as a colourless oil.

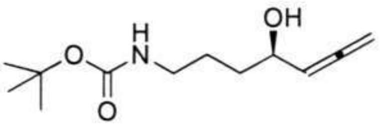
δ_H (400 MHz, $CDCl_3$), 6.83 (dq, J = 15.6, 6.9, 1H, -$CHCHCH_3$), 5.78 (dq, J = 15.6, 1.4, 1H, C$\underline{H}$$CHCH_3$), 5.74 (br s, 1H, NH), 4.44 (m, 1H, C$\underline{H}$(OH)(CCH)), 3.37 (m, 2H, CH_2NH-), 2.86 (d, J = 5.5, 1H, OH), 2.45 (d, J = 1.8, 1H, CC$\underline{H}$), 1.84 (dd, J = 6.9, 1.4, 3H, CH_3), 1.74 (m, 4H, CH_2CH_2).

δ_C (100 MHz, $CDCl_3$), 166.2, 140.1, 124.9, 84.6, 73.1, 61.9, 39, 34.4, 25.4, 17.7.

IR (cm^{-1}) 3289, 2871, 2113, 1668, 1620, 1548, 966.

MS (ESI +) *m/z* 181.99 ($[M]^+$), 204.06 ($[M+Na]^+$).

HRESIMS found 182.1172, calc. for $C_{10}H_{16}NO_2$ 182.1181 ($[M+H]^+$).



(*R*)-7-*t*-Butoxycarbonyl-4-hydroxyhept-1,2-diene ((*R*)-2.111).

A mixture of alkyne **(*R*)-2.107** (957 mg, 4.49 mmol), CuBr (322 mg, 2.25 mmol), diisopropylamine (1.34 mL, 9.43 mmol) and paraformaldehyde (326 mg, 11.23 mmol) in dioxane (20 mL) was heated at reflux for 2 h at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was allowed to cool to RT then air was bubbled through the reaction mixture for 1 h. The mixture was then diluted with EtOAc (10 mL) and sat. aq. NH_4Cl (10 mL), and filtered through a pad of celite washing with EtOAc (5 mL), The organic layer was separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with HCl (10 mL, 2M), water (10 mL) and brine (10 mL) before being dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a pale yellow oil (1.00 g, 99%), without need for further purification.

$[\alpha]^{23}_{D}$ +0.31 (*c* 1, CH_2Cl_2).

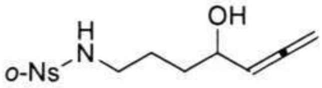
δ_H (400 MHz, $CDCl_3$), 5.24 (app q, *J* = 6.9, 1H, -C$\underline{H}$CCH$_2$), 4.87 (m, 2H, -CHCC$\underline{H}_2$), 4.59 (s, 1H, NH), 4.20 (br s, 1H, -CH(OH)-), 3.16 (br s, 2H, -C$\underline{H}_2$NH-), 1.81 (s, 1H, OH), 1.65-1.54 (m, 4H, -CH$_2$CH$_2$-), 1.26 (s, 9H, C(C$\underline{H}_3$)$_3$).

δ_C (100 MHz, $CDCl_3$), 206.9, 156.1, 94.7, 79.1, 77.7, 69.3, 40.3, 34.3, 28.4 (3C), 26.1.

IR (cm^{-1}), 3350, 2929, 1956, 1687.

MS (ESI +) *m/z* 127.4 ($[MH\text{-}Boc]^+$), 227.6 ($[M]^+$), 250.0 ($[M+Na]^+$), 476.8 ($[2M+Na]^+$).

HRESIMS found 228.1602, calc. for $C_{12}H_{22}NO_3$ 228.1600 ($[M+H]^+$).



***Rac-ortho*-Nitrobenzenesulfonylamino-4-hydroxyhept-1,2-diene (2.112).**

The title compound (242 mg, 74%) was obtained from alkyne (**2.108**), by the method described for **(*R*)-2.111**, giving the product as a pale yellow oil.

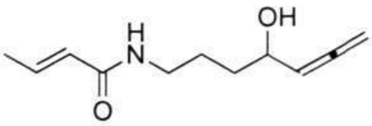
δ_H (400 MHz, $CDCl_3$), 8.13 (m, 1H, ArH), 7.87-7.84 (m, 1H, ArH), 7.76-7.71 (m, 3H, ArH), 5.54 (t, *J* = 5.8, 1H, NH), 5.19 (app q, *J* = 6.8, 1H, -C$\underline{H}$CCH$_2$), 4.87 (m, 2H, -CHCC$\underline{H_2}$), 4.17 (m, 1H, C$\underline{H}$(OH)), 3.14 (q, *J* = 6.8, 2H, CH_2NH), 1.75-1.55 (m, 4H, CH_2CH_2).

δ_C (100 MHz, $CDCl_3$), 206.7, 148.0, 133.6, 133.5, 132.8, 131.1, 125.4, 94.5, 69.0, 43.8, 34.0, 25.7.

IR (cm^{-1}), 3527, 3337, 3100, 2936, 1955, 1593, 1537

MS (ESI +) *m/z* 312.85 ($[M]^+$), 335.04 ($[M+Na]^+$).

HRESIMS found 313.0851, calc. for $C_{13}H_{17}N_2O_5S$ 313.0858 ($[M+H]^+$).



***Rac-N*-4-Hydroxyhept-1,2-diene-but-2-enamide (2.113).**

The title compound (113 mg, 76%) was obtained from alkyne (**2.109**), by the method described for **(*R*)-2.111**, giving the product as a yellow oil.

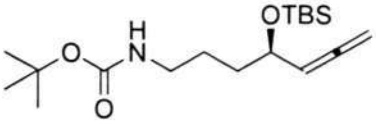
δ_H (400 MHz, CDCl$_3$) 6.84 (dq, *J* = 13.7, 6.8, 1H, -CHC$\underline{H}$CH$_3$), 5.77 (dq, *J* = 13.7, 1.4, 1H, -C$\underline{H}$CHCH$_3$), 5.62 (s, 1H, NH), 5.24 (app q, *J* = 6.4, 1H, C$\underline{H}$CCH$_2$), 4.87 (m, 1H, CHCC$\underline{H}_2$), 4.22 (m, 1H, C$\underline{H}$(OH)CH-), 3.36 (m, 2H, CH$_2$NH), 1.84 (dd, *J* = 6.8, 1.4, 3H, CHCHC$\underline{H}_3$), 1.64 (m, 4H, CH$_2$CH$_2$).

δ_C (100 MHz, CDCl$_3$), 206.9, 166.1, 139.8, 125.0, 94.7, 69.2, 39.2, 34.3, 25.7, 17.7 (additional carbon is layered with the CDCl$_3$ reference)

IR (cm-1), 3289, 3089, 2938, 2872, 1956, 1670

MS (ESI +) *m/z* 195.85 ([M]$^+$), 196.85 ([M+H]$^+$), 218.04 ([M+Na]$^+$).

HRESIMS found 196.1340, calc. for $C_{11}H_{18}NO_2$ 196.1338 ([M+H)$^+$).



(*R*)-7-*t*-Butoxycarbonyl-4-(*t*-Butyldimethylsilyloxy)hepta-1,2-diene ((*R*)-2.114).

A solution of allene **(*R*)-2.111** (1.08 g, 4.76 mmol) in THF (5 mL) was added to a solution of TBSCl (0.93 g, 6.18 mmol), imidazole (0.45 g, 6.66 mmol) and DMAP (6 mg, 0.01 mmol) in THF (15 mL). The reaction mixture was stirred overnight before being diluted with EtOAc (10 mL) and quenched by addition of sat. aq. NH$_4$Cl (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL) and then dried over MgSO$_4$. The solvent was removed *in vacuo* to give the crude product. Purification by column chromatography on silica gel, eluting with 15 % EtOAc/hexane gave the title compound as a colourless oil (1.30 g, 80%).

$[\alpha]^{19}_{D}$ +17.21 (*c* 1, CH_2Cl_2).

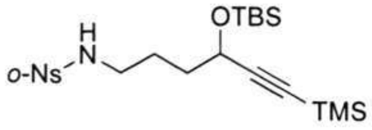
δ_H (400 MHz, $CDCl_3$), 5.08 (app q, *J* = 7.3, 1H, -$CHCCH_2$), 4.74 (m, 2H, -$CHCCH_2$), 4.56 (s, 1H, NH), 4.16 (app. q, *J* = 6.9, 1H, -CH(OH)CH-), 3.12 (br s, 2H, -CH_2NH-), 1.58 (m, 4H, -CH_2CH_2-), 1.44 (s, 9H, $C(CH_3)_3$, 0.88 (s, 9H, $Si(CH_3)_2C(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$-).

δ_C (100 MHz, $CDCl_3$), 207.3, 155.5, 94.6, 79.0, 77.3, 76.1, 71.1, 40.6, 35.7, 28.4 (3C), 25.8 (3C), 18.2, -4.3, -4.9.

IR (cm^{-1}), 2954, 1957, 1694.

MS (ESI +) *m/z* 241.3 ($[MH\text{-}Boc]^+$), 341.9 ($[M]^+$), 364.2 ($[M+Na]^+$).

HRESIMS found 242.2468, calc. for $C_{18}H_{36}NO_3Si$ 342.2464 ($[M+H]^+$).



Rac-7-ortho-Nitrobenzene-4-(t-butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-ynylsulfonamide (2.119).

The title compound (313 mg, 48%) was obtained from azide (**2.117**), by the method described for ***rac*-2.103**, giving the product as a yellow oil.

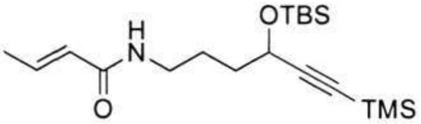
δ_H (400 MHz, $CDCl_3$), 8.14-8.11 (m, 1H, ArH), 7.88-7.85 (m, 1H, Ar), 7.74-7.72 (m, 2H, ArH), 5.31 (s, 1H, NH), 4.33 (t, *J* = 5.5, 1H, -CH(OTBS)CC-), 3.15 (q, *J* = 6.4, 2H, CH_2NH), 1.71-1.63 (m, 4H, CH_2CH_2), 0.87 (s, 9H, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.14 (s, 9H, $Si(C\underline{H}_3)_3$), 0.10 (s, 3H, $Si(C\underline{H}_3)_2C(CH_3)_3$), 0.07 (s, 3H, $Si(C\underline{H}_3)_2C(CH_3)_3$).

δ$_C$ (100 MHz, CDCl$_3$), 148.1, 133.8, 133.5, 132.7, 131.1, 125.4, 106.8, 89.3, 62.7, 43.6, 35, 25.8, 25.4, 18.2, -4.5, -5.01.

IR (cm^{-1}), 3353, 2956, 2171, 1540

MS (ESI +) *m/z* 484.67 ([M]$^+$), 507.13 ([M+Na]$^+$).

HRESIMS found 485.1959, calc. for $C_{21}H_{37}N_2O_5SSi_2$ 485.1962 ([M+H]$^+$).



N-4-(t-Butyldimethylsilyloxy)-6-(trimethylsilyl)hex-5-ynyl-but-2-enamide (2.118).

The title compound (400 mg, 74%) was obtained from azide **2.117**, by the method described for ***rac*-2.103**, giving the product as a yellow oil.

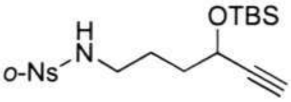
δ$_H$ (400 MHz, CDCl$_3$), 6.82 (dq, *J* = 15.1, 6.9, 1H, CHC$\underline{H}$CH$_3$), 5.77 (dq, *J* = 15.1, 1.8, 1H, C$\underline{H}$CHCH$_3$), 5.52 (s, 1H, NH), 4.38 (t, *J* = 6.0, 1H, C$\underline{H}$(OTBS)CH$_2$), 3.36 (m, 2H, -C$\underline{H}_2$NH), 1.84 (d, *J* = 6.9, 3H, CHCHC$\underline{H}_3$), 1.69 (m, 4H, CH$_2$CH$_2$), 0.89 (s, 9H, C(C$\underline{H}_3$)$_3$), 0.15 (s, 9H, TMS), 0.13 (s, 3H, Si(CH$_3$)$_2$), 0.11 (s, 3H, Si(CH$_3$)$_2$).

δ$_C$ (100 MHz, CDCl$_3$), 165.8, 139.6, 125.1, 107.1, 89.0, 63.0, 38.9, 35.6, 25.9, 25.3, 18.2, 17.7, -0.2, -4.5, -5.

IR (cm^{-1}) 3277, 3083, 2172, 1673, 1630.

MS (ESI +) *m/z* 367.96 ([M]$^+$), 369.00 ([M+H]$^+$), 390.08 ([M+Na]$^+$).

HRESIMS found 390.2266, calc. for $C_{19}H_{37}NO_2NaSi_2$ 390.2261 ([M+Na]$^+$).



Rac-7-_ortho_-Nitrobenzene-4-(_t_-butyldimethylsilyloxy)hex-5-ynylsulfonamide (2.121).

The title compound (221 mg, 83%) was obtained from alkyne (**2.119**), by the method described for **(_R_)-2.107**, giving the product as a yellow oil.

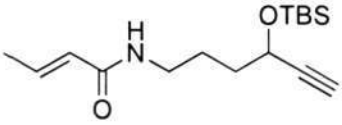
δ_H (400 MHz, $CDCl_3$), 8.15-8.13 (m, 1H, ArH), 7.88-7.85 (m, 1H, ArH), 7.76-7.71 (m, 2H, ArH), 5.31 (t, _J_ = 6.4, 1H, NH), 4.36 (m, 1H, $-CH_2C\underline{H}(OTBS)CCH$), 3.16 (m, 2H, CH_2NH), 2.36 (d, _J_ = 1.8, 1H, $-CC\underline{H}$), 1.70 (m, 4H, CH_2CH_2), 0.87 (s, 9H, $Si(CH_3)_2C(C\underline{H}_3)_3$), 0.11 (s, 3H, $Si(C\underline{H}_3)_2$), 0.08 (s, 3H, $Si(C\underline{H}_3)_2$).

δ_C (100 MHz, $CDCl_3$), 133.8, 133.5, 132.8, 131.1, 125.4, 84.7, 72.6, 62.0, 43.6, 35.1, 25.7 (3C), 25.2, 18.1, -4.7, -5.2.

IR (cm^{-1}), 3353, 3305, 2930, 2858, 2116, 1539

MS (ESI +) _m/z_ 412.93 ($[M]^+$), 435.08 ($[M+Na]^+$)

HRESIMS found 435.1385, calc. for $C_{18}H_{28}N_2O_5NaSiS$ 435.1386 ($[M+Na]^+$).



_N_-4-(_t_-Butyldimethylsilyloxy)hex-5-ynyl-but-2-enamide (2.120).

The title compound (274 mg, 85%) was obtained from alkyne (**2.118**), by the method described for **(_R_)-2.107**, giving the product as a yellow oil.

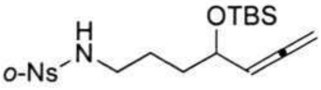
δ_H (400 MHz, $CDCl_3$), 6.82 (dq, J = 15.1, 6.9, 1H, $\mathrm{CHC\underline{H}CH_3}$), 5.76 (dq, J = 15.1, 1.4, 1H, $\mathrm{C\underline{H}CHCH_3}$), 5.51 (s, 1H, NH), 4.39 (dt, J = 5.5, 1.8, 1H, $\mathrm{\text{-}CH_2C\underline{H}(OTBS)CCH}$), 3.35 (m, 2H, $\mathrm{CH_2NH\text{-}}$), 2.39 (d, J = 2.3, 1H, $\mathrm{\text{-}CC\underline{H}}$), 1.84 (dd, J = 6.9, 1.8, 3H, $\mathrm{\text{-}CHCHC\underline{H}_3}$), 1.70 (m, 4H, $\mathrm{CH_2CH_2}$), 0.89 (s, 9H, $\mathrm{Si(CH_3)_2C(C\underline{H}_3)_3}$), 0.13 (s, 3H, $\mathrm{Si(C\underline{H}_3)_2}$), 0.11 (s, 3H, $\mathrm{Si(C\underline{H}_3)_2}$).

δ_C (100 MHz, $CDCl_3$), 165.9, 139.7, 125.0, 85.0, 72.5, 62.3, 39, 35.6, 25.7 (3C), 25.2, 18.2, 17.7, -4.6, -5.1.

IR (cm^{-1}), 3290, 2930, 2858, 2112, 1672, 1627

MS (ESI +) *m/z* 295.23 ($[M]^+$), 296.02 ($[M+H]^+$), 318.09 ($[M+Na]^+$).

HRESIMS found 318.1866, calc. for $C_{16}H_{29}NO_2NaSi$ 318.1865 ($[M+Na]^+$).



Rac-7-_ortho_-Nitrobenzenesulfonamide-4-(_t_-Butyldimethylsilyloxy)hepta-1,2-diene

(2.115).

The title compound (162 mg, 71%) was obtained from alkyne (**2.121**), by the method described for **(*R*)-2.111**, giving the product as a yellow oil.

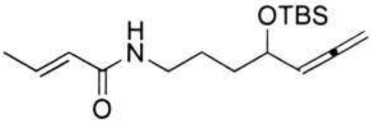
δ_H (400 MHz, $CDCl_3$), 8.15-8.12 (m, 1H, ArH), 7.87-7.85 (m, 1H, ArH), 7.76-7.71 (m, 2H, ArH), 5.28 (t, J = 6.0, 1H, NH), 5.02 (q, J = 6.8, 1H, $\mathrm{C\underline{H}CCH_2}$), 4.75 (ddd, J = 11.0, 6.8, 1.8, $\mathrm{CHCC\underline{H}_2}$), 4.70 (ddd, J = 11.0, 6.8, 2.3, 1H, $\mathrm{CHCC\underline{H}_2}$), 4.12 (m, 1H, $\mathrm{C\underline{H}(OTBS)CH}$), 3.12 (q, J = 6.9, 2H,$\mathrm{\text{-}C\underline{H}_2NH\text{-}}$), 1.64-1.50 (m, 4H, $\mathrm{CH_2CH_2}$), 0.85 (s, 9H, $\mathrm{Si(CH_3)_2C(C\underline{H}_3)_3}$), 0.03 (s, 3H, $\mathrm{Si(C\underline{H}_3)_2}$), 0.01 (s, 3H, $\mathrm{Si(C\underline{H}_3)_2}$).

δ_C (100 MHz, $CDCl_3$), 207.2, 148.1, 133.8, 133.6, 132.7, 131.1, 125.4, 94.4, 70.8, 67.1, 43.9, 35.3, 25.8, 25.6, 18.1, -4.3, -5.

IR (cm^{-1}), 2930, 2857, 1956, 1539

MS (ESI +) *m/z* 427.09 ($[M+H]^+$), 449.14 ($[M+Na]^+$).

HRESIMS found 427.1724, calc. for C19H31N2O5SiS 427.1723 ($[M+H]^+$).



N-4-(t-Butyldimethylsilyloxy)hepta-1,2-diene-but-2-enamide (2.116).

The title compound (203 mg, 71%) was obtained from alkyne (**2.120**), by the method described for **(*R*)-2.111**, giving the product as a yellow oil.

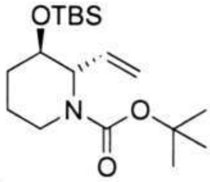
δ_H (400 MHz, $CDCl_3$), 6.84 (dq, *J* = 15.1, 6.8, 1H, $CHCH_3$), 5.79 (dd, *J* = 15.1, 1.7, 1H, $CHCHCH_3$), 5.5 (br s, 1H, NH), 5.11 (q, *J* = 6.7, 1H, $CHCCH_2$), 4.75-4.72 (m, 2H, $CHCCH_2$), 4.17 (m, 1H, CH(OTBS)), 3.34-3.32 (m, 2H, CH_2N), 1.85 (d, *J* = 6.8, 3H, CH_3), 1.59-1.56 (m, 4H, CH_2CH_2), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$) 207.3, 165. 9, 139.6, 125.1, 94.5, 71.1, 67.0, 39.3, 35.8, 25.8, 24.5, 18.1, 17.7, -4.3, -5.0.

IR (cm^{-1}), 3286, 3078, 2954, 2856, 1955, 1674, 1633, 1552

MS (ESI +) *m/z* 309.86 ($[M]^+$), 310.94 ($[M+Na]^+$), 332.13 ($[M+Na]^+$).

HRESIMS found 310.2205, calc. for $C_{17}H_{32}NO_2Si$ 310.2202 ($[M+H]^+$).



(2*S*,3*R*)-1-*t*-Butyloxycarbonyl-3-(*t*-butyldimethylsilyloxy)-2-vinylpiperidine

((*R*)-2.122)

Allene **(*R*)-2.114** (500 mg, 1.47 mmol) was dissolved in CH_2Cl_2 (2 mL) and held over activated 4Å mol. sieves for 5 min. The allene solution was then added via cannula to a solution of $AuCl_3$ (22.2 mg, 0.07 mmol) and $CaCO_3$ (146.8 mg, 1.47 mmol) in acetonitrile (8 μL, 0.016M) and CH_2Cl_2 (8 mL), in the absence of light (prior to addition the solution was a bright yellow colour). After 1 h TLC showed complete consumption of the starting material. The reaction mixture was filtered through celite washing with CH_2Cl_2 (5 mL) before being concentrated *in vacuo* to give the crude product, which was purified by flash chromatography on silica gel eluting with 5 % EtoAc/hexane to give the title compound as a colourless oil (0.494 g, quant.).

$[\alpha]^{22}_{D}$ -5.48 (*c* 1, CH_2Cl_2),

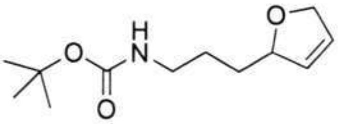
δ_H (400 MHz, $CDCl_3$), 5.72 (ddd, *J* = 17.2, 10.6, 4.8, 1H, $-CH\underline{H}CH_2$), 5.18 (dt, *J* = 10.6, 1.4, 1H, $-CHC\underline{H}_aH_b$), 5.09 (dt, *J* =17.2, 1.8, 1H, $-CHCH_a\underline{H}_b$), 4.64 (s, 1H, $-C\underline{H}CHCH_2$), 4.02 (br d, *J* = 11.4, 1H, $-CH_2N-$), 3.85 (q, *J* = 2.6, 1H, -CH(OTBS)), 2.81 (dt, *J* = 13.7, 3.2, 1H, $-CH_2N-$), 1.99-1.82 (m, 1H, $CH_2C\underline{H_2}CH_2$), 1.6-1.48 (m, 2H, $-CH_2CH(OTBS)$), 1.44 (s, 9H, $C(CH_3)_3$), 0.89 (s, 9H, $C(CH_3)_3$), 0.08 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$).

δ_C (100 MHz, $CDCl_3$), 155.8, 134.2, 116.4, 79.2, 68.5, 60.3, 39.0, 28.5 (3C), 27.5, 25.8 (3C), 19.1, 18.1, -4.9, -5.0.

IR (cm^{-1}), 2953, 2930, 2886, 2857,1694.

MS (ESI +) *m/z* 240.3 ([M-Boc]$^+$), 341.9 ([M]$^+$), 364.1 ([M+Na]$^+$).

HRESIMS found 342.2474, calc. for $C_{18}H_{36}NO_3Si$ 342.2467 ([M+H]$^+$).

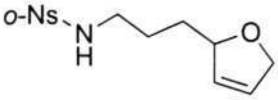


_t_-Butyl 3-(2,5-dihydrofuran-2-yl)propylcarbamate (2.134).

Dihydrofuran formed when opportunistic moisture is present.

δ_H (400 MHz, $CDCl_3$), 5.89 (m, 1H, CHCH), 5.75 (m, 1H, CHCH), 4.84 (br s, 1H, NH), 4.67-4.56 (m, 3H, $CHOCH_2$), 3.14 (br d, *J* = 5.1, 2H, CH_2NH), 1.64-1.52 (m, 4H, CH_2CH_2), 1.43 (s, 9H, $C(CH_3)_3$).

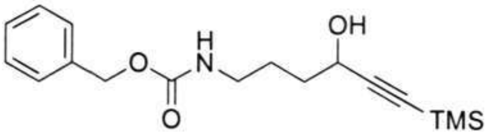
δ_C (125 MHz, $CDCl_3$), 156.0, 129.5, 126.7, 85.7, 79.1, 75.1, 40.6, 33.0, 28.4 (3C), 25.7.



***ortho*-Nitrobenzene 3-(2,5-dihydrofuran-2-yl)propylsulfonamide (2.123).**

Dihydrofuran formed when opportunistic moisture is present.

δ_H (400 MHz, $CDCl_3$), 8.13-8.11 (m, 1H, ArH), 7.84-7.82 (m, 1H, ArH), 7.74-7.71 (m, 2H, ArH), 5.88-5.86 (m, 1H, CHCH), 5.70-5.67 (m, 2H, CHCH, NH), 4.8 (br s, 1H, -C($\underline{H}$)OCH_2C), 4.61-4.59 (m, 2H, -C(H)$OC\underline{H}_2C$), 3.16-3.13 (m, 2H, CH_2NH), 1.66-1.62 (m, 4H, CH_2CH_2).



Benzyl 4-hydroxy-6-(trimethylsilyl)hex-5-ynylcarbamate (2.124).

The title compound (760 mg, 59%) was obtained from azide (**2.103**), by the method described for **(*R*)-2.104**, using benzyl chloroformate giving the product as a colourless oil.

δ_H (400 MHz, $CDCl_3$), 7.39-7.37 (m, 5H, ArH) 5.10 (m, 2H, C$\underline{H_2}$Ar), 4.84 (br s, 1H, NH), 4.40 (br t, *J* = 5.0, 1H, CHOH), 3.26 (br q, *J* = 6.4, 2H, CH_2NH), 1.94 (s, 0.5H, OH), 1.67-1.73 (m, 4H, CH_2CH_2), 1.58 (s, 0.5H, OH), 0.17 (s, 9H, TMS).

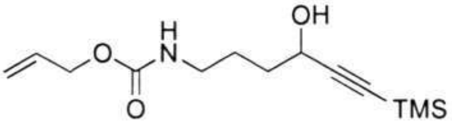
Significant peak broadening was observed, we attribute this to the formation of rotamers.

δ_C (100 MHz, $CDCl_3$), 156.4, 136.5, 128.5 (3C), 128.1 (2C), 106.3, 89.7, 66.6, 62.3, 40.6, 34.5, 25.6, -0.18 (TMS).

IR (cm^{-1}) 3341, 3034, 2956, 2170, 1697, 1529.

MS (ESI +) *m/z* 319.90 ($[M]^+$), 342.10 ($[M+Na]^+$).

HRESIMS found 320.1694, calc. for $C_{17}H_{26}NO_3Si$ 320.1682 ($[M+H]^+$).



Allyl 4-hydroxy-6-(trimethylsilyl)hex-5-ynylcarbamate (2.125).

The title compound (606 mg, 28%) was obtained from azide (**2.103**), by the method described for **(*R*)-2.104**, using allyl chloroformate giving the product as a colourless oil.

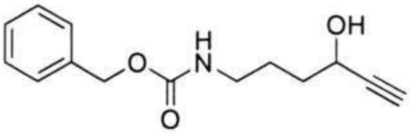
δ_H (400 MHz, $CDCl_3$), 5.92 (ddt, J = 16.7, 10.6, 5.0, 1H, CH_2=C$\underline{H}$=CH_2C), 5.30 (dd, J = 16.7, 1.2, 1H, C$\underline{H_2}$=CH=CH_2C), 5.21 (dd, J = 10.6, 1.2, 1H, CH_2=CH=CH_2C) 4.81 (br s, 1H, NH), 4.57 (d, J = 5.0, 1H, CH_2O), 4.40 (q, J = 5.6, 1H, C$\underline{H}$OH), 3.26 (q, J = 6.4, 2H, CH_2NH), 1.94 (br s,1H, OH), 1.68-1.75 (m, 4H, CH_2CH_2), 0.17 (s, 9H, TMS).

δ_C (100 MHz, $CDCl_3$), 156.3, 132.9, 117.6, 106.2, 89.8, 65.5, 62.4, 40.5, 34.5, 25.7, -0.16 (3C).

IR cm-1, 3343, 2956, 2872, 2170, 1701, 1527

MS (ESI +) *m/z* 270.03 ($[M+H]^+$), 292.03 ($[M+Na]^+$).

HRESIMS found 270.1538, calc. for $C_{13}H_{24}NO_3Si$ ($[M+H]^+$).



Benzyl 4-hydroxy-hex-5-ynylcarbamate (2.126).

The title compound (387 mg, 66%) was obtained from alkyne (**2.124**), by the method described for **(*R*)-2.107**, giving the product as a colourless oil.

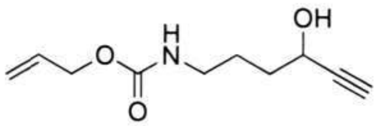
δ_H (400 MHz, $CDCl_3$), 7.35 (m, 5H, ArH), 5.09 (br s, 2H, $ArCH_2$), 4.86 (s, 1H, NH), 4.42 (m, 1H, CH_2C$\underline{H}$(OH)), 3.26 (q, J = 6.4, 2H, CH_2C$\underline{H_2}$NH), 2.47 (d, J = 1.8, CC$\underline{H}$), 1.80-1.61 (m, 4H, -C$\underline{H_2}$C$\underline{H_2}$-).

δ_C (100 MHz, $CDCl_3$), 156.6, 136.6, 128.6 (3C), 128.2 (2C), 84.6, 73.3, 66.8, 61.9, 40.7, 34.5, 25.7.

IR(cm^{-1}) 3293, 2948, 2114, 1691, 1525.

MS (ESI +) *m/z* 247.88 ([M]$^+$), 270.05 ([M+Na]$^+$).

HRESIMS found 248.1290, calc. for $C_{14}H_{18}NO_3$ 248.1287 ([M+H]$^+$).



Allyl 4-hydroxy-hex-5-ynylcarbamate (2.127).

The title compound (335 mg, 75%) was obtained from alkyne (**2.125**), by the method described for **(*R*)-2.107**, giving the product as a colourless oil.

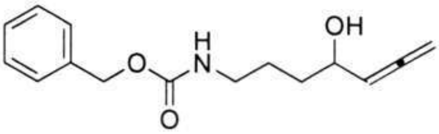
δ_H (300 MHz, CDCl$_3$), 5.92 (ddt, *J* = 17.2, 10.5, 5.3, 1H, CHCHCH$_3$), 5.30 (dd, *J* = 17.2, 1.4, 1H, CH$_2$CH), 5.21 (dd, *J* = 10.5, 1.4, 1H, CH$_2$CH), 4.83 (br s, 1H, NH), 4.56 (br d, *J* = 5.3, 2H, CH$_2$O), 4.43-4.40 (m, 1H, CH(OH)), 3.25 (app q, *J* = 6.4, 2H, CH$_2$NH), 2.47 (d, *J* = 2.1, (br s, 1H, OH), 1.80-1.63 (m, 4H, CH$_2$CH$_2$).

δ_C (100 MHz, CDCl$_3$), 156.4, 133.0, 117.8, 84.5, 73.4, 65.6, 61.9, 40.6, 34.5, 25.7.

IR (cm^{-1}), 3350, 2933, 2870, 2112, 1676, 1527.

MS (ESI +) *m/z* 197.91 ([M]$^+$), 220.05 ([M+Na]$^+$).

HRESIMS found 198.1125, calc. for $C_{10}H_{16}NO_3$198.1130 ([M+H]$^+$).



7-Benzyloxycarbonyl-4-hydroxyhept-1,2-diene (2.128).

The title compound (329 mg, 80%) was obtained from alkyne (**2.124**), by the method described for **(*R*)-2.111**, giving the product as a colourless oil.

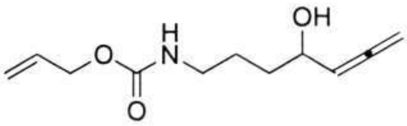
δ_H (400 MHz, CDCl$_3$), 7.36-7.26 (m, 5H, ArH), 5.23 (q, *J* = 6.4, 1H, C$\underline{H}$CCH$_2$), 5.09 (s, 2H, CH$_2$Ar), 4.86 (m, 2H, -CHCC$\underline{H_2}$), 4.20 (s, 1H, C$\underline{H}$(OH)CH), 3.24 (t, *J* = 6.4, 2H C$\underline{H_2}$NH-), 1.80-1.50 (m, 4H, C$\underline{H_2}$C$\underline{H_2}$).

δ_C (100 MHz, CDCl$_3$), 206.9, 156.3, 136.6, 128.5 (3C), 128.1 (2C), 94.7, 69.2, 66.6, 40.8, 34.2, 25.9. (missing carbon was layered under the reference CDCl$_3$)

IR (cm^{-1}), 3336, 2941, 1955, 1693, 1526

MS (ESI +) *m/z* 261.85 ([M]+), 284.07 ([M+Na]+).

HRESIMS found 262.1449, calc. for $C_{15}H_{20}NO_3$ 262.1443 ([M+H]$^+$).



7-Allyloxycarbonyl-4-hydroxyhept-1,2-diene (2.126).

The title compound (288 mg, 80%) was obtained from alkyne (**2.127**), by the method described for **(*R*)-2.111**, giving the product as a colourless oil.

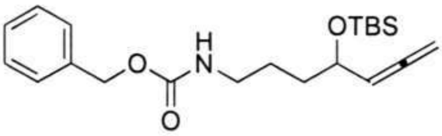
δ_H (400 MHz, $CDCl_3$), 5.91 (ddt, *J* = 16.2, 10.7, 5.6, 1H, $CHCH_3$), 5.33-5.19 (m, 3H, $C\underline{H}_2$=CH, $C\underline{H}CCH_2$), 4.91-4.87 (m, 2H, $CHCCH_2$), 4.55 (br d, *J* = 5.6, 2H, CH_2O), 4.20 (m, 1H, CH(OH)), 3.22 (app br d, *J* = 5.6, 2H, CH_2NH), 2.07 (br s, 1H, OH), 1.68-1.59 (m, 4H, CH_2CH_2).

δ_C (100 MHz, $CDCl_3$), 207.0, 156.4, 133.0, 117.7, 94.8, 69.2, 65.3, 40.5, 34.4, 31.0, 26.1.

IR (cm^{-1}), 3340, 2963, 1945, 1413, 1258

MS (ESI +) *m/z* 211.79 ($[M]^+$), 233.97 ($[M+Na]^+$).

HRESIMS found 234.1112, calc. for $C_{11}H_{17}NO_3Na$ 234.1106 ($[M+Na]^+$).



7-Benzyloxycarbonyl-4-(*t*-Butyldimethylsilyloxy)hepta-1,2-diene (2.130).

The title compound (378 mg, 80%) was obtained from alcohol (**2.128**), by the method described for **(*R*)-2.114**, giving the product as a pale yellow oil.

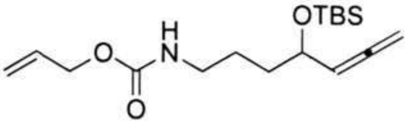
δ_H (400 MHz, $CDCl_3$), 7.36-7.30 (m, 5H, ArH), 5.14-5.05 (m, 3H, $ArC\underline{H}_2$, $C\underline{H}CCH_2$), 4.76 (ddd, *J* = 10.5, 6.4, 1.8, 1H, $-CHCC\underline{H}_2$), 4.72 (ddd, *J* = 10.5, 6.4, 1.8, 1H, $-CHCC\underline{H}_2$), 3.20 (m, $-C\underline{H}_2NH-$), 1.58 (m, 4H, $-C\underline{H}_2C\underline{H}_2-$), 0.87 (s, 9H, $-Si(CH_3)_2C(C\underline{H}_3)_3$), 0.04 (s, 6H, $Si(C\underline{H}_3)_2C(CH_3)_3$).

δ_C (100 MHz, $CDCl_3$), 207.2, 156.3, 136.6, 135.0, 128.5 (2C), 128.1 (2C), 94.6, 71.0, 66.6(2C), 41.0, 35.6, 25.8, 25.6, 18.1, -4.3, -5.0.

IR (cm^{-1}), 2930, 2857, 1956, 1697, 1529

MS (ESI +) *m/z* 375.89 ([M]+), 398.17 ([M+Na]+).

HRESIMS found 376.2307, calc. for $C_{21}H_{34}NO_3Si$ 376.2308 ($[M+H]^+$).



7-Allyloxycarbonyl-4-(*t*-Butyldimethylsilyloxy)hepta-1,2-diene (2.131).

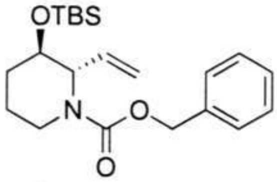
The title compound (970 mg, 63%) was obtained from alcohol (**2.138**), by the method described for **(*R*)-2.114**, giving the product as a colourless oil.

δ_H (300 MHz, $CDCl_3$), 5.92 (ddt, *J* = 16.7, 10.6, 5.6, 1H, $CHCH_2$), 5.30 (dd, *J* = 16.7, 1.3, 1H, $CHCH_2$), 5.20 (dd, *J* = 10.6, 1.3, 1H, $CHCH_2$), 5.09 (app q, *J* = 6.9, 1H, $CHCCH_2$), 4.74 (m, 2H, $CHCCH_2$), 4.55 (br d, *J* = 5.3, 2H, CH_2O), 4.17 (br d, *J* = 6.9, 1H, CH(OTBS)), 3.19 (m, 2H, CH_2NH), 1.63-1.48 (m, 4H, CH_2CH_2), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.05 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 207.3, 156.2, 133.0, 117.6, 94.6, 76.2, 71.1, 65.4, 41.0, 35.6, 31.0, 25.9 (3C), 18.2, -4.3, -4.9.

MS (ESI +) *m/z* 242.77 ($[M]^+$).

HRESIMS found 326.2141, calc. for $C_{17}H_{32}NO_3Si$ 326.2151 ($[M+H]^+$).

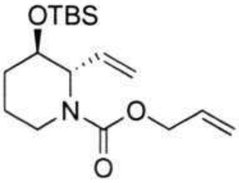


1-benzyloxycarbonyl-3-(*t*-butyldimethylsilyloxy)-2-vinylpiperidine (2.132).

The title compound (23 mg, 23%) was obtained from allene (**2.130**), by the method described for (***R*)-2.122**), giving the product as a colourless oil.

δ_H (400 MHz, CDCl$_3$), 7.34 (m, 5H, ArH), 5.77 (ddd, *J* = 15.4, 10.7, 4.7, 1H, CHCH$_2$), 5.24 (dd, 1H, *J* = 10.7, 5.3, 1H, CHCH$_2$), 5.2 (d, *J* = 12.6, 1H, AB pair CH$_2$Ar), 5.15 (br d, *J* = 15.4, 1H, CHCH$_2$), 5.12 (d, *J* = 12.6, 1H, AB pair CH$_2$Ar), 4.75 (br s, 1H, CH(CHCH$_2$)), 4.11 (br d, *J* = 12.8, 1H, CH$_2$N), 3.9 (app d, *J* = 2.4, 1H, CH(OTBS)), 2.94 (dt, *J* = 12.8, 2.9, 1H, CH$_2$N), 1.99-1.94 (m, 1H, CH$_2$), 1.59 (m, 2H, CH$_2$), 1.32 (m, 2H, CH$_2$), 0.86 (s, 9H, SiC(CH$_3$)$_3$), 0.04 (s, 6H, Si(CH$_3$)$_2$).

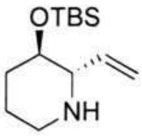
δ_C (100MHz, CDCl$_3$), 156.4, 137.1, 133.8, 128.4 (2C), 127.7 (2C), 127.6, 116.8, 68.4, 66.9, 60.2, 39.6, 27.3, 25.7 (3C), 19.0, 18.0, -4.9, -5.1.



2,3-Allyloxycarbonyl-3-(*t*-butyldimethylsilyloxy)-2-vinylpiperidine (2.133).

The title compound (58 mg, 36%) was obtained from allene (**2.131**), by the method described for (***R*)-2.122**, giving the product as a colourless oil.

All spectral data was identical to that of compound (***R*)-2.133**.



(2*S*,3*R*)-3-(*t*-Butyldimethylsilyloxy)-2-vinylpiperidine (2.165).

Trifluroacetic acid (642 μL, 8.33 mmol) was added to a solution of piperidine **(*R*)-2.167** (284 mg, 0.83 mmol) in CH_2Cl_2 (10 mL) dropwise, with external cooling. After completion of addition, the cold water bath was removed and the reaction mixture was allowed to stir for 2 h. At which point TLC analysis showed complete consumption of the starting material. The reaction mixture was quenched by addition of NaOH (5 mL, 2M). The organic layer was then separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL) before being dried over $MgSO_4$. The solvent was removed *in vacuo* to give the title compound as a brown oil (179 mg, 89%), which was used without further purification.

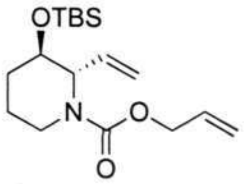
δ_H (400 MHz, $CDCl_3$), 5.86 (ddd, J = 17.7, 10.6, 7.3, 1H, $-CHC\underline{H}CH_2$), 5.34 (dd, J = 17.7, 10.6, 2H, $-CHC\underline{H_2}$, H_aH_b pair), 3.62 (dt, J = 13.7, 9.6, 4.1, 1H, $-CH_2NH$), 3.17 (m, 2H, -CHNH-, CH(OTBS)), 2.75 (dt, J = 16.0, 4.1, 1H, $-CH_2NH$), 2.04 (m, 1H, $CH_2C\underline{H_2}CH_2$), 1.83-2.00 (m, 2H, $C\underline{H_2}CH(OTBS)$), 1.45 (m, 1H, $CH_2C\underline{H_2}CH_2$), 0.86 (s, 9H, $C(CH_3)_3$), 0.07 (s, 3H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$).

δ_C (100 MHz, $CDCl_3$), 133.2, 121.2, 69.7, 64.3, 43.9, 32.9, 25.6 (3C), 21.6, 17.9, -4.4, -4.8.

IR (cm^{-1}), 3422, 2955, 2932, 2887, 2718, 1674.

MS (ESI +) *m/z* 242.10 ($[M+H]^+$).

HRESIMS found 242.1943, calc. for $C_{13}H_{28}NOSi$ 242.1940 ($[M+H]^+$).



(2*S*,3*R*)-Allyloxycarbonyl-3-(*t*-butyldimethylsilyloxy)-2-vinylpiperidine (*R*)-2.133.

Allyl chloroformate (114 μL, 1.08 mmol) was added to a solution of piperidine **2.165** (174 mg, 0.72 mmol) in CH_2Cl_2 (5 mL) containing sodium carbonate (113 mg, 1.08 mmol). TLC analysis showed complete consumption of the starting material after 3 h. The reaction mixture was quenched by addition of sat. aq. NH_4Cl (5 mL) and diluted by addition of CH_2Cl_2 (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL) before being dried over $MgSO_4$. The solvent was removed *in vacuo* to give the title compound as a pale yellow oil (215.6 mg, 92%), which was used without further purification.

$[\alpha]^{22}_D$ -2.90 (*c* 1, CH_2Cl_2).

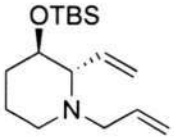
δ_H (400 MHz, $CDCl_3$), 5.92 (ddt, *J* =17.4, 10.6, 5.0, 1H, -$CH_2C\underline{H}CH_2$), 5.74 (ddd, *J* = 17.4, 10.6, 5.0, 1H, -$CHC\underline{H}CH_2$), 5.30-5.08 (m, 4H, $CHC\underline{H}_2$, $CHC\underline{H}_2$), 4.84 (br s, 1H, CHN), 4.64-4.52 (m, 2H, $OC\underline{H}_2CHCH_2$), 4.07 (br d, *J* = 16.0, 1H, CH_2N), 3.87 (q, *J* = 2.3, 1H, CH(OTBS)), 2.90 (dt, *J* = 16.0, 2.7, 1H, CH_2N), 2.03-1.88 (m, 1H, $CH_2C\underline{H}_2CH_2$), 1.67-1.53 (m, 2H, CH_2CH(OTBS)), 1.32 (br d, *J* = 12.8, 1H, $CH_2C\underline{H}_2CH_2$), 0.87 (s, 9H, *t*-Bu), 0.07 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$).

δ_C (100 MHz, $CDCl_3$), 156.0, 133.8, 133.3, 116.9, 116.7, 68.4, 65.8, 60.1, 39.5, 27.3, 25.7 (3C), 19.0, 18.0, -4.9, -5.1.

IR (cm^{-1}) 3085, 2952, 2857, 1699, 1463, 1254.

MS (ESI +) *m/z* 325.2 ([M]$^+$), 326.1 ([M+H]$^+$).

HRESIMS found 326.2141, calc. for $C_{17}H_{32}NO_3Si$ 326.2151 ([M+H]$^+$).



(2*S*,3*R*)-1-Allyl-3-(*t*-butyldimethylsilyloxy)-2-vinylpiperidine (2.166).

A solution of piperidine **(*R*)-2.133** (216 mg, 0.67 mmol) in THF (2 mL) was added via cannula to a solution of tetrakis(triphenylphosphine)palladium(0) (77 mg, 0.07 mmol) in THF (8 mL) in the absence of light. TLC analysis showed complete consumption of the starting material after 5 h. The reaction mixture was concentrated *in vacuo*, before being purified by flash chromatography on silica gel eluting with 5 % EtOAc/hexane to give the title compound as a colourless oil (159 mg, 85%).

$[\alpha]^{24}_{D}$ -35.25 (*c* 1, CH_2Cl_2).

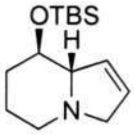
δ_H (400 MHz, $CDCl_3$), 5.83 (dddd, *J* = 17.4, 10.5, 8.2, 5.5, 1H, -$CH_2C\underline{H}CH_2$), 5.58 (ddd, *J* = 18.5, 9.6, 8.7, 1H, -CH($C\underline{H}CH_2$)), 5.24-5.20 (m, 2H, $CHCH_2$), 5.14-5.09 (dd, *J* = 18.5, 8.7, 2H, $CHCH_2$), 3.46 (ddt, *J* = 14.2, 5.5, 1.4, 1H, $NC\underline{H_2}CHCH_2$), 3.40 (ddd, *J* = 11.5, 8.7, 5.0, 1H, CH(OTBS)), 2.88 (dt, *J*= 11.5, 5.0, 1H, $NC\underline{H}(CHCH_2)$), 2.76 (dd, *J* = 14.2, 8.2, 1H, $NC\underline{H_2}CHCH_2$), 2.43 (t, *J* = 8.6, 1H, CH_2N), 1.97 (m, 1H, $C\underline{H_2}CH_2N$), 1.93 (dt, *J* = 15.1, 12.3, 3.2, 1H, CH_2N), 1.67-1.60 (m, 1H, CH_2CH(OTBS)), 1.53 (ddt, *J* = 13.7, 13.3, 5.0, 1H, $C\underline{H_2}$CH(OTBS)), 1.30 (m, 1H, $C\underline{H_2}CH_2N$), 0.85 (s, 9H, *t*-Bu), 0.02 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$).

δ_C (100 MHz, $CDCl_3$), 138.8, 135.0, 119.5, 117.6, 73.6, 71.7, 58.2, 51.5, 34.0, 25.9 (3C), 23.3, 18.1, -4.2, -4.3.

IR (cm^{-1}), 3078, 2894, 2790, 2710, 1642, 1471.

MS (ESI +) *m/z* 282.2 ([M+H]$^+$), 348.2 ([M+Na]$^+$).

HRESIMS found 282.2253, calc. for $C_{16}H_{32}NOSi$ 282.2253 ([M+H]$^+$).



(8*R*,8a*S*)-8-(*t*-Butyldimethylsilyloxy)-3,5,6,7,8,8a-hexahydroindolizine (2.62).

A solution of piperidine **2.166** (60 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) was added via cannula to a solution of tosic acid monohydrate (40 mg, 0.21 mmol) in CH_2Cl_2 (2 mL). The above solution was stirred at RT for 0.5 h, then a solution of Grubbs II catalyst (8.8 mg, 0.01 mmol) in CH_2Cl_2 (1 mL) was added via cannula. The reaction mixture was heated at reflux for 5 h, when TLC analysis showed complete consumption of the starting material. The reaction mixture was then diluted by addition of CH_2Cl_2 (5 mL), and quenched by addition of aq. NaOH (2 mL, 2M). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were dried over $MgSO_4$, before being concentrated *in vacuo* to give the title compound as a brown oil. Purification by column chromatography on silica gel, eluting with 5 % EtOAc/hexane and a trace of triethylamine gave the title compound as a colourless oil (39.4 mg, 73%).

$[\alpha]^{23}_D$ -59.58 (*c* 1, CH_2Cl_2),

δ_H (400 MHz, $CDCl_3$), 6.05 (dd, *J* = 6.4, 1.4, 1H, CHC$\underline{H}$CH), 5.88 (m, 1H, CHC$\underline{H}$CH$_2$), 3.63 (dddd, *J*= 13.3, 2.3, 2.3, 1.4, 1H, CH(OTBS)C$\underline{H}$), 3.46 (ddd, *J* = 13.7, 9.2, 4.4, 1H,

$CH_2C\underline{H}_2N$), 3.23 (dddd, *J* = 13.3, 8.7, 2.3, 2.3, 1H, $C\underline{H}(OTBS)$), 2.91 (dt, *J* = 11.4, 3.6, 1H, $NC\underline{H}_2CH$), 2.86 (m, 1H, CH_2), 2.39 (ddd, *J* = 11.4, 8.7, 6.4, 1H, $NC\underline{H}_2CH$), 1.93 (ddd, *J* = 11.9, 7.8, 4.4, 1H, $CH_2C\underline{H}_2N$), 1.68-1.64 (m, 2H, $C\underline{H}_2CH(OTBS)$), 1.33-1.19 (m, 1H, $C\underline{H}_2$), 0.89 (s, 9H, *t*-Bu), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$).

δ_C (100 MHz, $CDCl_3$), 131.6, 128.6, 74.1, 72.0, 58.0, 48.9, 34.4, 25.8 (3C), 24.5, 18.1, -4.3, -4.7.

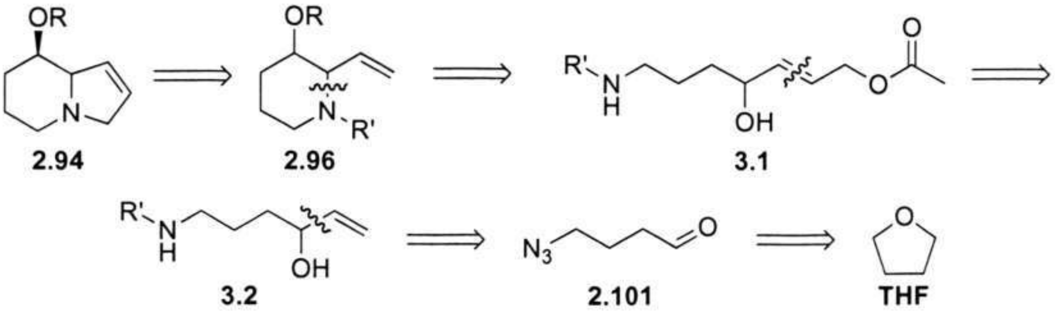
IR (cm^{-1}), 3081, 2884, 2778, 2713, 1470.

All data was consistent with that of the literature.[77]

Chapter 3: Tsuji -Trost Cyclisation route to Swainsonine.

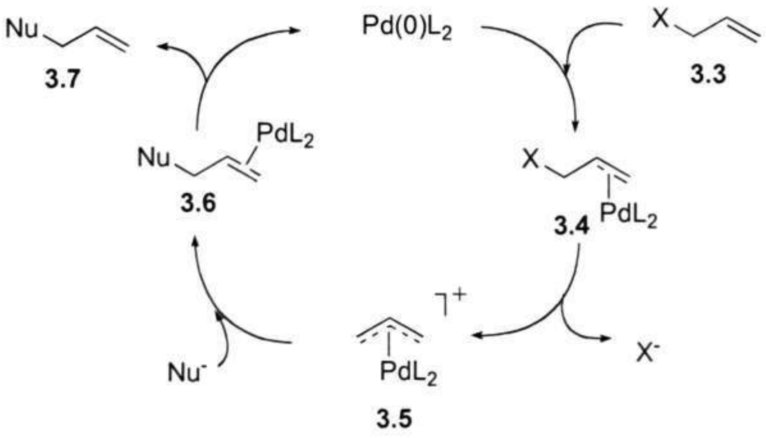
Rethinking our strategy and Reterosynthetic analysis.

With the cyclisation of the allene amines proving to be initially capricious, another method of cyclisation to furnish the piperidine core of the unsaturated indolizidine (**2.94**) was required (Scheme 124).



Scheme 124. Revised retrosynthetic analysis of a known (-)swainsonine intermediate.

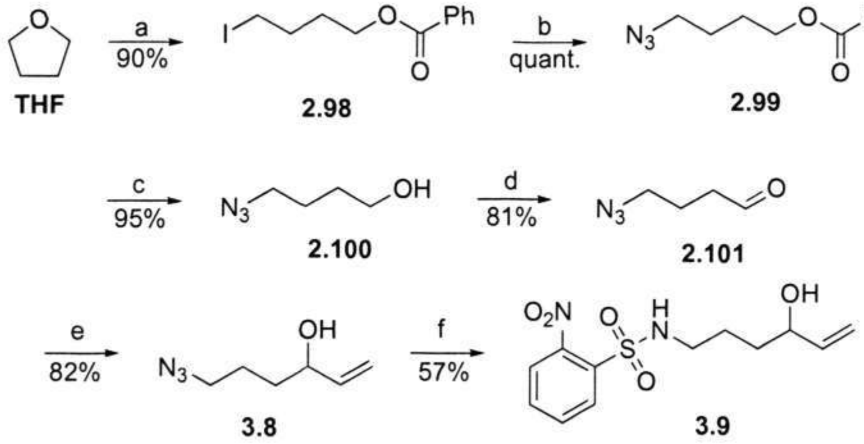
We envisioned that the piperidine (**2.96**) could be obtained from a Tsuji-Trost reaction of an allylic acetate (**3.1**). We thought that as there are no large substituents to direct the attack of the nucleophilic amine onto the π-allyl complex involved in a Tsuji-Trost reaction, that the diastereoselectivity was likely to be an issue. The regioselectivity could also prove to be a challenge as the η^3 π-allyl complex (**3.5**) generated can be attacked at any of the three carbon positions (Scheme 126), thereby generating three different sized rings (when the nucleophile is a pendant group to the π-allyl complex).



Scheme 125. General mechanism for Tsuji-Trost reaction.

The allylic acetate (**3.1**) could be obtained from a cross metathesis of an allylic alcohol (**3.2**) with an allylic alkene. The allylic alcohol (**3.2**) could be obtained from a Grignard addition to aldehyde (**2.101**), which was already known from chapter 2, and can be obtained on a multi-gram scale from THF in a few transformations (Scheme 124).

Results and Discussion

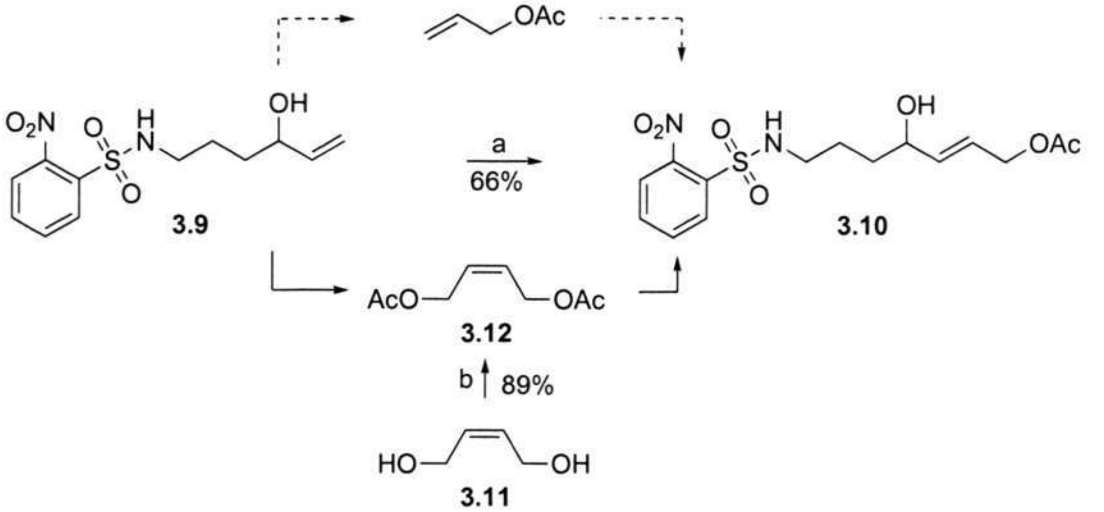


Reagents and Conditions: (a). BenzoylCl, NaI, CH_3CN. (b). NaN_3, DMF. (c). LiOH, THF:H_2O:MeOH. (d). IBX, DMSO. (e). $CH_2CHMgCl$, THF. (f). i. Zn, AcOH, THF, ii. NosylCl, Na_2CO_3, CH_2Cl_2

Scheme 126. Preparation of allylic alcohol.

The requisite 4-azidobutanal (**2.101**) was prepared by an identical procedure as in Chapter 2 (scheme 81), in 70% overall yield. Installation of the allyl group was possible by treatment with vinyl magnesium chloride, and afforded the vinyl alcohol (**3.8**) in 87% yield. Grignard additions are a common method of C-C bond formation, and are exceptionally simple to perform, especially when the Grignard reagent required is commercially available. Initially, we purchased vinyl magnesium chloride (1.6M soln. in THF), and reactions of the Grignard reagent with aldehyde (**2.101**) were carried out in THF at -78 °C but they produced a large amount of precipitate. Changing the solvent to ether allowed us to overcome this problem and provided the desired allylic alcohol (**3.8**) in 87 % yield. The IR spectrum provided proof of the azide, with a peak at 2097 cm^{-1}, and also the presence of the alcohol by a peak at 3402 cm^{-1}. The allylic double bond was observable as a doublet of doublet of doublets at 5.87 ppm, and two doublet of triplets at

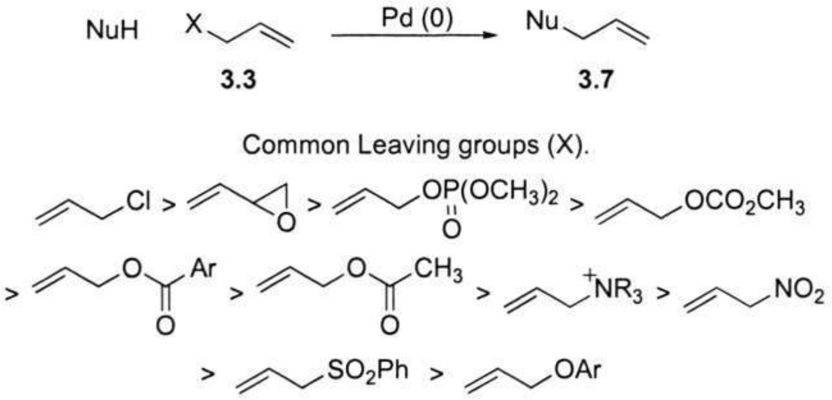
5.19, in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum displayed peaks at 140.7, and 115.2 ppm for the CH, CH_2 respectively, these were distinguished by pendant NMR technique. Surprisingly, this compound proved to be more unstable than the azido alkyne (**2.103**), if allowed to stand at room temperature the initially pale yellow oil would turn dark brown in little more than an hour. Care must therefore be taken to store allylic alcohol (**3.8**) at -78 °C until desired. With the allylic alcohol (**3.8**) in hand, we now turned our attention to reduction of the azide. Due to the success of the one-pot reduction protection of the alkyne (**2.103**), we chose to employ the same method here. Reduction of the azide with activated zinc and protection as the *o*-nitrobenzene sulfonamide proceeded in 43% yield initially. The use of this protecting group was prompted by the limited success of the nosyl allene (**2.115**) to give the dihydrofuran (**2.123**) but not the piperidine in the allene series, and also because it is a commonly employed method for the protection of amines due to the advantages previously discussed. The yield was improved when greater care was taken in the addition of the acid, and with rapid purification, giving the desired compound (**3.9**) in 72 % yield. We believe that the excess nosyl chloride leads to the formation of HCl, it is this that then causes the decomposition of the crude mixture on standing. Installation of the protecting group was verified by loss of the azide in the IR spectrum, and by the presence of the 8.10, 7.83, 7.72 ppm mulitiplets in the ^{1}H NMR spectrum, which are characteristic of the nosyl functionality. Confirmation was also possible from the ^{13}C NMR spectrum in which the characteristic aromatic carbons around the 133 ppm region were observed. The next transformation required a cross metathesis reaction to install the allylic acetate moiety. As mentioned previously cross metathesis has become one of the most powerful methods for the formation of C=C double bonds. The development of Grubbs II generation catalyst greatly improved cross metathesis reactions, due to its more robust nature.[144,145,146,51] In 1998 Grubbs and co-workers reported a general model for selectivity in olefin cross metathesis, within they reported that cross metathesis of a non-terminal olefin in the form of a diacetate (**3.12**) with an allylic alcohol. This reaction was akin to our desired reaction, providing access to an allylic acetate.[147] An advantage of using a non-terminal alkene was that it limits the possibility of byproducts such as dimers.



Reagents and Conditions: (a). Grubbs II, *cis*-butene-1,4-diacetate, CH_2Cl_2, 40 °C. (b). Ac_2O, K_2CO_3, DMAP, CH_2Cl_2, -1 °C.

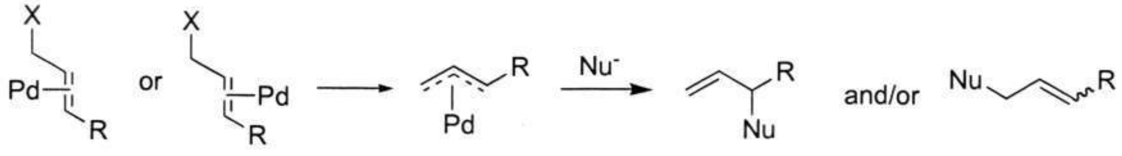
Scheme 127. Grubbs cross metathesis reaction.

The non-terminal alkene (**3.12**) was prepared by double acylation of commercially available *cis*-butene-1,4-diol (**3.11**), under basic conditions in 89 % (Scheme 127). With the diacetate (**3.12**) in hand our attention now turned to the cross metathesis (Scheme 127), our general procedure for cross metathesis used 1 equivalent of the allylic alcohol (**3.9**) and 2 equivalent of the diacetate (**3.12**) with Grubbs II catalyst at reflux. After a short period of time the appearance of the reaction mixture changed greatly, going from the deep red colour, one normally associates with Grubbs II, to a jet-black colour. We concluded that the allylic alcohol had decomposed, after purification by column chromatography the desired allylic acetate (**3.10**) was obtained in 28% yield. Careful control of the metathesis reaction conditions was required. Repetition of the reaction with gradual addition of the catalyst to a refluxing solution of allylic alcohol (**3.9**) in CH_2Cl_2, over a period of two hours allowed for an improved yield of 60 %. While gradual addition of a solution of Grubbs II at room temperature, gave the desired product in a 40 % yield. The compound was clearly identifiable by its ^{1}H spectrum, loss of the doublet of doublet of doublets and the two doublet of triplets that had be assigned as the terminal alkene. In their place was a multiplet at 5.74 ppm, which correlates to the two protons associated with the internal alkene. A triplet at 5.57 ppm (coupling constant of 6.4 Hz), which was assigned as the proton at the quaternary centre. The triplet coupled to a quartet at 3.13 ppm, which we have assigned as the neighbouring CH_2. The apparent doublet at 4.54 ppm was assigned as the CH_2 next to the acetate, and the methyl group was observed as a three proton singlet at 2.07 ppm. The change was also apparent in the ^{13}C NMR spectrum with the downfield shift and change in sign of the terminal alkene CH_2 carbon, as it becomes an internal CH deshielded by the acetate, a shift of 115 to 125 ppm. The stage was now set for the crucial intramolecular Tsuji-Trost reaction.



Scheme 128. Tsuji-Trost allylic alkylation reaction.

The Tsuji-Trost reaction is a palladium catalysed allylic alkylation (Scheme 128, Scheme 125 (mechanism)).[148] Here we are concerned primarily with its use in the formation of heterocycles by cyclisation reactions and many factors that need to be taken into account when performing this reaction.

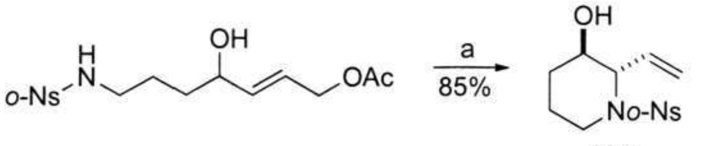


3.13 **3.14** **3.15** **3.16** **3.17**

Scheme 129. Tsuji-Trost issues.

Firstly to be able to obtain the allylation product from the Tsuji-Trost reaction, requires the generation of the π-allyl system (**3.15**), this can be achieved with a Pd(0) catalyst. Another procedure that also provides access to the allylation products, uses Pd(II) catalysis, but this sequence proceeds *via* nucleophilic attack on to the activated alkene. The use of palladium(0) is well established by the work of Trost,[149] and would be the most advantageous as this catalyst is easily prepared and the acetate leaving group should readily be displaced by the internal nucleophile (Scheme 128, Scheme 129). On forming the π-allyl complex there is the issue of the palladium co-ordinating to either face of the double bond (**3.13/3.14**), this rapid equilibrium could give rise to diastereomers. After loss of the acetate, the π-allyl complex (**3.15**) can also be attacked at different positions, each giving different products this can be dependent on the nucleophile.[150] The mechanism of addition is also variable, as the electrophilic intermediate can either be attacked by the nucleophile directly on to one of the carbon atoms or onto the palladium itself followed by migration. This is determined by the nature of the nucleophile, in our example the nucleophile is an amine and as such a soft nucleophile, the method of attack of a soft nucleophile has already been established as direct attack on to the carbon. Common reaction conditions for the preparation of palladium π-allyl systems use a palladium(0) catalyst, the most common being tetrakis(triphenylphosphine)palladium(0). This catalyst is soluble in organic solvents, the most common combination is with THF and in a 1-10 mol% loading. Tetrakis(triphenylphosphine)palladium(0), is commercially available, however, it is often of varying activity and it is best to prepare one's own.

This is possible by a simple reaction of palladium(II) chloride, triphenylphosphine and hydrazine to give tetrakis(triphenylphosphine)palladium(0).[151] Whilst stable for short periods of time in air, storage and use under an inert atmosphere and in the absence of light gives greater results.



3.10 **3.18**

Reagents and conditions: (a). Pd(PPh_3)$_4$ 5 mol%, TMG, THF.

Scheme 130. Our Tsuji-Trost cyclisation.

The initial cyclisation reaction used 5 mol % of tetrakis(triphenylphosphine)palladium(0) in THF with one equivalent of tetramethyl guanidine (TMG), the reaction proceeded in 85% yield, but with a longer reaction time (3 hours) than that of the allene cyclisation. The reaction mixture was concentrated and the palladium residue was removed by column chromatography to give the cyclised piperidine (**3.18**).

The cyclised product was clearly a mixture of diastereoisomers, with the major product observed at 5.75 ppm and the minor at 5.95 ppm as a 10:1 ratio, using the proton of the alkene C(2'). Initially the stereochemistry of the major product was inferred to be the *trans* piperidine (**3.18**), due to the similarity on comparison with the Boc piperidine (**2.127**).

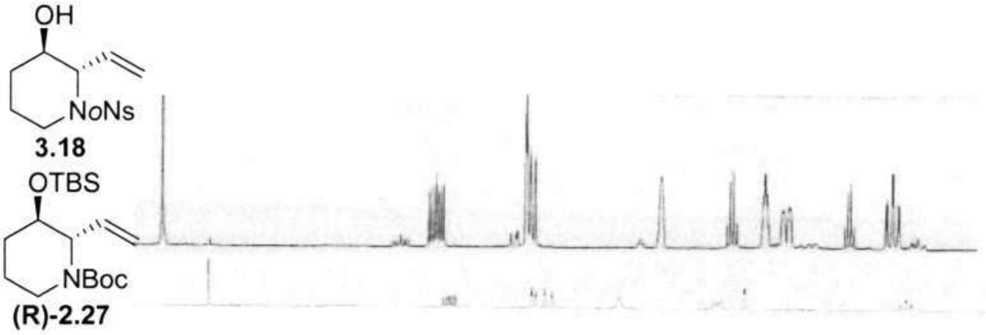
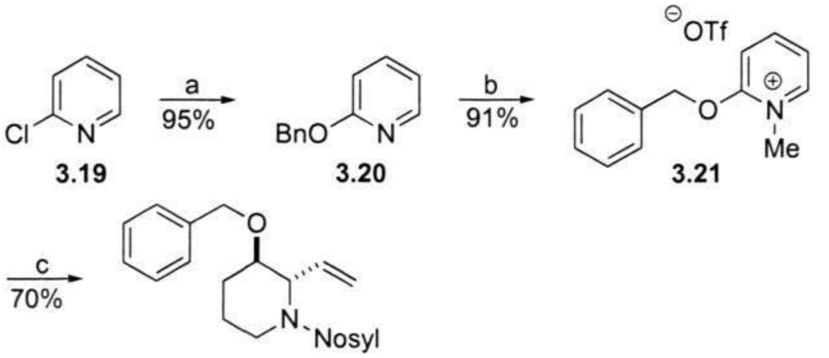


Figure 14. 1H NMR comparisons of the piperidines formed on cyclisation.

The intention now, was to protect the alcohol with the hope that we would be able to separate the diastereomers and confirm the conformation through NMR studies. Many methods for the protection of alcohols are available, yet we required a mild method of achieving either a TBS ether or a benzyl ether, as these two indolizidines are available as formal synthesis targets from Pyne's total synthesis (**2.63**, **2.48**).[75, 77] We chose to proceed with the formation of the benzyl ether, there formation in total synthesis usually use one of two methods. The S_N2 type reaction between an alkoxide and benzyl halide, a Williamson ether synthesis, or a benzyl trichloroacetimidate and acid otherwise know as Bundle reagents,[152] but recently a new protocol was reported by Dudley.[153,154] This procedure does not require any of the harsh acidic/ basic conditions, therefore greatly increasing the applicability of this protecting group. Dudley's procedure uses a stable, neutral organic salt, 2-benzyloxy-1-methylpyridinium triflate (**3.21**). This converts alcohols into benzyl ethers upon warming in the presence of a mild acid scavenger.



3.19 **3.20** **3.21** **3.22**

Reagents and conditions: (a). BnOH, NaOH, Tol. 111 °C. (b). MeOTf, Tol. 0 °C. (c). **3.18**, MgO, DCE, 83 °C.

Scheme 131. Benzylation of the piperidine.

The pyridinium salt was available after a two step synthesis. First coupling of benzyl alcohol and 2-chloropyridine (**3.19**) with sodium hydroxide and azeotropic removal of water gave 2-benzyloxypyridine (**3.20**), however, we used the cheaper $Bu_4N^+Br^-$ in the place of Dudley's 18-crown-6. This benzylated pyridine (**3.20**) was then converted to the triflate salt (**3.21**) by addition of methyl triflate at 0 °C. Treatment with our piperidine (**3.18**) in DCE and using MgO as the acid scavenger gave the desired benzylated crude product (**3.22**). Purification by column chromatography allowed for the isolation of the major isomer as a colourless solid in 70 % yield, however the minor product was only isolated as an oil. The colourless solid did allow us to obtain a single crystal X-ray analysis of structure.

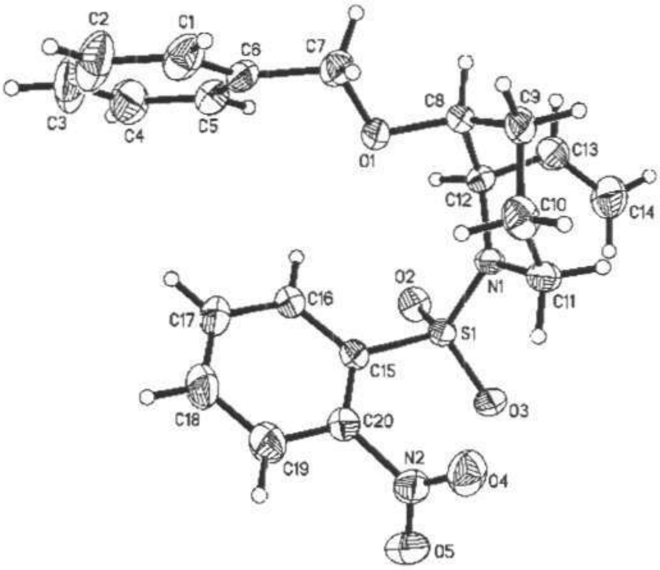
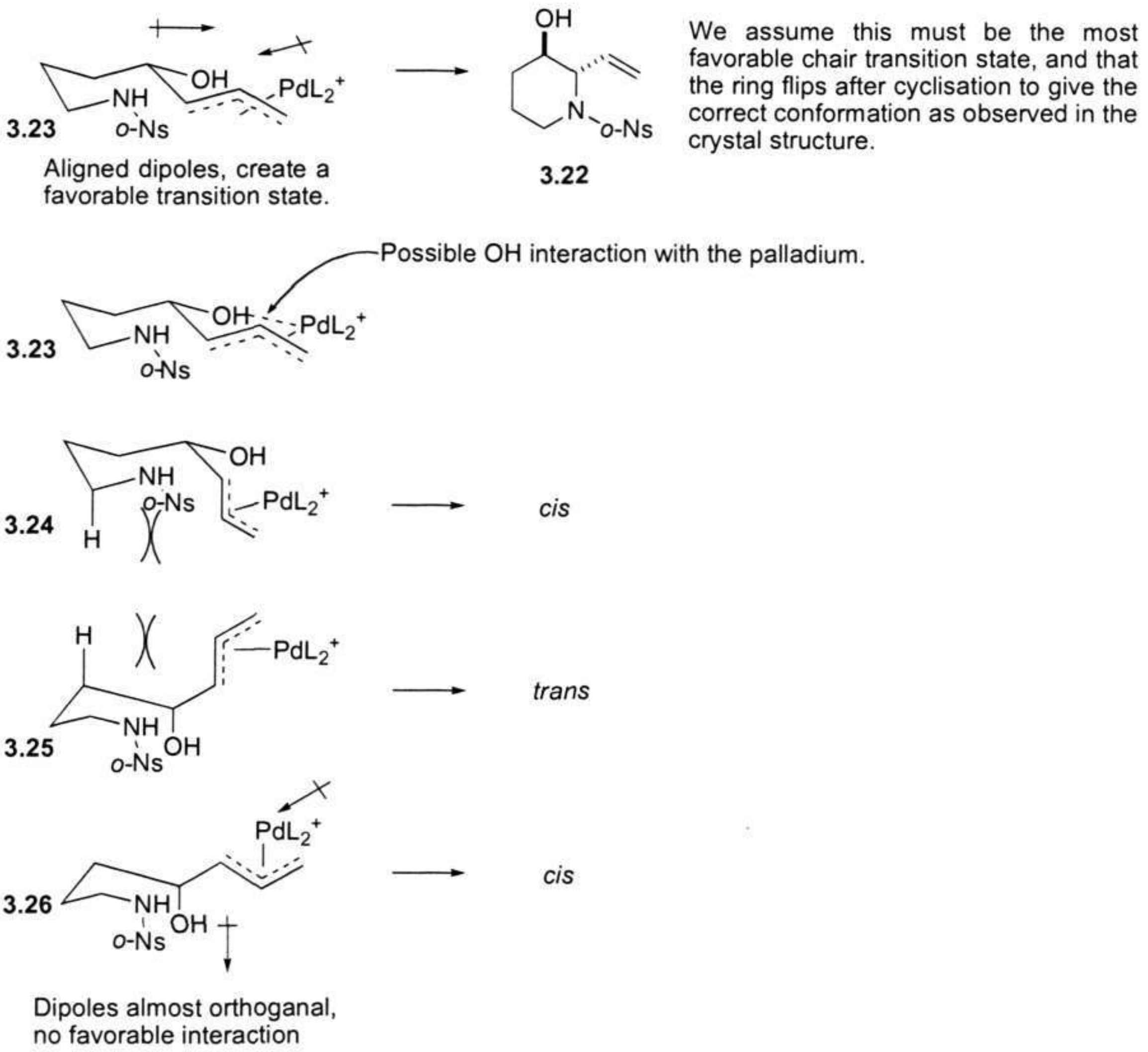


Figure 15. X-Ray structure of Piperidine (**3.22**).

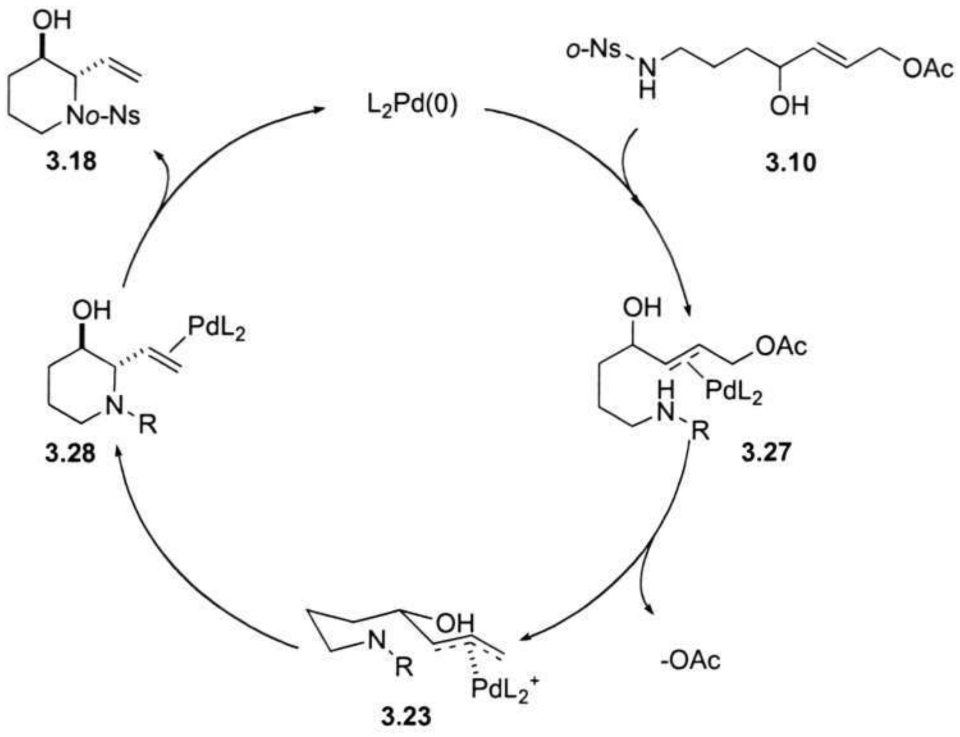
Clearly the crystal shows the hydroxyl group and the alkene in a *trans* relationship. This regiochemistry was interesting, as was the nucleophilic attack at the most hindered carbon of the palladium π-allyl system. The attack at the most hindered (proximal) carbon of the π-allyl system can be explained as the result of multiple factors.[155] Firstly the charge distribution in the palladium π-allyl cation, this will favour attack at the most substituted position. The formation of a 6 membered ring *via* a 6 *exo*-trig over an 8 *endo*-trig and the associate ring strain for the 6 and 8 membered rings. The 6 membered ring formation is representative of the above factors overwhelming the negative steric interaction associated with attack at the more hindered (substituted) carbon. The regiochemical outcome of the cyclisation, giving the *trans*-product in such a highly selective manner we postulate to be the result of an underlying chelation between the alcohol the palladium complex, these interactions could possibly help to maintain an ordered chair transition state such as (**3.23**) (Scheme 133). The interesting diaxial relationship of the alkene and the benzyl alcohol as seen in the crytal structure (Figure 15), has also been observed in the results of Martin and his *N*-acyl piperidines.[156]



Scheme 132. Chair transition states that led to the high level of *trans* diastereoselectivity.

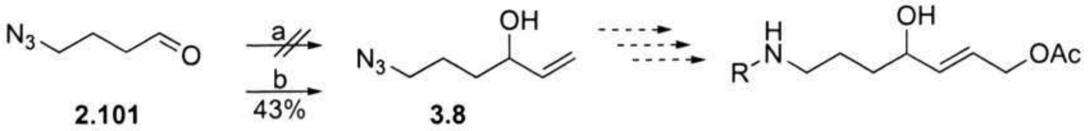
The slight erosion in the selectivity is observed as this chair conformation (**3.23**) is only the more favorable transition state. We were unable to find any corroborating evidence from the Cambridge X-ray crystal data base, to answer the question of whether there is any electronic interaction between the C-O bond and the C-M bond, and are therefore well aware of the speculative nature of our postulation.

The Tsuji-Trost reaction with palladium(0) and a soft nucleophile is known to follow the established catalytic cycle (Scheme 133).[157]



Scheme 133. Tsuji-Trost cyclisation mechanism.

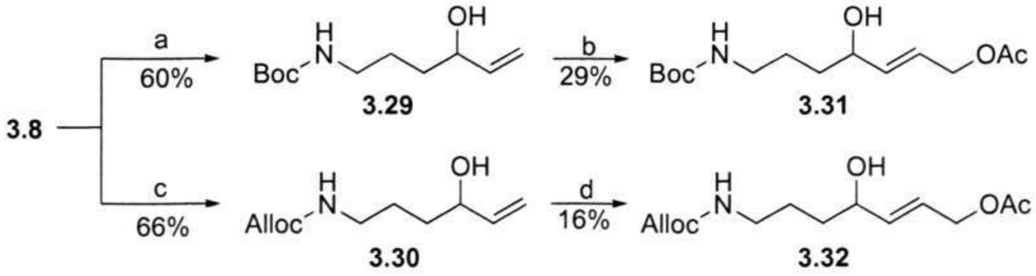
Further exploration of this cyclisation was then undertaken, with the success of the nosyl group, we chose to produce the allyloxycarbamate and *t*-buyloxycarbamates derivative and explore there applicability. As well as explore the effect of protecting the hydroxyl group prior to cyclisation.



Reagents and conditions: (a). $CH_2CHMgCl$, Et_2O. (b). $CH_2CHMgBr$, THF.
Scheme 134. Formation of the Alloc and Boc allylic acetates.

It was at this point that a problem was encountered, whilst initially we were able to obtain the allylic alcohol (**3.8**) using a commercially available Grignard reagent source (Aldrich). The second batch of Grignard reagents purchased proved to be unusable, Fluka bottles as replacements proved to be better. While the Aldrich Grignard reagents were vinyl magnesium chlorides, the Fluka bottles were vinyl magnesium bromides. Reactions of the vinyl magnesium bromides in ether were not as successful leading to the desired allylic alcohol (**3.8**) in 43 % yield, however, by changing the solvent to THF the desired allylic alcohol (**3.8**) was obtained in 89 % yield. Improvement was also attempted by formation of the Grignard reagent under the standard procedure, using vinyl bromide (1M solution in THF, commercially available) and magnesium. This resulted in the desired product being obtained in 83 % yield after addition of the aldehyde.

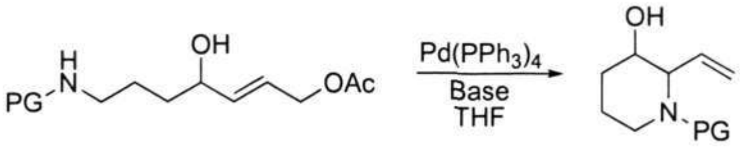
Now with a reliable method for the formation of the vinyl alcohol re-established our attention was focused on the preparation of the Alloc and Boc allylic acetate derivatives (**3.32**) and (**3.31**) (Scheme 135).



Reagents and conditions: (a). i. Zn, AcOH, THF, ii. Boc_2O, Na_2CO_3, CH_2Cl_2. (b). Grubbs II, *cis* butene diacetate, CH_2Cl_2. (c). i. Zn, AcOH, THF, ii. Allyl chloroformate, Na_2CO_3, CH_2Cl_2. (d). Grubbs II, *cis*-butene diacetate, CH_2Cl_2.

Scheme 135. Preparation of the carbamate derivatives.

Reduction of the azide (**3.8**) was accomplished using the established procedure, and gave the Boc allylic alcohol (**3.29**) in 59% yield. The allylic alcohol (**3.29**) was clearly identifiable from the ^1H NMR spectrum, with the terminal alkene observed as a doublet of doublet of doublets at 5.85 ppm, and the doublet of triplets at 5.22 and the doublet at 5.10 ppm. The Boc functionality was observed as a singlet at 1.43 ppm, integrating for 9 protons. The Boc group was also observed in the ^{13}C NMR spectrum with the carbonyl at 156.1 ppm, the ester carbon at 79.2 ppm and the three methyls at 28.4 ppm. Loss of the azide was observed by the change in the IR spectrum. The Alloc protected allylic alcohol (**3.30**) was obtained in 66% yield. The product was clearly identifiable from the ^1H and ^{13}C NMR spectra. Formation of the allylic acetate by Grubbs cross metathesis then gave the Boc allylic acetate (**3.31**) in 29 % yield. The Alloc allylic alcohol (**3.30**) also proved to be a difficult cross metathesis partner and as such the desired Alloc protected allylic acetate (**3.32**) was only obtained in 7 % yield. Poor results in cross metathesis reactions can be attributed to many factors including, the stability of the two alkenes and the propensity of terminal double bonds to undergo self cross metathesis, resulting in the formation of homodimers. Here we were already using a homodimer in the form of the *cis*-butene-1,4-diacetate (**3.12**). The use of such alkenes was reported to limit the formation of undesired self metathesis products. Although not always applicable a larger excess of the *cis*-butene-1,4 diacetate (**3.12**) may be helpful in reducing any non-isolated byproducts of dimerisation. The Alloc allylic alcohol (**3.30**) could also gives rise to the formation of a polymer as it posses two terminal alkenes, this may account for the low yield of the desired product. At this point in time optimization of the reaction procedure was not attempted, as both reactions had produced enough product to attempt their cyclisations.

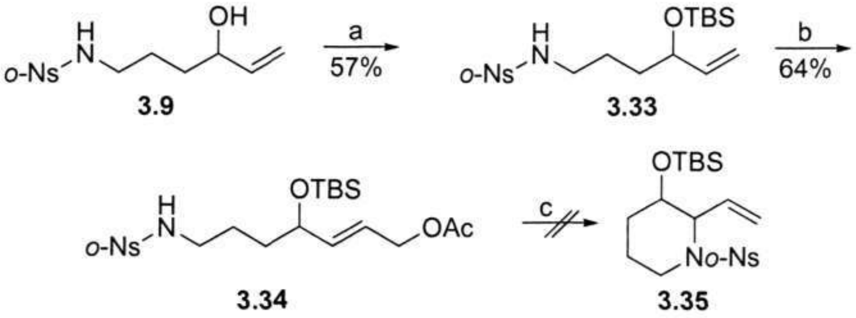


SM	PG	Base	Product
3.31	Boc	TMG	NR[a]
3.31	Boc	K^{t}BuO	NR
3.32	Alloc	TMG	NR[a]

[a] Starting material recovered.

Table 7. Tsuji-Trost cyclisation of the carbamates derivatives.

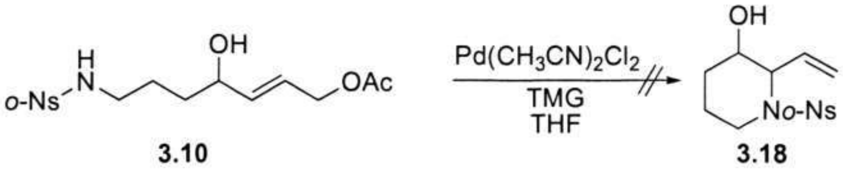
Cyclisation of the Alloc (**3.32**) and Boc (**3.31**) allylic acetates under identical conditions to those established with the nosyl example proved to be unsuccessful (Table 7). The reactions did, however, allow for recovery of starting material. We tried increasing the strength of the base by changing from TMG to potassium *t*-butoxide, but this also failed to provide any of the desired products. This unwillingness to cyclise suggests the reaction is very sensitive to the steric environment of around the nitrogen, maybe with the carbamates preventing the formation of a favourable chair transition state for cyclisation.



Reagents and Conditions: (a). TBSCl, Im., DMAP, THF. (b). Grubbs II, *cis*-butene diacetate, CH_2Cl_2. (C). $Pd(PPh_3)_4$, TMG, THF.

Scheme 136. Preparation of the protected secondary allylic alcohol.

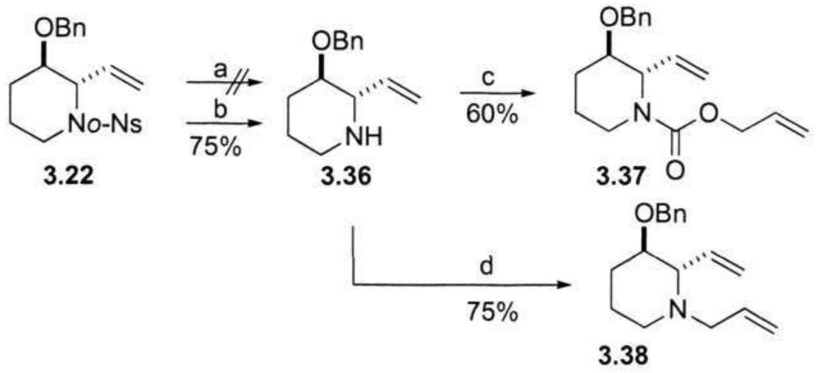
We then intended to address the question about what effect, if any, the size of the protecting group on the hydroxyl would have on the diasteroselectivity of cyclisation. We therefore chose to use a relatively large protecting group and prepared the TBS ether. We thought protection of the hydorxyl group prior to the cross metathesis reaction would be the most advantageous. As the protected product would be less polar than our original precursors to cyclisation and therefore should be much easier to purify from the ruthenium catalyst. Protection of alcohol (**3.9**) under the standard conditions that used imidazole as the base failed to proceed to completion after 24 hours. The reaction mixture was then warmed to 40 °C, which resulted in the formation of the silyl ether in 42% yield (unoptimized). The silyl protecting group was most clearly observed from the ^1H NMR spectrum with the characteristic singlets, loss of the broad OH in the IR spectrum was also observed. The Cross metathesis reaction with an excess of the *cis*-butene-1,4-diacetate (**3.12**), occurred in 64 % yield, providing the precursor to cyclisation (**3.34**). Use of the established cyclisation conditions that consisted of a 5 mol% catalyst loading of tetrakis(triphenylphosphine)palladium(0) and TMG were unsuccessful. We attempted to promote cyclisation by allowing the reaction mixture to stir for a longer duration of time and increasing the reaction temperature, however, both were unsuccessful. Fortunately the reaction conditions did allow for recovery of starting material. We postulate that by functionalising the hydroxyl group with such a large group as TBS, must have increased the steric interactions around the alkene. The increase steric interaction either, prohibits effective chelation of the palladium and therefore prevents formation of the π-allyl system. Or the large protecting group does not allow for the formation of a transition state in which the nucleophile is capable of approaching the π-allyl system. If the mechanism is as we have already discussed, functionalisation would also remove any ability the oxygen possess in assisting in the formation of an ordered transition state.



Scheme 137. Pd(II) allylation attempt.

As both, protection of the hydroxyl group and the use of different protecting groups for the amine prevented the Tsuji-Trost reaction from taking place, we now thought to explore the effect of a different catalytic system. As previously mentioned Pd(II) is also capable of providing the allylated products by nucleophilic attack onto an the activated alkene. A readily available source of Pd(II) was bis(acetonitrile)dichloropalladium(II). However, on substituting this catalyst for the tetrakis(triphenylphosphine)palladium(0) that we used in our established reaction conditions failed to provide any of the desired product. The use of more forcing conditions such as, increasing the reaction temperature to 50 °C, and then to refluxing THF, also failed to bring about cyclisation. We therefore concluded that our initial cyclisation conditions were sufficient, especially as we are able to obtain the desired piperidine (**3.18**) as a single diastereomer after protection as the benzyl ether (**3.22**), therefore no further optimization was attempted and the Pd(II) cyclisation was not pursued any further.

With the single diastereomer of piperidine (**3.22**) now in hand, the 5-membered ring of the indolizidine (**2.48**) was to be installed. By drawing on the conclusions obtained from the allene route, where in the final stage the ring closing metathesis required the formation of a quaternary salt (Table 6), we thought we should explore the ring closing metathesis of a protected amine. Which Pyne has already demonstrated by ring closing a Boc protected amino diene with Grubbs catalyst, without difficulty. We envisioned that by protecting our piperidine amine with an Alloc functionality (**3.38**), we would be able to perform the ring closing metathesis directly generating a 7 membered ring (**3.39**). The 7 membered ring could then be contracted by exposure to tetrakis(triphenylphosphine)palladium(0).



Reagents and conditions: (a). Pyrrolidine, MeOH:CH_3CN. (b). K_2CO_3, EtSH, DMF. (c). Allyl chlorofomate, Na_2CO_3, CH_2Cl_2. (d). Allyl Bromide, NaOH, Tol.

Scheme 138. Preparation of the diene for ring closing metathesis.

Before being able to do Alloc the amine the nosyl protecting group needed to be removed. The most common methods involve malodorous conditions using a thiol and base, we desired mild conditions initially and therefore, we first attempted used an excess of pyrrolidine in a methanol-acetonitrile solvent mixture. However these conditions failed to remove our protecting group and we were forced to turn to a thiol route. Available to us was ethanethiol, the use of thiols needs to be accompanied by a base, Cs_2CO_3 or K_2CO_3 are the most commonly used. Here we chose to use ethanethiol and K_2CO_3 in DMF and found these conditions were capable of removing the nosyl group in 75% yield. The ^1H NMR spectrum of the desired piperidine (**3.36**) varied greatly from that of the starting material and a COSY NMR spectrum was obtained. As an explanation for such a substantial change in the NMR spectrum, we propose that it is possible that the ring flips after deprotection, placing the two substituents diequatorial.

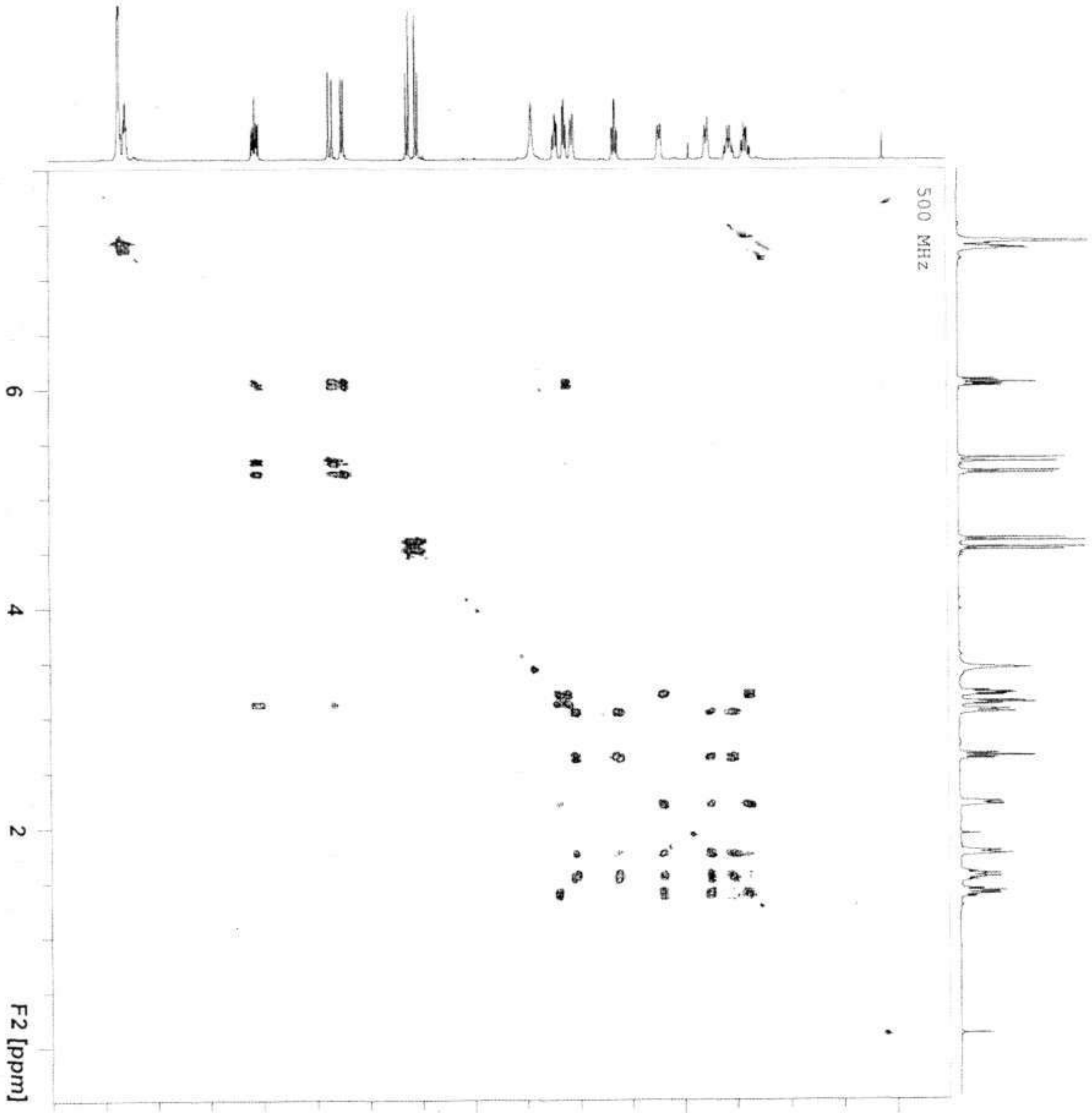
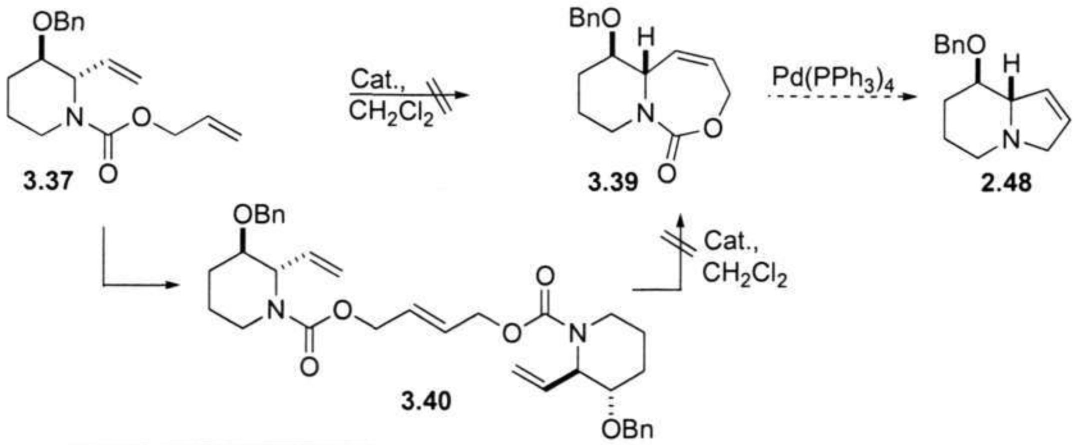


Figure 16. COSY NMR spectrum of the free piperidine (**3.36**).

The proton 2' was the most identifiable as the doublet of doublet of doublets at 6.04 ppm, this showed a cross peak with the broad triplet at 3.10 ppm, which we assigned as the proton of C(2). This broad triplets only other coupling was to the doublet of doublet of doublets at 3.19 ppm which we assigned as the proton of C(3) α to OBn. This proton coupled to two others at 2.19 and 1.38 ppm, which we assigned as the protons of C(4). The proton of C(4) coupled to the two protons of C(5) at 1.75 and 1.53 ppm and this left two other protons at 3.19 and 3.03 ppm unassigned. We have assigned these as the two protons of C(6), as they coupled only to the two protons of C(5), confirming our assignment.

With the free amine **(3.36)** in hand protection as the Alloc was now necessary. By using the standard procedure where allyloxychloroformate and a base react with the amine gave the desired product **(3.37)** in 83% (Scheme 139). The desired product was easily identifiable by the change in the ^{1}H spectrum, which becomes more complex as the Alloc functionality overlays the alkene and benzyl CH_2. The proximal proton of the Alloc was clearly identifiable at 5.92 ppm and the proximal proton of the alkene C(2') were both observed at 5.73 ppm. The four distal protons associated with the two alkenes all coalesce. With the Alloc protecting group now installed, the ring closing metathesis was attempted. The formation of medium sized 5- and 6-membered rings *via* Grubbs RCM is well established in the literature with little difficulty associated with their formation.[158,159] However, when looking at forming larger rings such as 8-, 9- and 10-membered, the reactions become more challenging and are rarely achieved with Grubbs I catalyst, with the use of Grubbs II usually being more successful.[160,161] The predominance for dimerisation is also more pronounced therefore there is a greater need for higher dilution. The use of the slow addition technique (of the catalyst) can help to minimize any dimerisation reactions. The formation of 7-membered ring does not commonly appear to be problematic and we assumed that our ring closing metathesis reaction would be as achievable even without a high dilution factor.

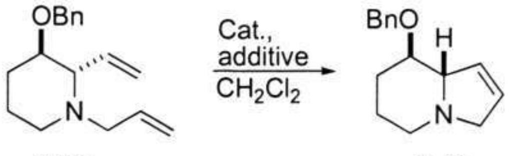


compound	Cat.	Loading	Conc.	Conditions	Product
3.37	Grubbs I	5 mol%	0.01	RT	-^{a}
3.37	Grubbs I	5 mol%	0.01	Reflux	**3.40**
3.40	Grubbs II	5 mol%	0.1	Reflux	-^{a}
3.37	Grubbs II	5 mol%	0.01	Reflux	**3.40**
3.37	Grubbs II	5 mol%	0.001	Reflux	**3.40**^{a}

^{a}Starting material was recovere.

Table 8. Ring closing metathesis conditions.

Ring closing metathesis reactions of (**3.37**) with the less reactive Grubbs I catalyst were unsuccessful, allowing for recovery of the starting material only. Such a result was not unexpected due the increased difficulty associated with formation of a larger ring size. The use of more forcing conditions were also unsuccessful and led to the formation of the homodimer (**3.40**). This was identified from the ^{1}H NMR spectrum but was not rigorously characterized, such homodimers have been reported to cyclise upon themselves when exposed to forcing conditions. Therefore the homodimer was expose to Grubbs II catalyst at a high concentration, but this did not lead to the formation of the desired product. We assume that the alkene is in an axial position and that the Alloc group is also in a quasi axial position, in the place where the nosyl group was observed in the crystal structure (Figure 15), the two dienes are therefore on opposite sides of the molecule.[162] Any transition state that would then place the two alkenes in close proximity would be very strained. Reactions with Grubbs II catalyst with a moderate dilution also led to the formation of the homodimer, but by increasing the dilution and adding the catalyst slowly over 24 hours we reduced the rate of dimerization but also failed to obtain the desired product, recovering mainly starting material (**3.37**). With the formation of the 7-membered ring proving to be a challenge we chose to proceed by forming the 5-membered ring directly. Any remaining Alloc allylic acetate (**3.37**) could be converted to the allylated compound (**3.38**) by an identical manner as demonstrated for the compound ((***R***)-**2.138**) in Scheme 121. However, with no compound in hand at the time allylation of the free piperidine (**3.36**) was attempted directly. Here, the benzyloxy piperidine (**3.36**) was exposed to the standard allylating conditions and the desired allylated piperdine (**3.38**) was obtained in 74% yield. This high yield was in dramatic contrast to the allylation of the TBS ether (**2.170**) equivalent from Chapter 2, which only allylated in 28% yield. The large silyl group must therefore be the stumbling block, providing a large steric interaction that prevents alkylation of the nitrogen. The desired allylated piperidine (**3.38**) was readily identifiable from the now simplified ^{1}H NMR spectrum, as the two alkenes no longer coalesced, with the diene (**3.38**) in hand the ring closing metathesis reaction could now be attempted.



3.38 **2.48**

Cat	Loading	Additive	Yield %
Grubbs I	5 mol%	-	-[a]
Grubbs I	5 mol%	Tosic Acid	56[b]

[a]Starting material was recovere. [b]Isolated yield.

Table 9. Revised ring closing metathesis conditions.

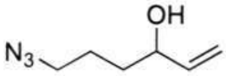
Ring closing metathesis under standard condition with Grubbs I catalyst and no Lewis acid failed to provide any desired product. Again this was attributed to the catalyst coordinating to the NH of the piperidine (**3.38**), preventing any reaction from taking place. The addition of 1 equivalent of tosic acid allowed for coordination of the amine as previously mentioned in Chapter 2. The tosic acid complexed of diene (**3.38**) then reacted with 5 mol% of Grubbs I catalyst to provide the desired indolizidine (**2.48**) in 56 %

isolated yield. An additional fraction of the desired product was also isolated but contained a significant amount of impurity that could be traced to a plasticiser impurity (Table 9). This completed a second formal synthesis of *rac*-swainsonine (**2.1**), the characterization of the benzyloxy indolizidine (**2.48**) was in good consistency with that of Pyne's in the literature.

In summary, we have achieved a highly diastereoselective cyclisation of an allylic acetate (**3.10**) under Tsuji-Trost cyclisation conditions, providing access to the piperidine (**3.18**) in high yield. The high level of selectivity we have attributed to the formation of a favored transition state (**3.23**) in which an oxygen-palladium interaction provided a stabilizing effect. This cyclisation has been utilized in a racemic formal synthesis of a know intermediate (**2.48**) from Pyne's total synthesis of (-)-swainsonine. We are continuing our research in the area to include the formation of both 5- and 7-membered heterocycles *via* an identical cyclisation reaction, and explore the selectivity observed, our research continues.

Chapter 3: Tsuji -Trost Cyclisation route to Swainsonine

Experimental Section



6-Azidohex-1-en-3-ol (3.8).

Vinyl magnesium bromide (29 mL, 1.6M) was added dropwise to a solution of 4-azidobutanal **2.101** (4.05 g, 36 mmol), in diethyl ether (80 mL) at -78 °C. The reaction mixture was stirred at this temperature for 1 h at which point TLC analysis showed complete consumption of the starting material. The reaction was quenched by addition of sat. aq. NH_4Cl (20 mL), before allowing to warm to room temperature, and the volatilities were removed *in vacuo*. The residue was extracted with ether (3x30 mL), the combined organics were then washed with brine and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a yellow oil (4.15 g, 82%).

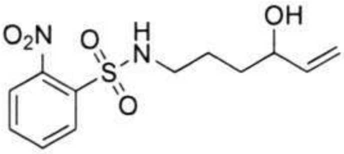
δ_H (400 MHz, $CDCl_3$), 5.87 (ddd, *J* = 17.2, 10.5, 6.4 1H, $CHCH_2$), 5.19 (dd, *J* = 17.2, 10.5, 2H, $CHCH_2$), 4.12 (m, 1H, CH(OH), 3.32 (m, 2H, CH_2N_3), 1.66-1.60 (m, 4H, CH_2CH_2),

δ_C (100 MHz, $CDCl_3$), 140.7, 115.2, 72.6, 51.4, 45.8, 33.9, 24.8

IR (ν/cm^{-1}) 3392, 2933, 2872, 2096, 1641

MS (ESI +) *m/z* 164.8 ($[M+Na]^+$)

HRESIMS found 164.0795, calc. for $C_6H_{11}N_3ONa$ 164.0800 ($[M+Na]^+$).



***N-ortho*-Nitrobenzenesulfonyl-(4-hydroxy-5-enyl)-amide (3.9).**

A solution of azide **3.8** (4.53 g, 32.13 mmol) in THF (60 mL) was cooled with an ice water bath. Freshly activated zinc (10.5 g, 160.6 mmol) was added to the reaction mixture cautiously (portionwise), followed by portionwise addition of acetic acid (7.34 mL, 128.5 mmol), the reaction mixture was stirred for 2 h and allowed to warm to RT. TLC analysis showed complete consumption of the starting material. The reaction mixture was quenched by addition of Na_2CO_3 (8.54 g, 128.5 mmol) with vigorous stirring. The mixture was filtered through a pad of celite washing with CH_2Cl_2 (40 mL). The reaction mixture was then placed back into the cold water bath and Na_2CO_3 (8.54 g, 128.5 mmol) was added followed by *ortho*-nitrobenzene solfunyl chloride, (8.54 g, 38.55 mmol). The reaction mixture was allowed to warm to RT and left to stir overnight. The reaction mixture was filtered through a pad of celite washing thoroughly with EtOAc. The solvent was then removed *in vacuo* to give the crude product. Purification by flash chromatography on silica gel eluting with 40 % EtOAc/hexane, gave the title compound as a viscous, yellow oil (4.18 g, 57%).

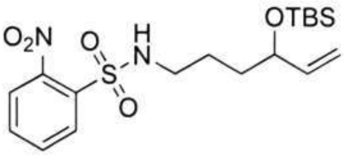
δ_H (400 MHz, $CDCl_3$), 8.10 (m, 1H, ArH), 7.83 (m, 1H, ArH), 7.71(m, 2H, ArH), 5.79 (ddd, J = 17.2, 10.5, 6.0, 1H, $CHCH_2$), 5.13 (dd, J = 17.2, 10.5, 2H, $CHCH_2$), 4.08 (m, 1H, CHOH), 3.12 (q, J = 6.4, 2H, CH_2NH), 1.68-1.48 (m, 4H, CH_2CH_2)

δ_C (100 MHz, $CDCl_3$), 148.0, 140.5, 133.7, 133.5, 132.7, 131.0, 125.3, 115.0, 72.5, 43.7, 33.5, 25.6

IR (ν/cm^{-1}) 3530, 3347, 3096, 1721, 1537, 1162.

MS (ESI +) *m/z* 300.42 ($[M]^+$), 322 ($[M+Na]^+$)

HRESIMS found 323.0678, calc. for $C_{12}H_{16}N_2O_5SNa$ 323.0678 ($[M+Na]^+$).



N-(4-*t*-Butyldimethylsilyloxy)-5-enyl-*ortho*-nitrobenzenesulfonamide (3.33).

A solution of alcohol **3.9** (0.5 g, 1.67 mmol) in THF (2 mL) was added to a solution of TBSCl (0.33 g, 2.17 mmol), imidazole (0.15 g, 2.17 mmol) and DMAP (0.002 g, 0.02

mmol) in THF (2 mL). The reaction mixture was stirred overnight before being diluted with EtOAc (10 mL) and quenched with sat. aq. NH_4Cl (10 mL). The organic layer was separated and the aqueous layer was extracted into EtOAc (3x10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL) before being dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the crude product. Purification by column chromatography on silica gel, eluting with 10 % EtOAc/hexane gave the title compound as a colourless oil (393 mg, 57%)

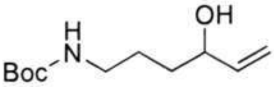
δ_H (400 MHz, $CDCl_3$), 8.14 (m, 1H, ArH), 7.86 (m, 1H, ArH), 7.74(m, 2H, ArH), 5.7 (ddd, *J* = 17.2, 10.4, 5.8, 1H, $CHCH_2$), 5.26 (t, *J* = 6.1, 1H, NH), 5.02 (dd, 2H, *J* = 17.2, 10.4, $CHCH_2$), 3.11 (q, *J* = 5.8, 1H, CH(OH)), 3.11 (q, *J* = 6.1, 2H, CH_2NH), 1.62-1.42 (m, 4H, CH_2CH_2), 0.85 (s, 9H, $Si(CH_3)_2C(CH_3)_3$), 0.01 (s, 6H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 148.0, 141.0, 133.9, 133.4, 132.7, 131.1, 125.4, 114.2, 73.0, 44.0, 34.6, 25.8 (3C), 25.2, 18.2, -4.4, -4.9

IR (ν/cm^{-1}) 3353, 2954, 2857, 1542, 1360, 1168

MS (ESI +) *m/z* 437.14 ($[M+Na]^+$), 414.24 ($[M]^+$).

HRESIMS found 415.1714, calc. for $C_{18}H_{31}N_2O_5SiS$ 415.1723 ($[M+H]^+$).



t-Butyl 4-hydroxyhex-5-enylcarbamate (3.29).

The title compound (450 mg, 60%) was obtained from azide **3.8**, by the method described for (**3.39**), using di-*tert*-butyl dicarbonate, giving the product as a colourless oil.

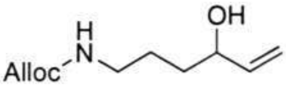
δ_H (400 MHz, $CDCl_3$), 5.85 (ddd, *J* = 17.0, 10.5, 5.5, 1H, $CHCH_2$), 5.22 (dt, *J* = 17.0, 1.4, 1H, $CHCH_2$), 5.1 (d, *J* = 10.5, 1H, $CHCH_2$), 4.61 (s, 1H, NH), 4.12 (q, *J* = 5.5, 1H, CH(OH)), 3.15 (br s, 2H, CH_2NH), 1.83 (br s, 1H, OH), 1.62-1.51 (m, 4H, CH_2CH_2), 1.43 (s, 9H, $C(CH_3)_3$).

δ_C (100 MHz, $CDCl_3$), 156.1, 141.0, 114.8, 79.1, 72.8, 40.3, 33.9, 28.4, 26.0.

IR (ν/cm^{-1}) 3358, 2978, 2931, 2870, 1693, 1520, 1365

MS (ESI +) *m/z* 215 ([M]$^+$), 237.9 ([M+Na]$^+$)

HRESIMS found 238.1423, calc. for $C_{11}H_{21}NO_3Na$ 238.1419 ([M+Na]$^+$).



Allyl 4-hydroxyhex-5-enylcarbamate (3.30).

The title compound (466 mg, 66%) was obtained from **3.8**, by the method described for **(3.30)**, using allyl chloroformate, giving the product as a colourless oil.

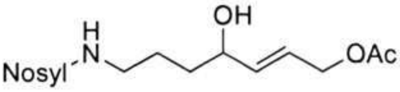
δ_H (400 MHz, $CDCl_3$), 5.91-5.80 (m, 2H, $C\underline{H}CH_2$/ $OCH_2C\underline{H}CH_2$), 5.32-5.1 (m, 4H, $CHC\underline{H_2}$/ $CHC\underline{H_2}$), 4.86 (br s, 1H, NH), 4.55 (br d, *J* = 7.1, 2H, OCH_2CHCH_2), 4.13 (q, *J* = 7.9, 1H, CH(OH)), 3.21 (app. q, *J* = 8.2, 2H, CH_2NH), 1.73-1.48 (m, 4H, CH_2CH_2).

δ_C (100 MHz, $CDCl_3$), 156.4, 141.0, 133.0, 117.7, 115.0, 72.9, 65.6, 40.9, 33.9, 26.0.

IR (ν/cm^{-1}) 3343, 2940, 2872, 1713, 1682, 1531, 1257

MS (ESI +) *m/z* 200.0 ([M+H]$^+$).

HRESIMS found 222.1107, calc. for $C_{10}H_{17}NO_3Na$ 222.1107 ([M+Na]$^+$).



7-(*ortho*-Nitrobenzenesulfonamide)-4-hydroxyhept-2-enyl acetate (3.10)

A solution of allylic alcohol **3.9** (500 mg, 1.67 mmol) and *cis*-butene-1,4-diacetate (573 mg, 3.33 mmol) in CH_2Cl_2 (5 mL) was heated at reflux. A solution of Grubbs II catalyst (43 mg, 5mol%) in CH_2Cl_2 (5 mL) was then added slowly over a 5 h. period, the reaction mixture was held at this temperature overnight. The reaction mixture was allowed to cool to RT, before silica gel (2 g) was added. The volatilities were removed *in vacuo*, to give the crude mixture absorbed onto silica gel. This was then transferred to a silica gel column and purified, eluting with 20% EtOAc/hexane to give the title compound as a yellow oil (409 mg, 66%).

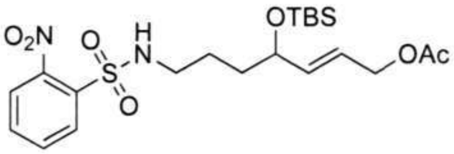
δ_H (400 MHz, $CDCl_3$), 8.13 (m, 1H, ArH), 7.85 (m, 1H, ArH), 7.74 (m, 2H, ArH), 5.74 (m, 2H, CHCH), 5.57 (t, *J* = 6.4, 1H, NH), 4.54 (br d, *J* = 4.1, 2H, CH_2OAc), 4.14 (br s, 1H, CH(OH)), 3.13 (q, *J* = 6.4, 2H, CH_2NH), 2.07 (s, 3H, $C(O)CH_3$), 1.79 (br s, 1H, OH), 1.7-1.53 (m, 4H, CH_2CH_2).

δ_C (100 MHz, $CDCl_3$), 170.9, 148.2, 136.7, 133.8, 133.6, 132.9, 131.2, 125.4, 125.0, 71.5, 64.2, 43.7, 33.7. 25.7, 21.1.

IR (ν/cm^{-1}) 3519, 3335, 2945, 1730, 1540, 1163.

MS (ESI +) *m/z* 372.0 ($[M]^+$), 186 ($[M\text{-}Ns]^+$).

HRESIMS found 395.0870, calc. for $C_{15}H_{20}N_2O_7NaS$ 395.0889 ($[M+Na]^+$).



7-(*ortho*-nitrobenzenesulfonamide)-4-(*t*-butyldimethylsilyloxy)-hept-2-enyl acetate

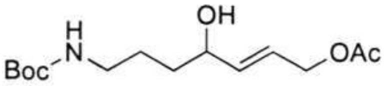
(3.34)

The title compound (218 mg, 64%) was obtained from allylic ether **3.33**, by the method described for (**3.10**), giving the product as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$), 8.14 (m, 1H, ArH), 7.88 (m, 1H, ArH), 7.76 (m, 2H, ArH), 5.66 (br s, 2H, CHCH), 5.27 (t, *J* = 6.2, 1H, NH), 4.51 (br d, *J* = 3.7, CH_2OAc), 4.11 (br q, *J* = 4,1, 1H, CH(OH)), 3.10 (q, *J* = 6.2, 2H, CH_2NH), 2.05 (s, 3H, $C(O)CH_3$), 1.6-1.4 (m, 4H, CH_2CH_2) 0.85 (s, 9H, $SiC(CH_3)_3$), 0.01 (s, 3H, $Si(CH_3)_2$), -0.01 (s, 3H, $Si(CH_3)_2$).

δ_C (100 MHz, $CDCl_3$), 170.8, 148.1, 137.3, 133.8, 133.5, 132.8, 131.1, 125.4, 123.9, 71.8, 64.3, 43.9, 34.6, 25.8, 25.2, 21, 18.2, -4.4, -4.9

IR (ν/cm^{-1}) 3329, 2952, 2886, 1744, 1752, 1168



7-(*t*-butoxycarbonylamino)-4-hydroxyhept-2-enyl acetate (3.31).

The title compound (194 mg, 29%) was obtained from allylic alcohol **3.31**, by the method described for (**3.10**), giving the product as a colourless oil

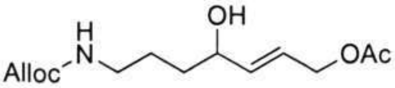
δ_H (400 MHz, CDCl$_3$), 5.78 (m, 2H, CHCH), 4.57 (br s, 1H, NH), 4.55 (app. d, *J* = 5.0, 2H, CH$_2$OAc), 4.17 (br s, 1H, CH(OH)), 3.15 (br s, 2H, CH$_2$NH), 2.07 (s, 3H, C(O)CH$_3$), 1.85 (br s, 1H, OH), 1.58-1.55 (m, 4H, CH$_2$CH$_2$), 1.44 (s, 9H, ^{t}Bu).

δ_C (100 MHz, CDCl$_3$), 173.5, 138.6, 129.2, 125.6, 70.6, 62.8, 58.4, 31.3, 25.6 (3C), 23.2, 17.8, 17.7

IR (ν/cm^{-1}) br 3373, 2977, 2873, 1738, 1691, 1563, 1249.

MS (ESI +) *m/z* 287.17 ([M+H]$^+$), 310.12 ([M+Na]$^+$)

HRESIMS found 288.1811, calc. for $C_{14}H_{26}NO_5$ 288.1811 ([M+H]$^+$).



7-(allyloxycarbonylamino)-4-hydroxyhept-2-enyl acetate (3.32).

The title compound (21 mg, 16%) was obtained from allylic alcohol **3.30**, by the method described for (**3.10**), giving the product as a pale yellow oil.

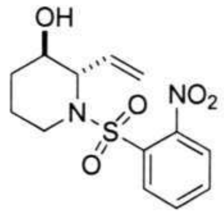
δ_H (300 MHz, CDCl$_3$), 5.92 (ddt, *J* = 17.2, 10.5, 5.1, 1H, CH$_2$C$\underline{H}$CH$_2$), 5.78-5.76 (m, 2H, CHCH), 5.25 (ddt, *J* = 17.2, 10.5, 1.5, 2H, -CH$_2$CHC$\underline{H_2}$), 4.86 (br s, 1H, NH), 4.56-4.54 (m, 4H, -CH$_2$O, -CH$_2$O), 4.16 (br s, 1H, CH(OH)), 3.21 (app. q, *J* = 6.0, NHCH$_2$), 2.07 (s, 3H, C(O)CH$_3$), 1.60-1.55 (m, 4H, CH$_2$CH$_2$).

δ_C (100 MHz, CDCl$_3$), 170.8, 156.4, 136.9, 132.9, 124.6, 117.6, 71.6, 65.5, 64.2, 40.7, 33.8, 25.9, 20.9

IR (ν/cm^{-1}) br 3339, 3082, 2940, 2872, br 1700, br 1531, br 1242.

MS (ESI +) *m/z* 272.0 ($[M+H]^+$), 294.12 ($[M+Na]^+$).

HRESIMS found 272.1501, calc. for $C_{13}H_{22}NO_5$ 272.1498 ($[M+H]^+$).



1-*ortho*-Nitrobenzenesulfonyl-3-hydroxy-2-vinylpiperidine (3.18).

A solution of allylic acetate **3.10** (389 mg, 1.05 mmol) in THF (5 mL), was added via cannula to a solution of tetrakis(triphenylphosphine)palladium(0) (60 mg, 5 mol%) in THF (5 mL) in the absence of light. Tetramethyl guanidine (131 μL, 1.05 mmol) was then added and the reaction was followed by TLC analysis till completion (4 h). The reaction mixture was then concentrated *in vacuo*, before being purified by flash chromatography on silica gel, eluting with 30% EtOAc/hexane to give the title compound as a colourless oil (280 mg, 85%).

Major isomer

δ_H (400 MHz, $CDCl_3$), 8.12-8.05 (m, 1H, ArH), 7.71-7.62 (m, 3H, ArH), 5.75 (ddd, J = 17.1, 10.9, 5.0, 1H, $CHCH_2$), 5.23 (ddd, J = 17.1, 10.9, 1.1, 2H, $CH\underline{H_2}$), 4.51 (br s, 1H, $C\underline{H}CHCH_2$), 3.94 (dt, J = 3.2, 2.9, 1H, CH(OH)), 3.83 (br d, J = 13.1, 1H, $-CH_2N-$), 3.24 (dt, J = 13.1, 2.9, 1H, $-CH_2N-$), 1.98-1.85 (m, 1H, $CH_2C\underline{H_2}CH_2$), 1.78-1.63 (m, 2H, $C\underline{H_2}CH(OH)$), 1.49 (m, 1H, $CH_2C\underline{H_2}CH_2$).

δ_C (100 MHz, $CDCl_3$), 148.0, 133.7, 133.4, 132.0, 131,8, 131.1, 124.3, 124.1, 118.9, 67.5, 61.6, 41.9 , 25.6, 19.0

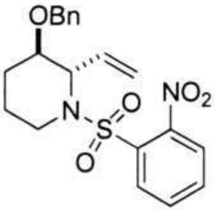
IR (ν/cm^{-1}) 3549, 3021, 1719, 1542, 1371, 1163.

MS (ESI +) *m/z* 268.9 ($[M+H]^+$), 290.9 ($[M+Na]^+$)

HRESIMS found 290.0825, calc. for 290.0827 ($[M+Na]^+$).

Minor isomer of (3.18).

δ_H (400 MHz, $CDCl_3$), 8.12-8.05 (m, 1H, ArH), 7.71-7.62 (m, 3H, ArH), 5.95 (ddd, *J* = 17.0, 10.7, 6.3, 1H, C$\underline{H}$CH$_2$), 2.81 (dd, *J* = 17.0, 10.7, 2H, CHC$\underline{H}_2$). 4.62 (br s, 1H, C$\underline{H}$CHCH$_2$), 3.89 (m, 1H, CH(OH)), 3.59 (m, 1H, CH_2N), 3.10 (dt, *J* = 13.2, 2.8, 1H, CH_2N), 1.98-1.45 (m, 4H, CH_2).



1-*ortho*-Nitrobenzenesulfonyl-3-(benzyloxy)-2-vinylpiperidine (3.22).

A solution of piperidine **3.18** (280 mg, 0.90 mmol) in dichloroethane (1 mL) was added to a solution of 2-benzyloxy-1-methylpyridinium triflate (600 mg, 1.80 mmol) and MgO (71 mg, 1.80 mmol) in dichloroethane (1 mL). The reaction mixture was heated at reflux for 21 h at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was then cooled to RT and filtered through a pad of celite. The filtrate was concentrated *in vacuo* to give the crude product. Purification by column chromatography on silica gel, eluting with 5% EtOAc/hexane gave the title compound as a colourless solid (253 mg, 70%).

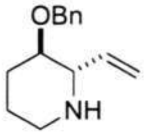
δ_H (400 MHz, $CDCl_3$), 8.20 (d, *J* = 7.7, 1H, ArH), 7.62-7.55 (m, 2H, ArH), 7.47-7.34 (m, 6H, ArH), 5.78 (ddd, *J* = 17.3, 10.7, 4.4, 1H, $CHCH_2$), 5.34 (ddd, *J* = 17.3, 10.7, 1.8, 2H, $CHCH_2$), 4.83 (br s, 1H, $CHCHCH_2$), 4.54 (d, *J* = 11.4, 1H, AB pair CH_aH_bAr), 4.46 (d, *J* = 11.4, 1H, AB pair CH_aH_bAr), 3.79 (br d, *J* = 13.5, 1H, -C$\underline{H}_2$N-), 3.65 (app. d, *J* = 2.6, 1H, C$\underline{H}$(OBn), 3.32 (dt, *J* = 13.5, 3, 1H, -C$\underline{H}_2$N-), 2.05-1.91 (m, 2H, CH(OBn)C$\underline{H}_2$C$\underline{H}_2$), 1.64 (dt, *J* = 13.5, 2.5, 1H, -C$\underline{H}_2$CH$_2$N-), 1.47-1.43 (m, 1H, CH(OBn)C$\underline{H}_2$CH$_2$).

δ_C (100 MHz, $CDCl_3$), 148.1, 137.9, 134.2, 132.7, 132.6, 131.3, 130.5, 128.3 (2C), 127.6 (2C), 127.5, 123.6, 118.5, 74.2, 70.2, 58.4, 41.4, 23.1, 18.9

IR (ν/cm^{-1}), 2943, 1543, 1372, 1164.

MS (ESI +) *m/z* 403.06 ([M+H]$^+$), 311.04 ([M-Bn]$^+$), 216.13 ([M-Ns]$^+$), 186.02 ([Ns]$^+$), 140.13 ([Ns-NO$_2$]$^+$), 91.08 ([Bn]$^+$).

HRESIMS found 311.0686, calc. for $C_{13}H_{15}O_5N_2S$ 311.0683 ([M-Bn]$^+$).



3-(Benzyloxy)-2-vinylpiperidine (3.36).

To a solution of piperidine **3.22** (315 mg, 0.78 mmol) in DMF (4 mL), was added K_2CO_3 (0.87 g, 6.27 mmol) and ethanethiol (308 μL, 3.92 mmol). The reaction mixture was stirred for 1 h at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was quenched by addition of sat. aq. NH_4Cl (10 mL) and stirred vigorously for 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), before being dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the crude product. Purification by column chromatography on silica gel, eluting with 80% EtOAc/hexane then 10% MeOH/CH_3Cl plus one drop of Et_3N, gave the title compound as a pale yellow oil (127 mg, 75%).

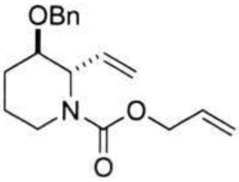
δ_H (500 MHz, $CDCl_3$), 7.31-7.23 (m, 5H, ArH), 6.04 (ddd, J = 17.3, 10.5, 6.6, 1H, $CHCH_2$), 5.27 (dd, J = 17.3, 10.5, 2H, $CHCH_2$), 4.59 (d, J = 11.7, 1H, AB pair CH_aH_bAr), 4.50 (d, J = 11.7, 1H, AB pair CH_aH_bAr), 3.46 (s, 1H, NH), 3.19 (ddd, J = 10.5, 8.8, 4.2, 1H, -CH(OBn)-), 3.1 (br t, J = 8.8, -$C\underline{H}(CHCH_2)$-), 3.03 (dt, J = 11.9, 2.9, 1H, -CH_2NH-), 2.62 (dt, J = 11.9, 2.9, 1H, -CH_2NH-), 2.19 (m, 1H, -$C\underline{H_2}CH(OBn)$-), 1.75 (dt, J = 13.6, 3.6, 1H, $CH_2C\underline{H_2}CH_2$), 1.53 (app. ddt, J = 13.6, 6.4, 3.6, 1H, $CH_2CH_2CH_2$), 1.38 (app. ddt, J = 12.8, 10.5, 4.2, 1H, -$C\underline{H_2}CH(OBn)$-).

δ_C (100 MHz, $CDCl_3$), 138.6, 138.6, 128.2 (2C), 127.6 (2C), 127.4, 115.8, 78.8, 71.1, 64, 45.5, 30.3, 24.9.

IR (ν/cm^{-1}), 3449, 2938, 2864, br 1640, 1453, 1099.

MS (ESI +) *m/z* 218.29 ($[M+H]^+$)

HRESIMS found 218.1534, calc. for $C_{14}H_{20}NO$ 218.1545 ($[M+H]^+$).



1-Allyloxycarbonyl-3-(benzyloxy)-2-vinylpiperidine (3.37).

To a solution of piperidine **3.36** (50 mg, 0.23 mmol) in CH_2Cl_2 (2.5 mL) was added Na_2CO_3 (36 mg, 0.35 mmol) and allyl chloroformate (37 μL, 0.35 mmol). The reaction mixture was stirred for 2 h, at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was quenched by addition sat. aq. NH_4Cl, the organic layer was separated and the aqueous layer was extracted with EtOAc (3x5 mL). The combined organics were then washed with water (5 mL) and brine (5 mL), before being dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a colourless oil (42 mg, 60%), which was used without further purification.

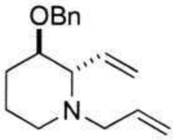
δ_H (300 MHz, $CDCl_3$), 7.33-7.26 (m, 5H, ArH), 5.92 (ddt, *J* = 15.2, 10.1, 5.1, 1H, $COCH_2C\underline{H}CH_2$), 5.73 (ddd, *J* = 17.3 10.7, 4.5, 1H, $C\underline{H}{=}CH_2$), 5.28 (ddd, *J* = 15.2, 2.1, 1.2, 1H, $CHC\underline{H_2}$), 5.23 (ddd, *J* = 10.2, 2.1, 1.2, 1H, $CHC\underline{H_2}$), 5.16 (ddd, *J* = 10.7, 2.0, 1.1, 1H, $CHC\underline{H_2}$), 5.15 (ddd, *J* = 17.3, 2.0, 1.1, 1H, $CHC\underline{H_2}$), 5.05 (br s, 1H, $C\underline{H}CHCH_2$), 4.66 (d, *J* = 12, 1H, AB pair CH_aH_bAr), 4.61 (br d, *J* = 5.1, 2H, $OC\underline{H_2}CHCH_2$), 4.52 (br d, *J* = 12, 1H, AB pair CH_aH_bAr), 4.08 (br d, *J* = 13.8, 1H, $-C\underline{H_2}N-$), 3.58 (app. d, *J* = 2.6, 1H, CH(OBn)), 2.97 (dt, *J* = 13.8, 3.2, 1H, $-CH_2N-$), 2.02-1.85 (m, 2H, $C\underline{H_2}C\underline{H_2}CH_2N$), 1.66-1.59 (m, 1H, CH_2CH_2N), 1.41-1.36 (m, 1H, $C\underline{H_2}CH(OBn)$).

δ_C (100 MHz, $CDCl_3$), 156.0, 138.7, 133.8, 133.2, 128.3 (2C), 127.5 (3C), 117.0 (2C), 76.6, 74.4, 70.2, 65.9, 39.5, 24.5, 19.5.

IR (ν/cm^{-1}), 3086, 2946, 2865, 1693, 1378.

MS (ESI +) *m/z* 302.17 ($[M+H]^+$), 324.17 ($[M+Na]^+$).

HRESIMS found 324.1591, calc. for $C_{18}H_{23}NO_3Na$ 324.1576 ($[M+Na]^+$).



1-Allyl-3-(benzyloxy)-2-vinylpiperidine (3.38).

To a solution of piperidine **3.36** (46 mg, 0.21 mmol) in toluene (1 mL) was added NaOH (17 mg, 0.43 mmol) and allyl bromide (40 μL, 0.43 mmol). The reaction mixture was stirred vigorously for 2 h, at which point TLC analysis showed complete consumption of the starting material. The reaction mixture was diluted by addition of EtOAc (5 mL) and quenched by addition of sat. aq. NH_4Cl (2 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2x5 mL). The combined organic layers were then washed with brine (5 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* to give the title compound as a pale yellow oil (40 mg, 75%), which was used without further purification.

δ_H (300MHz, $CDCl_3$), 7.32-7.24 (m, 5H, ArH), 5.84 (dddd, *J* = 18.2, 10.1, 7.9, 5.3, 1H, $CH_2C\underline{H}CH_2$), 5.72 (ddd, *J* = 16.8, 10.6, 8.9, 1H, $CHC\underline{H}CH_2$), 5.31 (dd, *J* = 16.8, 7.7, 1H, $CHCHC\underline{H_2}$), 5.30 (dd, *J* = 10.6, 7.7, 1H, $CHCHC\underline{H_2}$), 5.12, (dd, *J* = 18.6, 1, 1H, $CH_2CHC\underline{H_2}$), 5.11, (dd, *J* = 10.1, 1, 1H, $CH_2CHC\underline{H_2}$), 4.56 (d, *J* = 11.7, 1H, AB pair CH_aH_bAr), 4.50 (d, *J* = 11.7, 1H AB pair CH_aH_bAr), 3.46 (ddt, *J* = 13.9, 5.3, 1.6, 1H, $NC\underline{H_2}CHCH_2$), 3.21 (ddd, *J* = 10.4, 8.3, 4.4, 1H, -$C\underline{H}$(OBn)-), 2.89 (dt, *J* = 11.5, 2.8, 1H, CH_2N), 2.79 (dd, *J* = 13.9, 7.9, 1H, $NC\underline{H_2}CHCH_2$), 2.65 (dd, *J* = 8.9, 8.4, 1H, -$C\underline{H}CHCH_2$), 2.17-2.07 (m, 1H, -CH_2), 1.99 (dt, *J* = 11.5, 2.8, 1H, -$CH_2C\underline{H_2}N$-), 1.77- 1.68

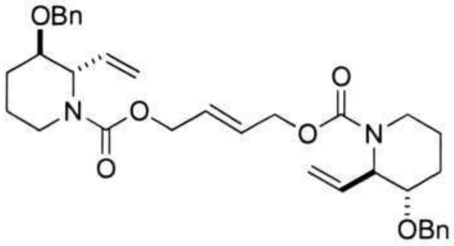
(m, 1H, -C<u>H</u>$_2$-), 1.50 (dtt, *J* = 12.5, 12.5, 4.0, 1H, -C<u>H</u>$_2$), 1.31 (ddt, *J* = 12.5, 10.4, 4.0, 1H, -C<u>H</u>$_2$CH(OBn)-).

δ_C (100 MHz, CDCl$_3$), 138.8, 138.1, 135.0, 128.2 (2C), 127.8 (2C), 127.4, 119.4, 117.7, 78.1, 71.5, 71.1, 58, 51.2, 29.6, 23.

IR (ν/cm^{-1}) 3078, 3031, 2937, 2794, 1642, 1454, 1101

MS (ESI +) *m/z* 257.46 ([M]$^+$), 258.18 ([M+H]$^+$), 280.41 ([M+Na]$^+$).

HRESIMS found 258.1861, calc. for $C_{17}H_{24}NO$ 258.1858 ([M+H]$^+$).

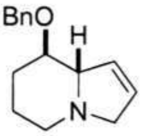


Compound (3.40).

This undesired compound was not rigorously characterized.

δ_H (300 MHz, CDCl$_3$), 7.35-7.24 (m, 10H, ArH), 5.79 (br s, 1H, CH=CH), 5.70 (ddd, *J* = 17.4, 10.6, 4.4, 2H, CHC<u>H</u>CH$_2$), 5.18 (dd, *J* = 17.4, 10.6, 4H, CHCHC<u>H</u>$_2$), 5.03 (br s, 1H, CH=CH), 4.76-4.53 (m, 6H, OC<u>H</u>$_2$-, C<u>H</u>$_a$H$_b$Ar), 4.51 (d, *J* = 12.1, 2H, AB pair CH$_a$<u>H</u>$_b$Ar), 4.05 (br s, 2H, C<u>H</u>CHCH$_2$), 3.57 (br s, 2H,), 2.95 (br t, *J* = 12.3, 2H, CH$_2$N), 1.9-1.26 (m, 10H, C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$N).

The spectrum was significantly broadened due to rotamers, the difference in chemical shift for the alkene protons is also attributed as due to slow rotation of the rotamers.



(8, 8a)-8-Phenylmethoxy-2,3-dehydroindolizine (2.48).

A solution of piperidine **3.38** (25 mg, 0.01 mmol) in CH_2Cl_2 (3 mL) was added via cannula to a solution of tosic acid monohydrate (19 mg, 0.01 mmol) in CH_2Cl_2 (2 mL). The above solution was stirred at RT for 0.5 h, then a solution of Grubbs I catalyst (4 mg, 5 mol%) in CH_2Cl_2 (1 mL) was added via cannula. The reaction mixture was heated at reflux for 12 h, when TLC analysis showed complete consumption of the starting material. The reaction mixture was then diluted by addition of CH_2Cl_2 (5 mL), and quenched by addition of aq. NaOH (2 mL, 2M). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic layers were dried over $MgSO_4$, before being concentrated *in vacuo* to give the title compound as a brown oil. Purification by column chromatography on silica gel, eluting with 1% $MeOH/CH_2Cl_2$ gave the title compound as a colourless oil (13 mg, 56%).

δ_H (300 MHz, $CDCl_3$), 7.36-7.22 (m, 5H, ArH), 6.16 (br d, $J = 6.1$, 1H, CHCH), 5.91 (m, 1H, CHCH), 4.73 (d, $J = 12.5$, 1H, AB pair CH_2Ar), 4.52 (d, $J = 12.5$, 1H, AB pair CH_2Ar), 3.62 (br d, $J = 15.4$, 1H, C$\underline{H}$N), 3.24 (dt, $J = 9$, 4.1, 1H, CH(OBn), 3.24-3.22 (m, 1H, CH2), 3.06-2.91 (m, 2H,), 2.41 (dt, $J = 8.4$, 3.7, 1H, CH_2N), 2.25-2.20 (m, 1H, CH_2), 1.73-1.53 (m, 2H, CH_2), 1.40-1.11 (m, 1H, CH_2).

δ_C (100 MHz, $CDCl_3$), 138.8, 131.3, 128.7, 128.2, 127.5 (2C), 127.4 (2C), 78.4, 72.1, 71.0, 57.6, 48.8, 30.4, 24.2

All data is consistent with that of the literature.[75]

References

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[1] Lin, Y.-Y., Risk, M., Ray, S. M., Engen, D. V., Clardy, J., Golik, J., James, J. C., Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.
[2] Nicolaou, K. C., Theodorakis, E. A., Rutjes, F. P. J. T., Tiebes, J., Sato, M., Untersteller, E., Xiao, X.-Y. *J. Am.Chem. Soc.* **1995**, *117*, 1171. Nicolaou, K. C., Theodorakis, E. A., Rutjes, F. P. J. T., Tiebes, J., Sato, M., Untersteller, E. *J. Am.Chem. Soc.* **1995**, *117*, 1173. Nicolaou, K. C., Hwang, C.-K., Duggan, M. E., Nugiel, D. A., Abe, Y., Bal Reddy, K., DeFrees, S.a., Reddy, D. R., Awartani, R. A. *J. Am.Chem. Soc.* **1995**, *117*, 10227. Nicolaou, K. C., Theodorakis, E. A., Rutjes, F. P. J. T., Tiebes, J., Sato, M., Untersteller, E., Xiao, X.-Y., Hwang, C.-K., Duggan, M. E., Yang, Z. *J. Am.Chem. Soc.* **1995**, *117*, 10239. Nicolaou, K. C., Rutjes, F. P. J. T., Theodorakis, E. A., Tiebes, J., Untersteller, E. *J. Am.Chem. Soc.* **1995**, *117*, 10252.
[3] Nicolaou, K. C., Prasad, C. V. C., Somers, P. K., Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.
[4] Baldwin, J. E. *J. Chem. Soc., Chem. Comm.* **1976**, 734.
[5] Bravo, F., McDonald, F. E., Neiwert, W. A., Do, B., Hardcastle, K., I. *Org. Lett.* **2003**, *5*, 12, 2123.
[6] Valentine, J. C., McDonald, F. E., Neiwert, W. A., Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586.
[7] Lambertin, F., Wende, M., Quirin, M. J., Taran, M., Delmond, B. *Eur. J. Org. Chem.* **1999**, 6, 1489
[8] Wang, Z., Tu, Y., Frohn, M., Zhang, J., Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.
[9] Trost, B. M., Rhee, Y. H. *Org. Lett.* **2004**, *6*, 23, 4313.
[10] Peng, Z, -H., Li, Y.-L., Wu, W. –L., Liu, C.-X., Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1*. **1996**, 1057.
[11] Trost, B. M., Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 11, 2528.
[12] Hori, N., Matsukura, H., Matsuo, G., nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811.
[13] Nicolaou, K. C., Hwang, C. K. Marron, B. E., Defees, S. A., Couladouros, E. A., Abe, Y., Carroll, P. J., Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040.
[14] Mori, Y., Yaegashi, K., Furukawa, H. *J. Am. Chem. Soc.* **1996**, 118, 8158.
[15] McErlean, C. S. P., Willis, A. C., *Synlett*, **2009**, *2*, 233
[16] Nicolaou, K. C., Prasad, C. V. C., Hwang, C. K., Duggan, M. E., Veale, C. A. *J. Am. Chem. Soc.* **1989**, 111, *14*, 5321
[17] Tojo, G., Fernández, M., *Oxidation of Alcohols to Aldehydes and Ketones,* Springer, U.S., **2006**.
[18] Ireland, R. E., Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
[19] Frigerio, M., Santagostino, M. *Tetrahedron Lett.* **1994**, *35,* 8019.
[20] Frigerio, M., Santagostino, M., Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
[21] Dess, D. B., Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
[22] Bowden, K., Heilbron, I. M., Jones, E. R. H., Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.
[23] Collin, J. C., Hess, W. W., Franks, F. J. *Tetrahedron Lett.* **1968**, 3363.
[24] Corey, E. J., Schmidt, G. *Tetrahedron Lett.* **1979**, *5*, 399.
[25] Corey, E. J., Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
[26] Huang, S. L., Omura, K., Swern, D. *J. Org. Chem.* **1976**, *41*, 3329.
[27] Griffith, W. P., Ley, S. V., Whitcombe, G. P., White, A. D. *J. Chem. Soc. Chem. Commun.* **1987**, 1625.
[28] Ley, S. V., Norman, J., Griffith, W. P., Marsden, S. P. *Synthesis,* **1994**, 639.

---

[29] Carlsen, P. H. J., Katsuki, T., Martin, V. S., Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

[30] Miranda Moreno, M. J. S., Sá e Melo, M. L., Campos Neves, A. S. *Tetrahedron Lett.* **1991**, *32*, 3201.

[31] Brummond, K. M., DeForrest, J. E., *Synthesis,* **2007**, 6, 795.

[32] Schuster, H. F., Coppola, G. M., *Allenes in Organic Synthesis,* John Wiley and Sons: New York, **1984**.

[33] Brandsma, L., *Synthesis of Acetylenes, Allenes and Cumulenes: Methods and Techniques,* Elsevier: Oxford, **2004**.

[34] Crabbé, P., André, D., Fillion, H. *Tetrahedron Lett.* **1979**, 20, 893.

[35] Searles, S., Li, Y., Nassim, B., Lopes, M.-T. R., Tran, P. T., Crabbé, P. *J. Chem. Soc., Perkin Trans. 1.* **1984**, 747.

[36] Siemsen, P, Livingston, R. C., Diederich, F. *Angew. Chem., Int. Ed.* **2002**, *39*, 2632.

[37] Bates, R. W., Satcharoen, V. *Chem. Soc. Rev.* **2002**, 31, 12.

[38] Claesson, A., Shalberg, C., Luthman, K. *Acta Chem. Scand. B.* **1979**, 309.

[39] Olsson, L.-I., Claesson, A., *Synthesis*, **1979**, 743.

[40] Walkup, R. D., Guan, L., Mosher, M. D., Kim, S. W., Kim, Y. S., *Synlett*, **1993**, 88.

[41] Marshall, J. A., Sehon C. A. *J. Org. Chem.* **1995**, 5966.

[42] Arredondo, V. M., Tian, S., McDonald, F. E., Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633.

[43] Arredondo, V. M., McDonald, F. E., Marks, T. J. *Organometallics,* **1999**, *18*, 1949.

[44] Jonasson, C., Horváth, A., Bäckvall, J.-E. *J. Am. Chem. Soc.* **2000**, *122*, 9600.

[45] Snider, B. B., He, F. *Tetrahedron Lett.* **1997**, *38*, 5453.

[46] Shaw, R., Lathbury, D., Anderson, M., Gallagher, T. *J. Chem. Soc. Perkin Trans. 1.***1991**, 659.

[47] Audin, P., Doutheau, A., Gore, J. *Tetrahedron Lett.* **1982**, *23*, 42, 4337.

[48] Gallagher, T., *J. Am. Chem. Soc., Perkin Trans. 1.* **1984**, 1554.

[49] Zhang, Z., Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 283.

[50] Bates, R. W., Song, P. *Tetrahedron*, **2007**, *63*, 4497.

[51] Grubbs, R. H., Chang, S. *Tetrahedron*, **1998**, *54*, 4413.

[52] Grubbs, R. H., Trnka, T. M., *Acc. Chem. Res.* **2001**, *34*, 18.

[53] Schuster, M., Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036.

[54] Cannon, S. J., Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.

[55] Betancort, J. M., Martín, V. S., Padrón, J. M., Palazón, J. M., Ramírez, M. A., Soler, M. A. *J. Org. Chem.* **1997**, *62*, 4570.

[56] Pappo, R., Allen, D. S., Lemieux, R. U., Johnson, W. S. *J. Am. Chem. Soc.* **1956**, *21*, 478.

[57] Minato, M., Yamamoto, K., Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766.

[58] Shing, T. K. M., Zhong, Y-L. *J. Org. Chem.* **1997**, *62*, 2622.

[59] D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd Ed., Pergamon Press, Oxford, 1988.

[60] Heumann, L. V., Keck, G. E. *Org. Lett.* **2007**, *9*, 21, 4275.

[61] Miyashita, M., Yoshikoshi, A., Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 23, 3772.

[62] Guengerich, F. P., DiMari, S. J., Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055.

[63] Schneider, M. J., Ungemach, F. S., Broquist, H. P., Harris, T. M. *Tetrahedron,* **1983**, 39, *1*, 29.

[64] Colegate, S. M., Dorling, P. R., Huxtable, C. R. *Aust. J. Chem.* **1979**, 32, 2257.

[65] Skelton, B. W., White, A. H. *Aust. J. Chem.* **1980**, *33*, 435.

[66] Molyneux, R. J., James, L. F. *Science*, **1982**, *216,* 190.

[67] Hino, M., *et al*, *J. Antibiotics,* **1985**, *38*, 926.

[68] Nemr, A. E. *Tetrahedron,* **2000**, *56*, 8579.

---

[69] Pyne, S. G., *Curr. Org. Synth.* **2005**, *2*, 39.

[70] Ali, M., H., Hough, L., Richardson, A. C. *J. Am. Chem., Chem. Comm.* **1984**, 447.

[71] Ali, M., H., Hough, L., Richardson, A. C. *Carbohydrate Research,* **1985**, *136*, 225.

[72] Adams, C. E., Walker, F. J., Sharpless, K. B. *J. Am. Chem.* **1985**, *50*, 422.

[73] Naruse, M., Aoyagi, S., Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358.

[74] Herradon, B., *Tetrahedron Asymmetry*, **1991**, 2, 83.

[75] Diels, O., Alder, K., *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.

[76] Nicolaou, K. C., Snyder, S. A., Montagnon, T., Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668.

[77] Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650.

[78] Lindsay, K. B., Pyne, S. G., *J. Org. Chem.* **2002**, *67*, 7774.

[79] Lindström, U. M., Somfai, P. *Synthesis,* **1998**, 109.

[80] Pyne, S. G., Au, C. W. G. *J. Org. Chem.* **2006**, *71*, 7079.

[81] Evans, P., Leffray, M., *Tetrahedron,* **2003**, *59*, 7973

[82] Petasis, N. A., Zavialov, I. A., *J. Am. Chem. Soc.* **1998**, *120*, 11798

[83] Buschmann, N., Rückert, A., Blechert, S., *J. Org. Chem.* **2002**, *67*, 4325

[84] De Vicente, J., Arrayas, R. G., Canada, J., Carretero, J. C., *Synlett*, **2000**, 53

[85] Buschmann, N., Rückert, A., Blechert, S. *J. Org. Chem.* **2002**, *67*, 4325

[86] Trost, B. E., Patterson, D. E., *J. Org. Chem.* **1998**, *63*, 1339.

[87] Stragies, R., Blechert, S., *Tetrahedron*, **1999**, *55*, 8179

[88] Mukai, C., Sugimoto, Y., Miyazawa, K., Yamaguchi, S., Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281.

[89] Oku, A., Harada, T., Kita, K. *Tetrahedron lett.* **1982**, *6*, 681.

[90] Frigerio, M., Santagostino, M. *Tetrahedron Lett.* **1994,** *35*, 8019.

[91] Ley, S. V., Norman, J., Griffith, W. P., Marsden, S. P. *Synthesis*, **1994**, 639.

[92] Verkruijsse, H. D., De Graaf, W., Brandsma, L., *Synth. Commun.* **1988**, *18,* 132.

[93] Kolb, H. C., Finn, M. G., Sharpless, K. B., *Angew. Chem. Int. Ed.* **2004**, *11*, 40, 2021.

[94] Huisgen, R. Proc. of the Chem. Soc. **1961**, 357.

[95] Bates. R. W., Satchareon, V., *Synlett*, **2001**, 532

[96] Hurst, D. T., McInnes, A. G., *Can. J. Chem.* **1965**, *43*, 2004

[97] Kocieñski, P. J., *Protecting Groups,* **1994**, Thieme, New York.

[98] Greene, T. W., Wuts, P. G. M., *Protective Groups in Orgainic Synethesis*, **1991**, Wiley, New York.

[99] Searles, S., Li, Y., Nassim, B., Lopes, M-T. R., Crabbé, *J. Chem. Perkin. Trans. I.* **1984**, 747.

[100] Lee P. H.; Kim, H.; Lee, K. ; Kim, M.; Noh, K.; Kim, H.; Seomoon, D. *Angew. Chem. Int. ed.* **2005**, *44*, 1840.

[101] Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* **1999**, *64,* 2992.

[102] Dieter, K. R., Yu, H. *Org. Lett.* **2001**, *3*, 3855.

[103] Fox, D. N. A., Gallagher, T. *Tetrahedron*, **1990**, *46*, 4697.

[104] Lathbury, D., Vernon, P., Gallagher, T. *Tetrahedron*, **1986**, *27*, 49, 6009.

[105] Fox, D.N.A., Lathbury, D., Mahon, M. F., Molly, K. C., Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652.

[106] Bates R. W., Rama-Devi, T., Ko, H-H. *Tetrahedron*, **1995**, *51*, 47, 12939.

[107] Hashmi, S. K., *Chem. Rev.* **2007**, *107*, 3180 (and references here in).

[108] Neipp, C. E., Martin, S. F. *Tetrahedron Lett.* **2002**, *43*, 1779.

[109] Morita, N., Krause, N. *Organic Lett.* **2004**, *6*, 22, 4121.

[110] Gockel, B., Krause, K. *Organic Lett.* **2006**, *8*, 20, 4485.

[111] Carlsen, P H. J., Katsuki, T., Martin, V. S., Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 2936

---

[112] Hashmi, S. K., Weyrauch, J. P., Rudolph, M., Kurpejovic, E. *Angew. Chem., Int. Ed.* **2004**, 43, 6545.

[113] Toste, F. D., Shapiro, N. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244.

[114] Hyland, C. J., Hegedus, L. S. *J. Org. Chem.*, **2006**, *71*, 8658.

[115] Zhang, Z., Liu, C., Kinder, R. E., Han, X., Qian, H., Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066.

[116] Zhang, Z., Bender, C. F., Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 15, 2887.

[117] Yang, C-Y., Lin, G-Y, Liao, H-Y., Datta, S., Liu, R-S. *J. Org. Chem.* **2008**, *73*, 4907.

[118] Pu, L. *Tetrahedron,* **2003**, *59*, 9873.

[119] Marshall, J. A., Bourbeau, M. P. *Org. Lett.* **2003**, *5*, 18, 3197

[120] Bach, J., Berenguer, R., Garcia, J., Loscertales, T., Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 9021.

[121] Shi, Y-J., Cai, D., Dolling, U.-H., Douglas, A. W., Tschaen, D. M., Verhoeven, T. R. *Tetrahedron Lett.* **1994**, *35*, 6409.

[122] Midland, M. M., McLoughlin, J. I., Gabriel, J. *J. Org. Chem.* **1989**, *54*, 159.

[123] Satcharoen, V., McLean, N. J., Kemp, S. C., Camo, N. P., Brown, R. C. D. *Org. Lett.* **2007**, *9*, 10, 1867.

[124] Corey, E. J., Bakshi, R. K., Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

[125] Corey, E. J., Helal, C. *Angew. Chem. Int, Ed.* **1998**, *37*, 1986.

[126] Singh, V. K. *Synthesis*, **1991**, 605.

[127] Jones, T. K., *et. al., J. Org. Chem.* **1991**, *56*, 763.

[128] Gilmore, N. J., Jones, S. *Tetrahedron, Asymmetry*, **2003**, *14*, 2115.

[129] Corey, E. J., Helal, C. J., Magriotis, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 10938.

[130] Corey, E. J., Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 50, 9153.

[131] Navath, S. R., Pabbisetty, K. B., Hu, L. *Tetrahedron Lett.* **2006**, *47*, 389.

[132] Caelier, F., Enjalbal, C. *Tetrahedron Lett.* **1996**, *37*, 5131.

[133] Guibé, O. D. F., Balavoine, G., Lavielle, S., Marquet, A. *J. Am. Chem. Soc.* **1987**, *52*, 22, 4993.

[134] Martinez, P. G., Bessolin, M., Guilbé, Albericio, F. *J. Chem. Soc., Perkin Trans. I.* **1999**, 2871.

[135] Banks, R. L., Bailey, G. C., Ind. Eng. Chem. Prod. Res. Dev. 3, **1964**,170

[136] Schrock, R. R., Murdzek, J. S., Bazan, G. C., Robbins, J., DiMare, M., O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

[137] Fu, G. C., Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426.

[138] Fu, G. C., Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324.

[139] Fu, G. C., Nguyen, S. T., Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.

[140] Yang, Q., Xiao, W.-J., Yu, Z., *Org. Lett.* **2005**, 7, 871

[141] Ott, M. M., Little, D. *J. Org. Chem.* **1997**, *62*, 1610.

[142] Prado, M. A. F. *et al., Synth. Comm.* **2003**, *33*, 463.

[143] Hudliky, T. *et al. J. Am. Chem. Soc.* **1986**, *108*, 3755.

[144] Connon, S. J., Blechert, S., *Angew. Chem. Int. Ed.* **2003**, *42*, 1900.

[145] Schuster, M., Blechert., S., *Angew. Chem. Int. Ed.* **1997**, *36*, 2036.

[146] Tina, M., Grubbs, R. H., *Acc. Chem. Res.* **2001**, *34*, 18.

[147] Grubbs, R. H., O'Leary, D. J., Blackwell, H. E, Washenfelder, R. A., *Tetrahedron Lett.* **1998**, *39*, 7427.

[148] Hyland, C., *Tetrahedron*, **2005**, *61*, 3457

[149] Trost, B. M., Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

[150] Trost, B. M., Weber, L., Strege, P. E., Fullerton, T. J., Dietsche, T. J. *J. Am Chem. Soc.* **1978**, 3416

[151] Heck, R. F. *Palladium Reagents in Organic synthesis*, Academic Press Ltd., London **1987**

---

[152] Bundle, D. R., Iversen, T. *J. Chem. Soc. Chem. Commun.* **1981**, 1240

[153] Dudley, G. B., Poon, K. W. *J. Org. Chem.* **2006**, *71*, 3923.

[154] Poon, K. W. C., House, S. E., Dudley, G. B. *Synlett,* **2005**, 3142.

[155] Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1173.

[156] Neipp, C. E., Martin, S. F. *Tetrahedron Lett.* **2002**, *43*, 1779.

[157] Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules,* University Science Books, Mill Valley, California, **1994**.

[158] Armstrong, S. K., *J. Chem. Soc. Perkin Trans 1.* **1998**, 371.

[159] Phillips, A. J., Abell, A. D. *Aldrichimica Acta*, **1999**, *32,* 3, 75.

[160] Fürstner, A., Langemann, K. *Synthesis,* **1997**, 792.

[161] Schmalz, H.-G., *Angew. Chem. Int. Ed.* **1995**, *34*, 1833.

[162] Neipp, C. E., Martin, S. F., *J. Org. Chem.* **2003**, *68*, 8867.