Acid-catalysed hydroaminations

Piotr M Rutkowski

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Declaration

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This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended. The views expressed are my own.

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"The most spiritual men, as the strongest, find their happiness where others would find their destruction: in the labyrinth, in hardness against themselves and others, in experiments. Their joy is self-conquest: asceticism becomes in them nature, need, and instinct. Difficult tasks are a privilege to them; to play with burdens that crush others, a recreation. Knowledge - a form of asceticism. They are the most venerable kind of man: that does not preclude their being the most cheerful and the kindliest. "

- Friedrich Nietzsche

"There is no success without hardship."

- Sophocles

"They asked me how well I understood theoretical chemistry. I said I had a theoretical degree in chemistry. They said welcome aboard."

- unknown

Abstract

This thesis describes the use of Brønsted acid catalysis to promote 6-*exo*-trig cyclisations in the synthesis of *N*-heterocyclic compounds.

In Chapter one, a general overview of alkaloid structures is given, together with a number of general ways for their synthesis, with a particular focus on the Bischler-Napieralski and Pictet-Spengler methods. Hydroamination as a synthetic method is then briefly reviewed to set into context the present project to develop and optimize an acid-catalysed hydroamination method as an alternative protocol to the Picted-Spengler reaction.

Chapter two describes different synthetic routes towards the construction of 2-vinylphenylethylamines and their subsequent cyclisations into tetrahydroisoquinoline alkaloids *via* the acid-catalysed hydroamination methodology. Key aspects of the diastereochemical outcome of the reaction are discussed, as well as the spectral features and limitations of the researched chemistry.

Chapter three describes application of the acid-catalysed hydroamination in the making of more complex, polycyclic structures. Synthesis of polymethoxylated tetrahydroisoquinolines, benzhydryl derivatives and a relay synthesis of racemic salsolidine is described. An attempt to synthesise racemic alkaloid, crispine, is briefly discussed, as well as synthesis of an aporphine and a berberine skeleton.

Chapter four covers the attempt to extend the acid-catalysed hydroamination chemistry to unprotected indoles and trans-annular cyclisations. Future work and areas of chemistry in which the acid-catalysed hydroamination underperformed or failed to deliver the desired results altogether are briefly discussed.

Chapter five contains the experimental remarks and characterisation data.

Acknowledgements

I would like to thank my supervisor Professor David W Knight for his support and wisdom throughout my studies at Cardiff University.

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I would also like to say a big thank you to my mother and my brother for all their support and love throughout my life.

I'd like to thank my wonderful wife Tatyana for being there for me and for everything else.

Last but not least, I would like to dedicate this thesis to my son, Gabriel.

Table of contents

Abbreviations and acronyms

Several abbreviations and acronyms have been used throughout this thesis that may not be familiar to the reader. They are listed below:

Ac	acetyl
app.	apparent
APCI	atmospheric pressure chemical ionisation
Ar	aromatic
b.p.	boiling point
Boc	*tert*-butyloxy carbonyl
br.	broad
Bu	butyl
Bz	benzoyl
cat.	catalytic
CI	chemical ionisation
COSY	correlation spectroscopy
cy	cyclohexane
d	day(s)
d	doublet
DCM	dichloromethane
dd	double doublet
dt	double triplet
DEPT	distortionless enhancement by polarization transfer
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
EI	electron ionisation
eq.	equivalent(s)
ES	electrospray
ether	diethyl ether
Et	ethyl
EWG	electron withdrawing group
g	gram
GC	gas chromatography

Δ	heat
h	hour(s)
HMBC	heteronuclear multiple quantum coherence
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectroscopy
HSQC	heteronuclear single quantum coherence
Hz	hertz
IR	infra-red
J	coupling constant
k	kilo
kg	kilogram
lit.	literature
m	*meta*
m	multiplet
M	molar
mCPBA	3-chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
μmol	micromole(s)
min.	minute(s)
mL	millilitre(s)
mmol	millimole(s)
m.p.	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
nOESY	nuclear Overhauser enhancement spectroscopy
Ns	*para*-nitrobenzenesulfonyl
o	*ortho*
p	page
p	*para*
Ph	phenyl
Pr	propyl
ppm	parts per million
py	pyridine
q	quartet
r.t.	room temperature
sept	septet

σ	sigma
s	singlet
t	triplet
td	triple doublet
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TLC	thin layer chromatography
tol.	toluene
Ts	toluenesulfonyl
UV	ultra-violet
w/w	weight for weight

Chapter 1: Introduction

1.1 Heterocycles

Heterocycles form a vast family of organic compounds. Their characteristic feature is the presence of at least one lone pair of electrons on a non-carbon atom within the ring structure. Nitrogen, oxygen and sulfur containing heterocycles such as the four-membered azetidines **1**, furans **2**, pyridines **3**, or thiiranes **4**, (Scheme 1) are by far the most abundant in nature and industry. However, phosphorus,[1] arsenic[2] and several other[3] atoms that do not carry a lone pair, such as silicon,[4] or boron, are also known to form heterocyclic ring systems with carbon.

1 **2** **3** **4**

Scheme 1. Heterocyclic rings: azetidine, furan, pyridine and thiirane.

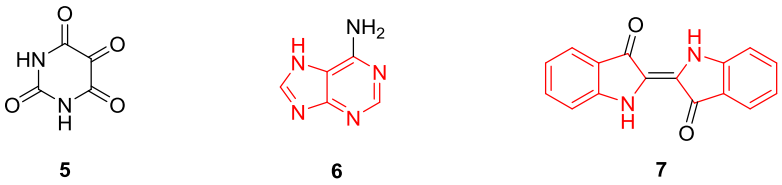
The presence of the lone pair on a heteroatom in such structures provides a basis for hydrogen bonding, coordination, increased reactivity and resonance properties of the molecules. This very important group of compounds was shown to possess a wide range of biological properties and to play central roles in the world and within our lives. Heterocyclic moieties can be found in DNA, amongst the vast majority of pharmaceuticals, dyes and agricultural products, as well as in hormones and vitamins.

Studies of heterocyclic systems comprise an important part in the history of organic chemistry. Several of those compounds were made and characterised some two hundred years ago, yet due to their anomalous reactivity profiles they proved quite elusive to study and categorise. For a long period, heterocycles were not included in most introductory level organic chemistry books. Alan Katritzky had influence on introducing perhaps the first, basic, comprehensive courses[5] in heterocyclic chemistry and was a key contributor in this field.

Major changes in the world of science began in 1828 with Wöhler's revolutionary production of urea from inorganic materials, which was a very important step in the development of organic chemistry. Until that finding, many believed in vitalism, a doctrine stating that there is a fundamental difference between biological organisms and other matter and that living entities contain some special, non-physical element often referred to as "vital spark". Even though urea was first detected and described by several scientists (Boerhaave, Rouelle, Berzelius, Prout) more than fifty years before Wöhler's breakthrough discovery, it is still an extremely important compound used primarily as a fertiliser and produced in excess of 150 million tonnes per year.

The few initial heterocyclic compounds were first produced soon after and isolated in the early 19th century; Brugnatelli's synthesis of alloxan **5** from uric acid and Wöhler and Liebig's synthesis of purines **6** and pyrimidines being the first two examples (Scheme 2).[6] Further, important discoveries by Perkin allowed a synthesis of benzofuran,[7] proved that indole formed the core of the indigo dye **7**[8] and

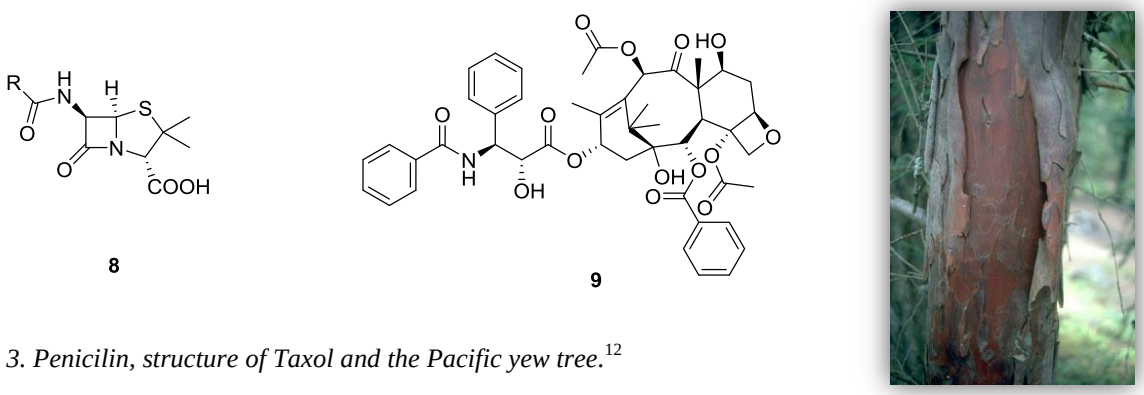
that pyrrole, isolated by Perkin and described by Anderson,[9] was an important constituent of hemin, bilirubin and chlorophyll.



5 **6** **7**

Scheme 2. Alloxan, adenine (with purine core highlighted) and indigo (with indole core highlighted).

Heterocyclic chemistry has been an active area of research for over two centuries and the last few decades conveyed some major improvements, especially in terms of analysis, synthesis and applications of heterocyclic compounds. A great number of projects and patents of industrial giants such as Bayer, Pfizer, BASF and GSK are based on heterocycles and the work around them never stops. A good example is aripiprazole,[10] one of the top ten best-selling drugs in 2013[11] making over $6,400,000,000 (6.4 billion dollars) during the same year, sold as an antipsychotic drug used to tread schizophrenia, depression and bipolar disorder. A few more famous examples, due to their important position in history and structural complexities are penicillin **8** and taxol **9** (Scheme 3). In 1945, Florey, Fleming and Chain shared a Nobel Prize for their ground-breaking work on penicillin. It was proved to be a very effective antibacterial drug and its discovery began the modern era of antibiotic research. Mass production of this famous drug began in the same year. Interestingly, the chemical structure of penicillin was first determined by Dorothy Hodgkin - also in 1945. Her work in the field of analytical chemistry was recognized somewhat later and culminated in her receiving Nobel Prize in 1964, "for her determinations by X-ray techniques of the structures of important biochemical substances."



8 **9**

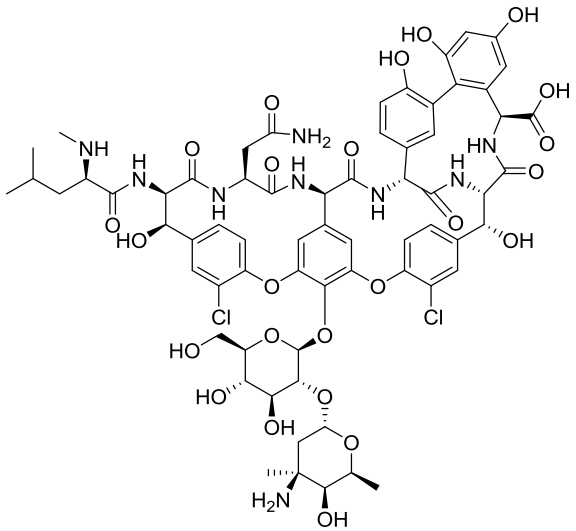
Scheme 3. Penicilin, structure of Taxol and the Pacific yew tree.[12]

Taxol **9**,[13] which was discovered in 1962 and first isolated in 1964-1967 from a Pacific yew tree species, is used cancer therapy[14] and in HIV-associated Kaposi's sarcoma.[15] It is still one of the most effective anti-cancer drugs available and functions by inhibiting mitosis through stabilisation of microtubules, through boosting the polymerisation of tubulin.[16] The material was incredibly difficult to come by in its early stages of development; processing 1200 kg of tree bark delivered roughly 28 kg of

crude extract, which was then further processed to provide only 10 g of the pure material. This amounted to approximately 0.00083%, which rendered the process very inefficient.

Reports of taxol's interesting biological properties, *i.e.* anti-leukemia in mice,[17] caused a rapid increase in demand and it was calculated that 360,000 trees would be required annually to satisfy only the USA's needs. This stimulated organic chemists to devise a way for accessing taxol synthetically and prompted several companies to get involved. The future saw Bristol-Meyers Squib (BMS) obtaining almost exclusive rights to study and manufacture taxol for a number of years, in collaboration with Robert Holton's group in Florida. Extensive efforts were undertaken to address the supply issue and the problem was resolved by the group of Potier, who managed to isolate 10-deacetylbaccatin from the needles of European Yew. This highly functionalised precursor of taxol could be isolated in large quantities from a cheap and sustainable source and allowed production of taxol in a short semi-synthesis. Not soon after, BMS patented an improved, semi-synthetic process to the drug, one not relying on destroying Pacific yew trees and thus quenching the controversial, ecological debate over taxol's manufacture. The molecule was also accessed completely synthetically; two earliest, elegant syntheses, by Holton[18,19] and Nicolaou[20,21,22,23], were published in 1994. More recently, emphasis was put on the biosynthesis of taxol[24] and the relatively expensive, semi-synthetic pathway is being abandoned for the cheaper and more economically viable biotechnological[25] production of taxol on industrial scale by plant cell cultures.

Vancomycin **10** (Scheme 4) is a very effective antibiotic used in the treatment of problematic bacterial infections. It is most effective against Gram-positive bacteria and belongs to the family of glycopeptide antibiotics. The structure of vancomycin is relatively big and contains 66 carbons and 24 oxygens; its molecular mass is almost 1.5 kDa. The mechanism through which the drug exhibits its anti-bacterial properties was deciphered and reported recently.



10

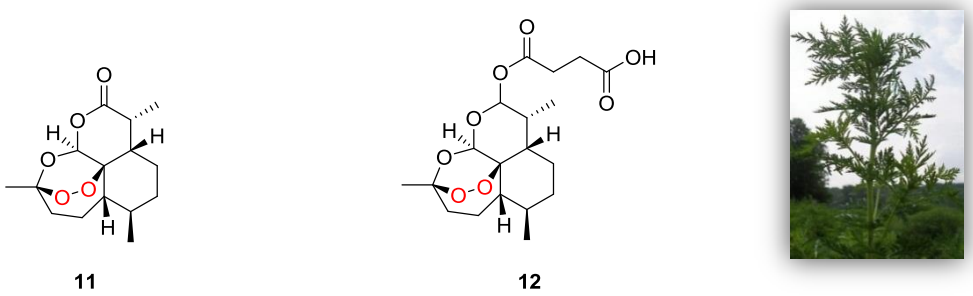
(1S,2R,18R,19R,22S,25R,28R,40S)-48-{[(2S, 3R,4S,5S,6R)-3-{[(2S,4S,5S,6S)- 4- amino-5-hydroxy-4,6-dimethyloxan-2-l]oxy}-4,5-dihydroxy-6-(hydroxyl methyl)oxan-2-yl]oxy}- 22- (carbamoylmethyl)- 5,15-dichloro- 2,18,32,35,37- pentahydroxy- 19- [(2R)- 4-methyl-2-(methylamino)pentanamido]- 20,23,26,42, 44-pentaoxo-7,13-dioxa-21,24,27,41,43-pentaaza octacyclo[26.14.2.23,6.214,17.18,12.129,33.010,25.0 34,39]pentaconta- 3,5,8(48),9,11,14,16,29 (45),30,32,34,36,38,46,49- pentadecaene- 40-carboxylic acid

Scheme 4. Vancomycin and its systematic (IUPAC) name.

Vancomycin is involved in inhibiting the growth of bacterial cell walls and can form a five-point binding interaction with specific proteins in the outer wall of Gram-Positive bacteria. The cell walls of gram-negative organisms are composed of different proteins and do not bind efficiently to vancomycin and thus are resistant.

The first total synthesis of vancomycin was reported in 1999 by Nicolaou and concluded an effort that spanned many years and required considerable research by several synthetic groups, for example Rao's, Boger's, Evans' and many others.[26] At the present time, most investigation is carried out in an attempt to synthesise analogues of vancomycin which exhibit a similar spectrum of antimicrobial activity against both vancomycin-sensitive and vancomycin resistant bacteria.[26]

Another important heterocyclic molecule often classified as an oxygen-based sesquiterpene, Artemisinin **11**, belongs to a new generation of drugs used in the treatment[27] of malaria (Scheme 5). Its recent rediscovery[28] goes back to the 1960s, as in the case of taxol. Conversely, the earliest historical records of its use go back over two millennia.[29] They were found in a collection of antique prescriptions uncovered in ancient, Chinese tombs originating from the Han Dynasty. Its unusual structural feature, a peroxide bridge, is believed to be crucial in its mechanism of action, most likely based on formation of oxygen free radicals.



Scheme 5. Artemisinin and artesunate with the peroxide bridge highlighted and Artemisia annua,[30] *the parent plant.*

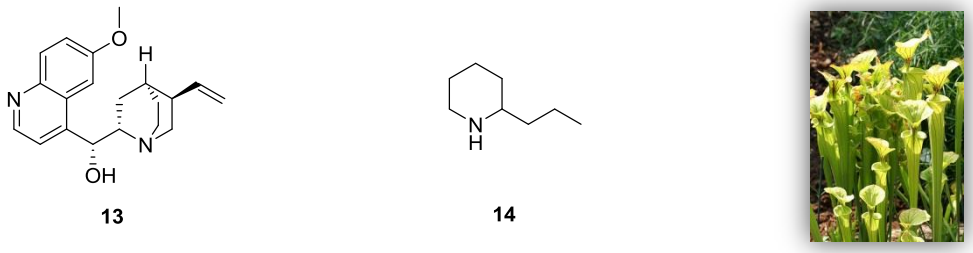
At the moment, there is no general, accepted mechanism through which Artemisinin **11** acts. The active species, dihydroartemisinin, is nonetheless believed to act whilst the parasites are inside red blood cells. One of the possible mechanisms involves action of iron in heme on the peroxide bridge which in turn could potentially generate iron-oxo species ultimately resulting in a sequence of reactions that generate oxygen radicals that kill the parasite.[31] High demand for this molecule prompted many chemists and engineers to look for faster and more efficient methods for extractions of Artemisinin from natural sources, using less toxic solvents and more sustainable methods.[32] A review published in 2010 by Lapkin covers a number of well-known and emerging technologies for extraction of Artemisinin from plant material, *i.e.* with super-critical carbon dioxide or ionic liquids.[33] Artemisinin itself has relatively low bioavailability; a number of more water or lipid soluble, semisynthetic derivatives has been screened, namely artesunate or artemether. Artesunate **12** is an ester derivative of the parent compound and due to the presence of a carboxylic acid group shows much higher water solubility and can be administered intravenously. Artemether, in turn, has an ether functionality which renders it more lipophilic and

increases its oral bioavailability. Malaria is one of the major causes of death worldwide as over one million people die as a result of the disease annualy and drugs from the Artemisinin family have a profound impact on controlling outbreaks of the disease and reducing the mortality rates. Artemisinin combination therapy (ACT) has played an imperative role in treatment of uncomplicated malaria over the past ten years and is now the recommended first-line treatment.[34] Unfortunately, the efficiency of the treatment could be threatened by malaria's resistance towards Artemisinin, and the first reports of tolerance to the treatment were recently reported in Cambodia.[35]

To summarise, the history of heterocyclic compounds is over two hundred years old and they still play a very important role and have a profound impact on mankind in modern life. They range from very simple and inactive compounds to extremely complex, very active biological molecules and powerful drugs. Finally, the research in heterocyclic chemistry never stops and immense quantities of literature are published regularly, describing advances in design, synthesis, application and understanding of heterocycles.

1.2 Alkaloids

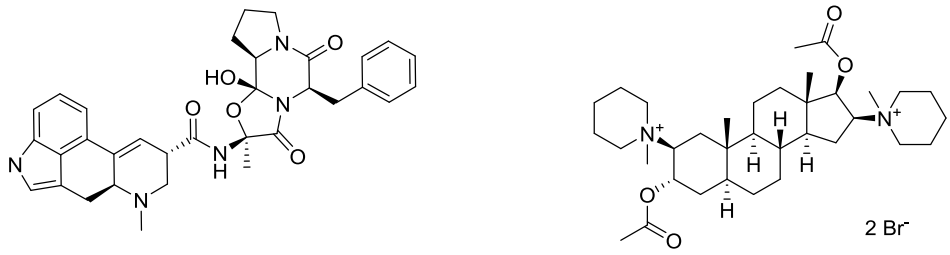
Alkaloids are a large group of chemical compounds which are best defined as containing a basic nitrogen atom and are produced by various different organisms including plants, animals, fungi and bacteria. Isolation of morphine, quinine **13** (Scheme 6) and strychnine between 1804 and 1820 began the era of studies of alkaloids, leading in 1886 to a first total synthesis of coniine **14**[36] by Ladenburg, a neurotoxin fatal to humans in quantities less than 0.2 g.



Scheme 6. Quinine and (racemic) coniine with its parent plant: Sarracenia flava.[37]

Alkaloids have been used by humans for over four thousand years and have played an incredibly important role in the history of humanity, as mankind has always sought to cure diseases and alleviate pain. A plethora of different pharmacological properties they possess is the key motive behind why they were used in tribal rituals, as recreational drugs, but also as analgesics, antibacterials or local anesthetics. It is also in our nature to seek remedies for coughs, runny noses or fevers, depression or to stay awake when needed and, in different ways, different properties of various alkaloids have helped mankind to stay alive and in control of their lives. Simultaneously, in recent times, a broad variety of medicine based on

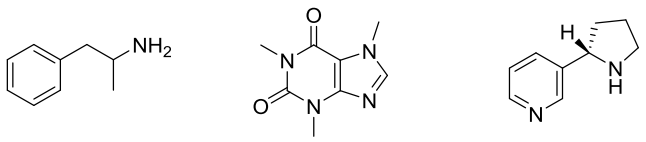
alkaloids such as anti-inflammatory, analgesic or antidepressant are available over the counter. Some alkaloids are incredibly potent and even very small doses can induce a substantial biological response in living organisms. Exceeding certain, tolerable limits for a drug can cause serious side effects such as headaches, confusion, pains, nausea and also death.[38] Compounds from the family of ergot alkaloids[39] such as ergotamine **15** (Scheme 7), which are amongst the most important toxins in human history, are known to have a harmful effect on many living creatures, from herbivorous insects to large mammals.[40] In small, carefully controlled doses, however, it can be used in management of migraines[41] and in treatment of tumours.[42]



15 **16**

Scheme 7. Ergotamine and pancuronium bromide.

Darker and grimmer aspects of alkaloids were also explored by scientists and compounds such as pentobarbital and pancuronium bromide **16**[43] (marketed under the name Pavulon) are two infamous compounds used in a deadly cocktail of chemicals during capital punishment[44] procedure in the USA.[45] The lethal cocktail is designed to induce unconsciousness, paralysis, cardiac arrest and death, and is introduced in three steps, as mixing all the compounds together would cause them to precipitate. During the Second World War, many aircraft pilots were given amphetamine **17** (Scheme 8) to keep them awake and sharpen their senses during extremely long flights in difficult and demanding conditions. The typical and very well known everyday examples of stimulant alkaloids include caffeine **18** and nicotine **19**, present in coffee and tobacco, respectively.



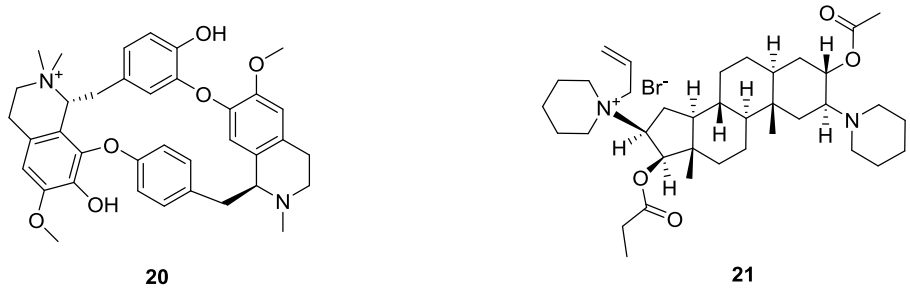
17 **18** **19**

Scheme 8. Important alkaloids: caffeine, nicotine and amphetamine.

The psychoactive opioid drug morphine, first isolated in 1804 is, alongside heroin, codeine and oxycodone, one of at least fifty different alkaloids present in the opium poppy and is still the most widely used pain-relieving drug in clinical medicine. Its mode of action involves direct interaction with the central nervous system and it thus alleviates pain. Remarkably, the infamous recreational drug, heroin, is

itself inactive, but inside the human body it is converted into 6-acetylmorphine.[46] When administered intravenously, heroin is almost four times more potent than morphine. Opioid drugs create an intense feeling of relaxation and euphoria and are used recreationally. Regular use, however, is associated with tolerance and physical dependence on the drug develops fast.

Another example is lacing arrows with toxic alkaloids, for instance tubocurarine **20** (Scheme 9), which was a crucial implement used to hunt and incapacitate prey by South American Indians.



Scheme 9. Tubocurarine and rapacuronium bromide.

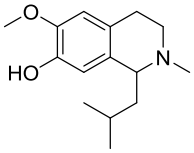
Tubocurarine **20** and rapacuronium bromide **21** are neuromuscular-blocking drugs and cause paralysis of skeletal muscles.[47] Tubocurarine does not easily cross the mucous membranes and, subsequently, consumption of the contaminated flesh does not produce any negative effects. It belongs to a family of tetrahydroisoquinoline alkaloids (*vide infra*), an important group of compounds displaying interesting biological properties.

1.3 Tetrahydroisoquinolines

The bicyclic isoquinoline **22** and 1,2,3,4-tetrahydroisoquinoline **23** (THIQ) ring systems are incorporated into a vast amount of compounds (Scheme 10); over a thousand of these alkaloids have been described to date. Various natural and synthetic analogues of THIQs display different biological and physiological activities and form a very important family of bioactive compounds. They have played an important role in traditional, oriental medicine and are still of great interest in the modern, pharmacological world.

Scheme 10. Isoquinoline and tetrahydroisoquinoline cores.

Typical examples of simple isoquinoline alkaloids, which are often substituted at the C(1) position with a carbon chain, are lophocerine **24**, the biosynthesis of which was described in 1968,[48] and salsoline **25**[49], a cytotoxin selective towards dopamine neurons. Salsolinol[49] and norsalsolinol,[50] metabolites of salsoline, were proven to be endogenous neurotoxins and might be responsible for Parkinson's disease (Scheme 11).



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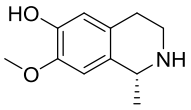

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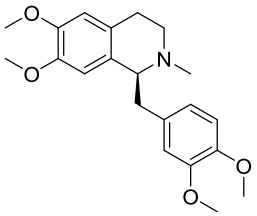
Scheme 11. Lophocerine and salsoline.

Laudanosine **26** (Scheme 12) is a tetrahydroisoquinoline alkaloid that interacts with the central nervous system and has stimulating properties.[51] It is also a metabolite of an important drug, atracurium, a quaternary amine, *bis*-benzyltetrahydroisoquinoline muscle relaxant similar to tubocurarine **20**, used along with anaesthetics during tracheal intubation procedures, surgery or artificial respiration.[52] Since it was shown that laudanosine **26** has epileptogenic and cardiovascular effects, further studies were carried out to show whether it could potentially cause seizures and other, unwanted side-effects. Further studies showed, however, that the plasma levels of laudanosine are too low to cause any adverse effects, especially related to seizures, and that atracurium is a safe drug.



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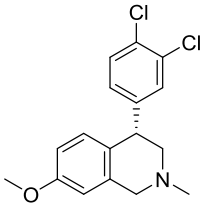

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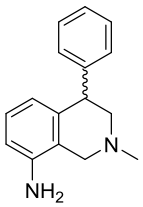

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Scheme 12. (S)-Laudanosine, (S)-diclofensine and racemic nomifensine

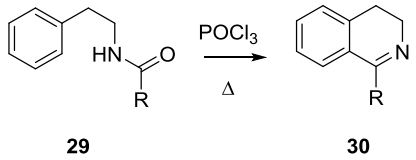
Diclofensine **27**[53] and nomifensine **28**[54] are two significant isoquinoline alkaloids discovered in the 60s and 70s.[55] It was shown that the mechanism of action of nomifensine involves increasing the available norepinephrine and dopamine by blocking their respective reuptake transporters and both compounds were investigated for use as antidepressants.[56] Successful human trials were run in the 1980s.[57] Relatively few side effects of diclofensine made it the drug of choice in treatment of symptoms associated with depressions. It was later discovered that nomifensine could cause haemolytic anaemia, a condition related to abnormal breakdown of red blood cells, and between 1990 and 1992 both drugs were withdrawn from the market. Another important property of the compounds was their mechanism of action, which is parallel to the mechanism of recreational drugs such as cocaine. Concerns about their

high abuse potential played a major role in retracting the approval for the drugs and removing them from the market.

Typical chemistry employed in the synthesis of those alkaloids would often feature Bischler-Napieralski or Pictet-Spengler reactions.

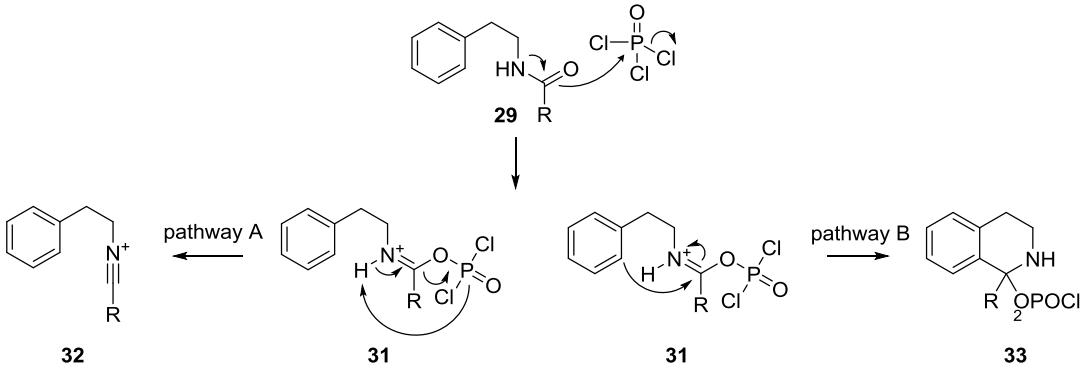
1.4 Bischler-Napieralski

The Bischler-Napieralski[58] reaction was first discovered in 1893 and allows preparation of 3,4-dihydroisoquinolines **29** by reacting β-arylethylamides **30** or β-arylethylcarbamates with a strong dehydrating agent (Scheme 13). Phosphoryl chloride, phosphorus pentoxide, zinc chloride and a number of strong Brønsted and Lewis acids can be used in catalytic or in stoichiometric quantities to induce the desired transformation.



Scheme 13. The Bischler-Napieralski reaction.

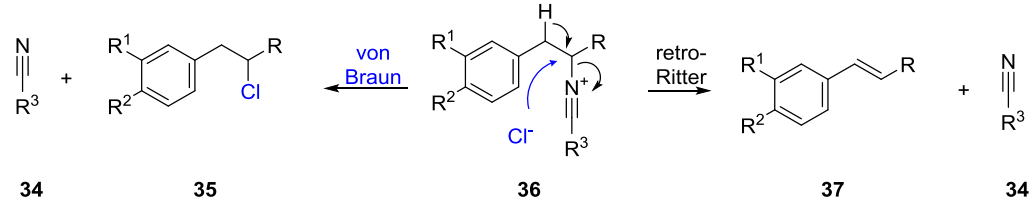
This classic and important reaction allowed access to the isoquinoline skeleton and synthesis of many complex molecules, for example in Woodward's reserpine[59] synthesis. Two possible intermediates are proposed for the transformation, involving reaction of the β-arylethylamide **29** with phosphoryl chloride. The first reaction leads to the formation of **31**, which then converts to either a nitrilium species **32** or a dichlorophosphinic intermediate **33** (Scheme 14), depending on the exact reaction conditions and the reagents used.



Scheme 14. Two possible mechanisms of a Bischler-Napieralski reaction.

The main difference between the two pathways lies in the carbonyl elimination step. In the pathway A, the carbonyl group leaves prior to the cyclisation and the ring-closure occurs via the nitrilium

intermediate **32**. In the second instance, pathway B, the cyclisation occurs prior to the exclusion of the amide group, which is eliminated at a later step. The existence of pathway A was reported by Fodor and Nagubandi and they postulate that the initial step in the mechanism involves dehydration of the amide to form nitrilium salt.[60] The formation of styrenes **37** in a *retro*-Ritter side reaction (Scheme 15) provides evidence for intermediacy of the nitrilium intermediates **36** in the reaction and can be rationalised by formation of a stable, highly conjugated system. A second product formed in the reaction is nitrile **34**.

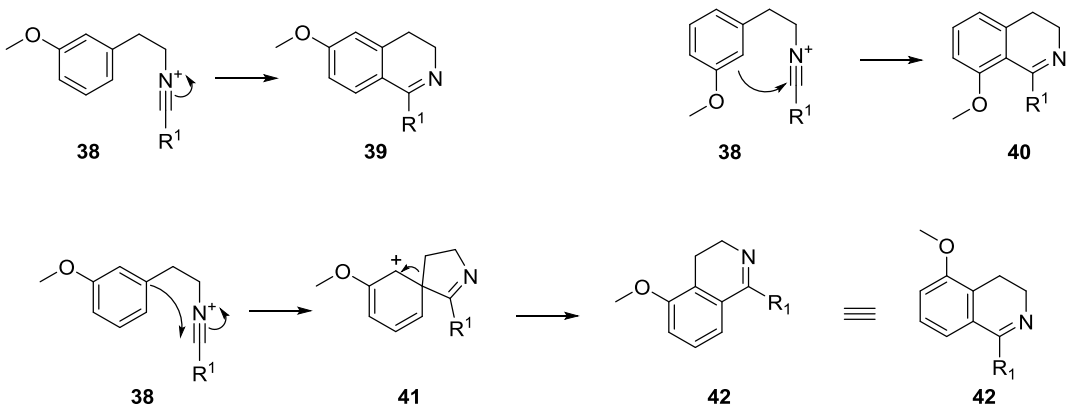


34 **35** **36** **37** **34**

Scheme 15. Formation of styrenes in a retro-Ritter reaction.

Products arising from the von Braun reaction[61], alkyl chlorides **35**, were also detected in the reaction mixtures and are most likely the result of decomposition of the same intermediate **36**. Fodor also found that Lewis acids increase the rates of Bischler-Napieralski reactions, which delivers further indication of nitrilium salt intermediacy.

A crucial step in the mechanism of the reaction is the electrophilic aromatic substitution and rearomatisation, which afford the protonated, cyclised product. As a general rule, the more electron-rich, activated substrates perform much better than electron-poor ones. Nonetheless, even the activated methoxy-substituted analogues require extensive heating and the standard reaction conditions for the Bischler-Napieralski reaction often involve prolonged reflux in toluene or xylene. This is a major drawback of the reaction and the non-activated, electron-poor substrates are well known to give poor yields – if any. Another downside of this classic reaction is that mono-substituted analogues **38** can give rise to different, difficult to separate isomers **39** and **40** (Scheme 16), depending on the reaction pathway, in a typical non-selective *ortho* vs *para* electrophilic aromatic substitution reaction.



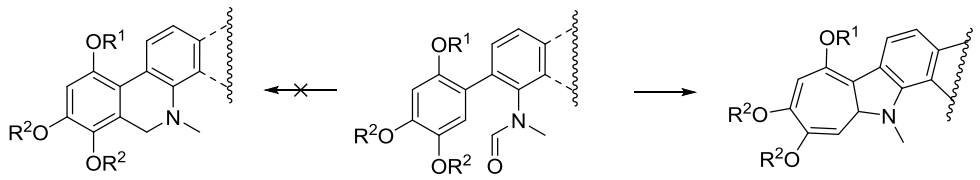
38 **39** **38** **40**

38 **41** **42** **42**

Scheme 16. Routes to different isomers in the electrophilic aromatic substitution.

Another reported side-product in the Bischler-Napieralski reaction is the regioisomer **42**, which presumably results from an *ipso* attack of the aromatic carbon to give the *spiro*-intermediate **41**, which then rearranges to give **42**.

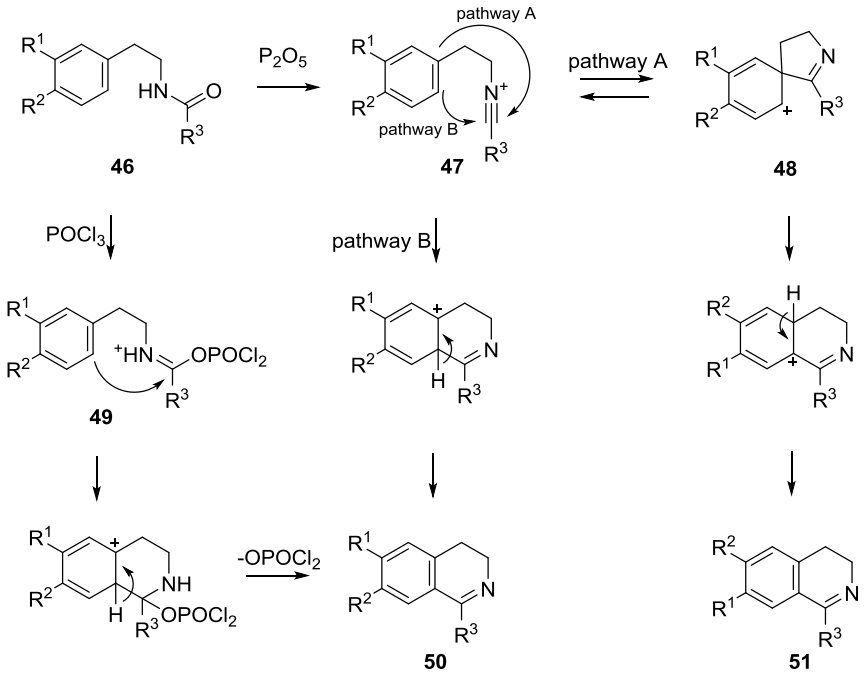
An interesting and unprecedented anomalous behaviour of the reaction was reported by Yamaguchi (Scheme 17), where evidence for a $POCl_3$-mediated carbon insertion into a benzene ring is described. Instead of the expected tetrahydroisoquinoline derivative **43** a rearranged product was observed, allowing the synthesis of azaazulenes **45** (7-5 rings, which are valence isomers of the 6-6 isoquinolines) from precursors **44**.[62]



Scheme 17. Anomalous Bischler-Napieralski reaction.

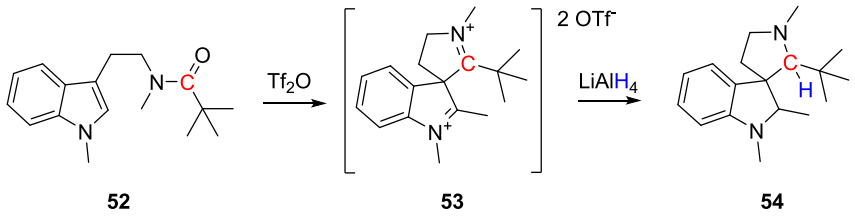
The mechanism involves an initial *ipso* attack onto the formyl carbon followed by abnormal ring expansion and is a direct result of the particular substitution pattern of the electron-donating groups on the benzene ring of **44**. Various analogues with different substituents on the ring system proved to follow a different reaction pathway and gave the expected tetrahydroisoquinolines or, in some extreme cases, de-formylated procucts.

Abnormal reaction products were also studied by Sato, Doi and Shirai (Scheme 18).[63] In their work, they showed that reactions of similar substrates **46** with phosphorus pentoxide in toluene indeed proceed via the nitrilium intermediates **47**. The authors, however, obtained a mixture of two different products, **50** and **51**, and to rationalise the formation of the minor product **51**, they invoke the existence of the *spiro*-intermediate **48**. Interestingly, reactions of the same set of substrates (*e.g.* **46)** with phosphoryl chloride go through the dichlorophosphinic acid esters **49** and give only one product, **50**.



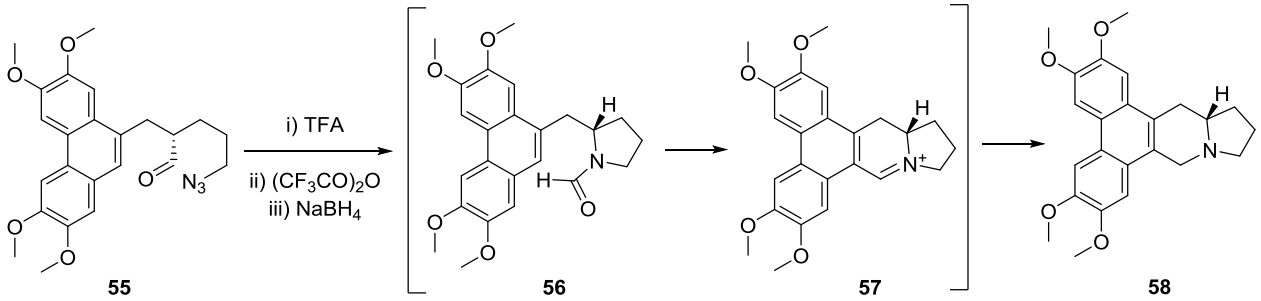
Scheme 18. Doi's mechanistic investigation into the Bischler-Napieralski reaction.

Comparable *spiro* intermediates **53** were previously reported by Medley and Movassaghi,[64] who were able to obtain spirocyclic indolines **54** in an interrupted variation of the Bischler-Napieralski cyclisation (Scheme 19) starting from **52**.



Scheme 19. Interrupted Bischler-Napieralski reaction.

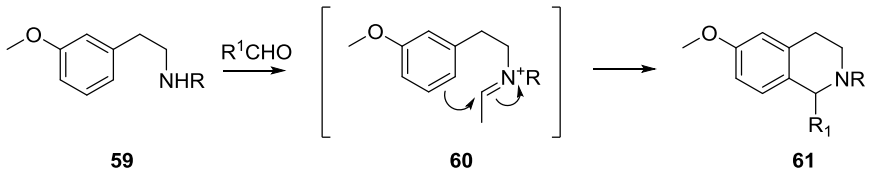
The Bischler-Napieralski synthesis continues to be the primary method of making dihydroisoquinolines and form an interesting research theme. A large number of papers on this topic are published every year describing various modifications such as microwave-assisted variants[65], solid phase synthesis[66], reactions in ionic liquids,[67] or as important steps in total syntheses of various natural products such as a potent anti-cancer and anti-inflammatory agent (*S*)-tylophorine,[68] made in a one-pot Schmidt/Bischler-Napieralski/imine reduction in 84% yield starting from the precursor **55**, via the formamide **56** and imine **57**, to give the final product **58** after the reduction (Scheme 20). A Bischler-Napieralski reaction was also used to construct the THIQ skeleton in the early steps of a synthesis of a close relative of morphine, (-)-thebaine.[69]



Scheme 20. Wang's synthesis of (S)-tylophorine.

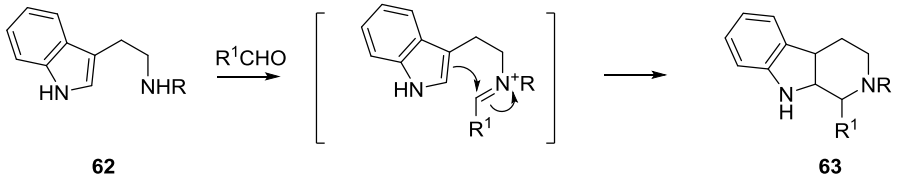
1.5 Pictet-Spengler Reaction

The Pictet-Spengler[70] reaction (Scheme 21) is very closely related to the Bischler-Napieralski and involves reaction of a phenylethylamine **59** with an aldehyde or a ketone to form an imine **60**, followed by ring-closure to form a new carbon-carbon bond. Concomitant re-aromatisation by proton loss yields the tetrahydroisoquinoine **61**. The reaction is generally catalysed by protic or Lewis acids; in addition, a number of thermally-mediated examples have been reported in the literature.



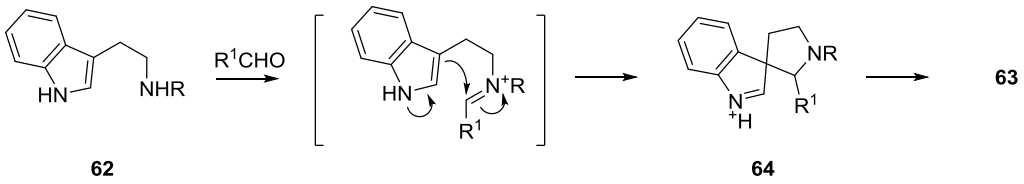
Scheme 21. Classic Pictet-Spengler reaction.

The Pictet-Spengler transformation was discovered in 1911 and quickly became the standard method of synthesizing tetrahydroisoquinoline alkaloids **61** and in 1928 it was also successfully extended to indoles **62** (Scheme 22) and opened up an easy pathway to the carboline moiety **63**.



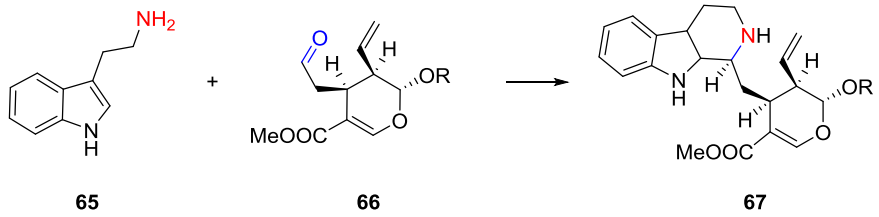
Scheme 22. Classic Pictet-Spengler synthesis of a carboline moiety.

The reaction can be classified as an intramolecular Mannich reaction, where the reactive imine (iminium) intermediate is trapped, instead of by an enol, by a benzene ring. The Pictet-Spengler reaction mechanism has been studied under acid-catalysed and superacid-catalysed conditions and a clear correlation had been found between the strength of the acid employed in the reaction and its efficiency. In 1987 the reaction mechanism was probed in more detail by Bailey,[71] who reported the existence of *spiro*-intermediates **64** (Scheme 23) involved in the reaction.



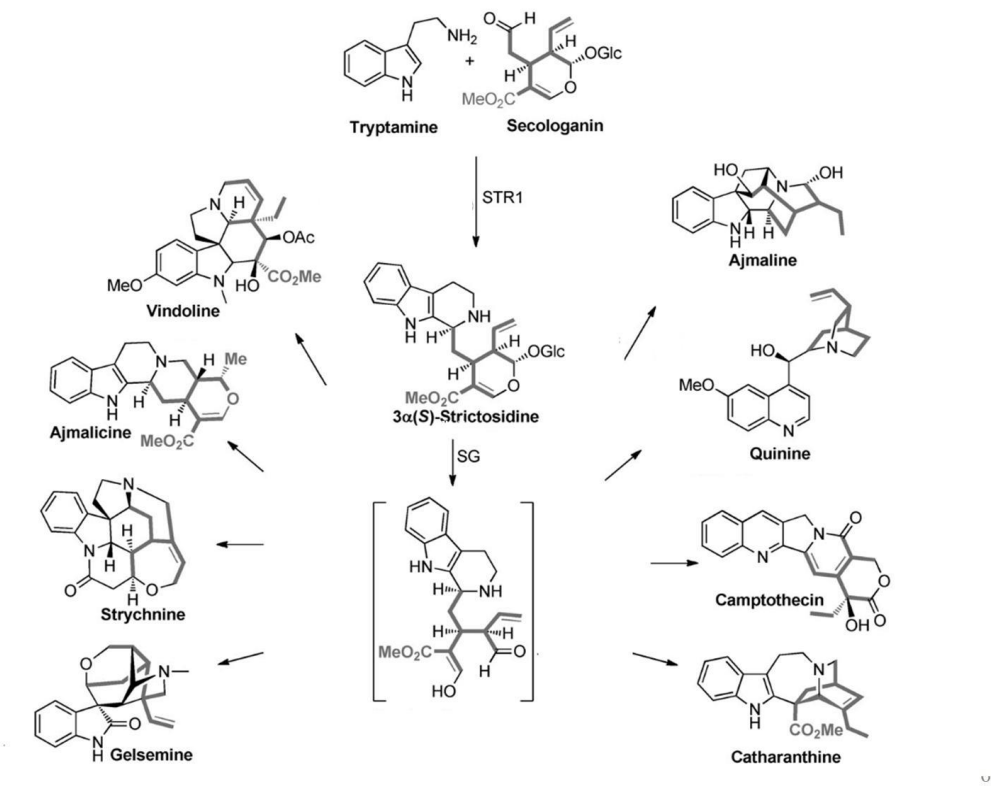
Scheme 23. Spiro-intermediates in the Pictet-Spengler synthesis of carbolines.

In 1977 Stöckigt and Zenk showed that nature also uses the Pictet-Spengler reaction to synthesize alkaloids. In their report, the first enzymatic condensation of tryptamine **65** and secologanin **66** in the presence of the strictosidine synthase (STR1) enzyme was shown, the first "Pictet-Spenglerase".[72] Since then, it was reported that the occurrence of THIQ alkaloids in humans most likely is related to their synthesis *in situ*; consequently, enzymes catalysing Pictet-Spengler reactions are also, reportedly, present in humans.[73]



Scheme 24. Condensation of tryptamine and secologanin to strictosidine.

The product of the enzymatic transformation, strictosidine **67**,[74] was synthesized on a relatively large scale, derivatized and compared to an authentic standard and its absolute configuration was established to be (*R*). Strictosidine was also proven to be an important biological intermediate in the synthetic pathway of the indole and bisindole cores[75] and to many important compounds from *Aspidosperma, Iboga* and *Corynanthe*[76] families. Experiments where ^{14}C labelled strictosidine was fed to carefully selected families of plants revealed that it occupies a central position in the synthesis of complex indole and monoterpenoid alkaloids (Scheme 25). A detailed study of the mechanism of strictosidine synthase was published in 2008 by Stöckigt *et al.*, fourty years after its initial discovery.[77]



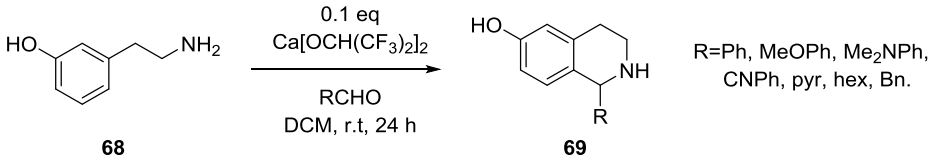
Scheme 25. Involvement of strictosidine in biosynthesis of various alkaloids.

The strictosidine skeleton is incorporated into quinine,[78] the first effective anti-malarial used for many years, gelsemine,[79] a structurally rare and complex alkaloid with a cage-like structure, the highly toxic alkaloid strychnine,[80] a member of heteroyohimbine alkaloids and a cardiovascular agent ajmalicine,[81] the anti-tumour[82] and anti-cancer drug camptothecin,[83] vindoline, a precursor to the anti-cancer agent vinblastine,[84] and many others.

Work in the area of Pictet-Spengler chemistry is mainly focused on achieving good stereochemical control of the reaction and investigating the scope and extending the synthetic methodology to produce enantioenriched substances. Studies also revealed that, in some cases, the condensation proceeds under non-acidic, non-classical conditions.[85] This was a substantial improvement to the original method, as some of the substrate amines and more likely aldehydes could be acid-labile.[76]

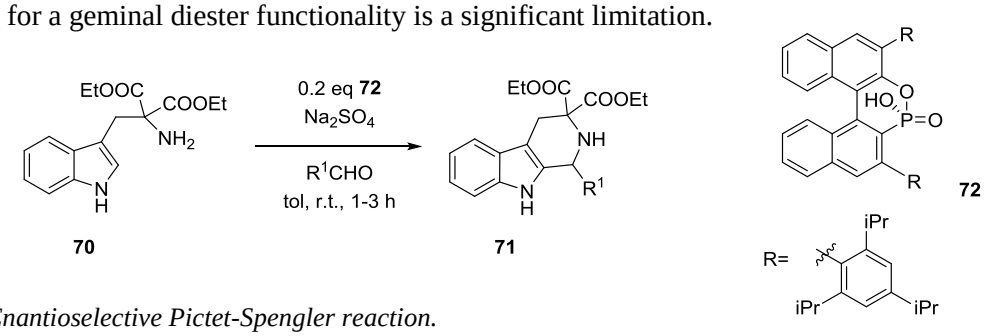
Due to the common electrophilic aromatic substitution step, both Bischler-Napieralski and Pictet-Spengler reactions suffer from the same problems. Aromatic compounds which contain electron-donating substituents are the most reactive substrates for the reaction. Electron-poor rings react very slowly or not at all, reactions of ring-substituted substrates produce mixture of isomers and harsh reaction conditions are required to push the reaction to completion.[86] The vast majority of THIQ alkaloids present in nature are highly decorated with methoxy groups, which is quite fortunate. Nonetheless, the methodology is not universal and modified protocols of the classic reaction are still being researched, in the hope to increase the efficiency and the substrate scope.

An interesting calcium-catalysed Pictet-Spengler reaction was reported by Stambuli (Scheme 26) and is a comparatively very mild protocol.[87] The reaction performs very well even at room temperature and provides good to excellent yields of THIQs **69** from phenylethylamine substrates **68** for a range of aldehydes. Notably, the hydroxyl-group activation is required; less activated substrates such as tryptamine were also exposed to the reaction conditions, however, only the resultant imine could be detected and no cyclisation took place.



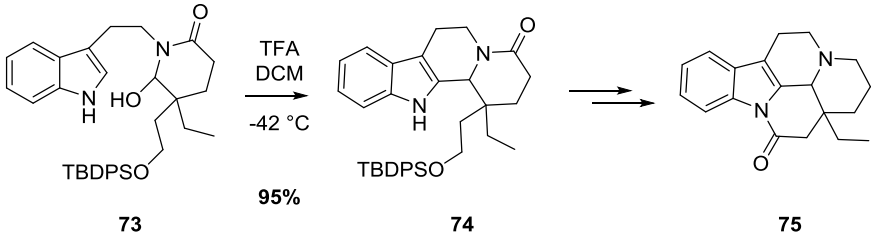
Scheme 26. Calcium-catalysed Pictet-Spengler reaction.

An enantioselective version of the reaction has been developed by List who reported in 2006 that it can deliver enantioenriched tetrahydro-β-carbolines **71** in good to excellent yields (Scheme 27). Chiral, BINOL-based phosphoric acids **72** served as the catalysts in the reaction and produced good to excellent enantioselectivities. A number of aliphatic and aromatic aldehydes are tolerated, which is a major improvement on previous work in this area. The major drawback of this protocol is the necessity for the two ester groups on substrate **70** which, according to the authors, provide the required Thorpe-Ingold[88] steric compression required for the cyclisation to occur. Further functionalisation via decarboxylation is naturally possible, as is selective hydrolysis of the *trans* ester group; nevertheless the requirement for a geminal diester functionality is a significant limitation.



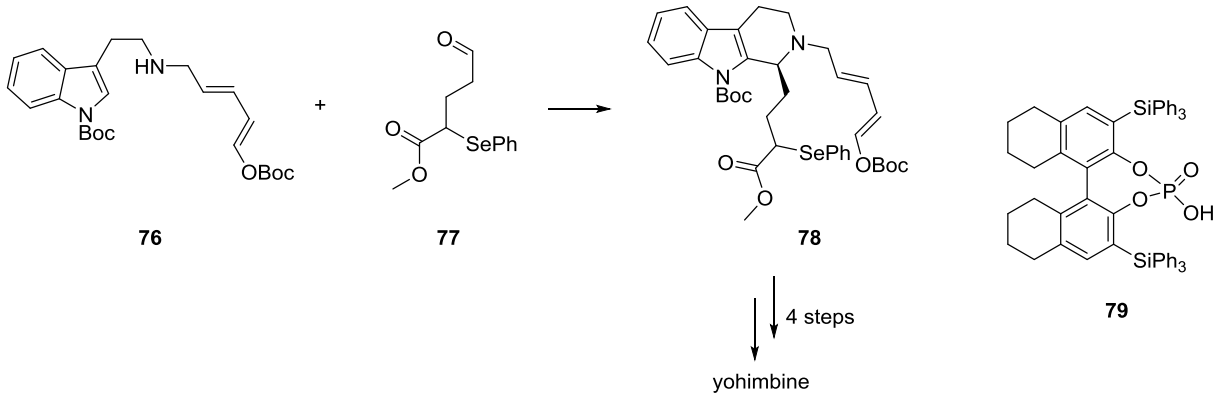
Scheme 27. Enantioselective Pictet-Spengler reaction.

The Pictet-Spengler reaction has been a central reaction employed in synthesis of numerous tetrahydroisoquinoline and β-carboline natural products. Cyclisation of the hydroxy-lactam **73** to the corresponding intermediate **74** is an elegant example of this chemistry (Scheme 28) and allowed assembling the desired tetracyclic core *en route* to a total synthesis of (-)-eburnamonine **75**.[89]



Scheme 28. Synthesis of eburnamonine.

In a recent paper by Hiemstra, the enantioselective Pictet-Spengler reaction was successfully applied in the synthesis of yohimbine (Scheme 29) from an indole derivative **76** and aldehyde **77**.[90] As before, the catalyst of choice was a BINOL-phosphoric acid derivative **79**,[91] producing a 92:8 enantiomeric ratio of the desired final product **78** in 88% yield.



Scheme 29. Hiemstra's yohimbine synthesis.

Interestingly, a similar approach was also applied to facilitate Sato's synthesis of (-)-corynantheidine,[92] where the *cis*-selective Pictet-Spengler reaction delivered a β-carboline intermediate in 74% yield.

1.6 Baldwin's Rules

According to literature resources, 90% of all the molecules discovered in nature to date contain either a carbocyclic or heterocyclic ring.[93] It is therefore important for chemists to understand what rules govern the key bond-forming processes and whether it is possible to control them and apply successfully in synthesis. Due to the large amount of different cyclisation modes *i.e.* carbon/oxygen/nitrogen ring closure onto a carbonyl/double/triple bonds in an *endo* or *exo* fashion (Scheme 30), forming a 3-7 membered rings, substantial consideration needs to be done before certain trends become obvious. Understanding why certain reactions perform better than others is also quite a challenge. The key set of such rules[94] was published in 1976 by Baldwin and still remain one of the most cited articles in the history of the RSC Chemical Communications journal. The guidelines not only provide the now widely accepted nomenclature required to describe and categorise such transformations and processes, but also go into more detail and describe the information behind regioselectivity in the ring-closure reactions. The physical centre of the rules lies within the requirements of the transition state and thus is based on the kinetic favourability of a reaction. In order to achieve cyclisation, a molecule needs to adopt a certain conformation, which allows optimal overlap of suitable orbitals and leads to the reaction product. The optimal trajectory of approach for a nucleophilic atom onto a digonal, sp systems is 120°, 105-109° - the

Bürgi-Dunitz angle - for trigonal cyslisations and 180° for an sp^3 centre, which is the classical S_N2 backside approach angle. Since the outcome of a cyclisation relies on the stereochemical requirements for the transition state of a particular transformation, some reactions occur very slowly or not at all. In some cases the length of the linking chain prevents the cyclising atom from being able to access the site of attack at a desired angle and the activation energy for accessing a certain transition state geometry will be high and may prevent the reaction from happening. Baldwin's rules describe ring-closures in three ways: by the number of atoms in the new ring (*3,4,5* etc.), by position of the bond that is being broken relative to the new bond (*endo* broken bond is within the new ring, *exo* if the broken bond is outside of the new ring system) and by geometry of the electrophilic site (*tet*, *trig*, *dig*, corresponding to sp^3, sp^2 and sp geometries, respectively.). The nomenclature introduced by Baldwin (Scheme 30) takes the form A-B-C, where the three abovementioned parameters correspond to the A, B and C letters, i.e. 6-*endo*-trig for a cyclisation in which a 6-membered ring is formed (6-*endo*-trig), the bond which is being broken is inside the new ring system (6-*endo*-trig) and the electrophilic site has sp^2 geometry (6-*endo*-trig).

Scheme 30. Example of an exo and endo reaction (left); 5-endo-trig and 5-endo-dig cyclisations (right).

To sum up, the stereochemical requirements for certain types of cyclisation reactions to occur vary between different systems and Baldwin's rules summarise those trends and restrictions.

For tetrahedral systems:

i.	3 to 7-*exo*-tet	favoured
ii.	5 to 6-*endo*-tet	disfavoured

For trigonal systems:

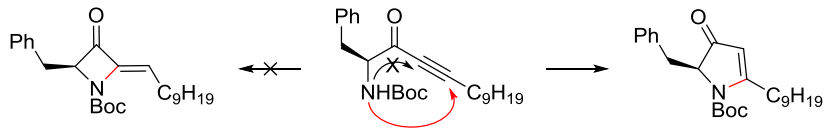
i.	3 to 7-*exo*-trig	favoured
ii.	3 to 5-*endo*-trig	disfavoured
iii.	6 to 7-*endo*-trig	favoured

For digonal systems:

i.	3 to 4-*exo*-dig	disfavoured
ii.	5 to 7-*exo*-dig	favoured
iii.	3 to 7-*endo*-dig	favoured

This thesis will be mainly concerned with overall 6-*exo*-trig cyclisations, which are all favoured in formation of 3 to 7 membered ring systems driven by anionic or radical processes.

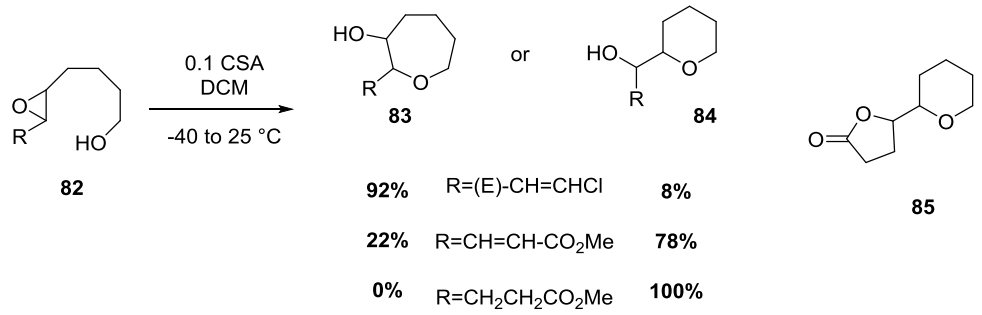
In some cases the outcome of a cyclisation reaction can be predicted intuitively, as in the mercury acetate catalysed cyclisation of nitrogen onto the triple bond in the synthesis of (+)-preussin **81** in ~80% yield (Scheme 31) from the aminoalkyne **80**.[95] Formation of a four-membered ring in the product **79** would create substantial ring strain and consequently it is plausible to assume that a five-membered product of the reaction would be much more stable and require meeting much lower activation energy for the transition state. Not all reactions, however, are as instinctive as the above mentioned one and quite often the result of radical or cationic cyclisations are much harder to predict. Rules for ring-closure of cyclic aldol reaction substrates involving enolate intermediates have also been described.[96]



79 **80** **81**

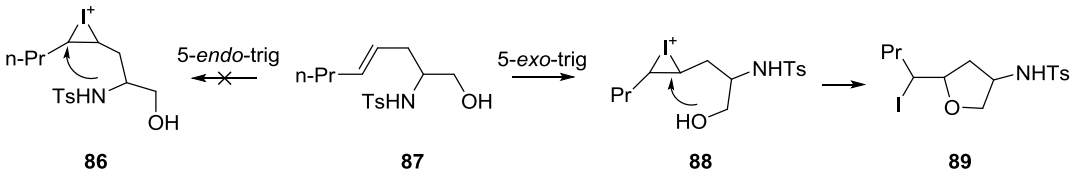
Scheme 31. 4-exo-dig vs. 5-endo-dig cyclisations in the synthesis of Preussin (new bond in red).

Not all cyclisations conform to the Baldwin's rules at first sight and exceptions are known. More complex, polyfunctional (*i.e.* highly conjugated, within a rigid ring system or with a restricted access to the electrophilic site) systems sometimes follow the "seemingly" disfavoured reaction pathway; this is due to the specific properties and structural features of a molecule and results in lowering of the activation barriers for the disfavoured pathway and the associated transition states. Also, due to their larger orbital radii, different bond lengths and availability of d electrons reactions of third-row and larger elements (i.e. sulfur) can yield the "disfavoured" reaction product, as they can access geometrical conformations which are much more difficult to occur for second row elements (i.e. carbon, nitrogen).[97] During his initial studies on oxepanes, tetrahydrofurans and tetrahydropyrans, in a project directed towards the synthesis of brevetoxins, Nicolaou published his findings on *6-endo vs 5-exo*[98] and *7-endo vs 6-exo*[99] epoxide-ring opening with a hydroxyl group and showed that outcome is dependent on the steric as well as electronic properties of the substrate **82** (Scheme 32). In the oxepane **83** *vs* tetrahydropyran **74** experiment (*7-endo vs 6-exo*), introducing a remote ester moiety helped trapping the alcohol **85**, resulting from *6-exo-trig* cyclisation in 100% selectivity (70% yield). However, using the same chain-length ester but an α,β-unsaturated one, increases the charge-stabilisation on the furthest epoxide carbon and increases its electrophilicity; this caused 22% of *7-endo* adduct formation. More π-rich, chlorine-substituted double bond caused the selectivity to shift to 92% in favour of the *7-endo* product.



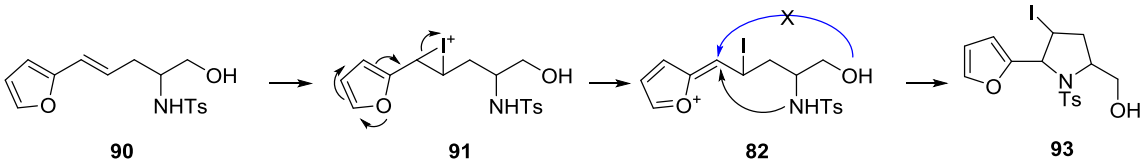
Scheme 32. Nicolaou's work on exceptions to Baldwin's rules.

Another important finding by Knight, Redfern and Gilmore showed that a furan moiety conjugated to the alkenyl cyclisation site can also have an impact on the outcome of ring formation.[100] Building on their previous research in the area of synthesising pyrrolidines and prolines,[101] they synthesized a series of alkenyl sulfonamides and attempted their cyclisation. In the case of unsubstituted analogues the reaction proceeded via the 5-*endo*-*trig* pathway, yielding **86** (Scheme 33). Introduction of an alcohol group in the molecule **87** opened up a new possible pathway, 5-*exo*-trig, which is more favourable according to Baldwin's rules, and the cyclisation does not proceed through the sulfonamide and yields a tetrahydrofuran **89**, via the iodonium intermediate **88**, instead.



Scheme 33. 5-exo-dig vs 6-exo-dig cyclisation.

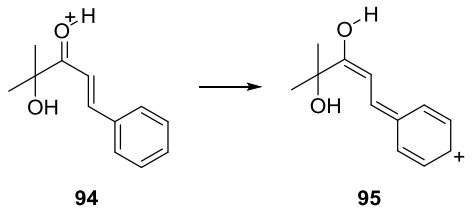
This was on the other hand, not the case for furan-substituted substrates such as **90** and the apparent 5-*exo* pathway is favoured over the 5-*endo* pathway. However, the cyclisation is also controlled by the substituent on the double bond and, in this case, involvement of the furan oxygen lone pair (Scheme 34). Presumably, the iodonium intermediate **91** is ring-opened by the oxygen, forming a highly electrophilic system **82** which can now undergo a 5-*exo*-dig to form **93**, or the less favoured 6-*exo*-dig (in blue) pathway.



Scheme 34. Knight's 5-exo-trig sulfonamido THF synthesis.

In conclusion, this type of arrangement is an example of a multifunctional, complex system that, upon closer inspection, follows the Baldwin's rules. A similar observation was also made by Baldwin himself in a publication describing base- and acid-catalysed cyclisation reactions of various

hydroxyenones **94** (Scheme 35), where an apparent disfavoured transformation (5-*endo*-trig) occurs via a conjugated transition state **95** and is hence best categorized as a 5-*exo*-trig process.[102]

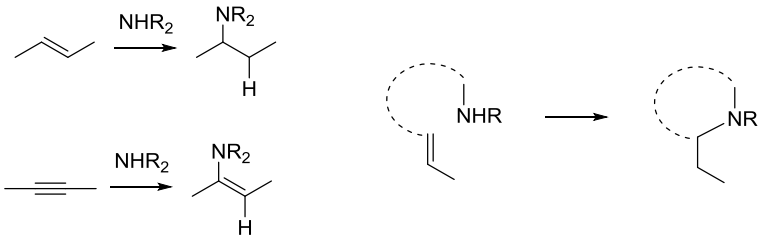


94 **95**

Scheme 35. Cyclisation reactions of hydroxyenones.

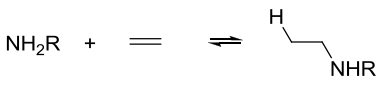
1.7 Hydroamination

In a hydroamination reaction, an N-H functionality is added across an unsaturated carbon-carbon bond of an alkene, alkyne or an allene (Scheme 36). The transformation can be carried out between two species in an intermolecular fashion to furnish an amine, or in an intramolecular fashion to give an *N*-heterocyclic ring.



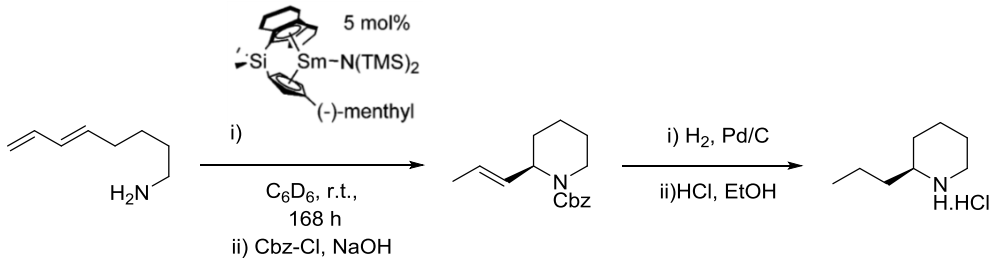
Scheme 36. Inter- and an intramolecular hydroamination.

Hydroamination reactions can be highly atom-efficient reaction process that can be used in an intramolecular or intermolecular fashion to create *N*-heterocyclic compounds. The high activation barrier of the reaction[103] stems possibly from the electrostatic repulsion of the π-bond and the nitrogen lone pair. The thermodynamics of a hydroamination are close to neutral,[104] however, the intermolecular reaction is entropically unfavourable and, according to several reviews, should benefit from being performed at lower temperatures. Logic behind this reasoning invokes the temperature dependence of the equilibrium constant of an exothermic reaction. Increasing the temperature of an exothermic reaction decreases the value of the equilibrium constant. This implies that as the temperature is increased, the position of the equilibrium will move to the left (Scheme 37). Opposite behaviour would be expected if the reaction was endothermic.



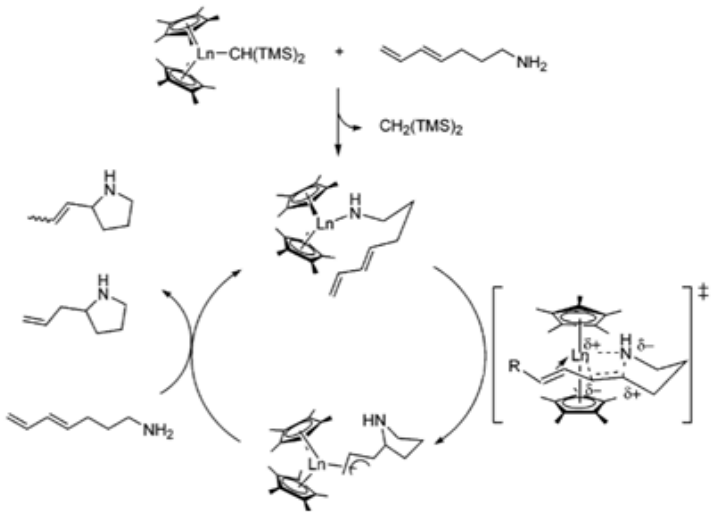
Scheme 37. Equilibrium in an intermolecular hydroamination.

Two common approaches to effect a hydroamination reaction are often adopted and involve activation of either the π-system or the amine. The activation of alkenes is usually done with transition metals and a number of procedures describing the to use of aluminium,[105] zirconium,[106] palladium,[107] gold,[108] bismuth,[109] yttrium,[110] and indium [111] are known. The mechanism of organolanthanide-catalysed hydroamination is a well-studied topic and high turn-over frequencies and excellent stereoselectivities are some of the striking features of this methodology. Use of intelligent ligand-design allowed for development of enantioselective hydroaminations, as exemplified by concise synthesis of (+)-coniine[112] (Scheme 38) employing a catalyst of high complexity.



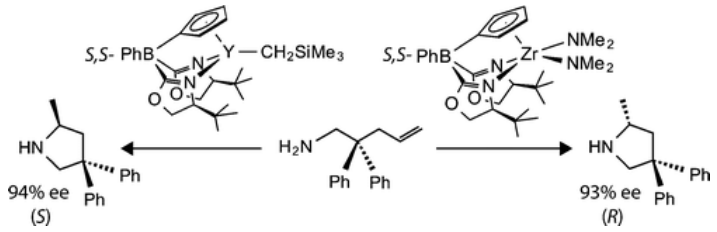
Scheme 38. Coniine synthesis.

The initial samarium complex-catalysed reaction proceeds in 91% yield and affords the carboxybenzyl-protected product in 63% ee. The mechanism of the reaction is believed to proceed via an initial association of the amine with the lanthanide complex, followed by a four-point transition state (Scheme 39) leading to the olefin insertion. Note that a diene moiety is required for the reaction to take place and that simple alkenes have a different reactivity profile. The final step involves protonolysis of the Ln-C bond and yields the cyclised product.



Scheme 39. Catalytic cycle of "lanthanocene" hydroamination reaction.

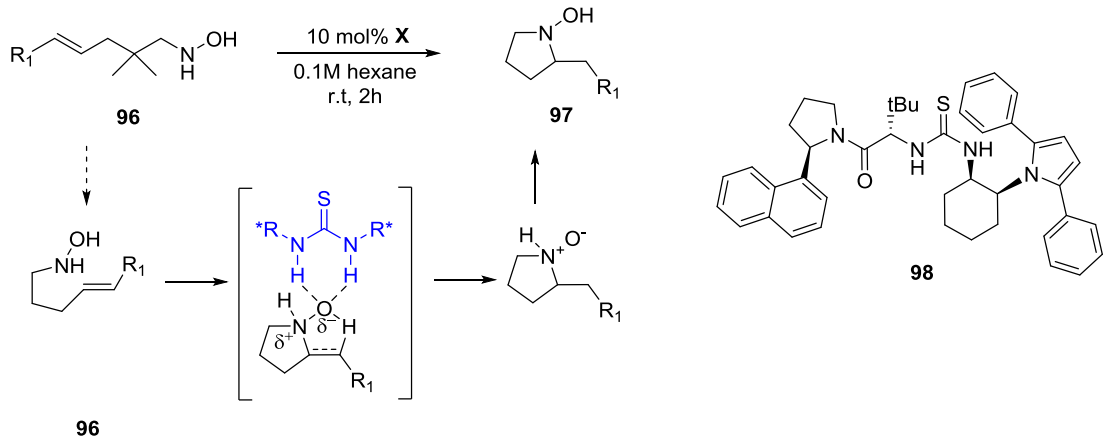
Very good yields and enantioselectivities were recently reported by Sadow in his hydroamination protocol for synthesis of 2-methylpyrrolidines from unactivated alkenyl amines.[113] Oxazolinylborate-based species are used as the catalysts with either ytterbium or zirconium, to provide the hydroamination products in excellent yields and enantioselectivities. A thought-provoking phenomenon was also observed by the authors, specifically, two opposite enantiomers could be produced in a reaction with identical oxazolinylborate ligands but when different metals are used. The absolute configuration of the ligand was identical in both cases and thus an issue of different mechanistic pathways, depending on the metal, was highlighted (Scheme 40).



Scheme 40. Sadow's ytterbium and zinc hydroamination.

Hydroamination approaches utilising alkali metals including lithium[114] and calcium,[115] developed by Ward and his group at Cardiff University, rely on deprotonation of the amine (to give N^-), which renders it nucleophilic enough to attack the double bond. In many cases, however, stoichiometric quantities of metals are required in the reaction[116] and the substrate scope is very limited. Subsequently, no universal method to afford a hydroamination is available and this specific research field remains very active, as there is still need for new, efficient amination processes. Since the shift from stoichiometric to catalytic metal quantities in synthesis, the topic was reviewed a number of times, recently by Beller and Múller[117] in 1999.

Recently, more emphasis is also being put on developing hydroaminations performing well at ambient temperature[118] and delivering enantioenriched products (Scheme 41).[119] In a recent publication by Jacobsen, a reverse Cope hydroamination[120] of bis-homoallylic hydroxylamines **96** catalysed by thiourea species **98** was reported. The reaction provides access to enantioenriched, substituted pyrrolidines **97** and does it at room temperature and very good overall yields.



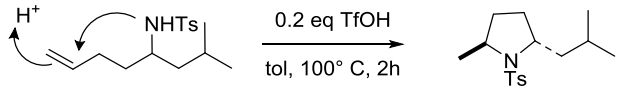
Scheme 41. Jacobsen's reverse Cope hydroamination.

Good to excellent enantioselectivities were obtained in the reaction, however, the reaction scope seems limited, as only alkyl and arylphenyl/halophenyl substituents were reported. The complex nature of the catalyst employed and a possible lack of functional group tolerance is making this reaction, at least in its current state, not very useful.

1.8 Acid-catalysed intramolecular hydroamination

Trifluoromethanesulfonic[121] (triflic) acid, first reported in 1954, is a super acid, which by definition implies that it is stronger than sulfuric acid. It belongs to a special family of compounds and is one of the strongest known Brønsted[122] acids and has a pKa of approximately -12.[123] Another way of measuring the strength of a Brønsted acid is related to the rate at which it exchanges aromatic hydrogens and it has been reported that the proton-exchange rate of triflic acid in benzene is more than 220 billion times faster (2.2×10^{11}) than with trifluoroacetic acid. Apart from its high acidity, its important features also involve high thermal stability and resistance to oxidation and reduction. Unlike sulfuric and halo-sulfuric acids, triflic acid does not induce sulfonylations of unsaturated systems. This important set of properties make this acid an important reagent in organic synthesis and chemists continue to employ its special reactivity to find new and interesting applications. Trifluoromethanesulfonic acid was demonstrated to be an effective catalyst in Friedel-Crafts reactions, cationic polymerisations[124] of alkenes,[125] ethers and siloxanes, Diels-Alder[126] reactions, as well as various rearrangements and cycloadditions,[127] and oxygen or nitrogen cyclisations. The high reactivity of triflic acid makes it sensitive to water. It fumes in humid air and upon reaction with water, forms a stable monohydrate: $CF_3SO_3H.H_2O$. This is a significant drawback and triflic acid-catalysed reactions need to be carried out under inert atmosphere and anhydrous conditions.

Since a vast number of nitrogen-containing heterocycles are synthesized from amino-olefins, the intramolecular hydroamination protocol is of great interest to many organic chemists. One of the first examples in the area of acid-catalysed intramolecular hydroamination of alkene sulfonamides **99** was reported by Hartwig and Schlummer (Scheme 42) in 2002.[128]

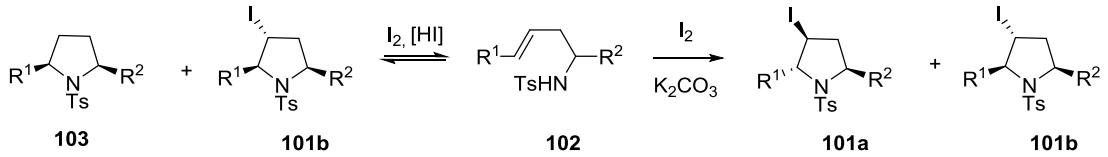


99 **100**

Scheme 42. Hartwig's acid-catalysed hydroamination.

The reaction affords substituted pyrrolidines **100** which are important synthetic intermediates and natural products, as their core is incorporated into such important compounds as nicotine, cocaine and proline. The overall yields are good to excellent; however, the substrate scope is quite limited. Upon extension of the chemistry to styryl double bonds, the electron-rich substrates underwent decomposition and the electron poor ones did not undergo cyclisation at all.

Acid-catalysed hydroamination chemistry is a very central research topic within the Knight group and is a result of previous research into iodocyclisations (Scheme 43).[129] An observation was made that formation of iodopyrrolidines **102** proceeds to give a mixture of diastereomers **101a** and **101b** in the presence of base but a single diastereomer **101a** is formed if the reaction is carried out without base.[130] This was thought to occur due to the presence of hydroiodic acid causing a proton-induced ring-opening and cyclisation, effectively pushing the equilibrium towards the thermodynamic *cis*-product **101b**.



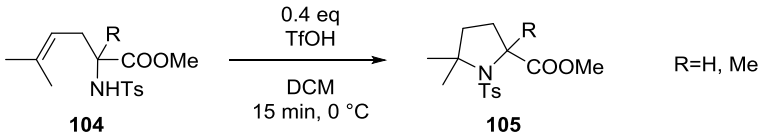
103 **101b** **102** **101a** **101b**

Scheme 43. Iodocyclisations of homoallylic sulfonamides.

When such iodine-induced cyclisations were performed in the absence of base, deiodinated reaction products **103** were also observed. Since these by-products could not be formed through deiodination, this pointed towards a different reaction mechanism – one that does not involve formation of iodonium intermediate. One of the possibilities was that direct acid-catalysed cyclisation was occurring to a small degree.

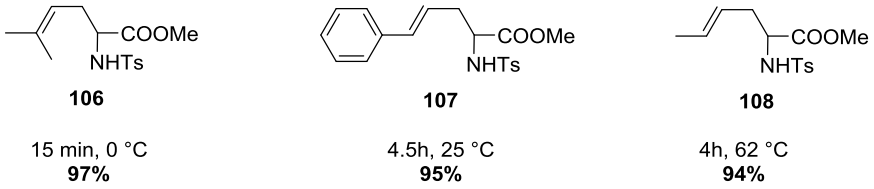
Interestingly, hydroiodic acid-catalysed intermolecular hydroamination and hydroarylation was reported by Marcseková in 2007. The electronic properties of the olefin and of the amine were found to play important roles in the selectivity of the reaction. Addition of hydrogen iodide to the olefin followed by a nucleophilic substitution was postulated as a possible reaction mechanism

Contemporaneously, Haskins and Knight showed that tosic acid, triflic and sulfuric acid catalyse the overall 5-*endo*-trig cyclisations[131] and the methodology has been utilized to synthesize numerous heterocyclic compounds (Scheme 44), for example, pyrrolidines **105** from prenyl derivatives **104** in excellent yields.



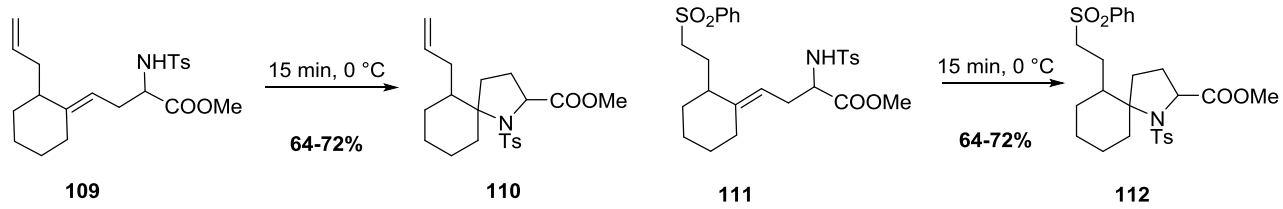
Scheme 44. Knight's acid-catalysed hydroamination procedure.

This was an improvement on the iodine-mediated cyclisations, as catalytic amounts of acid could have been used instead of ~3.0 equivalents of molecular iodine. The reaction was found to need stoichiometric quantities of tosic acid to go to completion and require temperatures in excess of 70 °C. Fortunately, further optimisation of the reaction conditions showed that the reaction performs very well with sub-stoichiometric amounts of triflic acid with chloroform or dichloromethane as solvent and that full conversion of the prenyl derivatives to the pyrrolidines is achieved in 15 minutes at 0 °C. No cyclisation was observed at -78 °C and slow conversion of about 70% in 6h was observed at -40 °C. The general conditions adopted for the reaction were 0.4 equivalents of triflic acid at 0 °C. Lowering the quantity of acid to 0.1 or 0.03 equivalents resulted in a drastic drop in yield, which could indicate the sensitivity of the reaction to trace amounts of water. Further optimisation involved syntheses of analogues **106**, **107** and **108** with different substituents on the olefin and probing the performance (Scheme 45).



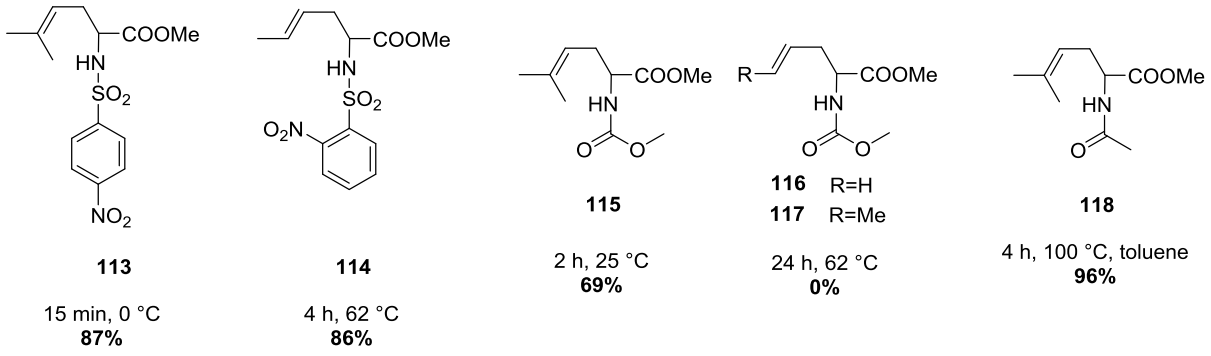
Scheme 45. Optimisation of hydroamination (yields of corresponding products are given).

A clear trend in the reactivity could be observed, related to the generation of a more or less stable carbenium ion. The highly stabilised tertiary cations arising from prenyl analogues **106** required low temperature and short reaction times to achieve full conversion and products could be obtained in 97% yield. Cinnamyl derivatives and thus the secondary benzylic cations, for example **107**, needed more forcing conditions and substantially longer reaction times and products were synthesized in 95% yield. The least stable, secondary olefins **108** could only be cyclised at significantly higher temperature of 62 °C; a yield of 94% was obtained, nevertheless. Additional experimentation showed that non-enolisable aldehydes, remote double bonds and sulfonyl groups were tolerated under the reaction conditions (Scheme 46). Dienes **109** and **111** were successfully cyclised to the corresponding pyrrolidine derivatives **110** and **112** in 64-72% yield.



Scheme 46. Acid catalysed hydroaminations.

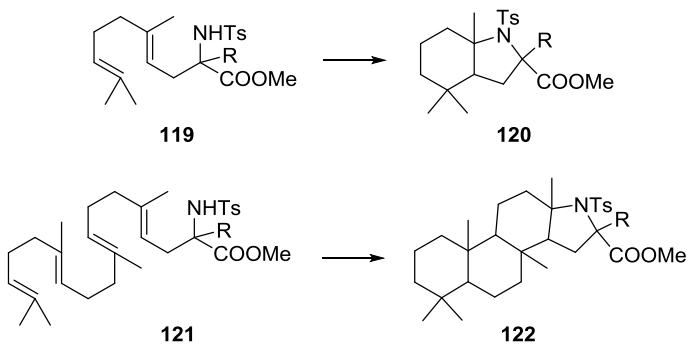
Additional development involved probing the nitrogen-protecting group and it was discovered that nitrophenylsulfonyl (nosyl) protecting groups, first introduced by the Fukuyama group, work very well. Nosyl protecting groups are much easier to remove as they are prone to an *ipso* attack by a thiolate ion and thus can be removed with thiols, including thioacetic or thioglycolic acid. Even though there are a large number of protocols available in the arsenal of synthetic chemists to remove tosyl protecting groups, usually involving Birch-like reducing conditions, the reactions often do not perform very well. Somewhat lower yields were obtained in comparison to the tosyl series, but efficient cyclisation of nosyl derivatives **113** and **114** was nonetheless an improvement (Scheme 47).



Scheme 47. Acid catalysed hydroaminations (yields of corresponding products are given).

Unfortunately, carbonyl protecting groups such as carbamates and amides do not perform in the cyclisations all that well. Carbamate substrates are limited to the most reactive, prenyl derivatives **115**. More forcing reaction conditions are required, 2h at 25 °C, in comparison to the tosyl-protected compounds (*i.e.* **106**), which cyclise in 15 min at 0 °C. No product could be obtained in an attempt to cyclise the cinnamyl and crotyl derivatives **116** and **117**. Also, much more forcing reaction conditions involving refluxing in toluene had to be applied to transform the acetyl-protected, prenyl substrate **118**.

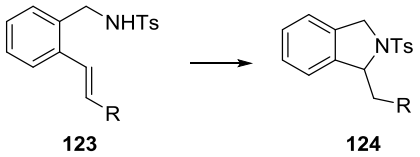
This methodology was also applied to synthesis of more complex molecules in a cascade cyclisation of a polyalkene to form larger cyclic systems (Scheme 48).[132]



Scheme 48. Hydroamination of polyene substrates.

Geranyl **119** (and farnesyl, not shown) derivatives cyclised in approximately 80 – 90% yield to give the corresponding polyclic structures **120**. The chemistry was also used in the synthesis of aza-steroids **122**, which could be successfully obtained from the geranylgeranyl substrates **121**. Unfortunately, the obtained products were obtained in various diastereochemical ratios, approximately 3:1 to 3:2 for geranyl and 3:3:1:1 for farnesyl products. The diastereomeric composition of the azasteroids could not be accurately determined, due to the complexity of the NMR data.

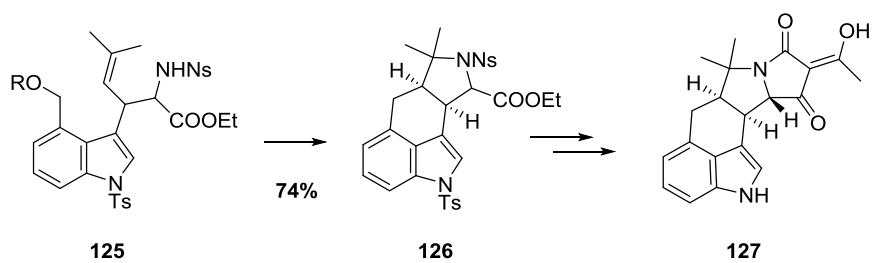
The acid-catalysed intramolecular hydroamination methodology was also extended to the synthesis of isoindolines (Scheme 49). Henderson and Knight reported that cyclisations of 2-alkenylarylmethylamine derivatives **123** gave isoindolines **124**, most likely via benzylic carbenium ion generation.[133]



Scheme 49. Synthesis of isoindolines.

As before, the tosyl group was chosen as the nitrogen-activating group. Exposure of the substrates **123** to catalytic (~ 0.5 eq.) quantities of triflic acid in dichloromethane resulted in smooth transformation into the corresponding isoindolines **124** in very good yields.

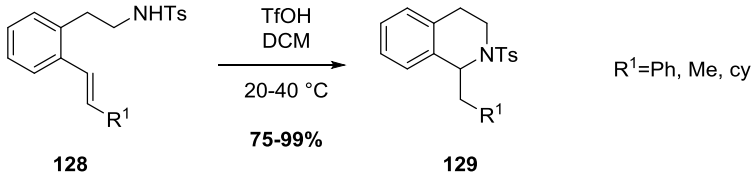
After initial probing of the scope and limitations of this methodology, an idea arose to prove its utility in a synthesis of more complex targets. More recently, Knight's hydroamination was effectively applied in the synthesis of a pentacyclic alkaloid, α-cyclopiazonic acid **127** (Scheme 50).[134]



Scheme 50. Synthesis of α-cyclopiazonic acid.

The key step involved a cascade cyclisation of a nosyl-protected nitrogen in **125** onto a double bond and terminating on a protected, benzylic alcohol, presumably via a carbenium-ion intermediate. The transformation delivered the desired tetracyclic product **126** in 74% yield, which was further developed to the target material **127**.

Establishing that the acid catalysed hydroamination performs well in the area of synthesis of crowded amines, focus was put on extending it to the production of other alkaloid cores. Since a clear relationship between the outcome of the cyclisation and the relative stability of the postulated carbocationic intermediate was observed, it was envisioned that the benzylic stabilisation could provide the extra reactivity – as in the synthesis of isoindolines. In 2012, Henderson reported the synthesis of tetrahydroisoquinoline ring system **129** from the corresponding 2-vinylphenylethylamines **128** (Scheme 51).[135]



Scheme 51. Synthesis of tetrahydroisoquinolines.

These encouraging results prompted further research in this field and permitted gaining access to an important and valuable moiety in an unconventional, yet effective way and delivered a number of novel chemical compounds relatively quickly.

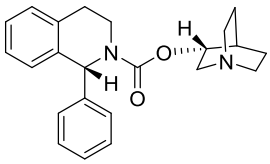
1.9 Conclusions

A vast number of academic institutions and chemical companies work in the area of *N*-heterocyclic chemistry. Acid catalysed hydroamination has a potential of delivering complex, high value compounds in a transformation which is very efficient and atom-economical. An important advantage of the Knight hydroamination over the classical methods developed for synthesis of heterocyclic compounds is that it is not as sensitive to unactivated substrates. In fact, none of the compounds reported by Henderson had any electron-donating substituents on the ring. The requirement for an electron-rich ring on the cyclising substrate could, therefore, be somewhat alleviated, making Knight's methodology the preferred technique for synthesis of numerous alkaloids.

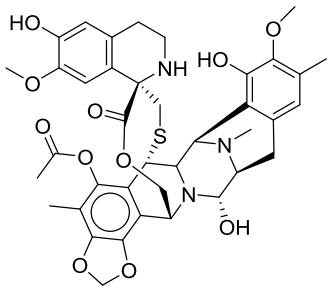
Chapter 2: Synthesis of tetrahydroisoquinolines.

2.1 Tetrahydroisoquinolines

Tetrahydroisoquinoline alkaloids often exhibit strong biological responses and belong to an important class of chemical compounds. They have been extensively studied for their muscle-relaxing (*vide supra*), antidepressing and antidopaminergic effects,[136] neurotoxic and cytotoxic properties,[137] and many others.[138] A number of important drug molecules which are currently being prescribed to patients contain the tetrahydroisoquinoline moiety. Solifenacin **130** (Scheme 52) is a muscarinic receptor antagonist[139] and by 2008 it had been used in almost 50 countries worldwide and prescribed to over 2.2 million patients for the treatment of Overactive Bladder Syndrome.[140] Another important drug which presently, in December 2014, is in Phase III trials for treatment of ovarian cancer and Phase II for prostate cancer is Trabectedin **131**.[141] Its structure comprises of 3 tetrahydroisoquinoline moieties and a total of 8 rings, including a 10-membered heterocyclic macrocycle. In 1996, Corey published the first total synthesis of trabectedin, employing a series of exotic Pictet-Spengler-type cyclisations to construct the THIQ moieties.[142]



130



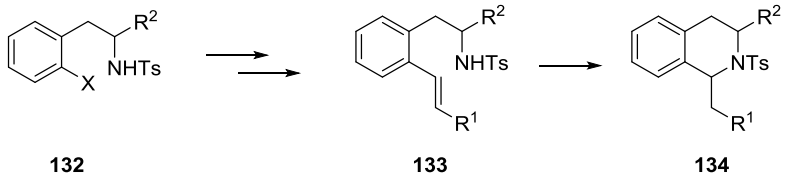
131

Scheme 52. Solifenacin and trabectedin.

Alkaloids from the tetrahydroisoquinoline family constitute a valuable group of bioactive chemical compounds. The classic methods of synthesising these compounds, the Bischler-Napieralski and Pictet-Spengler reactions, are somewhat limited in their scope and efficiency and there is a need for development of new, more universal routes to access the THIQ skeleton.

Knight's acid-catalysed hydroamination methodology has the potential for delivering the THIQ products without the necessity for electron-donating substituents on the ring of the substrate, which is a requirement in the Pictet-Spengler and Bischler-Napieralski reactions. In the synthesis of α-cyclopiazonic acid and in the synthesis of isoindoline and other, simple isoquinoline systems, the cyclisations onto stable benzylic cations were largely successful. Installing the double bond on intermediate **132**, prior to formation of the THIQ heterocyclic part, to form **133**, ensures the necessary C-C bond is in place; subsequent hydroamination provides the ring-closed product **134** (Scheme 53). An additional advantage over the classic methodology is the selectivity; the *ortho* substitution almost guarantees only one regioisomer as the sole product of the reaction. It is possible, however, that the suggested *spiro*-

intermediates (*vide supra*), which play an important role in some of the postulated Pictet-Spengler reaction mechanisms, could also potentially prove problematic under the superacid-catalysed reaction conditions and lead to unwanted byproducts.



132 **133** **134**

Scheme 53. Knight's hydroamination in the synthesis of THIQ alkaloids.

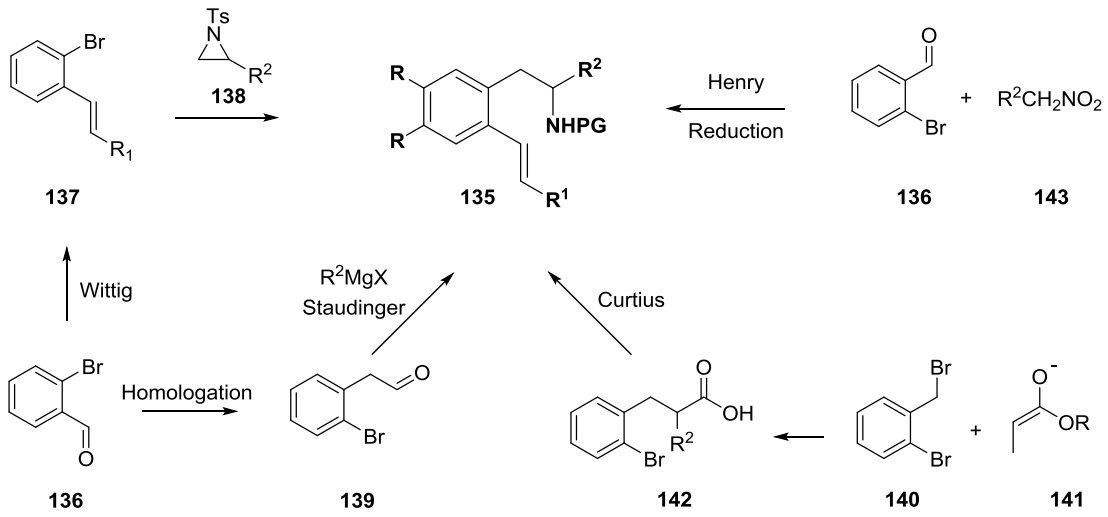
It needs to be noted that the synthetic scheme depicted above is largely different from the classical approach to molecules of this type. It was speculated that the R^1 substituent will now most probably have a large effect on the reaction rate and that the steric compression introduced by R^2 might also play an important role. The substituents *para* to the vinyl moiety will also have an influence on the rate of the reaction, however, most likely it will not govern the overall outcome of the transformation, as it is usually the case in electrophilic aromatic substitution-driven reactions, such as Bischler-Napieralski and Pictet-Spengler.

The topic of this thesis will mainly describe synthesis, substituent effect and nitrogen protecting group influence on the outcome of 6-*exo*-trig cyclisations of 2-vinylphenylethylamines **133** to the corresponding tetrahydroisoquinoline alkaloids **134**.

2.2 Preparative Chemistry

The ability to quickly and efficiently make any of the starting materials for any planned reaction is an important part of any synthesis, especially if a large library of compounds needs to be synthesized or an extensive optimisation of the reaction performed. The efficiency of a particular chemical reaction becomes not as important if one cannot access the required compounds to accomplish it; thus, to some extent a reported chemical procedure is only as good as the accessibility of the starting material for it.

In the early stages of the project an emphasis was put on developing a comprehensive set of organic reactions which would allow construction of the desired 2-vinylphenylethylamines **133**. The main idea was to access a set of synthetic methodologies which would permit manipulation of various parts of the precursor **135**: the groups present on the ring (R), the substituents on the double bond (R^1) and on the phenylethyl chain (R^2) and the protecting group (PG) on the nitrogen (Scheme 54). Since a universal procedure granting access to all the needed precursors for the acid-catalysed cyclisation could not be found, several diverse approaches were defined and are depicted below.



Scheme 54. Preparative chemistry behind the synthesis of the cyclisation precursors.

It was envisioned that the synthesis of the required cyclisation precursors could start with functionalization of 2-bromobenzaldehyde **136**. The vinyl group could be installed in a standard double-bond formation reaction, such as Wittig, Petersen or Julia. The 2-vinyl substrate **137** could be then used to ring-open a substituted *N*-tosylaziridine **138** to yield the final target **135** in only two steps.

Homologation of 2-bromobenzaldehyde to phenylacetaldehyde derivative **139** followed by functionalization with a Grignard reagent, conversion to the amine and installation of the double bond in a Heck,[143] Suzuki[144] or Stille[145] reaction would provide the desired precursor **135**, albeit in a minimum of 7 steps.

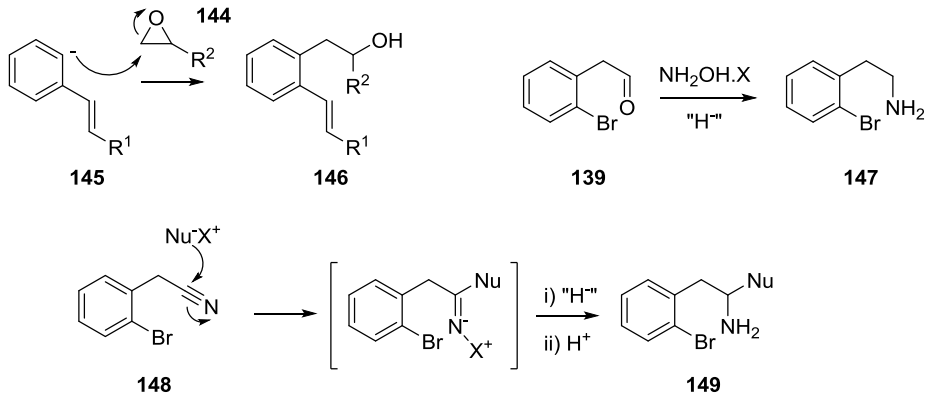
Condensation of 2-bromobenzylbromide **140** with enolates **141** followed by hydrolysis could afford phenylpropionic acids **142**, which after Curtius rearrangement and introduction of the double bond would furnish the final product **135**.

Another useful approach involved condensation of a nitroalkene **143** with 2-bromobenzaldehyde **136**, which after dehydration, reduction, protection and introduction of the olefin could afford the target molecule **135**.

All the aforementioned routes were tested experimentally and their synthetic value examined. The efficiency, scope, limitations and strengths and weaknesses of the procedures will be discussed in greater detail later in this chapter.

There are many other possible routes which potentially could deliver the necessary substrates **135** (Scheme 55), for example, ring-opening of an epoxide **144** by intermediate **145**,[145] followed by further elaboration of the phenethyl alcohol **146**, a simple reductive amination of homobenzylic aldehydes **139** to

access the unsubstituted analogues **147**, or addition of nucleophiles to phenylacetonitriles **148** and reductive work-up to afford primary amines **149**.

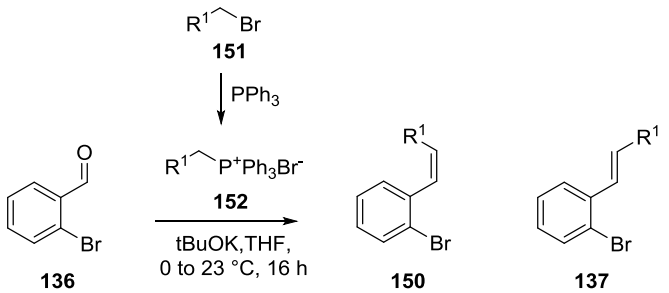


Scheme 55. Alternative routes for the synthesis of the cyclisation precursors.

2.3 Aziridine route

Aziridines are the nitrogen equivalents of epoxides. Their biological properties[146], synthesis[147] and reactions[148] have been reviewed many times, more recently in 2014 by Degennaro and Luisi.[149] The ring-opening of an aziridine reagent is an established methodology used for introducing an ethylamine moiety.[150] One of the major areas of research where aziridines are frequently used is the ring-opening of *N*-sulfonyl aziridine-2-carboxylate esters with carbon nucleophiles as a method for preparation of aminoacids.[151]

One of the major drawbacks of the aziridine route is the inability to tolerate any highly electrophilic, reactive functional groups as they would react in preference to the aziridine. Consequently, the carbonyl group of 2-bromobenzaldehyde **136**, which was the starting material of choice mainly due to its availability and low price, had to be functionalised prior to the ring-opening reaction. Fortuitously, the 2-vinylbromoarenes **137**/**150** could be synthesized in a Wittig reaction of **136** (Scheme 56) with various phosphonium salts **152**, which were either commercially available or made in the laboratory in a very good yield from the respective alkyl halides **151**.

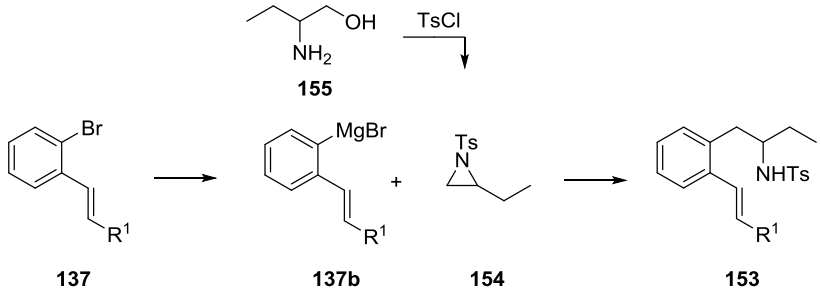


Scheme 56. Synthesis of 2-vinylbromoarenes.

The Wittig reaction delivered the products mostly in very good to excellent yields, although as a mixture of inseparable *cis* **150** and *trans* **137** isomers. A very interesting publication by Gilheany covers some of the basic aspects of *E/Z* selectivities in Wittig reactions.[152] The publication also reveals that column chromatography causes slow isomerisation of the olefins from *cis* to *trans*. Similar behaviour was observed in several cases for a number of stilbene derivatives in our laboratory, where the initial Wittig product would be synthesized as a 10:1 mixture of *cis* and *trans* isomers and taking the olefin through to the next synthetic steps would change the mixture's composition to 7:1 *cis* and *trans* and later to 4:1 *cis* and *trans*. The accurate isomeric ratios are reported in the experimental section.

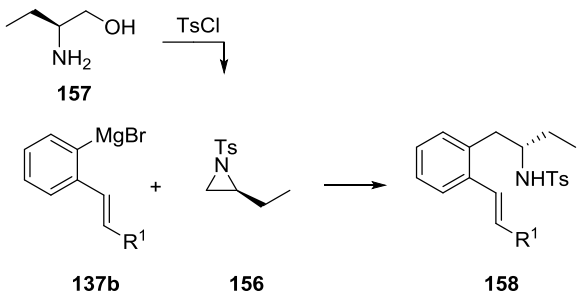
It was realized that the stereochemistry of the double bond could prove problematic if the reactivity of substrates under hydroamination conditions was different. It was later discovered that this was indeed the case. On the other hand, it was a good opportunity to study the effect of the double bond geometry on performance of the cyclisation reactions.

The main benefit of the synthetic route to tetrahydroisoquinoline **153** involving the ring-opening of an aziridine **154** with a Grignard reagent **137b** was the quick installation of the phenylethylamine chain, including the tosyl protecting group, in one step (Scheme 57).



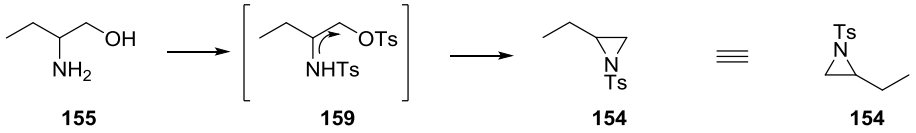
Scheme 57. Aziridine route to the 2-vinylphentylethylamines .

Aziridines can be accessed in many different ways and the preparation of substituted aziridines usually involves nitrene insertions into alkenes, via aza-Darzens type reactions or Mitsunobu reactions of β-hydroxy-α-aminoesters. The *N*-tosyl aziridines such as **154** used in the synthesis of tetrahydroisoquinolines were prepared by a one-pot double tosylation and concomitant ring-closure of 1,2-aminoalcohols **155**. In addition, aziridines have also been used as sources of chirality in stereocontrolled reactions and can be used to access enantiomerically pure cyclisation precursors **156** (Scheme 58). Optically active aziridines can be synthesized via cyclisation of the 1,2-aminoalcohols **157**, which are in turn derived from their respective aminoacids and can be purchased in enantiomerically enriched forms. A range of racemic and optically pure *N*-tosyl aziridines are also commercially available and would potentially allow synthesis of 2-vinylethylamines such as compound **158**.



Scheme 58. Aziridine route to the optically pure 2-vinylphentylethylamines .

According to some literature sources, synthesis[153] of aziridines from their respective aminoalcohols is an easy, one step, one-pot procedure (Scheme 59) yielding 86 – 93% of the desired aziridine product on a 1 to 10 g scale.[154] When attempted in the laboratory, however, the yields obtained were poor (30 – 45 %) and the purification painstakingly slow and costly, mostly due to large amounts of toluenesulfonic acid and tosyl chloride present in the crude reaction mixture. Another major problem was related to the conversion of the tosylated aminoalcohol **159** into the aziridine **154**.

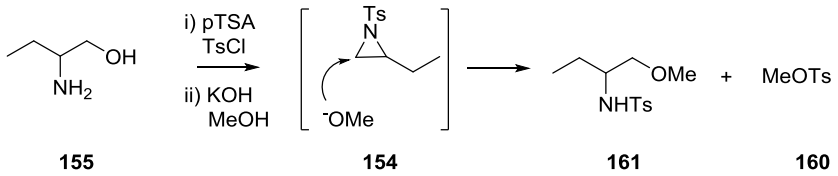


Scheme 59. One-pot aziridine synthesis.

Analysis of the crude reaction mixtures showed the aziridine as well as the *mono*- and *bis*-tosylated material present, which would not ring-close, even at prolonged reaction times or mild heating. This is in accordance with several other publications, where the reported yields for synthesis of aziridines from 1,2-aminoalcohols vary between approximately 40 and 60 %.[155]

Several experiments were carried out in an attempt to try and improve the yield for aziridine synthesis - unfortunately, no major improvement could be attained. Changing the solvent from dichloromethane to acetonitrile[156] had almost no effect; attempts to mediate the ring-closure with a stronger base, *e.g.* sodium hydroxide in methanol, resulted in formation of large quantities of methyl tosylate **160**, which could not be separated. The idea of using a strong, inorganic base to achieve the ring-closure was inspired by a publication by Daub and Overman, who reported a sequential *bis*-tosylation of a 1,2-aminoalcohol to obtain the product using pyridine as solvent, followed by a separate cyclisation/elimination step with KOH in methanol, to yield an aziridine.[157] A literature search revealed that Di Vitta and Marzorati encountered similar problems and could only obtain 60% yield of a very similar aziridine, unless phase-transfer catalysis was employed, in which case their yields had reached >90% but significant problems associated with purification of the final product arose.[158] Increasing the reaction time or the temperature of the original, reaction performed in dichloromethane caused an

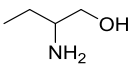
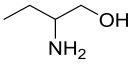
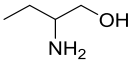
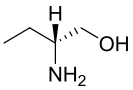
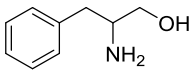
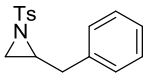
increased formation of unidentified impurities and in the case of NaOH/MeOH reaction, the ring-opened product **161**[159] was mainly detected (Scheme 60).



Scheme 60. Side products in the aziridine synthesis.

Reactions using potassium carbonate[158] in methanol or dichloromethane both at low and high temperatures also did not provide any better results and either incomplete conversion or complex reaction mixtures, which were difficult to purify by means of column chromatography, were obtained.

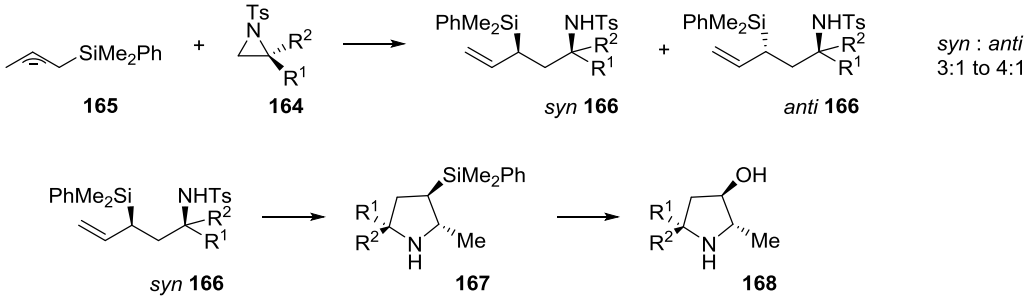
Further optimisation showed that the ring-closure can be induced by careful reaction of the crude residue after removal of DCM with KOH in MeOH at low temperature. Stirring for 90 minutes at 0 to 21 °C and monitoring by ^{1}H NMR spectroscopy allowed improving the yield by roughly 10 - 15%. The only other minor improvement to the original procedure was reducing the equivalents of tosyl chloride and triethylamine from 2.5 and 3.0 to 2.05 and 2.1 respectively. No drop in yield and no major changes in the reaction rate were observed. In the end, by careful column chromatography purification it was possible to obtain a 60% yield of the aziridine (Table 1), of pristine purity. It was also decided that, in other cases, yields of 40-60% are acceptable, since 1 g of the aminoalcohol generates 1 g of the aziridine, assuming ~35% reaction yield.

Aminoalcohol		Conditions	Aziridine		Yield
155		2.5 TsCl 3.0 NEt_3 DCM, r.t, 24h	**154**		40%
155		2.5 TsCl 3.0 NEt_3 DCM, r.t, 24h, then KOH/EtOH	**154**		44%
155		2.05 TsCl 2.1 NEt_3 DCM, r.t, 24h	**154**		60%
157		2.05 TsCl 2.1 NEt_3 DCM, r.t, 24h	**157**		39%
162		2.05 TsCl 2.1 NEt_3 DCM, r.t, 24h	**163**		56%[a]

[a] - After recrystallization from ethanol.

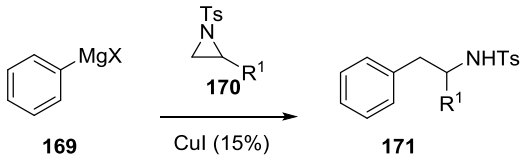
Table 1. Aziridine synthesis.

Application of the aziridine ring-opening with nucleophiles such as phenylthiolates and azides is a known strategy in synthesis of *N*-heterocycles.[160] Another interesting example involving a ring opening of enantiopure aziridine **164** with allylsilyllithium intermediate **165** was reported by Kagoshima *et al.* and yielded a mixture of *syn*- and *anti*- stereoisomers **166** (Scheme 61).[161] Subsequent cyclisation of a single diastereomer **166** and conversion of the silicon group of intermediate **167** to an alcohol afforded tetrasubstituted pyrrolidines **168** in enantiomerically enriched forms.



Scheme 61. Ring-opening of aziridine followed by cyclisation to a pyrrolidine.

The presence of an appropriate electron-withdrawing group on the aziridine nitrogen is necessary for an effective ring opening reaction. Several protecting groups employed to assist in the nucleophilic attack on the aziridine ring, which serve as activators, are often sulfonamides, diphenylphosphinyl and diethoxyphosphoryl groups. Carbonyl protecting groups and also more reactive groups, *i.e.* nosyl, are too electrophilic and react with the nucleophile. An interesting publication by Nenajdenko describes the synthesis of racemic and optically pure aryl and heteroaryl ethylamines utilising the aforementioned approach (Scheme 62).[162] Reactions of a series of aryl and heteroaryl Grignard reagents **169** with *N*-sulfonylaziridines **170** in presence of catalytic amounts of copper iodide were investigated. It was envisioned that this methodology could very quickly provide the desired precursors **171**.

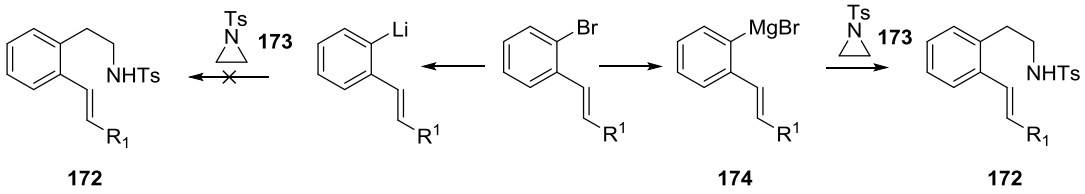


Scheme 62. Ring opening of aziridines by Nenajdenko.

In the vast majority of cases reported in the paper, only a single reaction product was detected; the only exception being 3-indolylmagnesium bromide producing a regioisomeric mixture of two ring-opened compounds. The two products came from the attack of the nucleophile on both aziridine ring-carbons, and their ratios varied from 1:1 to 3:1, depending on the aziridine employed. The authors postulate that the difference in the reactivity for this particular substrate stems from the fact that diethyl

ether was used as solvent instead of tetrahydrofuran, due to issues with solubility of 3-indolylmagnesium bromide. In all other experiments very good yields were obtained, ranging from 64 to 89% and only a single product was detected, arising from the attack of the Grignard reagent at the less substituted carbon of the aziridine. Interestingly, the authors also mention that various other organometallic reagents, such as lithium and zinc derivatives, were also tested but only with the Grignard reagents were they able to generate the ring-opened products. No explanation for this phenomenon was provided in the publication; however, the Lewis acidity of magnesium could potentially be invoked.

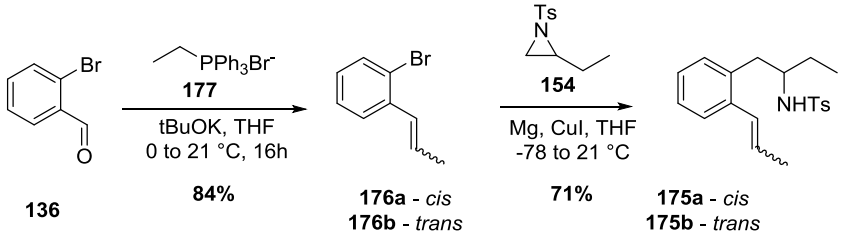
The yields of ring-opening reaction products **172** of *N*-tosyl aziridines **173** with 2-vinylbenze Grignard reagents **174** (Scheme 63) were generally very good and compare very well with the yields reported in the original paper.



Scheme 63. Ring opening of aziridines with lithium and magnesium reagents.

Unsuccessful generation of several Grignards, however, brought several test experiments to confirm whether the lithiated organometallic intermediates indeed do not react under the reported reaction conditions to give the phenylethylamine products. Since the lithium-halogen exchange process is relatively simple, it would be highly advantageous to be able to carry out the process using either a magnesium intermediate or a lithiated species. Unfortunately, only very small quantities of the desired products could be observed and thus the attempts to facilitate the reaction via the lithiation method were abandoned. For substrates from which it was difficult to make a Grignard reagent, an efficient alternative methodology was developed and is discussed later.

The first cyclisation precursor was synthesized as a mixture of *cis* **175a** and *trans* **175b** isomers from the two *cis* and *trans* alkenes **176a** and **176b** obtained in a Wittig reaction of 2-bromobenzaldehyde **136** and ethyltriphenylphosphonium bromide **177**, and successive reaction with the 2-ethyl-*N*-tosyl aziridine **154** (Scheme 64). Very good yields were obtained for both steps.

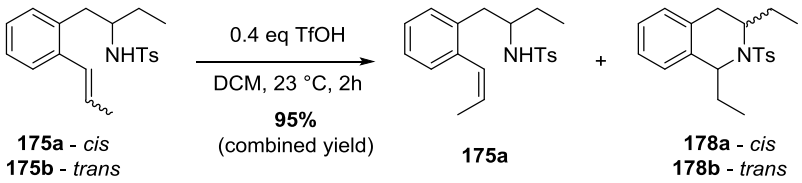


Scheme 64. Synthesis of the cyclisation precursors.

In the original procedure reported by Nenajdenko, two equivalents of the Grignard reagent are used per one equivalent of the aziridine. The authors do not comment on why such an excess of the nucleophile was used. In the laboratory, an observation was made that occasionally, small quantities of the unreacted aziridine (~5 – 10%) were present after the completed reaction, even though two equivalents of the nucleophile were used. The unreacted or dehalogenated aryl bromide could be easily separated by column chromatography; however, the residual aziridine would often co-elute with the product of the reaction and was somewhat difficult to remove. On this basis it was decided that no further optimisation of the ring-opening reaction will be undertaken and the 2:1 ratio of Grignard to aziridine will be used, predominantly because the aryl halides were the cheaper and more readily available starting materials and that the full consumption of the aziridine allowed for easier isolation of the final reaction products.

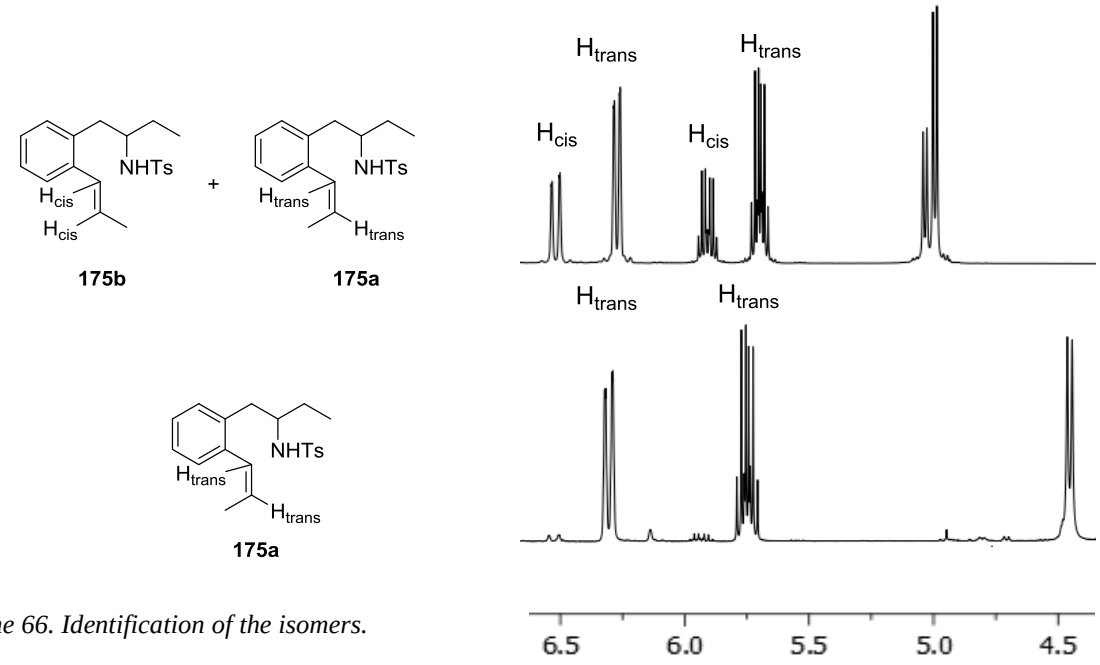
The *E*/Z mixture of the first cyclisation precursor, **175a** and **175b**, was then exposed to the standard hydroamination conditions described below. It should be noted that for all cyclisation reactions carried out above 0 °C, the addition of triflic acid to the substrate in solvent occurred after initial cooling to 0 °C, after which the reaction mixture was stirred for a further 5 minutes at the same temperature and then warmed up to the temperature reported. This approach was employed to minimise the outcome of any exothermic effects associated with brief existence of high-concentration triflic acid droplets during the addition. The initial step concerning the pre-cooling, addition of triflic acid and 5-minutes stir at 0 °C will be omitted for all further cyclisation reactions discussed.

Previous reaction conditions used to afford triflic acid-catalysed hydroaminations employed 0.4 equivalents of acid in a chlorinated solvent such as dichloromethane or chloroform and temperatures of 0 to 68 °C. To accurately define the reactivity of the new system, most of the preliminary experiments were designed to explore the low-end of the reactivity window of the substrate. Later it was also shown that low temperature allows accessing the kinetic product of the reaction in substantially higher quantities. Thus, stirring of the first substrate **175a**/**175b** in dichloromethane with 0.4 equivalents of trifluoromethanesulfonic acid at 0 °C for several hours showed very little conversion and that almost no reaction was occurring (Scheme 65). The small quantity of product **178a**/**178b** (*vide infra*) which could be observed (<10 %) was attributed to the initial cyclisation occurring due to the "hot-spots" present for a very short time immediately after the addition of neat triflic acid. Fortunately, increasing the temperature to 23 °C (room temperature) showed that cyclisation does occur and uncovered an interesting phenomenon.



Scheme 65. Cyclisation reaction.

Out of the two isomers present in the reaction mixture, **175a** and **175b**, only the *trans* isomer **175b** cyclised at 23 °C to give the final product as a mixture of *cis* and *trans* diastereoisomers **178a** and **178b**. The *cis* isomer **175a** of the starting material was separated in 55% yield from the product by column chromatography and easily identified using NMR spectroscopy, as one pair of the resonances coming from the *trans* double bond (d, *J* 16 Hz) disappeared, leaving the other pair of the peaks (d, *J* 12 Hz) intact (Scheme 66). The NH peak was found to drift and could be found around ~4.5-5.0 ppm.



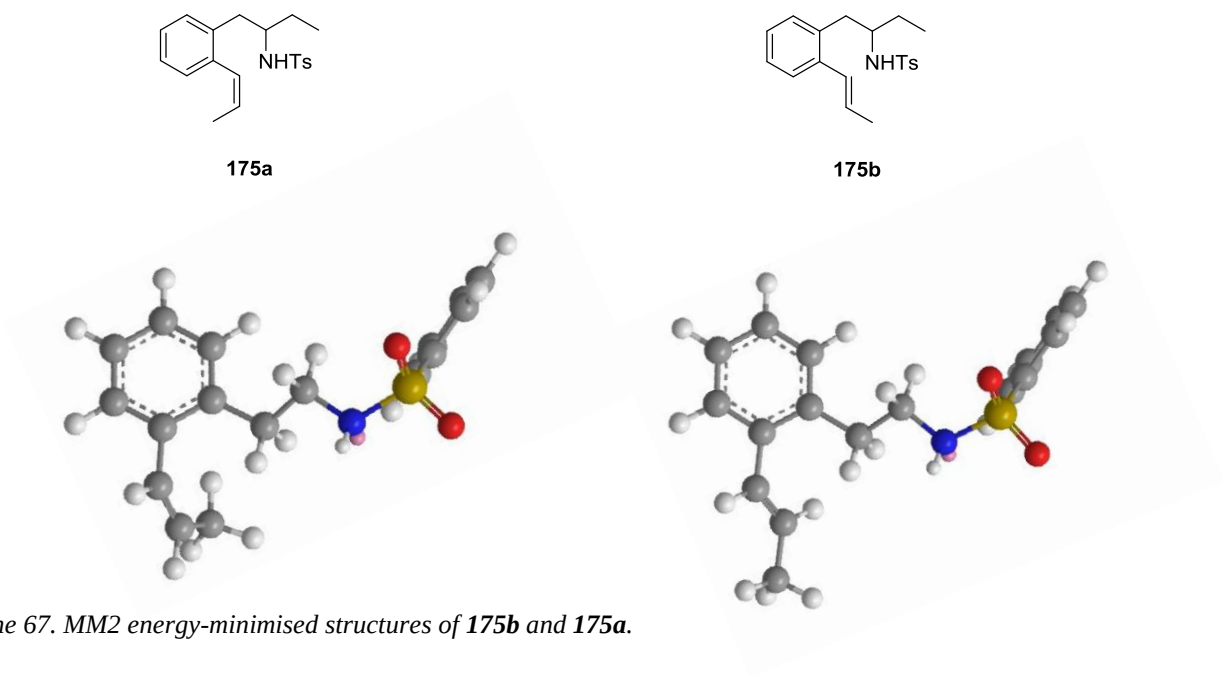
Scheme 66. Identification of the isomers.

This result was somewhat surprising, as it was anticipated that the *cis* double bond is more strained and more open towards the nitrogen attack and also for the postulated intramolecular proton transfer between the sulfonamide and the olefin. It was speculated that the difference in the reactivity could come from the steric interactions between the methyl group of the *cis* isomer and the benzene ring, perhaps twisting the π-system out of conjugation and affecting the approach of the nitrogen.

2.4 Computational Study

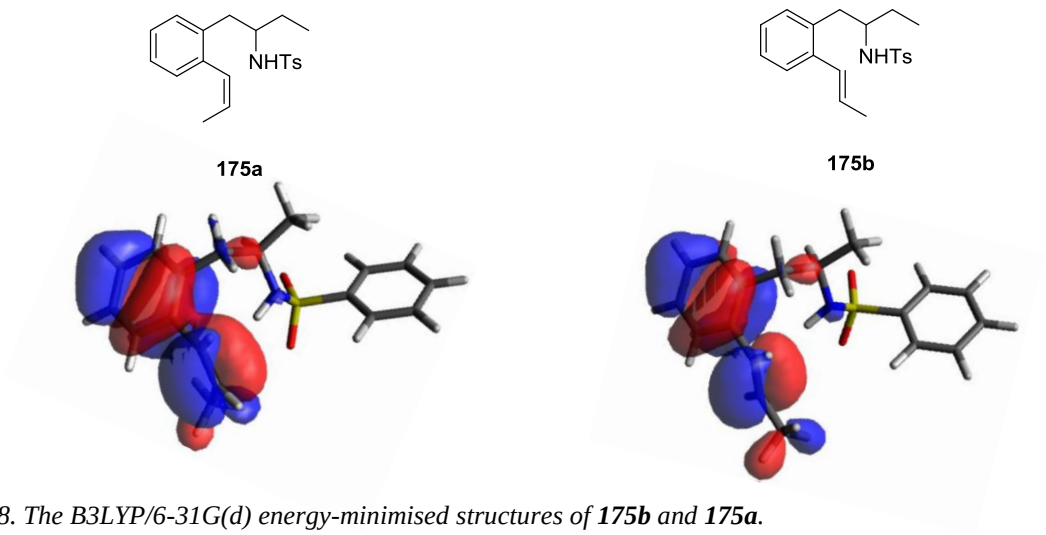
Often, a detailed visual analysis of a compound can deliver important information about it, such as its conformation, bond angles and interatomic distances. It was thought that the position of the double

bond with respect to the benzene ring could have a major influence on the outcome of the cyclisation. A computational analysis of the energy-minimised structures for the *trans* and *cis* isomers **175a** and **175b** indicated that the dihedral angle between the phenyl ring and methyl group varies very little between the two compounds. Values of 49° and 65° for *trans* and *cis* were obtained from ChemDraw3D MM2 force field analysis (Scheme 67), showing a difference of 15° between the two angles.



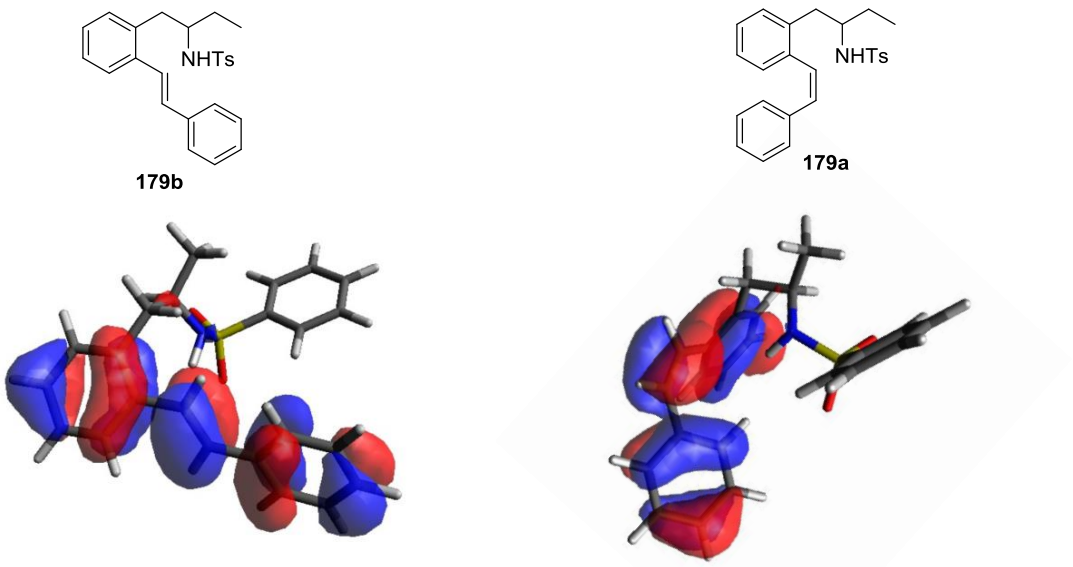
*Scheme 67. MM2 energy-minimised structures of **175b** and **175a**.*

More advanced density functional theory (DFT) calculations,[163] namely B3LYP/6-31G(d), (Scheme 68) gave very similar outcome and angles of 36° for *trans* and 51° for *cis* were obtained. The two values for the tetrahedral angles were approximately 15° smaller than the MM2-calculated ones; however, the overall difference between the *cis* and *trans* dihedral angles was also 15°, which compares with ChemDraw calculations reasonably well. The calculations also revealed that the *trans* form is 8 kJ per mol more stable than the *cis*, which is opposite to the kinetic behaviour observed in hydroaminations.



*Scheme 68. The B3LYP/6-31G(d) energy-minimised structures of **175b** and **175a**.*

The two most unanticipated structural features observed for the energy-minimised structures of *trans* was how large the dihedral angle between the ring and the olefin was. Even though it was predicted that the *ortho*-substitution pattern would possibly introduce some degree of steric interactions between the two ring substituents, the entire π-system was expected to remain flat and the benzene ring to be in conjugation with the alkene.



*Scheme 69. MM2 energy-minimised structures of **179b** and **179a**.*

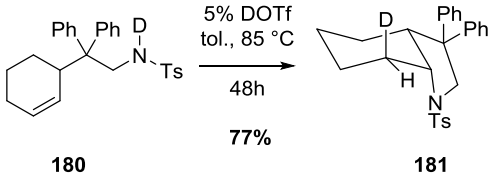
Similar relationship between the bond angles was also observed in the structures of B3LYP/6-31G(d) optimised stilbene derivatives **179a** and **179b** (Scheme 69),[163] which was again unanticipated, especially for the *trans* form, as the two rings were expected to exist in full cross-conjugation through the double bond.

Future work in this are could potentially involve modelling of possible transition states and looking into the protonation barriers. These, however, are notoriously difficult to calculate due to changes in charge and require accurate models of solvent, which introduces further problems. A literature screen revealed that a very interesting, detailed, mechanistic study of an analogous cyclisation reaction on a similar system was published by Widenhoefer.

2.5 Reaction Mechanism

Screening the literature for acid-catalysed hydroamination mechanisms pointed towards only several relevant papers, mostly based on computational calculations for transition states predicted for intermolecular reactions of unactivated amines with simple olefins, frequently using metal catalysts. One, very relevant paper by Widenhoefer describes a detailed, mechanistic examination of an intramolecular,

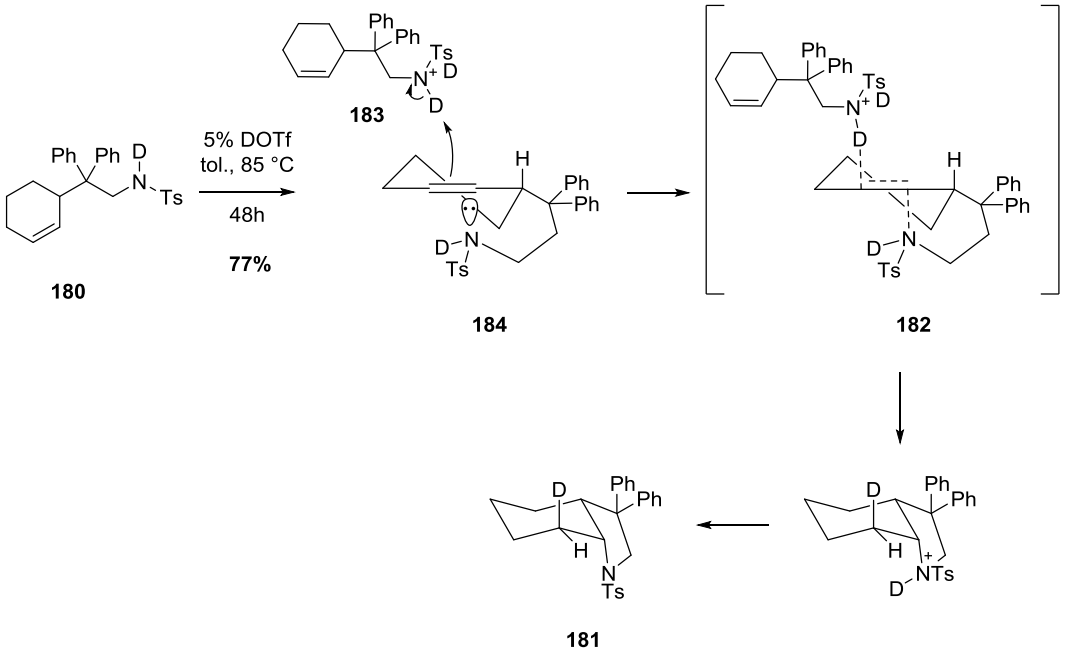
transannular, acid-catalysed hydroamination of **180** with trifluoromethanesulfonic acid to yield the product **181** (Scheme 70).[164]



180 **181**

Scheme 70. Widenhoefer's hydroamination study.

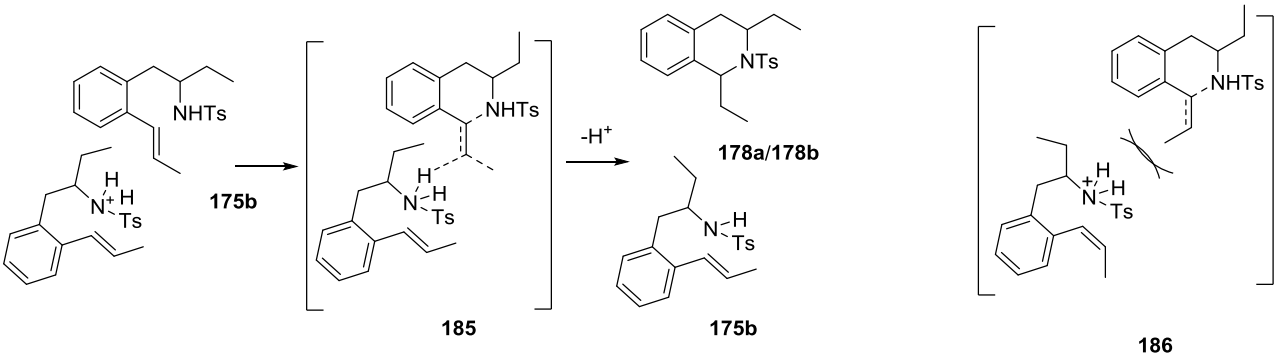
Absence of the alkene isomerisation in the unreacted starting material and the lack of deuterium incorporation in the alkene bond argue against a mechanism including simple protonation of the olefin followed by trapping by sulfonamide. Widenhoefer also discredits the hydroamination mechanism originally proposed by Hartwig, where a rapid, intramolecular proton transfer between the sulfonamide and the olefin occurs, followed by the cyclisation of nitrogen on the carbocation. The mechanism is rejected on the basis that *anti* stereoselectivity is observed in the product (Scheme 71).



Scheme 71. Widenhoefer's proposed hydroamination mechanism.

Subsequently, according to Wiedenhoefer, the transition state for the reaction involves an initial pre-association state **182** of a molecule of protonated sulfonamide **183** and a neutral molecule **184**. An intermolecular, irreversible proton-transfer along the double bond then occurs between the two species, together with the formation of a C-N bond (Scheme 72). If the reaction indeed proceeds via the *anti* transition state **182**, this pre-association mechanism could to some extent explain why the **175a** *cis* olefin reacts slower. The *trans* isomer **175b** in transition state **185** is potentially more open than the

corresponding *cis* isomer **175a** for which the steric interactions in the transition state **186** would make the process higher in energy and thus render the substrate less reactive in the cyclisation.



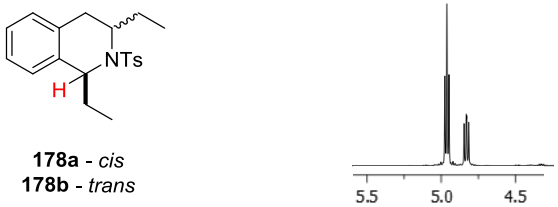
Scheme 72. Wiedenhoefer's postulated hydroamination mechanism extended to Knight's hydroamination.

Further, more detailed information, including deuterium labelling studies and kinetic isotope effect calculations, which are key pieces of the puzzle that led to understading the mechanism of this transformation, can be found in the original paper.

2.6 Cyclisations

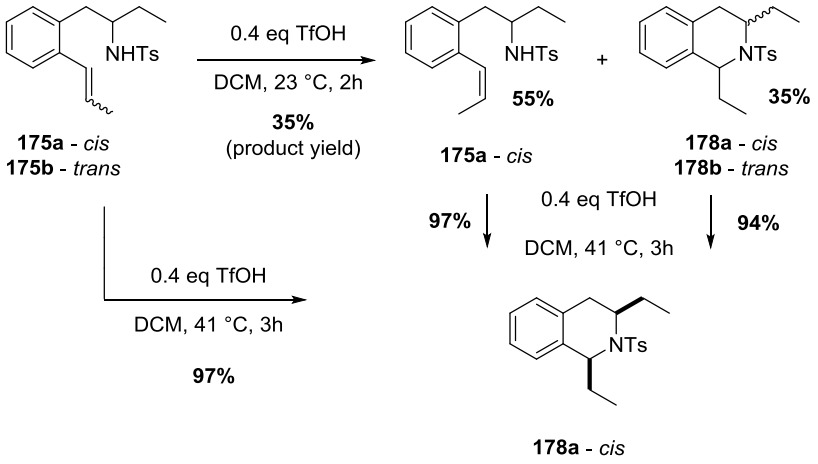
As mentioned before, apart from the *cis* isomer **175a** recovered from the reaction mixture, the cyclised product could also be isolated. The tetrahydroisoquinoline compound was separated as a 2:1 mixture of two diastereoisomers in 35% yield, later assigned as *cis* **178a** and *trans* **178b**. The overall yield of the unreacted starting material and the product were 55% and 35%, and, therefore, very good.

The ^{1}H NMR spectrum of the isolated product showed complete disappearance of the olefin resonances, as well as the N-H signal. Correspondingly, two distinctive sets of two triplets were observed for the two ethyl groups, two methyl groups' signals coming from the tosyl group and two distinctive ABX resonances for the benzylic CH_2-CH-N system. Another characteristic set of peaks was observed at 4.7 - 5.0 ppm, where sharp resonances corresponding to the benzylic CH, next to the nitrogen appeared (Scheme 73), also in 2:1 ratio. It was therefore clear that those two groups of peaks correspond to the two diastereoisomers.



Scheme 73. Characteristic benzylic resonance.

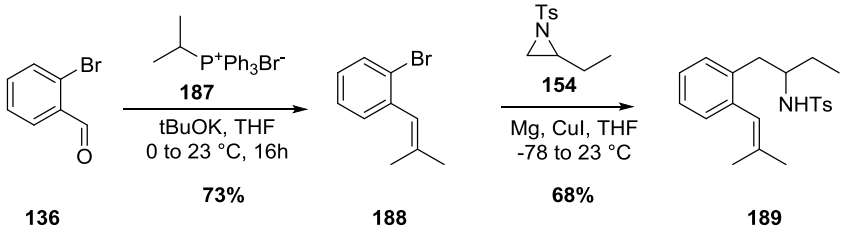
The diastereomeric outcome of the reaction was the next issue to be probed. In the following experiments it was established that one of the stereosimers is the thermodynamic product of the hydroamination reaction



Scheme 74. Equilibration in the hydroamination reaction.

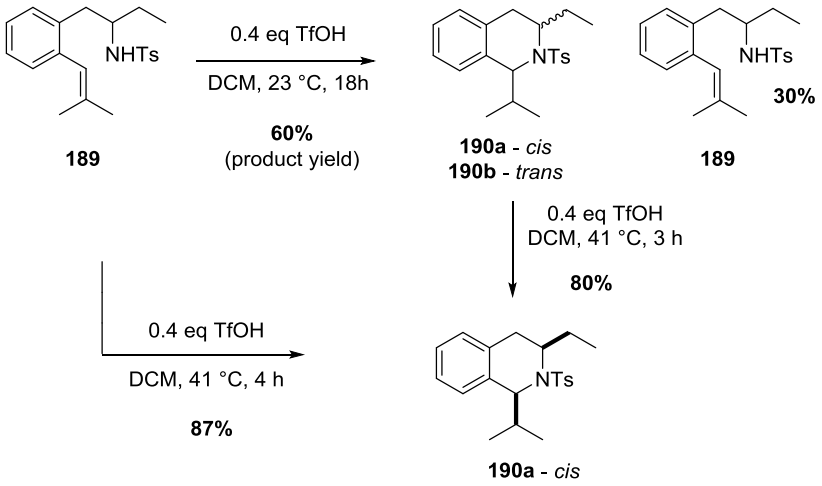
Reaction of the starting material **175a** and **175b** with 0.4 eq. of triflic acid in refluxing dichloromethane for 3 hours furnished the cyclised tetrahydroisoquinoline as a single diastereoisomer (Scheme 74). Subsequently, it was discovered that treating the separated, unreacted *cis* isomer **175a** with triflic acid at 41 °C also gives the thermodynamic product as a single reaction product. In addition, when the 2:1 mixture of the already cyclised product **178a** and **178b** was reacted under the more forcing conditions, again only single reaction product **178a** was observed. In conclusion, the reaction at room temperature afforded roughly 2:1 *trans* to *cis* mixture of the cyclised products, most probably exclusively from the *trans* starting material **175b**. The less reactive *cis* alkene **175a** was converted to the product under similar reaction conditions but at higher temperature and yielded the thermodynamic product **178a** exclusively. The minor, thermodynamic isomer **178a** could also be solely obtained by exposing either the mixture of the *E*/*Z* starting materials, or the diastereomeric mixture of tetrahydroisoquinolines **178a** and **178b** to triflic acid at elevated temperatures.

With the Widenhoefer reaction mechanism in mind it was decided to probe whether more sterically hindered precursors would cyclise successfully. Using almost the same preparative chemistry as before, 2-bromobenzaldehyde **136** was reacted with phosphonium salt **187** and the product **188** was obtained in 73% in a Wittig reaction (Scheme 75). The bromoolefin **188** was used in an aziridine ring-opening reaction to quickly deliver the desired precursor **189**.



Scheme 75. Cyclisation reaction.

It was anticipated that the reaction will be very sluggish or not occur at all at room temperature; however, the reaction of the cyclisation precursor **189** with 0.4 equivalents of triflic acid in dichloromethane at room temperature gave the cyclised product **190** as a mixture of diastereoisomers in approximately 54% yield by NMR, after 5 hours (Scheme 76). Interestingly, extending the reaction time to 18 hours improved the overall conversion by only a few percent and the reaction seemed to have equilibrated.



Scheme 76. Equilibration in the hydroamination reaction.

Similarly as before, at low temperature the cyclised product was obtained as a mixture of two diastereomers, this time in 1:1 ratio and in 60% yield. The product **190** was then reacted with triflic acid at higher temperature. As before, a single diastereoisomer **190a** was obtained exclusively, after 4 hours at 41 °C in 80% yield. Applying the more forcing reaction conditions to the starting material **189** also resulted in complete conversion to the single diastereoisomer **190a**, which was obtained in 87% yield as colourless crystals. An X-Ray structure (Figure 1) was obtained from a single crystal of an analytical sample of compound **190a** and confirmed the stereochemichal assignment of the thermodynamic isomer as *cis*.

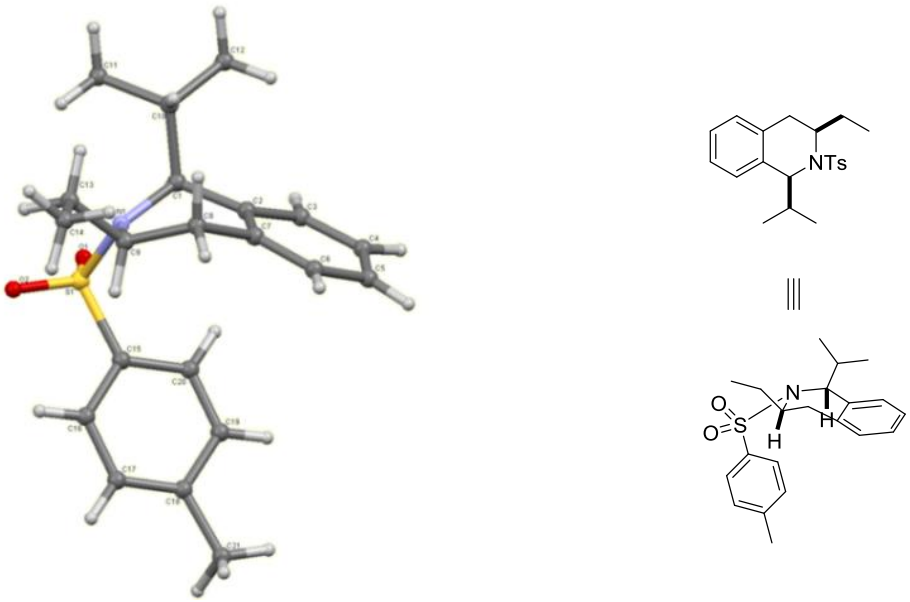


*Figure 1. An X-ray of the thermodynamic isomer **190a**.*

2.7 Diastereochemistry and Spectral Analysis

It can be clearly seen from the X-ray analysis that both substituents are on the same side of the piperidine ring. Interestingly, due to the presence of the double bond and the nitrogen atom, the shape of the six-membered ring is distorted and resembles a traditional boat configuration, rather than a cyclohexane or cyclohexene shape. It was also somewhat surprising to see one of the ring hydrogens from the tosyl group pointing directly into the aromatic ring of tetrahydroisoquinoline. To help establish that the two *pseudo*axial protons of the piperidine ring are *cis*, a nOe signal between the two was expected. Yet, no interaction was observed. The fact that the tosyl group "wedges" itself in between the two protons effectively pushing the two protons apart could explain why no nOe was detected. It is possible, however, that the *pseudo*equatorial substituents are somewhat brought together, as the nitrogen pulls the ring down. Incidentally, it was possible to detect an nOe interaction between one of the diastereomeric protons of the benzylic CH_2 group, and the CH proton of the isopropyl group (Figure 2). The benzylic hydrogen displaying the nOe enhancement is most likely the equatorial one (*J* 7.3), as the resonance from the other benzylic hydrogen is slightly broader (*J* 11.1) and therefore belongs to the benzylic, axial hydrogen.

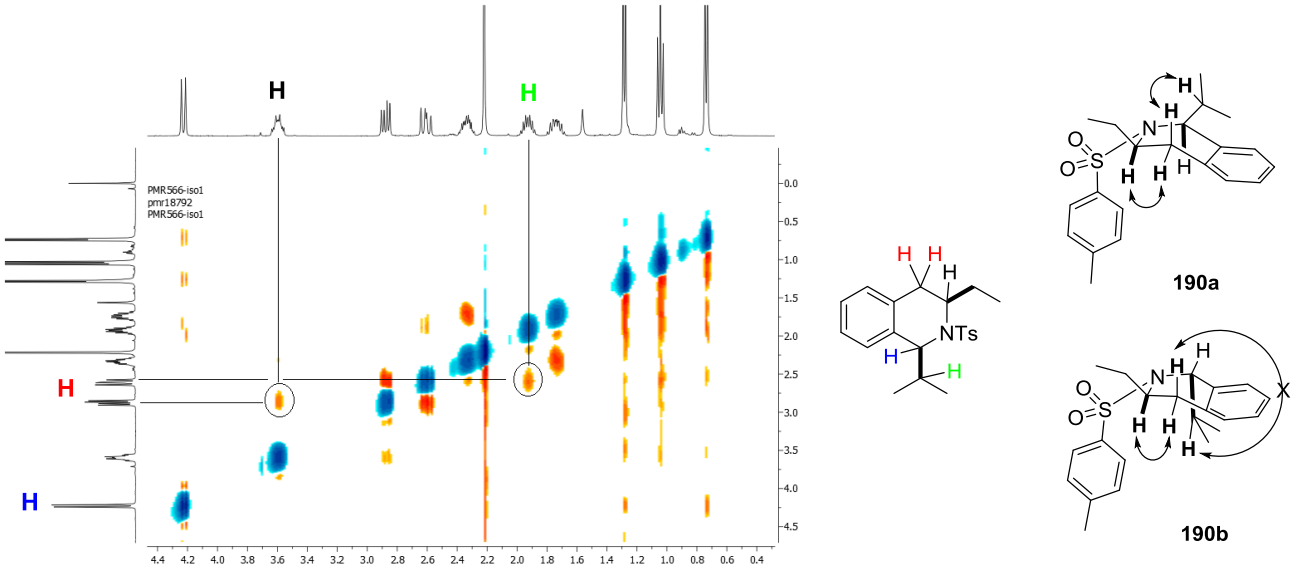


*Figure 2. Important through-space interactions of compound **190a**.*

The second, broader resonance, most probably from the benzylic hydrogen displaying the diaxial coupling, correlates strongly to the neighbouring hydrogen atom next to the nitrogen. The assigned NMR signals are relatively strong and the observed Overhauser enhancement is relatively strong. Since it would be impossible for those two pairs of hydrogens to interact through space if the two piperidine substituents, ethyl and isopropyl, were on the opposite sides of the ring as in **190b** (Figure 2), this supports the *cis* configuration of the thermodynamic stereoisomer **190a**.

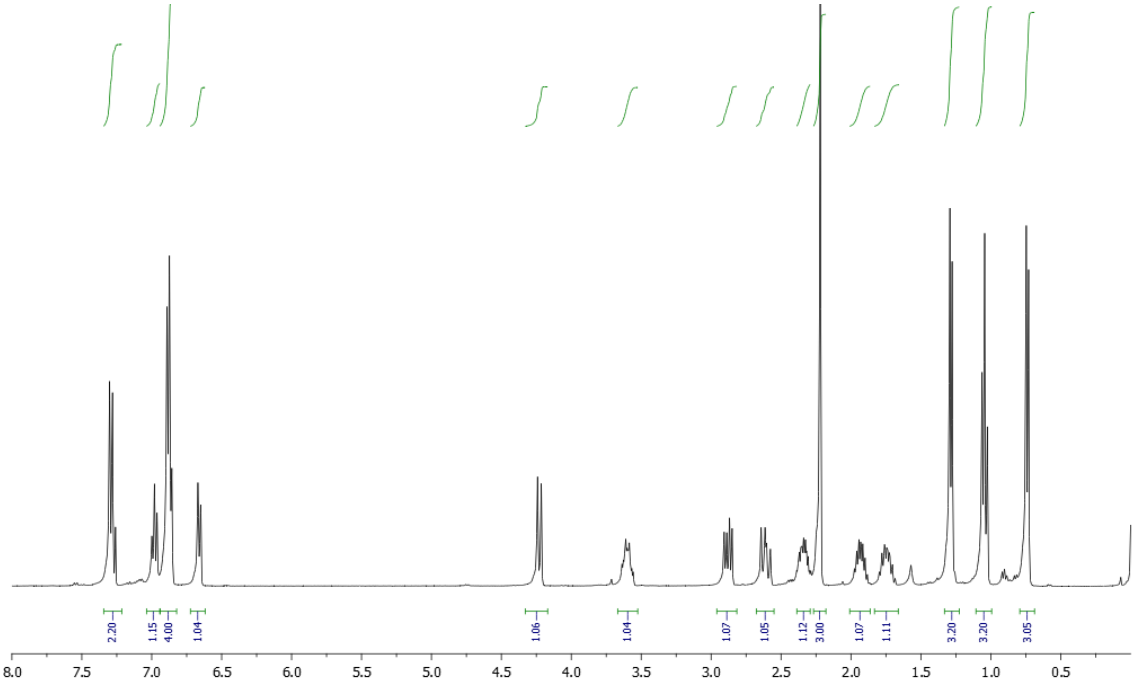


*Figure 3. ^{1}H NMR spectrum of **190a**.*

The resonances on the ^{1}H NMR spectrum of compound **190a** are relatively easy to read, as almost no overlaps occur (Figure 3). Two doublets at 0.74 and 1.28 ppm with *J* value of 6.5 Hz can undoubtedly be assigned to the two methyl groups of the isopropyl moiety. The triplet at 1.04 ppm, *J* 7.5 Hz in between the two doublets, comes from the isolated methyl group on the ethyl substituent. Additionally, all these resonances integrate to 3 protons. The characteristic singlet at 2.22 ppm can also be unambiguously assigned to the CH_3 group of the tosyl moiety.

Further downfield, at 1.75 and 2.32 ppm are the two signals from the two diastereotopic protons of the distal CH_2 group, attached to methyl and NCH moiety. These resonances were identified as possible double-double-quartets and should in theory display a total of 16 overlapping lines (as do dddd). Even though only 10 out of the 16 lines could be identified, careful analysis of the multiplet revealed that there are indeed 16 lines hidden within the resonance. Clear "shoulders" on some peaks could be observed and eventually deconstructed to unveil a doublet quartet of doublets. Extracting the smallest coupling constant (between the outmost peak and the next one) helped with initial establishment of the quartet coupling. This could be done with a ruler, simply by measuring the distance between the first and second peak and then appropriately fitting it onto signals, working backwards to create a coupling tree. A graphic representation of the coupling tree is shown and the black, violet, green and red quartets analysed.

A journal article describing systematic procedures allowing more detailed analysis of first-order ^{1}H NMR spectra was published by Hoye.[165] It discusses three slightly different approaches for extracting *J* values from a diverse range of resonances, *i.e.* doublets, doublets of doublets, ddds, dddds and briefly covers interpretation of ddddds. Various examples are also shown and interactions between dissimilar protons are pointed out. In combination with general knowledge of ^{1}H NMR spectroscopy, information

about the structure of the compound being investigated and thorough analysis, the publication provides a practical set of guidelines which allows for a deeper understanding of multiplets, especially useful for beginner chemists and analysts. A few years later, in another paper by Hoye,[166] a very simple approach to quickly find a *J* value was shown, simply based on the relative distances between specific peaks in a single resonance. According to the publication, the distance between the first and the second peak for a dddd is always J_1, the J_2 value is the distance between the first and third peak and the next coupling constant is unravelled by skipping the resonance formed from addition of J_1 and J_2 values and taking the distance to the next one. Such approach does not necessarily function very well when applied on its own, but to a certain degree speeds up the process of peak analysis, when combined with other, thorough methods.

In the case of the 1.75 ppm resonance of **190a**, the signal is composed of four quartets, each of 1:3:3:1 ratio. These four quartets can be further disconnected to a doublet of doublets and the resultant dd becomes a doublet (Figure 4). The quartet coupling constant is the smallest and can be easily observed on the NMR spectrum and equals the distance between the first and second peaks, which is 7.3 Hz. The two doublet couplings cannot be directly extracted but "travelling" up and down the disconnection tree and choosing distances between the appropriate peaks allowed to determine that the two *J* values are 9.6, from the vicinal N-CH coupling, and 13.5 Hz, the larger value coming from the geminal coupling.

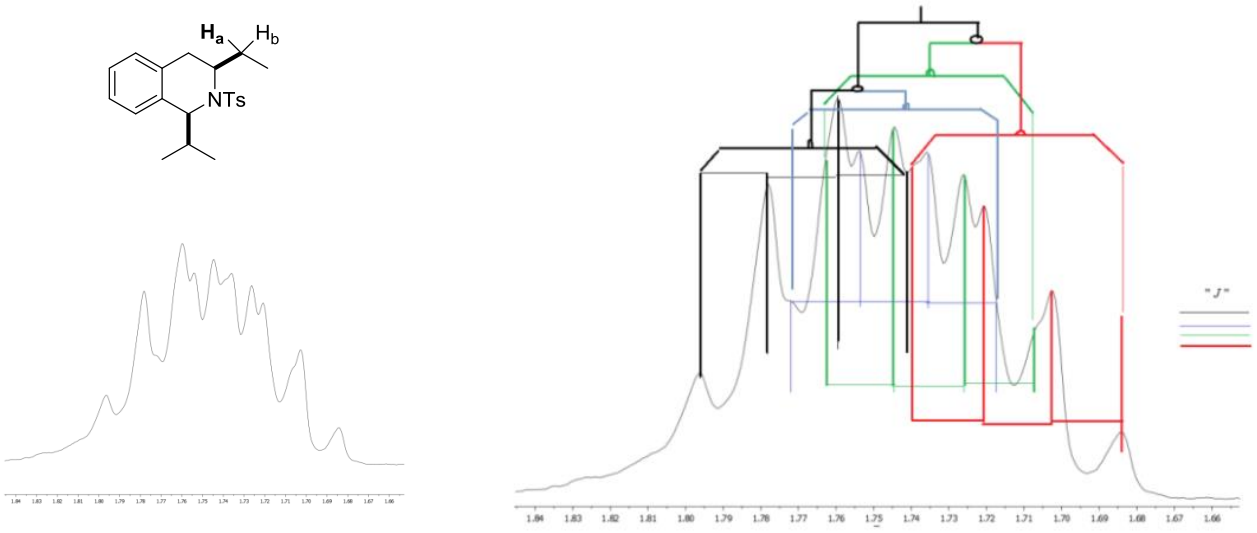


*Figure 4. Resonance at 1.75 ppm from ^{1}H NMR spectrum of compound **190a**.*

The width of the whole resonance, from the first to the last peak is 45.11 Hz. It is known that the sum of all the coupling constants is equal to the width of the resonance in Hz. Since the H_a hydrogen of **190a** couples to three protons of the methyl group, the "quartet" coupling constant needs to be multiplied by 3 and the other *J* values added only once. Thus, 3 x 7.4 + 9.6 + 13.5 = 45.3 (Hz), which corresponds very well to the 45.11 Hz observed for the multiplet.

The other resonance for the diastereomeric CH_2 group appears at 2.33 ppm. At the first inspection, the shape of the peak does not resemble a standard dddd or ddq pattern. Careful and thorough analysis allowed deciphering the signal (Figure 5) and showed the hidden configuration.

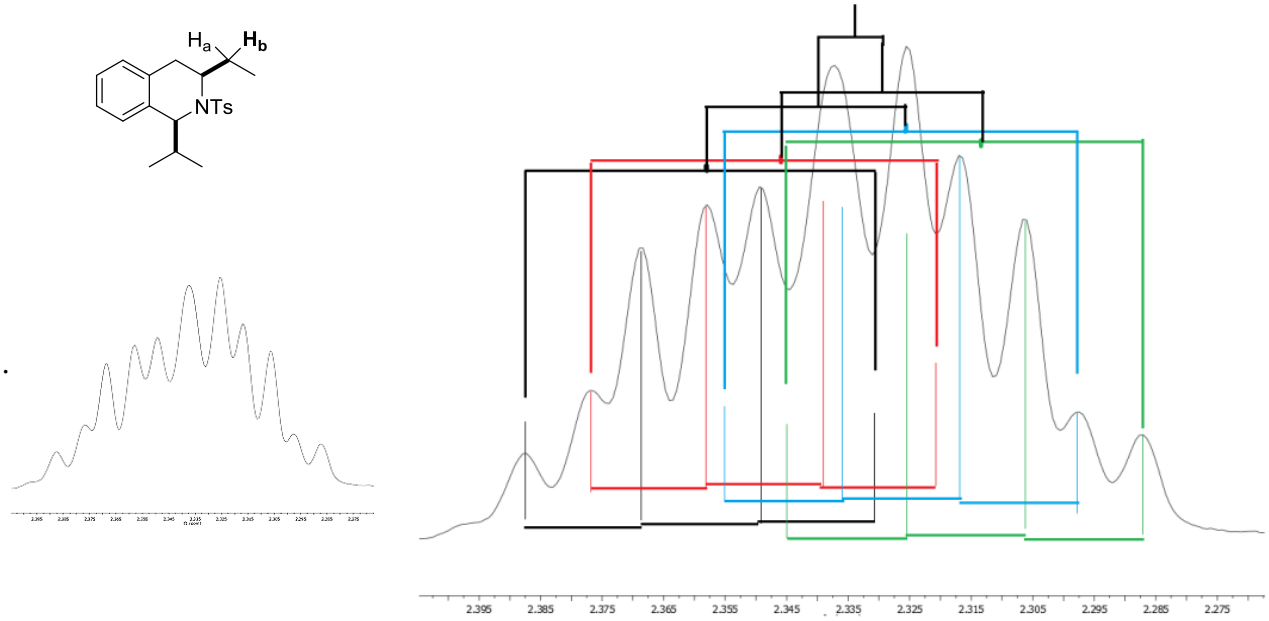


*Figure 5. Resonance at 2.33 ppm from ^1H NMR spectrum of compound **190a**.*

Just as its sibling H_a, the signal of the H_b proton could be taken apart to a double-doublet of quartets. The largest, geminal coupling was 13.5 Hz, which naturally matches the coupling of H_a. Unsurprisingly, the quartet coupling was found to be 7.5 Hz (7.4 Hz for H_a) and the smallest, doublet coupling constant was 4.3 Hz. To confirm the analysis the arithmetical calculation was carried out: 3 x 7.5 + 4.3 + 13.5 = 40.3 (Hz). The width of the peak was found to be 40.18 Hz, which corresponds to the calculated value of 40.3 Hz very well.

The next peak in the analysis was the signal belonging to the CH of the isopropyl group at 1.93 ppm (Figure 6). The proton in question couples to two CH_3 groups, which appear as two triplets with *J* of 6.5 Hz, and also with a benzylic CH, which in turn appears as a doublet with *J* of 10.6 Hz. The resulting doublet of septets, which upon closer inspection appears to look more like symmetric doublet of quartets or a ddq, could be deciphered relatively easy. Careful investigation confirmed that the coupling constants were in agreement and were found to be 6.5 and 10.6 Hz, as expected.

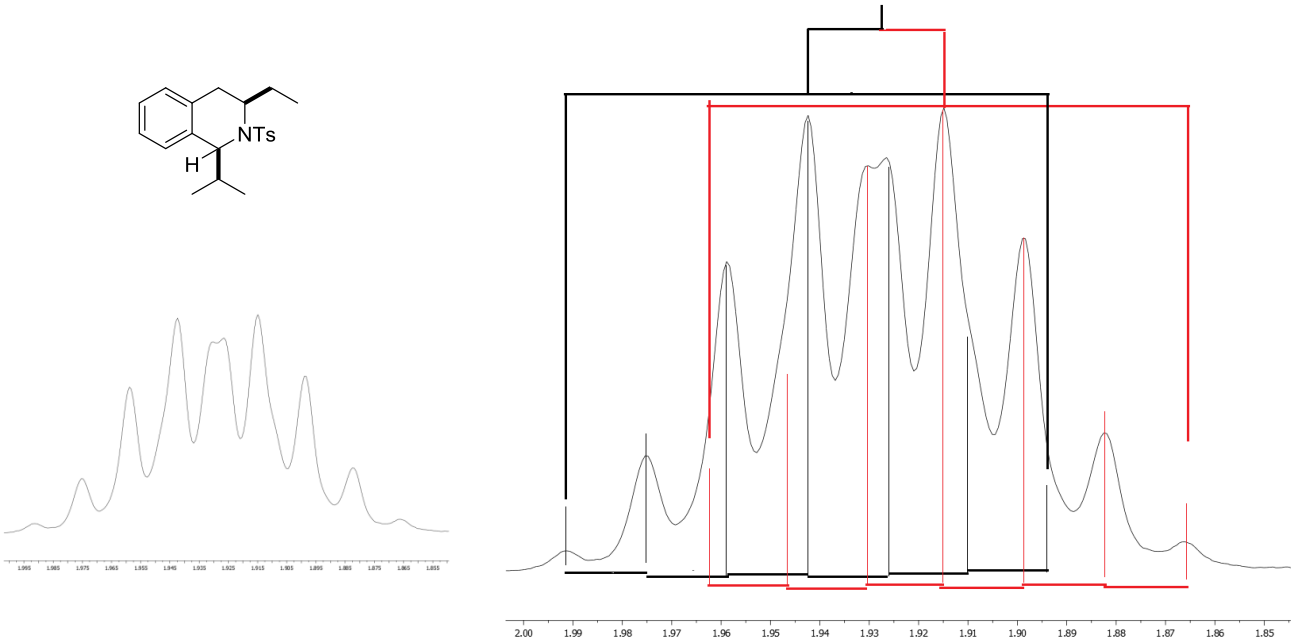


*Figure 6. Resonance at 1.93 ppm from ^{1}H NMR spectrum of compound **190a**.*

The benzylic AB protons of the cyclised compound **190a** presented themselves as a set of two very well defined double doublets (Figure 7). They were also very useful, as they straightforwardly delivered the important AX, BX and AB coupling constants, potentially valuable in confirming the stereochemistry of the compound.

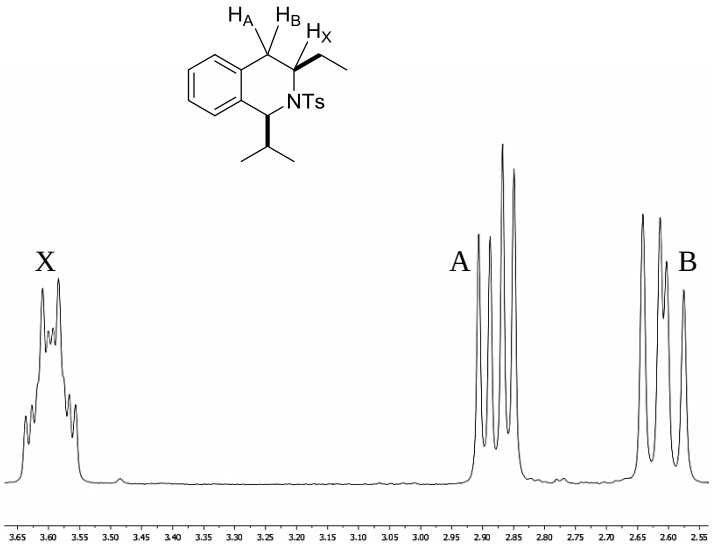


*Figure 7. The ABX system at 2.50 – 3.60 ppm from ^{1}H NMR spectrum of compound **190a**.*

The geminal coupling for the benzylic CH_2, found in both A and B proton resonances, was found to be 15.3 Hz. The smaller, *pseudo*axial-*pseudo*equatorial AX coupling at 2.86 ppm was determined to be 7.3 Hz, whereas the slightly larger, *pseudo*diaxial BX coupling of the 2.61 ppm resonance was 11.1 Hz. This information proved beneficial in resolving the coupling constants of the H_X proton, which should appear as a dddd resonance on the proton NMR. (Figure 8).

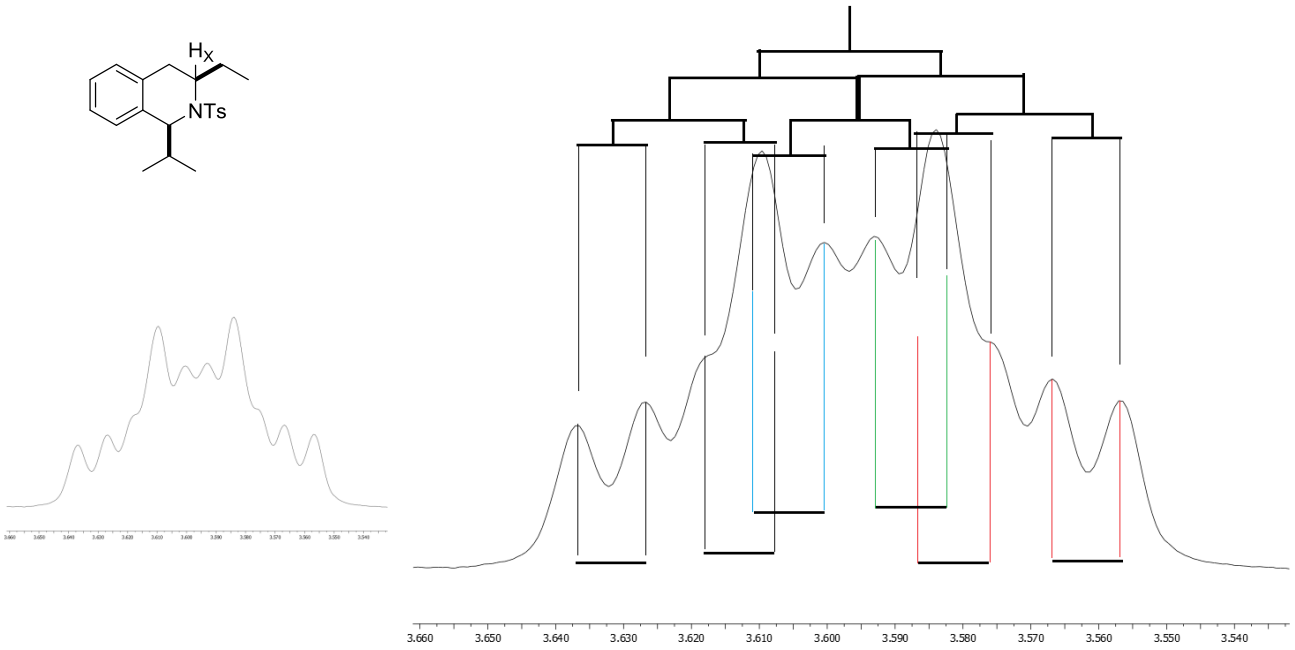


Figure 8. The 3.59 resonance of the ABX system at 3.60 ppm from ^1H NMR spectrum of compound ***190a****.*

As anticipated, the *J* values for the H_X proton matched the resonances already observed. The four coupling constants extracted were 4.0, 7.4, 10.5 and 10.5 Hz. The width of the peak was found to be 32.0 Hz and related well to the calculated value of 32.4 Hz. Two out of four values matched the previously extracted coupling constants of 4.3 and 7.5 Hz, for the $C\underline{H}_{2a+b}CH_3$. Due to the peak broadening and averaging of peaks during the analysis, the remaining two coupling constants, 9.7 and 11.1 Hz observed in the ABX system, could be averaged to 10.5 and 10.5. Since 10.5 + 10.5 = 21.0 and 9.7 + 11.1 = 20.8, this explains why mathematically the resonance appears to have been resolved accurately. Due to the fact that the broadening of the lines cannot be avoided and that the peak indeed appears to have four couplings of 4.3, 7.5, 10.5 and 10.5 Hz, extraction of the coupling constants from less overlapped resonances can aid with accurate determination of *J* values. Resonances as the previously mentioned AB protons deliver some of the desired numbers in great accuracy. Consequently, it was decided that the more accurate values derived from unambiguous signals will be reported, unless impossible otherwise.

The final and possibly most important and characteristic signal for compound **190a** was the benzylic proton next to nitrogen at 4.25 ppm (Figure 9). It appeared as a doublet and shared the coupling constant of 10.9 Hz with the doublet of septets already described. Signal from this proton appears furthest downfield, not counting the aromatic protons.

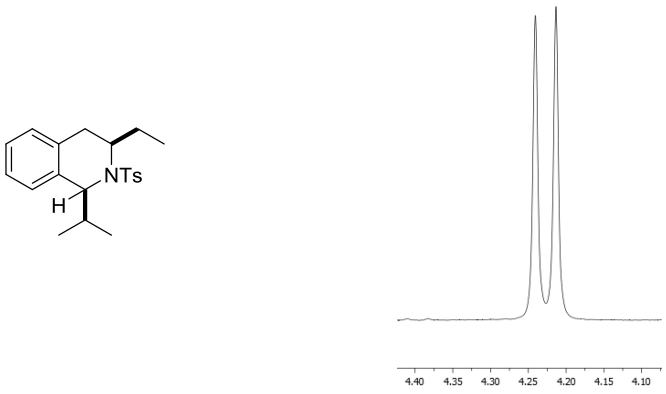


*Figure 9. The benzylic CH resonance at 4.25 ppm from ^{1}H NMR spectrum of compound **190a**.*

For majority of the reported compounds, as much as possible of the aromatic region of the proton NMR spectrum was fully interpreted, in terms of integration and coupling constants. Not all of the ring-hydrogens were definitely and unambiguously assigned, as it was deemed unnecessary.

Two sets of doublets with a *J* value of ~8 Hz and integrating to a total of 4 protons, characteristic for the tosyl group, could be easily found for most compounds. They appear at 6.87 and around 7.30 ppm for compound **190a**, however the right-most tosyl signal overlaps with two signals out of the two doublets and the two triplets from the four *ortho* and *para* protons on the tetrahydroisoquinoline ring (Figure 10). The second tosyl doublet could be seen but not clearly described due to an overlap with another aromatic signal.

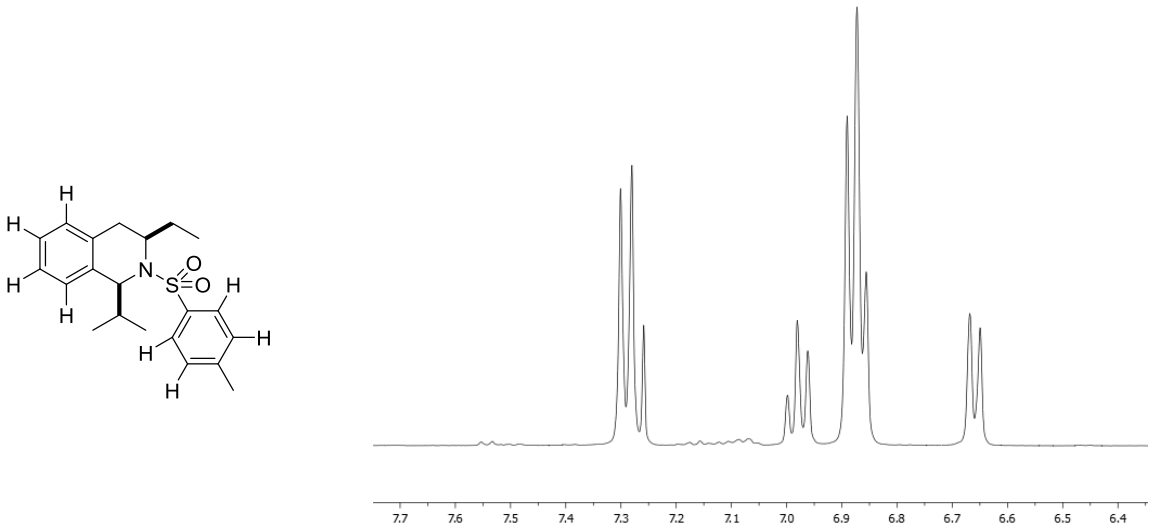


*Figure 10. The aromatic resonances of compound **190a**.*

Several, complex peaks were deconstructed in this way, to show a general approach and prove that if needed, it could be done. This was found to be tremendously time consuming, as there are several of such composite peaks present in a single isomer and in some cases identification of two isomers arising from one hypothetical reaction would deliver several of such peaks. In many cases, the coupling constants extracted from the highly overlapping or coinciding resonances were found to be inaccurate. Focus was put on extracting coupling constants from the more "simple" resonances, which also delivered valuable and more precise information about the structure.

To establish a quick and robust method allowing fast discrimination between the *cis* and *trans* tetrahydroisoquinolines several trends were analysed. It was hypothesised that ^{1}H NMR shifts of one of the diastereoisomers could point towards a specific isomer. In many cases the signal from the benzylic hydrogen next to the nitrogen of the *trans* isomer (Figure 11) was the furthest downfield aliphatic signal. It was later established that there is a number of exceptions to this rule and that it can be only used as a guide. Unfortunately, thorough analysis of several compounds proved that the shifts could not be predicted and do not follow any pattern.

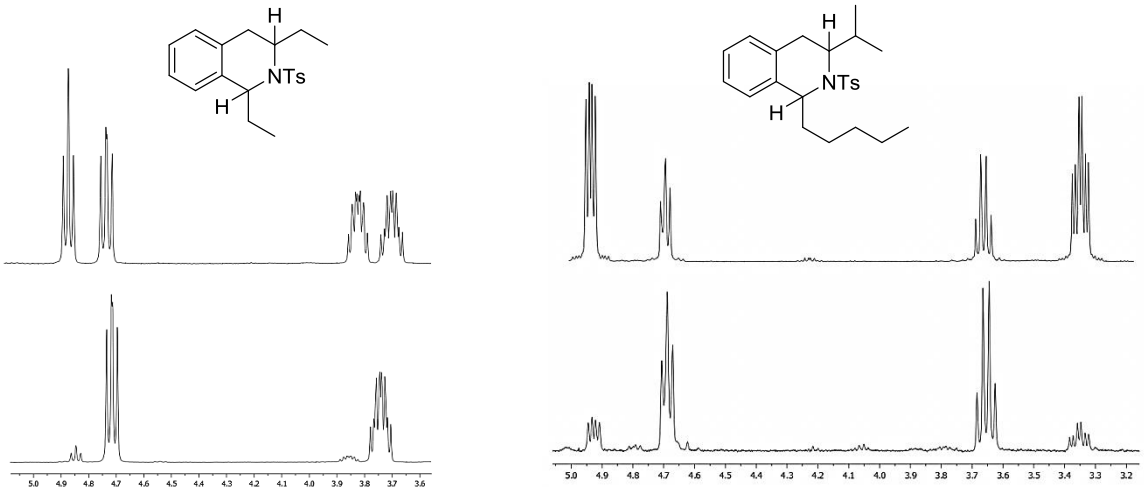


*Figure 11. The resonances of compounds **190** and **191**; cis isomer on the bottom.*

It was previously reported by Cook and Mokry that the ^{13}C NMR signals of β-carbolines follow a specific pattern.[167] Namely, the C1 and C3 of a *cis* 1,3-disubstituted-1,2,3,4-tetrahydro-β-carboline are downfield relatively to the C1 and C3 resonances of the *trans* isomer. This relationship was applied more recently by Sato and co-workers to establish the stereochemistry of a carboline derivative in their synthesis of (-)-corynantheidine.[92] The reported difference between the two signals for the two isomers was approximately 4 ppm, which is relatively large. In an attempt to apply similar rules to the tetrahydroisoquinoline derivatives synthesized in the laboratory it was observed that the resonances of the C1 and C3 carbons of *cis* and *trans* isomers occasionally follow a similar pattern, for instance compound

190, yet quite often tend to be very close to each other and frequently overlap (Figure 12). Analysis of tetrahydroisoquinoline **191** revealed an opposite trend, where the C1/C3 resonances of the *cis* isomer are upfield of those of the *cis*. In conclusion, all the efforts to quickly differentiate between the isomers based on information from NMR spectra did not provide a fast method for their assignment.

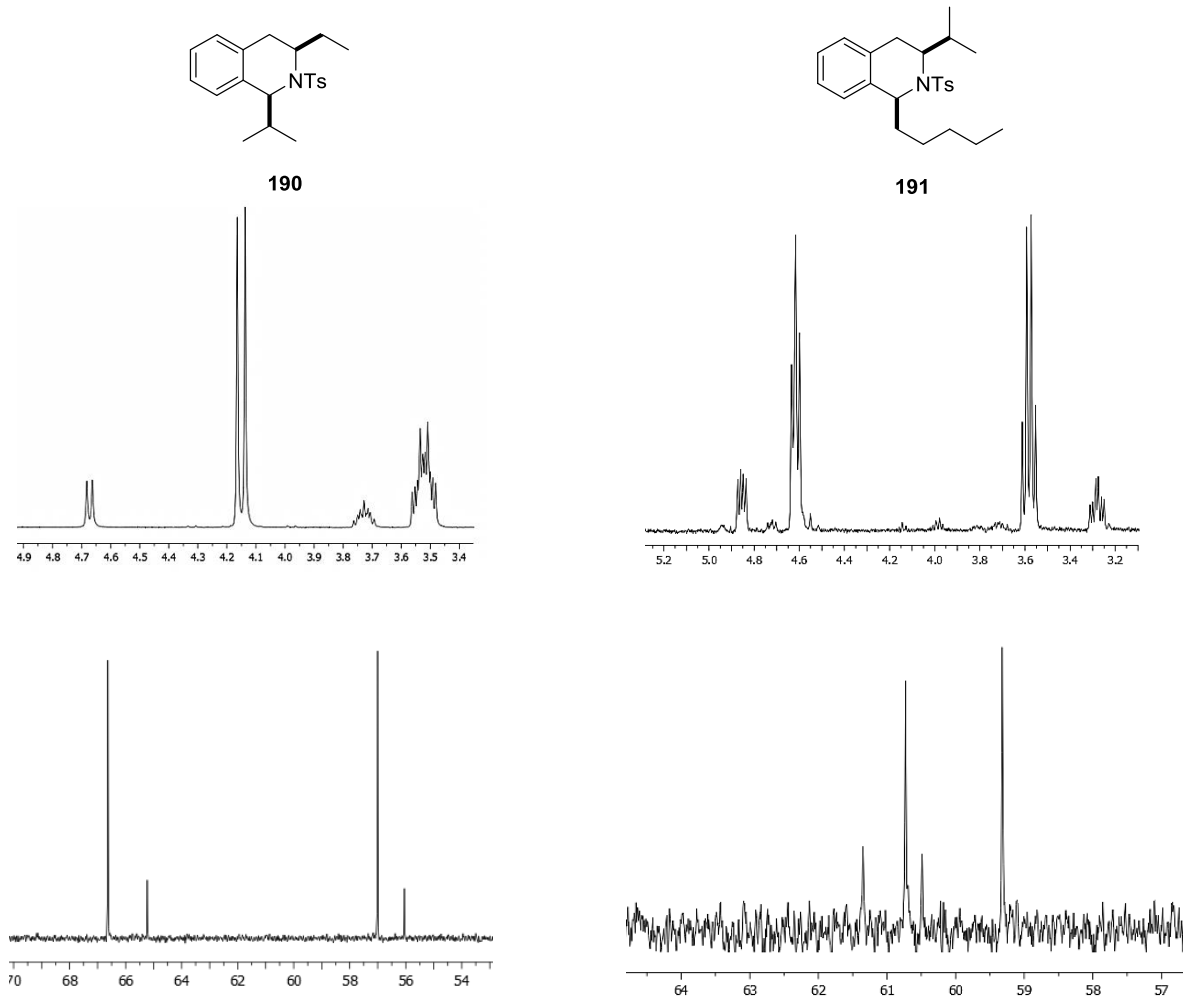
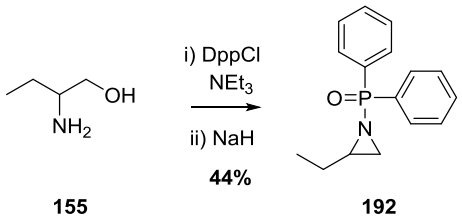


*Figure 12. The spectra of compounds **190** and **191**, C1 and C3 resonances on the bottom.*

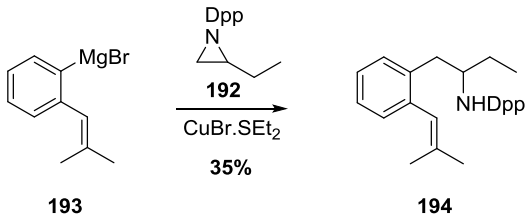
2.8 Hydroamination Scope

The use of diphenylphosphinyl (Dpp) group as an alternative activating group for ring-opening of the aziridine ring allowed the assessment of its synthetic utility in the acid-catalysed cyclisations of the prepared substrates into the *N*-Dpp protected THIQ alkaloids. 2-ethyl-*N*-diphenylphosphinyl aziridine **192** was synthesized from the corresponding 1,2-aminobutanol **155** in 44% yield (Scheme 77). Remarkably, due to its sluggishness, the reported synthesis of such *N*-Dpp aziridines involves a two-step process: a *bis*-phosphinylation in presence of excess triethylamine followed by cyclisation induced with 5 equivalents of sodium hydride.[168]



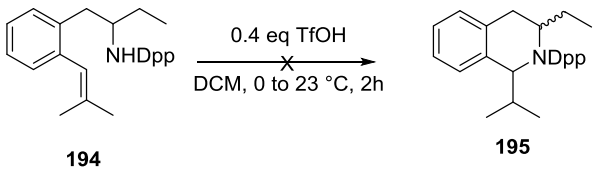
Scheme 77. Synthesis of N-Dpp aziridine.

The ring-opening protocol of *N*-Dpp aziridines **192** was explored by Cantril and is somewhat different to the procedure used for reacting *N*-tosyl aziridines. Reactions of such diphenylphosphinyl aziridines with ethylmagnesium bromide yield no product even in refluxing THF and exposure to lithium nucleophiles, higher-order cuprates or methanol and $BF_3.OEt_2$ only yield the products arising from attack at phosphorus.[169] Fortunately, addition of catalytic amount of $CuBr.SEt_2$ to an excess of Grignard reagent (~ 5 eq.) in THF, followed by heating under reflux for several hours afforded the ring-opened product in good yield. When applied to the synthesis of cyclisation precursors, ring opening of aziridine **192** with excess (2-(2-methylprop-1-en-1-yl)phenyl)magnesium bromide **193** afforded the ring-opened product **194** in 35% yield (Scheme 78).



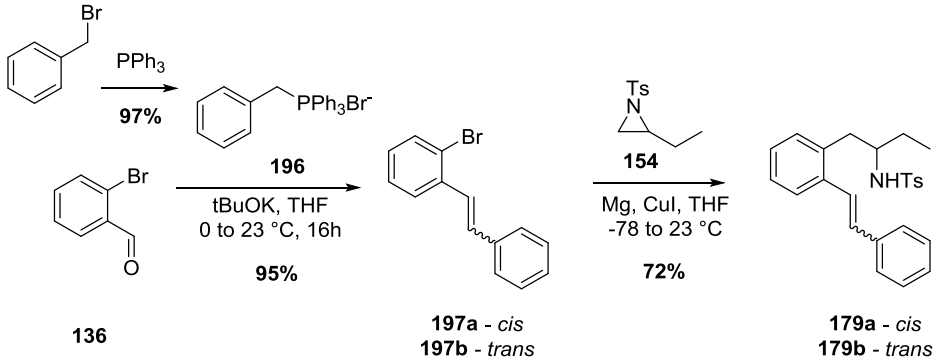
Scheme 78. Ring-opening of N-Dpp aziridine.

The synthesis and reactions of diphenylphosphinyl-protected aziridines allowed entry into phenylethyl-*N*-diphenylphosphinyl amines **194** and their reactivity in hydroamination reactions could be probed. Regrettably, at 0 °C no reaction was observed after 15-30 minutes. Extending the reaction time beyond 1 hour or increasing the temperature to 23 °C produced only a complex mixture (Scheme 79) and the product **195** could not be seen. Proton NMR analysis of the crude sample showed only broad, undefined peaks and nothing meaningful could be isolated by column chromatography. It was decided that *N*-Dpp activating group does not trigger the cyclisation and that only extensive decomposition occurs.



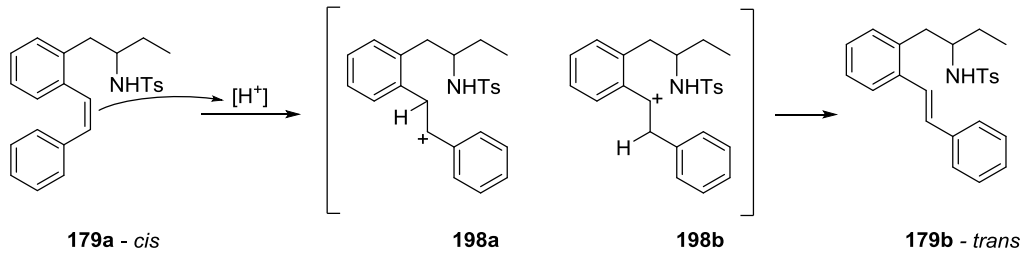
Scheme 79. Cyclisation attempt on a N-Dpp protected substrate.

The purpose of the next reactions was to probe the reactivity of stilbene derivatives. A Wittig reaction of 2-bromobenzaldehyde **136** with benzyltriphenylphosphonium bromide **196**, made from benzyl bromide, afforded the brominated stilbene derivative **197** as a 1:5 mixture of *E* and *Z* isomers in 95% yield. Ring-opening of the aziridine **154** afforded the desired cyclisation precursor **179a**/**179b** as a 1:5 mixture of *E* and *Z* isomers in 72% yield (Scheme 80).



*Scheme 80. Synthesis of the stilbene substrate **179**.*

A cyclisation attempt using the standard reaction conditions of 0.4 equivalents of triflic acid in dichloromethane at 0 °C did not deliver any product. Similarly, at room temperature only the starting material could be recovered. Refluxing the substrate **179** in dichloromethane with the same amount of acid showed slow isomerisation of the *cis* **179a** into the more stable isomer **179b** (Scheme 81).



*Scheme 81. Isomerisation of the stilbene substrate **179a**.*

This result was very puzzling, as it was anticipated that the isomerisation most likely occurred via the carbocationic species **198a** and **198b** NH_{cis} (Scheme 81). Therefore, it was reasonable to expect for the carbenium ion to be trapped by the nitrogen atom. Strangely, the tetrahydroisoquinoline product was not observed in refluxing dichloromethane. Repeating the reaction under more forcing conditions, in 1,2-dichloroethane as solvent and at 60 °C, showed that full reisomerisation could be achieved. Several distinctive resonances could be followed by ^{1}H NMR to observe the complete

reisomerisation of **179a** into **179b** (Figure 13; note: the ^{1}H NMR spectra were taken on differet spectrometers).

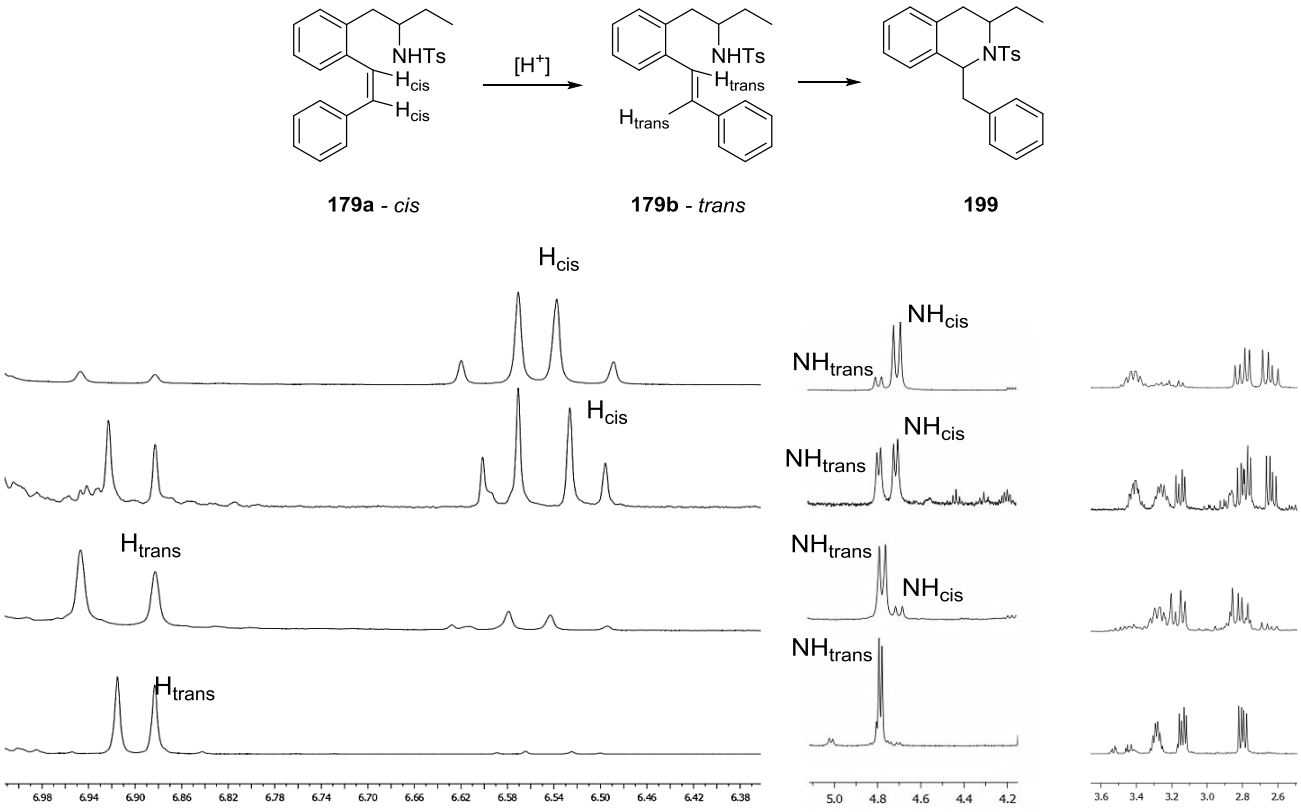
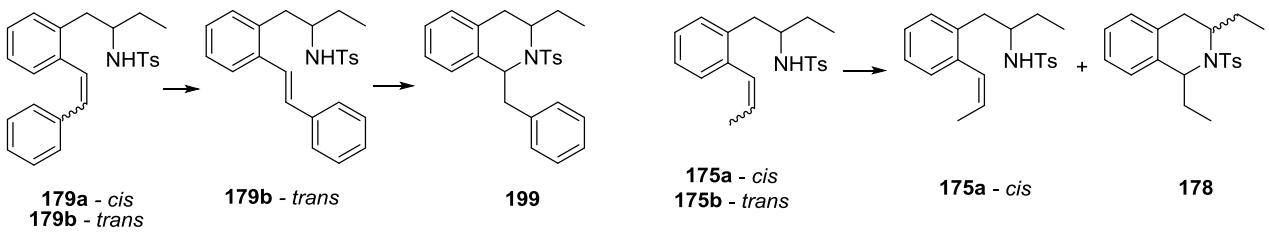


*Figure 13. Relevant ^{1}H NMR resonances of compound **179** isomerisation (spectra ran on different machines).*

The figures above show the most noteworthy resonances in the transformation of the *cis* isomer **179a** into the *trans* isomer **179b**, as the reisomerisation proceeded, top to bottom. First left hand side part shows the disappearance of the two "roofing" doublet resonances from the two *cis* hydrogens of **179a** at 6.53 ppm and appearance of one of the doublets from the *trans* isomer **179b** at 6.89 ppm. The second and third spectra fragments show the same trend, but for the NH peaks (~4.8 ppm) and the ABX system (3.4 – 2.6 ppm). Identical observations could be also made for the singlets arising from methyl of the tosyl group. Remarkably, very small quantities of product could be observed in the reaction mixture but upon prolonged refluxing either equilibration was observed or poor yields were obtained.

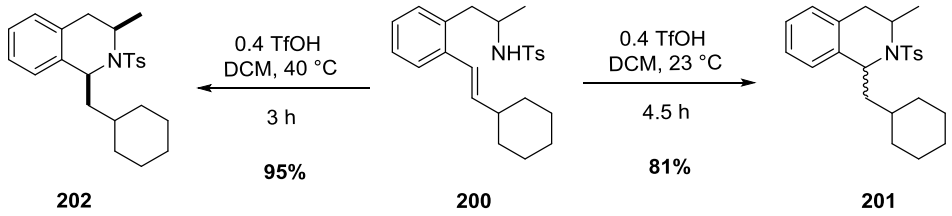
This phenomenom of the *cis* isomer interconverting to *trans* prior to cyclisation does not correspond accurately to the properties of the *cis/trans* alkyl-substituted isomers, where the *cis* isomer was more reactive than the *trans*.

Briefly, the styryl *cis* isomer converts to *trans* isomer and then can be cyclised at higher temperature, whereas in the vinylalkyl series the *trans* isomer reacts first leaving the *cis* isomer untouched (Scheme 82), which then can be successfully cyclised under slightly more forcing conditions.



Scheme 82. Reisomerisation during hydroamination.

The issue associated with unusual reactivity of *cis* and *trans* isomers of the synthesized substrates could be overcome by designing a route to deliver exclusively the more stable *trans* compound which is described in the next part. Furthermore, to ascertain that the lower reactivity of the stilbene substrates comes from the electronic and not steric effects, a cyclohexane derivative **200** was also synthesized.



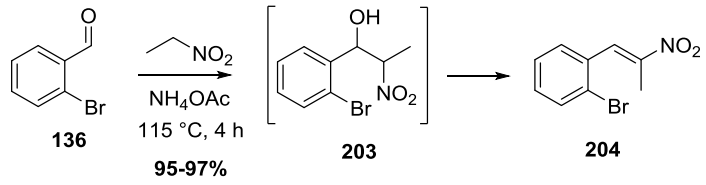
Scheme 83. Cyclisation of cyclohexyl derivative.

The acid-catalysed cyclisation proceeded very well and at room temperature, as it was the case with the alkyl derivative **175**. Similarly as before, a 2:1 mixture of diastereoisomers **201** was obtained, in 81% yield, the major product being the kinetic, *trans* product (Scheme 83). Exposure of the starting material to triflic acid in refluxing dichloromethane resulted in formation of the thermodynamic *cis* product in approximately 20:1 ratio favouring the *trans* material and the final product **202** was isolated in an overall 95% yield. Extended reflux allowed pushing the thermodynamic equilibrium towards a single reaction product and a single recrystallisation delivered the *cis* product **202** exclusively.

The two main advantages of the aziridine route are its shortness and very good reaction yields. Several important limitations exist, especially related to the protecting group and potential presence of other, reactive functionalities. First of all, only tosylated, diphenylphosphinyl aziridines could be successfully ring-opened with an organometallic reagent. Further limitations are imposed by the reaction procedure. Functional groups such as alcohols, amines, ketones, esters and a few others would not survive the reaction conditions.

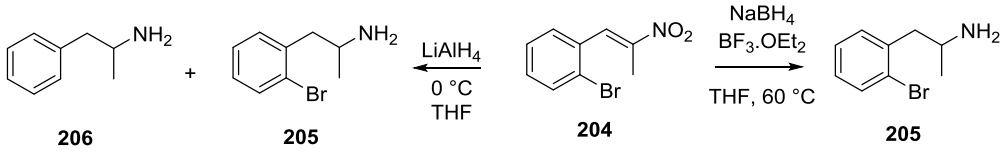
2.9 Henry Route

The second route which effectively delivered a number of cyclisation precursors was based on a nitro-aldol reaction. It was thought that the amine group could be installed via the aldehyde functional group and a subsequent coupling reaction would provide the olefin functionality. The phenylethylamine chain was installed in a Henry reaction of 2-bromobenzaldehyde **136** with nitroethane, followed by *in situ* dehydration of **203** to nitroalkene **204** (Scheme 84).[170]



Scheme 84. Henry reaction.

The Henry reaction involved 4 hour reflux in nitroethane as solvent at 115 °C and it was remarkably clean. Washing with water and removal of the solvent on rotary evaporator (60 °C, 5 mbar) delivered 102% yield of the crude product contaminated with ~5% nitroethane (HPLC analysis). Further azeotropic drying with toluene and overnight drying in a vacuum oven delivered essentially pure nitroalkene in 97% yield. The olefin as well as the nitro group was then reduced with lithium aluminium hydride to yield the primary amine **205** (Scheme 85).



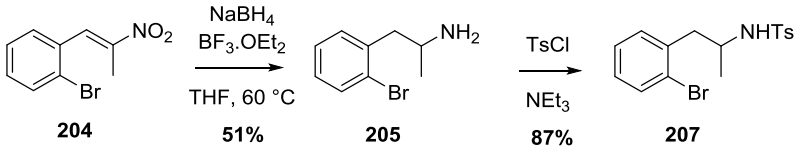
Scheme 85. Reduction of nitroalkene.

Small quantities of the debrominated material **206** were detected after isolation of the primary amine in an acidic work-up after the LAH reduction. This impurity was found to be very difficult to remove by column chromatography. A Kugelrohr distillation was attempted to remove the residual amphetamine **206** (lit.[171] b.p. 81-86 °C/10-12 mm) from the reaction mixture. Majority of the unwanted compound could be removed at ~100 °C/20 mm; still, traces of **206** were present in the distillation base, even after careful and slow distillation of approximately 50% of the entire mixture.

Another, milder approach towards an effective and clean reduction of the brominated nitroalkene **204** was deemed necessary. An interesting article discussing several different procedures used for conversion of nitroalkenes into phenylethylamines was published by Collins.[172] Fortunately, a very similar compound to **204**, a *para*-iodophenyl nitroalkene derivative, was reduced in 84% yield to the primary amine in Kabalka's reported synthesis of iodo-amphetamines.[173] The procedure involved slow, *in*

situ release of borane from a heated mixture of sodium borohydride and boron trifluoride diethyl etherate in tetrahydrofuran at 60 °C over several hours, followed by quenching and isolation with hydrochloric acid and base. A comprehensive review on the topic of synthesis and selective reduction of conjugated nitroalkenes was later written by Kabalka.[174]

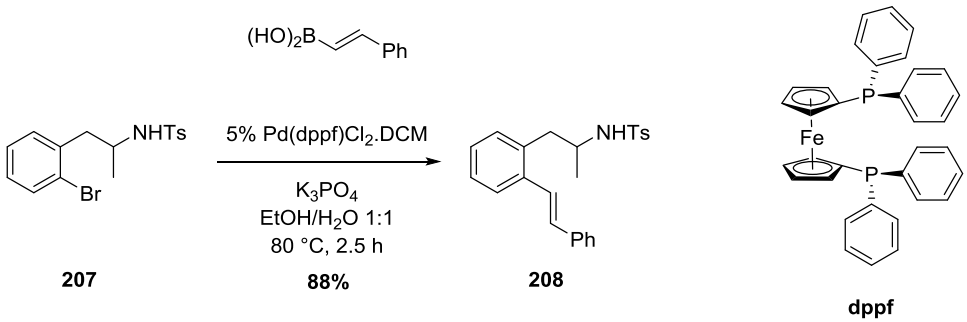
Attempts to apply this methodology in the reduction of nitroalkene **204** were largely successful and delivered the desired product, albeit in 51% yield, opposed to 84% conveyed for a similar substrate (Scheme 86).



*Scheme 86. Reduction of nitroalkene **204**.*

The reason behind the lower yields in Kabalka's reduction remains unknown. In most cases, the reaction followed by an acid-base work-up delivered relatively pure amines in good yields, *i.e.* 85% purity by HPLC and 65% mass recovery. The primary amines were usually used without any purification, as the next step involved protection of the amine. Tosylation of the amine **205** furnished the sulfonamide **207** in 87% yield. Most impurities carried over from the previous steps could be removed by a simple acid and base wash, yielding a reasonably pure compound, which could be further purified by column chromatography. Importantly, no debrominated side-product **206** was detected after applying Kabalka's method.

One of the drawbacks associated with this methodology is that both the Henry reaction and the reduction are potentially explosive. Nitroalkenes are highly energetic compounds and may combust explosively, releasing large quantities of gases.[175] Borane-oxygen mixtures are also explosive and reported to be very dangerous, especially at higher temperatures.[176] In June 2002 an explosion of a 250-pound borane-tetrahydrofuran drum on one of the Pfizer sites nearly demolished an entire warehouse and injured five employees.[177] Necessary precautions need to be taken whilst carrying out this type of chemistry, especially on larger scales when temperature control and avoiding thermal runaways is much more difficult. After the reduction, the protected sulfonamide **207** was reacted under modified Suzuki coupling conditions (Scheme 87), reported by Knight and Henderson, to afford **208**.[178]

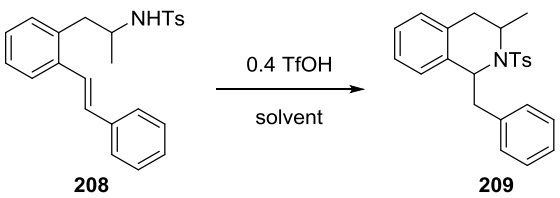


Scheme 87. Suzuki coupling reaction conditions.

The original, published procedure used catalyst pre-mixes and microwave heating for 30 minutes at 100 °C. In the laboratory it was proved that the microwave conditions are not necessary and that the reaction goes to completion at 80 °C in approximately two hours. The catalyst load was reduced to 5%. The quick reaction time implied that the amount of catalyst used could be dropped even further, however, it was decided that since 5% guaranteed good yields and quick reaction times, it would be adopted as the default load. The species used to enable the C-C bond formation was the (1,1'-bis(diphenylphosphino) ferrocene)palladium(II) dichloride, which is a popular catalyst in coupling reaction. The dppf ligand has a wide bite angle of 99 degrees and its bulkiness assists in the reductive elimination step and improves the cross coupling catalytic cycle.[179]

2.10 Optimisation of the Hydroamination Reaction

With the *trans*-exclusive compound **208**, it was possible to carry out a comprehensive solvent screen. Literature search revealed that nitromethane, dioxane, toluene and several other solvents are often used in acid-catalysed hydroaminations, Pictet-Spengler and Bischler-Napieralski reactions. A parallel set-up of 10 reactions in which 200 mg of substrate **208** was reacted with 0.4 equivalents of triflic acid in 2 mL of a solvent and the conversion plotted against time (Figure 14). It needs to be noted that the conversion does not correspond to the yield of the product but to the ratio of starting material to <u>all</u> products. Therefore, it more accurately corresponds to the rate of disappearance of starting material and not the rate of product formation. The temperatures at which the reactions were carried out varied from solvent to solvent. If no conversion was observed after 1 hour, the temperature would be increased by 10 – 20 °C, up to the boiling point of the solvent.



208 **209**

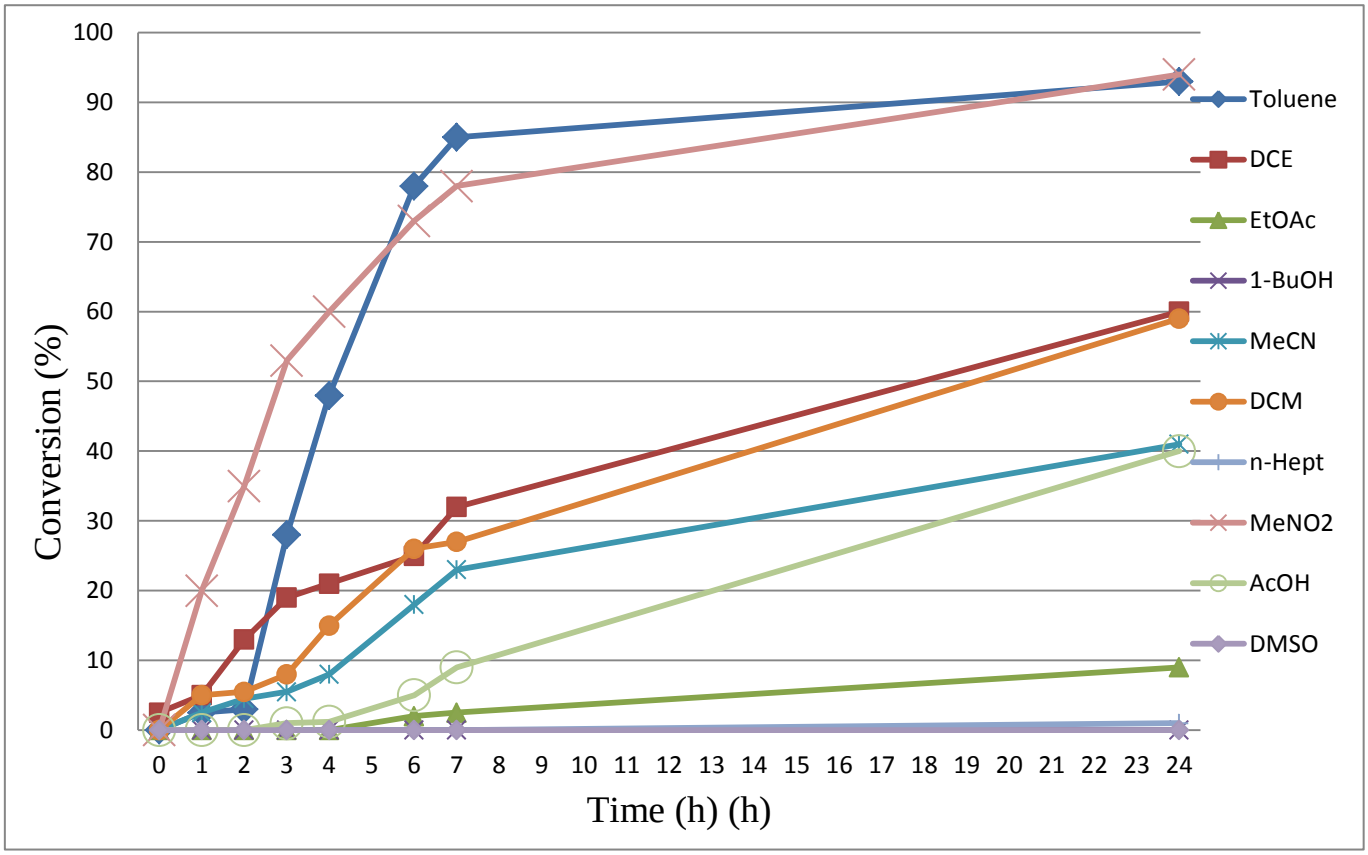
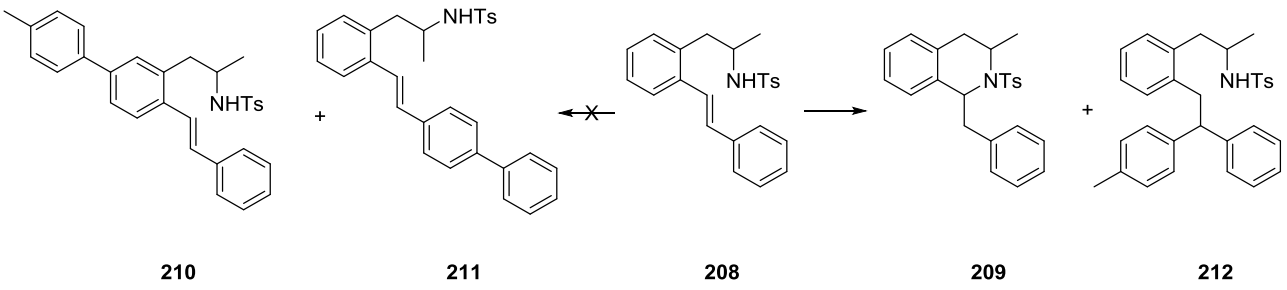


*Figure 14. Solvent screen in the hydroamination of **208**.*

The two most promising results point towards toluene reaction and nitromethane as potential solvents for the cyclisation. Both reactions were run at 70 °C. Even though over 90% of the starting material was consumed in both cases, large amount of impurities were formed in the process. Column chromatography of the toluene reaction product gave only 32% isolated yield of the product **209** and 37% of an unknown impurity. Proton and carbon NMR analysis of the unknown showed an extra singlet for an arylmethyl group, several new aliphatic and aromatic signals, and new ^{13}C NMR resonances. Mass spectrometry demonstrated that the mass of the molecular ion (484.2) corresponds directly to the mass of the starting material and the mass of toluene added together (391 + 92 + H^+ = 484). It was subsequently ascertained that the impurity was made in a Friedel-Crafts type reaction. Initially, it was expected that its structure could be **210** or **211** (Scheme 88) but further analysis of ^{13}C NMR and COSY/HSQC data helped unravel the most fitting structure, which is **212**.



Scheme 88. Impurity formation in the toluene reaction.

The two ABX systems of **212** could be easily identified and their connectivity was confirmed by COSY. The downfield shift of the hydrogen flanked by two phenyl moieties, from the usual benzylic 3.0 ppm towards 4.2 ppm additionally confirmed the assignment of the structure. The NH doublet was still present in the ^{1}H NMR spectrum and was confirmed by showing no correlation to any of the carbons on HSQC spectrum. The olefinic signals could not be seen but could have possibly been overlapping with other aromatic protons.

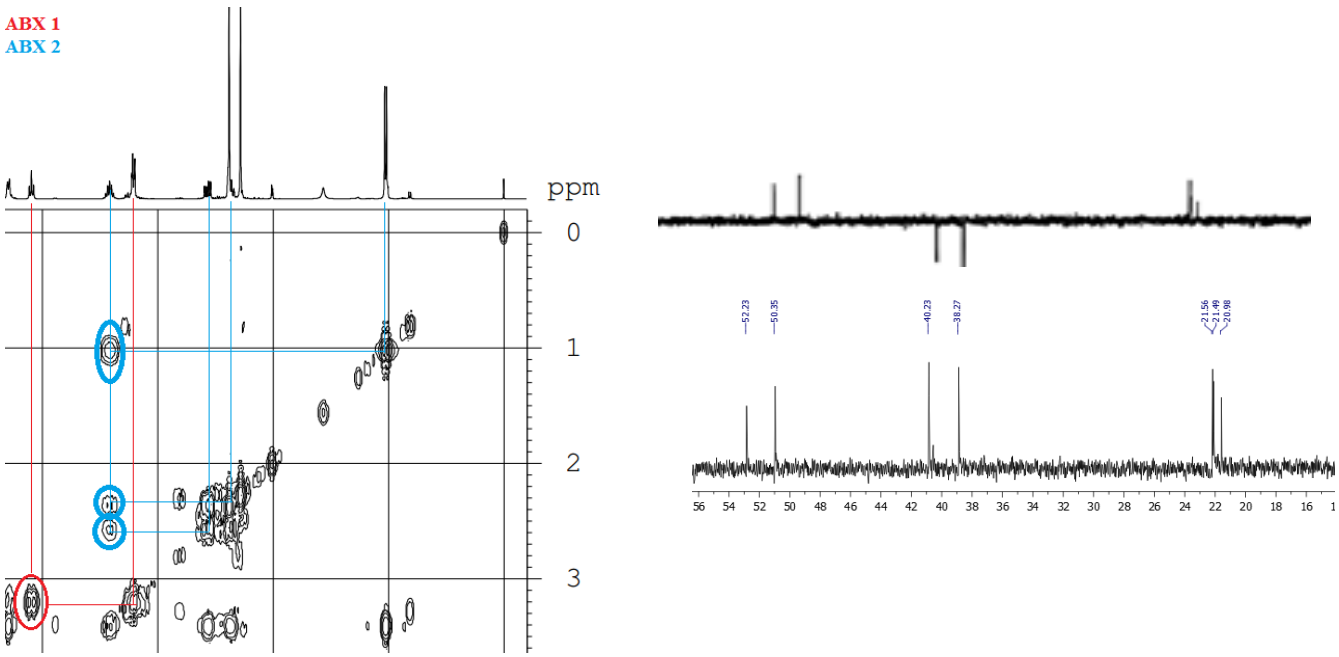


*Figure 15. Fragment of the COSY and ^{13}C NMR DEPT-135 spectrum of compound **212**.*

Additionally, three CH_3, two benzylic CH_2 and two CH aliphatic peaks were observed in the ^{13}C NMR spectrum and further confirm the structure (Figure 15). It was a largely unanticipated result, as toluene is often used as solvent in this type of reaction with strong acids.

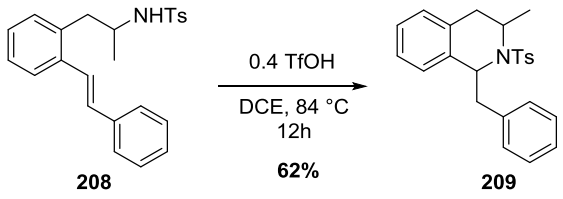
The the nitromethane cyclisation was much more complicated and a large number of impurities could be seen by HPLC, structures of which were not identified. HPLC analysis of the crude reaction mixture after 24 hours at 70 °C mass showed approximately 25% of the tetrahydroisoquinoline product **209** and ~70% of various side-products . Nevertheless, isolation of the reaction product gave the cyslised material in 23% yield.

Surprisingly, the reaction performed in dichloromethane at 41 °C showed lower initial conversion rate than the 1,2-dichloroethane reaction at 70 °C but after 24 hours both reactions equilibrated at approximately 50% conversion. Column chromatography purification of both reaction mixtures led to a 43% yield from the 1,2-dichloroethane and 33% of **209** from the dichloromethane reaction. This was somewhat disappointing, as it was hoped that the chlorinated solvents would perform much better. It was

noted, however, that the quality of the cyclised material slowly degraded during the extended reaction times and it was hoped that the yields could be increased by careful monitoring of the reaction times. Further optimisation of the 1,2-dichloroethane reaction resulted in observation that the reaction reaches 70% conversion after 10-12 hours and higher yields of the product could be isolated by stopping the reaction at this stage.

The reaction in ethyl acetate provided approximately 10% yield after 24 hours reflux. Butanol, heptane, acetic acid and dimethylsulfoxide produced no product at all. In addition to the 10 parallel experiments, another 5 reactions were performed using mixtures of 1,2-dichloroethane and heptane as solvent. An originally predicted trend was observed, where the addition of heptane slowed the hydroamination and was therefore undesireable.

After re-establishing that 1,2-dichloroethane is the optimal solvent for hydroamination of substrates requiring harsh reaction conditions, screening of different Lewis and Brønsted acids was carried out. Unfortunately out of nine acids, triflic acid, sulfuric acid, trimethylsilyl triflate (TMSOTf), bismuth triflate, gadolinium triflate, zinc triflate, potassium triflate, polyphosphoric acid and methanesulfonic acid, only triflic acid and TMSOTf showed any observable cyclisation. Doubling the amount of triflic acid to 0.8 equivalents roughly doubled the rate of conversion but did not result in a cleaner reaction.

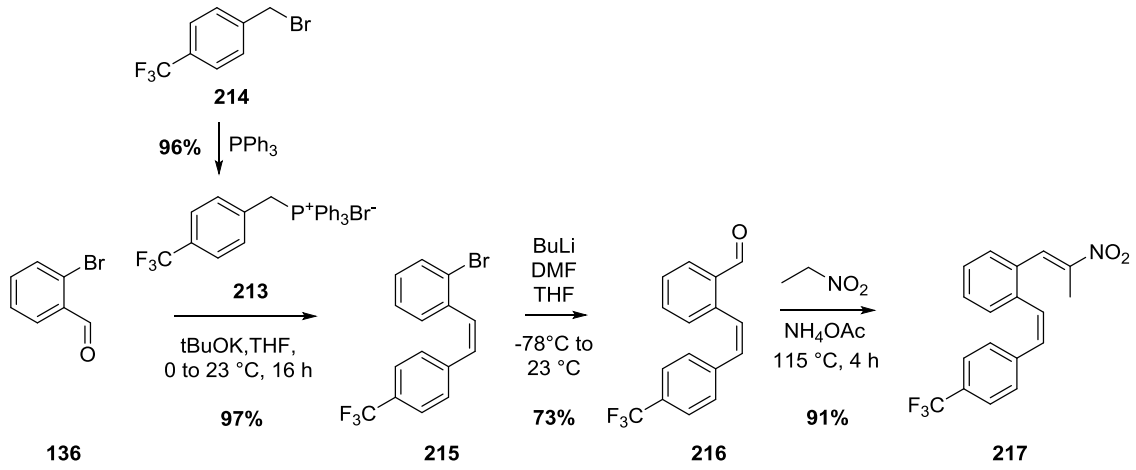


Scheme 89. Optimised cyclisation.

In conclusion, the solvent and the acid screen firmly established that the initial acid, solvent and temperature used were the optimal conditions and were later extended to 1,2-dichloroethane solvent. Careful monitoring by TLC and HPLC helped synthesising the 1-benzyl tetrahydroisoquinoline **209** (Scheme 89).

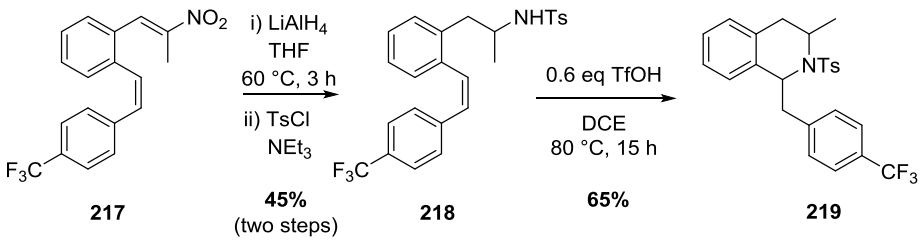
2.11 Cyclisations

To show that additional functionalities are tolerated under Knight's hydroamination conditions, we decided to look at halogenated substrates. Synthesis of the triphenylphosphonium salt **213** from the commercially available *p*-trifluoromethylbenzyl bromide **214** in 96% yield and subsequent reaction with 2-bromobenzaldehyde in a Wittig reaction yielded the olefin **215** as a *cis* and *trans* mixture in 97% (Scheme 90). Following a formylation with butyllithium and dimethylformamide which delivered the aldehyde **216** in 73% yield, the nitroalkene **217** could be obtained in 91% yield in a Henry reaction.



*Scheme 90. Synthesis of intermediate **217** via the Henry reaction.*

Reduction with lithiumaluminium hydride and protection with tosyl chloride furnished the cyclisation precursor **218** in 45% yield over two steps. Slightly more forcing reaction conditions had to be applied to achieve the final transformation into the tetrahydroisoquinoline **219**, 0.6 equivalents of triflic acid were used for 15 hours at 80 °C and gave the cyclised material in a good 65% yield, as a predominantly *cis* isomer (Scheme 91).

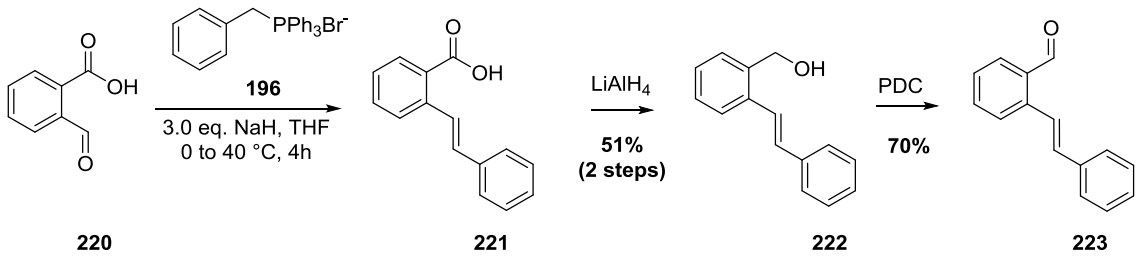


*Scheme 91. Synthesis of intermediate **219** via the reduction and tosylation.*

The 1-benzylisoquinoline compounds form an important sub-group of isoquinolines and tetrahydroisoquinolines.[180] Several important alkaloids *e.g.* laudanosine **26** (*c.f.* page 9) and papaverine[181]

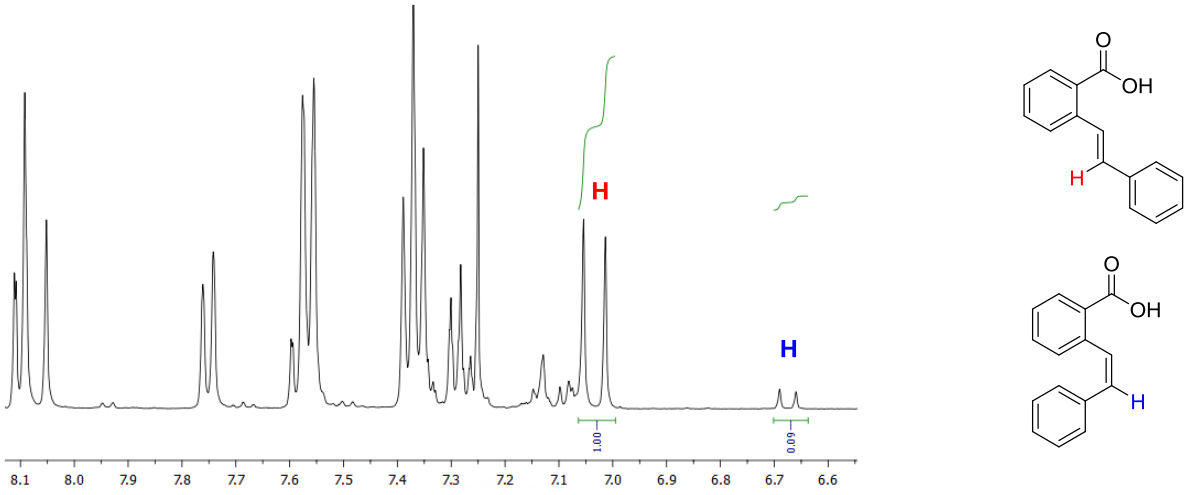
belong to the aforementioned family of bioactive molecules and therefore such compounds are of large synthetic interest.

Another synthetic route utilising the Henry reaction was designed and allowed synthesis of essentially *trans* olefins, *via* Wittig chemistry (Scheme 92).



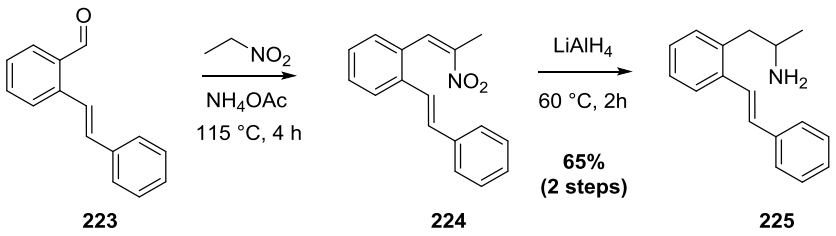
Scheme 92. Different synthesis towardsthe trans-stilbene isomers.

Using excess sodium hydride as the base in a Wittig reaction between 2-formylbenzoic acid **220** and phosphonium salt **196** afforded the carboxylic acid **221** in good yield. Integration of the appropriate peaks on ^{1}H NMR spectrum proved that the isomer ratio of *cis* and *trans* compounds was approximately 1:10 (Scheme 93). Compound **221** was reduced with lithium aluminium hydride without further purification and delivered the alcohol **222** in overall 51% yield.



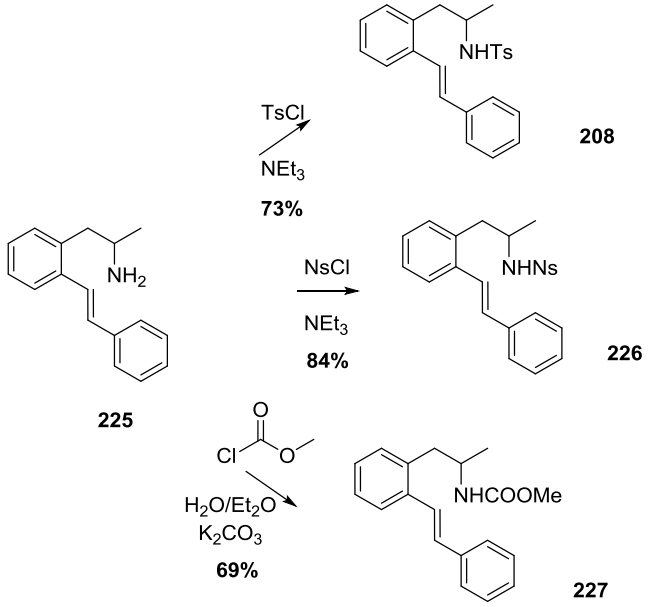
*Scheme 93. Fragment of ^{1}H NMR of compound **16**.*

Finally, pyridinium dichromate[182] oxidation of alcohol **222** gave the aldehyde **223**, which was then converted to the primary amine **225** in a Henry reaction to nitroalkene **224** followed by reduction.



Scheme 94. Different synthesis towards the trans isomers.

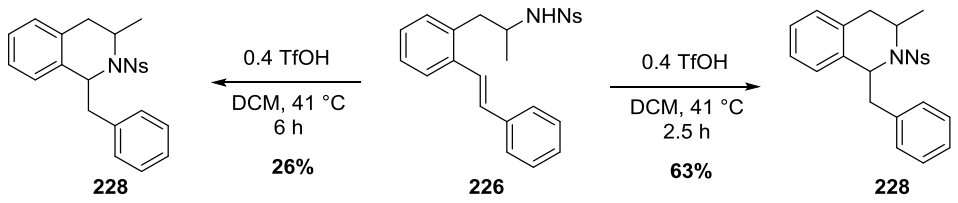
Refluxing the nitroalkene in tetrahydrofuran with 3.0 equivalents of lithium aluminium hydride followed by basic work-up gave the pure amine, which was in turn converted to three cyclisation precursors, already synthesized sulfonamide **208**, nosyl-protected **226** and the carbamate **227** (Scheme 95).



Scheme 95. Different syntheses towards the trans isomers.

All of the carbamate precursors, as well as the cyclised carbamate-protected tetrahydroisoquinolines, showed some interesting spectral features. Several broad signals in the proton and carbon NMR spectra indicated that these species exist as conformational isomers, which arise when the rotation about a specific, single bond is somewhat hindered. Unhindered resonances of hydrogens distant to the obstructed single bond in question remained well-defined. In the case of the rotameric carbamates synthesized in our laboratory the energy barrier required to overcome the interconversion between them was found to be relatively low. Usually, heating an NMR sample to 50 °C or sometimes 90 °C usually caused the broad signals to coalesce. The rotameric properties of such molecules will not be further discussed and the relevant information about their spectral features can be found in the experimental section.

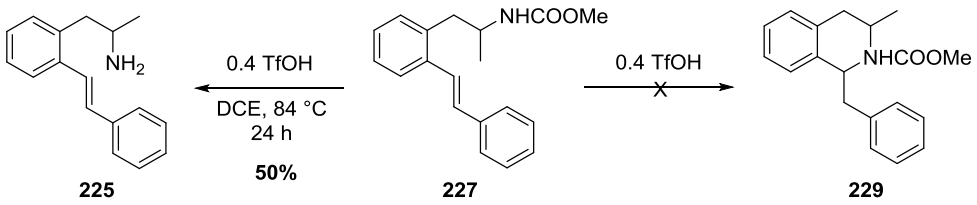
In the hydroamination reaction, the nosyl-protected substrate **226** behaved slightly differently to its sibling precursor **208**, which cyclised at 85 °C in 1,2-dichloroethane in 12 hours. Nosyl group seemed to have a slightly more activating effect and was also to some extent more delicate. Cyclisation of **226** occurred smoothly at 41 °C in dichloromethane over 2.5 hours and produced tetrahydroisoquinoline **228** in 56% yield (Scheme 96) as a single diastereoisomer.



*Scheme 96. Cyclisation of the nosyl derivative **226**.*

Extending the reaction time to 6 hours dropped the isolated yield to only 26%, unmistakably demonstrating higher fragility of the protecting group. Increasing the temperature also did not improve the initial outcome and carrying out the reaction at 60 °C for one hour resulted in extensive decomposition.

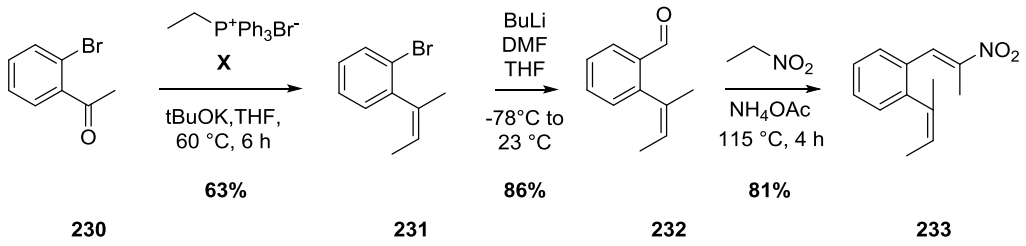
Attempts to cyclise the carbamate derivative **227** were met with failure. At temperatures up to 60 °C no reaction was observed. Prolonged reflux in dichloroethane resulted in removal of the carbamate moiety and the primary amine **225** was recovered in 50% yield (Scheme 97).



*Scheme 97. Cyclisation of the carbamate derivative **227**.*

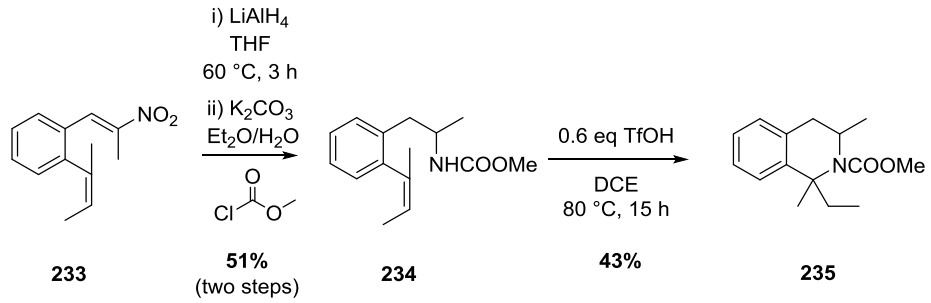
The COOMe protecting group is much less activating than a sulfonamide and thus the carbamate substrate **227** did not undergo cyclisation. On the other hand, Knight's group had ample success in applying carbamate-protected amines in synthesis of functionalised heterocycles.[131] To establish whether this is a more general phenomenon and whether the carbamate protecting group cannot be used in this chemistry, it was chosen to access cyclisation precursors which would potentially require less forcing conditions to cyclise. From past experience it was already known that the alkyl substituents on the olefin have an important on the reaction and it was decided that such carbamates needed to be prepared.

All precursors synthesized so far did not have a second substituent on the benzylic olefin carbon. It was expected that introducing additional steric hindrance on the double bond may thwart the cyclisation reaction. To probe the behaviour of more sterically demanding precursors a synthetic route starting from 2-bromoacetophenone **230** was designed (Scheme 98). Wittig reaction in refluxing tetrahydrofuran gave the desired bromoaryl olefin **231** in 64% yield, which was subsequently formylated with butyllithium and dimethylformamide to give aldehyde **232** in 86% yield.



*Scheme 98. Synthesis of intermediate **233** via the Henry reaction.*

Subsequent Henry reaction supplied the intermediate **233** in a very good, 81% yield. Reduction of the nitroalkene **233** to the corresponding amine and protection with methyl chloroformate provided the carbamate product **234** in 51% yield over two steps. Attempts to cyclise substrate **234** only gave a modest amount of product **235**. Optimised reaction conditions provided 43% isolated yield (Scheme 99) of the final product as a 3:1 mixture of diastereoisomers. Increasing or decreasing the amount of acid from the standard 0.4 equivalents, running the reaction at higher or lower temperatures and for prolonged periods of time did not have any significant effect on the outcome of the transformation. An observation was made that the reaction equilibrates at roughly 3:2 ratio of starting material to product and it was impossible to push the reaction to completion.



*Scheme 99. Synthesis of alkaloid **235**.*

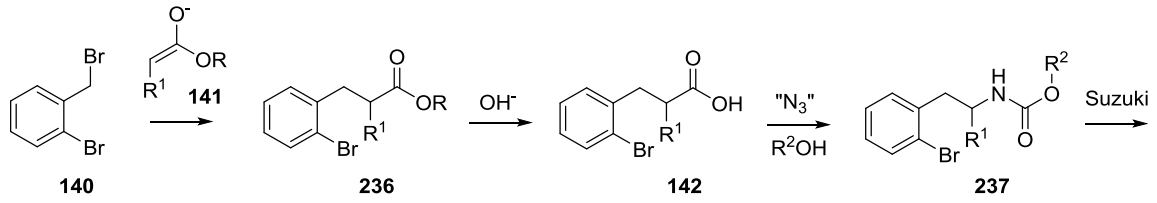
In all the cyclisation attempts, no side-products or impurities were detected and the starting material could be separated from the product giving an overall mass balance of over 90% and reacted again to deliver the same 3:2 mixture of starting material and final product. The diastereomeric ratio of

the cyclised material remained constant even after prolonged reaction times and a single diastereoisomer could not be isolated.

Due to time constraints and only a small amount of material available it was impossible to probe the chemistry of the equivalent, tosylated substrate.

2.12 Curtius Route

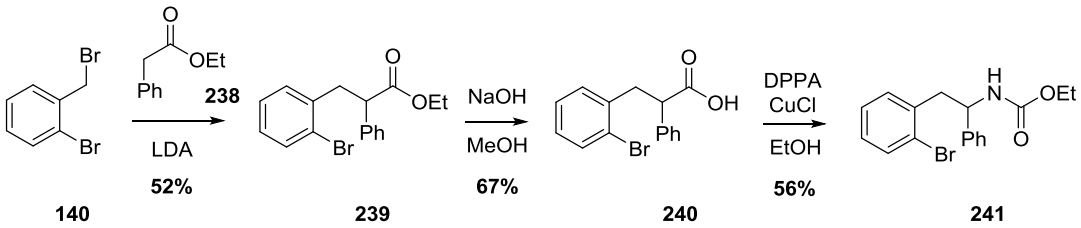
It was envisioned that the wanted compounds could be prepared in a relatively short sequence involving an enolate **141** condensation with the 2-bromobenzyl bromide **140** to yield ester **236**, followed by hydrolysis to the acid **140** and Curtius[183] rearrangement to yield the carbamate **237**. Functionalisation with the already established Suzuki coupling would deliver the cyclisation precursors (Scheme 100).



Scheme 100. Envisioned synthesis of thecarbamate precursors.

Due to the large amount of cheap, commercially available esters it was possible to generate a number of different cyclisation substrates. Freshly prepared lithium diisopropylamide[184] was used to generate the enolate anions **140**.[185] The condensation process was found to be relatively poor yielding, most likely due to the steric hindrance introduced by the *ortho* bromine substituent on the electrophile. Screening the literature revealed that often large excess of the benzyl bromide is used to facilitate the condensation and that many a time yields vary between 40 and 60%.[186] In the laboratory, though, it was decided that a 1:1 ratio of the nucleophile to the electrophile will be used.

Condensation of methyl phenylacetate **238** with 2-bromobenzyl bromide yielded the ester product **239** (Scheme 101) in 52% yield. The product of the initial reaction was purified by column chromatography for yield purposes; however, the majority of the condensation reactions were taken through to the hydrolysis step without any purification as the pure carboxylic acid would later be isolated in high purity in an acid-base work-up.



Scheme 101. Synthesis of the carbamate precursors.

The ester **239** was converted to the carboxylic acid derivative **240** in 67% yield. It was noticed that the hydrolysis reaction was relatively slow, as after 6 hours at room temperature it was only 60% complete by ^{1}H NMR analysis. The reaction could be pushed to completion by increasing the temperature to 40-60 °C, which did not seem to have any negative impact on the formation of impurities and the overall outcome of the reaction. Curtius rearrangement facilitated with diphenylphosphoryl azide and a catalytic amount of copper chloride afforded the 2-bromocarbamate derivative **241**. High temperature NMR analysis ran at 50 °C, allowed resolving some of the resonances for the rotamers (Figure 16).

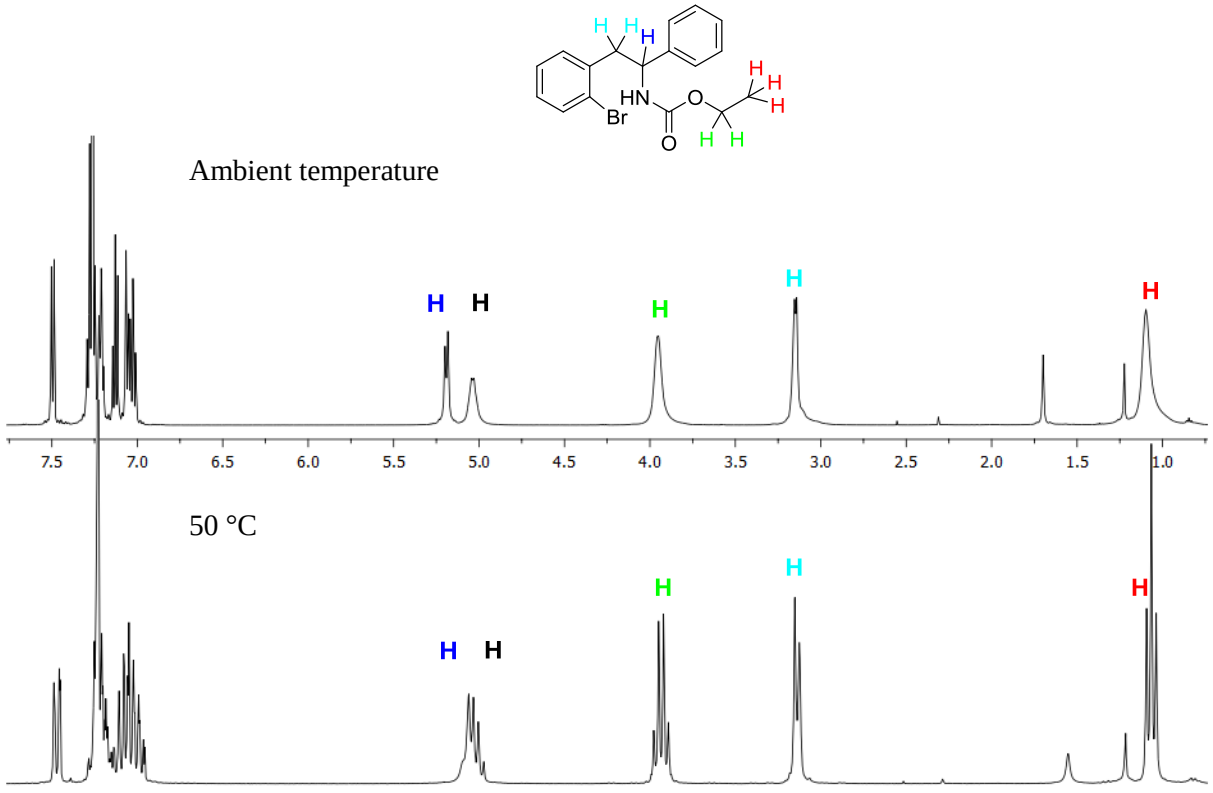
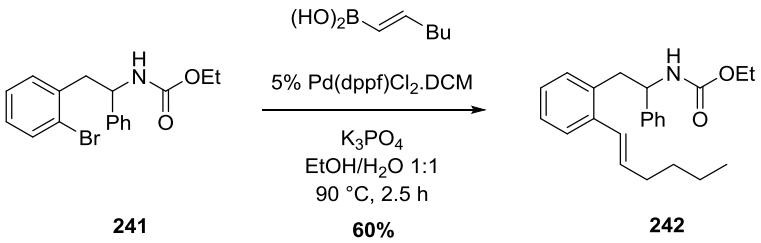


*Figure 16. Rotameric behaviour of compound **241**.*

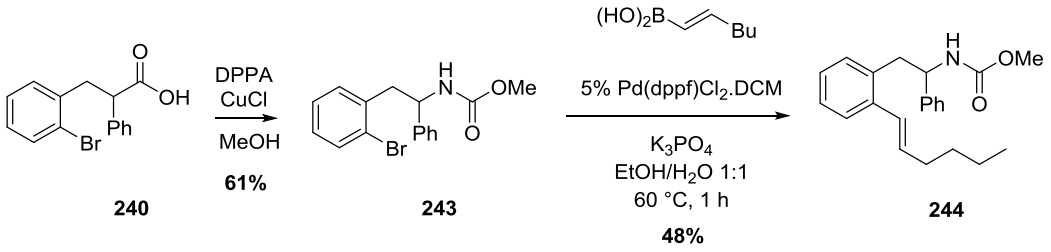
The final step of the synthesis involved setting up of the olefin group and the Suzuki coupling (Scheme 102) delivered the final product **242** in 60% yield.



*Scheme 102. Suzuki reaction of **241**.*

The overall yield of **242** for the entire sequence, starting from benzyl bromide, was only 12%. The reactions, however, were relatively quick and easy to perform and the availability and low cost of the starting materials are definitely beneficial in this system.

The relatively modest yield obtained in the Suzuki coupling of **241** to **242** seemed slightly suspicious and it was believed that the carbamate protecting group was slowly being removed. In an experiment conducted at lower temperature with carbamate **243** from a different Curtius reaction and for a shorter reaction time a similar yield 48% of the product **244** was obtained (Scheme 103). Further analysis of the ^{1}H NMR spectra of the crude reaction mixtures for both Suzuki reactions revealed that the main reason behind the low yields was incomplete conversion of the starting material.

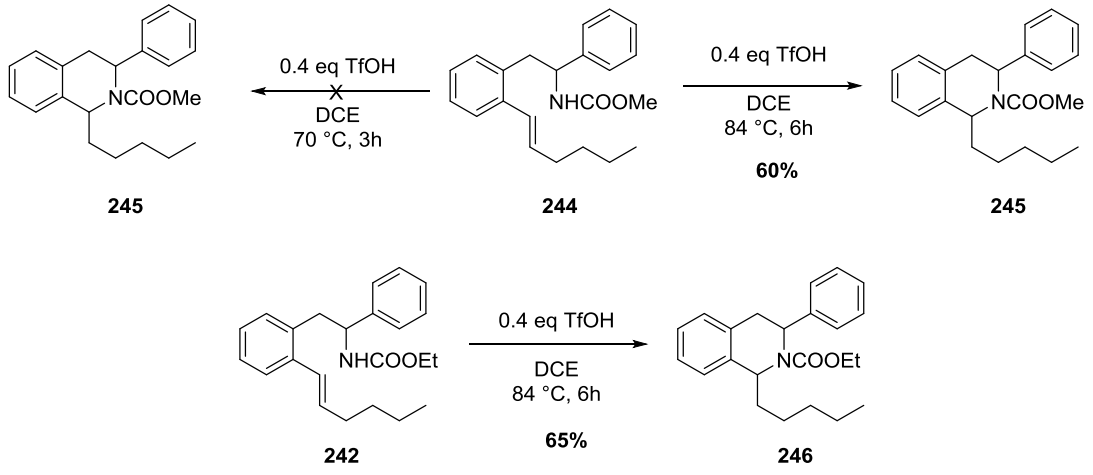


240 **243** **244**

Scheme 103. Synthesis of the carbamate precursors via Suzuki reaction and Curtius rearrangement.

Relatively harsh conditions had to be applied to affect the cyclisation of compounds **242** and **244**. Small amount of the product and mainly unchanged starting material could be recovered after stirring of the substrates at 70 °C for 3 hours with 0.4 equivalents of triflic acid (Scheme 104).

This was somewhat disappointing; previously, it was already established that carbamate protecting group was being slowly removed under more forcing reaction conditions. Fortunately, increasing the temperature to 84 °C and extending the time of the reaction to 6 hours delivered both reaction products **245** and **246** in 60-65% yield. Ratio of 3:2 of the two possible diastereoisomers was obtained in both instances. As before, prolongued reaction times did not have any impact on the composition of the final product.

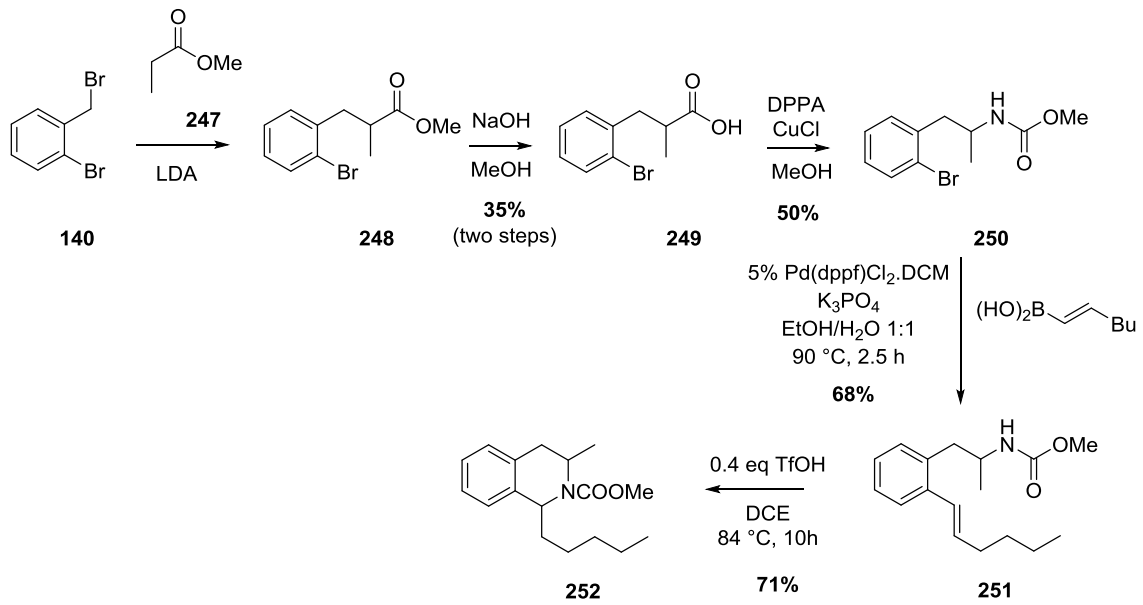


245 **244** **245**

242 **246**

Scheme 104. Synthesis of the carbamate cyclisation products.

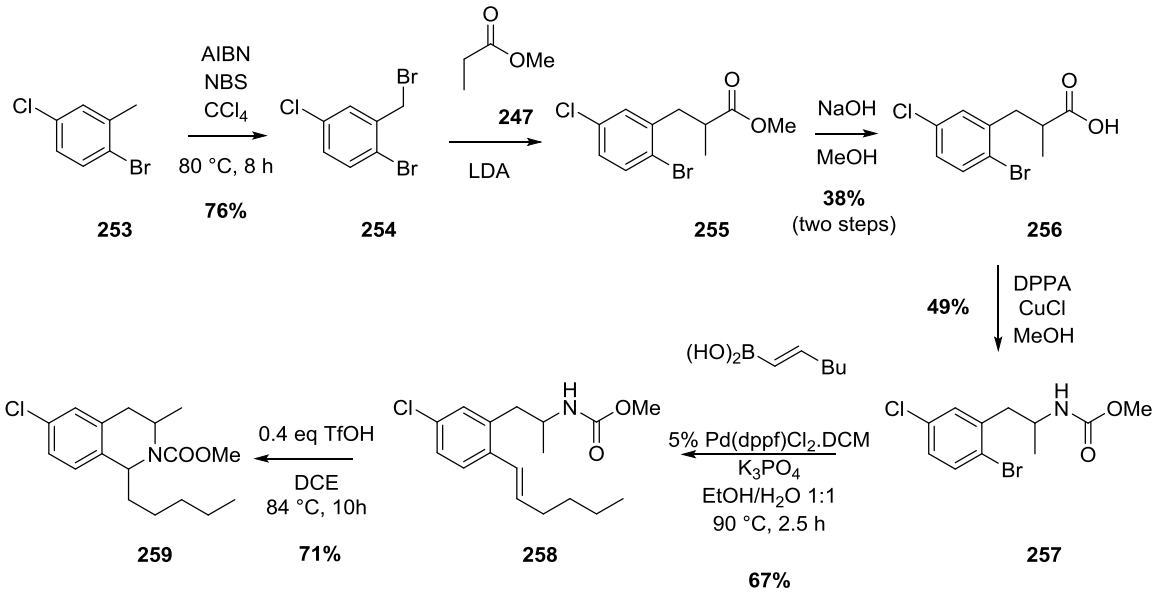
Substrates with a methyl substituent instead of the phenyl group were synthesized in the same way. Condensation of 2-bromobenzylbromide **140** with methyl propionate **247** and subsequent hydrolysis of the ester **248** furnished the carboxylic acid derivative **249** in 35% yield over two steps (Scheme 105).



Scheme 105. Synthesis of the carbamate cyclisation products.

The carbamate **250** was obtained in a Curtius rearrangement in 50% yield, followed by a Suzuki reaction with 1-hexenylboronic acid to give the desired substrate **251** in 68% yield. Monitoring the cyclisation reaction of **251** by TLC showed that it is somewhat slower than the transformation of the phenyl substituted precursor **242** and **244**. This could be due the larger Thorpe-Ingold effect which the phenyl group of **242**/**244** exerts over the methyl group in **251**. Allowing for a total of 10 hours reaction time at 84 °C successfully delivered the product **252** in 71% yield, this time in a 3:1 ratio of diastereoisomers.

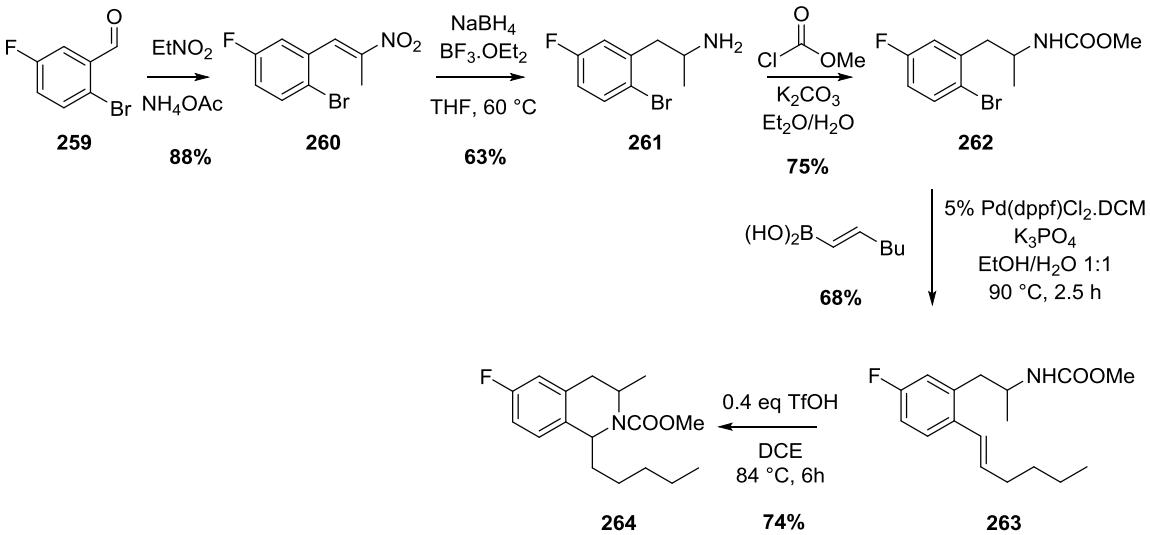
Higher functionalization of the tetrahydroisoquinoline aromoatic ring was one of the goals of the project and introducing substituents such as halogens was highly desirable. It was predicted that the same methodology could potentially supply the desired molecules but due to the small number of commercially available, substituted 2-bromobenzyl bromides, an extra step was necessary (Scheme 106).



Scheme 106. Synthesis of the carbamate cyclisation products.

Radical bromination[187] of 2-bromotoluene derivate **253** with *N*-bromosuccinimide provided the halogenated 2-bromo-5-chlorophenyl compound **254** in 76% yield. Condensation with methyl propionate **247** to **255** and base hydrolysis gave the carboxylic acid **256** in 50% yield. Further elaboration by a Curtius rearrangement provided the carbamate **257** in a modest, 49% yield and was then coupled with 1-hexenylboronic acid to give **258** in 67% yield under standard Suzuki coupling conditions. Cyclisation occurred smoothly and delivered the cyclised product **259** in 71% yield in and a 4:1 ratio of the diastereoisomers, indicating no major difference in reactivities towards acid-catalysed hydroamination between the chloro-substituted **258** and unsubstituted compound **251**.

Similarly, a fluorinated analogue **264** was synthesized, starting from the commercially available 2-bromo-5-fluorobenzaldehyde **259** and a Henry reaction with nitroethane (Scheme 107). The nitroalkene **260** was obtained in 88% yield and was immediately reduced to the primary amine **261** in 63% yield. Protection with methyl chloroformate under Schotten-Bauman conditions furnished compound **262** in 75% yield, which was then reacted in a Suzuki coupling to deliver the cyclisation precursor **263** in 68% yield.



Scheme 107. Synthesis of the carbamate cyclisation products via the Henry reaction.

Similarly as before, the carbamate substrate **263** smoothly converted to the fluorinated tetrahydroisoquinoline derivative **264** as a 2:1 mixture of diastereoisomers in 74% yield, using 0.4 equivalents of triflic acid at 84 °C for 6 hours. The fluorinated compound displayed some interesting features on the ^{13}C NMR spectra. Long distance couplings between the fluorine and carbon, of up to four bonds could be seen resulting in splitting of all the ring carbons (Figure 17).

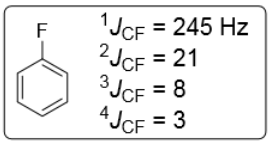
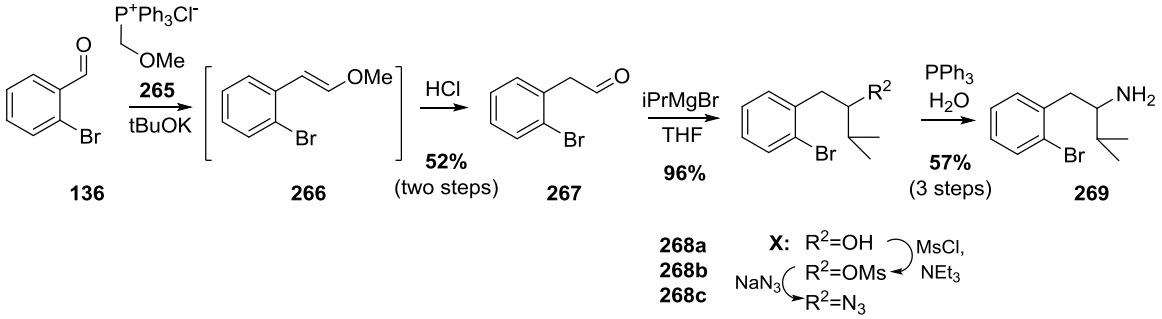


Figure 17. Approximate coupling constant values for fluorine and carbon.

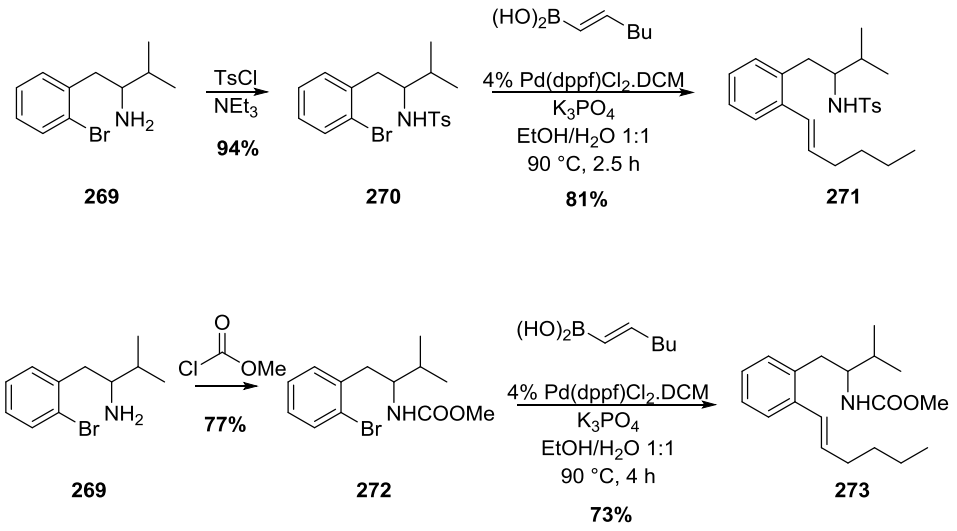
2.13 Homologation Route

One more route for the synthesis of carbamates and tosylates was investigated, in order to expand the substrate scope and extend the approachability of hydroamination chemistry. Homologation reaction of 2-bromobenzaldehyde based on a Wittig reaction with the phosphine salt **265** yielded intermediate **266** which was treated with acid and gave the phenylacetaldehyde derivative **267** in 52% yield (Scheme 108).[188] Condensation of **267** with isopropylmagnesium bromide reagent provided the alcohol **268a** in 96% yield, which was converted to the primary amine **269** in 57% yield via a three step mesylation/azidation/Staudinger reaction reaction sequence.



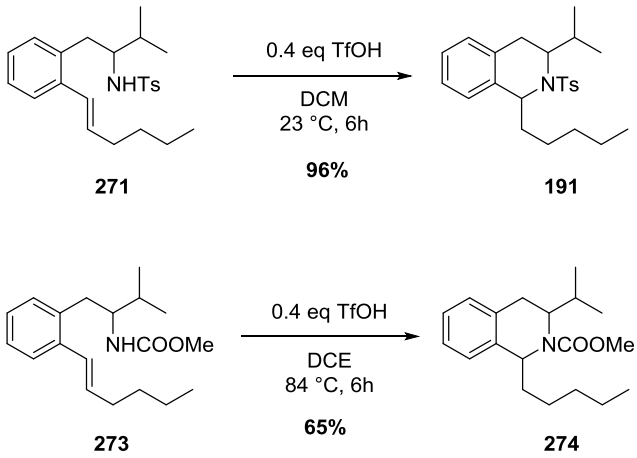
Scheme 108. Synthesis of the cyclisation substrates via benzaldehyde homologation.

Protection of the nitrogen of compound **269** with tosyl chloride delivered the sulfonamide **270** in 94% yield and reaction with methyl chloroformate gave a 77% yield of the carbamate species **272**. Suzuki coupling of the two substrates with 1-hexenylboronic acid afforded the cyclisation precursors **271** and **273** in 81% yield for the sulfonamide and 73% for the carbamate (Scheme 109).



Scheme 109. Synthesis of the cyclisation substrates via benzaldehyde homologation.

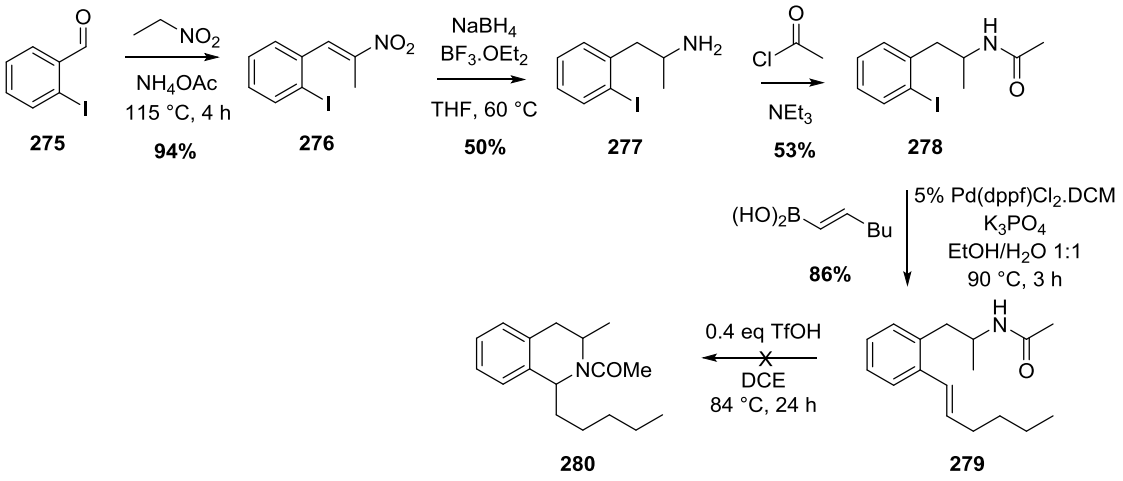
Direct comparison of the cyclisation reactions of substrates **271** and **273**, which differ by the protecting group only, confirmed the reactivity trends observed before. The more reactive sulfonamide **271** cyclised smoothly when exposed to 0.4 equivalents of triflic acid at room temperature for 5 hours and provided the tetrahydroisoquinoline **191** in 96% yield (Scheme 110) as a 3:1 mixture of isomers. The carbamate precursor **273** proved more challenging to cyclise and only 53% conversion by ^{1}H NMR spectroscopic analysis was observed after 3.5 hours at 84 °C, with the same quantity of triflic acid. Extending the reaction time to 7 hours delivered the cyclised material **274** in 65% isolated yield, as a 5:1 mixture of diastereoisomers.



Scheme 110. Cyclisation of carbamate and sulfonamide substrates.

The largely effective application of hydroamination chemistry in the synthesis of carbamate tetrahydroisoquinolines prompted a search for an alternative carbonyl protecting group. A simple acetyl moiety was expected to behave similarly. It was also of interest to test whether the Suzuki coupling carried out on an iodoarene instead of a bromoarene would allow for reducing the reaction temperature

and time and potentially to obtain higher yields of the transformation. Using the Henry route allowed quick access into the iodinated nitroalkene **276** from iodobenzaldehyde **275** (Scheme 111), which was reduced under Kabalka's reaction conditions to **277** and reacted with acetyl chloride to give compound **278**.



Scheme 111. Synthesis and cyclisation attempt of the acetyl-protected substrate.

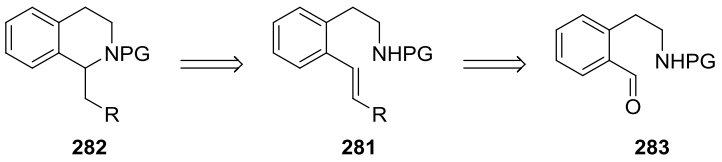
The Suzuki reaction of iodide **278** with 1-hexenylboronic acid performed better that the similar couplings executed on bromoarenes. Conversion of 50% was observed after only 45 minutes at 40 °C, which was very encouraging. The best yield was nevertheless obtained under the standard reaction conditions usually employed for the transformation. Reaction time of 2 hours at the temperature of 90 °C with 5% palladium catalyst and 1.5 equivalents of boronic acid delivered the cyclisation substrate **279** in 86% yield. Unfortunately, no conversion to **280** was observed in the cyclisation reaction, even after 24 hours at 84 °C and 0.8 equivalents of triflic acid.

2.14 Functionalised Aldehyde Route

The carbonyl group is highly abundant amongst organic molecules and is possibly the most important functionality, which is common to compounds such as aldehydes, ketones, carboxylic acids, esters, amides, lactones, acid anhydrides and carbonates. Carbonyl group chemistry is involved in a huge number of various reactions, such as aldol-type condensations, reductions like Luche, Mozingo, Wolff-Kischner, Clemmensen or Tebbe, disproportionations such as Cannizaro or Tishchenko, double-bond forming reactions of Wittig, Peterson and Julia type, reactions with cyanides, hydroxylamines, sulfur nucleophiles or hydration to hemiacetals and acetals. One of the most reactive but also a relatively stable carbonyl group is an aldehyde. Acetaldehyde and formaldehyde are key components of several important industrial polymerisations and are soluble and water. Aldehydes of higher molecular mass are unreactive

towards water, albeit they may form geminal diols through the hydration process, as well as undergo autoxidation with oxygen in the air. They can be accessed in many ways, *i.e.* formylation, ozonolysis, Nef reaction, Wittig homologation and in oxidation of primary alcohols with mild oxidants.

The main topic of this work revolves around the synthesis and cyclisations of 2-vinylphenylethylamines **281** to produce the tetrahydroisoquinoline scaffold **282** (Scheme 112).



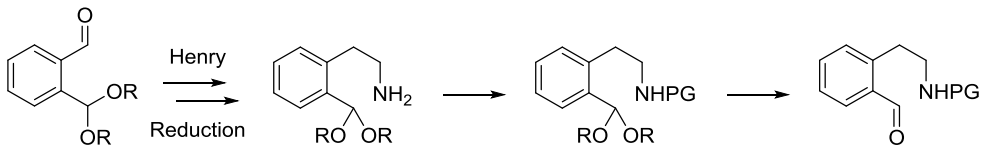
282 **281** **283**

Scheme 112. Retrosynthetic analysis of tetrahydroisoquinoline synthesis.

All the routes designed to access the cyclisation precursors **281** suffered from a fairly limited flexibility in the step of introduction of the olefin. Late functionalization of the compounds from the Henry and the Curtius routes relied on the Suzuki coupling and therefore was restricted by the availability of vinylboronic acids. The route involving ring-opening of an aziridine proceeds via the Grignard reagent of the bromoolefin and thus is constrained to unfunctionalised substrates.

It was conceived that accessing compound **283** could greatly increase the number of synthetic transformations available to perform in the ultimate goal to access more complex cyclisation substrates **281** and the hydroamination products **282**.

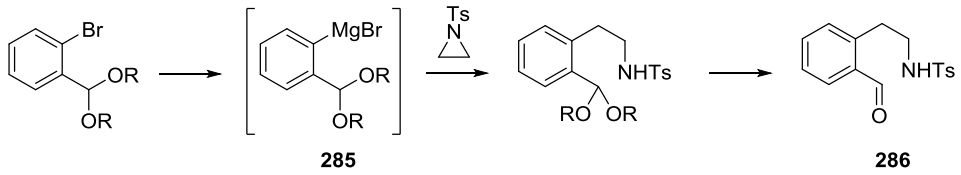
Two primary routes intended to supply the chosen intermediate **284** were designed. The first approach (Scheme 113) involved synthesis of a protected phthalaldehyde **285** followed by introduction of the ethylamine chain in a Henry reaction, lithium aluminium hydride reduction, installation of the protecting group and removal of the acetal moiety to afford **284**. This approach would potentially permit manipulation of the protecting group on the ethylamine chain and also allow setting up the alkene.



285 **284**

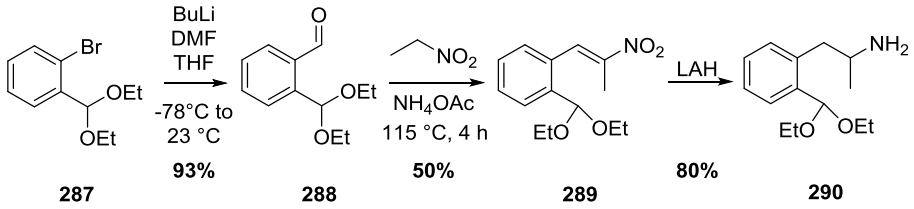
*Scheme 113. Synthesis of intermediate **284** via the Henry reaction.*

The second method was somewhat shorter and relied on the ring-opening of an aziridine with Grignard reagent **285** and removal of the acetal group to produce **286** (Scheme 114).



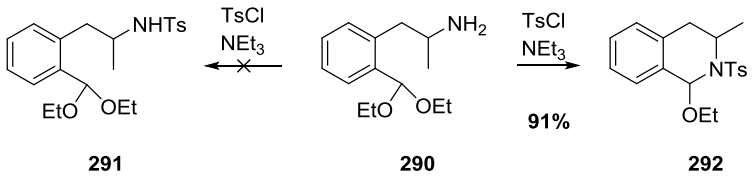
*Scheme 114. Synthesis of intermediate **286** via ring-opening of an aziridine.*

The initial reaction in route one involved formylation of the 2-bromoacetal **287** with butyllithium and dimethylformamide, and proceeded smoothly to deliver the aldehyde **288** in 93% isolated yield (Scheme 115). The Henry reaction proved difficult and a large number of different impurities could be detected by TLC and ^{1}H NMR analysis. The acetal moiety proved somewhat fragile under the reaction conditions and was possibly being slowly deprotected with the traces of acetic acid present in the reaction mixture. The nitroalkene **289** was the major component of the reaction mixture but it took some effort to isolate it in pure form.



*Scheme 115. Synthesis of intermediate **290** via the Henry reaction.*

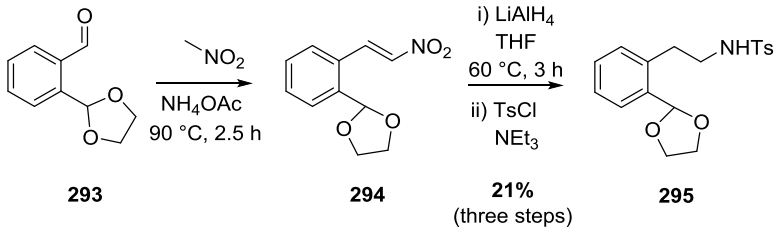
Reduction of the crude nitroalkene **289** delivered the primary amine **290** in 88% yield after an acid- work-up. An attempted tosylation of intermediate **290** delivered surprising results, as none of the sulfonamide acetal **291** could be isolated from the reaction mixture. The major product of the transformation was the cyclised tetrahydroisoquinoline **292** (Scheme 116). The structure was confirmed by ^{1}H NMR analysis where only one ethoxy moiety could be detected, no NH peaks were seen and the presence of the tosyl group was confirmed.



*Scheme 116. Synthesis of THIQ **292** in a tosylation reaction.*

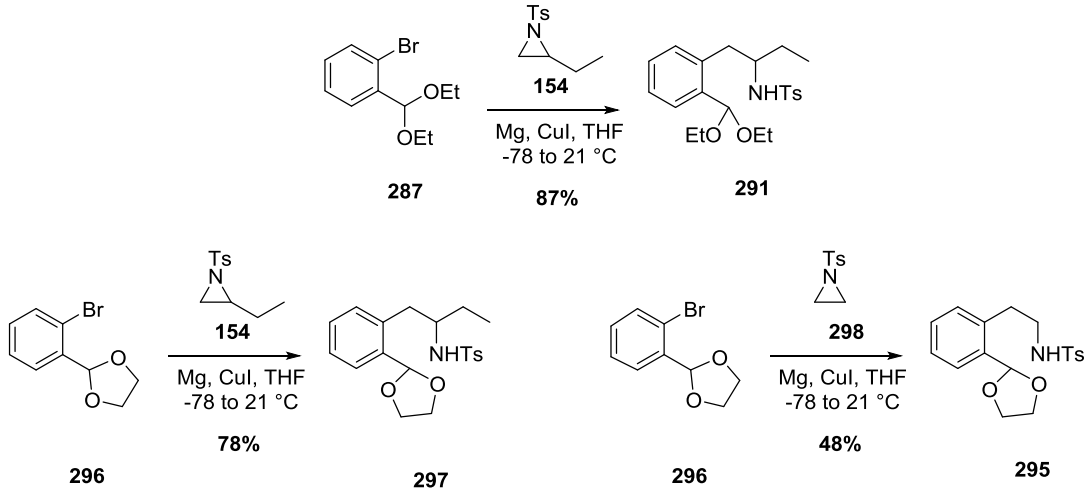
Since the final product **292** of the scheme was of no value at this stage, the whole sequence was repeated with an ethylene acetal-protected benzaldehyde, in hope that the problem of the nitrogen cyclisation onto the ethoxy group could be avoided.

A short optimisation of the reaction conditions proved that the route can deliver the product but in a low yield. The commercially available benzaldehyde **293** could be reacted with nitromethane in presence of ammonium acetate, the nitroalkene **294** reduced with LAH and the primary amine subsequently protected with tosyl chloride to yield the desired intermediate **295** (Scheme 117).



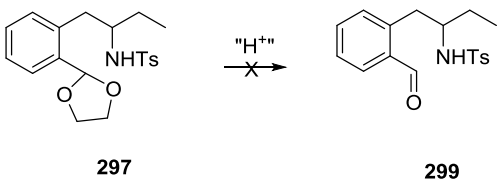
*Scheme 117. Synthesis of intermediate **295** via the Henry reaction, reduction and tosylation.*

This time it was possible to isolate the tosylated compound **295**, however in a poor overall yield. The purification process was also quite problematic, and since the obtained results were not satisfying, it was decided that the second route, involving ring-opening of an aziridine will be tested. The obvious limitation of this methodology was the requirement for the tosyl group on the aziridine. Nevertheless, the synthesis consists of only two synthetic steps (Scheme 118) to reach **291**, **297** and **295**, starting from the synthesized or commercially available aziridines **154** and **298**, and the 2-bromobenzaldehyde acetals **287** and **296**.



Scheme 118. Synthesis of intermediates via the Henry reaction.

The ring opening reactions were largely successful and delivered the phenylethylamines **295** and **297** in very good yield. The lower, 48% yield does not reflect the performance of the reaction and was caused by low solubility of the product **295** in diethyl ether. This resulted in loss of material due to crystallisation of **295** on silica during purification. The next step involved deprotection of the acetal moiety, which was first attempted on the intermediate **297**.

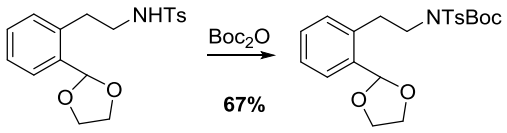


297 **299**

*Scheme 119. Deprotection of intermediate **295**.*

A number of different reagents and solvents have been employed to facilitate the desired transformation of **297** to **299**. In the case of pyridinium *p*-toluenesulfonate, being used, no conversion was observed even after stirring for 18 hours. In the case of hydrochloric acid in tetrahydrofuran and water or acetone as solvent at room temperature, only complex reaction mixtures could be obtained (Scheme 119). The hemiacetal or the free aldehyde formed in the course of the reaction are probably too reactive in presence of the amine group undergo condensation-type reactions, leading to formation of byproducts. In any case, the aldehyde group could not be detected by ^{1}H NMR analysis at any point.

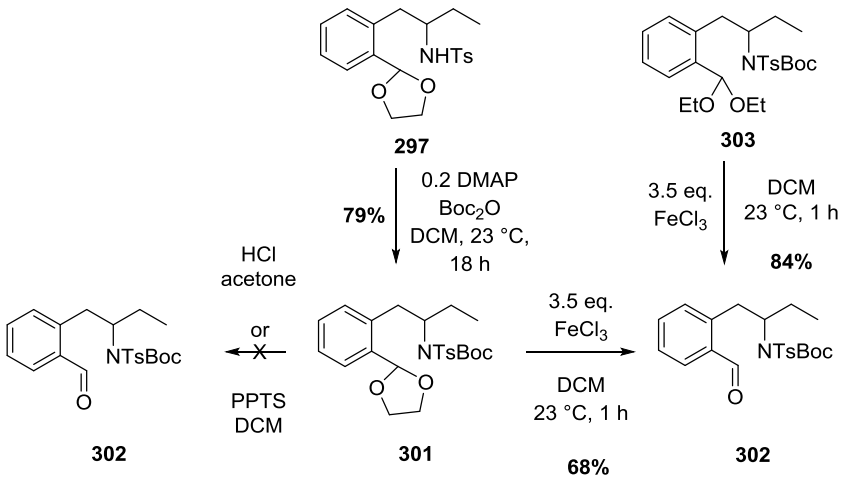
It was decided that another protecting group should be introduced on the nitrogen to block it and reduce the nucleophilicity of the amine. The first group of choice was the *t*-butoxycarbonyl moiety and could be easily installed in a reaction with BOC anhydride (Scheme 120) to give compound **300** in 67% yield.



295 **300**

Scheme 120. Protection of sulfonamide with Boc-anhydride.

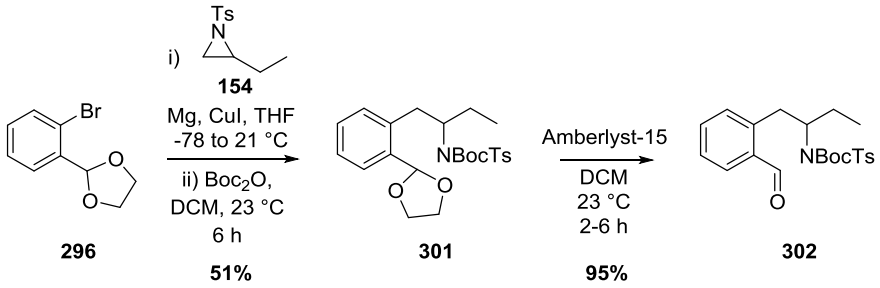
Interestingly, the reaction would not proceed without dimethylaminopyridine and a minimum of 0.2 equivalents of DMAP was required to achieve a sensible conversion rate. Thus, the doubly protected acetal **301** could be obtained smoothly in 92% isolated yield.



*Scheme 121. Synthesis of the BOC protected intermediate **301** and subsequent deprotection.*

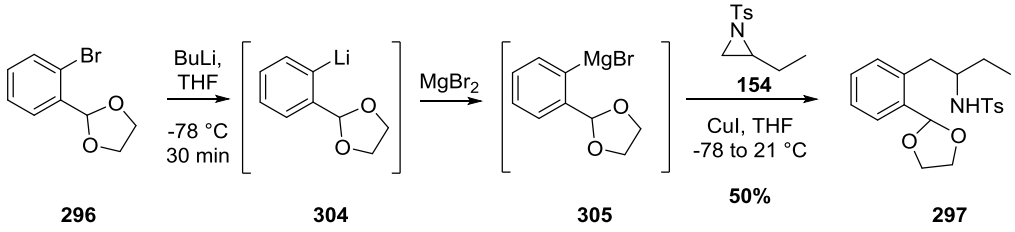
Exposing the intermediate **301** or **303** to the reaction conditions previously used to remove an acetal moiety, namely: HCl in a mixture of water, THF and acetone or PPTS in dichloromethane showed that no reaction was taking place, even after prolonged stirring and warming. Attempts to use stronger acids, such as trifluoroacetic acid in dichloromethane and sulfuric acid in a mixture of water and acetone, resulted mainly in removal of the BOC group. Fortunately, the acetal group could be selectively cleaved with 3.5 equivalents of iron (III) chloride hexahydrate in dichloromethane at room temperature for several hours (Scheme 121).[189] Under these conditions, the doubly protected benzaldehyde intermediate **302** was found to be relatively stable and, importantly, further deprotection of the Boc group did not occur. Even though TLC and ^{1}H NMR analysis of the reaction showed complete conversion to the aldehyde, yield of only 71% per cent could be obtained. This reflects the issues associated with formation of large quantities of a slurry and brown precipitate during the work up stage. To increase the practicality of the reaction, it was further optimised to run with 1.1 equivalents of the reagent, which improved the yields and reduced the amount of solid present during the work-up stage.

In a single experiment it was also shown that the ring-opening of the aziridine **154** with **296** and the nitrogen protection could be carried out in one step to give intermediate **301**. The yield obtained was good (51%) and it was decided that this protocol would not be further optimised. Overall, we were able to install the phenylethylamine chain and two protecting groups in a single step, which was highly advantageous. To further increase the usefulness of this synthetic sequence, it was decided that a greener protocol was required for the acetal deprotection step. Screening of several reagents showed that using 10-25 weight% of amberlyst-15 in either dichloromethane or acetone and water delivered the desired aldehyde **302** in almost quantitative yield (Scheme 122).[190]



*Scheme 122. Synthesis of intermediate **302** via the aziridine route.*

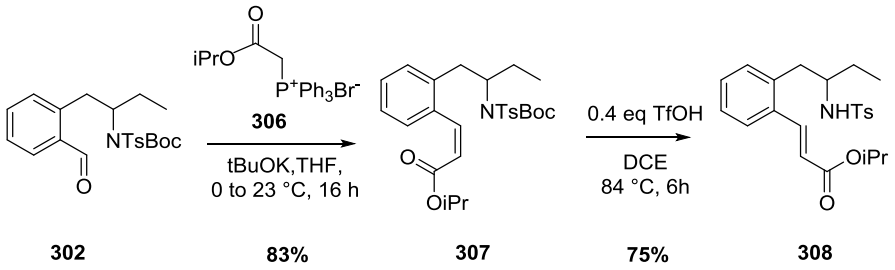
The procedure of ring-opening of the aziridines exclusively relied on utilisation of Grignard reagents. Previous experiments showed that lithiated species cannot be used in place of halomagnesium compounds, which was an important limitation. It was envisioned, however, that the desired Grignard reagents could be synthesized in a sequential lithium-halogen exchange followed by addition of magnesium bromide. In an experiment where the aryl bromide **296** was first lithiated to **304** and then converted to its magnesium bromide derivative **305** by addition of solid magnesium bromide, a good yield of the ring-opened product **297** was obtained (Scheme 123).



*Scheme 123. Synthesis of intermediate **297** via lithiation-magnesiation.*

It was therefore possible to carry out the standard aziridine ring-opening reaction but with pre-formation of the Grignard reagent via lithium halogen exchange and addition of magnesium bromide. This opened the door towards the substrates from which the magnesio-reagents could not be formed, *i.e.* highly electron-rich, dimethoxy substituted compounds.

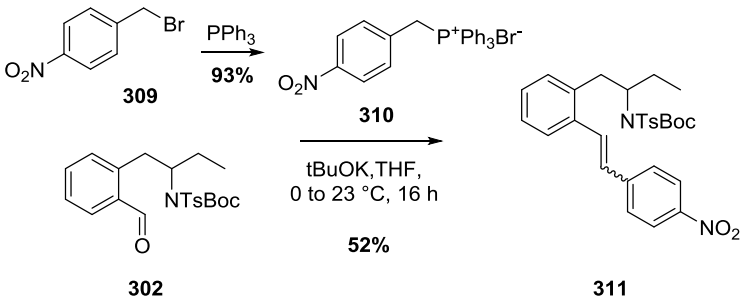
The first idea to exploit the aldehyde moiety with the ethylamine chain already installed involved carrying out a Wittig-type reaction with a phosphonium salt **306** containing an ester, to synthesize intermediate **307** (Scheme 124). The standard reaction conditions employed before worked very well and delivered the product in 83% isolated yield, as a mixture of *cis* and *trans* isomers. It was anticipated that compound **307** would undergo a smooth acid catalysed deprotection and cyclisation in a Michael fashion. It was surprising to see that only the deprotection of the Boc group and isomerisation of the double bond from *cis* to *trans* was observed, yielding product **308**. Even in refluxing dichloroethane no tetrahydroisoquinoline could be detected.



*Scheme 124. Synthesis of intermediate **307** via the Wittig reaction.*

The failure in the attempted cyclisation of compound **308** could have been caused by the triflic acid preferentially protonating the ester group and effectively preventing the cyclisation from occurring. The low reactivity of the ester system also correlated to the problematic cyclisations of the previously described stilbene derivatives. Electron-withdrawing groups present on the double bond have a strongly deactivating effect and in case of the substrate **307**, perhaps can completely stop the reaction from happening.

Encouragement from the good performance of the Wittig reaction prompted synthesis of a number of cyclisation precursors which due to their structural properties had been previously impossible to make. Synthesis of the phosphonium salt **310** from the commercially available *p*-nitrobenzyl bromide **309** and sequential reaction with the benzaldehyde intermediate **302** delivered a cyclisation intermediate possessing a nitro group.

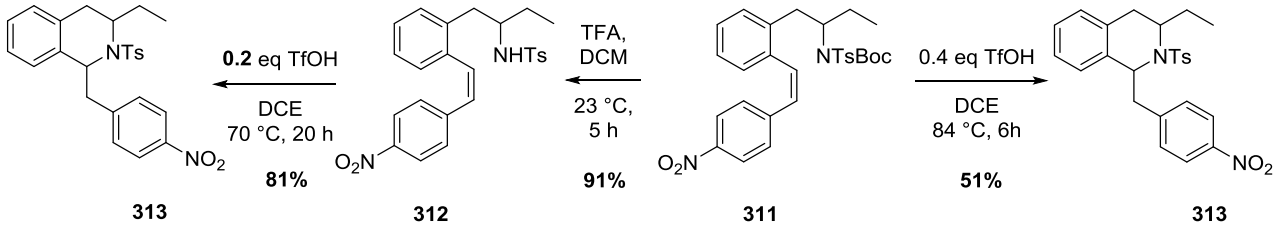


*Scheme 125. Synthesis of intermediate **311**.*

Previous attempts to access similar compounds possessing a nitro group were met with failure as the formation of a Grignard reagent could not be successfully initiated. The phosphine salt **310** was synthesized from the commercially available 4-nitrobenzyl bromide **309**. Accessing the substrate through the novel, functionalised aldehyde approach proved effective and compound **311** was cyclised in a good 51% yield to the corresponding tetrahydroisoquinoline **313**.

To probe if the Boc group has any influence on the cyclisation progress we have decided to remove the carbamate with TFA in dichloromethane, which gave the sulfonamide **312** in 91% yield

(Scheme 126). Running the cyclisation under optimised reaction conditions and with only 0.2 equivalents of triflic acid led to the cyclised product **313** in 81% yield, or in 74% over two steps.



*Scheme 126. Synthesis of tetrahydroisoquinoline **313**.*

Generally, better cyclisation yields were obtained during the optimisation process if the Boc-free compound **312** was used. It therefore seemed as the Boc group plays an important role in the reaction and the overall outcome of the reaction to some extent depends on its presence.

2.15 Conclusions

Probing of a number of different synthetic routes towards the hydroamination substrates allowed efficient synthesis of various cyclisation precursors, which were smoothly converted to 1,3-substituted THIQ alkaloids. Different alkyl- and phenyl- substituted analogues were synthesized, with a carbamate, tosyl or a nosyl protecting group on the nitrogen. Separation and careful spectroscopic analysis of diastereoisomers, along with X-ray evidence, proved that the thermodynamic product of the hydroamination was the 1,3-*cis* stereoisomer.

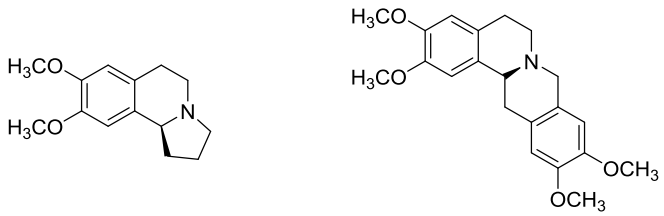
Literature search on the mechanism of acid-catalysed hydroamination proved inconclusive, however, a pre-association mechanism, postulated by Wiedenhoefer, appears to be the most convincing. Analysis of the energy-minimised structures of substrates with *cis* and *trans* olefin bonds accounted for the difference in reactivities between the two isomers. Furthermore, comparison of the vinyl-isopropyl and vinyl-phenyl substituted aminoalkenes showed that steric factors play a minor role in the reaction and that the electronic properties of the alkene bond have a crucial impact on the reaction. Electron poor π-bonds, *e.g.* with a phenyl or an ester substituent, performed poorly and either did not work at all or required very harsh conditions to cyclize.

A variety of different solvents and catalysts was screened in an attempt to find better catalyst or solvent system for the hydroamination reaction. Ultimately, it was shown that a combination of 0.4 equivalents of triflic acid and dichloromethane or 1,2-dichloroethane as solvent work best and delivered the tetrahydroisoquinolines in good yields.

Chapter 3: Application to Synthesis of Natural Products

3.1 Introduction

Growing general interest in tetrahydroisoquinoline chemistry in the context of natural products, building blocks and pharmaceuticals has resulted in fast development of a large variety of synthetic approaches delivering these compounds. Different alkaloids in this family have shown diverse biological activities, *e.g.* inflammatory,[191] neuromuscular transmission blocking,[192] and enzyme inhibitory[193] properties. Compounds such as the pyrroloisoquinoline (S)-crispine A **314** (Scheme 127), first isolated in 2002 by Zhao and co-workers, have been shown to posses anticancer properties against several human cancer cells.[194] (*S*)-Xylopinine **315** belongs to the protoberberines, a large family of alkaloids characterised by their tetracyclic skeleton with an incorporated tetrahydroisoquinoline core. Tetrahydroprotoberberines often possess antimicrobial, antitumour and antileukemic properties.[195]



314 **315**

Scheme 127. Crispine A and xylopinine.

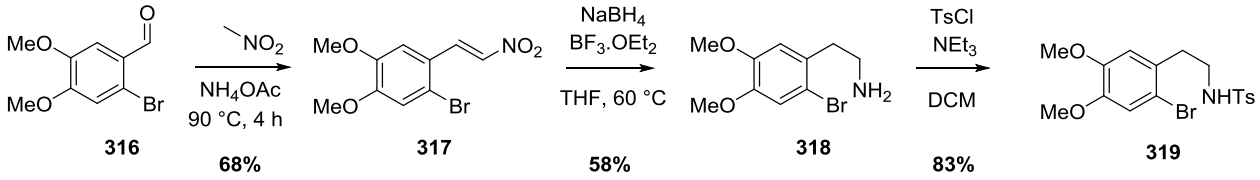
The past decade saw advances in the area of tetrahydroisoquinoline synthesis. Enantioselective Pictet-Spengler reaction,[196] procedures involving operations such as cyanations on 3,4-dihydroisoquinolines,[197] functionalisation of dihydroisoquinolines *N*-oxides[198] or catalytic asymmetric hydrogenations[199] of 3,4-dihydroisoquinolines have been applied in this area. The ongoing research in the field of THIQ is still very dynamic and many journal articles covering their syntheses are published annually.

3.2 Methoxylated Analogues

A large number of tetrahydroisoquinoline, benzyltetrahydroisoquinoline and other isoquinoline natural products contain alkoxy groups on one or several rings. The hydroxy, methoxy and methylenedioxy substituents on ring A are usually located at the same positions, as in crispine A or xylopinine (Scheme 127). After proving the utility of hydroamination in the synthesis of unsubstituted and electron-poor tetrahydroisoquinolines it was important to test whether this synthetic methodology could be used to access molecules resembling natural products.

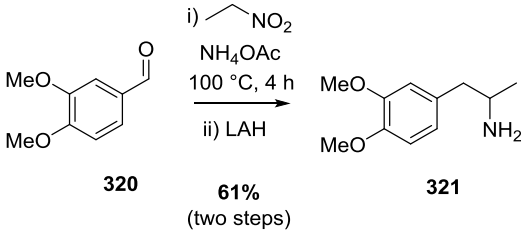
It was anticipated that the substituted analogues could be accessed from veratraldehyde **316** via the already established Henry sequence. Reaction of **316** with nitromethane delivered the nitroalkene **317** in 68% yield. It was observed that the veratraldehyde reaction performs much worse in comparison to the

unsubstituted aldehydes. Fortunately, the products could be purified relatively easily by repeated recrystallization from petrol/ethyl acetate mixtures. Kabalka's reduction protocol was employed to access the amine **318** in 58% yield, which was then used without purification in a tosylation reaction to deliver sulfonamide **319** (Scheme 128).



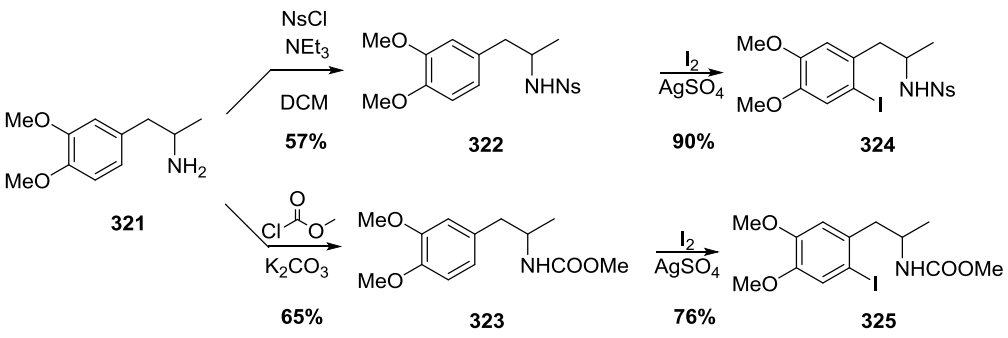
Scheme 128. Synthesis of methoxylated compounds.

To avoid the laborious Kabalka reduction protocol of halogenated nitroalkenes, a synthetic route was also devised where the iodine substituent was introduced at a later stage, after the initial installation of the phenylethylamine chain. Thus, the 3,4-dimethoxyamphetamine **321** was accesed in a two step process by a Henry reaction followed by reduction with lithium aluminium hydride in 61% yield (Scheme 129).



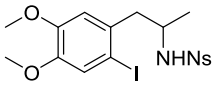
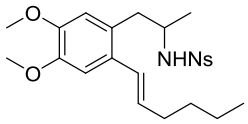
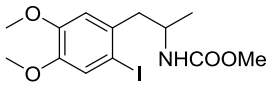
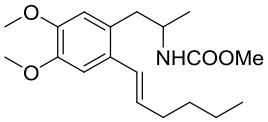
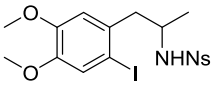
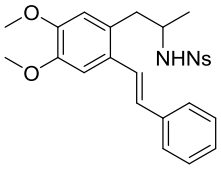
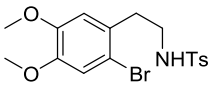
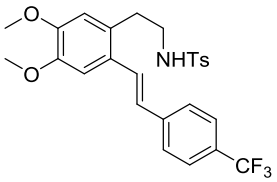
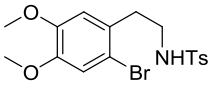
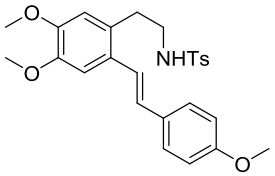
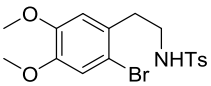
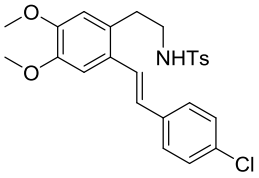
Scheme 129. Synthesis of methoxylated compounds.

The primary amine was then converted to nosyl derivative **322** and carbamate **323** in 57% and 65% yield, respectively. Both compounds were then iodinated using molecular iodine and silver sulfate. This protocol was found to be very efficient and high yielding and produced the iodinated sulfonamide **324** in 90% and the carbamate **325** in 76% yield (Scheme 130).



Scheme 130. Synthesis of iodinated methoxylated compounds.

The prepared series of nosyl, tosyl and carbamate methoxy- haloarenes were then functionalised using the Suzuki reaction. It was anticipated that, due to the electron-rich nature of the coupling substrates, the rate of palladium insertion into the carbon-bromine and carbon-iodine bonds could be much slower or that the reaction would not proceed at all. Fortunately, all of the palladium couplings performed worked well and delivered compounds of interest in relatively good yields. The results are summarised in the table below (Table 2).

Starting Material		Final Product		Yield[a]
324		**326**		72%
325		**327**		54%
324		**328**		82%
319		**329**		77%
319		**330**		53%
319		**342a**		77%

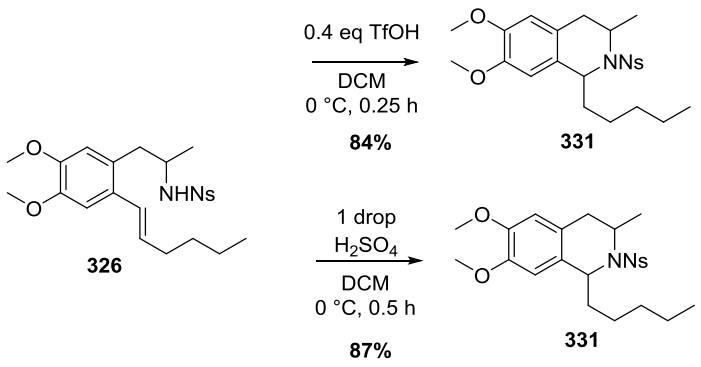
[a] Yields for products isolated after column chromatography.

Table 2. Suzuki coupling of methoxylated compounds.

The yields obtained in the palladium coupling reactions were acceptable. Analysis of the crude reaction mixtures showed no decomposition and most likely further optimisation of the reaction conditions could improve the conversion and the yield for the reation.

3.3 Cyclisations

It was correctly predicted that the electron donating substituents on the benzene ring would have a drastic effect on the outcome of the hydroamination reaction. Less forcing conditions could be applied to afford the bicyclic product, however, some of the precursors were found to be more prone towards decomposition. The cyclisation reaction of sulfonamide **326** proceeded to completion in less than 15 minutes at 0 °C with 0.4 equivalents of triflic acid and delivered the tetrahydroisoquinoline **331** in 84% yield (Scheme 131).



*Scheme 131. Cyclisation of compound **326**.*

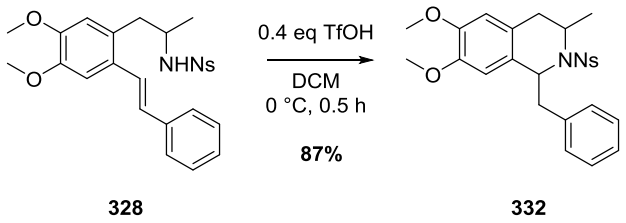
Interestingly, ^{1}H NMR experiments proved that full conversion to the product could also be achieved at -20 °C after 20 minutes and at -40 °C after approximately 1 hour.

At this stage it was also demonstrated that the electron-rich substrates could be cyclised with sulfuric acid as the catalyst, which is insoluble in organic solvents usually employed for this transformation and was also somewhat harder to quantify. Compound **326** was cyclised with a drop of sulfuric acid in dichloromethane in 30 minutes to furnish tetrahydroisoquinoline **331** in 87% yield.

To quantify sulfuric acid more accurately, a series of measurements were taken where a drop of sulfuric acid was discharged from a syringe and its mass accurately determined each time. Twenty readings gave an average mass of a "drop" to be 12 mg, which corresponds to 0.12 mmol. Generally, 1 drop of sulfuric acid was used per 100 mg of a compound with molecular mass between 300 and 500 Daltons. This is approximately 0.5 equivalents of the acid per 1.0 equivalent of the substrate and therefore corresponds well to the triflic acid-catalysed reaction conditions. The cyclisation rate of triflic acid-catalysed reactions was found to be faster than of the corresponding sulfuric acid reactions, most likely

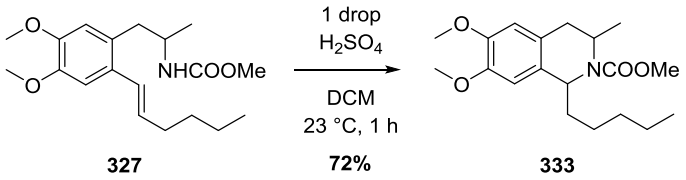
due to the fact that the second reaction is heterogenous. Most of the time, even when the reaction was vigorously stirred, the drop of sulfuric acid could be seen in the reaction flask.

The second reaction in the series involved a stilbene derivative **328**. As before, switching from an alkyl to a phenyl substituent on the double bond caused the reaction to be more sluggish. The compound was also slowly decomposing if the reaction temperature was raised above 0 °C or upon prolongued stirring (Scheme 132). A small quantity of brown precipitate, insoluble in organic solvents, could be detected. Nevertheless, the optimised reaction conditions delivered the benzyltetrahydroisoquinoline **332** in 87% yield.



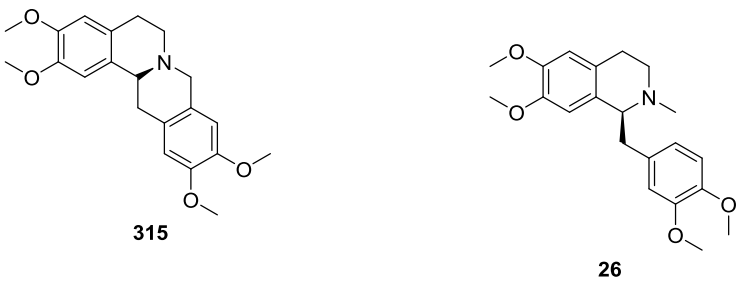
*Scheme 132. Cyclisation of compound **328**.*

Hydroamination reaction of the electron-rich carbamate analogue **327** proved to be somewhat difficult. Similarly as before, higher temperature was required to cyclise the corresponding carbamate equivalent of **326**. No reaction was seen at temperaures close to 0 °C and the corresponding cyclised product **333** was formed in 72% yield and a 2:1 mixture of diastereoisomers, after 1 hour at room temperature (Scheme 133). Only approximately 75% conversion by NMR was observed after 1 hour of stirring in acid, however, extending the reaction time to 2 or 3 hours resulted in a drastic drop in yield (<50 %) and formation of a number of unidentified impurities.



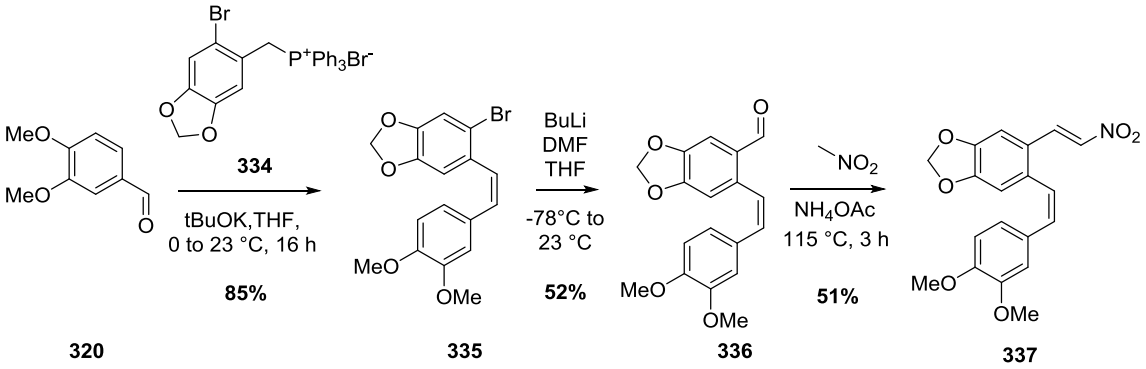
*Scheme 133. Cyclisation of compound **333**.*

The results obtained were encouraging and introducing alkoxy substituents on the second benzene ring became a priority. Increasing the scope of the hydroamination to highly substituted and electron rich compounds would possibly permit synthesis of interesting, biologically active compounds such as the previously mentioned xylopinine **315** and laudanosine **26** (Scheme 134).



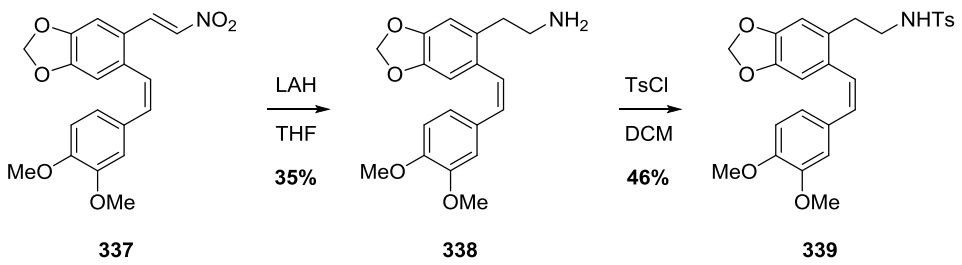
Scheme 134. Xylopinine and laudanosine.

Due to the limited availability of the boronic acids, another route enabling relatively quick synthesis of methoxylated tetrahydroisoquinoline alkaloids was defined. As before, veratraldehyde **320** served as a cheap and commercially available starting material and was reacted with phosphine salt **334** in a Wittig reaction to deliver the alkene **335** in 85% yield (Scheme 135). It was later shown that the low yield of a number of Wittig reactions was caused by poor quality potassium *tert*-butoxide used to form the ylide.



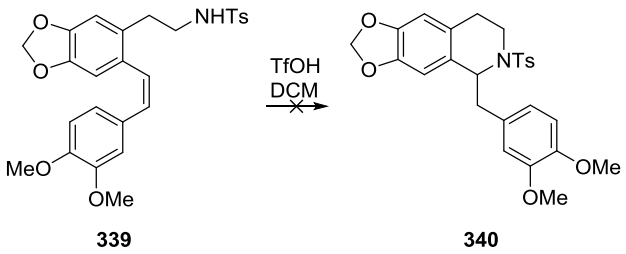
Scheme 135. Synthesis of electron-rich hydroamination precursors.

The bromide **335** was then transformed into the aldehyde **336** in 52% yield by a lithium-halogen exchange formylation reaction with dimethylformamide used as the source of the carbonyl group. Henry reaction with nitromethane afforded the nitroalkene **337** in 51% yield, which was subsequently reduced to an amine with lithium aluminium hydride to **338** and tosylated to furnish sulfonamide **339** (Scheme 136) in a modest, 40% yield over two steps.



Scheme 136. Synthesis of electron-rich hydroamination precursors.

Regrettably, the standard triflic acid-catalysed reaction resulted in decomposition of the starting material. The cyclisation step required a lot of optimization (Scheme 137), as the substrate was extensively decomposing, forming a thick, black residue which could not be purified. Lowering the reaction temperature to -20 °C did not improve the outcome in any way and carrying out the treaction at -50 °C completely stopped the process; in this case only unreacted starting material was recovered. It was, therefore, decided that any potential reactivity window between -20 and -50 °C was too small and optimising the reaction was not desirable. Attempt to use weaker acids such as trichloroacetic acid, sulfuric acid, trifluoroacetic acid proved largely ineffective. The problem was overcome by using pTSA in toluene.

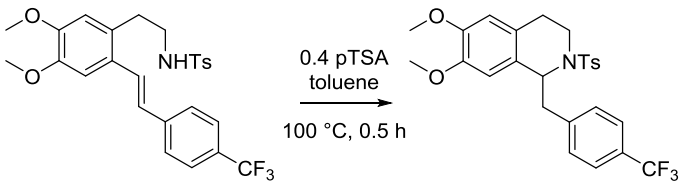


339 **340**

Acid	Temp.	Time	Yield
TfOH	0°C	15 min	decomp.
TfOH	-20 °C	15 min	decomp.
TfOH	-50 °C	1 h	no reaction
TFA	25°C	1h	no reaction
TCA	25°C	1h	no reaction
H_2SO_4	-20	15 min	no reaction
pTSA	60°	5h	10%
pTSA	75°C	24h	41%

Scheme 137. Optimisation of the cyclisation reaction.

A small amount of the cyclised material could be obtained in a reaction with 1.0 equivalent of *p*-toluenesulfonic acid at 75 °C. The optimised conditions involved heating the substrate with 0.5 equivalents of pTSA in toluene to 100 °C for 0.5 h. Further analysis of the crude reaction mixtures showed that *trans* starting material fully converts to give the product **340**, however, the *cis* isomer remains unreacted. Since approximately 40% of the cyclisation precursor existed in the *trans* from, it was unsurprising to see the the yield of the reaction close to 40% as well. This was previously observed in a similar system (Scheme 82, pg. 61), where a much higher temperature was required to cyclize compound **179** to **199**. It was concluded that the problem could be potentially avoided if the synthesized starting material **339** was exclusively *trans.* This idea was later successfully proved to be true via the Suzuki methodology and several polysubstituted, electron-rich tetrahydroisoquinolines were synthesized. The first tetrahydroisoquinoline synthesized in a pTSA-catalysed reaction was the trifluoromethylated compound **341** which gave the cyclic product in 95% yield (Scheme 138).



329 **95%** **341**

Scheme 138. Synthesis of electron-rich hydroamination products.

Similarly to compound **264** (Scheme 107), interesting spectral features could be observed in the ^{13}C NMR spectrum of compound **341**; carbons up to four bonds away from the fluorines (Figure 18) of the -CF_3 group were split into quartets. The *J* values for the couplings fitted well into the ranges previously reported (Figure 18) and ranged between 3 and 250 Hz.

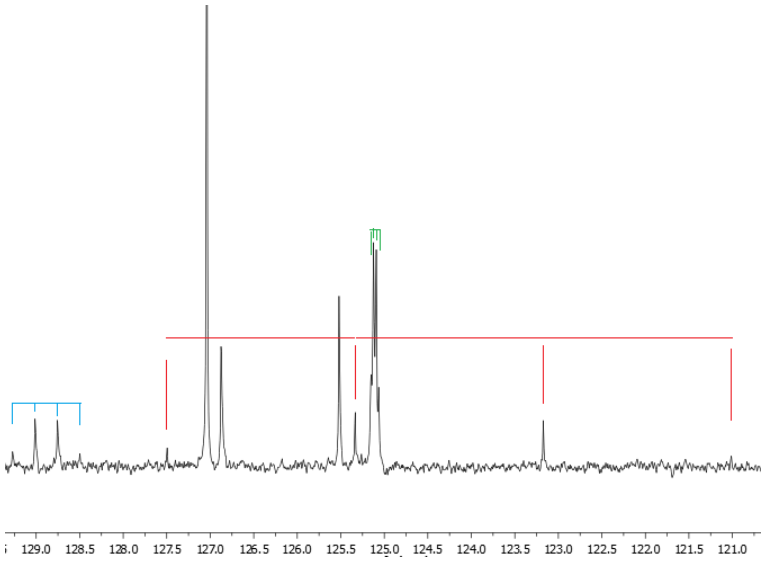
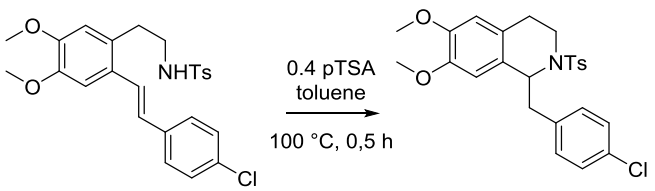


Figure 18. Splitting patterns due to carbon-fluorine coupling.

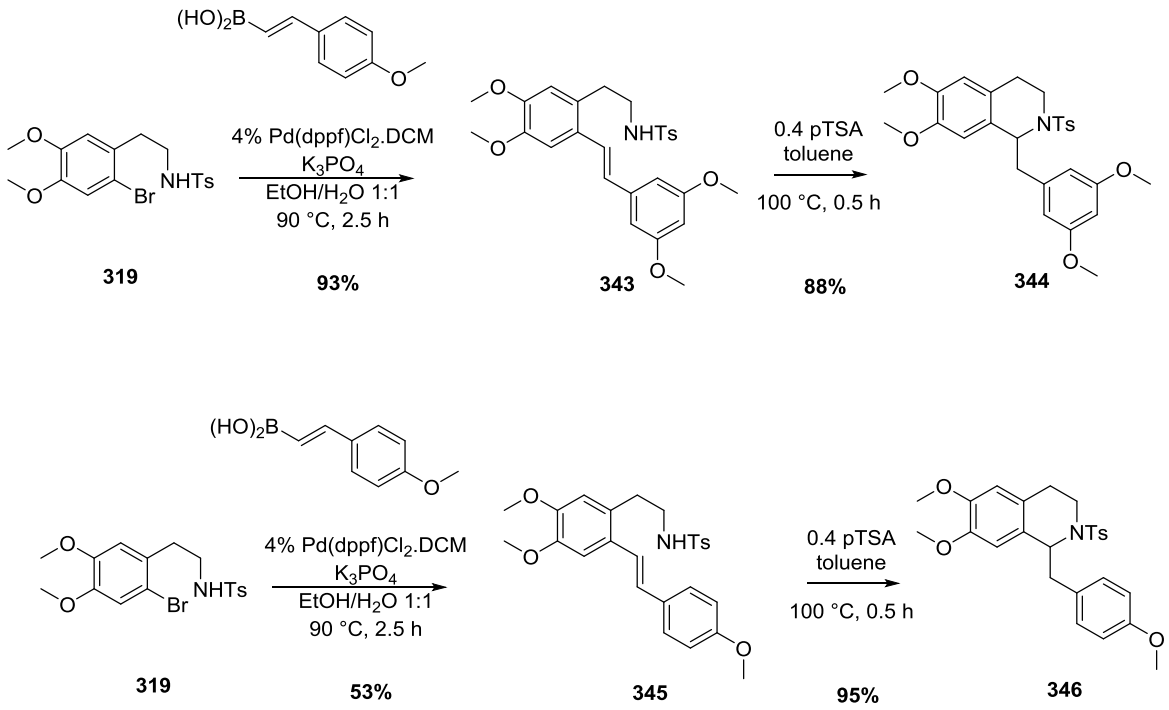
It was soon discovered that this methodology is very general and tolerates different substituents on the second benzene ring. Predictably, the chlorinated derivative **330** also cyclised under the same reaction conditions and gave tetrahydroisoquinoline **342** in 95% isolated yield (Scheme 139).



330 **95%** **342**

*Scheme 139. Synthesis of electron-rich hydroamination product **342**.*

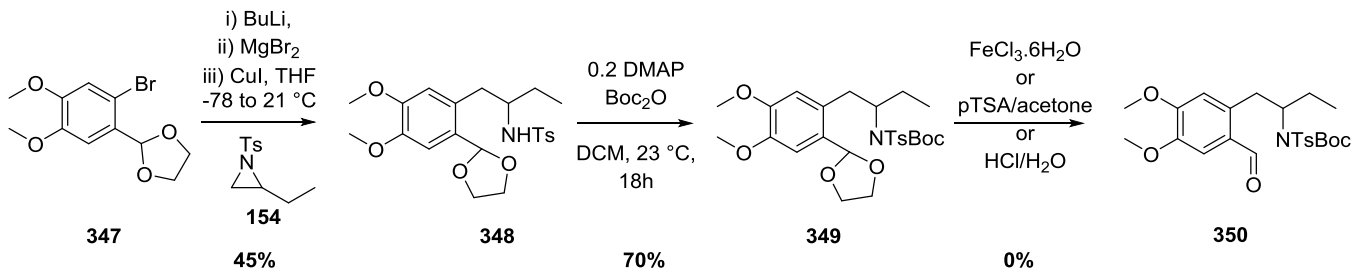
The highly electron-rich substrates **343** and **345** were also accessed through the Suzuki coupling in a 93% and 53% yield respectively, and were quickly converted to their cyclised counterparts **344** in 88% and **346** in 95% yield (Scheme 140).



Scheme 140. Synthesis of electron-rich hydroamination products.

3.4 A formal total synthesis of (*R/S*)-salsolidine

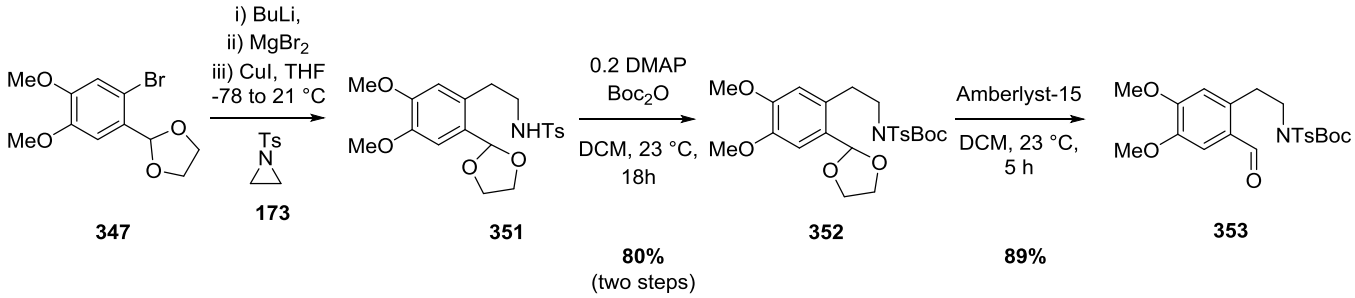
The synthesis of polyalkoxy substituted tetrahydroisoquinolines was also successfully extended to the previously described functionalised aldehyde route. Acetal protection of 2-bromoveratraldehyde cleanly delivered the bromo-derivative **347** which was converted to the sulfonamide **348** in a one-pot lithium-halogen exchange followed by an *in situ* formation of a Grignard via addition of solid magnesium bromide and finally ring-opening of an aziridine **154** in an overall 45% yield. The sulfonamide **348** was then protected with a Boc group to furnish doubly-protected amine **349** which could not be efficiently deprotected to deliver **350** (Scheme 141). The substrate was exposed to a number of different reagents in an attempt to remove the acetal but only extensive decomposition or complex reaction mixtures containing multiple products could be obtained.



Scheme 141. Functionalised aldehyde synthesis.

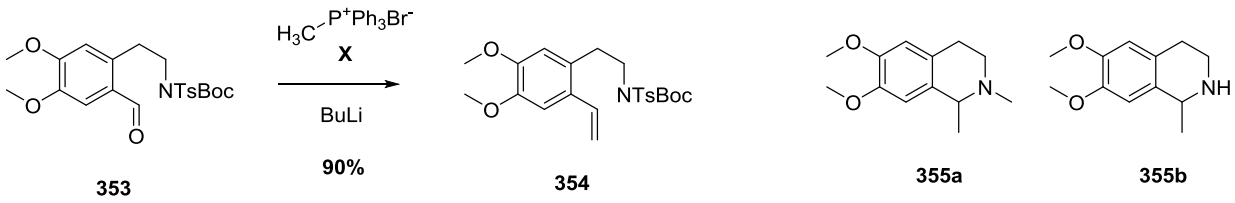
It was later discovered that amberlyst-15 provides a very clean and efficient transformation of acetals such as **349** into their corresponding aldehydes; this methodology was applied to acetal **352** to yield aldehyde **353**.

To sum up, the acetal **349** can be accessed in a relatively short sequence of reactions. The installation of the acetal was not a problem, as well as the introduction of the Boc group and most probably removal of the dioxolane at the end. The protecting-group manipulations were the price to pay to access a highly functionalised and dynamic intermediate such as **350**. Unfortunately, due to intensive experimentation and time constraints no further synthesis using compound **350** was carried out; however, a similar set of transformations was used to access compound **353**, which differs only by not having an ethyl substituent on the ethylamine chain.



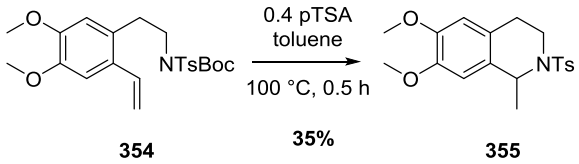
Scheme 142. Functionalised aldehyde synthesis.

(*R*/*S*)-Carnegine[200] **355a** and (*R*/*S*)-salsolidine **355b** are a simple, model tetrahydroisoquinoline alkaloids and often serve as test molecules for new THIQ-making methodologies. In an attempt to access racemic carnegine through Knight's hydroamination the aldehyde **353** was transformed into the alkene **354** in a simple Wittig reaction (Scheme 142).



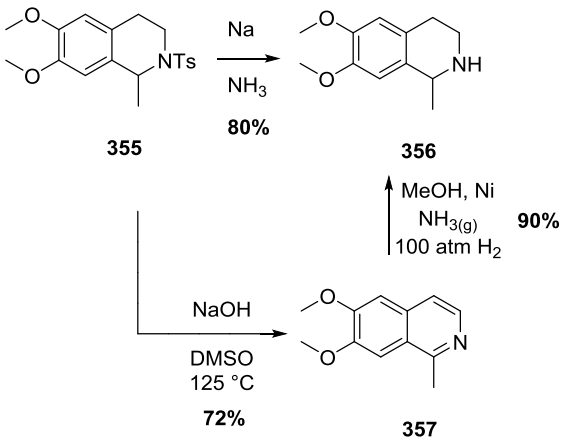
Scheme 143. Synthesis of electron-rich hydroamination products (left) and carnegine and salsolidine (right).

The subsequent cyclisation of the Boc protected sulfonamide **354** under the standard pTSA-catalysed reaction conditions gave the tetrahydroisoquinoline **355** in only 35% yield and a number of impurities which could be isolated but were not identified (Scheme 144). This relatively poor result might be due to the Boc interfering with the hydroamination or due to the higher reactivity of the terminal double bond.



Scheme 144. Synthesis of racemic salsolidine precursor.

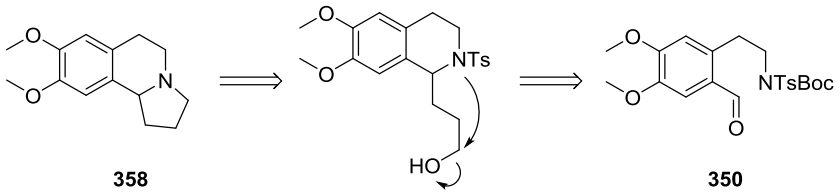
Exposing the isolated cyclisation product **355** to the reaction conditions for 24 hours resulted in its full recovery, thus proving its stability. Due to time constraints the cyclisation reaction was never fully optimised. Nevertheless, the reductive deprotection of the sulfonamide **355** under dissolving-metal reaction has been previously reported by Ponzo and Kaufman and a formal synthesis (Scheme 145) was therefore established.[201] The amine **356** could also be accessed in a two step process involving a one-pot elimination and aromatisation of the B ring with sodium hydroxide in hot DMSO reported by Shi and co-workers,[202] followed by high-pressure hydrogenation of isoquinoline **357** over Raney Nickel.[203]



Scheme 145. Relay synthesis of racemic salsolidine.

3.5 Crispine

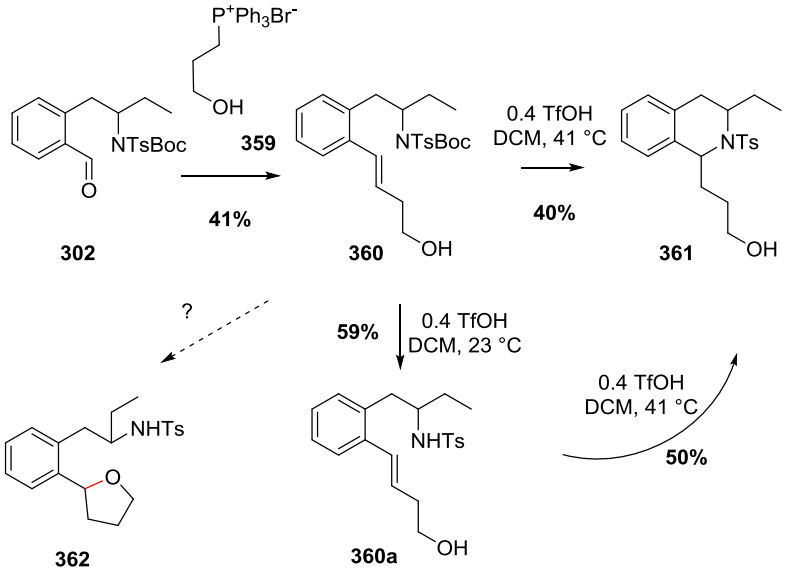
A similar approach was used in an attempted synthesis of (*R/S*)-crispine **358**, where the installation of a four-carbon chain with an alcohol group would be used to form the five-membered ring in the final product (Scheme 146).



Scheme 146. Retrosynthetic analysis of crispine.

The initial effort was directed towards probing the behaviour of the alcohol group under acid-catalysed hydroamination conditions. It was plausible to expect that a primary alcohol might dehydrate when treated with a strong acid, or cyclize onto the double bond to form an oxygen heterocycle.

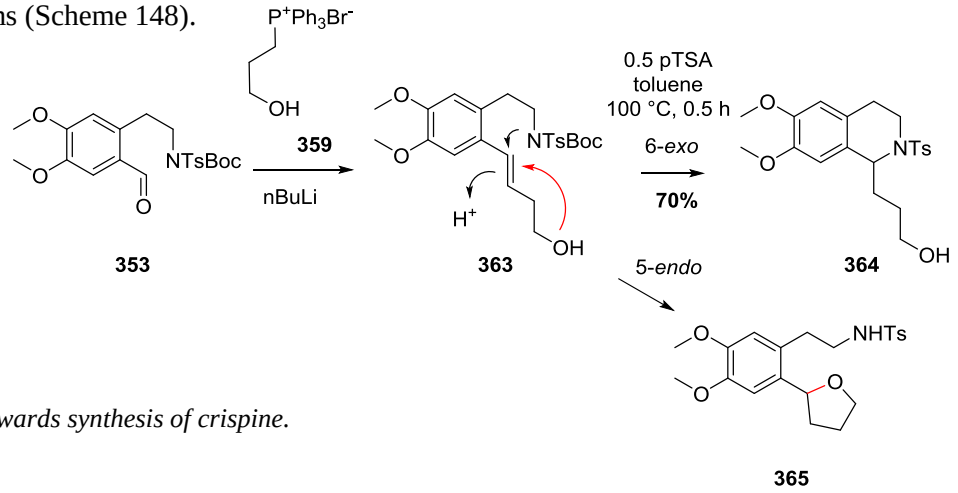
Happily, the alcohol **360** could be easily accessed in a simple Wittig reaction of aldehyde **302** and phosphine salt **359** to furnish the cyclisation precursor in 41% yield. Exposing **360** to 0.4 equivalents of triflic acid in dichloromethane at ambient temperature gave only the deprotected product **360a** in 59% yield. However, more forcing conditions delivered the desired cyclic product **361** in 40% yield. Additionally, reacting the deprotected compound **360a** with triflic acid in refluxing dichloromethane also gave the desired tetrahydroisoquinoline **360**, in somewhat higher yield of 50% (Scheme 147).



Scheme 147. Towards synthesis of crispine.

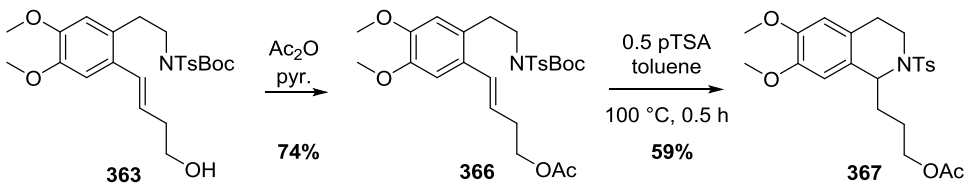
A considerable effort was dedicated to proving the true structure of **361**. Extensive analysis of the chemical shifts and connectivity ascertained that the cyclised compound was indeed a tetrahydroisoquinoline formed in a 6-*exo* fashion and not a tetrahydrofuran **362**, which could arise from a 5-*endo*-trig cyclisation of the oxygen onto the alkene. With this data, the research then shifted to the dimethoxybenzene analogues.

It was possible to synthesise the alcohol **363** in a Wittig reaction of aldehyde **353** and phosphine salt **359**, however in only 18% yield (Scheme 146). Taking the Boc-protected sulfonamide straight to the hydroamination, which could be triggered under less forcing conditions than hydroamination of **360**, delivered the cyclised product **364** in 70% yield. As before, it was noticed that the cyclisation reaction could also potentially occur through the oxygen atom, via the 5-*endo* pathway, to give a furan product **365**. Careful analysis of the 2D NMR spectrum revealed that the product was indeed a nitrogen heterocycle **361**. In both cases this was somewhat unsurprising, as all (3 to 7)-*exo*-trig cyclisations are favoured according to the Baldwin's rules, whereas all (3 to 5)-*endo* cyclisations are disfavoured in trigonal systems (Scheme 148).



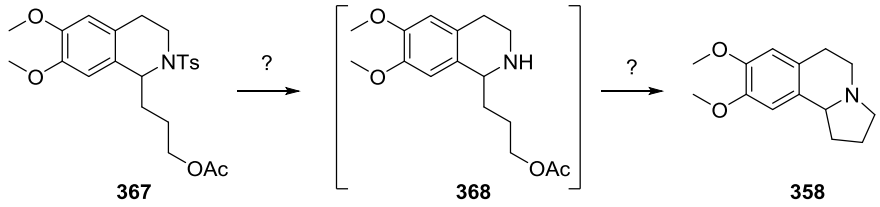
Scheme 148. Towards synthesis of crispine.

The next steps involved deprotection of the sulfonamide group and intramolecular cyclisation. It was highly possible that the alcohol group would interfere with the harsh reaction conditions required to remove a tosyl group. The issue could be overcome by introducing a protecting group on the oxygen atom, which would additionally block the suspected 5-endo cyclisation. An acetate protecting group could also serve as a leaving group and induce the 5-membered pyrrole ring-closure at a later stage. Protection of the alcohol **363** with acetic anhydride was achieved in 66% yield to give the cyclisation precursor **366**. The hydroamination proceeded smoothly and delivered the acetate protected tetrahydroisoquinoline **367** (Scheme 149) in 59% yield.



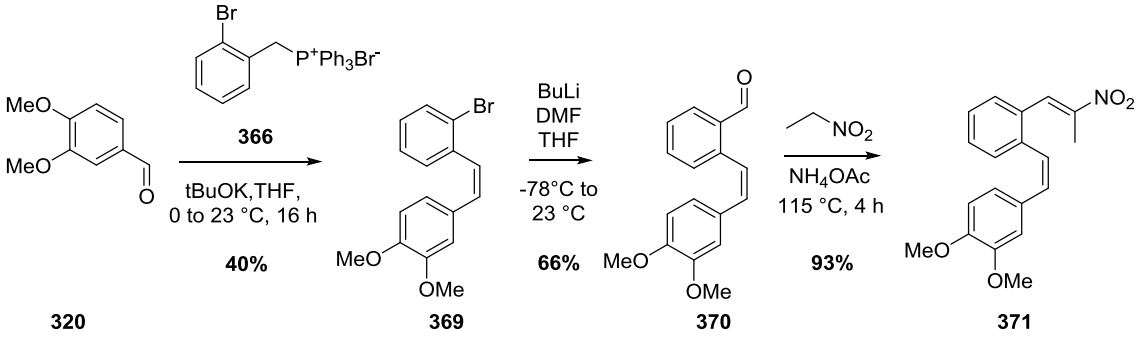
Scheme 149. Towards the synthesis of crispine.

The final step of the synthesis was supposed to involve a deprotection of the tosyl group to the intermediate **368** and a simultaneous cyclisation of the nitrogen atom onto the acetate carbon would deliver the racemic crispine **358**. Regrettably, the detosylation attempts were ineffective and due to time limitations the final product could not be synthesized (Scheme 150).



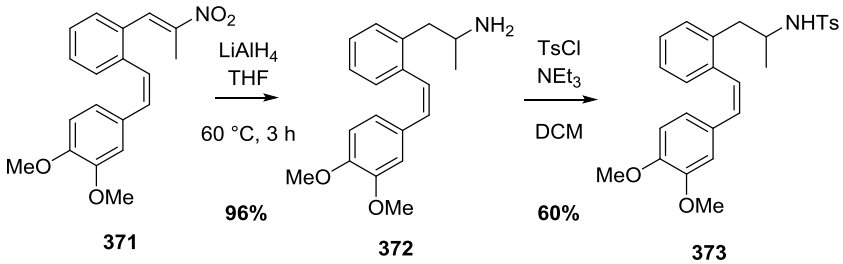
Scheme 150. Final steps in the synthesis crispine.

Another area of research involved synthesis of a stilbene-type precursor decorated with methoxy substituents on the bottom ring, but not the top. It was anticipated that the reduced reactivity would cause problems and that the cyclisation might occur via the 7-*endo* instead of 6-*exo* fashion and potentially produce a 7-membered ring.



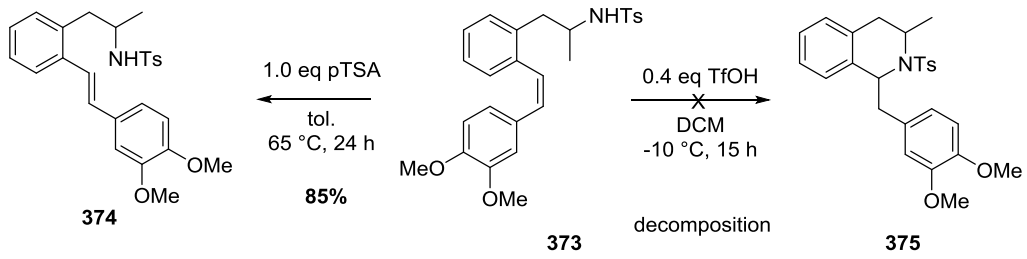
*Scheme 151. Synthesis of intermediate **371** via the Wittig and Henry reactions.*

Previously established methodology was used to access the cyclisation precursor **374**. Wittig reaction of bromoveratral **320** and 2-bromobenzyltriphenylphosphonium bromide **366** (Scheme 152) delivered the alkene **369** in a modest, 40 % yield. The 2-bromostilbene derivative **369** was then formylated to **370** in 66% yield and transformed into nitroalkene **371** in 93% yield via a condensation with nitroethane. Subsequent reduction with LAH furnished the primary amine **372** in 96% yield, followed by tosylation to the final compound **373** in 60% yield (Scheme 152).



*Scheme 152. Synthesis of intermediate **373** via the Henry reaction.*

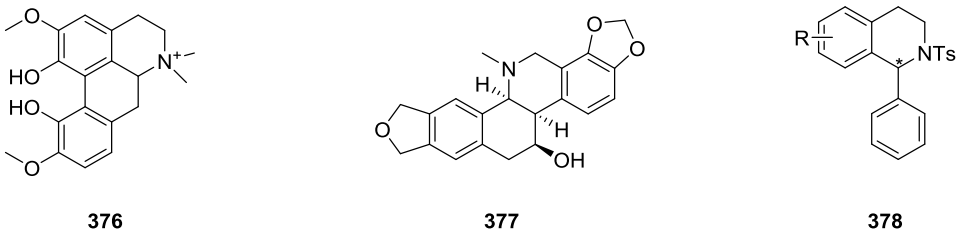
Unfortunately, attempts to cyclise the sulfonamide derivative **373** were met with failure. Even under carefully controlled conditions only complex reaction mixtures containing multiple products could be obtained. The desired tetrahydroisoquinoline **375** was not observed by ^{1}H NMR spectroscopy and the mixtures were not analysed further. Further optimisation attempts did not afford any major reaction product. In a series of overnight experiments where *p*-toluenesulfonic acid was employed at 65 or 100 °C, a complete isomerisation to the *trans* isomer **377** was observed; yet no tetrahydroisoquinoline product could be detected.



*Scheme 153. Attempted cyclisation of **373**.*

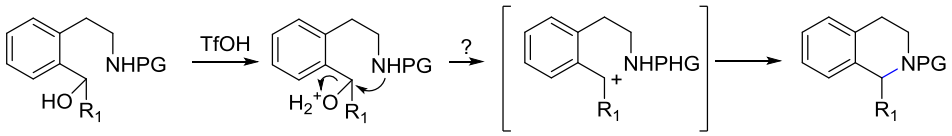
3.6 Benzhydryl Analogues

Apart form ability to interact on central nervous system and antitumour and antimicrobial properties, several tetrahydroisoquinoline derivatives, such as chelidoneme **377** and magnoflorine **378**, are known for their anti-HIV activity (Scheme 154).[204] Compounds such as **378** have been recently accessed in an iridium complex-catalysed hydrogenation/tosylation of the corresponding imines.[205] Another recent publication by Efange and co-workers revealed that 1-aryl tetrahydroisoquinolines also display antimalarial properties.[206]



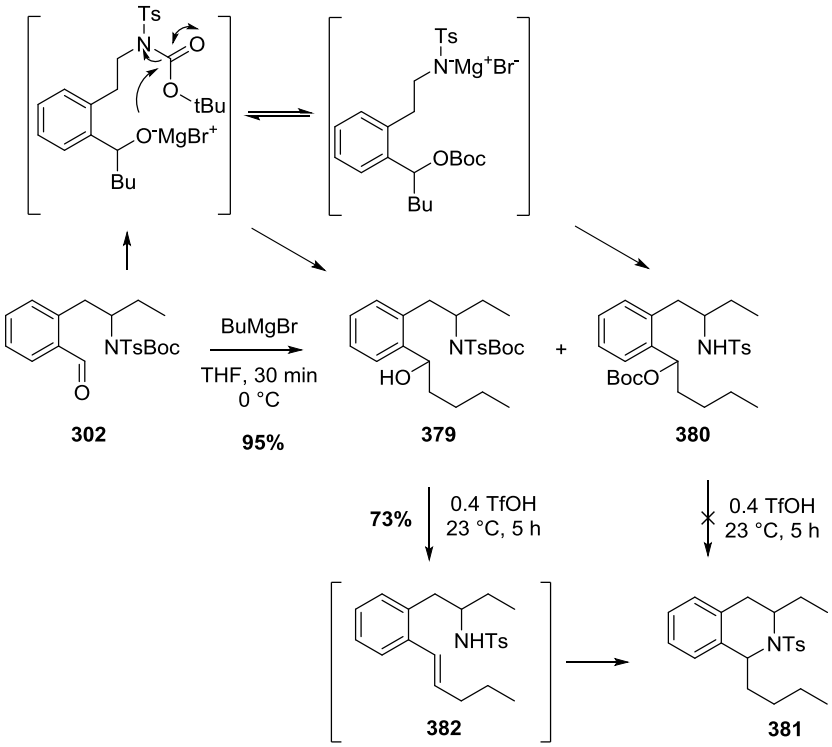
Scheme 154. Structures of chelidoneme and magnoflorine.

It was envisioned that perhaps a double bond is not required to generate a carbocation on the benzylic position to facilitate a hydroamination reaction. Instead, a departing molecule of water would serve as a leaving group (Scheme 155).



Scheme 155. Hydroamination reaction terminating on a benzylic alcohol.

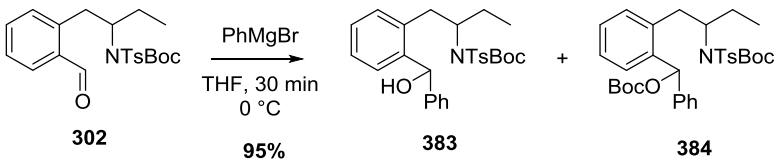
With the previously synthesized aldehyde **302** it was possible to quickly test the idea. First, it was attempted to synthesise a substrate which could potentially dehydrate during the cyclisation. Condensation of aldehyde **302** with butylmagnesium bromide delivered the alcohol **379** in approximately 40% yield. It was discovered that the Boc group migrates between the nitrogen and oxygen (Scheme 156).



Scheme 156. Boc group migration in a condensation reaction.

At first it was expected that the presence of the Boc group on either of the heteroatoms will not have any major influence on the outcome of the cyclisation reaction. It was later discovered that the final product could **378** only be obtained from the N-Boc protected material **379** and that the O-Boc substrate **380**, when exposed to triflic acid, produces only very small amounts of product **381**. Separation of compound **379** and subsequent reaction with a catalytic amount of triflic acid delivered the product **381** in 73% yield. Interrupting the cyclisation reaction before reaching completion showed that it occurs *via* the dehydrated alkene **382**. The initial rate of dehydration was relatively fast with the cyclisation occurring relatively slow. This was possibly caused by the water coming from the dehydration step and could be overcome by using larger quantities of triflic acid (0.8 – 1.2 eq.) to afford the transformation.

The next substrate tested was designed not to dehydrate in the process, with no hydrogens available for elimination. Condensation of the aldehyde **302** with phenylmagnesium bromide delivered a mixture of two products, **383** and **384** in a good overall yield (Scheme 157).



Scheme 157. Boc group migration in a condensation reaction.

As before, however, only modest quantities of product **385** could be isolated if a mixture of both of the condensation products **383** and **384** were exposed to hydroamination conditions (Scheme 156). Extending the reaction time had no positive effect on the outcome of the transformation. An attempt to use TFA to afford deprotection and cyclisation resulted in similar results and only delivered the product in very low quantities (Figure 19) amongst several impurities which were not identified.

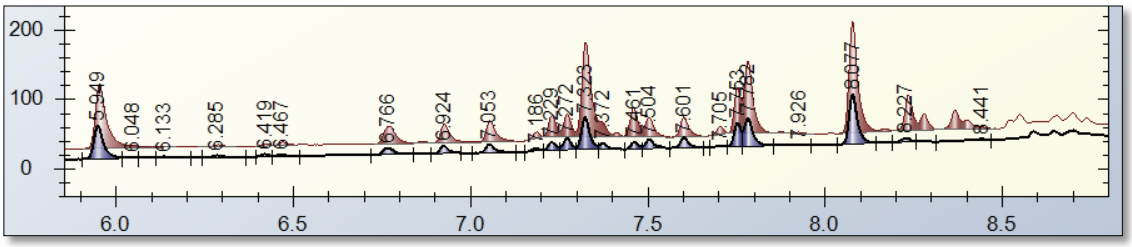
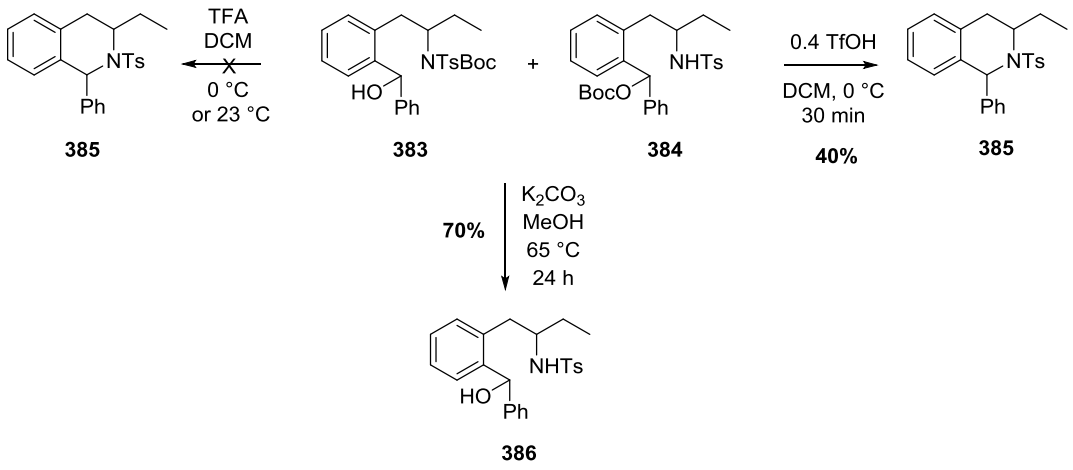


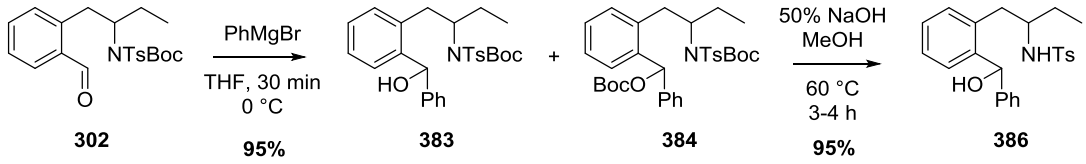
*Figure 19. HPLC trace of the crude mixture of a TFA (red) and TfOH (blue) reaction of crude **380/381.***
Product at 7.75/7.78 min.

It was decided that the methodology would benefit from a short and simple procedure allowing for a complete removal of the Boc group; therefore, it was then attempted to cleave off the Boc protecting group from both the nitrogen and oxygen in a single step. Attempts to optimise the acid-catalysed deprotection did not deliver any positive results and a base-catalysed approach was then tried. A reaction with potassium carbonate in methanol under reflux conditions successfully delivered the product **386** as a single species (Scheme 156), although in a relatively long reaction time. This was unsatisfactory, as it was more desirable to design a faster and more robust transformation which could be employed as a short and simple, post work-up procedure after the condensation reaction.



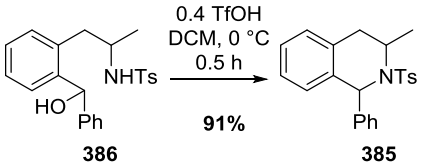
Scheme 158. Boc group deprotection attempt.

During further optimisation process it was determined that concentrated sodium hydroxide in methanol at 60 °C cleanly produced the deprotected cyclisation substrate **386** in a virtually quantitative yield (Scheme 159). Most importantly, no purification was required.



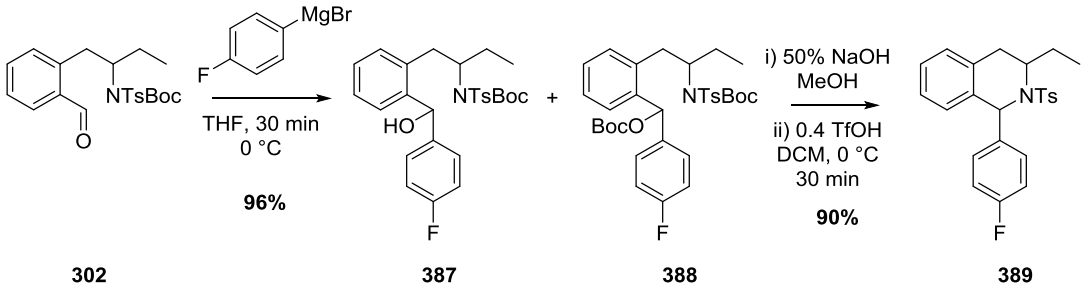
Scheme 159. Optimised Boc deprotection.

The cyclisation reaction of substrate **386** proceeded very fast and delivered the 1-aryl tetrahydroisoquinoline **385** in 90% yield (Scheme 160) as a predominantly single diastereoisomer.



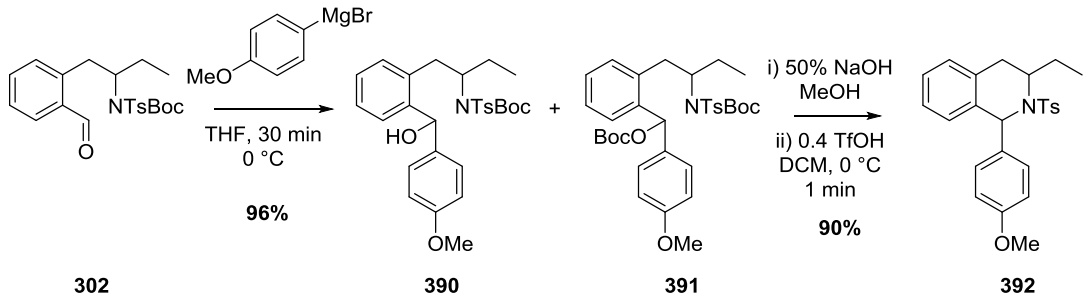
Scheme 160. Optimised benzhydryl cyclisation.

With the new, optimised conditions it was possible to synthesise several of the benzhydryl analogues and perform their cyclisation. Reaction of the aldehyde **302** with 4-fluorophenylmagnesium produced the mixture of Boc protected products **387** and **388** which were then converted to the fluorinated tetrahydroisoquinoline **389** in 90% yield over two steps (Scheme 161).



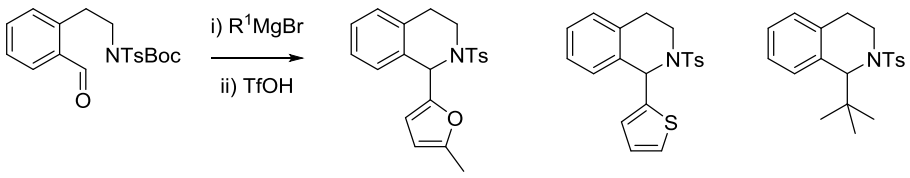
Scheme 161. Fluoroaryl benzhydryl cyclisation.

Similarly, reaction of the aldehyde **302** with 4-methoxyphenylmagnesium bromide gave compounds **390** and **391** as a mixture which was treated with sodium hydroxide and then triflic acid to provide the THIQ product **392** in an overall 86% yield over 3 steps (Scheme 162). Interestingly, the activating properties of the methoxy group allowed for the reaction to reach completion in one minute and gave the product as a single diastereoisomer.



Scheme 162. Synthesis and cyclisation of a methoxylated benzhydryl derivative.

The ultimate goal of this approach was to introduce a heterocyclic moiety in the 1-position to potentially synthesise a novel family of compounds and access a new, previously unexplored chemical space (Scheme 163). The reaction conditions used to achieve the hydroamination reaction are relatively mild and it is highly possible that moieties such as 2-methylfuran or thiophene would survive the transformation.



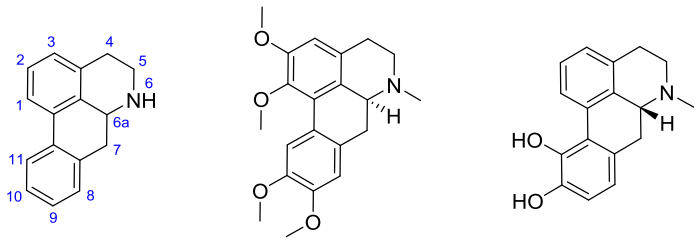
Scheme 163. Potential future work in the benzhydryl family.

In conclusion, a short synthesis of 1-aryl substituted tetrahydroisoquinoline alkaloids was devised. The starting material (aldehyde **302**) can be accessed in 3 steps from commercially available

acetals of 2-bromobenzaldehyde and 1-tosyl aziridines in a good yield. The condensation of the aldehyde with a Grignard reagent and subsequent removal of the Boc protecting group was optimised, as well as the final cyclisation to afford several 1-aryl tetrahydroisoquinoline alkaloids in very good yields.

3.7 Aporphine Skeleton

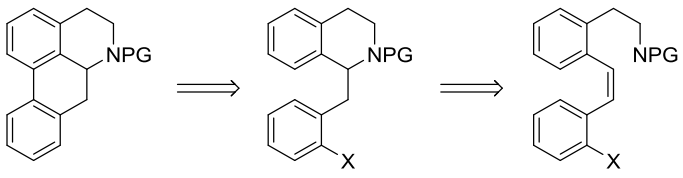
The aporphine nucleus consists of four 6-membered rings, including one nitrogen atom – as in **393**. They form a family of compounds which often possess divergent biological properties and exert anticolvunsant activity. Glaucine **394** is an aporphine alkaloid found in several species of *Papaveraceae* family[207] which displays antifungal and anti-inflammatory properties and is used as antitussive medicine in several countries.[208] It is also a psychoactive drug and can produce hallucinogenic effects. Nuciferine **395** is a pharmacologically active compound which acts by blocking dopamine receptors and can induce sedation, hypothermia and catalepsy.[209]



393 **394** **395**

Scheme 164. Aporphine alkaloids.

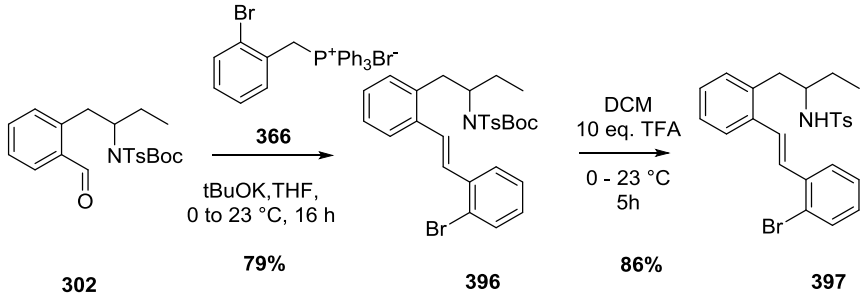
It was envisioned that the acid catalysed hydroamination methodology could be applied to build the tetrahydroisoquinoline part of an aporphine moiety. Cyclisation of substrate **398** would deliver the intermediate **397** which would then need to be ring-closed. Often, a Pschorr reaction, the intramolecular variant of the Gomberg-Bachman[210] reaction, or a radical tin-mediated coupling would be employed to connect such two rings to form a biaryl system; however, a literature search revealed that a palladium-mediated ortho-arylation[211] reaction should easily furnish the tetracyclic core of **396**. A simple retrosynthetic analysis is shown below (Scheme 165).



396 **397** **398**

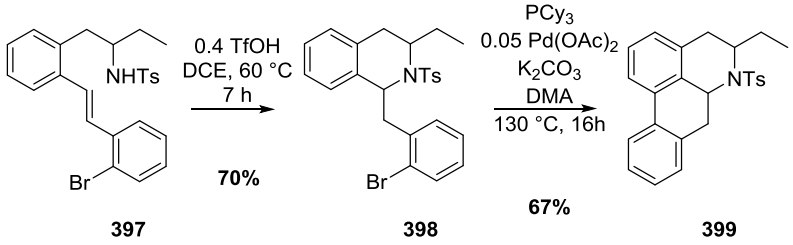
*Scheme 165. Retrosynthetic analysis of compound **396**.*

The synthesis started with preparation of the cyclisation substrate **397**, which was assembled in two steps *via* a Wittig reaction of aldehyde **302** to give alkene **396**, which was isolated in 79% yield. Subsequent deprotection of the Boc group with excess of trifluoroacetic acid delivered compound **397** in 86% yield.



*Scheme 166. Synthesis of cyclisation precursor **397**.*

The cyclisation reaction in presence of 0.4 equivalents of triflic acid in refluxing dichloroethane proceeded smoothly and tetrahydroisoquinoline **398** was obtained in 70% yield as a 9:1 mixture of isomers. Ortho-arylation with palladium acetate in dimethylacetamide gave compound **399** in 67% yield (Scheme 167). The yield of the final step could most likely be improved, since a large amount of literature covering the topic of inter- and intramolecular arylations is published every year.



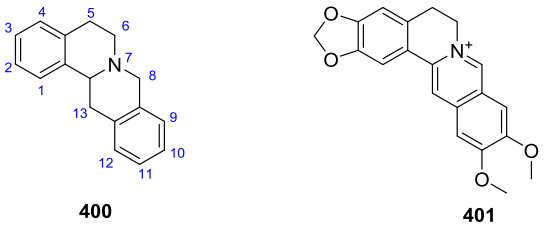
*Scheme 167. Synthesis of cyclisation precursor **397**.*

In conclusion, the previously synthesized aldehyde intermediate **302** was transformed into the aporphine derivative **399** in four steps. Yields for each transformation were over 65% and the final product **399** was synthesized in 32% yield, starting from **302**.

3.8 Berberinone and Berberine Alkaloids

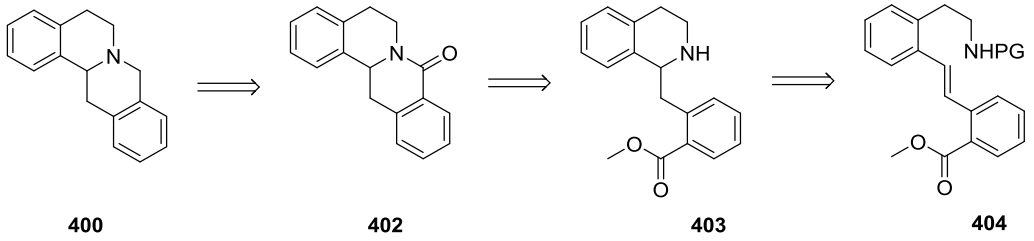
Another fused, heterocyclic ring system which was synthesized *via* the Knight's hydroamination methodology was berberine core **400**. The actual berberine alkaloid **401** (Scheme 168), which belongs to the protoberberine alkaloids family and is also known as umbellatine, can be found in the roots, stems and bark of several families of plants, *e.g. berberis*, *Coptis chinensis* or *Phellodendron amurense*. Berberine

is a dietary supplement available without prescription and has been used as traditional medicine in China. Pharmacologically, it was shown to exhibit a wide range of various activies such as antifungal[212] and anti-inflammatory[213], antitumour[214] and anticancer.[215] Berberine has also been shown to reduce elevated blood glucose[216] and has been successfully applied in the treatment of type 2 diabetes[217] and dyslepidemia.



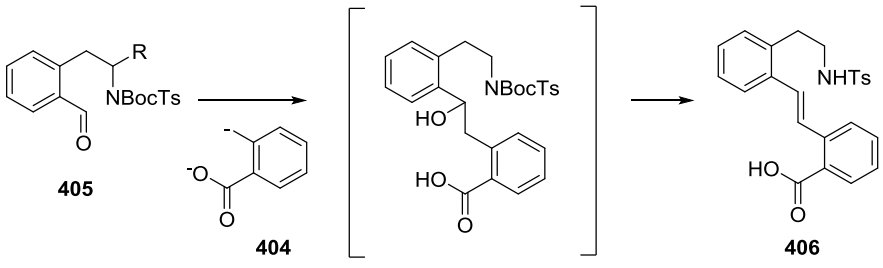
Scheme 168. Berberine core and barberine alkaloid.

It was thought that the berberine skeleton could be synthetically accessed *via* the reduction of berberinones **402**, which could be in turn made from tetrahydroisoquinolylbenzoate esters **403**. It was previously shown that remote esters survive the cyclisation conditions and thus exposing compounds such as **404** to triflic acid should result in formation of the tetrahydroisoquinoline heterocyclic system.



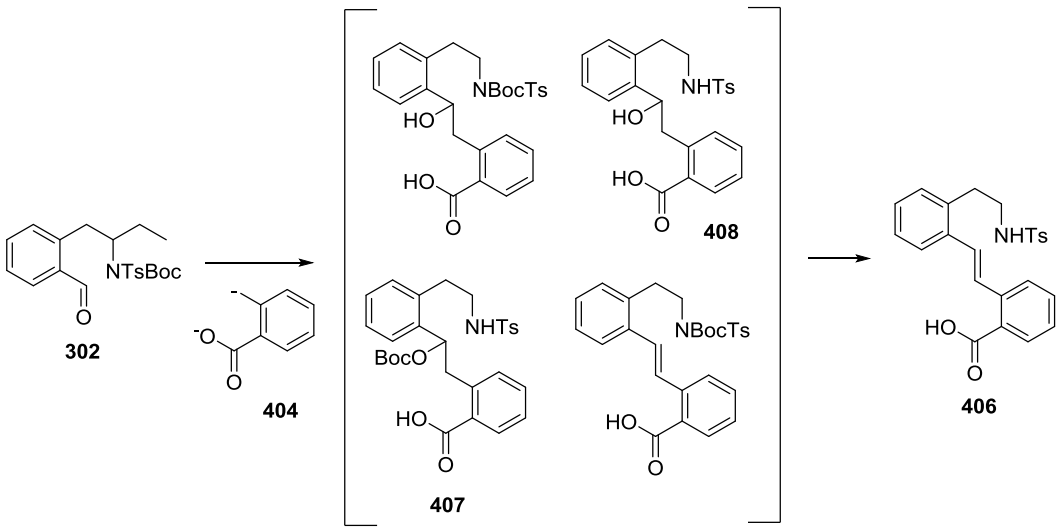
*Scheme 169. Synthesis of cyclisation precursor **397**.*

Closer examination of the synthetic routes to intermediate **403** (Scheme 170) revealed that a possible condensation of a dianion of *o*-toluic acid **404** with aldehyde intermediates **405**, followed by dehydration and deprotection would deliver the required cyclisation substrates **406**



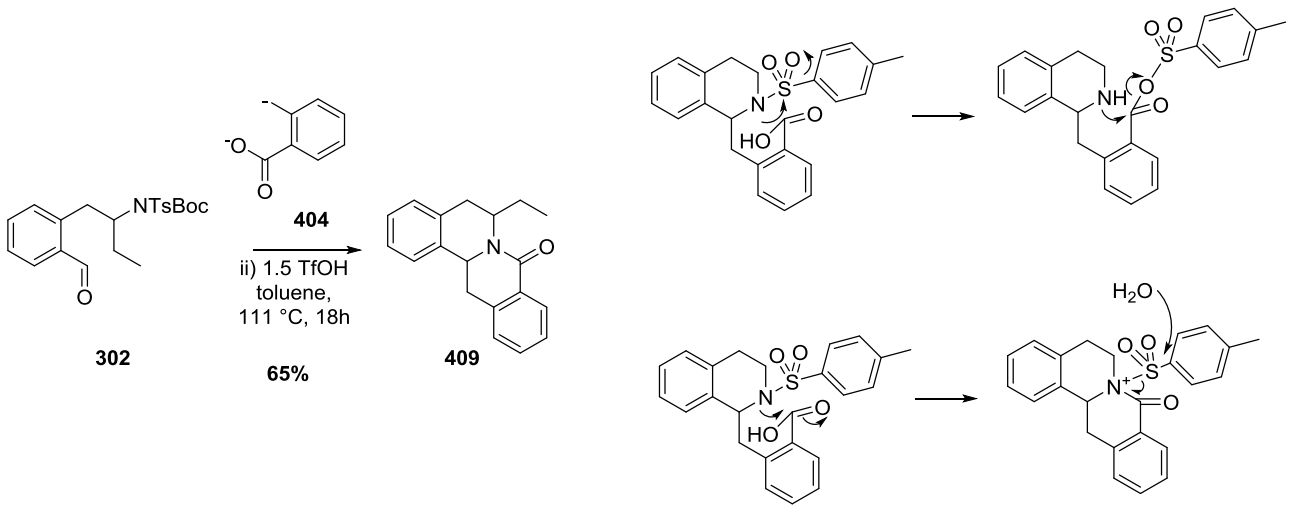
*Scheme 170. Synthesis of cyclisation precursor **397**.*

The condensation reaction was found to be self-titrating and relatively easy to perform. Excess of the deep-red dianion **404** would be prepared and then transferred *via* a cannula to a solution of aldehyde **302** until the red colour persisted.



Scheme 171. Condensation reaction.

Careful analysis of the crude mixture revealed that the condensation reaction proceeded very well but several different species were formed during the reaction (Scheme 171). The migration of the Boc group, previously reported in the benzhydryl series, was observed, as well as complete deprotection of the Boc group – most likely due to excess dianion **404** reacting with the carbonyl moiety of the carbamate group. Some dehydrated, alkene product could also be detected. Attempts to fully dehydrate and deprotect all compounds from the crude mixture to afford the final product **406** failed and only resulted in isolation of compounds **407** and **408**. Further optimisation revealed that the most effective way to access the target berberinone **409** involved exposing the entire crude mixture from the condensation reaction to 1.5 equivalents of triflic acid in refluxing toluene over 16-24 hours. This resulted not only in a global dehydration and Boc-deprotection, but also in a loss of the tosyl group during the cyclisation. Two possible mechanisms involving an intramolecular tosyl group loss and lactamisation followed by hydrolysis of tosyl group are shown below (Scheme 172). This treatment delivered the tetracyclic lactam **409** in 65% yield. The final product was obtained as a 4:1 mixture of diastereoisomers, however, a single recrystallization afforded exclusively the major, *cis*-isomer in an overall 45% yield.



Scheme 172. Two-step synthesis of a berberine moiety and two tentative mechanisms for loss of tosyl group.

An X-Ray crystal structure was obtained for the compound and ultimately proved that the thermodynamic product of the acid-catalysed hydroaminations is the 1,3-*cis* diastereoisomer. The hydrogen atom on the bridge is pointing in the opposite direction to the ethyl substituent on the carbon next to the nitrogen.

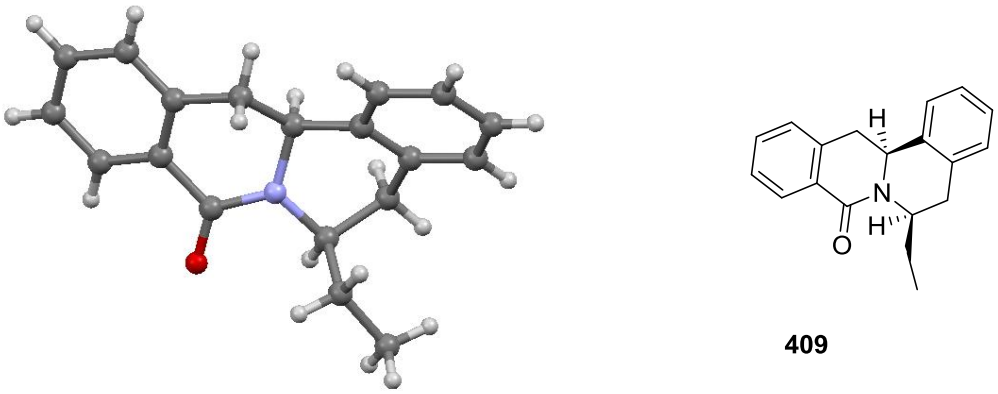
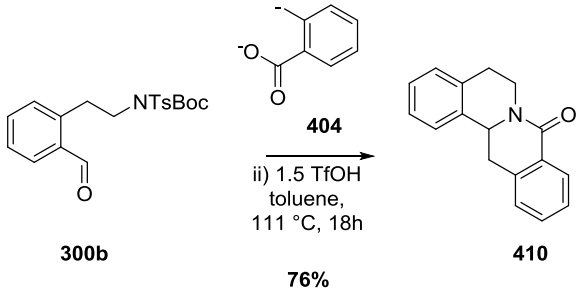


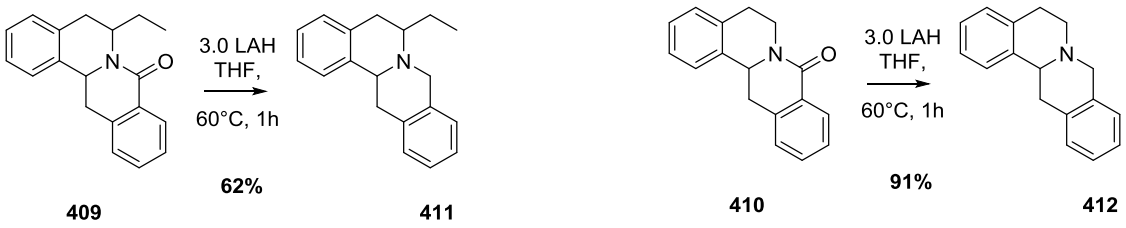
*Figure 20. X-Ray structure of berberinone **409**.*

An identical reaction sequence was applied to aldehyde **300b**. Condensation of **300b** with the dianion of *o*-toluic acid and subsequent treatment of the crude reaction mixture with triflic acid in refluxing toluene delivered the analogous berberinone **410** in a two process in 76% yield (Scheme 173).



*Scheme 173. Synthesis of berberinone **410**.*

The ultimate goal of the synthetic sequence was to reduce the berberinones to the corresponding berberines. This step is already known in the literature and the transformation was easily achieved using lithium aluminium hydride in refluxing tetrahydrofuran over 1 hour. The unsubstituted product **412** was obtained in 91% yield and the ethyl-substituted compound **411** was synthesized in 62% yield.



*Scheme 174. Reduction of berberinones **409** and **410** to berberines **411** and **412**.*

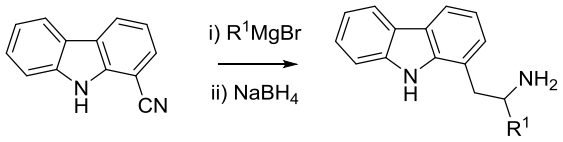
3.9 Conclusions

A modified protocol of Knight's hydroamination was successfully applied in the synthesis of a number of electron-rich, polymethoxylated THIQ alkaloids, analogues of which can often be found in nature. Efficacious hydroamination of a cyclisation substrate containing a terminal, monosubstituted double bond ultimately led to a short, formal synthesis of racemic salsolidine. A successful acid-catalyzed hydroamination carried out in presence of a free alcohol and, also, on a substrate with an acetate-protected OH group allowed accessing a synthetic intermediate which could potentially lead to synthesis of racemic crispine-A. A hydroamination of an *ortho*-bromo substituted derivative followed by an *ortho* arylation reaction opened up a synthetic pathway to a tetracyclic aporphine skeleton. Finally, a novel, double cyclisation involving a hydroamination step and a lactam formation from a tertiary, *N*-tosyl substituted nitrogen atom opened up an interesting synthetic pathway towards the berberinone alkaloids and eventually delivered berberines. These efforts ultimately proved that triflic acid catalysed, intramolecular *6-exo*-trig hydroamination of alkenes with activated amines is a powerful protocol that has been effectively used to access a variety of sterically hindered *N*-heterocyclic compounds.

Chapter 4: Challanges and Future Work

4.1 Addition to Grignard reagents

A large amount of time was dedicated to successfully perform an addition of a Grignard reagent to a homobenzylic nitrile[218], potentially yielding the corresponding substituted imine, which in turn could be reduced in a one pot-manner and would provide a quick access to the substituted phenylethylamines. The idea was based on a number of similar experiments previously reported in the literature (Scheme 175).[219]

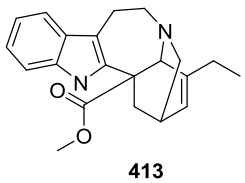


Scheme 175. Condensations of nitriles with Grignard reagents.

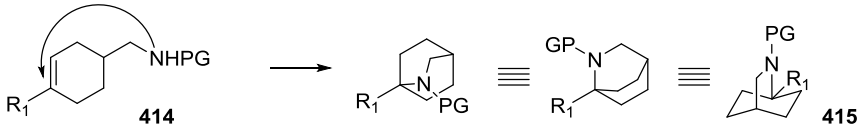
Unfortunately, none of the reactions performed delivered any of the desired products and only complex reaction mixtures or starting material could be recovered. Addition of copper,[220] changing the solvent or increasing the temperature had no positive effect on the reaction and no product could be observed at any point in any of the crude reaction mixtures. After extensive experimentation the nitrile route was abandoned. Interestingly, in case of the 2-iodobenzonitrile experiments, magnesium-halogen exchange was observed and the de-iodinated product was exclusively obtained in the reaction (Scheme).

4.2 Isoquinuclidines

Isoquinuclidines form a family of pharmacologically active compounds and are also valuable synthetic intermediates in the synthesis of alkaloids and various pharmaceutical products. A good example is catharantine **413**, which is a precursor in the biological and laboratory synthesis of vinblastine. Recently, the topic of trans-annular cyclisations (Scheme 180) of cyclohexene derivatives such as **414** is being revisited in the Knight group to access compounds such as **415**.

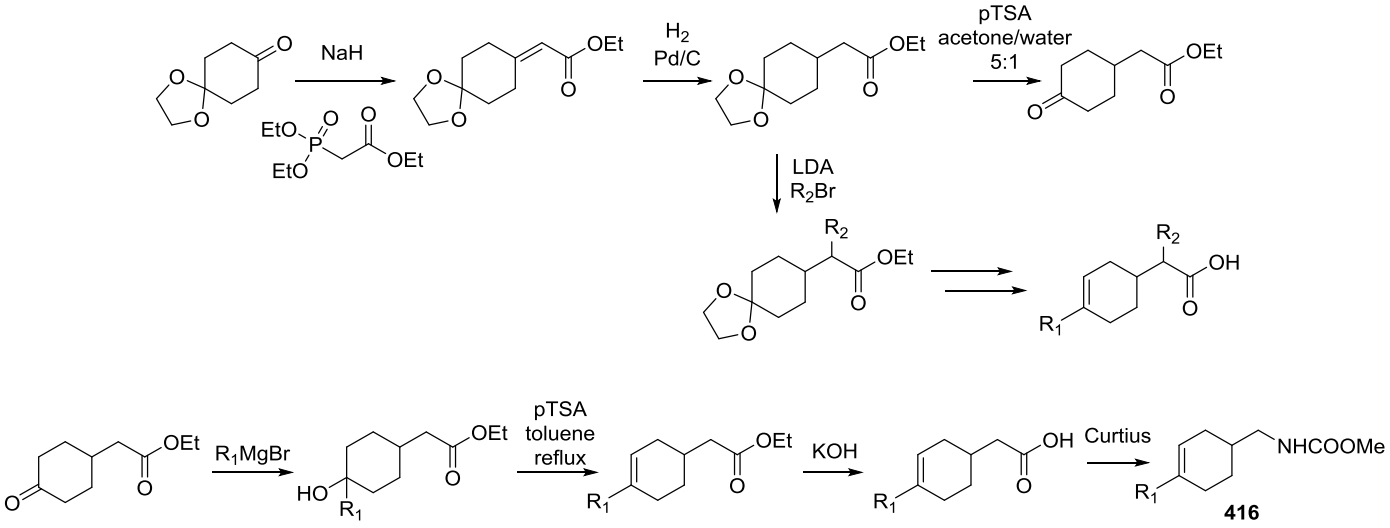


413



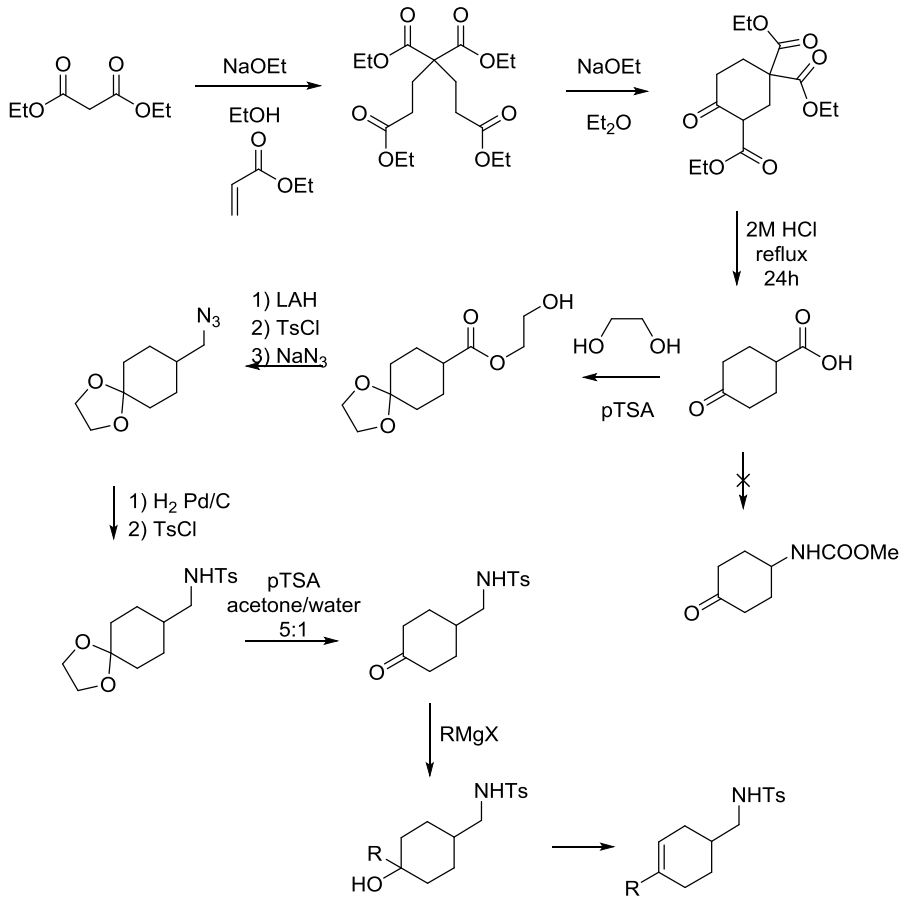
Scheme 180. Trans-annular cyclisations.

A lot of effort was dedicated towards developing a quick synthesis of cyclisation substrates to be able to quickly probe if the trans-annular cyclisations of these substrates would deliver the bicyclic products. The structure of these compounds looks relatively simple, as the basic skeleton is based on a cyclohexene ring and a single ethylamino- substituent. The synthesis of such compounds, however, is not trivial and often involves Birch reduction-type processes or long sequences of transformations (Scheme 181). The first route to the substrate **416** consisted of 7 steps and involved a Wittig reaction followed by hydrogenation, deprotection of the acetal group, condensation with a Grignard reagent, dehydration, hydrolysis and a Curtius rearrangement.



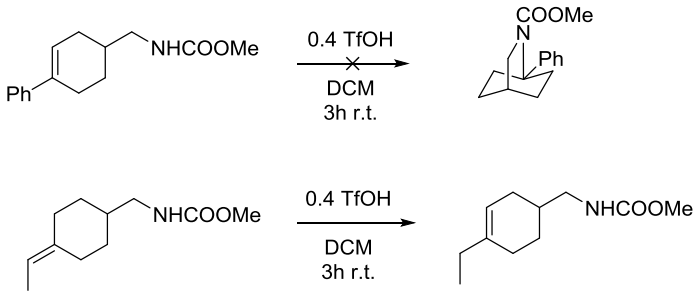
Scheme 181. Preparative chemistry: route 1.

The second route (Scheme 182), which was being developed parallel to the first one, was based on a double Michael addition of ethylacetoacetate to ethyl acrylate, a Dieckman cyclisation, decarboxylation, double protection of the acetal and ester, ester reduction, tosylation and azide displacement, hydrogenation to primary amine, protection with a tosyl group, acetal deprotection and then condensation followed by dehydration of the alcohol. That was approximately 10 synthetic steps.



Scheme 182.Preparative chemistry: route 2.

At this stage we have discovered that the synthesized compounds are very stable and indeed very resistant to the cyclisation (Scheme 183). Even under the most forcing conditions *i.e.* refluxing 1,2-dichloroethane or refluxing toluene with catalytic or excess quantities of triflic acid delivered no cyclised product whatsoever. No cyclisation and no decomposition was observed - only the starting material was recovered.



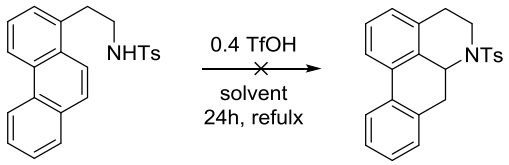
.

Scheme 183.Trans-annular cyclisation attempt.

This was very disappointing, as the Knight group had plenty of success[221] in the synthesis and hydroaminations of very similar molecules in the past.

4.3 Phenanthrenes

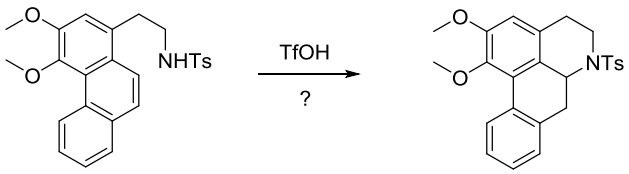
An alternative way which could lead to the tetracyclic hydroamination products was also examined by the Knight group. It was thought that cyclisation of phenanthrylethylamine compounds could deliver the aporphine alkaloids (Scheme 184). The synthesis of the cyclisation precursor was relatively straightforward and involved a ring-opening of an aziridine with a Grignard reagent derived form 2-bromophenanthrene.



Scheme 184.Phenanthrylethylamines - cyclisation attempt.

Unfortunately, no product could be obtained in the cyclisation, even under very harsh reaction conditions. Only starting material could be recovered after prolongued refluxing in dichloromethane or dichloroethane. A long reaction in toluene with excess triflic acid yielded only impurities which were later disovered to be Friedel-Crafts adducts from a reaction of the starting material with the solvent.

It was thought that the idea of obtaining an aporphine ring in a hydroamination reaction could be realized on a more reactive, methoxy-substituted substrate.



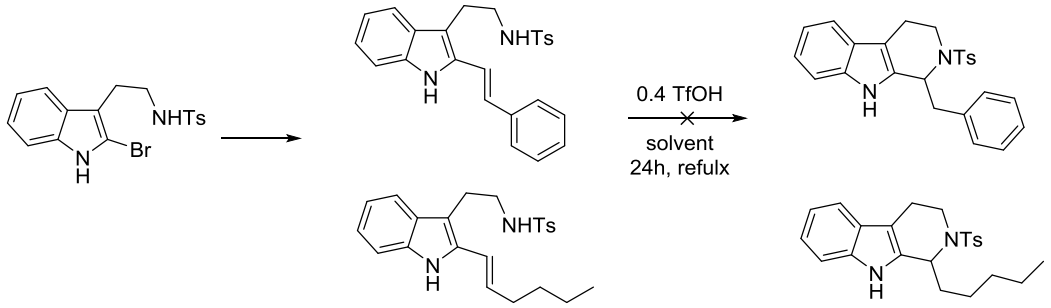
Scheme 184.Phenanthrylethylamines – alternative substrates.

Due to time constrictions, this was never attempted in the laboratory.

4.4 Indoles

An attempt was also made to extend the Knight's hydroamination chemistry to the synthesis of carbolines, as it was also the case with the classic Pictet-Spengler reaction. The starting material was

quickly accessed by tosylation and bromination of tryptamine, followed by a Suzuki reaction (Scheme 185).



Scheme 185.Indoles - cyclisation attempt.

Even though a full disappearance of starting material was observed during the hydroamination attempts, no product could be isolated. HPLC analysis of the crude reaction mixture revealed that the material formed during the reaction is extremely greasy and non-polar and most likely is a dimeric or polymeric derivative of the starting material. Further attempts to synthesise the product using molecular iodine or sulfuric acid also failed and this area of research was abandoned.

It is possible that the free N-H bond of the indole is responsible for much higher reactivity of the system and hence the inability of the hydroamination reaction to proceed. Protection of the nitrogen group with an electron withdrawing group, such as sulfonamides, could potentially lead to a successful cyclisation outcome. This was, however, never attempted in the laboratory.

4.5 Conclusions

Countless nitrogen-containing compounds are being synthesized every day by different academic groups, research institutions and industrial companies. New, more atom-efficient, greener and superior reaction protocols for synthesis of *N*-heterocycles are being developed. The area of intramolecular and intermolecular hydroamination, due to its atom-efficiency, is very popular and there is much more needed to be done in this particular field of research. Expanding the Knight's hydroamination to more advanced azasteroids, application in the synthesis of *spiro*-derivatives and accessing more advanced natural product are of high interest. More detailed investigation of the reaction mechanism, deuterium labelling studies and stereochemical outcome of the reaction would also be very interesting. Performing the reaction on more electron-poor cyclisation substrates and exposing analogues with fragile functional groups to the reaction conditions would expand the scope of the reaction.

In general, the novel hydroamination methodology could provide new synthetic pathways to a range of heterycyclic systems in the pharmaceutical sector. Overall, this chemistry is very useful in

synthesis of sterically hindered, cyclic amines, which can sometimes be difficult to prepare. There are, arguably, too many different themes and potential research areas within the topic to try and cover them all, which also demonstrates the potential synthetic utility of this transformation.

Chapter 5: Experimental

5.1 General Remarks

Reagents were obtained from Aldrich, Alfa Aesar, Lancaster, Across, Fluka, Rieke, and Fluorochem chemical companies and used as received unless otherwise stated. Solvents and reagents were purified according to the procedures of Armarego and Perrin.[222] Dichloromethane was dried by distilling over calcium hydride under a nitrogen atmosphere. Anhydrous tetrahydrofuran was obtained by refluxing over sodium with benzophenone as indicator, followed by distillation or from Sigma-Aldrich (99.9%, anhydrous) and titrated on a Karl Fischer still for water content below 0.05%. "Petrol" and "petroleum ether" refer to petroleum ether, b.p. 40-60 °C. All aqueous solutions were saturated unless otherwise stated. "Dried" refers to the addition of dried magnesium sulfate or sodium sulfate to remove trace amounts of water. "Filtered" refers to the removal of solid residues by gravity filtration of organic solutions through filter paper. "Evaporated" refers to the distillation of volatiles using a Büchi rotary evaporator attached to a 20 L Charles Austen pump operating at approx 15 mbar, heated with a water bath typically between 20 and 40 °C. "Degassed" refers to bubbling N_2 through the solvent for a minimum of 30 minutes. All reactions using air/moisture sensitive reagents were performed in oven-dried apparatus, under a nitrogen atmosphere. Solid carbon dioxide and an acetone bath (-78 °C), methanol-ice bath (-20 - -15 °C) and an ice-water bath (0 - 5 °C) were used to obtain low temperatures. Heated reactions were conducted in a stirred oil bath heated on a magnetically stirred hotplate. All reactions were followed and monitored by HPLC, TLC, ^{1}H NMR, ^{13}C NMR and mass spectrometry as appropriate. TLC analysis refers to analytical thin layer chromatography, using aluminium-backed plates coated with Merck Kieselgel 60 GF254. Product spots were viewed under 254/365 nm UV lamp, by developing in a 2% aqueous potassium permanganate solution or 5% solution of phosphomolybdic acid in ethanol. Column chromatography refers to flash column chromatography using head pressure by means of compressed air according to the procedure of Still,[223] and using Merck Kieselgel 60 H silica or Matrix silica 60. Melting points were recorded using a Kofler Heated Stage Micro Melting Point Apparatus and are uncorrected. Infra-red spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1600 series Fourier Transform Infrared Spectrometer, as liquid films between sodium chloride plates [film], unless otherwise stated, in which case samples were run as a solution in dichloromethane [DCM] between sodium chloride plates. All absorptions are quoted in wave numbers (cm^{-1}). Proton (^{1}H) NMR spectra were recorded using an Avance Bruker DPX 500 (500 MHz) instrument, with carbon (^{13}C) NMR spectra recorded at 126 MHz unless otherwise stated, in which case ^{1}H NMR spectra were recorded using an Avance Bruker DPX 400 instrument (400 MHz) with carbon (^{13}C) NMR spectra recorded at 101 MHz or an Avance Bruker DPX 250 instrument (250 MHz). Spectra were obtained as dilute solutions in deuterated chloroform, unless otherwise stated, in which case spectra were obtained in dilute solutions of fully deuterated methanol (CD_3OD). The chemical shifts were recorded relative to residual chloroform (7.26 ppm or 77.16 ppm) as an internal standard unless otherwise stated, in which case spectra were obtained in fully deuterated dimethyl sulfoxide (DMSO-d^6). Abbreviations used for the multiplicities are s (singlet), d (doublet), t

(triplet), q (quartet), bs (broad singlet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), quin (quintet), sext (sextet), sept (septet), m (unresolved multiplet), app. (apparent) or as a combination of these multiplicities. All coupling constants (*J*) are recorded in Hertz (Hz), are quoted as seen and are not adjusted. Assignments were made on the basis of chemical shift and coupling constant data using DEPT-90, DEPT-135, COSY, NOESY, HSQC and HMBC experiments where required. Mass spectrometric data were determined using a Waters GCT Premier instrument using electron ionisation (EI) unless otherwise stated, in which case such data were determined by a Waters LCT Premier XE instrument (LRMS) using atmospheric pressure chemical ionisation (APCI) or electrospray ionisation (ES). High resolution mass spectrometric data were determined with the molecular formula corresponding to the observed signal using the most abundant isotopes of each element. A literature reference associated with title of compound means it is not a novel compound and any data recorded in this thesis matches well with those reported in the associated references, unless otherwise stated.

5.2 General Procedures

General Procedure A1: Wittig Reaction with t-BuOK[224]

To a suspension of a triphenylphosphonium salt (1.0 – 2.5 eq.) in tetrahydrofuran (10 mL per 1 g phosphonium salt) at 0 °C was added solid potassium *tert*-butoxide (1.1 – 2.7 eq., 1.1 eq. of phosphine salt) portionwise, over five minutes. The reaction mixture was stirred for a further 0.5 h at 0 °C after which the aldehyde (1.0 eq.) was added as a solution in tetrahydrofuran (5 mL per 1 g aldehyde) dropwise, over 1-5 minutes. The cooling bath was removed and the mixture allowed to warm to room temperature overnight (~16 h). The reaction was quenched by addition of aqueous ammonium chloride (1 volume) and the separated aqueous layer extracted with ethyl acetate or diethyl ether (3 x 1 volume). The combined organic extracts were washed with brine, dried, filtered and evaporated.

General Procedure A2: Wittig Reaction with n-BuLi

To a suspension of a triphenylphosphonium salt (1.0 – 2.5 eq.) in tetrahydrofuran (10 mL per 1 g phosphonium salt) at -78 °C was added n-butyllithium (1.6 – 2.5 M in hexanes, 1.1 – 2.7 eq., 1.1 eq. of phosphine salt) dropwise, over five minutes. The reaction mixture was stirred for a further 0.5 h at -78 °C after which the aldehyde (1.0 eq.) was added as a solution in tetrahydrofuran (5 mL per 1 g aldehyde) dropwise, over 5 – 10 minutes. The cooling bath was removed and the mixture allowed to warm to room temperature overnight (~16 h). The reaction was quenched by addition of aqueous ammonium chloride (1 volume) and the separated aqueous layer extracted with ethyl acetate or diethyl ether (3 x 1 volume). The combined organic extracts were washed with brine, dried, filtered and evaporated.

General Procedure B: Sulfonamide Protection of an Amine

The amine (1.0 eq.) was dissolved in dry dichloromethane (1 mL per 1 mmol) and the solution cooled to 0 °C. Triethylamine (1.1 eq.) was added, followed by 4-(dimethylamino)pyridine (a few crystals, 1-2 mg) and methanesulfonyl chloride, *p*-nitrobenzenesulfonyl chlroride or *p*-toluenesulfonyl chloride (1.05 eq.). The cooling bath was removed and the reaction was allowed to warm to room temperature overnight (~16 h). The reaction mixture was then washed with water (1 volume), aqueous hydrochloric acid (2M, 1 volume) and aqueous sodium bicarbonate (1 volume), then dried, filtered and evaporated.

General Procedure C: Boc Protection of Sulfonamide

The sulfonamide (1.0 eq.) was dissolved in dry dichloromethane (1 mL per 1 mmol) at room temperature. Dimethylaminopyridine (0.3 eq.) and di-*tert*-butyl dicarbonate (1.2 eq.) were then added and the reaction mixture was allowed to stir at ambient temperature for 3 – 6 h. The reaction was quenched by addition of water and stirred vigorously for 0.5 h. The separated organic phase was then washed with water (2 x 1 volume), aqueous sodium bicarbonate (1 volume) and brine (1 volume), then dried, filtered and evaporated.

General Procedure D: Suzuki Reaction

The aryl bromide or iodide (1.0 eq.), a vinylboronic acid or vinylboronic pinacol ester (1.1-1.5 eq.), [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.01 – 0.1 eq.), potassium phosphate (2.0 – 3.0 eq.) were added sequentially to a degassed 1:1 water/ethanol solution (1ml per 100 mg aryl bromide/iodide) under an atmosphere of nitrogen and degassed for further 10 minutes. The mixture was then heated (40-100 °C) and stirred for the desired amount of time (1-12 h). Upon completion, the mixture was allowed to cool to ambient temperature and partitioned between dichloromethane (1 volume) and water (1 volume). The separated aqueous phase was extracted with dichloromethane (3 x 1 volumes) and the combined organic extracts washed with brine (1 volume), dried, filtered and evaporated.

General Procedure E: Preparation of LDA

To a stirred solution of diisopropylamine (1.0 eq.) in tetrahydrofuran (1 mL per 0.5 mL diisopropylamine) at -78 °C was added a solution of n-butyllithium (1.1 eq.). The mixture was kept at -78° C for 15 minutes and then at 0 °C for a further 15 minutes.

General Procedure F: Modified Kabalka's Nitroalkene Reduction

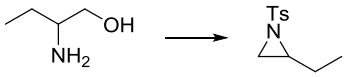
Monitoring of the internal reaction temperature is recommended if this reaction is carried out on large scale. To the suspension of sodium borohydride (4.75 eq) in tetrahydrofuran (10 mL per 10 mmol $NaBH_4$) under an atmosphere of nitrogen at 0 °C was added boron trifluoride diethyl etherate (6 eq.) dropwise, over several minutes (caution: exothermic!). The ice-bath was then removed and the reaction was stirred for 15 minutes. The nitroalkene (1 eq.) was then added as a solution in tetrahydrofuran (5 mL per 2 mmol nitroalkene) and the resulting mixture heated to reflux for 6 h. After cooling to room temperature, the reaction was quenched by slow (caution: exothermic!) addition of cold water (25 mL per 10 mmol nitroalkene), then acidified with hydrochloric acid (2M, 25 mL per 10 mmol of nitroalkene), heated to reflux for a further hour and allowed to cool to ambient temperature. The resulting aqueous solution was washed with diethyl ether (3 x 25 mL per 10 mmol nitroalkene) and then basified using aqueous sodium hydroxide (pH 14) and extracted with chloroform (3 x 25 mL per 10 mmol nitroalkene). The combined chloroform extracts were washed once with brine (1 volume), dried, filtered and evaporated.

General Procedure G: Fieser lithium aluminium hydride reduction work-up[225]

The reaction mixture was cooled to 0 °C and vigorous stirring applied. Carefully (caution: exothermic!), water (1 mL per 1 g LAH) was added dropwise, followed by 15% sodium hydroxide solution (1 mL per 1 g LAH) and again water (3 mL per 1 g LAH). The granular, inorganic precipitate was then filtered off on a Buchner funnel and the filter cake washed with diethyl ether. The resulting filtrate was then dried, filtered and evaporated.

5.3 Experimental Data

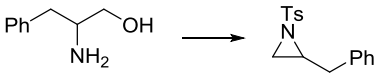
2-Ethyl-1-tosylaziridine[226] 154



155 154

2-Amino-1-butanol **155** (1.5 g, 16.83 mmol, 1.0 eq.) was dissolved in dichloromethane (20 mL) and the solution cooled to 0 °C. Triethylamine (5.11 g, 50.05 mmol, 3.0 eq.) was added, followed by DMAP (a few crystals, 1-2 mg) and *p*-toluenesulfonyl chloride (8.02 g, 42.08 mmol, 2.5 eq.). The cooling bath was removed and the reaction was allowed to warm to ambient temperature overnight (~16 h), and then washed with water (25 mL), HCl (2M, 25 mL) and aqueous sodium bicarbonate (25 mL), then dried, filtered and evaporated. The crude material was purified by column chromatography (ethyl acetate/petrol 1:5) to give the *aziridine* **154** (1.82g, 48%) as a colourless oil; δ_H (400 MHz) 7.82 (2H, d, *J* 8.3, 2 x ArH), 7.33 (2H, d, *J* 8.0, 2 x ArH), 2.69 (1H, m, CHN), 2.62 (1H, app. d, *J* 7.0, $CH_{2a}N$), 2.44 (1H, s, $ArCH_3$), 2.07 (1H, app. d, *J* 4.6, $CH_{2b}N$), 1.65 – 1.54 (1H, m, $C\underline{H}_{2a}CH_3$), 1.41 – 1.28 (1H, m, $C\underline{H}_{2b}CH_3$), 0.83 (1H, t, *J* 7.4, $CH_2C\underline{H}_3$); LRMS (EI^+) m/z 225 ($[M]^+$, 5%), 155 ($[Ts]^+$ 45%), 70 ($[M\text{-}Ts]^+$ 100%); HRMS (APCI) calculated for $C_{11}H_{16}NO_2S$ $[M+H]^+$ 226.0902, found 226.0891.

2-Benzyl-1-tosylaziridine[227] 163

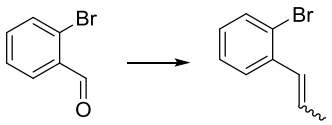


162 163

2-Amino-3-phenylpropan-1-ol (2.0 g, 13.23 mmol, 1.0 eq.) was dissolved in acetonitrile (40 mL) and the solution cooled to 0 °C. Triethylamine (4.02 g, 39.69 mmol, 3.0 eq.) was added, followed by dimethylaminopyridine (150 mg) and *p*-toluenesulfonyl chloride (6.30 g, 33.07 mmol, 2.5 eq.). Cooling bath was removed and the reaction was allowed to warm to room temperature overnight (~16 h). The reaction was then concentrated under reduced pressure and partitioned between ethyl acetate (40 mL) and ammonium chloride (30 mL). The organic phase was then washed with water (25 mL), 2M HCl (25 mL) and sodium bicarbonate (25 mL), then dried, filtered and evaporated. The crude material was purified by recrystallization from ethanol to give the *aziridine* **163** as a white solid (2.12g, 56%); m.p. 90 - 93 °C (lit. m.p.[227] 94-95 °C); δ_H 7.71 (2H, d, *J* 8.3, 2 x ArH), 7.24 (2H, d, *J* 8.4, 2 x ArH), 7.21 – 7.18 (3H, m, 3 x ArH), 7.18 (1H, d, *J* 1.8, ArH), 7.08 (1H, d, *J* 2.0, ArH), 7.07 - 7.05 (1H, m, ArH), 2.99 – 2.97 (1H, m, NCH), 2.83 (1H, dd, *J* 14.9 and 5.2, NCH_{2a}), 2.72 (2H, dd, *J* 15.2 and 7.0, NCH_{2b}), 2.72 - 2.71 (1H, m,

$ArCH_{2b}$), 2.45 (3H, s, $ArCH_3$), 2.18 (1H, d, *J* 4.5, $ArCH_{2b}$); δ_C 144.4 (C), 137.15 (C), 135.1 (C), 129.7 (2 x ArCH), 128.9 (2 x ArCH), 128.6 (2 x ArCH), 128.0 (2 x ArCH), 126.65 (ArCH), 41.3 (NCH), 37.65 (NCH_2), 33.0 ($ArCH_2$), 21.7 ($ArCH_3$).

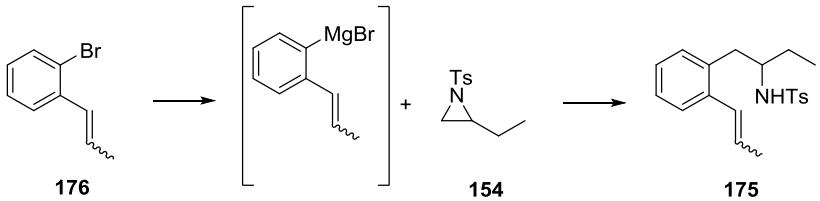
(*E/Z*)-1-Bromo-2-(prop-1-en-1-yl)benzene[228, 229] 176



136 176

Ethyltriphenylphosphonium bromide (2.74 g, 7.39 mmol) was treated with potassium *tert*-butoxide (1.02 g, 9.06 mmol) and 2-bromobenzaldehyde **136** (1.24 g, 6.72 mmol) according to general procedure A1. The crude material was purified by column chromatography to yield *alkene* **176** (1.16 g, 88%) as a a pale yellow oil and as a 4:3 mixture of *Z* and *E* isomers; *major (Z)-isomer* δ_H 7.59 (1H, d, *J* = 8.0 Hz, ArH), 7.32-7.28 (2H, m, ArH), 7.10 (1H, m, ArH), 6.49 (1H, d, *J* 11.4, ArC<u>H</u>=CH), 5.90 (1H, dq, *J* 11.6 and 7.1, ArCH=C<u>H</u>), 1.79 (3H, dd, *J* 7.1 and 1.7,CH_3); *minor (E)-isomer* δ_H 7.53 (1H, d, *J* 8.0, ArH), 7.48 (1H, d, *J* 7.8, ArH), 7.24 (2H, m, ArH), 7.04 (1H, m, ArH), 6.74 (1H, d, *J* 15.6, ArC<u>H</u>=CH), 6.19 (1H, dq, *J* 15.5 and 6.7, ArCH=C<u>H</u>), 1.94 (3H, dd, *J* 6.6 and 1.6, CH_3).

(*E/Z*)-4-Methyl-*N*-(1-(2-(prop-1-en-1-yl)phenyl)butan-2-yl)benzenesulfonamide 175

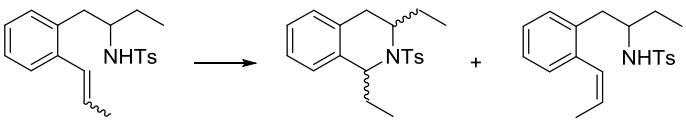


176 154 175

Magnesium turnings (95 mg, 3.91 mmol, 2.2 eq.) were dry-stirred under an atmosphere of nitrogen for 24 hours and then suspended in tetrahydrofuran (5 mL). The suspension was treated with a crystal of iodine and 1-bromo-2-(prop-1-en-1-yl)benzene **176** (700 mg, 3.56 mmol, 2.0 eq.) was added as a solution in tetrahydrofuran (3 mL). The reaction was stirred for a further 30 minutes, during which time decolourisation and disappearance of most of the magnesium turnings was observed. The solution was then cooled to -40 °C and copper (I) iodide (102 mg, 0.533 mmol, 0.3 eq.) was added. After a further 30 minutes the reaction mixture was cooled to -78 °C and 2-ethyl-1-tosylaziridine **154** (400 mg, 1.78 mmol, 1.0 eq.) in tetrahydrofuran (2 mL) was added. After 15 minutes, the reaction mixture was warmed to 0 °C and stirred for another 1.25 h, then quenched by aqueous ammonium chloride (10 mL) and the blue aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with

brine (10 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (dichloromethane/petrol, 1:1) to give *sulfonamide* **175** (751 mg, 71%) as colourless glass and as a 3.1:1 mixture of *Z* and *E* isomers; ν_{max} 3282 (br, NH); *major* (*Z*)*-isomer* δ_H (400 MHz) 7.58 (2H, d, *J* 8.2, 2 x ArH), 7.19 - 7.12 (3H, m, 3 x ArH), 7.09 (2H, d, *J* 7.1, 2 x ArH), 7.00 - 6.98 (1H, m, ArH), 6.35 (1H, d, *J* 11.4, ArC<u>H</u>=CH), 5.80 (1H, dq, *J* 11.5 and 7.0, ArCH=C<u>H</u>), 4.56 (1H, d, *J* 7.6, NH), 3.32 - 3.29 (1H, m, NCH), 2.69 (1H, dd, *J* 13.5 and 7.5, $ArCH_{2a}$), 2.63 (1H, dd, *J* 13.5 and 7.3, $ArCH_{2b}$), 2.39 (3H, s, $ArCH_3$), 1.64 (3H, dd, *J* 7.0 and 1.7, CH=CHC<u>H</u>$_3$), 1.55 - 1.46 (1H, m, $CH_3C\underline{H}_{2a}$), 1.45 – 1.33 (1H, m, $CH_3C\underline{H}_{2b}$), 0.81 (3H, t, *J* 7.4, $CH_2C\underline{H}_3$); δ_C (101 MHz) 143.0 (C), 137.85 (C), 136.7 (C), 136.2 (C), 130.35 (ArCH), 130.0 (ArCH), 129.55 (2 x ArCH), 128.7 (ArCH=C), 128.1 (ArCH=C), 127.1 (2 x ArCH), 127.05 (ArCH), 126.3 (ArCH), 56.2 (ArCH), 38.7 (CH_2), 27.7 (CH_2), 21.6 ($ArCH_3$), 14.3 (CH_3), 9.7 (CH_3); LRMS (EI^+) m/z 343 ($[M]^+$, 6%), 213 ($[n\text{-}PrNHTs]^+$, 100%), 172 ($[M–NH_2Ts]^+$, 10%); HRMS calculated for $C_{20}H_{25}NO_2S$ $[M]^+$ 343.1606, found 343.1600; *minor (E)-isomer* δ_H (400 MHz) 7.29 (1H, d, *J* 7.6, ArH), 6.94 (1H, d, *J* 7.5, ArH), 6.56 (1H, d, *J* 15.5, ArC<u>H</u>=CH), 5.98 (1H, dq, *J* 15.3 and 6.6, ArCH=C<u>H</u>), 4.51 (1H, d, 7.5, NH), 2.84 (1H, dd, *J* 13.8 and 6.9, $ArCH_{2a}$), 2.72 (1H, dd, *J* 13.7 and 7.5, $ArCH_{2b}$), 2.39 (3H, s, $ArCH_3$), 1.90 (3H, dd, *J* 6.6 and 1.5, CH=CHC<u>H</u>$_3$), 0.77 (3H, d, *J* 7.5, CH_2CH_3) only 10 distinct peaks; δ_C (101 MHz) 143.0 (C), 137.6 (C), 137.3 (C), 134.6 (C), 130.75 (ArCH), 128.5 (ArCH=C), 128.2 (ArCH=C), 127.0 (ArCH), 127.0 (ArCH), 126.9 (ArCH), 126.3 (ArCH), 56.1 (ArCH), 38.9 (CH_2), 27.6 (CH_2), 18.85 (CH_3), 9.7 (CH_3) only 16 distinct peaks; HRMS calculated for $C_{20}H_{25}NO_2S$ $[M]^+$ 343.1606, found 343.1609

1,3-Diethyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 178



175 **178** **175**

Method 1:

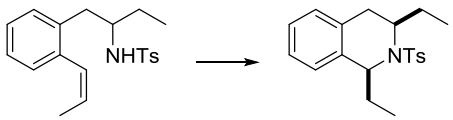
The sulfonamide **175** (127 mg, 0.370 mmol, 1.0 eq.) was dissolved in dichloromethane (1.3 mL) under atmosphere of nitrogen and the solution cooled to 0 °C. To this was added triflic acid (22 mg, 0.148 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then kept at 21 °C for 2 hours. It was then cooled to room temperature and quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/dichloromethane 1:1) to give unreacted starting material **175** (70 mg, 55%) as the *cis* isomer and *sulfonamide* **178** (51 mg, 40%) as a clear oil, as a mixture of 1:2 *cis* and *trans* diastereomers; ν_{max} 3055 (br., NH); *major (trans)-diastereoisomer* δ_H 7.65 (2H, d, *J* 8.3, 2 x ArCH), 7.16 (2H, d, *J* 8.1, 2 x ArCH), 7.15 – 7.10 (2H, m, ArH), 7.06 – 7.02 (2H, m,

ArH), 4.85 (1H, t, *J* 6.9, ArCHN), 3.89 – 3.82 (1H, m, $ArCH_2C\underline{H}$), 2.85 (1H, dd, *J* 15.9 and 4.5, $ArCH_{2a}$), 2.65 (1H, dd, *J* 15.9 and 6.7, $ArCH_{2b}$), 2.36 (3H, s, $ArCH_3$), 2.03 – 1.91 (2H, m, 1'-CH_{2a} and 1''-CH_{2a}), 1.78 – 1.65 (1H, m, 1'-CH_{2b}), 1.31 – 1.20 (1H, m, 1''-CH_{2b}), 0.84 (3H, t, *J* 7.4, 2'-CH_3), 0.79 (3H, t, *J* 7.4, 2''-CH_3); δ_C 142.65 (C), 140.1 (C), 137.4 (C), 133.6 (C), 129.4 (2 x ArCH), 128.9 (ArCH), 127.1 (ArCH), 127.0 (2 x ArCH), 126.9 (ArCH), 126.75 (ArCH), 126.2 (ArCH), 60.8 (CH), 56.2 (CH), 32.0 (CH_2), 30.35 (CH_2) , 26.6 (CH_2), 21.5 ($ArCH_3$), 11.4 (CH_3), 10.7 (CH_3); *minor (cis)-diastereoisomer* ν_{max} 3054 (br, NH); δ_H 7.41 (2H, d, *J* 8.3, 2 x ArCH), 7.04 – 6.98 (2H, m, 2 x ArH), 6.97 (2H, d, *J* 8.0, 2 x ArH), 6.89 (1H, d, *J* 7.2, ArH), 6.83 (1H, d, *J* 7.0, ArH), 4.72 (1H, dd, *J* 8.6 and 6.9, $ArC\underline{H}N$), 3.78 – 3.74 (1H, m, $ArCH_2C\underline{H}$), 2.73 (1H, dd, *J* 15.8 and 7.2, $ArCH_{2a}$), 2.58 (1H, dd, *J* 15.8 and 8.5, $ArCH_{2b}$), 2.25 (3H, s, $ArCH_3$), 2.11 (1H, m, 1''-CH_{2a}), 1.86 (1H, m, 1'-CH_{2a}), 1.78 – 1.65 (2H, m, 1'-CH_{2b} and 1''-CH_{2b}), 1.09 (3H, t, *J* 7.4, 2'-CH_3), 1.03 (3H, t, *J* 7.5, 2''-CH_3); δ_C 142.65 (C), 137.5 (C), 136.8 (C), 132.8 (C), 129.1 (2 x ArCH), 128.2 (ArCH), 127.3 (2 x ArCH), 126.95 (ArCH), 126.7 (ArCH), 126.0 (ArCH), 60.2 (CH), 55.7 (CH), 32.2 (CH_2), 31.6 (CH_2), 30.1 (CH_2), 21.4 ($ArCH_3$), 11.7 (CH_3), 10.7 (CH_3); HRMS calculated for $C_{20}H_{25}NO_2S$ $[M]^+$ 343.1606, found 343.1607.

Method 2:

The sulfonamide **175** (127 mg, 0.370 mmol, 1.0 eq.) was dissolved in dichloromethane (1.3 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (22 mg, 0.148 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to reflux at 41 °C for 3 hours, then cooled to ambient temperature and quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined extracts dried, filtered and evaporated to give *sulfonamide* **178** (123 mg, 97%) as a clear oil and as a single *cis* diastereoisomer. All data obtained were in accordance with those reported before.

1,3-Diethyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 178

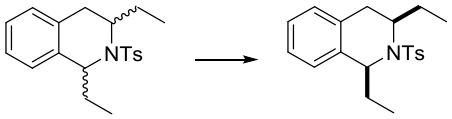


175 **178**

The *cis*-sulfonamide **175** (51 mg, 0.149 mmol, 1.0 eq.) isolated from the previous reaction was dissolved in dichloromethane (0.5 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (9.0 mg, 0.059 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to reflux at 41 °C for 3 hours, then cooled to ambient temperature and quenched with aqueous potassium carbonate (1 mL), extracted with dichloromethane (3 x 3 mL) and the combined organic

extracts dried, filtered and evaporated to give *sulfonamide* **178** (49 mg, 96%) as a clear oil, as a single *cis* diastereoisomer. All data obtained were in accordance with those reported before.

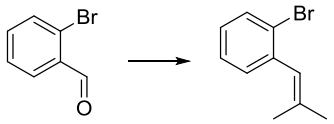
1,3-Diethyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 178



178 **178**

The 1:2 mixture of the *cis* and *trans* sulfonamide **178** (50 mg, 0.146 mmol, 1.0 eq.) from previous experiment was dissolved in dichloromethane (0.5 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (9 mg, 0.059 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to reflux at 41 °C for 3 hours, then cooled to room temperature and quenched with aqueous potassium carbonate (1 mL), extracted with dichloromethane (3 x 2 mL) and the combined organic extracts dried, filtered and evaporated to give *sulfonamide* **178** (47 mg, 94%) as a clear oil, as a single *cis* diastereoisomer. All data obtained were in accordance with those reported before.

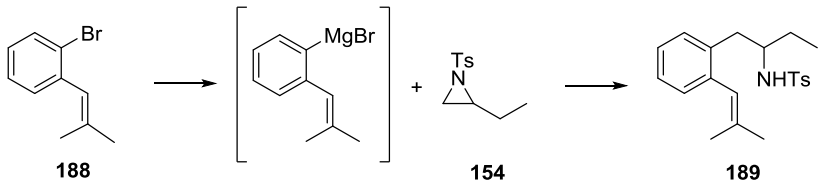
(*E*/*Z*)-1-Bromo-2-(2-methylprop-1-en-1-yl)benzene[230] 188



136 **188**

Isopropyltripthenylphosphonium iodide (16.13 g, 37.3 mmol) was treated with potassium *tert*-butoxide (5.09 g, 45.4 mmol) and 2-bromobenzaldehyde **136** (6.00 g, 32.43 mmol) according to general procedure A1. The crude material was purified by column chromatography (petrol) to yield *alkene* **188** (5.00 g, 73%) as a a pale yellow oil; δ_H (250 MHz) 7.58 (1H, d, *J* 7.8, ArH), 7.34 – 7.22 (2H, m, 2 x ArH), 7.14 – 7.04 (1H, m, ArH), 6.28 (1H, s, ArCH=C), 1.96 (3H, d, *J* 1.3, CH_3), 1.78 (1 H, d, *J* 1.2, CH_3); δ_C (63 MHz) 138.8 (C), 136.9 (C), 132.5 (ArCH), 131.1 (ArCH), 127.75 (ArCH), 126.9 (ArCH), 124.9 (ArCH), 124.35 (C-Br), 26.3 (CH_3), 19.4 (CH_3).

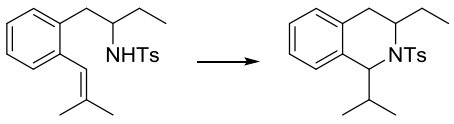
4-Methyl-*N*-(1-(2-(2-methylprop-1-en-1-yl)phenyl)butan-2-yl)benzenesulfonamide 189



188 154 189

Magnesium turnings (143.3 mg, 5.90 mmol, 2.2 eq.) were dry-stirred under an atmosphere of nitrogen for 24 hours and then suspended in tetrahydrofuran (5 mL). The suspension was treated with a crystal of iodine and 1-bromo-2-(2-methylprop-1-en-1-yl)benzene **188** (1.13 g, 5.36 mmol, 2.0 eq.) added as a solution in tetrahydrofuran (5 mL). The reaction was stirred for a further 30 minutes, during which time decolourisation and disappearance of the most magnesium turnings was observed. The solution was then cooled to -40 °C and copper (I) iodide (153 mg, 0.804 mmol, 0.3 eq.) was added. After further 30 minutes, the reaction mixture was cooled to -78 °C and 2-ethyl-1-tosylaziridine **154** (603 mg, 2.68 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) was added. After 15 minutes the reaction mixture was warmed to 0 °C and stirred for another 1.25 h. The reaction was quenched by addition of aqueous ammonium chloride (10 mL) and the blue aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine, dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/dichloromethane, 1:1) to give *sulfonamide* **189** (1.02 g, 68%) as an off-yellow oil; ν_{max} 3275 (br, NH); δ_H 7.47 (2H, d, *J* 8.3, 2 x ArH), 7.16 (2H, d, *J* 8.0, 2 x ArH), 7.13 (1H, dd, *J* 7.4 and 1.3, ArH), 7.07 – 7.02 (2H, m, 2 x ArH), 6.97 (1H, dd, *J* 7.7 and 1.1, ArH), 6.16 (1H, s, ArCH=C), 4.59 (1H, d, *J* 7.4, NH), 3.33 – 3.25 (1H, m, NCH), 2.68 (1H, dd, *J* 11.8 and 5.3, $ArCH_{2a}$), 2.64 (1H, dd, *J* 11.8 and 5.3, $ArCH_{2b}$), 2.38 (3H, s, $ArCH_3$), 1.90 (3H, d, *J* 1.3, $:CCH_3$), 1.61 (3H, d, *J* 1.1, $:CCH_3$), 1.52 – 1.44 (1H, m, $CH_3C\underline{H}_{2a}$), 1.45 – 1.36 (1H, m, $CH_3C\underline{H}_{2b}$), 0.79 (3H, t, *J* 7.4, $CH_2C\underline{H}_3$); δ_C 142.9 (C), 138.1 (C), 137.95 (C), 136.4 (C), 136.3 (C), 130.3 (ArCH), 130.1 (ArCH), 129.5 (2 x ArCH), 127.0 (2 x ArCH), 126.6 (ArCH), 126.29 (ArCH), 123.9 ($Ar\underline{C}H$=CH), 56.3 (CH), 38.6 ($ArCH_2$), 27.7 (CH_2), 26.1 (CH_3), 21.6 ($ArCH_3$), 19.25 (CH_3), 9.7 (CH_3); HRMS (APCI) calculated for $C_{21}H_{28}NO_2S$ $[M+H]^+$ 358.1841, found 358.1828.

3-Ethyl-1-isopropyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 190



189 190

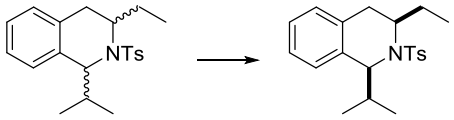
Method 1:

The sulfonamide **189** (92 mg, 0.258 mmol, 1.0 eq.) was dissolved in dichloromethane (1.0 mL) under atmosphere of nitrogen and cooled to 0 °C, to which was added triflic acid (16 mg, 0.103 mmol, 0.4 eq.). The resultant solution was stirred for 5 minutes at 0 °C and then allowed to reach 21 °C for 18 hours. The reaction mixture was then cooled to room temperature and quenched with saturated potassium carbonate solution (2 mL), extracted with dichloromethane (3 x 5 mL), dried, filtered and evaporated. The crude reaction mixture was purified by column chromatography (petrol/dichloromethane 1:1) to give the unreacted starting material X (28 mg, 30%) and *tetrahydroisoquinoline* **190** (55 mg, 60%) as colourless crystals and as a 1:1 mixture of *cis* and *trans* diastereomers; *(cis)-diastereoisomer* m.p. 76 – 79 °C; δ_H 7.29 (2H, d, *J* 8.1, 2 x ArH), 6.98 (1H, t, *J* 7.4, ArH), 6.91 – 6.82 (4H, m, 4 x ArH), 6.66 (1H, d, *J* 7.4, ArH), 4.23 (1H, d, *J* 10.9, ArCHN), 3.60 (1H, dddd, *J* 4.3, 7.5, 9.7 and 11.1, $ArCH_2C\underline{H}$), 2.88 (1H, dd, *J* 15.3 and 7.3, $ArCH_{2a}$), 2.61 (1H, dd, *J* 15.3 and 11.1, $ArCH_{2b}$), 2.31 (1H, dqd, *J* 4.3, 7.5 and 13.5 $C\underline{H}_{2a}CH_3$), 2.22 (3H, s, $ArCH_3$), 1.93 (1H, d sept, *J* 6.5 and 10.6, $C\underline{H}(CH_3)_2$), 1.75 (1H, qdd, *J* 7.3, 9.6 and 13.5, $C\underline{H}_{2a}CH_3$), 1.28 (3H, d, *J* 6.5, $CHC\underline{H}_3$), 1.04 (3H, t, *J* 7.5, $CH_2C\underline{H}_3$), 0.74 (3H, d, *J* 6.5, $CHC\underline{H}_3$); δ_C 142.45 (C), 137.6 (C), 136.2 (C), 133.4 (C), 128.9 (2 x ArCH), 128.2 (ArCH), 127.6 (ArCH), 127.35 (2 x ArCH), 127.0 (ArCH), 125.4 (ArCH), 66.8 (NCH), 57.1 (CH), 33.8 (CH_2), 32.2 (CH_2), 31.5 (CH_2), 21.4 ($ArCH_3$), 20.7 (CH_3), 20.6 (CH_3), 10.7 (CH_3); *(trans)-diastereoisomer* δ_H 7.54 (2H, d, *J* 8.3, 2 x ArH), 7.14 – 7.09 (2H, m, 2 x ArH), 7.07 (2H, d, *J* 8.0, 2 x ArH), 6.91-6.85 (2H, m, 2 x ArH), 4.75 (1H, d, *J* 7.6, ArCHN), 3.80 (1H, dddd, *J* 5.4, 8.6, 10.7 and 11.5), 2.79 (1H, dd, *J* 16.4 and 4.8, $ArCH_{2a}$), 2.49 (1H, dd, *J* 16.4 and 8.5, $ArCH_{2a}$), 2.32 (3H, s, $ArCH_3$), 2.09 (1H, d sept, *J* 1.4 and 7.5, $C\underline{H}(CH_3)_2$), 1.44 – 1.35 (1H, m, $C\underline{H}_{2a}CH_3$), 1.04 (3H, d, *J* 6.7, $CHC\underline{H}_3$), 0.91 (3H, t, *J* 7.4, $CH_2C\underline{H}_3$), 0.82 (3H, d, *J* 6.7, $CHC\underline{H}_3$); δ_C 142.5 (C), 140.0 (C), 135.1 (C), 134.0 (C), 129.0 (2 x ArCH), 128.9 (ArCH), 128.3 (ArCH), 126.9 (ArCH), 126.8 (ArCH), 125.2 (ArCH), 65.2 (NCH), 56.1 (CH), 32.3 (CH_2), 26.9 (CH_2), 21.3 ($ArCH_3$), 20.43 (CH_3), 18.99 (CH_3), 11.66 (CH_3); HRMS (APCI) calculated for $C_{21}H_{28}NO_2S$ $[M+H]^+$ 358.1841, found 358.1824.

Method 2:

The sulfonamide **189** (112 mg, 0.313 mmol, 1.0 eq.) was dissolved in dichloromethane (1.1 mL) under atmosphere of nitrogen and cooled to 0 °C, to which was added triflic acid (19 mg, 0.125 mmol, 0.4 eq.). The resultant solution was stirred for 5 minutes at 0 °C and then heated to 41 °C for 4 hours. The reaction mixture was then cooled to ambient temperature and quenched with saturated potassium carbonate solution (2 mL), extracted with dichloromethane (3 x 2 mL), dried, filtered and evaporated to give *tetrahydroisoquinoline* **190** (97 mg, 87%) as colourless glass, as a 19:1 mixture of *cis* and *trans* diastereomers. All data obtained were in accordance with those reported before.

3-Ethyl-1-isopropyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 190

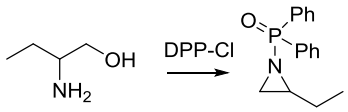


190 **190**

The sulfonamide product **190** (50 mg, 0.140 mmol, 1.0 eq.) from the previous reaction was dissolved in dichloromethane (0.5 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (8.4 mg, 0.056 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to reflux at 41 °C for 3 hours then cooled to ambient temperature and quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 2 mL) and combined organic extratcs dried, filtered and evaporated to give *sulfonamide* **190** (40 mg, 80%) as colourless crystals, as a 95:5 mixture of *cis* and *trans* diastereomers. Analytical sample of the *cis* isomer was obtainer by vapour diffusion recrystallization from diethyl ether in a petroleum ether chamber. All data obtained were in accordance with those reported before.

The sulfonamide product **190** (5 mg, 0.014 mmol, 1.0 eq.) from the first reaction was dissolved in dichloromethane (0.1 mL) under atmosphere then heated to 84 °C for 5 hours. The reaction mixture was then cooled to room temperature dried, filtered and evaporated to give *sulfonamide* **190** (4 mg, 80%) as colourless glass, as a 19:1 mixture of *cis* and *trans* diastereomers. All data obtained were in accordance with those reported before.

(2-Ethylaziridin-1-yl)diphenylphosphine oxide 192

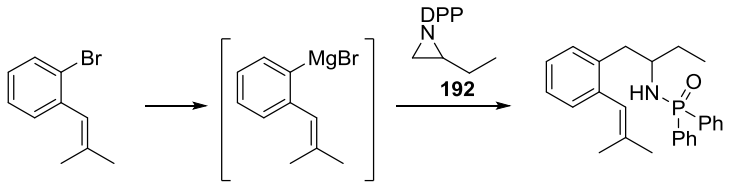


155 **192**

A solution of 2-amino-1-butanol **155** (0.8 g, 8.98 mmol, 1.0 eq.) in tetrahydrofuran (20 mL) was cooled to 0 °C. Triethylamine (2.77 g, 27.39 mmol, 3.05 eq.) was added, followed by diphenylphosphinic chloride (4.85 g, 18.41 mmol, 2.05 eq.). The cooling bath was removed and the reaction allowed to warm to ambient temperature overnight (~16 h) and then cooled to 0 °C. Sodium hydride (3.59 g, 89.8 mmol, 10 eq.) was slowly added and the reaction stirred for a further 20 hours at ambient temperature. The reaction was carefully quenched with dropwise addition of a 1:1 water and tetrahydrofuran solution (20 mL), followed by addition of diethyl ether (50 mL). The organic phase was then washed with water (20 mL), HCl (2M, 20 mL) and aqueous sodium bicarbonate (20 mL), then dried, filtered and evaporated. The crude material was purified by column chromatography (ethyl acetate/petrol 95:5) to give *aziridine* **192** as an off-yellow, viscous oil (1.136 g, 44%); δ_H (400 MHz) 7.89 – 7.82 (4H, m, 4 x ArH), 7.47 – 7.33 (6H,

m, 6 x ArH), 2.67 – 2.55 (1H, m, NCH), 2.45 (1H, ddd, *J* 17.5, 5.9 and 1.1, NCH_{2a}), 1.87 (1H, ddd, *J* 12.4, 3.5 and 1.1, NCH_{2b}), 1.54 – 1.37 (2H, m, $CH_3C\underline{H}_2$), 0.73 (3H, t, *J* 7.5, $C\underline{H}_3CH_2$).

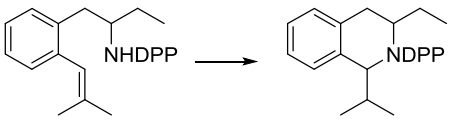
N-(1-(2-(2-Methylprop-1-en-1-yl)phenyl)butan-2-yl)-P,P-diphenylphosphinic amide 194



188 **194**

Magnesium turnings (110 mg, 4.53 mmol, 4.2 eq.) were dry-stirred under an atmosphere of nitrogen for 24 hours and then suspended in tetrahydrofuran (5 mL). The suspension was treated with a crystal of iodine and 1-bromo-2-(2-methylprop-1-en-1-yl)benzene **188** (925 mg, 4.38 mmol, 4.0 eq.) was added as a solution in tetrahydrofuran (5 mL). The reaction was stirred for a further 30 minutes, during which time decolourisation and disappearance of the most magnesium turnings was observed. The solution was then cooled to -40 °C and copper (I) bromide dimethylsulfide (4.5 mg, 0.022 mmol, 0.02 eq.) was added. After a further 30 minutes, the reaction mixture was cooled to -78 °C and (2-ethylaziridin-1-yl)diphenylphosphine oxide **192** (315 mg, 1.10 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) was added. After 15 minutes the reaction mixture was heated to reflux and stirred for another 5 hours. The reaction was quenched by addition of aqueous ammonium chloride (10 mL) and the blue aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine, dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate, 1:1) to give *phosphinamide* **194** (156 mg, 35%) as an off-yellow oil. δ_H 7.82 – 7.85 (2H, m, 2 x ArH), 7.54 (2H, m, 2 x ArH), 7.47 – 7.43 (1H, m, ArH), 7.42 – 7.37 (3H, m, 3 x ArH), 7.30 – 7.24 (2H, m, 2 x ArH), 7.22 (1H, dd, *J* 7.3 and 1.6, ArH), 7.19 (1H, td, *J* 7.4 and 1.7, ArH), 7.14 (1H, dd, *J* 7.4 and 1.4, ArH), 7.11 (1H, dd, *J* 7.2 and 1.1, ArH), 6.11 (1H, s, ArC$\underline{H}$=CH), 3.23 – 3.12 (1H, m, NCH), 2.86 (1 H, ddd, *J* 13.5, 5.9 and 2.2, $ArCH_{2a}$), 2.73 (1H, dd, *J* 13.6 and 7.9, $ArCH_{2b}$ and NH), 2.73 (1H, br s, NH), 1.75 (3H, d, *J* 1.1, $:CCH_3$), 1.67 (1H, m, $CH_3C\underline{H}_{2a}$), 1.61 – 1.52 (1H, m, $CH_3C\underline{H}_{2b}$), 1.46 (1H, d, *J* 1.0, $:CCH_3$), 0.94 (3H, t, *J* 7.4, $C\underline{H}_3CH_2$); δ_C 138.4 (C), 137.7 (C), 135.9 (C), 133.2 (d, *J* 45.7, C), 132.5 (d, *J* 9.4, ArCH), 132.0 (d, *J* 9.2, ArCH), 131.7 (d, *J* 2.7, ArCH), 131.5 (d, *J* 2.7, ArCH), 130.4 (d, *J* 36.9, ArCH), (s), 128.5 (d, *J* 5.6, ArCH), 128.4 (d, *J* 5.8, ArCH), 126.3 (d, *J* 27.7, ArCH), 123.95 (s, ArCH=$\underline{C}$), 54.4 (d, *J* 1.6, NCH), 40.4 (d, *J* 7.3, $ArCH_2$), 30.3 (d, *J* 3.1, $\underline{C}H_2CH_3$), 26.0 (CH_3), 19.0 (CH_3), 10.0 (CH_3); HRMS calculated for $C_{26}H_{31}NOP$ $[M+H]^+$ 404.2143, found 404.2132.

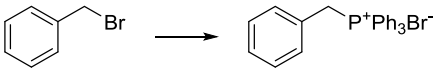
(3-Ethyl-1-isopropyl-3,4-dihydroisoquinolin-2(1H)-yl)diphenylphosphine oxide 195



194 195

The phosphinamide **194** (27 mg, 0.067 mmol, 1.0 eq.) was dissolved in dichloromethane (0.3 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (4 mg, 0.027 mmol, 0.4 eq.). The resulting solution was stirred for 30 minutes at 0 °C and quenched with aqueous potassium carbonate solution (2 mL), extracted with dichloromethane (3 x 5 mL), dried, filtered and evaporated. The desired product could not be detected in the reaction mixture.

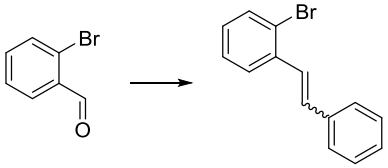
Benzyltriphenylphosphonium bromide[231] 196



196

A solution of benzyl bromide (7.0 g, 41.25 mmol) and triphenylphosphine (12.3 g, 45.0 mmol) in toluene (120 mL) was heated at 110 °C for 24 hours.[232] The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by vacuum filtration, washed with toluene (2 x 50 mL) and diethyl ether (50 mL) to yield *salt* **196** (17.7 g, 99%) as white powder, which was used without further purification.

(*E*/*Z*)-1-Bromo-2-styrylbenzene[233] 197

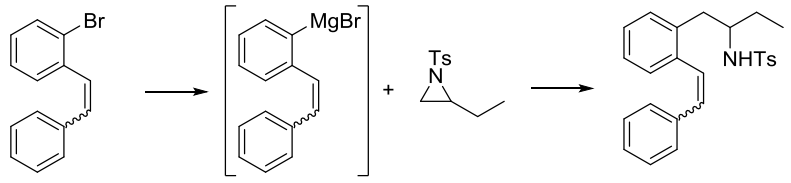


136 197

Benzyltriphenylphosphonium bromide **196** (17.7 g, 40.85 mmol) was treated with potassium *tert*-butoxide (5.35 g, 47.66 mmol) and 2-bromobenzaldehyde (6.3 g, 34.04 mmol) according to general procedure A1. The crude material was purified by column chromatography (petrol/dichloromethane 9:1) to yield *alkene* **197** (8.47 g, 96%) as an 83:17 mixture of *cis* and *trans* isomers; *major (cis)-isomer* δ_H 7.69 (1H, m, ArH), 7.30 – 7.25 (4H, m, 4 x ArH), 7.25 – 7.21 (2H, m, ArH), 7.19 – 7.15 (2H, m), 6.74

(2H, ABq, *J* 12.1, ArC<u>H</u>=C<u>H</u>); *minor (trans)-isomer* δ_H 7.52 (1H, d, *J* 16.2, ArC<u>H</u>=CH), 7.08 (1H, d, *J* 16.2, ArCH=C<u>H</u>); only 2 distinctive signals.

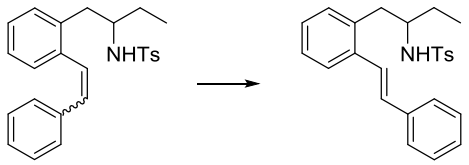
(*E*/*Z*)-4-Methyl-*N*-(1-(2-styrylphenyl)butan-2-yl)benzenesulfonamide 179



197 **154** **179**

Magnesium turnings (83 mg, 3.40 mmol, 2.2 eq.) were dry-stirred under an atmosphere of nitrogen for 24 hours and then suspended in tetrahydrofuran (5 mL). Suspension was treated with a crystal of iodine and 1-bromo-2-styrylbenzene **197** (800 mg, 3.09 mmol, 2.0 eq.) added as a solution in tetrahydrofuran (3 mL). The suspension was stirred for a further 30 minutes, during which decolourisation and disappearance of most magnesium turnings was observed. The solution was then cooled to -40 °C and copper (I) iodide (88 mg, 0.464 mmol, 0.3 eq.) was added. After further 30 minutes, the reaction mixture was cooled to -78 °C and 2-ethyl-1-tosylaziridine **154** (348 mg, 1.55 mmol, 1.0 eq.) in tetrahydrofuran (2 mL) was added. After 15 minutes the reaction mixture was warmed to 0 °C and stirred for another 1 hour. The reaction was quenched by addition of aqueous ammonium chloride solution (10 mL) and the blue aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine, dried, filtered and evaporated. The crude material was purified by column chromatography (dichloromethane/petrol, 1:1) to give *sulfonamide* **179** (460 mg, 74%) as colourless glass, as a 5:1 mixture of *cis* and *trans* isomers; ν_{max} 3291 (br, NH); *major (cis)-isomer* δ_H 7.64 (2H, d, *J* 8.3, 2 x ArH), 7.17 (1H, s, CHAr), 7.14 (4H, m, ArH), 7.13 – 7.09 (1H, m, ArH), 7.09 – 7.02 (5H, m, ArH), 6.55 (2H, ABq, J_{AB} 12.2, C<u>H</u>=C<u>H</u>), 4.66 (1H, d, *J* 7.8, NH), 3.42 (1H, dddd, *J* 14.5, 8.0, 6.5 and 5.4, $ArCH_2C\underline{H}$), 2.79 (1H, dd, *J* 13.7 and 6.5, $ArCH_{2a}$), 2.65 (1H, dd, *J* 13.8 and 8.0, $ArCH_{2b}$), 2.38 (3H, s, $ArCH_3$), 1.55 – 1.44 (1H, m, $CH_3C\underline{H}_{2a}$), 1.37 – 1.32 (1H, m, $CH_3C\underline{H}_{2a}$), 0.73 (3H, t, *J* 7.4, $C\underline{H}_3CH_2$); δ_C 143.1 (C), 138.0 (C), 137.45 (C), 136.7 (C), 135.9 (C), 131.3 (<u>C</u>H=CH), 130.7 (ArCH), 129.8 (ArCH), 129.6 (2 x ArCH), 129.0 (2 x ArCH), 128.95 (CH=<u>C</u>H), 128.3 (2 x ArCH), 127.6 (ArCH), 127.4 (ArCH), 127.2 (2 x ArCH), 126.85 (ArCH), 55.9 (CH), 39.4 (CH_2), 27.5 (CH_2), 21.6 ($ArCH_3$), 9.7 (CH_3); LRMS (EI^+) m/z 405 ($[M]^+$, 80%), 234 ($[M\text{-}Ts]^+$, 72%), 213 ($[n\text{-}PrNHTs]^+$, 100%); HRMS calculated for $C_{25}H_{27}NO_2S$ $[M]^+$ 405.1763, found 405.1759.

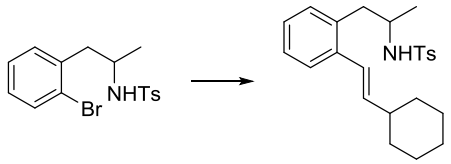
(*E*)-4-Methyl-*N*-(1-(2-styrylphenyl)butan-2-yl)benzenesulfonamide 179



179 **179**

The sulfonamide **179** (150 mg, 0.370 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (1.5 mL) under atmosphere of nitrogen and cooled to 0 °C, to which was added triflic acid (24 mg, 0.149 mmol, 0.4 eq.). The resultant solution was stirred for 5 minutes at 0 °C and then heated to 70 °C for 3 hours. The reaction mixture was quenched with saturated potassium carbonate solution (2 mL), extracted with dichloromethane (3 x 5 mL), dried, filtered and evaporated to give *sulfonamide* **179** (132 mg, 88%) as a viscous, clear oil, as a sinlge *trans* isomer; ν_{max} 3280 (br, NH); δ_H 7.61 (2H, d, *J* 7.3, 2 x ArH), 7.53 (1H, d, *J* 7.7, ArH), 7.50 (2H, d, *J* 8.3, 2 x ArH), 7.43 - 7.39 (2H, m, 2 x ArH), 7.41 (1H, d, *J* 15.7, ArCH=C), 7.33 – 7.28 (1H, m, ArH), 7.22 (1H, m, ArH), 7.15 (1H, td, *J* 7.4 and 1.3, ArH), 7.06 – 7.01 (3H, m, 3 x ArH), 6.90 (1H, d, *J* 15.9, ArCH=C), 4.68 (1H, d, *J* 7.2, NH), 3.28 (1H, m, NCH), 3.14 (1H, dd, *J* 13.8 and 6.2, $ArCH_{2a}$), 2.80 (1H, dd, *J* 13.8 and 8.2, $ArCH_{2b}$), 2.34 (3H, s, $ArCH_3$), 1.52 – 1.42 (1H, m, $CH_3C\underline{H}_{2a}$), 1.40 – 1.31 (1H, m, $CH_3CH_{\underline{2b}}$); 0.69 (3H, t, *J* 7.4, CH_3); δ_C 143.0 (C), 138.0 (C), 137.5 (C), 136.8 (C), 135.7 (C), 131.1 (ArCH), 131.0 (ArCH), 129.77 (ArCH), 129.42 (ArCH), 128.77 (ArCH), 127.84 (ArCH), 127.54 (ArCH), 127.11 (ArCH), 127.0 (ArCH), 126.8 (ArCH), 126.0 (ArCH), 125.85 (ArCH), 56.0 (CH), 39.8 ($ArCH_2$), 27.0 (CH_2), 21.5 ($ArCH_3$), 9.7 (CH_3); HRMS calculated for $C_{25}H_{27}NO_2S$ $[M]^+$ 405.1763, found 405.1755.

(*E*)-*N*-(1-(2-(2-Cyclohexylvinyl)phenyl)propan-2-yl)-4-methylbenzenesulfonamide 200

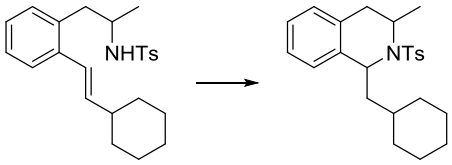


207 **200**

A solution of *N*-(1-(2-bromophenyl)propan-2-yl)-4-methylbenzenesulfonamide **207** (600 mg, 1.0 eq.) in ethanol/water (1:1, 6 mL) was treated with 2-cyclohexylvinylboronic acid (300 mg, 1.2 eq.), K_3PO_4 (691 mg, 2.0 eq) and Pd(dppf)Cl_2.DCM (66.5 mg, 0.05 eq) at 80 °C for 2.5 hours according to General Procedure D. The crude material was purified by column chromatography (petrol/diethyl ether 1:1) to give the *sulfonamide* **200** (531 mg, 82%) as a colourless oil; ν_{max} 3420 (br, NH); δ_H 7.54 – 7.50 (2H, d, *J* 8.3, 2 x ArH), 7.30 (1H, d, *J* 7.7, ArH), 7.14 (2H, d, *J* 7.9, 2 x ArH), 7.13 (1H, m, ArH), 7.06 (1H, td, *J* 7.4 and 1.3, ArH), 6.95 (1H, dd, *J* 7.5 and 1.1, ArH), 6.46 (1H, d, *J* 15.6, ArCH=C), 5.88 (1H, dd, *J* 15.7 and 7.1, ArCH=C$\underline{H}$), 4.74 (1H, d, *J* 6.8, NH), 3.47 – 3.38 (1H, m, NCH), 2.85 (1H, dd, *J* 13.8 and 7.3,

$ArCH_{2a}$), 2.68 (1H, dd, *J* 13.8 and 7.0, $ArCH_{2b}$), 2.39 (3H, s, $ArCH_3$), 2.17 – 2.09 (1H, m, ArCH=CH-C<u>H</u>), 1.83 – 1.75 (4H, m), 1.70 (2H, m), 1.39 – 1.29 (1H, m), 1.26 – 1.14 (2H, m), 1.12 (3H, d, *J* 6.5, $CH_2C\underline{H}_3$); δ_C 142.9 (C), 139.6 (ArCH=<u>C</u>H), 137.6 (C), 137.5 (C), 134.6 (C), 130.7 (ArCH), 129.6 (2 x ArCH), 127.1 (ArCH), 126.95 (3 x ArCH), 126.4 (ArCH), 124.7 (Ar<u>C</u>H=CH), 50.7 (NCH), 41.5 (CH), 41.2 (CH_2), 33.1 (CH_2), 26.25 (CH_2), 26.1 (CH_2), 21.9 (CH_3), 21.6 (CH_3); LRMS (EI^+) m/z 397 ($[M]^+$, 70%), 300 ($[M\text{-}CH_2cy]^+$, 90%), 242 ($[M\text{-}Ts]^+$, 90%), 198 ($[M\text{-}CH_3CH_2NHTs]^+$, 100%); HRMS ($EI^+$) calculated for $C_{24}H_{31}NO_2S$ $[M]^+$ 397.2076, found 397.2068.

1-(Cyclohexylmethyl)-3-methyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 201



200 **201**

Method 1:

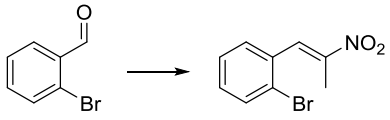
The sulfonamide **200** (99 mg, 0.25 mmol, 1.0 eq.) was dissolved in dichloromethane (1.0 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (15 mg, 0.1 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to reflux at 41 °C for 4 hours. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated to give *tetrahydroisoquinoline* **201** (80 mg, 81%) as a clear oil, as a 7:5 mixture of *trans* and *cis* isomers; *major (trans)-isomer* δ_H (400 MHz) 7.63 (2H, d, *J* 8.3, 2 x ArH), 7.15 (2H, d, *J* 8.0, 2 x ArH), 7.18 – 7.10 (2H, m, 2 x ArH), 7.06 – 6.91 (2H, m, 2 x ArH), 5.09 (1H, t, *J* 7.4, ArCHN), 4.17 – 4.08 (1H, m, $ArCH_2C\underline{H}$), 2.89 (1H, dd, *J* 15.9 and 4.7, $ArCH_{2a}$), 2.52 (1H, dd, *J* 15.9 and 7.4, $ArCH_{2b}$), 2.36 (3H, s, $ArCH_3$), 1.95-1.10 (13H, m), 1.20 (3H, d, *J* 6.7, $CH_2C\underline{H}_3$); δ_C 142.8 (C), 140.1 (C), 137.8 (C), 133.6 (C), 129.3 (2 x ArCH), 127.2 (2 x ArCH), 126.9 (ArCH), 126.8 (ArCH), 126.2 (ArCH), 57.0 (ArCHN), 49.3 ($ArCH_2\underline{C}H$), 45.4 ($ArCH_2$), 35.5 (CH_2), 34.3 (CH_2), 33.5 (CH_2), 33.2 (CH_2), 26.7 (CH_2), 26.3 (CH_2), 26.2 (CH_2), 21.5 (CH_3), 20.7 ($ArCH_3$); *minor (cis)-isomer* δ_H 7.38 (2H, d, *J* 8.3, 2 x ArH), 7.03 – 6.97 (2H, m, 2 x ArH), 6.95 (2H, d, *J* 8.0, 2 x ArH), 6.88 (1H, d, *J* 7.1, ArH), 6.80 (1H, dd, *J* 7.2 and 0.9, ArH), 4.90 (1H, dd, *J* 8.8, 6.6, ArCHN), 3.87 (1H, m, $ArCH_2C\underline{H}$), 2.77 (1H, dd, *J* 15.7 and 7.3, $ArCH_{2a}$), 2.69 (1H, dd, *J* 15.7 and 9.9, $ArCH_{2b}$), 2.24 (3H, s, $ArCH_3$), 1.96 - 1.90 (1H, m, CH_{2a}), 1.85 – 1.76 (3H, m, 2 x CH_{2b} and CH_{2c}), 1.76 – 1.62 (4H, m, CH_{2d} and 2 x CH_{2e} and CH_2), 1.58 – 1.52 (1H, m, $ArCHCH_2C\underline{H}$), 1.55 (3H, d, *J* 6.4, CH_3), 1.48 – 1.41 (1H, m, CH_{2c}), 1.35 – 1.23 (3H, m, CH_{2d} and 2 x CH_{2f}), 1.00 (1H, CH_{2b}), 0.91 (1H, m, CH_{2a}); δ_C 142.6 (C), 138.3 (C), 136.5 (C), 133.2 (C), 129.0 (2 x ArCH), 127.8 (ArCH), 127.3 (2 x ArCH), 127.0 (ArCH), 126.3 (ArCH), 126.1 (ArCH), 56.8 (ArCHN), 50.6 ($ArCH_2\underline{C}H$), 44.6

($ArCH_2$), 34.6 ($ArCH_2$), 34.0 (CH), 33.6 (CH_2), 33.15 (CH_2), 26.7 (CH_2), 26.4 (CH_2), 26.2 (CH_3), 26.1 (CH_2), 21.4 ($ArCH_3$).

Method 2:

The sulfonamide **200** (217 mg, 0.548 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (2.2 mL) under atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (33 mg, 0.219 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to reflux at 84 °C for 4.5 hours. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated to give *sulfonamide* **201** (206 mg, 95%) as a clear oil and as a 20:1 mixture of *cis* and *trans* isomers. All data obtained were in accordance with those reported before.

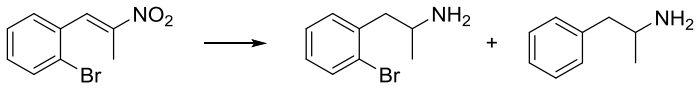
(*E*)-1-Bromo-2-(2-nitroprop-1-en-1-yl)benzene 204



136 **204**

To a solution of 2-bromobenzaldehyde **136** (17.6 g, 95.1 mmol, 1.0 eq) in nitroethane (100 g, 1.332 mol, 14 eq.) was added ammonium acetate (5.13 g, 66.6 mmol, 0.7 eq) and the mixture heated to reflux for 4 hours. The reaction was then allowed to cool to room temperature, and the solvent was removed *in vacuo* at 5 mbar pressure and at 60 °C for 1 hour. The crude reaction mixture was redissolved in toluene (100 mL) and the residual nitromethane distilled off azeotropically at 1 mbar and 60 °C. Drying overnight in a vacuum oven afforded *nitroalkene* **204** (22.32 g, 97%) as an orange oil which was used without further purification; δ_H (250 MHz) 8.15 (1H, s, ArCH=C), 7.69 (1H, dd, *J* 8.2 and 1.1, ArH), 7.46 – 7.38 (2H, m, 2 x ArH), 7.30 (2H, m, 2 x ArH), 2.34 (3H, d, *J* 1.1, CH_3).

1-(2-Bromophenyl)propan-2-amine 205

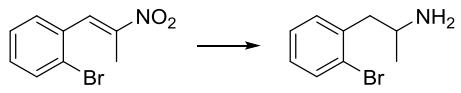


204 **205** **206**

To the solution of (*E*)-1-bromo-2-(2-nitroprop-1-en-1-yl)benzene **204** (0.40 g, 1.65 mmol, 1.0 eq.) in tetrahydrofuran (10 mL) at 0 °C under an atmosphere of nitrogen was added portionwise lithium aluminium hydride (207 mg, 5.46 mmol, 3.3 eq.) over 1 hour. The reaction mixture was allowed to stir for 1 hour at the same temperature after which it was quenched according to the General Procedure F to

yield an unseparable 8:1 mixture of *amine* **205** and *amine* **206**; *major (***205***)-amine* δ_H (400 MHz) 7.57 (1H, d, *J* 7.9, ArH), 7.40 – 7.19 (2H, m, 2 x ArH), 7.13 – 7.07 (1H, m, ArH), 3.35 – 3.25 (1H, m, NCH), 2.89 (1H, dd, *J* 13.3 and 5.5, $ArCH_{2a}$), 2.71 (1H, dd, *J* 13.2 and 7.9, $ArCH_{2b}$), 1.18 (2H, d, *J* 6.3, CH_3); *minor (***206***)-amine*: δ_H (400 MHz) 7.38 – 7.19 (5H, m, 5 x ArH), 3.25 – 3.15 (1H, m, NCH), 2.78 (1H, dd, *J* 14.7 and 5.8, $ArCH_{2a}$), 2.56 (1H, dd, *J* 13.2 and 8.1, $ArCH_{2b}$), 1.15 (3H, d, *J* 6.3, CH_3).

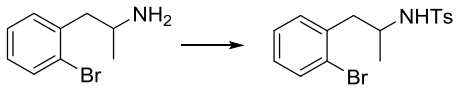
1-(2-Bromophenyl)propan-2-amine 205



204 **205**

A solution of 1-bromo-2-(2-nitroprop-1-en-1-yl)benzene **204** (22.2 g, 91.78 mmol, 1.0 eq.) in tetrahydrofuran was treated with sodium borohydride (920 mg, 24.3 mmol, 0.26 eq.) and boron trifluoride diethyl etherate (51.4 g, 367 mmol, 4.0 eq.) according to the General Procedure F to afford *amine* **205** (10.88 g, 51%) as a pale brown oil which was used without further purification. All data obtained were in accorded with those reported before.

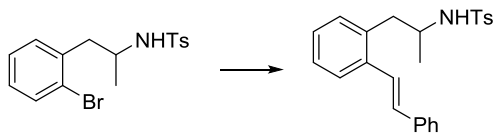
N-(1-(2-Bromophenyl)propan-2-yl)-4-methylbenzenesulfonamide 207



205 **207**

A solution of 1-(2-bromophenyl)propan-2-amine **205** (2.5 g, 11.68 mmol) in dichloromethane was treated with triethylamine, DMAP and *p*-tosyl chloride according to General Procedure B. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give the *sulfonamide* **207** (3.74 g, 87%) as a colourless glass; δ_H 7.55 (2H, d, *J* 8.3, 2 x ArH), 7.38 (1H, dd, *J* 8.0 and 1.1, ArH), 7.14 (2H, d, *J* 8.0, 2 x ArH), 7.16 – 7.12 (1H, m, ArH), 7.06 (1H, dd, *J* 7.6 and 1.7, ArH), 7.02 (1H, td, *J* 7.6 and 1.8, ArH), 4.59 (1H, d, *J* 7.5, NH), 3.69 – 3.55 (1H, m, NCH), 2.75 – 2.85 (2H, ABq, *J* 7.2, $ArCH_2$), 2.38 (3H, s, $ArCH_3$), 1.19 (3H, d, *J* 6.5, $CHC\underline{H}_3$); δ_C 143.0 (C), 137.6 (C), 137.25 (C), 133.1 (ArCH), 131.7 (ArCH), 129.6 (2 x ArCH), 128.4 (ArCH), 127.6 (ArCH), 127.1 (2 x ArCH), 124.8 (C-Br), 50.3 (NCH), 43.5 (CH_2), 22.3 ($ArCH_3$), 21.6 (CH_3).

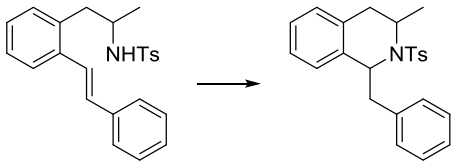
(*E*)-4-Methyl-*N*-(1-(2-styrylphenyl)propan-2-yl)benzenesulfonamide 208



207 **208**

A solution of *N*-(1-(2-bromophenyl)propan-2-yl)-4-methylbenzenesulfonamide **207** (3.00 g, 8.146 mmol, 1.0 eq.) in ethanol/water (1:1, 30 mL) was treated with 2-phenylvinylboronic acid (1.688 g, 11.404 mmol, 1.4 eq.), K_3PO_4 (3.45 g. 16.25 mmol, 2.0 eq.) and Pd(dppf)Cl_2.DCM (333 mg, 0.407 mmol, 0.05 eq) at 80 °C for 1.5 h according to General Procedure D. The crude material was purified by column chromatography (petrol/ethyl acetate 2:1) to give the *sulfonamide* **208** (2.81 g, 88%) as an off-orange glass; ν_{max} 3277 (br, NH); δ_H 7.60 (2H, d, *J* 7.8, 2 x ArH), 7.55 (3H, m, 3 x ArH), 7.42 (2H, t, *J* 7.7, ArH), 7.40 (1H, d, *J* 16.2, ArC<u>H</u>=CH), 7.34 – 7.29 (1H, m, ArH), 7.26 – 7.22 (1H, m, ArH), 7.20 – 7.13 (1H, m, ArH), 7.06 (3H, m, 3 x ArH), 6.91 (1H, d, *J* 16.0, ArCH=C<u>H</u>), 4.96 (1H, d, *J* 6.9, NH), 3.48 – 3.42 (1H, m, NCH), 3.20 (1 H, dd, *J* 13.7 and 6.1, $ArCH_{2a}$), 2.73 (1H, dd, *J* 13.7 and 8.4, $ArCH_{2b}$), 2.35 (3H, s, $ArCH_3$), 1.05 (3H, d, *J* 6.5, CH_3); δ_C 143.0 (C), 137.5 (C), 136.7 (C), 135.6 (C), 131.2 (ArCH), 131.1 (ArCH), 129.6 (2 x ArCH), 128.8 (2 x ArCH), 127.9 (ArCH), 127.65 (ArCH), 127.3 (ArCH), 127.05 (2 x ArCH), 126.9 (2 x ArCH), 126.1 (ArCH), 125.9 (ArCH), 50.5 (NCH), 41.95 (CH_2), 21.5 ($ArCH_3$), 21.05 (CH_3); LRMS m/z 396 ($[M]^+$, 35%), 300 ($[M\text{-}Tol]^+$, 33%), 220 ($[M\text{-}Ts]^+$, 98%), 198 ($[CH_3CH_2NHTs]^+$, 92%); HRMS (EI^+) calculated for $C_{24}H_{25}NO_2S$ $[M]^+$ 391.1606, found 391.1602.

1-Benzyl-3-methyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 209



208 **209**

Method 1:

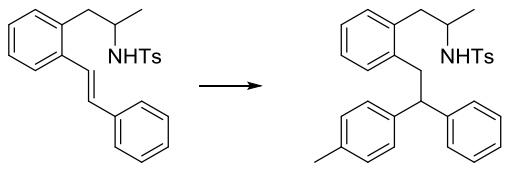
The sulfonamide **208** (200 mg, 0.511 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (2.0 mL) under atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (31 mg, 0.204 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 84 °C for 12 hours. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extratcs dried, filtered and evaporated to give *tetrahydroisoquinoline* **209** (124 mg, 62%) as a clear oil and as a 20:1 mixture of *cis* and *trans* isomers; *major (cis)-isomer* δ_H (400 MHz) 7.46 (2H, d, *J* 8.3, 2 x ArH), 7.35 – 7.15 (5H, m, 5 x ArH), 7.11 – 7.05

(3H, m, ArH), 7.03 (2H, d, *J* 8.1, 2 x ArH), 7.00 – 6.93 (1H, m, ArH), 6.87 (1H, t, *J* 7.4, ArH), 6.39 (1H, d, *J* 7.5, ArH), 5.13 (1H, dd, *J* 9.7 and 5.1, ArCHN), 3.96 (1H, m, $ArCH_2C\underline{H}N$), 3.38 (1H, dd, *J* 13.2 and 5.1, 1'-$C\underline{H}_{2a}$), 3.05 (1H, dd, *J* 13.2 and 9.7, 1'-$C\underline{H}_{2b}$), 2.89 (1H, dd, *J* 15.7, 6.9, 4-$C\underline{H}_{2a}$), 2.78 (1H, dd, *J* 15.7 and 9.0, 4-$C\underline{H}_{2b}$), 2.29 (3H, s, $ArCH_3$), 1.62 (3H, d, *J* 6.4, $CH_2C\underline{H}_3$); δ_C (101 MHz) 142.8 (C), 138.35 (C), 136.6 (C), 136.1 (C), 132.9 (C), 129.8 (2 x ArCH), 129.2 (2 x ArCH), 128.4 (2 x ArCH), 127.3 (2 x ArCH), 127.2 (ArCH), 127.2 (ArCH), 127.2 (ArCH), 126.6 (ArCH), 125.7 (ArCH), 60.4 (ArCHN), 50.3 ($ArCH_2\underline{C}HCH_3$), 44.7 (CH_2), 35.0 (CH_2), 25.5 ($ArCH_3$), 21.4 (CH_3); *minor (trans)-isomer* δ_H (400 MHz) 7.58 (2H, d, *J* 8.3, 2 x ArH), 7.29 – 6.88 (10H, m, 10 x ArH), 6.53 (1H, d, *J* 7.5, ArH), 5.08 (1H, dd, *J* 9.8 and 5.1, ArCHN), 4.38 – 4.30 (1H, m, $ArCH_2C\underline{H}CH_3$), 3.41 (1H, dd, *J* 13.0 and 5.1, 1'-$C\underline{H}_{2a}$), 2.89 (1 H, dd, *J* 12.7 and 3.6, 1'-$C\underline{H}_{2b}$), 2.86 (1H, m, 4-$C\underline{H}_{2a}$), 2.65 (1H, dd, *J* 15.4 and 5.0, 4-$C\underline{H}_{2b}$), 2.36 (3H, s, $ArCH_3$), 0.97 (1H, d, *J* 6.6, $CH_2C\underline{H}_3$); δ_C (101 MHz) 142.9 (C), 139.9 (C), 138.0 (C), 136.0 (C), 133.55 (C), 130.0, 129.6 (2 x ArCH), 129.0 (2 x ArCH), 128.5 (2 x ArCH), 128.25 (2 x ArCH), 127.9 (ArCH), 127.4 (ArCH), 127.3 (ArCH), 126.5 (ArCH), 126.0 (ArCH), 60.7 (ArCHN), 50.1 ($ArCH_2\underline{C}HCH_3$), 44.8 (CH_2), 36.2 (CH_2), 21.5 ($ArCH_3$), 20.5 (CH_3); HRMS calculated for $C_{24}H_{26}NO_2S$ $[M+H]^+$ 392.1684, found 392.1673.

Method 2:

The sulfonamide **208** (168 mg, 0.430 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (1.7 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (39 mg, 0.258 mmol, 0.6 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 60 °C for 3 hours. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated to give *tetrahydroisoquinoline* **209** (77 mg, 46%) as a clear oil, as a 2:1 mixture of *cis* and *trans* isomers. All data obtained were in accordance with those reported before.

1-Benzyl-3-methyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 212

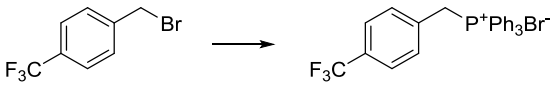


208 **212**

The sulfonamide **208** (200 mg, 0.511 mmol, 1.0 eq.) was dissolved in toluene (2.0 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (31 mg, 0.204 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 110 °C for 24 hours. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with

dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated to give *sulfonamide* **212** (64 mg, 32%) as a white foam; δ_H (400 MHz) 7.56 (2H, d, *J* 8.2, 2 x ArH), 7.25 – 7.19 (2H, m, 2 x ArH), 7.16 (2H, d, *J* 7.8, 2 x ArH), 7.19 – 7.09 (4H, m, 4 x ArH), 7.08 – 6.94 (7H, m, 7 x ArH), 6.91 (1H, dd, *J* 7.2 and 1.7, ArH), 6.89 – 6.84 (1H, m, dt, *J* 7.9 and 1.9, ArH), 4.29 (1H, d, *J* 7.3, NH), 4.11 (1H, t, *J* 7.5, $ArCH_2C\underline{H}Ar$), 3.49 – 3.37 (1H, m, NCH), 3.22 (2H, dd, *J* 7.5 and 2.8, $ArC\underline{H}_2CHAr$), 2.58 (1H, dd, *J* 14.1 and 7.0, $ArC\underline{H}_{2a}CHN$), 2.39 (3H, s, $ArCH_3$), 2.39 - 2.35 (1H, m, $ArC\underline{H}_{2b}CHN$), 2.30 (3H, s, $ArCH_3$), 1.04 (3H, d, *J* 6.4, $CHC\underline{H}_3$); δ_C (101 MHz), 144.45 (C), 143.0 (C), 141.3 (C), 138.7 (C), 137.6 (C), 135.6 (C), 130.2 (C), 130.0 (ArCH), 129.9 (ArCH), 129.6 (2 x ArCH), 129.1 (ArCH), 129.0 (ArCH), 128.3 (ArCH), 128.3 (ArCH), 128.05 (ArCH), 127.9 (ArCH), 127.9 (ArCH), 127.0 (2 x ArCH), 126.5 (ArCH), 126.2 (ArCH), 126.2 (ArCH), 126.1 (ArCH), 52.2 (CH), 50.35 (CH), 40.2 (CH_2), 38.3 (CH_2), 21.6 ($ArCH_3$), 21.5 ($ArCH_3$), 21.0 (CH_3); LRMS m/z 484 ($[M]^+$, 35%).

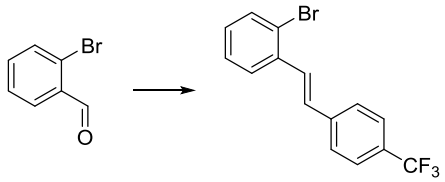
Triphenyl(4-(trifluoromethyl)benzyl)phosphonium bromide 213



214 **213**

A solution of *p*-(trifluoromethyl)benzyl bromide **214** (5.0 g, 20.92 mmol) and triphenylphosphine (6.31 g, 24.06 mmol) in toluene (50 mL) was heated to 65 °C for 12 hours and then at 111 °C for 3 hours.[232] The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by vacuum filtration, washed with toluene (2 x 50 mL) and diethyl ether (50 mL) to yield *salt* **213** (10.1 g, 96%) as white powder and used in the next step without further purification.

(*E*/*Z*)-1-Bromo-2-(4-(trifluoromethyl)styryl)benzene 215

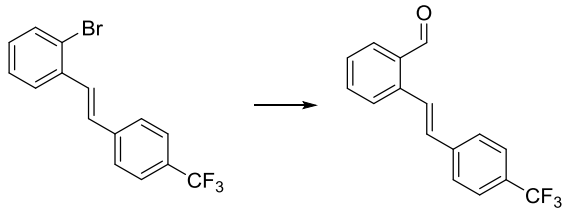


136 **215**

A suspension of *p*-(trifuoromethyl)benzyltriphenylphosphonium bromide **213**(2.00 g, 4.18 mmol) in tetrahydrofuran (15 mL) was treated with potassium *tert*-butoxide (596 mg, 5.32 mmol) and 2-bromobenzaldehyde **136** (644 mg, 3.48 mmol) according to general procedure A1. The crude product was purified by column chromatography (petrol/dichloromethane 9:1) to yield *alkene* **215** (1.089 mg, 80%) as an off-white glass and as a 7:1 mixture of *cis* and *trans* isomers; m*ajor (cis)-isomer* δ_H 7.53 – 7.50 (1H, m, ArH), 7.32 (2H, d, *J* 8.2, 2 x ArH), 7.12 (2H, d, *J* 8.0, 2 x ArH), 7.00 (1H, m, ArH), 6.68 - 6.57 (2H,

ABq, *J* 12.1, ArCH=CH); minor *(trans)-isomer* δ_H 7.45 (1H, d, *J* 16.2, ArCH=CH), 6.94 (1H, d, *J* 16.2, ArCH=CH), only 2 distinct signals.

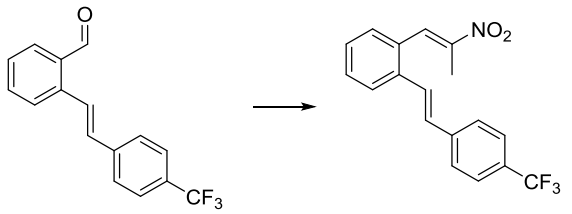
(*E*/*Z*)-2-(4-(Trifluoromethyl)styryl)benzaldehyde 216



215 **216**

To a solution of (E/Z)-1-bromo-2-(4-(trifluoromethyl)styryl)benzene (907 mg, 2.78 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) at -78 °C under an atmosphere of nitrogen was added n-butyllithium (1.9 M, 1.82 mL, 3.45 mmol, 1.1 eq.) over 10 minutes and the reaction stirred for a further 30 minutes at the same temperature. Dimethylformamide (0.61 mL, 7.85 mmol, 2.5 eq.) was added dropwise and the mixture allowed to warm to ambient temperature and stirred for a further 2 hours. The reaction was quenched by addition of aqueous ammonium chloride (10 mL) and the aqueous layer extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried, filtered and evaporated and the crude material purified by column chromatography (petrol/diethyl ether 1:4) to give *aldehyde* **216** (556 mg, 73%) as a yellow oil and as a 4.5:1 mixture of *cis* and *trans* isomers; ν_{max} 1697 (C=O); *major (cis)-isomer* δ_H (400 MHz) 10.25 (1H, s, CHO), 7.94 – 7.89 (1H, m, ArH), 7.66 – 7.63 (1H, m, ArH), 7.52 – 7.42 (2H, m, 2 x ArH), 7.40 (2H, d, *J* 8.2, ArH), 7.23 (1H, dd, *J* 6.9 and 1.3, ArH), 7.15 (1H, app. s, ArH), 7.15 (1H, d, *J* 12.7, ArCH=CH), 6.84 (1H, d, *J* 12.2, ArCH=CH); *minor (trans)-isomer* δ_H (400 MHz) 10.28 (1H, s, CHO), 8.19 (1H, d, *J* 16.2, ArCH=CH), 7.85 (1H, dd, *J* 7.6 and 1.3, ArH), 7.75 (1H, d, *J* 7.8, ArH), 7.08 (1H, d, *J* 16.2, ArCH=CH); only 5 distinct signals.

1-((*E*/*Z*)-2-Nitroprop-1-en-1-yl)-2-((*E*)-4-(trifluoromethyl)styryl)benzene 217

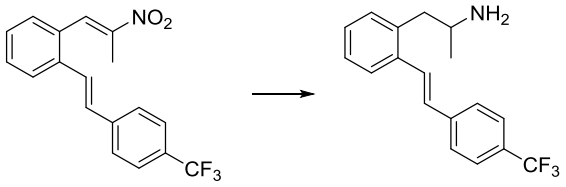


216 **217**

To a solution of (*E*/*Z*)-2-(4-(trifluoromethyl)styryl)benzaldehyde **216** (556 mg, 2.015 mmol, 1.0 eq) in nitroethane (1.16 g, 15.48 mmol, 8 eq.) was added ammonium acetate (89 mg, 1.161 mmol, 0.6 eq) and the mixture heated to 100 °C for 4 hours. The reaction was then allowed to cool to room temperature, and

the solvent was removed *in vacuo* at 5 mbar pressure and at 60 °C for 1 hour to afford the crude *nitroalkene* **217** (610 mg, 91%) as a brown oil and as a 4:1 mixture of *cis* and *trans* isomers; *major (cis)-isomer* δ_H 7.85 (1H, s, CH=CNO_2), 7.34 – 7.23 (4H, m, 4 x ArH), 7.22 – 7.12 (2H, m, 2 x ArH), 6.99 (2H, d, *J* 8.1, 2 x ArH), 6.72 (2H, s, ArC<u>H</u>=C<u>H</u>), 1.91 (3H, s, CH_3); *minor (trans)-isomer* δ_H 8.20 (1H, s, CH=CNO_2), 2.23 (3H, s, CH_3); only 2 distinct signals.

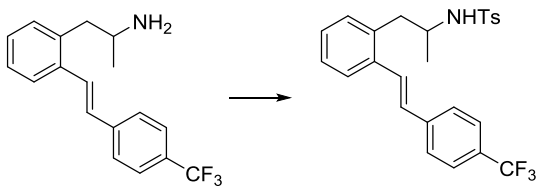
(*E*/*Z*)-1-(2-(4-(Trifluoromethyl)styryl)phenyl)propan-2-amine 218a



217 **218a**

To the solution of 1-((*E*/*Z*)-2-nitroprop-1-en-1-yl)-2-((*E*)-4-(trifluoromethyl)styryl)benzene **217** (610 mg, 1.83 mmol, 1.0 eq.) in tetrahydrofuran (10 mL) at 0 °C under an atmosphere of nitrogen was added portionwise lithium aluminium hydride (208 mg, 5.50 mmol, 3.0 eq) over 10 minutes. The reaction mixture was allowed to stir for 30 minutes at the 0 °C and heated to reflux for 2 h. The reaction was quenched according to the General Procedure F to yield *amine* **218a** (485 mg, 87%) as a dark, orange oil and as a 4:1 mixture of *cis* and *trans* isomers and was used in the next step without further purification; *major (cis)-isomer* δ_H (400 MHz) 7.33 (2H, d, *J* 8.2, 2 x ArH), 7.18 – 7.13 (2H, m, 2 x ArH), 7.11 (2H, d, *J* 8.3, 2 x ArH), 7.05 – 7.01 (2H, m, 2 x ArH), 6.79 (1H, d, *J* 12.2, ArCH=C<u>H</u>), 6.56 (1H, d, *J* 12.2, ArC<u>H</u>=CH), 3.24 – 3.13 (1H, m, NCH), 2.68 (1H, dd, *J* 13.5 and 6.2, $ArCH_{2a}$), 2.61 (1H, dd, *J* 13.5 and 7.6, $ArCH_{2b}$), 2.24-2.05 (2H, br. s, NH_2), 1.08 (1H, d, *J* 6.3, CH_3); *minor (trans)-isomer* δ_H (400 MHz) 7.42 (1H, d, *J* 16.0, ArCH=C<u>H</u>), 6.94 (1H, d, *J* 16.2, ArC<u>H</u>=CH); only 2 distinct signals.

(*E*/*Z*)-4-Methyl-*N*-(1-(2-(4-(trifluoromethyl)styryl)phenyl) propan-2-yl)benzenesulfonamide 218

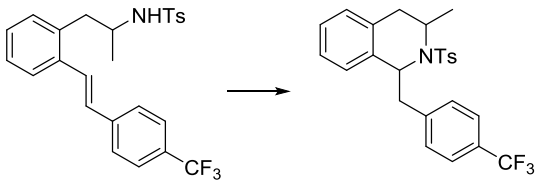


218a **218**

A solution of (*E*/*Z*)-1-(2-(4-(trifluoromethyl)styryl)phenyl)propan-2-amine **218a** (485 mg, 1.59 mmol) in dichloromethane (10 mL) was treated with triethylamine, DMAP and *p*-tosyl chloride according to

General Procedure B. The crude material was purified by column chromatography (petrol/diethyl ether 1:1) to give the *sulfonamide* **218** (378 mg, 52%) as an orange foam and as a 3:1 mixture of *cis* and *trans* isomers; m.p. 34 – 38 °C; ν_{max} 3572 (NH); *major (cis)-isomer* δ_H 7.62 (2H, d, *J* 8.3, 2 x ArH), 7.38 (2H, d, *J* 8.3, 2 x ArH), 7.17 (1H, m, ArH), 7.16 (2H, d, *J* 8.0, 2 x ArH), 7.14 – 7.02 (6H, m, 6 x ArH), 6.67 (1H, d, *J* 12.2, ArC<u>H</u>=CH), 6.58 (1H, d, *J* 12.2, ArCH=C<u>H</u>), 4.82 (1H, d, *J* 7.5, NH), 3.58 – 3.47 (1H, m, NCH), 2.86 (1H, dd, *J* 13.6 and 6.3, $ArCH_{2a}$), 2.59 (1H, dd, *J* 13.6 and 8.1, $ArCH_{2b}$), 2.37 (3H, s, $ArCH_3$), 1.03 (3H, d, *J* 6.5, CHC<u>H</u>$_3$); δ_C 143.2 (C), 140.1 (C), 137.6 (C), 136.5 (C), 135.8 (C), 131.15 (ArCH), 130.8 (ArCH), 129.8 (ArCH), 129.6 (2 x ArCH), 129.55 (ArCH), 129.4 (ArCH), 129.05 (2 x ArCH), 127.9 (ArCH), 127.0 (2 x ArCH), 126.95 (ArCH), 126.9 (ArCH), 125.1 (q, *J* 3.7, CF_3), 50.35 (NCH), 41.7 (CH_2), 21.5 ($ArCH_3$), 21.2 (CH_3); *minor (trans)-isomer* δ_H 6.94 (1H, d, *J* 16.0, ArC<u>H</u>=CH), 3.42 (1H, m, NCH), 3.27 (1H, dd, *J* 13.7 and 5.5, $ArCH_{2a}$), 2.70 (1H, dd, *J* 13.7 and 8.8, $ArCH_{2b}$), 2.34 (3H, s, $ArCH_3$), 1.00 (1H, d, *J* 6.5, CHC<u>H</u>$_3$); only 5 distinct signals; δ_C 143.1 (C), 140.8 (C), 137.3 (C), 135.9 (C), 131.3 (ArCH), 129.55 (2 x ArCH), 129.3 (ArCH), 128.8 (ArCH), 128.3 (ArCH), 128.15 (ArCH), 127.3 (ArCH), 126.95 (ArCH), 126.9 (2 x ArCH), 126.0 (ArCH),125.7 (q, *J* 3.8, CF_3), 50.5 (NCH), 42.1 (CH_2), 21.4 ($ArCH_3$), 20.6 (CH_3).

3-Methyl-2-tosyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroisoquinoline 219

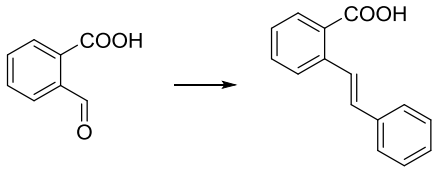


218 **219**

The sulfonamide **218** (75 mg, 0.163 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (0.8 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (15 mg, 0.098 mmol, 0.6 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 80 °C for 15 hours. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined extracts dried, filtered and evaporated to give *sulfonamide* **219** (49 mg, 65%) as a clear, viscous oil and as a 20:1 mixture of *cis* and *trans* isomers; *major (cis)-isomer* δ_H 7.53 (2H, d, *J* 8.3, 2 x ArH), 7.33 (2H, d, *J* 8.3, 2 x ArH), 7.12 (2H, d, *J* 7.2, 2 x ArH), 7.14 – 6.88 (3H, m, 3 x ArH), 6.92 (2H, d, *J* 7.8, 2 x ArH), 6.31 (1H, d, *J* 7.5, ArH), 5.02 (1H, dd, *J* 9.3 and 5.5, ArCHN), 3.85 (1H, ddq, *J* 8.9, 6.8 and 6.4 NC<u>H</u>CH_3), 3.31 (1H, dd, *J* 13.3 and 5.5, 1'-C<u>H</u>$_{2a}$), 3.00 (1H, dd, *J* 13.3 and 9.3, 1'-C<u>H</u>$_{2b}$), 2.79 (1H, dd, *J* 15.8 and 6.7, 4-C<u>H</u>$_{2a}$), 2.66 (1H, dd, *J* 15.8 and 8.9, 4-C<u>H</u>$_{2b}$), 2.18 (3H, s, $ArCH_3$), 1.50 (3H, d, *J* 6.4, CHC<u>H</u>$_3$). δ_C 143.05 (C), 142.3 (C), 139.45 (C), 135.6 (C), 133.4 (C), 130.0 (ArCH), 129.5 (ArCH), 129.0 (ArCH), 128.0 (ArCH), 127.1 (ArCH), 127.1 (ArCH), 126.05 (ArCH), 125.85 (ArCH), 125.2 (q, *J* 3.9, CF_3), 59.9 (ArCHN), 50.1 (CH), 44.65 (CH_2), 34.8 (CH_2), 25.3

($ArCH_3$), 21.4 (CH_3); *minor (trans)-isomer* δ_H 7.43 (2H, d, *J* 8.0, 2 x ArH), 7.36 (2H, d, *J* 8.8, 2 x ArH), 7.14 – 7.08 (2H, m, 3 x ArH), 6.96 (4H, m, 4 x ArH), 6.80 (1H, t, *J* 7.5, ArH), 6.48 (1H, d, *J* 7.5, ArH), 4.98 (1H, dd, *J* 8.5 and 5.0, ArCHN), 4.32 – 4.24 (1H, m, NCH), 3.41 (1H, dd, *J* 13.0 and 5.0, 1'-C$\underline{H}_{2a}$), 2.93 (1H, dd, *J* 12.9 and 8.6, 1'-C$\underline{H}_{2b}$), 2.84 (1H, dd, *J* 15.4 and 4.7, 4-C$\underline{H}_{2a}$), 2.59 (1H, dd, *J* 15.4 and 4.8, 4-C$\underline{H}_{2b}$), 2.30 (3H, s, $ArCH_3$), 0.89 (3H, d, *J* 6.6, CHC$\underline{H}_3$); δ_C 142.9 (C), 142.0 (C), 136.3 (C), 135.4 (C), 132.7 (C), 130.2 (2 x ArCH), 129.0 (ArCH), 127.5 (ArCH), 127.3 (ArCH), 127.0 (2 x ArCH), 126.9 (ArCH), 124.95 (q, *J* 3.8, CF_3), 61.0 (ArCH), 50.0 (CH), 44.4 (CH_2), 36.1 (CH_2), 21.3 ($ArCH_3$), 20.25 (CH_3).

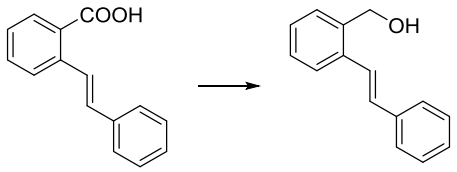
(*E*)-2-Styrylbenzoic acid[234] 221



220 **221**

To a suspension of benzyltriphenylphosphonium bromide **196** (3.46 g, 7.99 mmol, 1.20 eq.) in tetrahydrofuran (15 mL) at 0 °C under an atmosphere of nitrogen was added portionwise sodium hydride (60%, 0.80 g, 19.98 mmol, 3.0 eq.) and the reaction allowed to stir for one hour at the same temperature. A solution of 2-formylbenzoic acid **220** (1.0 g, 6.66 mmol, 1.0 eq.) in tetrahydrofuran (10 mL) was then added and the mixture heated to 40 °C for 1 hour. The reaction was cooled to 0 °C and quenched by slow addition of water and the separated aqueous layer washed with diethyl ether (2 x 20 mL). The combined aqueous extracts were acidified with HCl (2M, pH 1) and extracted with diethyl ether (2 x 20 mL) and the organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 2:1) to yield the *carboxylic acid* **221** (910 mg, 61%) as an off-white solid; m.p. 148-150 °C (lit. m.p.[234] 151-152 °C); δ_H (400 MHz) 8.12 – 8.09 (1H, m, ArH), 8.07 (1H, d, *J* 16.0, ArC$\underline{H}$=CH), 7.75 (1H, d, *J* 7.7, ArH), 7.58 (3H, m, ArH), 7.35 (3H, m, 3 x ArH), 7.28 (1H, m, ArH), 7.03 (1H, d, *J* 16.2, ArCH=C$\underline{H}$), 7.03 (1H, d, *J* 16.2); LRMS (EI^+) m/z 224 ($[M]^+$, 90%), 178 ($[M-CO_2]^+$, 70%), 85 (100%).

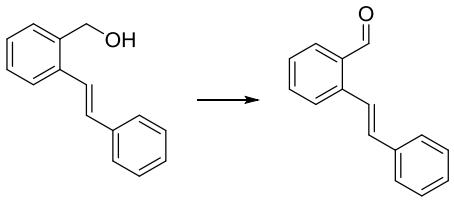
(*E*)-(2-Styrylphenyl)methanol[143] 222



221 **222**

To a solution of 2-styrylbenzoic acid **221** (170 mg, 0.76 mmol, 1.0 eq.) in tetrahydrofuran (3 mL) at 0 °C under an atmosphere of nitrogen was added portionwise lithium aluminium hydride (1.0 M in THF, 0.84 mL, 0.84 mmol, 1.1 eq.) and the mixture was allowed to warm to ambient temperature. The reaction mixture was allowed to stir for 4 hours after which it was quenched according to the General Procedure F to yield *alcohol* **222** (132 mg, 83%) as a white solid; m.p. 99-102 °C (lit. m.p.[143] 103 °C); ν_{max} 3349 (br., OH); δ_H (400 MHz) 7.67 (1H, d, *J* 7.5, ArH), 7.54 (2H, dd, *J* 8.1 and 0.9, 2 x ArH), 7.47 (1H, d, *J* 16.2, ArC<u>H</u>=CH), 7.42 – 7.32 (3H, m, 3 x ArH), 7.31 – 7.25 (3H, m, 3 x ArH), 7.06 (1H, d, *J* 16.2, ArCH=C<u>H</u>), 4.84 (2H, s, ArC<u>H</u>$_2$OH).

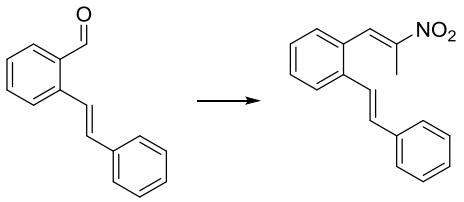
(*E*)-2-Styrylbenzaldehyde[235] 223



222 **223**

To a suspension of pyridinium dichromate (487 mg, 1.30 mmol, 1.6 eq.) in dry dichloromethane (10 mLs) was added a solution of 2-(styrylphenyl)methanol **222** (170 mg, 0.810 mmol, 1.0 eq.) in dichloromethane (5 mL).[236] After 4 hours diethyl ether (10 mL) was added and the reaction mixture filtered through a pad of Celite©. The solvent was removed *in vacuo* and the crude material purififed by silica chromatography (petrol/ethyl acetate 20:1) to yield *aldehyde* **223** (118 mg, 70%) as a white solid; m.p. 42-45 °C (lit. m.p.[237] 45 °C); ν_{max} 1694 (C=O); δ_H (250 MHz) 10.33 (1H, s, CHO), 8.09 (1H, d, *J* 16.2, ArC<u>H</u>=CH), 7.85 (1H, d, *J* 7.7, ArH), 7.72 (1H, d, *J* 7.7, ArH), 7.65 – 7.29 (7H, m, 7 x ArH), 7.08 (1H, d, *J* 16.2, ArCH=C<u>H</u>).

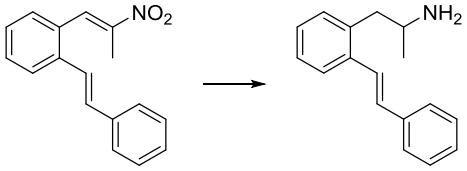
1-((*E*)-2-Nitroprop-1-en-1-yl)-2-((E)-styryl)benzene 224



223 **224**

To a solution of 2-styrylbenzaldehyde **223** (4.0 g, 19.23 mmol, 1.0 eq.) in nitroethane (28.9 g, 385 mmol, 20 eq.) was added ammonium acetate (1.26 g, 16.35 mmol, 0.85 eq.) and the mixture heated to reflux for 3 hours. The reaction was then allowed to cool to room temperature, and the solvent was removed *in vacuo* at 5 mbar pressure and at 60 °C for 1 h. The residue was suspended in dichloromethane (75 mL), washed with water (50 mL) and brine (50 mL), dried, filtered and evaporated to afford the crude *nitroalkene* **224** (4.68 g, 91%) as a brown oil and was used in the next step without further purification.

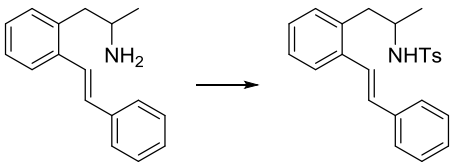
(*E*)-1-(2-Styrylphenyl)propan-2-amine 225



224 **225**

To the solution of 1-((*E*)-2-nitroprop-1-en-1-yl)-2-((*E*)-styryl)benzene **224** (4.18 g, 17.66 mmol, 1.0 eq.) in tetrahydrofuran (60 mL) at 0 °C under an atmosphere of nitrogen was added portionwise lithium aluminium hydride (2.15 g, 56.51 mmol, 3.2 eq) over 1 hour. The reaction mixture was allowed to stir for 1 hour at the same temperature and then heated to reflux at 65 °C for 2.5 hours. The reaction was then allowed to cool to room temperature after which it was quenched according to the General Procedure F to yield the *amine* **225** (3.02 g, 72%) as a deep-orange oil; δ_H 7.60 – 7.57 (1H, m, ArH), 7.46 (2H, d, *J* 7.7, 2 x ArH), 7.35 – 7.30 (3H, m, 3 x ArH), 7.25 – 6.99 (7H, m, 7 x ArH), 6.95 (1H, d, *J* 16.1, ArC<u>H</u>=CH), 3.20 – 3.12 (1H, m, NCH), 2.83 (1H, dd, *J* 13.6 and 5.6, $ArCH_{2a}$), 2.64 (1H, dd, *J* 13.6 and 8.0, $ArCH_{2b}$), 1.20 (2H, br s, NH_2), 1.08 (3H, d, *J* 6.3, CH_3); δ_C 137.6 (C), 136.5 (C), 130.8 (ArCH), 130.3 (ArCH), 129.0 (ArCH), 128.7 (2 x ArCH), 128.1 (ArCH), 127.65 (ArCH), 127.55 (ArCH), 126.75 (ArCH), 126.6 (2 x ArCH), 126.0 (ArCH), 48.1 (CH), 44.1 (CH_2), 23.8 (CH_3).

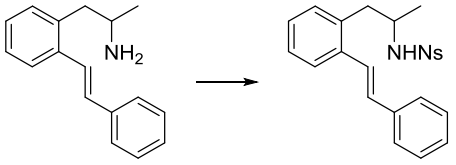
(*E*)-4-Methyl-*N*-(1-(2-styrylphenyl)propan-2-yl)benzenesulfonamide 208



225 **208**

A solution of (E)-1-(2-styrylphenyl)propan-2-amine **225** (321 mg, 1.35 mmol, 1.0 eq.) in dichloromethane was treated with triethylamine, DMAP and *p*-tosyl chloride according to General Procedure B. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give the *sulfonamide* **208** (386 mg, 73%) as a colourless glass. All data obtained were in accordance with those reported before.

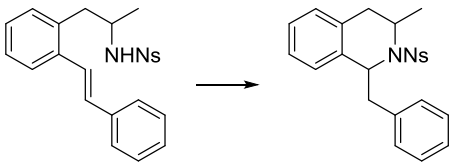
(*E*)-4-Nitro-*N*-(1-(2-styrylphenyl)propan-2-yl)benzenesulfonamide 226



225 **226**

A solution of (*E*)-1-(2-styrylphenyl)propan-2-amine (710 mg, 3.00 mmol, 1.0 eq.) in dichloromethane was treated with triethylamine, DMAP and *p*-nosyl chloride according to General Procedure B. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give the *sulfonamide* **226** (1.03 g, 84%) as a yellow foam; m.p. 49-52 °C; ν_{max} 3294 (NH); δ_H 8.01 (2H, d, *J* 8.9, 2 x ArH), 7.65 (2H, d, *J* 8.9, 2 x ArH), 7.56 – 7.51 (2H, m, 2 x ArH), 7.44 – 7.39 (3H, m, 3 x ArH), 7.35 – 7.31 (1H, m, ArH), 7.25 (1H, d, *J* 16.0, ArC<u>H</u>=CH), 7.21 (1H, dt, *J* 7.6 and 0.9, ArH), 7.13 (1H, dt, *J* 7.4 and 1.2, ArH), 7.02 (1H, dd, *J* 7.5 and 0.9, ArH), 6.82 (1H, d, *J* 16.0, ArCH=C<u>H</u>), 4.98 (1H, d, *J* 7.3, NH), 3.52 – 3.41 (1H, m, NCH), 3.01 (1H, dd, *J* 14.0 and 7.7, $ArCH_{2a}$), 2.82 (1H, dd, *J* 14.0 and 6.8, $ArCH_{2b}$), 1.20 (3H, d, *J* 6.5, CH_3); δ_C 149.7 (C), 145.8 (C), 137.1 (C), 136.5 (C), 135.1 (C), 131.4 (Ar<u>C</u>H=CH), 131.1 (ArCH), 129.0 (2 x ArCH), 128.25 (ArCH=<u>C</u>H), 128.0 (2 x ArCH), 127.8 (ArCH), 127.6 (ArCH), 126.8 (2 x ArCH), 126.2 (ArCH), 125.4 (ArCH), 124.1 (2 x ArCH), 51.2 (CH), 41.7 (CH_2), 22.2 (CH_3); HRMS (EI^+) calculated for $C_{23}H_{22}N_2O_4S$ $[M]^+$ 422.1300, found 422.1311.

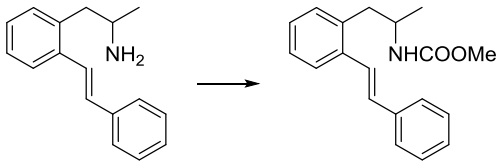
(*E*)-4-Nitro-*N*-(1-(2-styrylphenyl)propan-2-yl)benzenesulfonamide 228



226 **228**

The sulfonamide **226** (47 mg, 0.115 mmol, 1.0 eq.) was dissolved in dichloromethane (0.5 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (7 mg, 0.046 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 41 °C for 2.5 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated to give *tetrahydroisoquinoline* **228** (30 mg, 63%) as a yellow glass; ν_{max} 1559 (N=O); *major (cis)-isomer* δ_H 7.99 (2H, d, *J* 9.0, 2 x ArCH), 7.64 (2H, d, *J* 9.0, 2 x ArH), 7.28 – 7.22 (3H, m, 3 x ArH), 7.07 – 7.00 (3H, m, 3 x ArH), 6.95 (1H, d, *J* 7.4, ArH), 6.85 (1H, t, *J* 7.5, ArH), 6.35 (1H, d, *J* 7.5, ArH), 5.08 (1H, dd, *J* 9.5 and 5.7, ArCHN), 3.92 – 3.89 (1H, m, $ArCH_2C\underline{H}CH_3$), 3.35 (1H, dd, *J* 13.2 and 5.7, 1'-$C\underline{H}_{2a}$), 3.05 (1H, dd, *J* 13.2 and 9.5, 1'-$C\underline{H}_{2b}$), 2.92 (1H, dd, *J* 15.9 and 7.1, 4-$C\underline{H}_{2a}$), 2.83 (1H, dd, *J* 15.8 and 9.5, 4-$C\underline{H}_{2b}$), 1.64 (3H, d, *J* 6.4, CH_3); δ_C 149.65 (C), 145.05 (C), 137.7 (C), 135.7 (C), 132.7 (C), 129.7 (2 x ArCH), 128.6 (2 x ArCH), 128.45 (2 x ArCH), 128.1 (ArCH), 127.8 (ArCH), 127.2 (ArCH), 127.0 (ArCH), 126.1 (ArCH), 123.8 (2 x ArCH), 61.2 (ArCHN), 51.2 ($CH_3\underline{C}HN$), 44.0 (CH_2), 34.9 (CH_2), 25.8 (CH_3); HRMS (EI^+) calculated for $C_{23}H_{22}N_2O_4S$ $[M]^+$ 422.1300, found 422.1304; *minor (trans)-isomer* δ_H 5.23 (1H, t, *J* 7.3, ArCHN), 4.33 – 4.29 (1H, m, , $ArCH_2C\underline{H}CH_3$), 1.07 (3H, d, *J* 6.7, CH_3); only three distinctive signals; δ_C 129.9 (ArCH), 128.2 (ArCH), 61.5 (NCH), 50.4 ($CH_3\underline{C}HN$), 44.4 (CH_2), 20.2 (CH_3); only five distinctive signals.

Methyl-(E)-(1-(2-styrylphenyl)propan-2-yl)carbamate 227

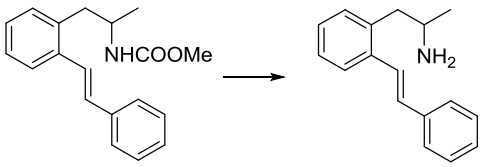


225 **227**

A solution of (*E*)-1-(2-styrylphenyl)propan-2-amine **227** (720 mg, 3.03 mmol, 1.0 eq.) in diethyl ether (4 mL) was cooled to 0 °C. Water (3 mL) and potassium carbonate (838 mg, 6.07 mmol, 2.0 eq.) was added, followed by dropwise addition of methyl chloroformate (344 mg, 3.64 mmol, 1.2 eq.). The cooling bath was removed and the reaction was allowed to warm to room temperature over 30 minutes. The separated

aqueous phase was then extracted with diethyl ether (3 x 5 mL) and the combined organic extracts washed with brine (5 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give *carbamate* **227** (618 mg, 69%) as a colourless glass; δ_H 7.54 (1H, d, *J* 7.6, ArH), 7.52 – 7.39 (3H, m, 2 x ArH and ArC<u>H</u>=CH), 7.28 – 7.24 (2H, m, 2 x ArH), 7.17 – 7.12 (2H, m, 2 x ArH), 7.09 (1H, dt, *J* 7.4 and 1.3, ArH), 7.03 (1H, d, *J* 7.3, ArH), 6.91 (1H, d, *J* 16.1, ArCH=C<u>H</u>), 4.59 (1H, d, *J* 7.5, NH), 3.87 (1H, br s, NCH), 3.47 (3H, s, OCH_3), 3.03 (1H, br dd, *J* 13.3 and 4.3, $ArCH_{2a}$), 2.64 (1H, br dd, *J* 11.5 and 8.1, $ArCH_{2b}$), 0.98 (3H, d, *J* 6.6, CH_3); δ_H (250 MHz, 50 °C) 7.59 – 7.54 (1H, m, ArH), 7.52 – 7.46 (2H, m, 2 x ArH), 7.51 – 7.48 (1H, m, ArC<u>H</u>=CH), 7.34 – 7.24 (2H, m, ArH), 7.23 – 7.16 (2H, m, 2 x ArH), 7.16 – 7.12 (1H, m, ArH), 7.12 – 7.03 (1H, m, ArH), 6.93 (1H, d, *J* 16.1, ArCH=C<u>H</u>), 4.46 (1H, br s, NH), 3.92 – 3.89 (1H, m, NCH), 3.51 (3H, s, OCH_3), 3.06 (1H, dd, *J* 13.6 and 5.4, $ArCH_{2a}$), 2.68 (1H, dd, *J* 13.5 and 7.9, $ArCH_{2a}$), 1.03 (3H, d, *J* 6.7, CH_3); δ_C 156.3 (C=O), 137.7 (C), 136.8 (C), 136.1 (C), 131.1 (ArCH), 130.6 (Ar<u>C</u>H=CH), 128.7 (2 x ArCH), 127.7 (ArCH), 127.5 (ArCH), 127.0 (ArCH), 126.8 (ArCH=<u>C</u>H), 126.2 (ArCH), 125.9 (ArCH), 51.9 (OCH_3), 48.0 (NCH), 40.3 ($ArCH_2$), 20.05 (CH_3); LRMS (EI^+) m/z 263 ($[M\text{-}OCH_3]^+$, 100%); HRMS calculated for $C_{19}H_{21}NO_2$ $[M]^+$ 295.1572, found 295.1565.

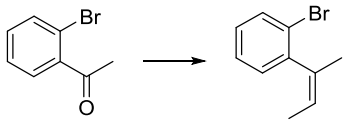
(*E*)-1-(2-Styrylphenyl)propan-2-amine 225



227 **225**

The sulfonamide **227** (101 mg, 0.342 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (1.0 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (21 mg, 0.137 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 84 °C for 24 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *amine* **225** (41 mg, 50%) as off-yellow oil. The sample showed identical spectroscopic and analytical data to the compound synthesized before.

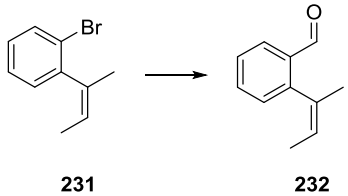
(*E*/*Z*)-1-Bromo-2-(but-2-en-2-yl)benzene[238] **231**



230 **231**

To the suspension of ethyltriphenylphosphonium bromide (12.59 g, 33.91 mmol, 2.7 eq.) in tetrahydrofuran (80 mL) at 0 °C was added solid potassium *tert*-butoxide (3.81 g, 33.91 mmol, 2.7 eq.) portionwise, over five minutes. The reaction mixture was stirred for a further 0.5 h at 0 °C after which 2-bromoacetophenone (2.5g, 12.56 mmol, 1.0 eq.) was added as a solution in tetrahydrofuran (25 mL) dropwise, over 5 minutes. The cooling bath was removed and the mixture heated to reflux for 6 hours. The reaction was quenched by addition of aqueous ammonium chloride (75 mL) and the separated aqueous layer extracted with ethyl acetate or diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine, dried, filtered and evaporated. The crude material was purified by column chromatography (petrol) to give *alkene* **231** (1.673 g, 63%) as a colourless oil and as a 4:1 mixture of *cis* and *trans* isomers; *major (cis)-isomer* δ_H 7.60 (1H, dd, *J* 8.5 and 1.2, ArH), 7.30 (1H, td, *J* 7.6 and 1.2, ArH), 7.15 – 7.10 (2H, m, 2 x ArH), 5.62 (1H, qq, 1.5 and 6.7, ArC=CH), 2.01 – 1.99 (3H, m, CH_3), 1.42 (3H, dq, *J* 6.7 and 1.5, CH_3); δ_C 143.0 (C), 136.9 (C), 132.65 (ArC=CH), 130.0 (ArCH), 128.1 (ArCH), 127.4 (ArCH), 123.2 (ArCH), 122.65 (C-Br), 24.45 (CH_3), 14.7 (CH_3); *minor (trans)-isomer* δ_H 7.55 (1H, dd, *J* 8.0 and 1.1, ArH), 7.26 (1H, td, *J* 7.5 and 1.2, ArH), 7.17 (1H, dd, *J* 7.6 and 1.8, ArH), 7.12 – 7.08 (1H, m, ArH), 5.48 (1H, qq, *J* 6.7 and 1.5, ArC=CH), 2.01 – 1.98 (3H, m, CH_3), 1.80 (3H, dq, *J* 6.8 and 1.1, CH_3); δ_C 146.6 (C), 137.0 (C), 130.2 (ArC=CH), 127.9 (ArCH), 127.2 (ArCH), 125.1 (ArCH), 122.4 (ArCH), 17.3 (CH_3), 13.9 (CH_3).

(*E*/*Z*)-2-(But-2-en-2-yl)benzaldehyde 232

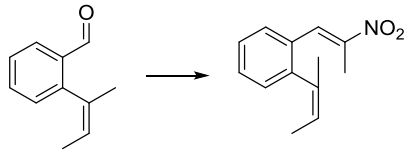


231 **232**

To a solution of 1-bromo-2-(but-2-en-2-yl)benzene **231** (1.55 g, 7.35 mmol, 1.0 eq.) in tetrahydrofuran (15 mL) at -78 °C under an atmosphere of nitrogen was added n-butyllithium (1.9 M, 4.64 mL, 8.82 mmol, 1.2 eq.) over 10 minutes and the reaction stirred for a further 30 minutes at the same temperature. Dimethylformamide (1.42 mL, 18.38 mmol, 2.5 eq.) was added dropwise and the mixture allowed to warm to ambient temperature and stirred for a further 2 hours. The reaction was quenched by addition of

aqueous ammonium chloride (15 mL) and the aqueous layer extracted with diethyl ether (3 x 15 mL). The combined organic extracts were dried, filtered and evaporated and the crude material purified by column chromatography (petrol/diethyl ether 15:1) to give *aldehyde* **232** (1.01 g, 86%) as a yellow oil and as a 5:1 mixture of *cis* and *trans* isomers; ν_{max} 1691 (C=O); *major (cis)-isomer* δ_H 10.07 (1H, d, *J* 0.7, CHO), 7.93 (1H, dd, *J* 7.8 and 1.2, ArH), 7.56 (1H, td, *J* 7.5 and 1.4, ArH), 7.37 (1H, t, *J* 7.6, ArH), 7.18 (1H, dd, *J* 7.7 and 0.7, ArH), 5.78 – 5.73 (1H, qq, *J* 6.7 and 1.4, ArC=CH), 2.05 – 2.04 (3H, m, CH_3), 1.36 (3H, dq, *J* 6.8 and 1.5, CH_3); δ_C 192.5 (CHO), 146.5 (C), 134.2 (ArC<u>C</u>H), 133.4 (C) 132.95 (C), 129.4 (ArCH), 127.2 (ArCH), 127.1 (ArCH), 125.0 (ArCH), 26.7 (CH_3), 14.8 (CH_3); *minor (trans)-isomer* δ_H 10.09 (1H, d, *J* 0.6, CHO), 7.87 (1H, dd, *J* 7.8 and 1.3, ArH), 7.50 (1 H, td, *J* 7.5 and 1.4, ArH), 7.33 (1H, t, *J* 7.6, ArH), 7.28 (1H, dd, *J* 7.7 and 0.7, ArH), 5.40 (1H, qq, *J* 6.7 and 1.4, ArC=CH), 2.06 – 2.03 (3H, m, CH_3), 1.82 (3H, dd, *J* 6.8 and 1.1, CH_3); δ_C 192.6 (CHO), 149.7 (C), 133.7 (C), 133.3 (ArC=<u>C</u>H), 132.9 (C), 129.0 (ArCH), 128.8 (ArCH), 127.6 (ArCH), 126.8 (ArCH), 18.5 (CH_3), 14.3 (CH_3).

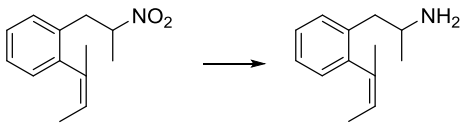
1-((*E*/*Z*)-But-2-en-2-yl)-2-((*E*)-2-nitroprop-1-en-1-yl)benzene 233



232 **233**

To a solution of (*E*/*Z*)-2-(But-2-en-2-yl)benzaldehyde **232** (920 mg, 5.75 mmol, 1.0 eq.) in nitroethane (3.45 g, 46.0 mmol, 8 eq.) was added ammonium acetate (266 mg, 3.45 mmol, 0.6 eq.) and the mixture heated to reflux for 3 hours. The reaction was then allowed to cool to room temperature, and the solvent was removed *in vacuo* at 5 mbar pressure and at 60 °C for 1 h. The residue was suspended in dichloromethane (75 mL), washed with water (50 mL) and brine (50 mL), dried, filtered and evaporated to afford the crude *nitroalkene* **233** (1.00 g, 81%) as a dark, brown oil, as a single *cis* isomer and was used in the next step without further purification; δ_H 7.91 (1H, s, ArCH=CNO_2), 7.34 – 7.30 (1H, m, ArH), 7.28 – 7.24 (2H, m, 2 ArH), 7.12 (1H, d, *J* 7.5, ArH), 5.57 (1H, qq, *J* 6.6 and 1.8, ArC=CH), 2.30 (3H, s, NO_2CCH_3), 1.88 – 1.86 (3H, m, CH_3), 1.22 (3H, dd, *J* 6.7 and 1.6, CH_3); δ_C 147.7 (C), 143.7 (C), 135.2 (C), 133.3 (ArC=<u>C</u>H), 130.5 (C), 129.9 (CH), 129.0 (CH), 128.9 (CH), 126.9 (CH), 124.5 (CH), 25.6 (CH_3), 14.8 (CH_3), 13.8 (CH_3).

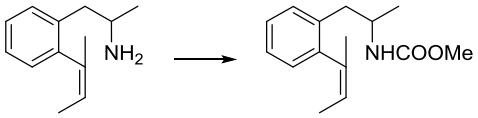
(*Z*)-1-(2-(But-2-en-2-yl)phenyl)propan-2-amine 234a



233 **234a**

To the solution of 1-(but-2-en-2-yl)-2-(-2-nitroprop-1-en-1-yl)benzene **233** (1.00 g, 4.61 mmol, 1.0 eq.) in tetrahydrofuran (15 mL) at 0 °C under an atmosphere of nitrogen was added portionwise lithium aluminium hydride (525 mg, 13.82 mmol, 3.0 eq) over 5 minutes. The reaction mixture was allowed to stir for 1 hour at the same temperature and then heated to reflux at 65 °C for 2.5 hours. The reaction was then allowed to cool to room temperature and quenched according to the General Procedure F to yield the *amine* **234a** (672 g, 77%) as a brown oil, as a single *cis* diastereoisomer and was used in the next step without further purification.

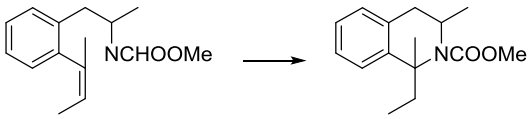
Methyl (*Z*)-(1-(2-(but-2-en-2-yl)phenyl)propan-2-yl)carbamate 234



234a **234**

A solution of 1-(2-(but-2-en-2-yl)phenyl)propan-2-amine (670 mg, 3.55 mmol, 1.0 eq.) in diethyl ether (7 mL) was cooled to 0 °C. Water (3 mL) and potassium carbonate (1.48 g, 10.64 mmol, 3.0 eq.) was added, followed by dropwise addition of methyl chloroformate (503 mg, 5.317 mmol, 1.5 eq.). The cooling bath was removed and the reaction was allowed to warm to ambient temperature over 30 minutes. The separated aqueous phase was then extracted with diethyl ether (3 x 5 mL) and the combined organic extracts washed with brine (5 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give *carbamate* **234** (400 mg, 66%) as an off-yellow oil which solidified upon standing to give long, white needles; m.p. 55 – 60 °C; δ_H 7.25 – 7.21 (1H, m, ArH), 7.21 – 7.18 (2H, m, 2 x ArH), 7.02 – 6.99 (1H, m, ArH), 5.58 (1H, q, *J* 6.6, ArC=CH), 4.51 (1H, br s, NH), 3.96 (1H, br s, NCH), 3.61 (3H, br s, OCH_3), 2.84 – 2.68 (1H, m, $ArCH_{2a}$), 2.69 – 2.51 (1H, m, $ArCH_{2b}$), 1.97 (3H, s, $ArCCH_3$), 1.38 (3H, dd, *J* 6.8 and 1.5, C=CHC<u>H</u>$_3$), 1.10 (3H, d, *J* 6.5, $NCHCH_3$); δ_C (126 MHz, $CDCl_3$) 156.3 (C=O), 142.0 (C), 136.8 (C), 135.55 (C), 129.5 (ArC=<u>C</u>H), 128.75 (ArCH), 126.7 (ArCH), 126.45 (ArCH), 122.6 (ArCH), 51.8 (OCH_3), 48.05 (NCH), 39.9 ($ArCH_2$), 25.8 (CH_3), 21.1 (CH_3), 14.8 (CH_3); HRMS calculated for $C_{15}H_{22}NO_2$ $[M+H]^+$ 248.1651, found 248.1641.

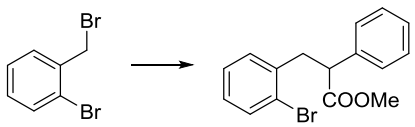
Methyl 1-ethyl-1,3-dimethyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 235



234 **235**

The carbamate **234** (70 mg, 0.283 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (0.7 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (17 mg, 0.113 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 80 °C for 15 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 4:1) to give *tetrahydroisoquinoline* **235** (30 mg, 43%) as a colourless glass and as a 4:1 mixture of *cis* and *trans* isomers; *major (cis)-isomer* δ_H 7.28 (1H, d, *J* 7.9, ArH), 7.24 (1H, t, *J* 7.5, ArH), 7.15 (1H, td, *J* 7.3 and 1.2, ArH), 7.03 (1H, d, *J* 7.5, ArH), 4.83 (1H, br s, NCH), 3.73 (3H, s, OCH_3), 3.10 (1H, dd, *J* 15.5 and 5.3, $ArCH_{2a}$), 3.06 – 3.04 (1H, m, $CH_3C\underline{H}_{2a}C$), 2.52 (1H, dd, *J* 15.4 and 2.1, $ArCH_{2b}$), 1.79 (3H, s, $ArCCH_3$), 1.49 (1H, dq, *J* 14.6 and 7.3, $CH_3C\underline{H}_{2b}C$), 1.01 (3H, d, *J* 6.8, $CHC\underline{H}_3$), 0.48 (3H, t, *J* 7.4, $C\underline{H}_3CH_2C$); δ_C 155.6 (C=O), 141.96 (C), 132.79 (C), 128.32 (ArCH), 126.62 (ArCH), 125.94 (ArCH), 125.70 (ArCH), 61.54 (C), 52.03 (OCH_3), 46.72 (NCH), 35.80 ($ArCH_2$), 27.28 (CH_2), 19.38 (CH_3), 8.35 (CH_3); *minor (trans)-isomer* δ_H 7.32 (1H, d, *J* 7.9, ArH), 7.26 – 7.13 (2H, m, 2 x ArH), 7.09 (1H, d, *J* 7.4, ArH), 4.70 (1H, br s, NCH), 3.73 (3H, s, OCH_3), 3.04 (2H, dd, *J* 15.1 and 7.5, $ArCH_{2a}$), 3.02 (1H, m, $CH_3C\underline{H}_{2a}C$), 2.56 (1H, dd, *J* 15.1 and 2.4, $ArCH_{2b}$), 2.05 (1H, dq, *J* 14.8 and 7.3, $CH_3C\underline{H}_{2b}C$), 1.57 (3H, s, $ArCCH_3$), 0.90 (3H, d, *J* 6.7, $CHC\underline{H}_3$), 0.69 (3H, t, *J* 7.4, $C\underline{H}_3CH_2C$); δ_C 141.2 (C), 133.6 (C), 129.2 (ArCH), 126.9 (ArCH), 126.1 (ArCH), 124.4 (ArCH), 62.1 (C), 52.0 (OCH_3), 47.7 (NCH), 35.9 ($ArCH_2$), 31.1 (CH_2), 20.15 (CH_3), 9.4 (CH_3); HRMS calculated for $C_{15}H_{22}NO_2$ $[M+H]^+$ 248.1651, found 248.1639.

Methyl 3-(2-bromophenyl)-2-phenylpropanoate 239

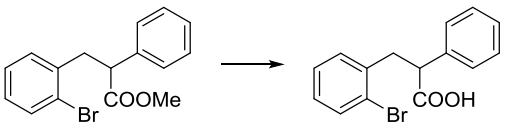


140 **239**

To a freshly made solution of lithium diisopropyl amide (3.67 mmol, 1.1 eq.) in tetrahydrofuran prepared according to General Procedure E at – 78 °C was added methyl phenylacetate (0.5 g, 3.33 mmol, 1.0 eq.) as a solution in tetrahydrofuran (1 mL) over 5 minutes. The reaction was allowed to stir for 30 minutes at

the same temperature and 2-bromobenzyl bromide (1.25 g, 5.00 mmol, 1.5 eq.) was added dropwise, as a solution in tetrahydrofuran (1 mL) over 5 minutes. The reaction was allowed to warm up to ambient temperature over 1 h and quenched with aqueous ammonium chloride (10 mL). The separated aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts washed with brine (20 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/dichloromethane 1:1) to give *ester* **239** (552 mg, 52%) as a colourless oil; ν_{max} 1736 (C=O), 1160 (C-O); δ_H (250 MHz) 7.54 (1H, dd, *J* 7.9 and 1.1, ArH), 7.35 – 7.27 (5H, m, 5 x ArH), 7.15 – 7.01 (3H, m, 3 x ArH), 4.05 (1H, dd, *J* 8.9 and 6.3, ArC<u>H</u>COOCH$_3$), 3.61 (3H, s, COOCH$_3$), 3.51 (1H, dd, *J* 13.6 and 8.9, ArCH$_{2a}$), 3.14 (1H, dd, *J* 13.6 and 6.3, ArCH$_{2b}$); δ_C 173.7 (C=O), 138.7 (C), 138.4 (C), 133.0 (ArCH), 131.65 (ArCH), 128.8 (2 x ArCH), 128.35 (ArCH), 128.0 (2 x ArCH), 127.6 (ArCH), 127.35 (ArCH), 124.8 (C-Br), 52.1 (OCH$_3$), 51.3 (CH), 40.35 (CH$_2$).

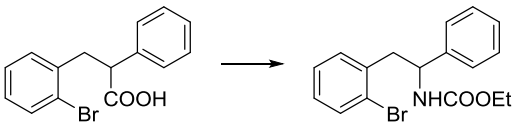
3-(2-Bromophenyl)-2-phenylpropanoic acid 240



239 **240**

To a solution of methyl 3-(2-bromophenyl)-2-phenylpropanoate **239** (552 mg, 1.73 mmol) in methanol (10 mL) at ambient temperature was added aqueous sodium hydroxide (1 mL) and the reaction mixture allowed to stir overnight. Diethyl ether (20 mL) was then added and the separated aqueous layer washed with diethyl ether (10 mL). The aqueous phase was then acidified with hydrochloric acid (2M, pH 14) and extracted with chloroform (3 x 10 mL). The combined chloroform extracts were dried, filtered and evaporated to yield the crude *carboxylic acid* **240** (354 mg, 67%) as a white glass; δ_H (250 MHz) 11.05 (1H, br s, COOH), 7.54 – 7.47 (1H, m, ArH), 7.33 – 7.20 (5H, m, 5 x ArH), 7.11 – 6.96 (3H, m, 3 x ArH), 4.03 (1H, dd, *J* 8.4 and 6.7, ArCH$_2$C<u>H</u>), 3.48 (1H, dd, *J* 13.7 and 8.5, ArCH$_{2a}$), 3.11 (1H, dd, *J* 13.7 and 6.6, ArCH$_{2b}$).

Ethyl (2-(2-bromophenyl)-1-phenylethyl)carbamate 241

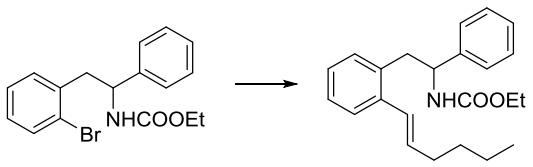


240 **241**

Diphenylphosphoryl azide (298 mg, 1.08 mmol, 1.1 eq.) and triethylamine (109 mg, 1.08 mmol, 1.1 eq.) were added to a solution of 3-(2-bromophenyl)-2-phenylpropanoic acid **240** (299 mg, 0.982 mmol, 1.0

eq.) in toluene (5 mL) under an atmosphere of nitrogen and the reaction mixture heated to reflux for 1 h. Copper (II) chloride (13 mg, 0.098 mmol, 0.1 eq.) and anhydrous ethanol (2.5 mL) were then added and the mixture heated under reflux for a further 1 h. The reaction mixture was concentrated *in vacuo* and partitioned between dichloromethane (10 mL) and water (10 mL). The separated aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with aqueous sodium bicarbonate (10 mL), brine (10 mL) and then dried, filtered and evaporated. The crude material was purified by column chromatography (dichloromethane) to yield *carbamate* **241** (146 mg, 56%) as a colourless oil; ν_{max} 3398 (br, NH), 1700 (C=O); δ_H 7.49 (1H, d, *J* 7.9, ArH), 7.31 – 7.23 (4H, m, 4 x ArH), 7.23 – 7.19 (1H, m, ArH), 7.13 (1H, td, *J* 7.5 and 1.2, ArH), 7.08 – 7.00 (2H, m, 2 x ArH), 5.19 (1H, br d, *J* 8.1, NH), 5.04 (1H, br s, NCH), 3.95 (2H, br s, OCH_2), 3.15 (2H, br d, *J* 6.0, $ArCH_2$), 1.14 (3H, br s, $OCH_2C\underline{H}_3$); δ_C 156.0 (C=O), 142.25 (C), 137.35 (C), 133.0 (ArCH), 131.5 (br ArCH), 128.7 (2 x ArCH), 128.4 (ArCH), 127.5 (ArCH), 127.4 (ArCH), 126.3 (ArCH), 125.1 (C), 60.95 (OCH_2), 55.5 (NCH), 43.2 (br. CH_2), 14.6 (CH_3); δ_H (250 MHz, 50 °C) 7.53 – 7.47 (1H, m, ArH), 7.32 – 7.17 (4H, m, 4 x ArH), 7.15 – 6.97 (3H, m, 3 x ArH), 5.08 (1H, d, *J* 6.8, NH), 5.13 – 4.97 (1H, m, NCH), 3.96 (2H, q, *J* 7.1, OCH_2), 3.17 (2H, d, *J* 6.6, $ArCH_2$), 1.10 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$).

Ethyl (*E*)-(2-(2-(hex-1-en-1-yl)phenyl)-1-phenylethyl)carbamate 242

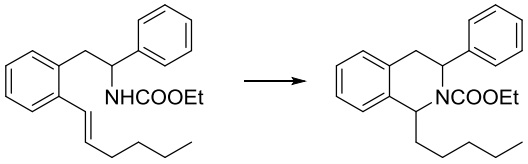


241 **242**

A solution of ethyl (2-(2-bromophenyl)-1-phenylethyl)carbamate **241** (111 mg, 1.0 eq.) in ethanol/water (1:1, 1 mL) was treated with 1-hexenylboronic acid (65 mg, 1.2 eq.), K_3PO_4 (165 mg, 2.0 eq) and $Pd(dppf)Cl_2$.DCM (9 mg, 0.10 eq) at 90 °C for 2.5 h according to General Procedure D. The crude material was purified by column chromatography (petrol/ethyl acetate 4:1) to give *carbamate* **242** (67 mg, 60%) as a colourless oil; ν_{max} 3392 (br, NH), 1701 (C=O); δ_H 7.40 (1H, d, *J* 6.9, ArH), 7.33 – 7.27 (2H, m, ArH), 7.26 – 7.17 (3H, m, ArH), 7.18 – 7.14 (1H, m, ArH), 7.08 (1H, td, *J* 7.5 and 1.3, ArH), 6.94 (1H, dd, *J* 7.6 and 1.0, ArH), 6.58 (1H, d, *J* 15.6, $ArC\underline{H}$=CH), 6.08 (1H, dt, *J* 15.4 and 6.9, ArCH=$C\underline{H}$), 5.09 (1H, br s, NH), 4.92 (1H, br. s, NCH), 4.02 (2H, d, *J* 6.6, OCH_2), 3.11 (2H, br. d, *J* 6.5, $ArCH_2$), 2.24 (2H, q, *J* 7.1, $ArCH=CHC\underline{H}_2$), 1.52 – 1.45 (2H, m, $ArCH=CHCH_2C\underline{H}_2$), 1.44 – 1.35 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.17 (3H, br s, $OCH_2C\underline{H}_3$), 0.95 (3H, t, *J* 7.2, $CH_2CH_2C\underline{H}_3$); δ_C 156.0 (C=O), 142.5 (C), 137.8 (C), 134.4 (C), 133.9 (ArCH=$\underline{C}$H), 130.5 (ArCH), 128.6 (2 x ArCH), 127.4 (ArCH), 127.4 (ArCH), 127.05 (ArCH), 126.9 (Ar$\underline{C}$H=CH), 126.5 (ArCH), 126.4 (ArCH), 60.9 (br, OCH_2), 56.3 (NCH) , 40.8

(br, $ArCH_2$), 33.1 (C=C<u>C</u>H<u>2</u>), 31.7 (<u>C</u>$H_2CH_2CH_3$), 22.45 (<u>C</u>H_2CH_3), 14.65 (OCH_2CH_3), 14.1 (CH_2<u>C</u>H_3); HRMS calculated for $C_{23}H_{29}NO_2$ $[M]^+$ 351.2198, found 351.2193.

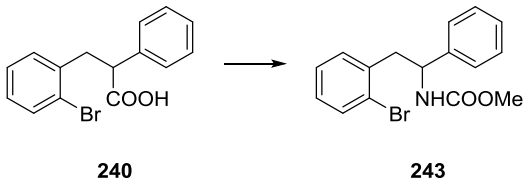
Ethyl 1-pentyl-3-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 246



242 **246**

The carbamate **242** (50 mg, 0.142 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (0.5 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (8.5 mg, 0.057 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 84 °C for 6 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 4:1) to give *tetrahydroisoquinoline* **246** (33 mg, 65%) as a yellowish glass and as a 2:1 mixture of isomers; ν_{max} 1698 (C=O); *major isomer* δ_H 7.21 – 7.12 (2H, m, 2 x ArH), 7.12 – 7.03 (5H, m, 5 x ArH), 6.89 – 6.75 (2H, m, 2 x ArH), 5.35 (1H, d, *J* 4.9, 1-CH), 5.15-5.17 (1H, m, 3-CH), 3.96 (2H, q, *J* 6.0, OCH_2), 3.56 (1H, dd, *J* 14.7 and 5.9, $ArCH_{2a}$), 2.83 (1H, m, $ArCH_{2b}$), 1.71 – 1.53 (2H, m, $ArCHC\underline{H}_2CH_2$), 1.43 – 1.11 (6H, m), 0.92 – 0.83 (6H, m, $OCH_2C\underline{H}_3$ and $CH_2CH_2C\underline{H}_3$); *minor isomer* δ_H 5.44 (1H, br. s, 3-CH), 5.01 (1H, br. d, *J* 6.9, 1-CH), 4.11 (2H, br s, OCH_2), 3.56 (1 H, dd, *J* 14.7, 5.9); only 4 distinct signals.

Methyl (2-(2-bromophenyl)-1-phenylethyl)carbamate 243

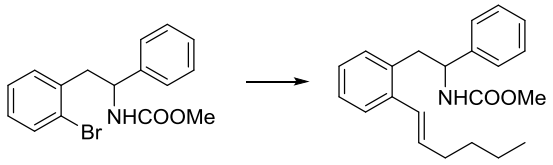


240 **243**

Diphenylphosphoryl azide (748 mg, 2.72 mmol, 1.15 eq.) and triethylamine (276 mg, 2.72 mmol, 1.15 eq.) were added to a solution of 3-(2-bromophenyl)-2-phenylpropanoic acid **240** (721 mg, 2.37 mmol, 1.0 eq.) in toluene (5 mL) under an atmosphere of nitrogen and the reaction mixture heated to reflux for 1 h. Copper (II) chloride (32 mg, 0.237 mmol, 0.1 eq.) and anhydrous methanol (2.0 mL) were then added and the mixture heated under reflux for a further 1 h. The reaction mixture was concentrated *in vacuo* and partitioned between dichloromethane (10 mL) and water (10 mL). The separated aqueous phase was

extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with aqueous sodium bicarbonate (10 mL), brine (10 mL) and then dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 3:1) to yield *carbamate* **243** (484 mg, 61%) as a colourless glass; ν_{max} 1702 (C=O); δ_H (400 MHz) 7.55 (1H, d, *J* 7.7, ArH), 7.37 – 7.24 (5H, m, 5 x ArH), 7.22 – 7.16 (1H, m, ArH), 7.14 – 7.06 (2H, m, 2 x ArH), 5.25 (1H, br s, NCH), 5.07 (1H, d, *J* 6.5, NH), 3.56 (3H, s, OCH_3), 3.19 (2H, d, *J* 7.2, $ArCH_2$); δ_C 156.3 (C=O), 142.2 (C), 137.2 (ArCH), 133.0 (ArCH), 131.4 (br C), 128.7 (2 x ArCH), 128.5 (ArCH), 127.6 (ArCH), 127.5 (ArCH), 126.3 (br ArCH), 125.1 (C), 55.7 (CH), 52.2 (OCH_3), 43.1 (CH_2); LRMS $(EI)^+$ *m/z* 259 ($[M\text{-}NHCOOCH_3]^+$, 25%), 178 ($[PhCHNHCOOMe]^+$, 70%), 162 (100%).

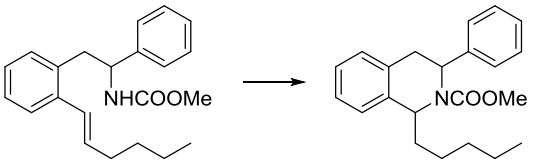
Methyl (*E*)-(2-(2-(hex-1-en-1-yl)phenyl)-1-phenylethyl)carbamate 244



243 **244**

A solution of methyl (2-(2-bromophenyl)-1-phenylethyl)carbamate (248 mg, 1.0 eq.) in ethanol/water (1:1, 2.5 mL) was treated with 1-hexenylboronic acid (142 mg, 1.2 eq.), K_3PO_4 (315 mg, 2.0 eq) and $Pd(dppf)Cl_2$.DCM (20 mg, 0.10 eq) at 60 °C for 1 h according to General Procedure D. The crude material was purified by column chromatography (petrol/ethyl acetate 4:1) to give the *carbamate* **244** (118 mg, 48%) as a colourless glass; ν_{max} 3392 (br, NH), 1696 (C=O); δ_H 7.31 (1H, d, *J* 7.7, ArH), 7.21 (2H, t, *J* 7.3, 2 x ArH), 7.16 – 7.14 (1H, m, ArH), 7.12 – 7.09 (2H, m, 2 x ArH), 7.07 (1H, d, *J* 7.6), 6.98 (1H, dt, *J* 7.6 and 1.2, ArH), 6.84 (1H, d, *J* 7.4, ArH), 6.50 (1H, d, *J* 15.6, ArC<u>H</u>=CH), 6.00 (1H, dt, *J* 15.4 and 6.9, ArCH=C<u>H</u>), 5.06 (1H, br s, NH), 4.83 (1H, br s, NCH), 3.49 (3H, s, OCH_3), 3.01 (2H, br d, *J* 6.5, $ArCH_2$), 2.15 (2H, q, *J* 7.2, CH=CHC<u>H</u>$_2$), 1.43 – 1.36 (2H, m, $CH_3CH_2C\underline{H}_2$), 1.32 (2H, ddq, *J* 14.1, 7.0 and 2.0, $CH_3C\underline{H}_2$), 0.87 (3H, t, *J* 7.2, CH_3); δ_C 156.3 (C=O), 142.4 (C), 137.75 (C), 134.3 (C), 133.95 (ArCH=<u>C</u>), 130.5 (ArCH), 128.6 (2 x ArCH), 127.45 (ArCH), 127.3 (ArCH), 127.1 (ArCH), 126.9 (Ar<u>C</u>H=C), 126.45 (ArCH), 126.4 (ArCH), 56.4 (NCH), 52.15 (OCH_3), 40.7 ($ArCH_2$), 33.1 (CH_2), 31.6 (CH_2), 29.8 (CH_2), 22.4 (CH_2), 14.1 (CH_3).

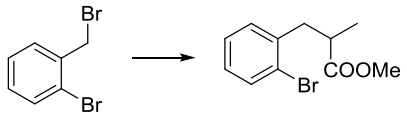
Methyl 1-pentyl-3-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 245



244 **245**

The carbamate **244** (52 mg, 0.154 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (0.5 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (9 mg, 0.062 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 84 °C for 6 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 4:1) to give *carbamate* **245** (31 mg, 60%) as a yellowish glass and as a 2:1 mixture of isomers; ν_{max} 1702 (C=O); *major isomer* δ_H (400 MHz) 7.19 – 7.17 (1H, m, ArH), 7.15 – 6.97 (3H, m, 4 x ArH), 6.97 – 6.86 (4H, m, 4 x ArH), 6.69 – 6.67 (1H, m, ArH), 5.23 (1H, br d, *J* 4.4, 3-CH), 5.00 (1H, br d, *J* 6.9, 1-CH), 3.44 – 3.38 (3H, br s, OCH_3), 3.38 (1H, m, $ArCH_{2a}$), 2.68 (1H, br d, *J* 14.9, $ArCH_{2b}$), 1.97 – 1.86 (2H, m, $ArCHC\underline{H}_2CH_2$), 1.34 – 1.00 (6H, m), 0.78 – 0.69 (6H, m); *minor isomer* δ_H (400 MHz) 5.29 (1H, s, 3-CH), 4.86 (1H, d, *J* 7.4, 1-CH), 3.59 (3H, s, OCH_3), 3.18 (1H, dd, *J* 15.6 and 7.8, $ArCH_{2a}$), 3.03 – 2.85 (1H, m, $ArCH_{2b}$), 1.86 – 1.76 (2H, m, $ArCHC\underline{H}_2CH_2$).

Methyl 3-(2-bromophenyl)-2-methylpropanoate 248

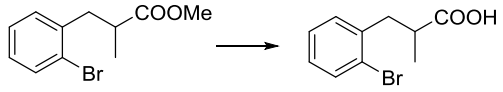


140 **248**

To a freshly made solution of lithium diisopropyl amide (22.23 mmol, 1.0 eq.) in tetrahydrofuran prepared according to General Procedure E at – 78 °C was added methyl propionate (1.95 g, 22.23 mmol, 1.0 eq.) as a solution in tetrahydrofuran (5 mL) over 5 minutes. The reaction was allowed to stir for 30 minutes at the same temperature and 2-bromobenzyl bromide (10.0 g, 40.1 mmol, 1.8 eq.) was added dropwise, as a solution in tetrahydrofuran (15 mL) over 5 minutes. The reaction was allowed to warm up to ambient temperature over 1 h and quenched with aqueous ammonium chloride (40 mL). The separated aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts washed with brine (20 mL), dried, filtered and evaporated to give the *ester* **248** (3.427 g, 60%) as a colourless oil; ν_{max} 1739 (C=O), 1152 (C-O); δ_H (250 MHz) 7.58 – 7.47 (1H, m, ArH), 7.19 (2H, m, 2 x ArH), 7.08 –

7.06 (1H, m, ArH), 3.63 (3H, s, OCH_3), 3.13 (1H, dd, *J* 12.5 and 6.7, $ArCH_{2a}$), 2.96 – 2.75 (2H, m, $ArCH_{2b}$ and $C\underline{H}COOCH_3$), 1.19 (3H, d, *J* 6.8, CH_3).

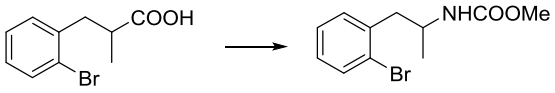
3-(2-Bromophenyl)-2-methylpropanoic acid[239] 249



248 **249**

To a solution of methyl methyl 3-(2-bromophenyl)-2-methylpropanoate **248** (3.427 mg, 13.34 mmol) in methanol (50 mL) at ambient temperature was added aqueous sodium hydroxide (4 mL) and the reaction mixture allowed to stir at 60 °C for 2h. The reaction was cooled to ambient temperature and diethyl ether (20 mL) was added and the separated aqueous layer washed with diethyl ether (10 mL). The aqueous phase was then acidified with hydrochloric acid (2M, pH 1) and extracted with chloroform (3 x 20 mL). The combined chloroform extracts were dried, filtered and evaporated to yield crude *carboxylic acid* **249** (1.88 g, 58%) as a white solid; δ_H 12.06 (1H, br. s, COOH), 7.57 (1H, d, *J* 7.8, ArH), 7.27 – 7.24 (2H, m, 2 x ArH), 7.12 – 7.09 (1H, m, ArH), 3.23 (1H, dd, *J* 13.6 and 6.9, $ArCH_{2a}$), 3.00 – 2.92 (1H, m, NCH), 2.85 (1H, dd, *J* 13.6 and 7.7, $ArCH_{2b}$), 1.26 (3H, d, *J* 7.0, CH_3); δ_C 182.7 (C=O), 138.6 (C), 133.1 (ArCH), 131.45 (ArCH), 128.3 (ArCH), 127.5 (ArCH), 124.9 (C-Br), 39.6 (CH), 39.4 (CH_2), 16.8 (CH_3); HRMS (ES^-)calculated for $C_{10}H_{11}BrO_2$ $[M-H]^-$ 240.9864, found 240.9868.

Methyl (1-(2-bromophenyl)propan-2-yl)carbamate 250

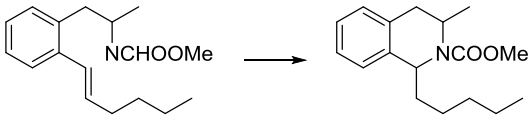


249 **250**

Diphenylphosphoryl azide (4.46 g, 16.22 mmol, 1.15 eq.) and triethylamine (1.64 g, 16.22 mmol, 1.15 eq.) were added to a solution of 3-(2-bromophenyl)-2-methylpropanoic acid **249** (3.20 g, 14.10 mmol, 1.0 eq.) in toluene (50 mL) under an atmosphere of nitrogen and the reaction mixture heated to reflux for 1 h. Copper (II) chloride (190 mg, 1.41 mmol, 0.1 eq.) and anhydrous methanol (20 mL) were then added and the mixture heated under reflux for a further 1 h. The reaction mixture was concentrated *in vacuo* and partitioned between dichloromethane (50 mL) and water (50 mL). The separated aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with aqueous sodium bicarbonate (10 mL), brine (10 mL) and then dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 4:1) to yield *carbamate* **250** (1.95 g, 50%) as a colourless glass; δ_H (400 MHz) 7.51 (1H, d, *J* 8.0, ArH), 7.21 (2H, app d, *J* 4.5, 2 x ArH), 7.10 – 7.01

(1H, m, ArH), 4.87 (1H, br s, NH), 4.10 – 3.98 (1H, br m, NCH), 3.58 (3H, s, OCH_3), 3.01 – 2.90 (1H, br. m, $ArCH_{2a}$), 2.85 (1H, br dd, *J* 13.5 and 6.7, $ArCH_{2a}$), 1.17 (3H, d, *J* 6.6, CH_3); δ_C (101 MHz) 156.4 (C=O), 138.0 (C), 132.95 (ArCH), 131.4 (ArCH), 128.2 (ArCH), 127.5 (ArCH), 125.1 (C-Br), 52.0 (OCH_3), 47.8 (CH), 42.6 (CH_2), 20.8 (CH_3).

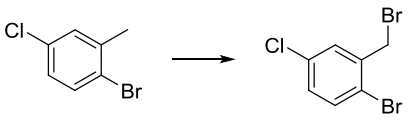
Methyl 3-methyl-1-pentyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 252



251 **252**

The carbamate **251** (57 mg, 0.207 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (0.6 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (12 mg, 0.083 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 84 °C for 10 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 4:1) to give *tetrahydroisoquinoline* **252** (41 mg, 60%) as a colourless glass and as a 4:1 mixture of isomers; ν_{max} 1697 (C=O), 1222 (C-O); *major isomer* δ_H 7.25 – 7.09 (2H, m, 2 x ArH), 7.06 (1H, br s, ArH), 4.72 (1H, br s, ArCHN), 4.41 (1H, br s, $ArCH_2C\underline{H}N$), 3.76 (3H, s, OCH_3), 3.23 (1H, dd, *J* 14.9 and 5.3, $ArCH_{2a}$), 2.55 (1H, br. d, *J* 13.6, $ArCH_{2b}$), 1.33 – 1.05 (8H, m, 4 x CH_2), 0.83 (6H, m, $CH_2C\underline{H}_3$ and $CHC\underline{H}_3$); δ_H (DMSO, 90 °C) 7.33 – 7.18 (4H, m, 4 x ArH), 4.73 (1H, dd, *J* 9.5 and 3.0, ArCHN), 4.39 – 4.35 (1H, m, $ArCH_2C\underline{H}N$), 3.72 (3H, s, OCH_3), 3.24 (1H, dd, *J* 15.0 and 5.3, $ArCH_{2a}$), 2.67 (1H, app d, *J* 15.0, $ArCH_{2a}$), 1.67 – 1.02 (8H, m, 4 x CH_2), 0.86 (6H, m, $CH_2C\underline{H}_3$ and $CHC\underline{H}_3$); δ_C 156.8 (C=O), 137.2 (C), 128.8 (ArCH), 127.4 (ArCH), 127.8 (ArCH), 126.2 (C), 126.0 (ArCH), 56.8 (ArCHN), 52.3 (OCH_3), 48.0 ($ArCH_2\underline{C}H$), 35.15 ($ArCH_2$), 31.7 (CH_2), 31.5 (CH_2), 25.8 (CH_2), 22.6 (CH_2), 19.9 (br. CH_3), 14.0 (CH_3); *minor isomer* δ_H 7.23 – 7.02 (4H, m, 4 x ArH), 5.18 (1H, br s, ArCHN), 4.13 (1H, br s, $ArCH_2C\underline{H}N$), 3.69 (3H, s, OCH_3), 2.97 (1H, dd, *J* 15.4 and 6.2, $ArCH_{2a}$), 2.81 (1H, dd, *J* 15.6 and 9.8, $ArCH_{2b}$), 1.98 – 1.42 (8H, m, 4 x CH_2), 1.39 (3H, d, *J* 6.3, $CHC\underline{H}_3$), 0.96 – 0.85 (3H, m, CH_2CH_3); δ_H (DMSO, 90 °C) 7.34 – 7.18 (4H, m, 4 x ArH), 5.13 (1H, br s, ArCHN), 4.10 – 4.01 (1H, br m, $ArCH_2C\underline{H}N$), 3.66 (1H, s, OCH_3), 3.07 (1H, dd, *J* 15.8 and 7.0, $ArCH_{2a}$), 2.85 (1H, dd, *J* 15.8 and 10.0, $ArCH_{2b}$), 1.88 – 1.42 (8H, m, 4 x CH_2), 1.39 (3H, d, *J* 6.2, $CHC\underline{H}_3$), 0.94 – 0.89 (3H, m, $CH_2C\underline{H}_3$); δ_C 56.6 (ArCHN), 52.4 (OCH_3), 47.9 ($ArCH_2\underline{C}H$), 34.95 ($ArCH_2$), 26.4 (CH_2), 22.5 (CH_2), 20.0 (CH3), 14.0 (CH_3); only 8 distinctive signals; HRMS calculated for $C_{17}H_{26}NO_2$ $[M+H]^+$ 276.1964, found 276.1964

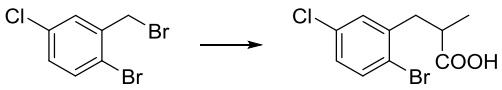
1-Bromo-2-(bromomethyl)-4-chlorobenzene[240] **254**



253 **254**

To a solution of 1-bromo-4-chloro-2-methylbenzene **253** (5.0 g, 24.3 mmol, 1.0 eq.) in carbon tetrachloride (100 mL) at ambient temperature was added *N*-bromosuccinimide (4.3 g, 24.3 mmol, 1.0 eq.) and AIBN (40 mg, 0.243 mmol, 0.01 eq.) and the solution was heated to reflux at 80 °C for 8 h. The reaction mixture was allowed to cool to ambient temperature, aqueous sodium bicarbonate (100 mL) was added and the mixture was stirred for a further 2 h. The separated organic phase was washed with brine (50 mL), dried, filtered and evaporated and the crude material purified by Kugelrohr distillation (185 – 210 °C, 20 mbar) to give *bromide* **254** (5.25 g, 76%) as a pale yellow oil; δ_H (250 MHz) 7.50 (1H, d, *J* 8.5, ArH), 7.45 (1H, d, *J* 2.5, ArH), 7.15 (1H, dd, *J* 8.5 and 2.5, ArH), 4.53 (2H, s, $ArCH_2$); δ_C (101 MHz) 138.7 (C), 134.5 (ArCH), 133.85 (C), 131.2 (ArCH), 130.3 (ArCH), 122.4 (C-Br), 32.4 (CH_2).

3-(2-Bromo-5-chlorophenyl)-2-methylpropanoic acid 256

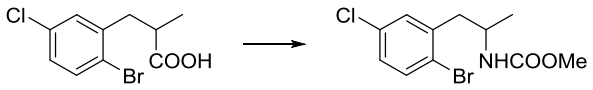


254 **256**

To a freshly made solution of lithium diisopropyl amide (23.83 mmol, 1.5 eq.) in tetrahydrofuran prepared according to General Procedure E at – 78 °C was added methyl propionate (2.10 g, 23.83 mmol, 1.5 eq.) as a solution in tetrahydrofuran (5 mL) over 5 minutes. The reaction was allowed to stir for 30 minutes at the same temperature and 1-bromo-2-(bromomethyl)-4-chlorobenzene **254** (4.52 g, 15.88 mmol, 1.0 eq.) was added dropwise, as a solution in tetrahydrofuran (15 mL) over 5 minutes. The reaction was allowed to warm up to ambient temperature over 1 h and quenched with aqueous ammonium chloride (40 mL). The separated aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts washed with brine (20 mL), dried, filtered and evaporated. The residue was dissolved in methanol (70 mL) at ambient temperature and aqueous aqueous sodium hydroxide (4 mL) was added and the reaction mixture allowed to stir at 60 °C for 2 h. The reaction was cooled to ambient temperature and diethyl ether (20 mL) was added and the separated aqueous layer washed with diethyl ether (10 mL). The aqueous phase was then acidified with hydrochloric acid (2M, pH 1) and extracted with chloroform (3 x 20 mL). The combined chloroform extracts were dried, filtered and evaporated to yield *carboxylic acid*

256 (1.69 g mg, 38%) as a yellow oil; ν_{max} 3468 (OH), 1741 (C=O); δ_H 10.75 (1H, br s, COOH), 7.45 (1H, d, *J* 8.5, ArH), 7.21 (1H, d, *J* 2.5, ArH), 7.06 (1H, dd, *J* 8.5 and 2.6, ArH), 3.14 (1H, dd, *J* 13.6 and 7.0, $ArCH_{2a}$), 2.93 – 2.85 (1H, m, NCH), 2.77 (1H, dd, *J* 13.6 and 7.6, $ArCH_{2b}$), 1.23 (3H, d, *J* 7.0, CH_3).

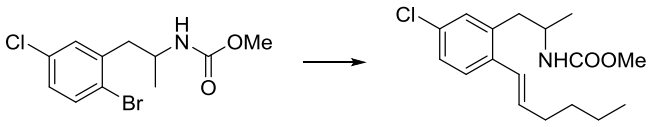
Methyl (1-(2-bromo-5-chlorophenyl)propan-2-yl)carbamate 257



256 **257**

Diphenylphosphoryl azide (1.83 g, 6.63 mmol, 1.15 eq.) and triethylamine (671 mg, 6.63 mmol, 1.15 eq.) were added to a solution of 3-(2-bromo-5-chlorophenyl)-2-methylpropanoic acid **256** (1.60 g, 5.77 mmol, 1.0 eq.) in toluene (30 mL) under an atmosphere of nitrogen and the reaction mixture heated to reflux for 1 h. Copper (II) chloride (77 mg, 0.57 mmol, 0.1 eq.) and anhydrous methanol (2.8 mL) were then added and the mixture heated under reflux for a further 1 h. The reaction mixture was concentrated *in vacuo* and partitioned between dichloromethane (50 mL) and water (50 mL). The separated aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with aqueous sodium bicarbonate (10 mL), brine (10 mL) and then dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 1:1) to yield *carbamate* **257** (1.95 g, 50%) as a colourless glass; ν_{max} 3350 (br, NH), 1681 (C=O), 1103 (C-O); δ_H 7.43 (1H, d, *J* 8.5, ArH), 7.20 (1H, d, *J* 1.9, ArH), 7.04 (1H, dd, *J* 8.5 and 2.6, ArH), 4.78 (1H, br. s, NH), 4.05 – 3.96 (1H, br. m, NCH), 3.59 (3H, s, OCH_3), 2.89 (1H, br. s, $ArCH_{2a}$), 2.82 (1H, dd, *J* 13.5 and 6.6, $ArCH_{2b}$), 1.17 (3H, d, *J* 6.6, CH_3); δ_C 156.35 (C=O), 139.9 (C), 133.9 (ArCH), 133.3 (C), 131.2 (ArCH), 128.3 (ArCH), 122.9 (C-Br), 52.0 (OCH_3), 47.6 (CH), 42.6 (CH_2), 20.8 (CH_3).

Methyl (*E*)-(1-(5-chloro-2-(hex-1-en-1-yl)phenyl)propan-2-yl)carbamate 258

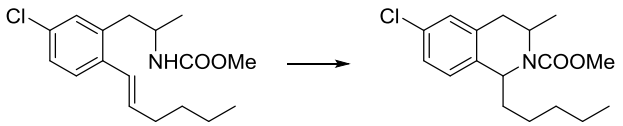


257 **258**

A solution of methyl (1-(2-bromo-5-chlorophenyl)propan-2-yl)carbamate **257** (148 mg, 1.0 eq.) in ethanol/water (1:1, 1.5 mL) was treated with 1-hexenylboronic acid (92 mg, 1.2 eq.), K_3PO_4 (205 mg, 2.0 eq) and Pd(dppf)Cl_2.DCM (8 mg, 0.04 eq) at 90 °C for 2.5 h according to General Procedure D. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give *carbamate* **258** (100 mg, 67%) as a pale yellow solid; m.p. 42 – 44 °C; ν_{max} 3348 (br, NH), 1700 (C=O); δ_H (400 MHz)

7.36 (1H, d, *J* 8.4, ArH), 7.14 (1H, dd, *J* 8.4 and 2.2, ArH), 7.08 (1H, d, *J* 1.9, ArH), 6.63 (1H, d, *J* 15.5, ArC<u>H</u>=CH), 6.08 (1H, dt, *J* 15.5 and 7.0, ArCH=C<u>H</u>), 4.62 (1H, br d, *J* 6.0, NH), 3.90 (1H, br m, NCH), 3.64 (3H, s, OCH_3), 2.94 (1H, dd, *J* 13.6 and 5.9, $ArCH_{2a}$), 2.63 (1H, br. dd, *J* 12.8 and 7.7, $ArCH_{2b}$), 2.24 (2H, dq, *J* 7.3 and 1.2, ArCH=CHC<u>H</u>$_2$), 1.50 – 1.42 (2H, m, CH_3CH_2C<u>H</u>$_2$), 1.37 (2H, ddq, *J* 14.1, 7.0 and 1.8, CH_3C<u>H</u>$_2CH_2$), 1.09 (3H, d, *J* 6.6, C<u>H</u>$_3$CHN), 0.93 (3H, t, *J* 7.2, C<u>H</u>$_3CH_2$); δ_C (101 MHz) 156.3 (C=O), 136.9 (C), 136.0 (C), 134.1 (Ar<u>C</u>H=C), 132.2 (C), 130.4 (ArCH), 127.5 (ArCH), 127.0 (ArCH), 126.4 (ArCH=<u>C</u>), 52.0 (OCH_3), 47.85 (NCH), 40.1 ($ArCH_2$), 33.1 (CH_2), 31.6 (CH_2), 22.4 (CH_2), 20.4 (CH_3), 14.1 (CH_3); HRMS calculated for $C_{17}H_{25}ClNO_2$ $[M+H]^+$ 310.1574, found 310.1563.

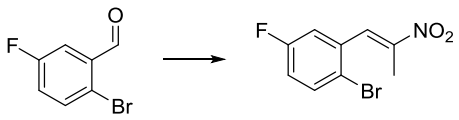
Methyl 6-chloro-3-methyl-1-pentyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 259



258 **259**

The carbamate **258** (41 mg, 0.134 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (0.4 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (8 mg, 0.054 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 84 °C for 10 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 4:1) to give *tetrahydroisoquinoline* **259** (31 mg, 76%) as a colourless glass and as a 3.5:1 mixture of isomers; ν_{max} 1699 (C=O); *major diastereoisomer* δ_H 7.18 – 7.15 (2H, m, 2 x ArH), 6.99 (1H, d, *J* 7.0, ArH), 4.73 (1H, br s, ArCHN), 4.39 (1H, br s, $ArCH_2C$<u>H</u>), 3.75 (3H, s, OCH_3), 3.20 (1H, dd, *J* 15.0 and 5.3, $ArCH_{2a}$), 2.52 (1H, br d, *J* 15.0, $ArCH_{2b}$), 2.00 – 1.80 (2H, m, ArCHC<u>H</u>$_2$), 1.34 – 1.02 (6H, m, 3 x CH_2), 0.90 (3H, m, C<u>H</u>$_3$CH), 0.82 (3H, t, *J* 6.8, C<u>H</u>$_3CH_2$); δ_C 156.1 (C=O), 135.9 (C), 132.8 (C), 129.0 (ArCH), 128.8 (ArCH), 126.35 (ArCH), 56.5 (ArNCH), 52.5 (OCH_3), 47.7 (N<u>C</u>HCH_3), 36.39 (CH_3), 36.8 (CH_2), 34.8 ($ArCH_2$), 31.6 (CH_2), 25.9 (CH_2), 22.7 (CH_2), 14.1 (CH_3); *minor diastereoisomer* δ_H 7.14 – 7.11 (2H, m, 2 x ArH), 7.03 (1H, d, *J* 8.0, ArH), 5.13 (1H, br s, ArCHN), 4.14 (1H, br s, $ArCH_2C$<u>H</u>), 3.70 (3H, s, OCH_3), 2.93 (1H, dd, *J* 15.7 and 6.7, $ArCH_{2a}$), 2.77 (1H, dd, *J* 15.8 and 9.5, $ArCH_{2b}$), 1.97 – 1.68 (2H, m, CH_2), 1.37 (3H, d, *J* 6.3, C<u>H</u>$_3$CH), 1.31 – 1.13 (6H, m, 3 x CH_2), 0.90 – 0.86 (3H, m, C<u>H</u>$_3CH_2$); δ_C 135.8 (C), 132.6 (C), 128.1 (ArCH), 127.85 (ArCH), 126.4 (ArCH), 56.5 (ArNCH), 47.7 (N<u>C</u>HCH_3), 36.5 (CH_2), 35.0 ($ArCH_2$), 31.8 (CH_2), 26.6 (CH_2), 22.5 (CH_2), 19.4 (CH_3), 14.15 (CH_3).

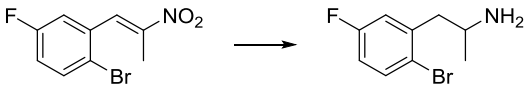
(*E*)-1-Bromo-4-fluoro-2-(2-nitroprop-1-en-1-yl)benzene 260



259 **260**

To a solution of 2-bromo-5-fluorobenzaldehyde (1.1 g, 5.42 mmol, 1.0 eq.) in nitroethane (7.4 g, 98.5 mmol, 20 eq.) was added ammonium acetate (304 mg, 3.94 mmol, 0.8 eq.) and the mixture heated to reflux for 3 hours. The reaction was then allowed to cool to room temperature, and the solvent was removed *in vacuo* at 5 mbar pressure and at 60 °C for 1 hour. The crude reaction mixture was redissolved in diethyl ether (100 mL), washed with water (3 x 25 mL), dried, filtered and evaporated. The crude material was recrystallized from hot hexane to give *nitroalkene* **260** (1.24 g, 88%) as a yellow solid; m.p. 56 – 59 °C; δ_H 8.04 (1H, s, ArC<u>H</u>=CH), 7.65 – 7.61 (1H, m, ArH), 7.04 (1H, d, *J* 8.5, ArH), 7.06 – 6.99 (1H, m, ArH), 2.33 (3H, d, *J* 1.1, CH_3); δ_C 161.7 (d, *J* 248.9, C-F), 149.9 (CH=<u>C</u>NO_2), 134.9 (d, *J* 8.1, FC-ArCH-<u>C</u>), 134.7 (d, *J* 8.2, FC-ArCH-Ar<u>C</u>H), 131.7 (<u>C</u>H=CNO_2), 119.0 (d, *J* 3.4, C-Br), 118.3 (d, *J* 22.4, FC-ArCH_a), 117.45 (d, *J* 23.9, FC-ArCH_b), 13.9 (CH_3).

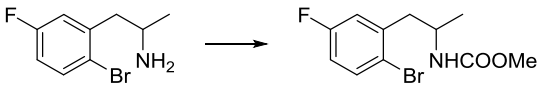
1-(2-Bromo-5-fluorophenyl)propan-2-amine 261



260 **261**

A solution of (*E*)-1-Bromo-4-fluoro-2-(2-nitroprop-1-en-1-yl)benzene **260** (1.24 g, 4.76 mmol, 1.0 eq.) in tetrahydrofuran was treated with sodium borohydride (855 mg, 22.61 mmol, 4.75 eq.), and boron trifluoride diethyl etherate (4.05 g, 28.56 mmol, 6.0 eq.) according to the General Procedure F to afford *amine* **261** (692 mg, 63%) as a brown oil; δ_H (250 MHz) 7.49 – 7.46 (1H, m, ArH), 6.98 – 6.95 (1H, m, ArH), 6.86 – 6.76 (1H, m, ArH), 3.34 – 3.19 (1H, m, NCH), 2.81 (1H, dd, *J* 13.3 and 5.6, ArCH_{2a}), 2.65 (1H, dd, *J* 13.3 and 7.8, ArCH_{2b}), 2.42 – 1.44 (2H, m, br s, NH_2), 1.14 (3H, d, *J* 6.3, CH_3); δ_C 161.78 (d, *J* 246.9, C-F), 141.3 (d, *J* 7.4, FC-ArCH-Ar<u>C</u>), 134.0 (d, *J* 8.1, FC-ArCH-Ar<u>C</u>H), 118.9 (d, *J* 3.1, C-Br), 118.2 (d, *J* 22.2, FC-ArCH_a), 115.1 (d, *J* 22.4, FC-ArCH_a), 47.0 (CH), 46.5 (CH_2), 23.5 (CH_3).

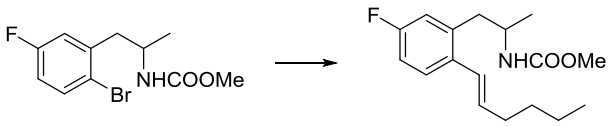
Methyl (1-(2-bromo-5-fluorophenyl)propan-2-yl)carbamate 262



261 **262**

A solution of 1-(2-bromo-5-fluorophenyl)propan-2-amine **261** (691 mg, 2.98 mmol, 1.0 eq.) in diethyl ether (4 mL) was cooled to 0 °C. Water (4 mL) and potassium carbonate (1.26 g, 9.04 mmol, 3.0 eq.) was added, followed by dropwise addition of methyl chloroformate (395 mg, 4.174 mmol, 1.4 eq.). The cooling bath was removed and the reaction was allowed to warm to ambient temperature over 30 minutes. The separated aqueous phase was then extracted with diethyl ether (3 x 5 mL) and the combined organic extracts washed with brine (5 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 1:1) to give *carbamate* **262** (651 mg, 75%) as an off-yellow oil; ν_{max} 3345 (br, NH), 1681 (C=O), 1058 (C-O); δ_H 7.49 – 7.46 (1H, m, ArH), 6.95 (1H, m, ArH), 6.83 – 6.79 (1H, m, ArH), 4.72 (1H, d, *J* 7.7, NH), 4.03 (1H, br d, *J* 6.2, NCH), 3.60 (3H, s, OCH_3), 2.92 (1H, br d, *J* 6.3, $ArCH_{2a}$), 2.84 (1H, dd, *J* 13.5 and 6.6, $ArCH_{2b}$), 1.19 (3H, d, *J* 6.6, CH_3); δ_C 161.8 (d, J 246.9, C-F), 156.2 (br s, C=O), 140.1 (d, J 7.4, C), 133.9 (d, J 8.0, ArCH), 119.0 (d, J 3.0, C-Br), 118.1 (d, J 22.4, ArH), 115.3 (d, J 22.4, ArCH), 52.0 (OCH_3), 47.6 (NCH), 42.7 (CH_2), 20.7 (CH_3).

Methyl (*E*)-(1-(5-fluoro-2-(hex-1-en-1-yl)phenyl)propan-2-yl)carbamate 263

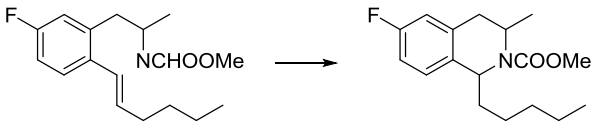


262 **263**

A solution of methyl (1-(2-bromo-5-fluorophenyl)propan-2-yl)carbamate **262** (441 mg, 1.0 eq.) in ethanol/water (1:1, 4 mL) was treated with 1-hexenylboronic acid (291 mg, 1.5 eq.), K_3PO_4 (645 mg, 2.0 eq) and Pd(dppf)Cl_2.DCM (41 mg, 0.05 eq) at 85 °C for 2 h according to General Procedure D. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give the *carbamate* **263** (301 mg, 68%) as a pale yellow oil; ν_{max} 3330 (br, NH), 1701 (C=O); δ_H 7.38 – 7.35 (1H, m, ArH), 6.87 – 6.86 (1H, m, ArH), 6.81 (1H, d, *J* 9.4, ArH), 6.62 (1H, d, *J* 15.5, ArC<u>H</u>=CH), 6.02 (1H, dt, *J* 15.4 and 7.0, ArCH=C<u>H</u>), 4.75 (1H, br s, NH), 3.92 (1H, br s, NCH), 3.63 (3H, s, OCH_3), 2.94 (1H, dd, *J* 13.6 and 6.1, $ArCH_{2a}$), 2.65 (1H, br dd, *J* 12.2 and 7.3, $ArCH_{2b}$), 2.23 (2H, qd, *J* 7.3 and 1.3, ArCH=CHC<u>H_2</u>), 1.49 – 1.41 (2H, m, CH_3CH_2C<u>H_2</u>), 1.37 (2H, dq, *J* 13.9 and 6.9, CH_3C<u>H_2</u>), 1.10 (2H, d, *J* 6.6, C<u>H_3</u>CH), 0.92 (3H, t, *J* 7.3, C<u>H_3</u>CH_2); δ_H (250 MHz, 50 °C) 7.39 – 7.35 (1H, m, ArH), 6.89 – 6.80 (2H, m, 2 x ArH), 6.62 (1H, d, *J* 15.6, ArC<u>H</u>=CH), 6.02 (1H, dt, *J* 15.5 and 6.9, ArCH=C<u>H</u>), 4.55 (1H, d, *J* 6.9, NH), 3.95 – 3.92 (1H, m, NCH), 3.64 (3H, s, OCH_3), 2.94 (1H, dd, *J* 13.7 and 6.2, $ArCH_{2a}$), 2.67 (1H, dd, *J* 13.7 and 7.5, $ArCH_{2b}$), 2.24 (2H, qd, *J* 7.1 and 1.2, ArCH=CHC<u>H_2</u>), 1.55 – 1.31 (4H, m, CH_3C<u>H_2</u>C<u>H_2</u>), 1.12 (3H, d, *J*

6.6, C<u>H</u>$_3$CH), 0.94 (3H, t, *J* 7.1, C<u>H</u>$_3$CH$_2$); δ_C 161.7 (d, *J* 245.5, C-F), 156.3 (C=O), 137.3 (d, *J* 7.2, Ar<u>C</u>-CH=CH), 133.7 (C), 133.3 (Ar<u>C</u>H=CH), 127.8 (d, *J* 8.0, FC-ArCH-Ar<u>C</u>H), 126.5 (ArC-CH=<u>C</u>H), 116.95 (d, *J* 21.0, FC-Ar<u>C</u>H$_a$), 113.7 (d, *J* 21.1, FC-Ar<u>C</u>H$_b$), 51.9 (OCH_3), 47.9 (NCH), 40.1 ($ArCH_2$), 33.0 (CH=CH<u>C</u>H$_2$), 31.6 (CH_2), 22.35 (CH_2), 20.4 (CH_3), 14.0 (CH_3); HRMS calculated for $C_{17}H_{25}FNO_2$ $[M+H]^+$ 294.1869, found 294.1858.

Methyl 6-fluoro-3-methyl-1-pentyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 264

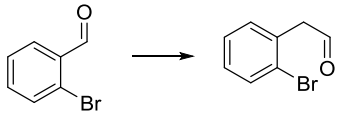


263 **264**

The carbamate **263** (83 mg, 0.283 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (0.8 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (17 mg, 0.113 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 84 °C for 6 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give *tetrahydroisoquinoline* **264** (62 mg, 75%) as a colourless glass and as a 2:1 mixture of isomers; ν_{max} 1699 (C=O), 1245 (C-O); *major diastereoisomer* δ_H 7.08 – 6.98 (1H, br m, ArH), 6.90 – 6.81 (2H, m, 2 x ArH), 4.70 (1H, br m, ArCHN), 4.40 (1H, br m, $ArCH_2C\underline{H}$), 3.75 (3H, s, OCH_3), 3.21 (1H, dd, *J* 15.0 and 5.3, $ArCH_{2a}$), 2.52 (1H, br d, *J* 13.8, $ArCH_{2b}$), 1.82 – 1.71 (2H, m, ArCHC<u>H</u>$_2$), 1.30 – 1.12 (6H, m, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 0.87 (3H, m, C<u>H</u>$_3$CH), 0.82 (3H, t, *J* 6.3, C<u>H</u>$_3$CH$_2$); δ_H (250 MHz, 50 °C) 7.10 – 6.97 (1H, m, ArH), 6.92 – 6.82 (2H, m, 2 x ArH), 4.74 (1H, dd, *J* 9.5 and 3.7, ArCHN), 4.46 – 4.33 (1H, m, $ArCH_2C\underline{H}N$), 3.75 (3H, s, OCH_3), 3.22 (1H, dd, *J* 15.0 and 5.3, $ArCH_{2a}$), 2.52 (1H, dd, *J* 15.1 and 2.1, $ArCH_{2b}$), 1.94 – 1.42 (2H, m, ArCHC<u>H</u>$_2$), 1.34 – 1.00 (6H, m, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 0.90 (3H, d, *J* 6.4, CHC<u>H</u>$_3$), 0.83 (3H, t, *J* 6.7, C<u>H</u>$_3$CH$_2$); δ_C 161.9 (d, *J* 245.4, C-F), 156.1 – 155.7 (br C=O), 136.0 (d, *J* 7.6, C), 133.0 (C) 128.8 (br ArCH), 115.8 (br ArCH), 113.0 (d, *J* 21.2, ArCH), 56.4 (br s, NCH), 52.5 (OCH_3), 47.7 (br s, CH), 36.8 (br s, CH_2) 35.3 (br s, Ar-CH_2), 31.8 (CH_2), 26.0 (CH_2), 22.7 (CH_2), 20.5 (CH_3), 14.1 (CH_3); *minor diastereoisomer* δ_H 7.08 – 6.98 (1H, br m, ArH), 6.90 – 6.81 (2H, m, 2 x ArH), 5.27 – 4.92 (1H, b s, ArCHN), 4.08 (1H, b s, $ArCH_2C\underline{H}$), 3.69 (3H, s, OCH_3), 2.94 (1H, br dd, *J* 15.4 and 6.2, $ArCH_{2a}$), 2.52 (1H, br. app d, *J* 13.8, $ArCH_{2b}$), 1.48 – 1.40 (2H, m, ArCHC<u>H</u>$_2$), 1.38 (3H, d, *J* 6.3, C<u>H</u>$_3$CH), 1.30 – 1.12 (6H, m, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 0.87 (3H, m, C<u>H</u>$_3$CH$_2$); δ_H (250 MHz, 50 °C) 7.10 – 6.98 (1H, m, ArH), 6.92 – 6.83 (2H, m, 2 x ArH), 5.14 – 5.12 (1H, m, ArCHN), 4.22 – 4.07 (1H, m, $ArCH_2C\underline{H}N$), 3.70 (3H, s, OCH_3), 2.94 (1H, dd, *J* 15.9 and 7.0, $ArCH_{2a}$), 2.79 (1H, dd, *J* 15.8 and 9.4, $ArCH_{2b}$), 1.94 – 1.44 (2H, m, ArCHC<u>H</u>$_2$), 1.39 (3H, d, *J* 6.3, C<u>H</u>$_3$CH), 1.35 – 1.00 (6H, m, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 0.90-0.78 (3H, m, C<u>H</u>$_3$CH$_2$); δ_C 161.8 (d, *J* 245.0, C-F), 156.1 – 155.8 (br C=O), 127.75 (br s, ArCH), 114.8 (br s, ArCH), 112.9 (d, *J* 21.8, ArCH), 56.4 (br s,

NCH), 52.6 (OCH_3), 47.7 (br s, CH), 20.4 (CH_3), 37.7 (br s, CH_3), 35.3 (br s, Ar-CH_2), 31.6 (CH_2), 26.55 (CH_2), 22.7 (CH_2), 14.2 (CH_3); HRMS calculated for $C_{17}H_{25}FNO_2$ $[M+H]^+$ 294.1869, found 294.1864.

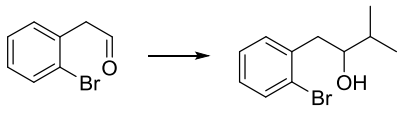
2-(2-Bromophenyl)acetaldehyde[241] 267



136 **267**

To a suspension of (methoxymethyl)triphenylphosphonium chloride (23.75 g, 69.27 mmol, 2.10 eq.) in tetrahydrofuran (80 mL) at 0 °C was added solid potassium *tert*-butoxide (7.77 g, 69.27 mmol, 2.10 eq.) portionwise, over five minutes. The reaction mixture was stirred for a further 0.5 h at 0 °C after which 2-bromobenzaldehyde **136** (6.0 g, 32.99 mmol, 1.0 eq.) was added as a solution in tetrahydrofuran (30 mL) dropwise, over 5 minutes. The cooling bath was removed and the mixture allowed to warm to ambient temperature overnight (~16 h). The reaction was quenched by addition of aqueous ammonium chloride (50 mL) and the separated aqueous layer extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered and evaporated. The residue was dissolved in tetrahydrofuran (150 mL) and HCl (2M, 25 mL), heated to reflux for 2.5 h and allowed to cool to ambient temperature. The separated aqueous layer was extracted with diethyl ether (50 mL) and the combined organic extracts washed with aqueous sodium bicarbonate (50 mL) and brine (50 mL) and filtered through a pad of silica. The mixture was then dried, filtered and evaporated and the crude material purified by column chromatography to give *aldehyde* **267** (3.41 g, 62%) as a colourless oil; ν_{max} 1709 (C=O); δ_H (250 MHz) 9.78 (1H, t, *J* 1.7, CHO), 7.64 (1H, dd, *J* 7.9 and 1.2, ArH), 7.39 – 7.30 (1H, m, ArH), 7.28 – 7.16 (2H, m, ArH), 3.89 (2H, d, *J* 1.7, $ArCH_2$).

1-(2-Bromophenyl)-3-methylbutan-2-ol 268a

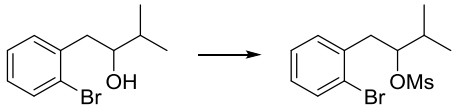


267 **268a**

To a solution of 2-(2-bromophenyl)acetaldehyde **267** (1.5 g, 7.54 mmol, 1.0 eq.) in tetrahydrofuran (10 mL) under an atmosphere of nitrogen at 0 °C was added isopropylmagnesium bromide (2.0M in Et_2O, 4.5 mL, 9.0 mmol, 1.2 eq.) and the mixture stirred for 30 minutes. The reaction was quenched by aqueous ammonium chloride (10 mL) and the separated organic layer extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried, filtered and evaporated to give

alcohol **268a** (1.76 g, 96%) as a white solid; m.p. 131 – 133 °C; δ_H (400 MHz) 7.54 (1H, dd, *J* 8.0 and 0.9, ArH), 7.29 – 7.21 (2H, m, 2 x ArH), 7.09 – 7.06 (1H, m, ArH), 3.68 (1H, ddd, *J* 9.8, 5.1 and 2.9, OCH), 3.07 (1H, dd, *J* 13.7 and 2.9, $ArCH_{2a}$), 2.65 (1H, dd, *J* 13.7 and 9.8, $ArCH_{2b}$), 1.78 (1H, d sept, *J* 5.0 and 6.8, $(CH_3)_2C\underline{H}$), 1.48 (1H, br s, OH), 1.02 (3H, d, *J* 6.8, $(C\underline{H}_3)_aCH$), 1.01 (3H, d, *J* 6.8, $(C\underline{H}_3)_aCH$); δ_C (101 MHz) 138.9 (C), 133.05 (ArCH), 131.9 (ArCH), 128.2 (ArCH), 127.5 (ArCH), 124.9 (C-Br), 75.8 (OCH), 40.9 ($ArCH_2$), 33.8 (CH), 18.8 (CH_3), 17.6 (CH_3).

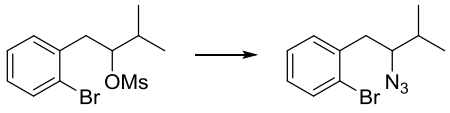
1-(2-Bromophenyl)-3-methylbutan-2-yl methanesulfonate 268b



268a **268b**

To a solution of 1-(2-Bromophenyl)-3-methylbutan-2-ol (759 mg, 3.12 mmol, 1.0 eq.) in dichloromethane (5 mL) at 0 °C was added methanesulfonyl chloride (394 mg, 3.44 mmol, 1.1 eq.), triethylamine (379 mg, 3.74 mmol, 1.2 eq.), DMAP (a few crystals) and the mixture allowed to stir overnight. The reaction was quenched by ammonium chloride and the separated organic layer washed with HCl (2M, 5 mL), aqueous sodium bicarbonate (5 mL), brine (5 mL) and dried, filtered and evaporated to give *sulfonamide* **268b** (960 mg, 96%) as a yellow oil; ν_{max} 1357 (S=O); δ_H (250 MHz) 7.57 (1H, dd, *J* 7.6 and 1.0, ArH), 7.33 – 7.24 (2H, m, 2 x ArH), 7.16 – 7.12 (1H, m, ArH), 4.85 (1H, ddd, *J* 10.2, 4.0 and 2.5, OCH), 3.15 (1H, dd, *J* 14.2 and 3.5, $ArCH_{2a}$), 2.97 (1H, dd, *J* 14.2 and 10.2, $ArCH_{2b}$), 2.32 (3H, s, SCH_3), 2.18 (1H, d sept, *J* 4.9 and 6.9, $(CH_3)_2C\underline{H}$), 1.12 (3H, d, *J* 6.9, $(C\underline{H}_3)_aCH$), 1.11 (3H, d, *J* 6.9, $(C\underline{H}_3)_bCH$).

1-(2-Azido-3-methylbutyl)-2-bromobenzene 268c

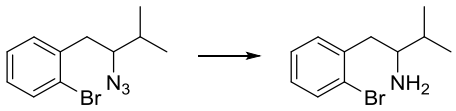


268b **268c**

To a solution of 1-(2-bromophenyl)-3-methylbutan-2-yl methanesulfonate **268b** (960 mg, 2.992 mmol, 1.0 eq.) in dimethylformamide (5 mL) at ambient temperature was added sodium azide (972 mg, 14.96 mmol, 5.0 eq.) and the mixture stirred at 40 °C for 16 h. The reaction was quenched by water (20 mL) and diethyl ether (30 mL) and the separated aqueous phase extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with water (3 x 10 mL) and brine (10 mL), dried, filtered and evaporated to yield *azide* **268c** (593 mg, 74%) as a brown liquid; δ_H (250 MHz) 7.54 (1H, dd, *J* 7.7 and

1.0, ArH), 7.32 – 7.19 (2H, m, 2 x ArH), 7.13 – 7.09 (1H, m, ArH), 3.52 (1H, ddd, *J* 9.9, 4.8 and 3.9, NCH), 3.09 (1H, dd, *J* 13.7 and 3.8, $ArCH_{2a}$), 2.72 (1H, dd, *J* 13.7 and 10.0, $ArCH_{2b}$), 1.89 (1H, d sept, *J* 4.7 and 6.8, $(CH_3)_2C\underline{H}$), 1.05 (3H, d, *J* 6.8, $(C\underline{H}_3)_aCH$), 1.04 (3H, d, *J* 6.8, $(C\underline{H}_3)_bCH$).

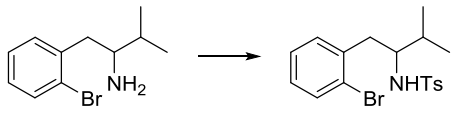
1-(2-Bromophenyl)-3-methylbutan-2-amine 269



X **X**

To a solution of 1-(2-azido-3-methylbutyl)-2-bromobenzene **268c** (591 mg, 2.21 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) was added triphenylphosphine (639 mg, 2.44 mmol, 1.1 eq.) and the resulting mixture stirred for 30 minutes. Water (0.8 g, 44.3 mmol, 18 eq.) was then added and the reaction mixture stirred for a further 2 hours at 50 °C. The solution was then partitioned between dichloromethane (10 mL) and water (10 mL) and the separated organic layer extracted with HCl (2M, 2 x 10 mL). The combined aqueous extracts were washed with dichloromethane (2 x 5 mL) and basified with aqueous sodium hydroxide (pH 14). The aqueous mixture was extracted with chloroform (3 x 10 mL) and the combined organic extracts were dried over sodium sulfate, filtered and evaporated to give *amine* **269** (460 mg, 86%) as a dark red oil; δ_H (250 MHz) 7.54 (1H, d, *J* 7.9, ArH), 7.28 – 7.20 (2H, m, 2 x ArH), 7.12 – 7.02 (1H, m, ArH), 3.02 (1H, dd, *J* 13.1 and 3.6, $ArCH_{2a}$), 2.96 – 2.87 (1H, m, NCH), 2.50 (1H, dd, *J* 13.0 and 9.6, $ArCH_{2b}$), 1.72 (1H, d sept, *J* 4.7 and 6.8, $(CH_3)_2C\underline{H}$), 1.16 (2H, br s, NH_2), 1.00 (2 x 3H, d, *J* 6.8 $(C\underline{H}_3)_2CH$).

N-(1-(2-Bromophenyl)-3-methylbutan-2-yl)-4-methylbenzenesulfonamide 270

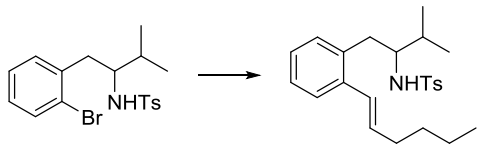


269 **270**

A solution of 1-(2-bromophenyl)-3-methylbutan-2-amine **269** (109 mg, 0.451 mmol) in dichloromethane was treated with triethylamine, DMAP and *p*-tosyl chloride according to General Procedure B. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give the *sulfonamide* **270** (168 mg, 94%) as a colourless glass; ν_{max} 3291 (br, NH), 1321 (S=O), 1162 (S=O); δ_H (250 MHz) 7.44 (2H, d, *J* 8.3, 2 x ArH), 7.32 – 7.27 (1H, m, ArH), 7.05 (2H, d, *J* 8.1, 2 x ArH), 7.08 – 6.91 (3H, m, 3 x ArH), 4.65 (1H, d, *J* 8.2, NH), 3.57 – 3.44 (1H, m, NCH), 2.84 (1H, dd, *J* 13.9 and 5.2, $ArCH_{2a}$), 2.60 (1H, dd, *J* 13.9 and 9.7, $ArCH_{2b}$), 2.36 (3H, s, $ArCH_3$), 1.98 (1H, d sept, *J* 3.5 and 6.9, $(CH_3)_2C\underline{H}$), 0.97

(3H, d, *J* 6.9, (C<u>H</u>$_3$)$_a$CH), 0.93 (3H, d, *J* 6.9, (C<u>H</u>$_3$)$_b$CH); δ_C (101 MHz) 142.6 (C), 137.5 (C), 132.95 (ArCH), 131.65 (ArCH), 129.5 (2 x ArCH), 128.1 (ArCH), 127.5 (ArCH), 126.8 (2 x ArCH), 124.7 (C-Br), 59.2 (NCH), 37.2 (CH_2), 32.2 (CH), 21.6 ($ArCH_3$), 17.95 (CH_3), 17.7 (CH_3).

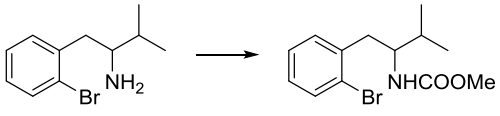
(*E*)-*N*-(1-(2-(Hex-1-en-1-yl)phenyl)-3-methylbutan-2-yl)-4-methylbenzenesulfonamide 271



270 **271**

A solution of methyl *N*-(1-(2-bromophenyl)-3-methylbutan-2-yl)-4-methylbenzenesulfonamide **270** (98 mg, 1.0 eq.) in ethanol/water (1:1, 1 mL) was treated with 1-hexenylboronic acid (47 mg, 1.5 eq.), K_3PO_4 (105 mg, 2.0 eq) and Pd(dppf)Cl_2.DCM (8 mg, 0.04 eq) at 100 °C for 5 h according to General Procedure D. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give the *sulfonamide* **271** (80 mg, 81%) as beige crystals; m.p. 56 – 59 °C; ν_{max} 3337 (br, NH); δ_H 7.44 (2H, d, *J* 8.3, 2 x ArH), 7.23 (1H, d, *J* 7.7, ArH), 7.12 – 7.06 (1H, m, ArH), 7.08 (2H, d, *J* 7.9, 2 x ArH), 7.03 – 7.01 (1H, m, ArH), 6.91 (1H, dd, *J* 7.5 and 1.0, ArH), 6.48 (1H, d, *J* 15.6, ArC<u>H</u>=CH), 5.91 (1H, dt, *J* 15.5 and 7.0, ArCH=C<u>H</u>), 4.60 (1H, d, *J* 7.3, NH), 3.32 – 3.27 (1H, m, NCH), 2.78 (1H, dd, *J* 14.0 and 6.5, $ArCH_{2a}$), 2.61 (1H, dd, *J* 14.0 and 8.5, $ArCH_{2b}$), 2.37 (3H, s, $ArCH_3$), 2.23 (1H, q, *J* 7.4, ArCH=CHC<u>H</u>$_2$), 1.99 – 1.89 (1H, d sept, *J* 3.2 and 6.9 $(CH_3)_2$C<u>H</u>), 1.51 – 1.43 (1H, m, CH_3CH_2C<u>H</u>$_2$), 1.43 – 1.35 (1H, m, CH_3C<u>H</u>$_2CH_2$), 0.98 – 0.94 (3H, t, *J* 7.4, NCHC<u>H</u>$_3$), 0.94 (3H, d, *J* 6.8, CH(C<u>H</u>$_3$)$_a$), 0.82 (3H, d, *J* 6.9, CH(C<u>H</u>$_3$)$_b$); δ_C 142.6 (C), 137.5 (C), 137.4 (C), 134.8 (C), 133.8 (ArCH), 130.5 (ArCH), 129.5 (ArCH), 127.2 (ArCH), 127.0 (ArCH), 127.0 (ArCH), 126.9 (ArCH), 126.5 (ArCH), 59.6 (NCH), 35.0 (CH_2), 33.1 (CH_2), 31.7 (CH_2), 30.8 (CH), 22.5 (CH_2), 21.6 (CH_3), 17.9 (CH_3), 17.4 (CH_3), 14.1 (CH_3); HRMS calculated for $C_{24}H_{34}NO_2S$ $[M+H]^+$ 400.2310, found 400.2298.

Methyl (1-(2-bromophenyl)-3-methylbutan-2-yl)carbamate 272

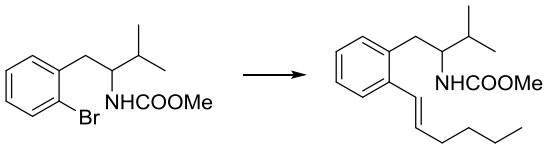


269 **272**

A solution of 1-(2-bromophenyl)-3-methylbutan-2-amine **269** (157 mg, 0.679 mmol, 1.0 eq.) in diethyl ether (1 mL) was cooled to 0 °C. Water (1 mL) and potassium carbonate (274 mg, 1.97 mmol, 3.0 eq.) was added, followed by dropwise addition of methyl chloroformate (85 mg, 0.909 mmol, 1.4 eq.). The cooling bath was removed and the reaction was allowed to warm to ambient temperature over 30 minutes.

The separated aqueous phase was then extracted with diethyl ether (3 x 5 mL) and the combined organic extracts washed with brine (5 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give *carbamate* **272** (150 mg, 77%) as a colourless oil; ν_{max} 3312 (bNH), 1689 (C=O); δ_H (250 MHz) 7.52 (1H, d, *J* 7.9, ArH), 7.24 – 7.19 (2H, m, ArH), 7.09 – 7.01 (1H, m, ArH), 4.66 (1H, br d, *J* 9.3, NH), 3.89 – 3.85 (1H, m, NCH), 3.52 (3H, s, OCH_3), 2.98 (1H, dd, *J* 14.0 and 4.7, $ArCH_{2a}$), 2.74 (1H, dd, *J* 13.9 and 10.1, $ArCH_{2a}$), 1.78 (1H, d sept, *J* 5.0 and 6.9 $(CH_3)_2C\underline{H}$), 0.99 (2 x 3H, d, *J* 6.8, 2 x CH_3); δ_C 155.7 (C=O), 137.3 (C), 131.8 (ArCH), 130.1 (ArCH), 127.0 (ArCH), 126.35 (ArCH), 124.0 (C-Br), 55.7 (OCH_3), 50.9 (NCH), 37.2 (CH), 31.0 (CH_2), 18.15 (CH_3), 16.7 (CH_3).

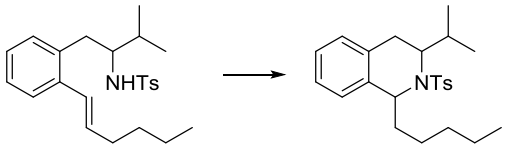
Methyl (*E*)-(1-(2-(hex-1-en-1-yl)phenyl)-3-methylbutan-2-yl)carbamate 273



272 **273**

A solution of methyl (1-(2-bromophenyl)-3-methylbutan-2-yl)carbamate **272** (197 mg, 1.0 eq.) in ethanol/water (1:1, 2 mL) was treated with 1-hexenylboronic acid (125 mg, 1.5 eq.), K_3PO_4 (277 mg, 2.0 eq) and Pd(dppf)Cl_2.DCM (21 mg, 0.04 eq) at 90 °C for 4 h according to General Procedure D. The crude material was purified by column chromatography (petrol/diethyl ether 3:1) to give the *carbamate* **273** (145 mg, 73%) as colourless oil; ν_{max} 3319 (br, NH), 1699 (C=O); δ_H 7.43 – 7.40 (1H, m, ArH), 7.18 – 7.08 (3H, m, 3 x ArH), 6.67 (1H, d, *J* 15.5, ArC$\underline{H}$=CH), 6.10 (1H, dt, *J* 15.5 and 6.9, ArCH=C$\underline{H}$), 4.61 (1H, br s, NH), 3.78 (1H, br s, NCH), 3.57 (3H, s, OCH_3), 2.88 (1H, dd, *J* 14.0 and 5.9, $ArCH_{2a}$), 2.69 (1H, br dd, *J* 13.4 and 8.8, $ArCH_{2a}$), 2.26 (2H, qd, *J* 7.3 and 1.3, ArCH=CHC$\underline{H}_2$), 1.83 (1H, br s, C$\underline{H}(CH_3)_2$), 1.53 – 1.46 (2H, m, $CH_3CH_2C\underline{H}_2$), 1.41 (2H, dq, *J* 14.1 and 7.1, $CH_3C\underline{H}_2$), 0.96 (9H, m, CH($C\underline{H}_3)_2$ and $C\underline{H}_3CH_2$); δ_C 156.8 (C=O), 137.6 (C), 135.6 (C), 133.5 (ArCH), 130.2 (ArCH), 127.5 (2 x ArCH), 126.8 (2 x ArCH), 126.7 (ArCH), 126.4 (ArCH), 57.0 (NCH), 51.9 (OCH_3), 35.6 ($ArCH_2$), 33.06 (CH_2), 31.6 (CH_2), 31.0 (CH), 22.3 (CH_2), 19.4 (CH_3), 17.35 (CH_3), 14.0 (CH_3).

3-Isopropyl-1-pentyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 191



271 **191**

Method 1:

The sulfonamide **271** (27 mg, 0.068 mmol, 1.0 eq.) was dissolved in dichloromethane (0.3 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (4 mg, 0.027 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then at ambient temperature for 6 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 3:1) to give *tetrahydroisoquinoline* **191** (26 mg, 96%) as a colourless glass and as a 2:1 mixture of *trans* and *cis* isomers; *major (trans)-diastereoisomer* δ_H 7.55 (2H, d, *J* 8.3, 2 x ArH), 7.05 (2H, d, *J* 8.1, 2 x ArH), 7.12 – 6.86 (3H, m, 3 x ArH), 6.83 (1H, d, *J* 7.5, ArH), 4.92 (1H, dd, *J* 9.3 and 5.1, ArCHN), 3.36 (1H, td, *J* 10.2 and 4.6, $ArCH_2C\underline{H}N$), 2.78 (1H, dd, *J* 16.5 and 4.6, $ArCH_{2a}$), 2.62 (1H, dd, *J* 16.4 and 10.1, $ArCH_{2b}$), 2.54 (1H, d sept, *J* 9.7 and 6.7, $C\underline{H}(CH_3)_2$), 2.31 (3H, s, $ArCH_3$), 1.95 – 1.71 (2H, m, CH_2), 1.50 – 1.17 (6H, m, 3 x CH_2), 1.11 (3H, d, *J* 6.8, $CH(C\underline{H}_3)_a$), 0.65 (3H, t, *J* 6.9, $CH_2C\underline{H}_3$), 0.82 (3H, d, *J* 6.7, $CH(C\underline{H}_3)_b$); δ_C 142.8 (C), 139.4 (C), 137.9 (C), 134.6 (C), 129.0 (2 x ArCH), 128.9 (ArCH), 127.5 (2 x ArCH), 126.6 (ArCH), 126.5 (ArCH), 126.1 (ArCH), 61.15 ($ArCH_2\underline{C}H$), 60.3 (ArCHN), 36.4 (CH_2), 31.6 (CH_2), 30.7 ($C\underline{H}(CH_3)_2$), 30.7 ($ArCH_2$), 26.1 (CH_2), 22.7 (CH_2), 21.6 ($ArCH_3$), 21.5 (CH_3), 20.3 (CH_3), 14.1 (CH_3); *minor (cis)-diastereoisomer* δ_H (400 MHz) 7.39 (2H, d, *J* 8.2, 2 x ArH), 6.96 (2H, d, *J* 8.0, 2 x ArH), 7.07 – 6.80 (3H, m, 3 x ArH), 6.70 (1H, d, *J* 7.4, ArH), 4.69 (1H, app t, *J* 7.1, ArCHN), 3.65 (1H, td, *J* 8.0 and 7.8, $ArCH_2C\underline{H}N$), 2.64 (1H, dd, *J* 8.0 and 3.8, $ArCH_2$), 2.26 (3H, s, $ArCH_3$), 2.26 – 2.19 (1H, m, $C\underline{H}(CH_3)_2$), 1.66 – 1.50 (2H, m, $ArCHCH_2CH_2C\underline{H}_2$), 1.41 – 1.23 (6H, m, 3 x CH_2), 1.13 (3H, d, *J* 6.9, $CH(C\underline{H}_3)_a$), 1.02 (3H, d, *J* 6.8, $CH(C\underline{H}_3)_b$), 0.88 (3H, t, *J* 6.9, $CH_2C\underline{H}_3$); δ_C (101 MHz) 142.7 (C), 137.5 (C), 136.5 (C), 133.1 (C), 129.1 (2 x ArCH), 128.1 (ArCH), 127.4 (2 x ArCH), 126.8 (ArCH), 126.7 (ArCH), 125.80 (ArCH), 60.5 ($ArCH_2\underline{C}H$), 59.1 (ArCHN), 37.2 (CH_2), 34.1 ($C\underline{H}(CH_3)_2$), 31.8 (CH_2), 28.3 ($ArCH_2$), 26.85 (CH_2), 22.7 (CH_2), 21.5 ($ArCH_3$), 20.45 (CH_3), 18.2 (CH_3), 14.3 (CH_3); HRMS calculated for $C_{24}H_{34}NO_2S$ $[M+H]^+$ 400.2310, found 400.2300.

Method 2:

The sulfonamide **271** (19 mg, 0.048 mmol, 1.0 eq.) was dissolved in dichloromethane (0.2 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (4 mg, 0.067 mmol, 1.4 eq.).

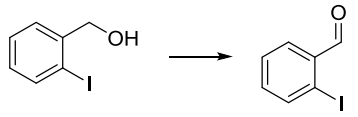
The resulting solution was stirred for 5 minutes at 0 °C and then at ambient temperature for 2.5 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 3:1) to give *tetrahydroisoquinoline* **191** (18 mg, 95%) as a colourless glass and as a 4:1 mixture of *cis* and *trans* isomers. All data obtained for the sample were in accordance with those reported before.

Methyl 3-isopropyl-1-pentyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 274

273 **274**

The carbamate **273** (51 mg, 0.168 mmol, 1.0 eq.) was dissolved in 1,2-dichloromethane (0.5 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (10 mg, 0.067 mmol, 0.4 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 84 °C for 10 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give *tetrahydroisoquinoline* **274** (33 mg, 65%) as a colourless glass and as a 5:1 mixture of isomers; ν_{max} 1699 (C=O); *major diastereoisomer* δ_H (400 MHz) 7.21 – 7.09 (3H, m, 3 x ArH), 7.09 – 7.02 (1H, m, ArH), 4.77 (1H, d, *J* 6.4, ArCHN), 4.01 (1H, br s, $ArCH_2C\underline{H}N$), 3.74 (3H, s, OCH_3), 3.03 (1H, dd, *J* 15.3 and 5.0, $ArCH_{2a}$), 2.88 – 2.80 (1H, br m, $ArCH_{2b}$), 1.52 – 1.45 (1H, br m, $C\underline{H}(CH_3)_2$), 1.39 – 1.05 (8H, m, 4 x CH_2), 0.83 (3H, t, *J* 6.9, $C\underline{H}_3CH_2$), 0.79 (3H, d, *J* 6.5, $CH(C\underline{H}_3)_a$), 0.59 (3H, d, *J* 6.8, $CH(C\underline{H}_3)_b$); δ_C (101 MHz) 156.8 (C=O), 138.1 (C), 134.6 (br s, C), 128.6 (ArCH), 127.3 (ArCH), 126.95 (ArCH), 126.0 (ArCH), 57.5 (ArCHN), 57.5 (br s, $ArCH_2\underline{C}H$), 52.6 (OCH_3), 37.9 ($\underline{C}H(CH_3)_2$), 31.6 ($ArCH_2$), 31.2 (br s, CH_2), 27.15 (CH_2), 25.75 (CH_2), 22.7 (CH_2), 19.8 (CH_3), 19.5 (CH_3), 14.1 (CH_3); *minor diastereoisomer* δ_H (400 MHz) 7.21 – 7.01 (4H, m, 4 x ArH), 5.13 (1H, br s, ArCHN), 3.69 (3H, s, OCH_3), 1.00 (3H, d, *J* 6.8, $CH(CH_3)_a$), 0.94 (3H, d, *J* 6.7, $CH(CH_3)_b$), 0.89 (3H, t, *J* 6.9, $CH_2C\underline{H}_3$); only 6 distinct signals; δ_C (101 MHz) 133.75 (C), 126.89 (ArCH), 126.24 (ArCH), 57.42 (CH), 52.63 (OCH_3), 31.96 (CH_2), 20.10 (CH_3), 18.46 (CH_3), 14.22 (CH_3); only 9 distinct signals; LRMS m/z 304 ($[M]^+$, 100%), 232 ($[M\text{-}NHCOOMe]^+$, 3%); HRMS ($APCI^+$) calculated for $C_{19}H_{30}NO_2$ $[M+H]^+$ 304.2277, found 304.2262

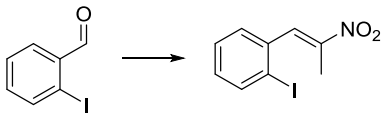
2-Iodobenzaldehyde[242] 275



275

To a suspension of pyridinium dichromate (25.7 g, 68.3 mmol, 1.0 eq.) in dry dichloromethane (70 mLs) at ambient temperature was added a solution of 2-iodobenzyl alcohol (10.0 g, 42.7 mmol, 1.6 eq.) in dichloromethane (30 mL) and the resulting mixture stirred for 4 h. Diethyl ether (50 mL) was added and the reaction mixture filtered through a pad of Celite©. The solvent was removed *in vacuo* and the crude material was purified by silica chromatography (petrol/ethyl acetate 20:1) to yield *aldehyde* **275** (8.49 g, 72%) as a white solid; m.p. 33-37 °C (lit. m.p.[243] 37-38 °C); ν_{max} 1697 (C=O); δ_H (400 MHz) 10.07 (1H, s, CHO), 7.96 (1H, d, *J* 7.9, ArH), 7.88 (1H, dd, *J* 7.7 and 1.7, ArH), 7.47 (1H, t, *J* 7.5, ArH), 7.29 (1H, td, *J* 7.6 and 1.8, ArH); δ_C (101 MHz) 196.0 (CHO), 140.7 (ArCH), 135.65 (ArCH), 135.2 (C), 130.4 (ArCH), 128.9 (ArCH), 100.9 (C-I).

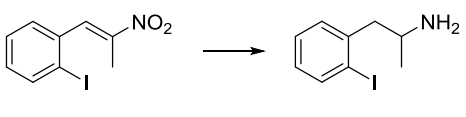
(*E*)-1-Iodo-2-(2-nitroprop-1-en-1-yl)benzene 276



275 **276**

To a solution of 2-iodobenzaldehyde **275** (3.5 g, 15.09 mmol, 1.0 eq.) in nitroethane (45.3 g, 528 mmol, 40 eq.) was added ammonium acetate (989 mg, 12.83 mmol, 0.85 eq.) and the mixture heated to reflux for 3 hours. The reaction was then allowed to cool to room temperature, and the solvent was removed *in vacuo* at 5 mbar pressure and at 60 °C for 1 hour. The crude reaction mixture was redissolved in dichloromethane (100 mL), washed with water (3 x 25 mL) and brine (25 mL), dried, filtered and evaporated to give *nitroalkene* **276** (4.08 g, 94%) as a yellow oil; δ_H (400 MHz) 8.01 (1H, s, ArC<u>H</u>=C), 7.94 (1H, dd, *J* 8.0 and 1.1, ArH), 7.45 – 7.41 (1H, m, ArH), 7.26 (1H, dd, *J* 7.7 and 1.4, ArH), 7.11 – 7.08 (1H, m, ArH), 2.28 (3H, d, *J* 1.1, CH_3); δ_C (63 MHz) 148.8 (C), 139.6 (ArCH), 136.9 (C), 136.8 (ArCH), 130.9 (ArCH), 129.8 (ArCH), 128.4 (ArCH), 99.9 (C-I), 13.8 (CH_3); HRMS calculated for $C_9H_8INO_2$ $[M]^+$ 288.9600, found 288.9596.

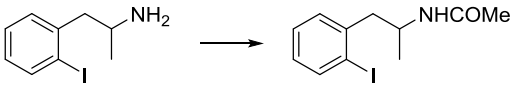
1-(2-Iodophenyl)propan-2-amine 277



276 **277**

A solution of 1-bromo-4-fluoro-2-(2-nitroprop-1-en-1-yl)benzene **276** (4.07 g, 14.09 mmol, 1.0 eq.) in tetrahydrofuran was treated with sodium borohydride (2.05 g, 54.10 mmol, 3.84 eq.), and boron trifluoride diethyl etherate (11.8 g, 83.26 mmol, 5.9 eq.) according to the General Procedure F to afford *amine* **277** (1.84 g, 50%) as a dark brown oil; δ_H (400 MHz) 7.83 (1H, dd, *J* 7.9 and 1.1, ArH), 7.28 (1H, dt, *J* 7.4 and 1.5, ArH), 7.22 – 7.20 (1H, m, ArH), 6.90 (1H, dt, *J* 7.7 and 1.8, ArH), 3.32 – 3.21 (1H, m, NCH), 2.83 (1H, dd, *J* 13.4 and 5.5, $ArCH_{2a}$), 2.67 (1H, dd, *J* 13.3 and 7.9, $ArCH_{2b}$), 1.16 (3H, d, *J* 6.3, CH_3).

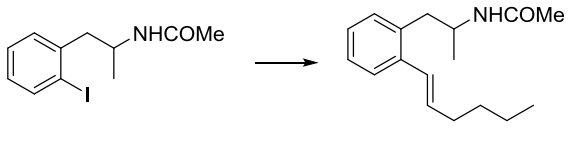
N-(1-(2-Iodophenyl)propan-2-yl)acetamide 278



277 **278**

A solution of 1-(2-iodophenyl)propan-2-amine **277** (620 mg, 2.38 mmol, 1.0 eq.) in dichloromethane (10 mL) was cooled to 0 °C. Triethylamine (360 mg, 3.56 mmol, 1.5 eq.) was then added, followed by acetyl chloride (204 mg, 2.61 mmol, 1.1 eq.) and the resulting mixture stirred for 0.5 h at 0 °C and 1 h at ambient temperature. The reaction mixture was quenched by water (10 mL) and the separated organic phase was washed with HCl (2M, 10 mL), aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *acetamide* **278** (382 mg, 53%) as a white solid; δ_H (400 MHz) 7.81 (1H, dd, *J* 7.9 and 1.1, ArH), 7.29 – 7.25 (1H, m, ArH), 7.22 (1H, dd, *J* 7.6, 1.9, ArH), 6.92 – 6.86 (1H, m, ArH), 5.59 (1H, d, *J* 7.4, NH), 4.37 – 4.25 (1H, m, NCH), 2.95 (1H, dd, *J* 13.9 and 7.7, $ArCH_{2a}$), 2.87 (1H, dd, *J* 13.9 and 6.5, $ArCH_{2b}$), 1.90 (3H, s, $C(O)CH_3$), 1.20 (3H, d, *J* 6.6, CH_3); δ_C 169.36 (C=O), 141.5 (C), 139.7 (ArCH), 130.4 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 101.6 (C-I), 46.7 ($ArCH_2$), 46.6 (NCH), 23.6 ($C(O)\underline{C}H_3$), 20.8 (CH_3); HRMS calculated for $C_{11}H_{14}INO$ $[M]^+$ 303.0120, found 303.0114.

(*E*)-*N*-(1-(2-(Hex-1-en-1-yl)phenyl)propan-2-yl)acetamide 279

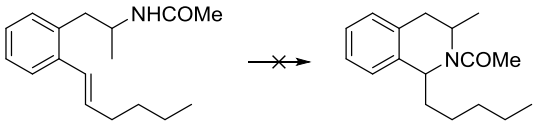


278 **279**

A solution of *N*-(1-(2-iodophenyl)propan-2-yl)acetamide **278** (477 mg, 1.0 eq.) in ethanol/water (1:1, 5 mL) was treated with 1-hexenylboronic acid (357 mg, 1.5 eq.), K_3PO_4 (792 mg, 2.0 eq) and

Pd(dppf)Cl_2.DCM (76 mg, 0.05 eq) at 90 °C for 3 h according to General Procedure D. The crude material was purified by column chromatography (petrol/ethyl acetate 1:3) to give the *acetamide* **279** (416 mg, 86%) as yellow oil; ν_{max} 3311 (NH), 1705 (C=O); δ_H 7.44 (1H, dd, *J* 7.6 and 1.2, ArH), 7.17 (1H, dt, *J* 7.4 and 1.6, ArH), 7.13 (1H, dt, *J* 7.3 and 1.6, ArH), 7.09 (1H, dd, *J* 7.4 and 1.6, ArH), 6.74 (1H, d, *J* 15.6 ArC<u>H</u>=CH), 6.11 (1H, dt, *J* 15.5 and 7.0, ArCH=C<u>H</u>), 5.69 (1H, d, *J* 7.6, NH), 4.25 – 4.16 (1H, m, NCH), 2.95 (1H, dd, *J* 13.7 and 6.0, $ArCH_{2a}$), 2.70 (1H, dd, *J* 13.7 and 7.6, $ArCH_{2b}$), 2.24 – 2.21 (2H, m, ArCH=CHC<u>H_2</u>), 1.89 (3H, s, C(O)CH_3), 1.49 – 1.42 (2H, m, CH_3CH_2C<u>H_2</u>), 1.39 – 1.36 (2H, m, CH_3C<u>H_2</u>CH_2), 1.09 (3H, d, *J* 6.6, CHC<u>H_3</u>), 0.93 (3H, t, *J* 7.2, CH_3C<u>H_2</u>); δ_C 169.4 (C=O), 137.5 (C), 135.1 (C), 133.3 (ArCH=<u>C</u>H), 130.6 (ArCH), 127.6 (ArCH), 126.8 (ArCH), 126.75 (ArCH), 126.1 (Ar<u>C</u>H=CH), 46.3 (NCH), 39.6 (CH_2), 33.1 (CH_2), 31.7 (CH_2), 23.45 (C(O)CH_3), 22.3 (CH_2), 20.1 (CH_3), 14.0 (CH_3).

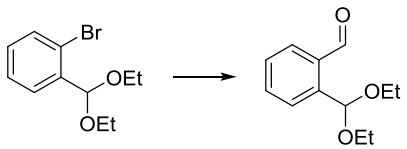
1-(3-Methyl-1-pentyl-3,4-dihydroisoquinolin-2(1H)-yl)ethan-1-one 280



279 **280**

The acetamide **279** (76 mg, 0.296 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (0.8 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (22 mg, 0.148 mmol, 0.5 eq.). The resulting solution was stirred for 5 minutes at 0 °C and then heated to 84 °C for 24 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. No product could be isolated.

2-(Diethoxymethyl)benzaldehyde[244] 288

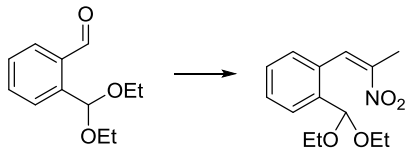


287 **288**

To a solution of 1-bromo-2-(diethoxymethyl)benzene **287** (5 g, 19.3 mmol, 1.0 eq.) in tetrahydrofuran (70 mL) at -78 °C under an atmosphere of nitrogen was added n-butyllithium (1.9 M, 12.2 mL, 23.16 mmol, 1.2 eq.) over 10 minutes and the reaction stirred for a further 30 minutes at the same temperature. Dimethylformamide (3.1 mL, 40.5 mmol, 2.1 eq.) was added dropwise and the mixture allowed to warm to ambient temperature and stirred for a further 2 hours. The reaction was quenched by addition of aqueous ammonium chloride (50 mL) and the aqueous layer extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried, filtered and evaporated and the crude material purified by column

chromatography (petrol/diethyl ether 1:4) to give *aldehyde* **288** (3.87 g, 93%) as a colourless oil; 10.52 (1H, s, CHO), 7.92 (1H, br. d, *J* 8.0, ArH), 7.69 (1H, br. d, *J* 8.0, ArH), 7.58 – 7.56 (1H, m, ArH), 7.47 (1H, br. t, *J* 8.0, ArH), 5.96 (1H, s, ArC<u>H</u>$(OEt)_2$), 3.72 (1H, q, *J* 7.0, OC<u>H_{2a}</u>CH_3), 3.69 (1H, q, *J* 7.0, OC<u>H_{2b}</u>CH_3), 3.59 (1H, q, *J* 7.0, OC<u>H_{2c}</u>CH_3), 3.56 (1H, q, *J* 7.0, OC<u>H_{2d}</u>CH_3), 1.23 (6H, t, *J* 7.0, 2 x OCH_2C<u>H_3</u>).

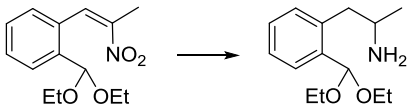
(*E*)-1-(Diethoxymethyl)-2-(2-nitroprop-1-en-1-yl)benzene 289



288 **289**

To a solution of 2-(diethoxymethyl)benzaldehyde **288** (3.87 g, 18.61 mmol, 1.0 eq.) in nitroethane (11.2 g, 149 mmol, 8 eq.) was added ammonium acetate (860 mg, 11.16 mmol, 0.6 eq.) and the mixture heated to reflux for 3 hours. The reaction was then allowed to cool to room temperature, and the solvent was removed *in vacuo* at 5 mbar pressure and at 60 °C for 1 hour. The crude reaction mixture was redissolved in dichloromethane (100 mL), washed with water (3 x 25 mL) and brine (25 mL), dried, filtered and evaporated to give *nitroalkene* **289** (4.14 g, 84%) as a black oil; δ_H (400 MHz) 8.23 (1H, s, ArCH=C), 7.53 (1H, dd, *J* 7.3 and 1.7, ArH), 7.30 – 7.22 (2H, m, 2 x ArH), 7.11 – 7.07 (1H, m, ArH), 3.48 (1H, q, *J* 7.1, OC<u>H_{2a}</u>CH_3), 3.46 (1H, q, *J* 7.1, OC<u>H_{2b}</u>CH_3), 3.39 (1H, q, *J* 7.0, OC<u>H_{2c}</u>CH_3), 3.37 (1H, q, *J* 7.1, OC<u>H_{2f}</u>CH_3), 2.14 (3H, d, *J* 1.1, CH_3), 1.07 (6H, t, *J* 7.1, 2 x OCH_2C<u>H_3</u>).

1-(2-(Diethoxymethyl)phenyl)propan-2-amine 290

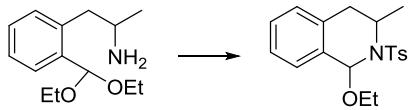


289 **290**

To the solution of 1-(diethoxymethyl)-2-(2-nitroprop-1-en-1-yl)benzene **289** (4.14 g, 15.64 mmol, 1.0 eq.) in tetrahydrofuran (60 mL) at 0 °C under an atmosphere of nitrogen was added portionwise lithium aluminium hydride (1.78 g, 46.9 mmol, 3.0 eq) over 10 minutes. The reaction mixture was allowed to stir for 30 minutes at the 0 °C and heated to reflux for 2 h. The reaction was quenched according to the General Procedure F to yield *amine* **290** (3.27 mg, 88%) as a dark, burgundy oil and was used in the next step without further purification; δ_H (250 MHz) 7.65 – 7.58 (1H, m, ArH), 7.31 – 7.17 (3H, m, 3 x ArH), 5.62 (1H, s, ArC<u>H</u>$(OEt)_2$), 3.70 – 3.45 (4H, m, 2 x OC<u>H_2</u>CH_3), 3.29 – 3.14 (1H, m, NCH), 2.85 (1H, dd, *J*

13.6 and 5.3, $ArCH_{2a}$), 2.67 (1H, dd, *J* 13.6 and 8.2, $ArCH_{2b}$), 2.10 – 1.90 (1H, br s, NH_2), 1.23 (6H, t, *J* 7.1, 2 x $OCH_2C\underline{H}_3$), 1.17 (3H, d, *J* 6.3, $CHC\underline{H}_3$).

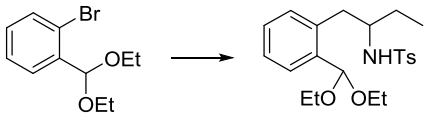
1-Ethoxy-3-methyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 292



290 **292**

A solution of 1-(2-(diethoxymethyl)phenyl)propan-2-amine (0.327 g, 1.380 mmol) in dichloromethane was treated with triethylamine, DMAP and *p*-tosyl chloride according to General Procedure B. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give the *tetrahydroisoquinoline* **292** (433 mg, 91%) as a colourless oil; δ_H (400 MHz) 7.51 (1H, d, *J* 8.3, 2 x ArH), 7.24 – 7.21 (1H, m, ArH), 7.18 – 7.15 (1H, m, ArH), 7.10 (2H, d, *J* 8.0, 2 x ArH), 6.98 – 6.92 (1H, m, ArH), 6.07 (1H, s, O-CH), 4.08 – 4.02 (1H, m, $NC\underline{H}CH_3$), 4.04 (1H, dq, 9.7 and 7.0, $OC\underline{H}_{2a}CH_3$), 3.81 (1H, dq, *J* 9.6 and 7.0, $OC\underline{H}_{2b}CH_3$), 2.59 (1H, dd, *J* 15.9, 5.1, $ArCH_{2a}$), 2.53 (1H, dd, *J* 15.9 and 6.4, $ArCH_{2b}$), 2.31 (1H, s, $ArCH_3$), 1.44 (3H, d, *J* 6.8, $CHC\underline{H}_3$), 1.28 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$).

N-(1-(2-(Diethoxymethyl)phenyl)butan-2-yl)-4-methylbenzenesulfonamide 291

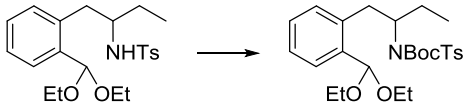


287 **291**

Magnesium turnings (475 mg, 19.56 mmol, 2.2 eq.) were dry-stirred under an atmosphere of nitrogen for 24 hours and then suspended in tetrahydrofuran (10 mL). The suspension was treated with a crystal of iodine and 1-bromo-2-(diethoxymethyl)benzene **287** (4.60 g, 17.8 mmol, 2.0 eq.) was added as a solution in tetrahydrofuran (10 mL). The reaction was stirred for a further 30 minutes, during which time decolourisation and disappearance of most of the magnesium turnings was observed. The solution was then cooled to -40 °C and copper (I) iodide (508 mg, 2.67 mmol, 0.3 eq.) was added. After further 30 minutes, the reaction mixture was cooled to -78 °C and 2-ethyl-1-tosylaziridine **154** (2.0 g, 8.89 mmol, 1.0 eq.) in tetrahydrofuran (10 mL) was added. After 15 minutes, the reaction mixture was warmed to 0 °C and stirred for a further 1.25 h. The reaction was quenched by aqueous ammonium chloride (30 mL) and the blue aqueous phase extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether, 1:1) to give *sulfonamide* **291** (3.13 g, 87%) as a colourless oil; ν_{max}

3235 (br, NH), 1331 (S=O), 1160 (S=O); δ_H (400 MHz) 7.55 (2H, d, *J* 8.3, 2 x ArCH), 7.26 (1H, m, ArH), 7.21 – 7.15 (2H, m, 2 x ArH), 7.13 (2H, d, *J* 8.1, 2 x ArH), 6.97 (1H, d, *J* 7.0, ArH), 6.08 (1H, s, ArC<u>H</u>$(OCH_2)_2$), 4.07 (1H, dq, *J* 9.6 and 7.1, $(OC\underline{H}_{2a}CH_3)_a$), 3.89 – 3.79 (1H, m, NCH) 3.88 – 3.78 (1H, m, $OC\underline{H}_2CH_3$), 3.72 (2H, q, *J* 7.0, $OC\underline{H}_2CH_3$), 2.50 (1H, dd, *J* 16.2 and 3.3, $ArCH_{2a}$), 2.42 (1H, dd, *J* 15.7 and 8.1, $ArCH_{2b}$), 2.34 (3H, s, $ArCH_3$), 2.00 – 1.86 (1H, m, $CHC\underline{H}_{2a}CH_3$), 1.62 – 1.50 (1H, m, $CHC\underline{H}_{2a}CH_3$), 1.29 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.24 (3H, t, *J* 7.0, $OCH_2C\underline{H}_3$), 0.95 (3H, t, *J* 7.4, $CHCH_2C\underline{H}_3$); δ_C (101 MHz) 143.3 (C), 137.9 (C), 133.5 (C), 132.3 (C), 129.7 (2 x ArCH), 128.85 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 127.1 (2 x ArCH), 126.6 (ArCH), 83.3 (CH), 64.0 (OCH_2), 53.65 (NCH), 30.9 (CH_2), 28.1 (CH_2), 21.6 ($ArCH_3$), 15.05 (CH_3), 11.1 (CH_3); HRMS calculated for $C_{22}H_{31}NNaO_4S$ $[M+Na]^+$ 428.1872, found 428.1882.

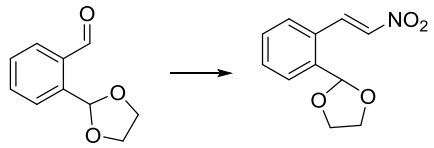
tert-Butyl (1-(2-(diethoxymethyl)phenyl)butan-2-yl)(tosyl)carbamate 303



291 **303**

A solution of *N*-(1-(2-(diethoxymethyl)phenyl)butan-2-yl)-4-methylbenzenesulfonamide **291** (2.38 g, 5.87 mmol, 1.0 eq.) in dichloromethane (25 mL) was treated with DMAP (143 mg, 1.17 mmol, 0.2 eq.) and Boc_2O (1.54 g, 7.04 mmol, 1.2 eq.) according to General Procedure C. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give the *carbamate* **303** (1.24 g, 82%) as a colourless oil; ν_{max} 3025, 1724 (C=O), 1353 (S=O), 1153 (S=O), 1088 (C-O); δ_H 7.57 (1H, d, *J* 7.2, ArH), 7.25 – 7.16 (3H, m, 3 x ArH), 7.07 (1H, t, *J* 6.8, ArH), 7.01 (3H, m, 3 x ArH), 5.63 (1H, s, C<u>H</u>(OCH_2CH_3)), 4.70 – 4.61 (1H, m, NCH), 3.63 – 3.48 (3H, m, 3 x $OC\underline{H}_2CH_3$), 3.47 – 3.39 (1H, m, $OC\underline{H}_2CH_3$), 3.28 (1H, dd, *J* 13.8 and 8.7, $ArCH_{2a}$), 3.21 (1H, dd, *J* 13.8 and 6.7, $ArCH_{2b}$), 2.30 (3H, s, $ArCH_3$), 2.08 – 1.94 (1H, m, CH_3CH_{2a}), 1.71 – 1.63 (1H, m, CH_3CH_{2b}), 1.33 (9H, s, $C(CH_3)_3$), 1.17 (3H, t, *J* 7.0, $OCH_2C\underline{H}_3$), 1.15 (3H, t, *J* 7.1, 3 x $OCH_2C\underline{H}_3$), 0.90 (3H, t, *J* 7.4, $CHCH_2C\underline{H}_3$); δ_C 151.1 (C=O), 143.4 (C), 137.75 (C), 137.2 (C), 131.35 (ArCH), 129.0 (2 x ArCH), 128.6 (ArCH), 128.2 (2 x ArCH), 127.0 (ArCH), 126.5 (ArCH), 100.2 (<u>C</u>$H(OCH_2CH_3)_2$), 84.1 (<u>C</u>$(CH_3)_3$), 62.2 (NCH) 62.1 (OCH_2), 62.0 (OCH_2), 35.7 (CH_2), 28.2 ($C(\underline{C}H_3)_3$), 26.3 ($ArCH_2$), 21.6 ($ArCH_3$), 15.4 (CH_3), 15.3 (CH_3), 11.6 (CH_3); HRMS (ES^-)calculated for $C_{27}H_{39}ClNO_6S$ $[M+Cl]^-$ 540.2187, found 540.2169

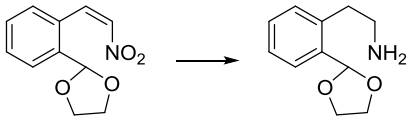
(*E*)-2-(2-(2-Nitrovinyl)phenyl)-1,3-dioxolane 294



293 **294**

To a solution of 2-(1,3-dioxolan-2-yl)benzaldehyde **293** (4.76 g, 26.74 mmol, 1.0 eq) in nitromethane (13.1 g, 214 mmol, 8 eq.) was added ammonium acetate (1.34 g, 18.72 mmol, 0.7 eq) and the mixture heated to 90 °C for 3 hours. The reaction was then allowed to cool to room temperature, and the solvent was removed *in vacuo* at 5 mbar pressure and at 60 °C for 1 hour. The crude reaction mixture was redissolved in dichloromethane (100 mL), washed with water (3 x 25 mL) and brine (25 mL), dried, filtered and evaporated to give crude *nitroalkene* **294** (5.63 g, 95%) as a brown oil (5.63 g, 95%); δ_H (400 MHz) 8.45 (1H, d, *J* 13.6, ArC<u>H</u>=CH), 7.57 (1H, dd, *J* 7.7 and 1.2, ArH), 7.49 – 7.46 (1H, m, ArH), 7.44 – 7.38 (1H, m, ArH), 7.41 (1H, d, *J* 13.7, ArCH=C<u>H</u>), 7.37 – 7.33 (1H, m, ArH), 5.87 (1H, s, ArC<u>H</u>$(OEt)_2$), 4.15 – 4.10 (2H, m, OC<u>H_2</u>CH_3), 4.04 – 3.99 (2H, m, OC<u>H_2</u>CH_3).

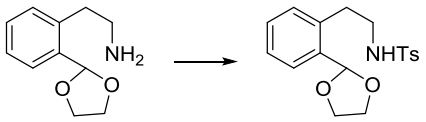
1-(2-(1,3-Dioxolan-2-yl)phenyl)ethan-1-amine 294a



294 **294a**

To the solution of **294** (4.76 g, 26.74 mmol, 1.0 eq.) in tetrahydrofuran (75 mL) at 0 °C under an atmosphere of nitrogen was added portionwise lithium aluminium hydride (525 mg, 13.82 mmol, 3.0 eq) over 5 minutes. The reaction mixture was allowed to stir for 1 hour at the same temperature and then heated to reflux at 65 °C for 2.5 hours. The reaction was then allowed to cool to room temperature and quenched according to the General Procedure F to yield the *amine* **294a** as a brown oil, and was used in the next step without further purification; δ_H (400 MHz) 7.56 – 7.47 (1H, m, ArH), 7.38 – 7.08 (3H, m, ArH), 5.93 (1H, s, ArC<u>H</u>$(OEt)_2$), 4.11 – 4.06 (2H, m, OC<u>H_2</u>CH_3), 4.00 – 3.95 (2H, m, OC<u>H_2</u>CH_3), 2.96 – 2.89 (1H, br m, $ArCH_2$), 2.85 – 2.80 (2H, br m, $ArCH_2C$<u>H_2</u>), 2.37 (2H, br s, NH_2).

2-(2-(1,3-Dioxolan-2-yl)phenethyl)-4-methylbenzenesulfonamide 295

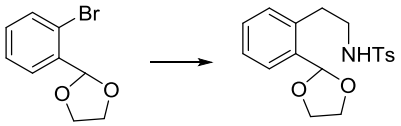


294a **295**

Method 1:

A solution of 1-(2-(1,3-dioxolan-2-yl)phenyl)ethan-1-amine **294a** from previous reaction (assumed: 25.46 mmol, 1.0 eq.) in dichloromethane was treated with triethylamine, DMAP and *p*-tosyl chloride according to General Procedure B. The crude material was purified by column chromatography (petrol/diethyl ether 1:1) to give the *sulfonamide* **295** (1.85 g, 22% over 2 steps) as a white solid; m.p. 108 – 112 °C; ν_{max} 3275 (br, NH), 1327 (S=O), 1159 (S=O), 1079 (C-O); δ_H 7.58 (2H, d, *J* 8.3, 2 x ArH), 7.50 (1H, dd, *J* 7.0 and 2.1, ArH), 7.25 – 7.19 (2H, m, 2 x ArH), 7.18 (2H, d, *J* 7.9, 2 x ArH), 7.03 (1H, dd, *J* 7.0 and 1.9, ArH), 5.85 (1H, s, (C<u>H</u>$(OCH_2)_2$), 5.37 (1H, t, *J* 5.3, NH), 4.17 – 4.11 (2H, m, CH(OC<u>H_{2a}</u>$)_2$), 4.07 – 4.01 (2H, m, (CH(OC<u>H_{2b}</u>$)_2$), 3.23 (2H, dd, *J* 12.3 and 6.8, NCH_2), 2.90 (2H, t, *J* 6.8, $ArCH_2$), 2.39 (3H, s, $ArCH_3$); δ_C 143.0 (C), 137.1 (C), 137.1 (C), 135.2 (C), 130.4 (ArCH), 129.6 (2 x ArCH), 129.6 (ArCH), 127.05 (2 x ArCH), 127.0 (ArCH), 126.8 (ArCH), 102.4 (<u>C</u>H$(OCH_2)_2$), 65.3 (CH(O<u>C</u>$H_2)_2$), 44.5 (NCH_2), 31.7 ($ArCH_2$), 21.6 ($ArCH_3$); HRMS calculated for $C_{18}H_{21}NNaO_4S$ $[M+Na]^+$ 370.1089, found 370.1087.

Method 2:

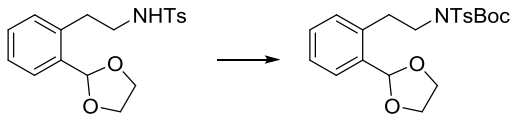


296 **295**

Magnesium turnings (542 mg, 22.30 mmol, 2.2 eq.) were dry-stirred under an atmosphere of nitrogen for 24 hours and then suspended in tetrahydrofuran (5 mL). The suspension was treated with a crystal of iodine and 2-(2-bromophenyl)-1,3-dioxolane **296** (4.64 g, 20.27 mmol, 2.0 eq.) was added as a solution in tetrahydrofuran (3 mL). The reaction was stirred for a further 30 minutes, during which time decolourisation and disappearance of most of the magnesium turnings was observed. The solution was then cooled to -40 °C and copper (I) iodide (579 mg, 3.04 mmol, 0.3 eq.) was added. After further 30 minutes, the reaction mixture was cooled to -78 °C and commercially available 1-tosylaziridine (2.0 g, 10.14 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) was added. After 15 minutes, the reaction mixture was warmed to 0 °C and stirred for another 1.25 h, then quenched by aqueous ammonium chloride (30 mL) and the blue aqueous phase extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered and evaporated. The crude material was purified by column

chromatography (petrol/diethyl ether 2:1) to give *sulfonamide* **295** (1.44 g, 41%) as white solid. All data obtained were in accordance with those reported previously.

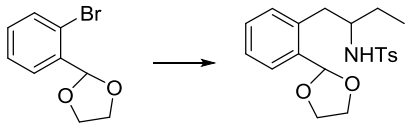
tert-Butyl (2-(1,3-dioxolan-2-yl)phenethyl)(tosyl)carbamate 300



295 **300**

A solution of 2-(2-(1,3-dioxolan-2-yl)phenethyl)-4-methylbenzenesulfonamide **295** (1.44 g, 41.38 mmol, 1.0 eq.) in dichloromethane (25 mL) was treated with DMAP (111 mg, 0.2 eq.) and Boc_2O (1.19 g, 1.2 eq.) according to General Procedure C. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give the *carbamate* **300** (1.24 g, 67%) as a pale yellow oil which solidified upon standing; m.p. 114 – 117 °C; ν_{max} 1728 (C=O), 1355 (S=O), 1155 (S=O); δ_H 7.82 (2H, d, *J* 8.3, 2 x ArH), 7.62 (1H, d, *J* 7.4, ArH), 7.36 – 7.28 (5H, m, 5 x ArH), 6.11 (1H, s, (C<u>H</u>$(OCH_2)_2$), 4.26 – 4.17 (2H, m, (CH(OC<u>H</u>$_{2a}$$)_2$), 4.13 – 4.04 (4H, m, (CH(OC<u>H</u>$_{2b}$$)_2$ and NC<u>H</u>$_2$), 3.29 – 3.23 (2H, m, $ArCH_2$), 2.45 (3H, s, $ArCH_3$), 1.39 (9H, s, $C(CH_3)_3$); δ_C 150.9 (C=O), 144.1 (C), 137.5 (C), 137.0 (C), 135.7 (C), 130.9 (ArCH), 129.4 (ArCH), 129.3 (2 x ArCH), 127.8 (2 x ArCH), 126.85 (ArCH), 126.8 (ArCH), 101.8 (<u>C</u>H$(OCH_2)_2$), 84.1 (<u>C</u>$(CH_3)_3$), 65.3 (NCH), 48.4 (CH_2), 33.5 (CH_2), 27.9 (C(<u>C</u>$H_3$$)_3$), 21.6 ($ArCH_3$).

N-(1-(2-(1,3-Dioxolan-2-yl)phenyl)butan-2-yl)-4-methylbenzenesulfonamide 297



296 **297**

Method 1:

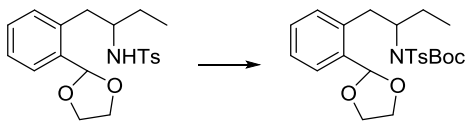
Magnesium turnings (1.25 g, 51.4 mmol, 2.7 eq.) were dry-stirred under an atmosphere of nitrogen for 24 hours and then suspended in tetrahydrofuran (10 mL). The suspension was treated with a crystal of iodine and 2-(2-bromophenyl)-1,3-dioxolane **296** (10.70 mg, 46.7 mmol, 2.46 eq.) was added as a solution in tetrahydrofuran (10 mL). The reaction was stirred for a further 30 minutes, during which time decolourisation and disappearance of most of the magnesium turnings was observed. The solution was then cooled to -40 °C and copper (I) iodide (1.33 g, 7.0 mmol, 0.37 eq.) was added. After further 30 minutes, the reaction mixture was cooled to -78 °C and 2-ethyl-1-tosylaziridine **154** (4.27 g, 18.98 mmol, 1.0 eq.) in tetrahydrofuran (10 mL) was added. After 15 minutes, the reaction mixture was warmed to 0 °C and stirred for a further 1.25 h, then quenched by aqueous ammonium chloride (30 mL) and the blue

aqueous phase extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether, 1:1) to give *sulfonamide* **297** (5.53 g, 78%) as colourless oil; δ_H 7.40 (1H, dd, *J* 7.7 and 1.1, ArH), 7.28 – 7.24 (2H, m, 2 x ArH), 7.12 (1H, td, *J* 7.6 and 1.1, ArH), 6.96 – 6.92 (3H, m and d *J* 8.0, 3 x ArH), 6.09 (1H, d, *J* 5.5, NH), 5.84 (1H, s, C<u>H</u>$(CH_2O)_2$), 4.26 – 4.24 (1H, m, OC<u>H</u>$_{2a}CH_3$), 4.23 – 4.20 (1H, m, OC<u>H</u>$_{2b}CH_3$), 4.14 – 4.06 (2H, m, OC<u>H</u>$_{2c}CH_3$ and OC<u>H</u>$_{2d}CH_3$), 3.28 – 3.21 (1H, m, NCH), 2.85 (1H, dd, *J* 14.1 and 10.3, $ArCH_{2a}$), 2.66 (1H, dd, *J* 14.1 and 4.4, $ArCH_{2b}$), 2.34 (3H, s, $ArCH_3$), 1.77 – 1.69 (2H, m, $CH_3C\underline{H}_2$), 0.95 (3H, t, *J* 7.4, $C\underline{H}_3CH_2$); δ_C 142.1 (C), 137.3 (C), 137.1 (C), 134.7 (C), 130.5 (ArCH), 129.5 (ArCH), 129.3 (2 x ArCH), 127.2 (ArCH), 126.7 (2 x ArCH), 126.3 (ArCH), 103.1 (Ar<u>C</u>H$(OCH_2)_2$), 65.4 (OCH_2), 65.3 (OCH_2), 57.2 (NCH), 35.3 ($ArCH_2$), 29.7 (CH_2), 21.5 ($ArCH_3$), 9.5 (CH_3).

Method 2:

To a solution of 2-(2-bromophenyl)-1,3-dioxolane (1.3 g, 5.67 mmol, 2.0 eq.) in tetrahydrofuran (20 mL) under an atmosphere of nitrogen at -78 °C was added n-butyllithium (2.4M, 2.48 mL, 5.95 mmol, 2.1 eq.) and the mixture stirred for 0.5 h. To the bright orange solution was then added solid magnesium bromide (1.10 g, 5.95 mmol, 2.1 eq.) and the resulting mixture stirred at 0 °C for 30 minutes and then cooled to -40 °C. Copper (I) iodide (160 mg, 0.85 mmol, 0.3 eq.) was then added and the reaction stirred for a further 30 minutes at -40 °C and then cooled to -78 °C. 2-Ethyl-1-tosylaziridine **154** (638 mg, 2.84 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) was then added, the solution stirred for 0.25 h at -78 °C and for a further 1h at 0 °C. The reaction was quenched by aqueous ammonium chloride (20 mL) and the separated blue aqueous phase extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts washed with brine (20 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 1:1) to give *sulfonamide* **297** (532 mg, 50%) as a colourless oil. All data obtained were in accordance with those reported previously.

tert-Butyl (1-(2-(1,3-dioxolan-2-yl)phenyl)butan-2-yl)(tosyl)carbamate 301



297 **301**

Method 1:

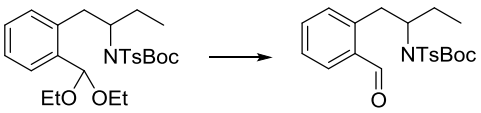
A solution of *N*-(1-(2-(1,3-dioxolan-2-yl)phenyl)butan-2-yl)-4-methylbenzenesulfonamide **297** (532 mg, 1.42 mmol, 1.0 eq.) in dichloromethane (10 mL) was treated with DMAP (35 mg, 0.2 eq.) and Boc_2O (372 mg, 1.2 eq.) according to General Procedure C. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give the *carbamate* **301** (533 g, 79%) as a pale yellow oil;

ν_{max} 1725 (C=O), 1352 (S=O), 1255 (C-O), 1153 (S=O); δ_H (400 MHz) 7.63 (1H, dd, *J* 7.7 and 1.2, ArH), 7.29 (3H, m, 3 x ArH), 7.19 (1H, td, *J* 7.4 and 1.4, ArH), 7.15 (1H, d, 7.0, ArH), 7.11 – 7.08 (1H, m, ArH), 6.10 (1H, s, C<u>H</u>$(OCH_2)_2$), 4.76 – 4.74 (1H, m, NCH), 4.18 – 4.11 (2H, m, OCH_2), 4.09 – 4.02 (2H, m, OCH_2), 3.39 (1H, dd, *J* 13.8 and 8.3, $ArCH_{2a}$), 3.30 (1H, dd, *J* 13.8 and 7.1, $ArCH_{2b}$), 2.37 (3H, s, $ArCH_3$), 2.13 – 1.99 (1H, m, C<u>H</u>$_{2a}CH_3$), 1.76 – 1.63 (1H, m, C<u>H</u>$_{2b}CH_3$), 1.39 (9H, s, $C(CH_3)_3$), 0.92 (3H, t, *J* 7.5, CH_2C<u>H</u>$_3$); δ_C 151.05 (C=O), 143.4 (C), 137.7 (C), 136.2 (C), 131.3 (C), 129.2, 129.0, 128.1, 126.8, 126.6, 101.55 ($CH(OCH_2)_2$), 84.0 ($\underline{C}(CH_3)_3$), 65.3 (2 x CH_2), 62.4 (NCH), 36.0 ($ArCH_2$), 28.1 ($C(\underline{C}H_3)_3$), 26.0 (CH_2), 21.6 ($ArCH_3$), 11.6 (CH_3); HRMS calculated for $C_{25}H_{34}NO_6S$ $[M+H]^+$ 476.2107, found 476.2095.

Method 2:

Magnesium turnings (258 mg, 10.6 mmol, 2.2 eq.) were dry-stirred under an atmosphere of nitrogen for 24 hours and then suspended in tetrahydrofuran (10 mL). The suspension was treated with a crystal of iodine and 2-(2-bromophenyl)-1,3-dioxolane **296** (2.21 g, 9.65 mmol, 2.0 eq.) was added as a solution in tetrahydrofuran (10 mL). The reaction was stirred for a further 30 minutes, during which time decolourisation and disappearance of most of the magnesium turnings was observed. The solution was then cooled to -40 °C and copper (I) iodide (276 mg, 1.45 mmol, 0.3 eq.) was added. After further 30 minutes, the reaction mixture was cooled to -78 °C and 2-ethyl-1-tosylaziridine **154** (4.27 g, 18.98 mmol, 1.0 eq.) in tetrahydrofuran (10 mL) was added. After 15 minutes, the reaction mixture was warmed to 0 °C and stirred for a further 1.25 h. Boc_2O (2.21 g, 10.14 mmol, 1.05 eq.) in tetrahydrofuran (10 mL) was then added and the solution stirred for 16 hours. The reaction was quenched by aqueous ammonium chloride (30 mL) and the blue aqueous phase extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether, 1:1) to give *sulfonamide* **301** (1.16 g, 51%) as a viscous, colourless oil. All data obtained were in accordance to those reported previously.

tert-Butyl (1-(2-formylphenyl)butan-2-yl)(tosyl)carbamate 302

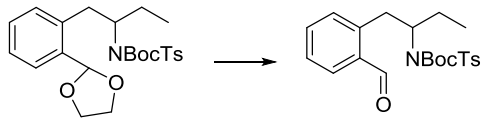


303 **302**

Method 1:

To a solution of *tert*-butyl (1-(2-(diethoxymethyl)phenyl)butan-2-yl)(tosyl)carbamate **303** (2.71 g, 5.52 mmol, 1.0 eq.) in dichloromethane (25 mL) at ambient temperature was added iron (III) chloride hexahydrate (5.22 g, 19.32 mmol, 3.5 eq.) and the resulting mixture stirred vigorously for 1 hour. The reaction was quenched by dropwise addition of aqueous sodium bicarbonate (25 mL) and the separated

aqueous phase extracted with dichloromethane (3 x 25 mL). The combined organic extracts were washed with aqueous sodium bicarbonate (25 mL), brine (25 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give *aldehyde* **302** (1.99 g, 84%) as a white solid; m.p. 75 – 77 °C; ν_{max} 3070, 2738 (CHO), 1723 (C=O), 1699 (C=O), 1350 (S=O), 1152 (S=O); δ_H 10.22 (1H, s, CHO), 7.87 – 7.80 (1H, m, ArH), 7.39 – 7.35 (2H, m, 2 x ArCH), 7.25 (3H, br. s, 3 x ArH), 7.05 (2H, d, *J* 8.0, ArCH), 4.74 – 4.71 (1H, m, NCH), 3.66 (1H, dd, *J* 13.3 and 5.5, $ArCH_{2a}$), 3.48 (1H, dd, *J* 13.1 and 9.9, $ArCH_{2a}$), 2.33 (3H, s, $ArCH_3$), 2.06 – 2.04 (1H, m, $CH_3C\underline{H}_{2a}$), 1.89 – 1.78 (1H, m, $CH_3C\underline{H}_{2b}$), 1.36 (9H, s, $C(CH_3)_3$), 0.97 (3H, t, *J* 7.5, CH_3); δ_C 192.7 (CHO), 150.9 (C=O), 143.5 (C), 141.3 (C), 137.5 (C), 134.6 (C), 133.7 (ArCH), 133.4 (ArCH), 132.6 (ArCH), 128.8 (2 x ArCH), 128.0 (2 x ArCH), 127.25 (ArCH), 84.1 ($\underline{C}(CH_3)_3$), 62.1 (NCH), 35.9 (CH_2), 28.0 ($C(\underline{C}H_3)_3$), 26.5 (CH_2), 21.5 ($ArCH_3$), 11.5 (CH_3); HRMS calculated for $C_{23}H_{29}NNaO_5S$ $[M+Na]^+$ 454.1664, found 454.1677.



301 **302**

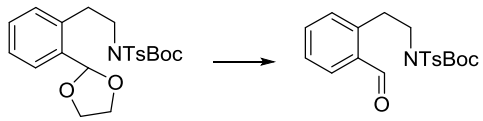
Method 2:

To a solution of *tert*-butyl (1-(2-(1,3-dioxolan-2-yl)phenyl)butan-2-yl)(tosyl)carbamate **301** (533 mg, 1.12 mmol, 1.0 eq.) in dichloromethane (10 mL) at ambient temperature was added iron (III) chloride hexahydrate (1.06 g, 7.87 mmol, 3.5 eq.) and the resulting mixture stirred vigorously for 1 hour. The reaction was quenched by dropwise addition of aqueous sodium bicarbonate (10 mL) and the separated aqueous phase extracted with dichloromethane (3 x 25 mL). The combined organic extracts were washed with aqueous sodium bicarbonate (10 mL), brine (10 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give *aldehyde* **302** (329 mg, 68%) as a white solid. All data obtained were in accordance to those reported previously.

Method 3:

To a solution of *tert*-butyl (1-(2-(1,3-dioxolan-2-yl)phenyl)butan-2-yl)(tosyl)carbamate **301** (100 mg, 0.211 mmol, 1.0 eq.) in dichloromethane (10 mL) at ambient temperature was added amberlyst-15 (20 mg, 20% wt.) and the resulting mixture stirred vigorously for 1 hour. The reaction was filtered and washed with aqueous sodium bicarbonate (10 mL) and the separated aqueous phase extracted with dichloromethane (3 x 25 mL). The combined organic extracts were washed with aqueous sodium bicarbonate (10 mL), brine (10 mL), dried, filtered and evaporated to give *aldehyde* **302** (66 mg, 95%) as a white solid. All data obtained were in accordance to those reported previously.

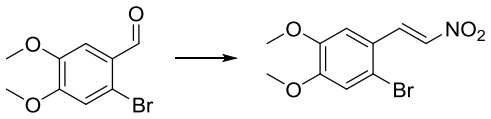
tert-Butyl (2-formylphenethyl)(tosyl)carbamate 300b



300 **300b**

To a solution of *tert*-butyl (1-(2-(1,3-dioxolan-2-yl)phenyl)butan-2-yl)(tosyl)carbamate **300** (1.00 g, 2.46 mmol, 1.0 eq.) in dichloromethane (20 mL) at ambient temperature was added iron (III) chloride hexahydrate (2.13 g, 7.87 mmol, 3.5 eq.) and the resulting mixture stirred vigorously for 1 hour. The reaction was quenched by dropwise addition of aqueous sodium bicarbonate (25 mL) and the separated aqueous phase extracted with dichloromethane (3 x 20 mL). The combined organic extracts were washed with aqueous sodium bicarbonate (20 mL), brine (20 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give *aldehyde* **300b** (710 mg, 78%) as a yellow oil; δ_H 10.34 (1H, s, CHO), 7.87 (1H, dd, *J* 7.7 and 1.3, ArH), 7.76 (2H, d, *J* 8.4, 2 x ArH), 7.55 (1H, td, *J* 7.5 and 1.5, ArH), 7.45 (1H, td, *J* 7.5 and 1.0, ArH), 7.40 (1H, d, *J* 7.5, ArH), 7.29 (2H, d, *J* 7.9, 2 x ArH), 4.15 – 4.11 (2H, t, 7.3, NCH_2), 3.50 (2H, t, *J* 7.3, $ArCH_2$), 2.44 (3H, s, $ArCH_3$), 1.29 (9H, s, $C(CH_3)_3$); δ_C 192.6 (CHO), 150.9 (C=O), 144.3 (C), 140.6 (C), 137.4 (C), 134.5 (C), 134.0 (ArCH), 132.3 (ArCH), 132.3 (ArCH), 129.3 (2 x ArCH), 128.0 (2 x ArCH), 127.4 (2 x ArCH), 84.3 ($\underline{C}(CH_3)_3$), 48.2 (CH_2), 33.5 (CH_2), 27.9 ($C(\underline{C}H_3)_3$), 21.7 ($ArCH_3$).

(*E*)-1-Bromo-4,5-dimethoxy-2-(2-nitrovinyl)benzene[245] 317



316 **317**

To a solution of 2-bromo-4,5-dimethoxybenzaldehyde (10.0 g, 40.8 mmol, 1.0 eq.) in nitromethane (20.0 g, 326 mmol, 8 eq.) was added ammonium acetate (1.89 g, 24.5 mmol, 0.6 eq.) and the mixture heated to 90 °C for 4 hours. The reaction was then allowed to cool to room temperature, and the solvent was removed *in vacuo* at 5 mbar pressure and at 50 °C for 0.25 h. The residue was suspended in dichloromethane (75 mL), washed with water (50 mL) and brine (50 mL), dried, filtered, evaporated and briefly triturated with petroleum ether to afford the crude *nitroalkene* **317** (7.96 g, 68%) as a yellow solid; δ_H (400 MHz) 8.35 (1H, d, *J* 13.6, ArC$\underline{H}$=CH), 7.51 (1H, d, *J* 13.6, ArCH=C$\underline{H}$), 7.10 (1H, s, ArH), 6.98 (1H, s, ArH), 3.92 (3H, s, OCH_3), 3.91 (3H, s, OCH_3).

2-(2-Bromo-4,5-dimethoxyphenyl)ethan-1-amine[246] 318

317 318

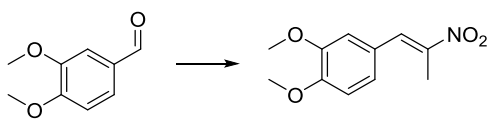
A solution of (*E*)-1-Bromo-4,5-dimethoxy-2-(2-nitrovinyl)benzene **317** (7.96 g, 27.7 mmol, 1.0 eq.) in tetrahydrofuran was treated with sodium borohydride (4.97 g, 131.3 mmol, 4.75 eq.), and boron trifluoride diethyl etherate (23.5 g, 165.9 mmol, 6.0 eq.) according to the General Procedure F to afford *amine* **318** (4.2 g, 58%) as a brown oil; δ_H (400 MHz) 7.00 (1H, s, ArH), 6.74 (1H, s, ArH), 3.85 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 2.95 (2H, t, *J* 6.9, NCH_2), 2.83 (2H, t, *J* 6.9, $ArCH_2$), 2.23 – 2.21 (1H, br s, NH_2).

***N*-(2-Bromo-4,5-dimethoxyphenethyl)-4-methylbenzenesulfonamide[247] 319**

318 319

A solution of 2-(2-bromo-4,5-dimethoxyphenyl)ethan-1-amine **318** (4.20 g, 16.16 mmol) in dichloromethane was treated with triethylamine, DMAP and *p*-tosyl chloride according to General Procedure B. The crude material was purified by column chromatography (petrol/diethyl ether 1:3) to give the *sulfonamide* **319** (5.55 g, 83%) as a white-orange solid; m.p. 114 – 116 °C, lit. m.p.[247] 127 – 128 °C (benzene); ν_{max} 3351 (br, NH); δ_H (400 MHz) 7.70 (2H, d, *J* 8.3, 2 x ArH), 7.26 (1H, d, *J* 8.2, 2 x ArH), 6.92 (1H, s, ArH), 6.66 (1H, s, ArH), 4.81 (1H, t, *J* 6.0, NH), 3.82 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.21 (1H, q, *J* 6.8, NCH_2), 2.84 (1H, t, *J* 7.0, $ArCH_2$), 2.41 (3H, s, $ArCH_3$); δ_C (101 MHz) 148.4 (C), 148.4 (C), 143.40 (C), 136.9 (C), 129.7 (2 x ArCH), 129.1 (C), 127.05 (2 x ArCH), 115.5 (ArCH), 114.1 (C-Br), 113.5 (ArCH), 56.2 (OCH_3), 56.1 (OCH_3), 42.9 (CH_2), 35.95 (CH_2), 21.55 ($ArCH_3$).

(*E*)-1,2-Dimethoxy-4-(2-nitroprop-1-en-1-yl)benzene[248] 321a



320 321a

To a solution of 3,4-dimethoxybenzaldehyde (2.0 g, 12.04 mmol, 1.0 eq.) in nitromethane (45.2 g, 602 mmol, 50 eq.) was added ammonium acetate (788 mg, 10.23 mmol, 0.85 eq.) and the mixture heated to

reflux for 4 hours. The reaction was then allowed to cool to room temperature, and the solvent was removed *in vacuo* at 5 mbar pressure and at 50 °C for 0.25 h. The residue was suspended in dichloromethane (75 mL), washed with water (50 mL) and brine (50 mL), dried, filtered and evaporated . The crude solid was briefly triturated with petroleum ether and then recrystallized from hot petrol/ethyl acetate (1:1) to afford the crude *nitroalkene* **321a** (1.96 g, 73%) as a yellow solid; δ_H (250 MHz) 8.07 (1H, s, ArCH=C), 7.09 (1H, dd, *J* 8.4 and 2.0, ArH), 6.94 (1H, d, *J* 8.5, ArH), 6.95 – 6.92 (1H, m, ArH), 3.94 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 2.49 (3H, d, *J* 0.9, CH_3).

1-(3,4-Dimethoxyphenyl)propan-2-amine[249] 321

321a **321**

To the solution of **321a** (1.96 g, 8.79 mmol, 1.0 eq.) in tetrahydrofuran (50 mL) at 0 °C under an atmosphere of nitrogen was added portionwise lithium aluminium hydride (1.33 g, 35.16 mmol, 4.0 eq) over 5 minutes. The reaction mixture was allowed to stir for 1 hour at the same temperature and then heated to reflux at 65 °C for 2.5 hours. The reaction was then allowed to cool to room temperature and quenched according to the General Procedure F to yield the *amine* **321** (1.43 g, 84%) as a beige oil, and was used in the next step without further purification; δ_H (250 MHz) 6.81 – 6.76 (1H, m, ArH), 6.73 – 6.67 (2H, m, 2 x ArH), 3.85 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.19 – 3.03 (1H, m, NCH), 2.65 (1H, dd, *J* 13.4 and 5.1, $ArCH_{2a}$), 2.41 (1H, dd, *J* 13.4 and 8.3, $ArCH_{2b}$), 1.80 – 1.70 (2H, br s, NH_2), 1.10 (3H, d, *J* 6.3, $CHC\underline{H}_3$).

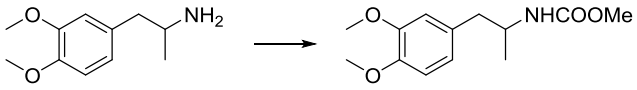
N-(1-(3,4-Dimethoxyphenyl)propan-2-yl)-4-nitrobenzenesulfonamide[250] 322

321 **322**

A solution of 1-(3,4-dimethoxyphenyl)propan-2-amine **321** (788 mg, 4.04 mmol) in dichloromethane was treated with triethylamine, DMAP and *p*-nosyl chloride according to General Procedure B. The crude material was purified by column chromatography (petrol/ethyl acetate 2:1) to give the *sulfonamide* **322** (848 mg, 57%) as a yellow solid; m.p. 69 – 72 °C; lit. m.p.[250] 74 – 81 °C; ν_{max} 3340 (br, NH), 1529 (N=O), 1345 (S=O), 1161 (S=O); δ_H 8.17 (2H, d, *J* 8.8, 2 x ArH), 7.75 (2H, d, *J* 8.8, 2 x ArH), 6.63 (1H, d, *J* 8.1, ArH), 6.50 (1H, dd, *J* 8.1 and 1.8, ArH), 6.44 – 6.42 (1H, m, ArH), 4.66 (1H, d, *J* 7.5, NH), 3.82

(3H, s, ArOC$\underline{H}_3$), 3.75 (3H, s, ArOC$\underline{H}_3$), 3.57 – 3.48 (1H, m, NCH), 2.72 (1H, dd, *J* 14.0 and 5.2, $ArCH_{2a}$), 2.49 (1H, dd, *J* 14.0 and 8.5, $ArCH_{2b}$), 1.25 (3H, d, *J* 6.5, CH_3); LRMS (EI^+) m/z 380 ($[M]^+$, 90%), 229 ($[EtNs]^+$, 99%), 151 ($[M\text{-}EtNs]^+$, 92%); HRMS calculated for $C_{17}H_{20}N_2O_6S$ $[M]^+$ 380.1042, found 380.1046.

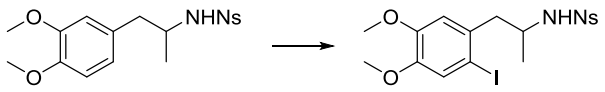
Methyl (1-(3,4-dimethoxyphenyl)propan-2-yl)carbamate 323



321 **323**

A solution of 1-(3,4-dimethoxyphenyl)propan-2-amine **321** (600 mg, 3.08 mmol, 1.0 eq.) in diethyl ether (4 mL) was cooled to 0 °C. Water (3 mL) and potassium carbonate (1.30 g, 9.33 mmol, 3.0 eq.) was added, followed by dropwise addition of methyl chloroformate (420 mg, 4.46 mmol, 1.45 eq.). The cooling bath was removed and the reaction was allowed to warm to room temperature over 30 minutes. The separated aqueous phase was then extracted with dichloromethane (3 x 5 mL) and the combined organic extracts washed with brine (5 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 2:1) to give *carbamate* **323** (510 mg, 65%) as a viscous beige oil; ν_{max} 3382 (br, NH), 1707 (C=O); δ_H (400 MHz) 6.79 (1H, d, *J* 8.3, ArH), 6.72 – 6.68 (2H, m, 2 x ArH), 4.54 (1H, br s, NH), 3.95 – 3.91 (1H, m, NCH), 3.86 (3H, s, ArOC$\underline{H}_3$), 3.85 (3H, s, ArOC$\underline{H}_3$), 3.64 (3H, s, $COOCH_3$), 2.78 (1H, br s, $ArCH_{2a}$), 2.61 (1H, dd, *J* 13.6 and 7.3, $ArCH_{2b}$), 1.11 (3H, d, *J* 6.6, CHC$\underline{H}_3$); LRMS (EI^+) m/z 253 ($[M]^+$, 20%), 221 ($[M\text{-}MeOH]^+$, 95%), 151 ($[M\text{-}EtNHCOOMe]^+$, 100%), 102 ($[EtNHCOOMe]^+$, 78%).

N-(1-(2-Iodo-4,5-dimethoxyphenyl)propan-2-yl)-4-nitrobenzenesulfonamide 324



322 **324**

To a solution of *N*-(1-(3,4-dimethoxyphenyl)propan-2-yl)-4-nitrobenzenesulfonamide **322** (500 mg, 1.32 mmol, 1.0 eq.) in methanol (10 mL) at 0 °C was added silver sulfate (492 mg, 1.58 mmol, 1.2 eq.) and solid iodine (401 mg, 1.58 mmol, 1.2 eq.) and the solution stirred at ambient temperature for 2.5 h. The reaction mixture was then cooled to 0 °C and poured over a 0 °C solution of aqueous sodium bicarbonate and aqueous sodium thiosulfate (1:1, 10 mL), stirred for 2 minutes and then filtered through a pad of Celite© and the filter cake washed with ethyl acetate (2 x 20 mL). The separated aqueous phase was extracted with ethyl acetate (2 x 20 mL) and the combined organic extracts washed with aqueous sodium

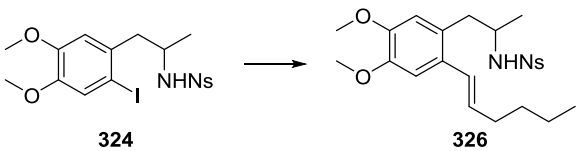
thiosulfate (10 mL), aqueous sodium bicarbonate (10 mL), brine (10 mL) and dried, filtered and evaporated to give *iodide* **324** (608 mg, 90%) as a yellow gum; ν_{max} 3309 (br, NH); δ_H 8.11 (2H, d, *J* 8.9, 2 x ArH), 7.71 (2H, d, *J* 9.0, ArH), 6.91 (1H, s, ArH), 6.42 (1H, s, ArH), 4.77 (1H, d, *J* 8.4, NH), 3.77 (3H, s, $ArOCH_3$), 3.75 (3H, s, $ArOCH_3$), 2.77 (1H, dd, *J* 14.3 and 4.5, $ArCH_{2a}$), 2.62 (1H, dd, *J* 14.3 and 10.3, $ArCH_{2b}$), 1.39 (3H, d, *J* 6.5, CH_3); δ_C 149.6 (C), 149.4 (C), 148.8 (C), 146.25 (C), 132.5 (C), 127.9 (ArCH), 123.95 (ArCH), 121.6 (ArCH), 113.3 (ArCH), 88.65 (C-I), 56.1 (OCH_3), 56.0 (OCH_3), 52.0 (NCH), 47.0 (CH_2), 23.6 (CH_3); HRMS calculated for $C_{17}H_{19}IN_2O_6S$ $[M]^+$ 506.0009, found 506.0026.

Methyl (1-(2-iodo-4,5-dimethoxyphenyl)propan-2-yl)carbamate 325

323 **325**

To a solution of methyl (1-(3,4-dimethoxyphenyl)propan-2-yl)carbamate **323** (500 mg, 2,00 mmol, 1.0 eq.) in methanol (10 mL) at 0 °C was added silver sulfate (748 mg, 2.40 mmol, 1.2 eq.) and solid iodine (608 mg, 2.40 mmol, 1.2 eq.) and the solution stirred at ambient temperature for 2.5 h. The reaction mixture was then cooled to 0 °C and poured over a 0 °C solution of aqueous sodium bicarbonate and aqueous sodium thiosulfate (1:1, 10 mL), stirred for 2 minutes and then filtered through a pad of Celite© and the filter cake washed with ethyl acetate (2 x 20 mL). The separated aqueous phase was extracted with ethyl acetate (2 x 20 mL) and the combined organic extracts washed with aqueous sodium thiosulfate (10 mL), aqueous sodium bicarbonate (10 mL), brine (10 mL) and dried, filtered and evaporated to give *iodide* **325** (573 mg, 76%) as a yellowish oil; ν_{max} 3373 (br, NH), 1702 (C=O); δ_H (250 MHz) 7.17 (1H, s, ArH), 6.69 (1H, s, ArH), 4.74 (1H, d, *J* 6.5, NH), 4.04 – 3.87 (1H, br m, NCH), 3.80 (6H, s, 2 x $ArOC\underline{H}_3$), 3.57 (3H, s, $COO\underline{C}H_3$), 2.87 (1H, br dd, *J* 13.1 and 7.5, $ArCH_{2a}$), 2.74 (1H, dd, *J* 13.8 and 6.8, $ArCH_{2b}$), 1.16 (3H, d, *J* 6.6, CH_3). δ_C 156.4 (C=O), 149.5 (C), 148.3 (C), 133.9 (C), 121.9 (ArCH), 113.05 (ArCH), 89.1 (C-I), 56.2 ($ArOCH_3$), 56.05 ($ArOCH_3$), 52.0 ($COO\underline{C}H_3$), 48.35 (NCH), 46.6 (br s, $ArCH_2$), 20.8 (CH_3); HRMS calculated for $C_{13}H_{19}IN_2O_6S$ $[M+H]^+$ 380.0359, found 380.0343.

(*E*)-*N*-(1-(2-(Hex-1-en-1-yl)-4,5-dimethoxyphenyl)propan-2-yl)-4-nitrobenzenesulfonamide 326

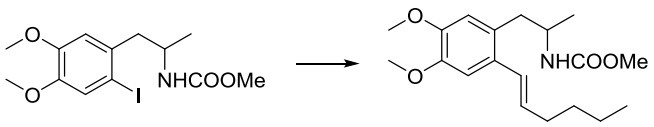


324 **326**

A solution of *N*-(1-(2-iodo-4,5-dimethoxyphenyl)propan-2-yl)-4-nitrobenzenesulfonamide **324** (150 mg, 1.0 eq.) in ethanol/water (1:1, 1.5 mL) was treated with 1-hexenylboronic acid (49 mg, 1.3 eq.), K_3PO_4

(126 mg, 2.0 eq) and Pd(dppf)Cl_2.DCM (21 mg, 0.10 eq) at 70 °C for 2 h according to General Procedure D. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give the *sulfonamide* **326** (99 mg, 72%) as a pale yellow foam; ν_{max} 3352 (br, NH); δ_H 8.09 (2H, d, *J* 8.9, 2 x ArH), 7.63 (2H, d, *J* 8.9, 2 x ArH), 6.64 (1H, s, ArH), 6.34 (1H, s, ArH), 6.32 (1H, d, *J* 15.6, ArC<u>H</u>=CH), 5.80 (1H, dt, *J* 15.4 and 7.0, ArCH=C<u>H</u>), 4.88 (1H, d, *J* 7.3, NH), 3.82 (3H, s, $ArOCH_3$), 3.76 (3H, s, $ArOCH_3$), 3.48 – 3.38 (1H, m, NCH), 2.73 (1H, dd, *J* 14.3 and 5.0, $ArCH_{2a}$), 2.57 (1 H, dd, *J* 14.3 and 9.6, $ArCH_{2b}$), 2.18 (2H, dt , *J* 7.0 and 7.0, C<u>H</u>$_2$CH=CH), 1.48 – 1.41 (2H, m, C<u>H</u>$_2$CH$_2$CH=CH), 1.38 – 1.36 (2H, m, CH$_3$C<u>H</u>$_2$), 1.31 (3H, d, *J* 6.4, C<u>H</u>$_3$CH), 0.95 (3H, t, *J* 7.2, C<u>H</u>$_3$CH$_2$); δ_C 149.6 (C), 148.3 (C), 148.1 (C), 146.0 (C), 132.6 (ArCH=<u>C</u>H), 129.45 (C), 127.8 (2 x ArCH), 126.5 (C), 126.4 (Ar<u>C</u>H=CH), 123.9 (2 x ArCH), 113.4 (ArCH), 108.9 (ArCH), 56.0 (OCH_3), 55.8 (OCH_3), 52.2 (NCH), 40.25 (CH_2), 33.1 (CH_2), 31.7 (CH_2), 23.3 (CH_3), 22.4 (CH_2), 14.0 (CH_3); HRMS calculated for $C_{23}H_{30}N_2O_6S$ $[M]^+$ 462.1825, found 462.1828.

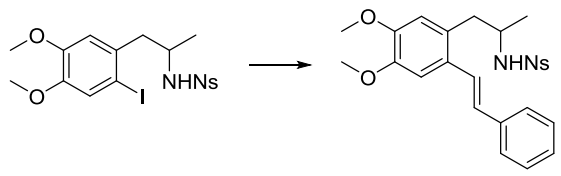
Methyl (*E*)-(1-(2-(hex-1-en-1-yl)-4,5-dimethoxyphenyl)propan-2-yl)carbamate 327



325 **327**

A solution of methyl (1-(2-iodo-4,5-dimethoxyphenyl)propan-2-yl)carbamate **325** (230 mg, 1.0 eq.) in ethanol/water (1:1, 2 mL) was treated with 1-hexenylboronic acid (101 mg, 1.3 eq.), K_3PO_4 (258 mg, 2.0 eq) and Pd(dppf)Cl_2.DCM (50 mg, 0.10 eq) at 80 °C for 1 h according to General Procedure D. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give the *carbamate* **327** (109 mg, 54%) as a yellow oil; δ_H 6.94 (1H, s, ArH), 6.60 (1H, d, *J* 15.4, ArC<u>H</u>=CH), 6.58 (1H, s, ArH), 6.02 – 5.98 (1H, dt, *J* 15.5 and 7.0, ArCH=C<u>H</u>), 4.64 (1H, br s, NH), 3.89 – 3.70 (1H, br s, NCH), 3.88 (3H, s, ArOC<u>H</u>$_3$), 3.84 (3H, s, ArOC<u>H</u>$_3$), 3.53 (3H, s, COOC<u>H</u>$_3$), 2.89 (1H, dd, *J* 13.8 and 6.0, $ArCH_{2a}$), 2.65 (1H, br s, $ArCH_{2b}$), 2.25 – 2.20 (2H, m, CH=CHC<u>H</u>$_2$), 1.50 – 1.42 (2H, m, CH$_3$CH$_2$C<u>H</u>$_2$), 1.39 – 1.35 (2H, m, C<u>H</u>$_2$CH$_3$), 1.09 (3H, d, *J* 6.6, NCHC<u>H</u>$_3$), 0.93 (3H, t, *J* 7.3, CH$_2$C<u>H</u>$_3$); δ_C 156.4 (C=O), 148.1 (C), 147.9 (C), 131.6 (ArCH=<u>C</u>H), 130.0 (C), 127.7 (C), 127.2 (Ar<u>C</u>H=CH), 113.7 (ArCH), 109.2 (ArCH), 56.1 (ArO<u>C</u>H$_3$), 56.0 (ArO<u>C</u>H$_3$), 52.0 (COO<u>C</u>H$_3$), 48.4 (NCH), 39.4 (br $ArCH_2$), 33.1 (CH_2), 31.8 (CH_2), 22.4 (CH_2), 20.2 (br. CH_3), 14.05 (CH_3); HRMS calculated for $C_{19}H_{30}NO_4$ $[M+H]^+$ 336.2175, found 336.2167

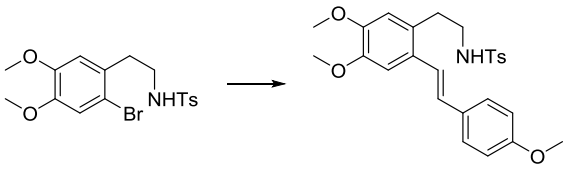
(*E*)-*N*-(1-(4,5-Dimethoxy-2-styrylphenyl)propan-2-yl)-4-nitrobenzenesulfonamide 328



324 **328**

A solution of *N*-(1-(2-iodo-4,5-dimethoxyphenyl)propan-2-yl)-4-nitrobenzenesulfonamide **324** (360 mg, 1.0 eq.) in ethanol/water (1:1, 4 mL) was treated with 1-phenylvinylboronic acid (150 mg, 1.5 eq.), K_3PO_4 (286 mg, 2.0 eq) and Pd(dppf)Cl_2.DCM (28 mg, 0.05 eq.) at 85 °C for 3 h according to General Procedure D. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give the *sulfonamide* **328** (268 mg, 82%) as a yellow foam; ν_{max} 3292 (br, NH); δ_H 8.04 (2H, d, *J* 8.8, 2 x ArH), 7.65 (2H, d, *J* 8.8, 2 x ArH), 7.51 (2H, d, *J* 7.5, 2 x ArH), 7.40 (2H, t, *J* 7.6, 2 x ArH), 7.33 – 7.28 (1H, m, ArH), 7.14 (1H, d, *J* 16.0, ArC<u>H</u>=CH), 6.90 (1H, s, ArH), 6.71 (1H, d, *J* 16.0, ArCH=C<u>H</u>), 6.47 (1H, s, ArH), 4.70 (1H, d, *J* 7.3, NH), 3.90 (1H, s, OCH_3), 3.83 (1H, s, OCH_3), 3.49 – 3.40 (1H, m, NCH), 2.89 (1H, dd, *J* 14.2 and 8.1, $ArCH_{2a}$), 2.79 (1H, dd, *J* 14.2 and 6.3, $ArCH_{2b}$), 1.23 (3H, d, *J* 6.5, CH_3); δ_C 149.8 (C), 148.9 (C), 148.5 (C), 146.0 (C), 137.3 (C), 129.6 (ArCH), 129.0 (2 x ArCH), 128.9 (C), 128.1 (ArCH), 128.0 (2 x ArCH), 127.8 (C), 126.6 (2 x ArCH), 125.2 (ArCH), 124.1 (2 x ArCH), 113.8 (ArCH), 108.8 (ArCH), 56.1 (OCH_3), 56.0 (OCH_3), 51.8 (NCH), 41.1 (CH_2), 22.5 (CH_3).

(*E*)-*N*-(4,5-Dimethoxy-2-(4-methoxystyryl)phenethyl)-4-methylbenzenesulfonamide 330

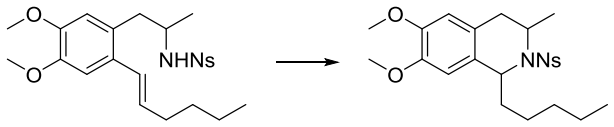


319 **330**

A solution of *N*-(2-bromo-4,5-dimethoxyphenethyl)-4-methylbenzenesulfonamide **319** (430 mg, 1.00 eq.) in ethanol/water (1:1, 4 mL) was treated with (4-methoxystyryl)boronic acid (268 mg, 1.5 eq.), K_3PO_4 (426 mg, 2.0 eq) and Pd(dppf)Cl_2.DCM (82 mg, 0.10 eq.) at 85 °C for 3 h according to General Procedure D. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give the *sulfonamide* **330** (259 mg, 53%) as a white foam; ν_{max} 3372 (br, NH); δ_H (400 MHz) 7.64 (2H, d, *J* 8.2, 2 x ArH), 7.43 (2H, d, *J* 8.7, 2 x ArH), 7.16 (2H, d, *J* 8.1, 2 x ArH), 7.07 (1H, d, *J* 16.1, ArCH=C<u>H</u>), 7.04 (1H, s, ArH), 6.89 (2H, d, *J* 8.7, 2 x ArH), 6.79 (1H, d, *J* 15.9, ArC<u>H</u>=CH), 6.58 (1H, s, ArH), 4.73 (1H, t, *J* 6.1, NH), 3.91 (3H, s, $ArOCH_3$), 3.83 (3H, s, $ArOCH_3$), 3.82 (3H, s, $ArOCH_3$), 3.14 (2H, dd, *J* 13.8 and 6.8, NCH_2), 2.91 (2H, t, *J* 7.2, $ArCH_2$), 2.35 (3H, s, $ArCH_3$); δ_C (101 MHz) 159.4 (C), 148.7 (C),

148.2 (C), 143.4 (C), 137.0 (C), 130.4 (C), 129.7 (2 x ArCH), 129.2 (C), 128.9 (CH=C), 128.1 (C), 127.8 (2 x ArCH), 127.1 (2 x ArCH), 123.2 (CH=C), 114.3 (2 x ArCH), 113.2 (ArCH), 108.8 (ArCH), 56.1 ($ArOCH_3$), 56.1 ($ArOCH_3$), 55.4 ($ArOCH_3$), 44.1 (CH_2), 33.55 (CH_2), 21.55 ($ArCH_3$);

6,7-dimethoxy-3-methyl-2-((4-nitrophenyl)sulfonyl)-1-pentyl-1,2,3,4-tetrahydroisoquinoline 331



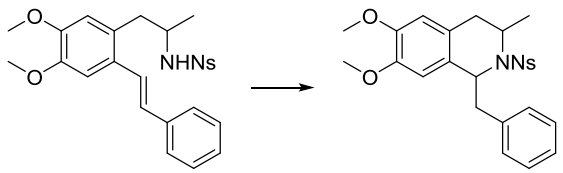
326 **331**

The sulfonamide **326** (20 mg, 0.043 mmol, 1.0 eq.) was dissolved in dichloromethane (0.2 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (2.5 mg, 0.017 mmol, 0.4 eq.). The resulting solution was stirred for 30 minutes at 0 °C and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 3:1) to give *tetrahydroisoquinoline* **331** (17 mg, 84%) as a colourless glass and as a 10:1 mixture of *cis* and *trans* diastereoisomers; *major (cis)-diastereoisomer* δ_H (250 MHz) 8.06 (2H, d, *J* 8.9, 2 x ArH), 7.72 (1H, d, *J* 9.0, 2 x ArH), 6.42 (1H, s, ArH), 6.38 (1H, s, ArH), 4.75 (1H, dd, *J* 8.7 and 6.1, ArCHN), 3.88 – 3.75 (1H, m, NCH), 3.78 (3H, s, $ArOCH_3$), 3.76 (3H, s, $ArOCH_3$), 2.70 (1H, dd, *J* 14.2 and 5.8, $ArCH_{2a}$), 2.61 (1H, dd, *J* 14.1 and 7.2, $ArCH_{2b}$), 1.95 – 1.78 (1H, m, CH_2), 1.74 – 1.58 (2H, m, CH_2), 1.55 (3H, d, *J* 6.4, $CHCH_3$), 1.50 – 1.14 (5H, m, CH_2), 0.90 (3H, t, *J* 6.3, CH_2CH_3); *minor (trans)-diastereoisomer* δ_H (250 MHz) 8.23 (2H, d, *J* 8.9, 2 x ArH), 7.93 (2H, d, *J* 9.0, 2 x ArH), 6.56 (1H, s, ArH), 6.47 (1H, s, ArH), 4.95 (1H, app t, *J* 6.9, ArCHN), 3.88 (3H, s, $ArOCH_3$), 3.81 (3H, s, $ArOCH_3$), 2.86 (1H, dd, *J* 16.0 and 4.6, $ArCH_{2a}$), 2.37 (1H, dd, *J* 15.8 and 6.8, $ArCH_{2b}$).

Method 2:

The sulfonamide **326** (42 mg, 0.083 mmol, 1.0 eq.) was dissolved in dichloromethane (0.2 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added sulfuric acid (1 drop, approx. 12 mg, 0.12 mmol, 1.2 eq.). The resulting solution was stirred for 30 minutes at 0 °C and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 1:2) to give *tetrahydroisoquinoline* **331** (18 mg, 87%) as a colourless glass and as a 10:1 mixture of *cis* and *trans* diastereoisomers. All data obtained were in accordance with those reported previously.

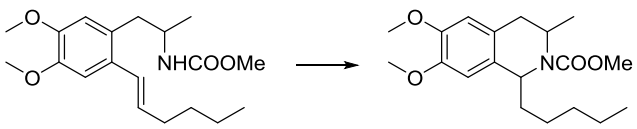
1-Benzyl-6,7-dimethoxy-3-methyl-2-nosyl-1,2,3,4-tetrahydroisoquinoline 332



328 **332**

The sulfonamide **328** (53 mg, 0.110 mmol, 1.0 eq.) was dissolved in dichloromethane (0.5 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (6.6 mg, 0.044 mmol, 0.4 eq.). The resulting solution was stirred for 30 minutes at 0 °C and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *tetrahydroisoquinoline* **332** (18 mg, 87%) as a yellow foam and as a 20:1 mixture of *cis* and *trans* diastereoisomers; *major (cis)-diastereoisomer* δ_H 8.09 (2H, d, *J* 8.9, 2 x ArH), 7.74 (2H, d, *J* 8.9, 2 x ArH), 7.30 – 7.20 (3H, m, 3 x ArH), 7.11 – 7.09 (2H, m, 2 x ArH), 6.46 (1H, s, ArH), 5.82 (1H, s, ArH), 5.06 (1H, dd, *J* 9.9 and 4.9, ArC<u>H</u>CH_2Ar), 4.05 – 3.97 (1H, app sext, *J* 6.9, $ArCH_2C\underline{H}CH_3$), 3.77 ($3H, s, OCH_3$), 3.45 ($3H, s, OCH_3$), 3.36 (1H, dd, *J* 13.2 and 4.9, $ArC\underline{H}_{2a}CHAr$), 3.02 (1H, dd, *J* 13.1 and 9.9, $ArC\underline{H}_{2b}CHAr$), 2.80 (1H, dd, *J* 15.8 and 6.9, $ArC\underline{H}_{2a}CHCH_3$), 2.68 (1H, dd, *J* 15.9 and 7.6, $ArC\underline{H}_{2b}CHCH_3$), 1.58 ($3H, d, J 6.5, CH_3$); δ_C 149.8 (C), 148.5 (C), 147.1 (C), 145.8 (C), 138.3 (C), 129.9 (2 x ArCH), 128.6 (2 x ArCH), 128.4 (2 x ArCH), 127.4 (C), 126.9 (ArCH), 124.1 (C), 124.0 (2 x ArCH), 111.45 (ArCH), 110.7 (ArCH), 60.1 (CH), 56.05 (OCH_3), 55.9 (OCH_3), 50.2 (CH), 45.1 (CH_2), 34.3 (CH_2), 25.0 (CH_3); *major (cis)-diastereoisomer* δ_H 8.16 (2H, d, *J* 8.9, 2 x ArH), 7.69 (2H, d, *J* 8.9, 2 x ArH), 7.30 – 7.20 (3H, m, 3 x ArH), 7.01 (2H, dd, *J* 6.5 and 2.9, 2 x ArH), 6.59 (1H, s, ArH), 6.09 (1H, s, ArH), 5.14 (1H, dd, *J* 7.6 and 7.0, ArC<u>H</u>CH_2Ar), 4.31 – 4.24 (1H, m, $ArCH_2C\underline{H}CH_3$), 3.85 ($3H, s, OCH_3$), 3.61 ($3H, s, OCH_3$), 1.11 ($3H, d, J 6.7, CH_3$); δ_C 150.8 (C), 148.9 (C), 147.2 (C), 138.3 (C), 129.95 (ArCH), 128.2 (ArCH), 127.5 (C), 126.9 (ArCH), 125.2 (ArCH), 124.2 (ArCH), 112.05 (ArCH), 110.7, 61.15 (CH), 56.1 (OCH_3), 56.0 (OCH_3), 50.4 (CH), 44.5 (CH_2), 35.6 (CH_2), 20.3 (CH_3); LRMS (EI_+) m/z 391 ($[M-CH_2Ph]^+$, 100%), 361 ($[M-PhNO_2]^+$, 3%); HRMS (ES^-) calculated for $C_{25}H_{26}BrClN_2O_6S$ $[M+Cl]^-$ 517.1200, found 517.1197.

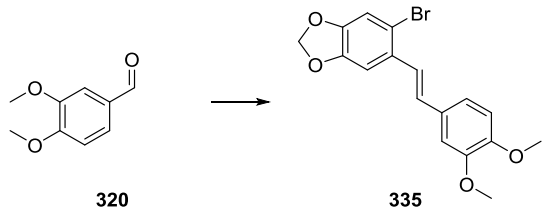
Methyl 6,7-dimethoxy-3-methyl-1-pentyl-3,4-dihydroisoquinoline-2(1H)-carboxylate 333



327 **333**

The carbamate **327** (31 mg, 0.093 mmol, 1.0 eq.) was dissolved in dichloromethane (0.3 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added sulfuric acid (1 drop, approx. 12 mg, 0.12 mmol, 1.2 eq.). The resulting solution was stirred for 30 minutes at 0 °C and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *tetrahydroisoquinoline* **333** (22 mg, 72%) as a colourless glass and as a 3:2 mixture of diastereoisomers; *major diastereoisomer* δ_H (400 MHz) 6.67 (1H, s, ArH), 6.64 (1H, s, ArH), 4.64 (1H, br s, 1-H), 4.37 (1H, d, 3-H), 3.88 (3H, s, $ArOCH_3$), 3.86 (3H, s, $ArOCH_3$), 3.74 (3H, s, $COOCH_3$), 3.17 (1H, dd, *J* 14.9, 5.2, $ArCH_{2a}$), 2.44 (1H, br s, $ArCH_{2b}$), 1.79 – 1.67 (2H, m, CH_2), 0.90 – 1.50 (6H, 3 x CH_2), 1.21 (3H, t, *J* 6.9, CH_3), 0.86 (3H, d, *J* 6.7, CH_3); *minor diastereoisomer* δ_H (400 MHz) 6.64 (1H, s, ArH), 6.59 (1H, s, ArH), 5.14 (1H, br. s, ArCHN), 4.05 (1H, s, 3-H), 3.86 (3H, s, $ArOCH_3$), 3.85 (3H, s, $ArOCH_3$), 3.69 (3H, s, $COOCH_3$), 2.89 (1H, br. s, $ArCH_{2a}$), 2.73 (1H, dd, *J* 15.4 and 9.6, $ArCH_{2b}$), 1.65 – 1.60 (2H, m, CH_2), 1.37 (3H, d, *J* 6.3, CH_3), 1.21 – 1.11 (3H, m, CH_3), 0.99 – 0.80 (6H, m, 3 x CH_2).

(*E*)-5-Bromo-6-(3,4-dimethoxystyryl)benzo[d][1,3]dioxole 335

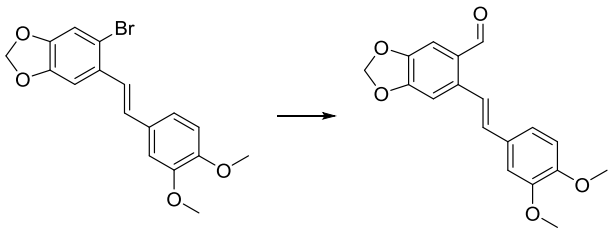


320 **335**

A suspension of ((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)triphenylphosphonium bromide **(**3.82 g, 7.46 mmol) in tetrahydrofuran (15 mL) was treated with potassium *tert*-butoxide (906 mg, 8.08 mmol) and 2-bromobenzaldehyde **136** (1.03 g, 6.22 mmol) according to general procedure A1. The crude product was purified by column chromatography (petrol/diethyl ether 2:1) to yield *alkene* **335** (1.915 g, 85%) as an off-white glass and as a 3:1 mixture of *cis* and *trans* isomers; m.p. 118-120 °C; ν_{max} 3004, 2917, 2850, 1266 (C-O), 1036 (C-O); *major (cis)-isomer* δ_H 6.77 (1H, dd, *J* 8.3, 1.8, ArH), 6.73 (1H, d, *J* 8.3, ArH), 6.69 (1H, s, ArH), 6.54 (1H, d, *J* 11.9, ArC<u>H</u>=CH), 6.42 (1H, d, *J* 11.9, ArCH=C<u>H</u>), 5.91 (2H, s,

OCH_2O), 3.85 (3H, s, $ArOCH_3$), 3.66 (3H, s, $ArOCH_3$); δ_C 148.46 (C), 147.55 (C), 147.0 (C), 131.4 (C), 130.6 (ArCH), 129.1 (C), 127.8 (ArCH), 122.0 (ArCH), 114.7 (C-Br), 112.5 (ArCH), 112.0 (ArCH), 110.9 (ArCH), 110.3 (ArCH), 101.4 (OCH_2), 55.8 (OCH_3), 55.6 (OCH_3); *minor (trans)-isomer* δ_H 7.24 (1H, d, *J* 16.0, ArC<u>H</u>=CH), 6.86 (1H, d, *J* 8.8, ArH), 6.83 (1H, d, *J* 16.1, ArCH=C<u>H</u>), 5.98 (2H, s, OCH_2O), 3.94 (3H, s, $ArOCH_3$), 3.90 (3H, s, $ArOCH_3$), only 6 distinct signals; δ_C (126 MHz, $CDCl_3$) 149.2 (C), 147.8 (C), 147.7 (C), 129.6 (ArCH), 125.5 (ArCH), 120.0 (ArCH), 112.8 (ArCH), 111.4 (ArCH), 109.2 (ArCH), 105.7 (ArCH), 101.6 (OCH_2), 56.0 (OCH_3), 55.9 (OCH_3), only 13 distinct signals; HRMS calculated for $C_{17}H_{16}BrO_4$ $[M+H]^+$ 363.0232, found 363.0237

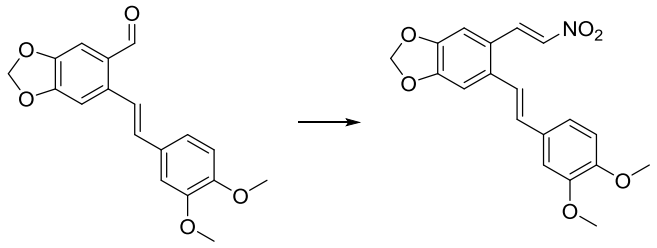
(*E*)-6-(3,4-Dimethoxystyryl)benzo[d][1,3]dioxole-5-carbaldehyde 336



335 **336**

To a solution of 5-bromo-6-(3,4-dimethoxystyryl)benzo[d][1,3]dioxole **335** (1.92 g, 5.28 mmol, 1.0 eq.) in tetrahydrofuran (20 mL) at -78 °C under an atmosphere of nitrogen was added n-butyllithium (1.5 M, 3.74 mL, 5.81 mmol, 1.1 eq.) over 10 minutes and the reaction stirred for a further 30 minutes at the same temperature. Dimethylformamide (1.23 mL, 15.8 mmol, 3.0 eq.) was added dropwise and the mixture allowed to warm to ambient temperature and stirred for a further 2 hours. The reaction was quenched by addition of aqueous ammonium chloride (20 mL) and the aqueous layer extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried, filtered and evaporated and the crude material purified by column chromatography (petrol/diethyl ether 1:1) to give *aldehyde* **288** (859 mg, 52%) as a yellow oil, as a 2:1 mixture of *cis* and *trans* isomers; ν_{max} 1711 (C=O); *major (cis)-isomer* δ_H 10.12 (1H, s, CHO), 7.37 (1H, s, ArH), 6.75 (1H, d, *J* 12.1, ArC<u>H</u>=CH), 6.72 (1H, d, *J* 12.2, ArCH=C<u>H</u>), 6.72 (1H, s, ArH), 6.70 (1H, d, *J* 1.4, ArH), 6.58 (2H, s, OCH_2O), 3.83 (3H, s, $ArOCH_3$), 3.60 (3H, s, $ArOCH_3$); δ_C 190.0 (CHO), 152.6 (C), 148.8 (C), 148.5 (C), 147.6 (C), 139.2 (C), 133.6 (ArCH), 128.45 (C), 123.7 (ArCH), 122.5 (ArCH), 112.1 (ArCH), 111.0 (ArCH), 109.7 (ArCH), 106.7 (ArCH), 102.0 (OCH_2), 55.8 (OCH_3), 55.5 (OCH_3); *minor (trans)-isomer* δ_H (400 MHz) 10.24 (1H, s, ArCHO), 6.93 (1 H, d, *J* 8.0, ArCH), 6.80 (1H, dd, *J* 8.0 and 0.8, ArCH), 6.62 (1H, s, ArCH), 6.14 (2H, s, OCH_2O), 3.83 (3H, s, $ArOCH_3$), 3.62 (3H, s, $ArOCH_3$); HRMS calculated for $C_{17}H_{16}BrO_4$ $[M+H]^+$ 363.0232, found 363.0237.

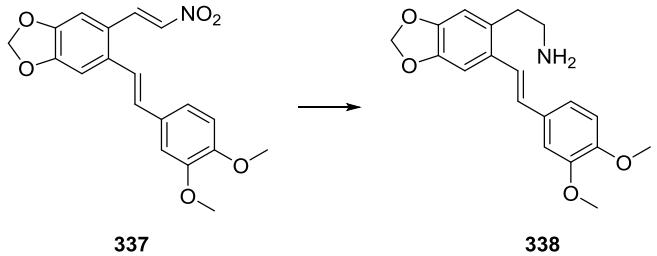
5-((*E*)-3,4-Dimethoxystyryl)-6-((*E*)-2-nitrovinyl)benzo[d][1,3]dioxole 337



336 **337**

To a solution of 6-(3,4-dimethoxystyryl)benzo[d][1,3]dioxole-5-carbaldehyde **336** (859 mg, 2.75 mmol, 1.0 eq.) in nitromethane (1.7 g, 27.5 mmol, 10 eq.) was added ammonium acetate (128 mg, 1.65 mmol, 0.6 eq.) and the mixture heated to reflux for 3 hours. The reaction was then allowed to cool to room temperature, and the solvent was removed *in vacuo* at 5 mbar pressure and at 60 °C for 1 h. The residue was suspended in dichloromethane (25 mL), washed with water (50 mL) and brine (50 mL), dried, filtered and evaporated to afford the crude *nitroalkene* **233** (500 mg g, 51%) as a viscous, red oil, as a single *cis* isomer and was used in the next step without further purification; δ_H 8.10 (1H, d, *J* 13.5, ArC<u>H</u>=CHNO$_2$), 7.23 (1H, d, *J* 13.5, ArCH=C<u>H</u>NO$_2$), 6.88 (1H, s, ArH), 6.71 (1H, s, ArH), 6.68 (1H, d, *J* 11.9, ArC<u>H</u>=CH), 6.62 (1H, d, *J* 8.3, ArH), 6.60 – 6.57 (1H, m, ArH), 6.48 (1H, d, *J* 12.0, ArH), 6.47 (1H, d, *J* 1.8, ArH), 5.96 (2H, s, OCH$_2$O), 3.75 (3H, s, OCH$_3$), 3.54 (3 H, s, OCH$_3$); δ_C 151.1 (C), 148.75 (C), 148.5 (C), 147.65 (C), 137.3 (ArCH), 135.8 (ArCH), 134.0 (ArCH), 125.0 (ArCH), 122.4 (ArCH), 112.05 (ArCH), 111.05 (ArCH), 110.1 (ArCH), 106.1 (ArCH), 102.0 (OCH$_2$), 55.8 (OCH$_3$), 55.55 (OCH$_3$).

(*E*)-2-(6-(3,4-Dimethoxystyryl)benzo[d][1,3]dioxol-5-yl)ethan-1-amine 338

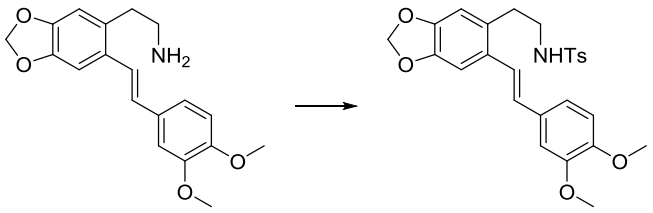


337 **338**

To the solution of 5-(3,4-dimethoxystyryl)-6-(2-nitrovinyl)benzo[d][1,3]dioxole **337** (500 mg, 1.41 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) at 0 °C under an atmosphere of nitrogen was added portionwise lithium aluminium hydride (161 mg, 4.23 mmol, 3.0 eq) over 5 minutes. The reaction mixture was allowed to stir for 1 hour at the same temperature and then heated to reflux at 65 °C for 2.5 hours. The

reaction was then allowed to cool to room temperature and quenched according to the General Procedure F to yield the *amine* **338** (160 mg, 35%) as a brown oil which was used in the next step without further purification; δ_H (400 MHz) 6.77 – 6.73 (3H, m, 3 x ArH), 6.69 (1H, s, ArH), 6.66 (1H, d, *J* 1.6, ArH), 6.55 – 6.50 (2H, m, 2 x ArH), 5.91 (1H, s, OCH_2O), 3.86 (3H, s, $ArOCH_3$), 3.61 (1H, s, $ArOCH_3$), 2.90 (2H, t, *J* 7.2, $ArCH_2C\underline{H}_2N$), 2.72 (2H, t, *J* 7.2, $ArCH_2$), 1.71 (2H, br. s, NH_2).

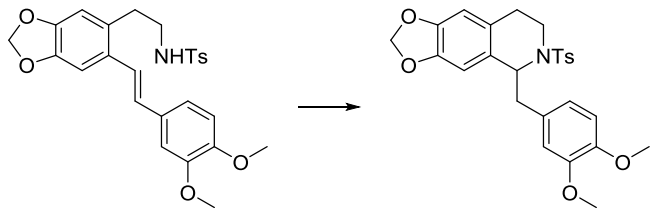
(*E*)-*N*-(2-(6-(3,4-Dimethoxystyryl)benzo[d][1,3]dioxol-5-yl)ethyl)-4-methylbenzenesulfonamide 339



338 **339**

A solution of (E)-2-(6-(3,4-dimethoxystyryl)benzo[d][1,3]dioxol-5-yl)ethan-1-amine **338** (1.26 g, 3.85 mmol, 1.0 eq.) in dichloromethane was treated with triethylamine, DMAP and *p*-tosyl chloride according to General Procedure B. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give the *sulfonamide* **339** (860 mg, 46%) as a colourless glass; δ_H 7.54 (2H, d, *J* 8.3, 2 x ArH), 7.08 (2H, d, *J* 8.2, 2 x ArH), 7.05 – 7.01 (2H, m, 2 x ArH), 7.04-7.02 (1H, m, ArH), 6.57 – 6.55 (1H, m, ArH), 6.50 (1H, d, *J* 1.7, ArH), 6.31 (1H, d, *J* 12.0, $ArC\underline{H}$=CH), 6.25 (1H, d, *J* 11.9, ArCH=C$\underline{H}$), 5.74 (2H, s, OCH_2O), 4.92 (1H, t, *J* 6.2, NH), 3.70 (3H, s, OCH_3), 3.44 (1H, s, OCH_3), 2.98 – 2.93 (1H, m, $ArCH_2C\underline{H}_2N$), 2.58 (1H, t, *J* 7.4, $ArC\underline{H}_2CH_2N$), 2.25 (3H, s, $ArCH_3$); δ_C 149.0 (C), 148.5 (C), 148.4 (C), 148.3 (C), 146.9 (C), 146.45 (C), 143.3 (C), 137.1 (C), 136.9 (C), 130.9 (ArCH), 129.6 (2 x ArCH), 127.0 (2 x ArCH), 127.0 (ArCH), 126.5 (ArCH), 122.1 (ArCH), 111.8 (ArCH), 110.9 (ArCH), 109.7 (ArCH), 101.0 (OCH_2), 55.8 (OCH_3), 55.4 (OCH_3), 43.6 (NCH_2), 33.65 ($ArCH_2$), 21.4 ($ArCH_3$); HRMS (ES^-) calculated for $C_{26}H_{26}NO_6S$ $[M-H]^-$ 480.1481, found 480.1501.

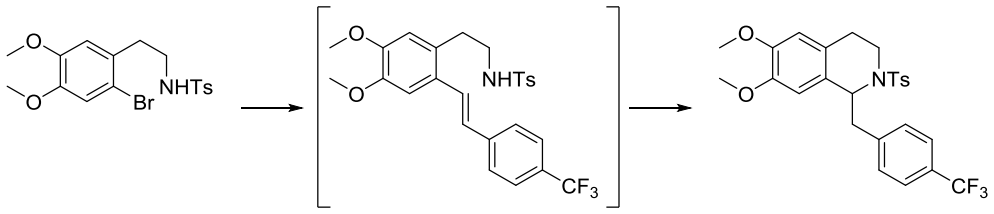
5-(3,4-Dimethoxybenzyl)-6-tosyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g] isoquinolinebenzenesulfonamide 340



339 **340**

The sulfonamide **339** (105 mg, 0.218 mmol, 1.0 eq.) was dissolved in toluene (2.1 mL) under an atmosphere of nitrogen at 0 °C. To this was added *p*-toluenesulfonic acid (46 mg, 0.240 mmol, 1.1 eq.). The resulting solution was heated to 65 °C, stirred for 18 hours and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *tetrahydroisoquinoline* **340** (43 mg, 41%) as a viscous, off-yellow glass; δ_H 7.42 (2H, d, *J* 8.2, 2 x ArH), 7.06 (2H, d, *J* 8.0, 2 x ArH), 6.65 (1H, d, *J* 8.1, ArH), 6.50 (1H, dd, *J* 8.2, 1.9, ArH), 6.42 (1H, d, *J* 1.8, ArH), 6.35 (1H, s, ArH), 6.30 (1H, s, ArH), 5.81 (1H, dd, *J* 3.7 and 1.3, ArH), 4.99 (1H, t, *J* 6.3, NCH), 3.79 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.47 – 3.42 (1H, ddd, *J* 4.8, 5.8 and 13.5, 3-CH_{2a}), 3.28 – 3.19 (1H, ddd, *J* 5.0, 9.9 and 13.5, 3-CH_{2b}), 2.95 (2H, d, *J* 6.3, 1'-CH_2), 2.48 (1H, ddd, *J* 15.9, 7.9 and 4.4, 4-CH_{2a}), 2.28 (3H, s, $ArCH_3$), 2.24 (1H, dt, *J* 16.0 and 4.4, 4-CH_{2b}). δ_C 148.7 (C), 147.9 (C), 146.45 (C), 145.8 (C), 143.0 (C), 137.1 (C), 130.0 (C), 129.35 (2 x ArCH), 128.8 (C), 127.1 (2 x ArCH), 126.5 (C), 121.9 (ArCH), 113.0 (ArCH), 111.0 (ArCH), 108.4 (ArCH), 107.2 (ArCH), 100.8 (OCH_2), 57.85 (NCH), 55.85 (OCH_3), 55.7 (OCH_3), 44.1 (CH_2), 39.9 (CH_2), 27.3 (CH_2), 21.4 (CH_3); HRMS calculated for $C_{26}H_{28}NO_6S$ $[M+H]^+$ 482.1637, found 482.1631

6,7-Dimethoxy-2-tosyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroisoquinoline 341

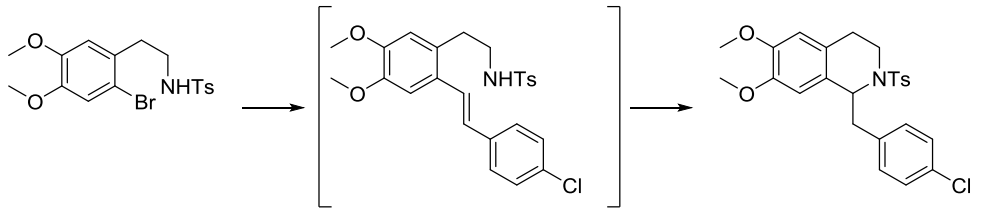


319 **329** **341**

A solution of *N*-(2-bromo-4,5-dimethoxyphenethyl)-4-methylbenzenesulfonamide **319** (200 mg, 1.00 eq.) in ethanol/water (1:1, 2 mL) was treated with (4-trifluoromethylstyryl)boronic acid (121 mg, 1.2 eq.), K_3PO_4 (198 mg, 2.0 eq) and Pd(dppf)Cl_2.DCM (19 mg, 0.05 eq.) at 85 °C for 3 h according to General Procedure D. The crude material was purified by filtration through a silica plug (petrol/diethyl ether 1:6) to give the *sulfonamide* **329** (181 mg, 77%) as a white solid which was used without further purification; m.p. 53-56 °C.

The sulfonamide **329** (175 mg, 0.347 mmol, 1.0 eq.) was dissolved in dichloromethane (1.7 mL) under an atmosphere of nitrogen at 0 °C. To this was added triflic acid (21 mg, 0.139 mmol, 0.4 eq.). The resulting solution was allowed to warm up to room temperature and stirred for 6 hours and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 1:3) to give *tetrahydroisoquinoline* **341** (165 mg, 95%) as a white solid; ν_{max} 3063, 2860, 1325 (S=O), 1246 (Ar-O), 1159 (S=O); δ_H 7.42 – 7.38 (4H, m, 4 x ArH), 7.08 (2H, d, *J* 8.0, 2 x ArH), 7.03 (2H, d, *J* 8.1, 2 x ArH), 6.38 (1H, s, ArH), 6.05 (1H, s, ArH), 5.03 (1H, t, *J* 6.9, ArCHN), 3.72 (3H, s, $ArOCH_3$), 3.60 – 3.53 (1H, m, $ArCH_2C\underline{H}_{2a}N$), 3.55 (3H, s, $ArOCH_3$), 3.34 (1H, ddd, *J* 13.6, 10.2 and 4.7, $ArCH_2C\underline{H}_{2b}$), 3.16 (1H, dd, *J* 13.4 and 6.6, $ArC\underline{H}_{2a}CH$), 3.03 (1H, dd, *J* 13.4 and 7.1, $ArC\underline{H}_{2b}CH$), 2.58 (1H, ddd, *J* 16.2, 10.2 and 6.0, $ArC\underline{H}_{2a}CH_2N$), 2.38 (1H, app. dt, *J* 16.2 and 4.3, $ArC\underline{H}_{2b}CH_2N$), 2.26 (3H, s, $ArCH_3$); δ_C 148.1 (C), 147.1 (C), 143.2 (C), 142.0 (C), 137.0 (C), 130.3 (2 x ArCH), 129.4 (2 x ArCH), 128.9 (q, *J* 32.0, $\underline{C}$-CF_3) 127.0 (2 x ArCH), 126.9 (C), 125.1 (q, *J* 3.9, 2 x $Ar\underline{C}H$-C-CF_3), 124.8 (q, *J* 271.0, CF_3), 111.4 (ArCH), 110.05 (ArCH), 57.4 (NCH), 55.8 ($ArOCH_3$), 55.7 ($ArOCH_3$), 44.1 (CH_2), 39.9 (CH_2), 26.8 (CH_2), 21.4 ($ArCH_3$); HRMS calculated for $C_{26}H_{26}F_3NNaO_4S$ $[M+Na]^+$ 528.1448, found 528.1432.

6,7-Dimethoxy-2-tosyl-1-(4-(trifluoromethyl)benzyl)-1,2,3,4-tetrahydroisoquinoline 342

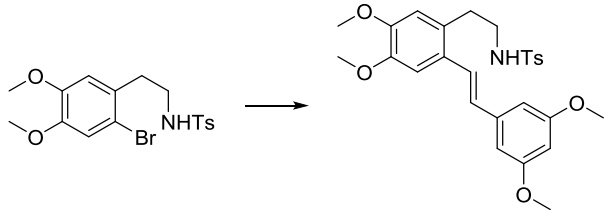


319 **342a** **342**

A solution of *N*-(2-bromo-4,5-dimethoxyphenethyl)-4-methylbenzenesulfonamide **319** (450 mg, 1.00 eq.) in ethanol/water (1:1, 4.5 mL) was treated with (4-chlorostyryl)boronic acid (230 mg, 1.2 eq.), K_3PO_4 (446 mg, 2.0 eq) and Pd(dppf)Cl_2.DCM (43 mg, 0.05 eq.) at 85 °C for 2.5 h according to General Procedure D. The crude material was purified by filtration through a silica plug (petrol/diethyl ether 1:5) to give the *sulfonamide* **342a** (337 mg, 77%) as a white solid which was used without further purification; m.p. 129-132 °C.

The sulfonamide **342a** (170 mg, 0.352 mmol, 1.0 eq.) was dissolved in dichloromethane (1.7 mL) under an atmosphere of nitrogen at 0 °C. To this was added triflic acid (21 mg, 0.141 mmol, 0.4 eq.). The resulting solution was allowed to warm up to room temperature and stirred for 6 hours and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 1:3) to give *tetrahydroisoquinoline* **342** (165 mg, 95%) as a white solid; m.p. 117-120 °C; HRMS calculated for $C_{25}H_{26}ClNNaO_4S$ $[M+Na]^+$ 494.1169, found 494.1166.

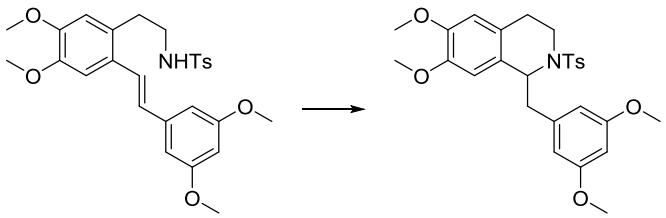
(*E*)-*N*-(2-(3,5-Dimethoxystyryl)-4,5-dimethoxyphenethyl)-4-methylbenzenesulfonamide 343



319 **343**

A solution of *N*-(2-bromo-4,5-dimethoxyphenethyl)-4-methylbenzenesulfonamide **319** (1.00 g, 1.00 eq.) in ethanol/water (1:1, 10 mL) was treated with 2-(3,5-dimethoxyphenyl)vinylboronic acid (813 mg, 1.2 eq.), K_3PO_4 (991 mg, 2.0 eq) and Pd(dppf)Cl_2.DCM (95 mg, 0.05 eq.) at 85 °C for 1.5 h according to General Procedure D. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give the *sulfonamide* **343** (1.079 g, 93%) as a beige solid; m.p. 145-146 °C; δ_H (400 MHz) 7.64 (2H, d, *J* 8.2, 2 x ArH), 7.24 (1H, d, *J* 15.9, ArC<u>H</u>=CH), 7.19 (2H, d, *J* 8.0, 2 x ArH), 7.07 (1H, s, ArH), 6.79 (1H, d, *J* 15.9, ArCH=C<u>H</u>), 6.68 (2H, d, *J* 2.1, 2 x ArH), 6.59 (1H, s, ArH), 6.40 (1H, s, ArH), 4.45 (1H, t, *J* 6.1, NH), 3.93 (3H, s, $ArOCH_3$), 3.86 (3H, s, $ArOCH_3$), 3.84 (6H, s, 2 x $ArOCH_3$), 3.14 (2H, dd, *J* 13.8 and 6.9, $ArCH_2$), 2.94 (2H, app. t, *J* 7.1, NCH_2), 2.36 (3H, s, $ArCH_3$); δ_C (101 MHz) 161.2 (2 x C), 149.2 (C), 148.3 (C), 143.5 (C), 139.65 (C), 137.1 (C), 129.8 (2 x ArCH), 129.4 (ArCH=C), 128.8 (C), 128.5 (C), 127.15 (2 x ArCH=C), 125.9 (ArCH), 113.2 (ArCH), 109.0 (ArCH), 104.75 (ArCH), 100.1 (ArCH), 56.2 (OCH_3), 56.1 (OCH_3), 55.6 (2 x OCH_3), 44.2 (CH_2), 33.8 (CH_2), 21.6 ($ArCH_3$).

1-(3,5-Dimethoxybenzyl)-6,7-dimethoxy-2-tosyl-1,2,3,4-tetrahydroisoquinoline 344



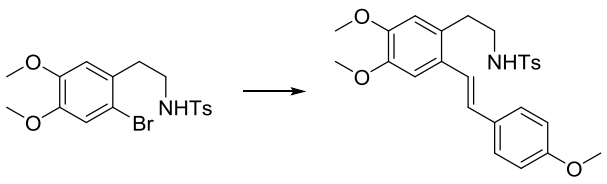
343 **344**

The sulfonamide **343** (119 mg, 0.239 mmol, 1.0 eq.) was dissolved in toluene (1.2 mL) under an atmosphere of nitrogen at 0 °C. To this was added *p*-toluenesulfonic acid (27.3 mg, 0.143 mmol, 0.6 eq.). The resulting solution was heated to 100 °C for 1 hour and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated to give *tetrahydroisoquinoline* **344** (105 mg, 88%) as a viscous, colourless glass; δ_H (400 MHz) 7.53 (2H, d, *J* 7.9, 2 x ArH), 7.13 (2H, d, *J* 7.9, 2 x ArH), 6.45 (1H, s, ArH), 6.32 (1H, s, ArH), 6.21 (2H, s, 2 x ArH), 6.18 (1H, s, ArH), 5.11 (1H, t, *J* 6.7, ArCHN), 3.79 (3H, s, $ArOCH_3$), 3.73 – 3.63 (1H, m, $ArCH_2C\underline{H}_{2a}N$), 3.71 (6H, s, 2 x $ArOCH_3$), 3.65 (3H, s, $ArOCH_3$), 3.44 – 3.34 (1H, m, $ArCH_2C\underline{H}_{2b}N$), 3.12 (1H, dd, *J* 13.2 and 6.0, $ArC\underline{H}_{2a}CHAr$), 2.95 (1H, dd, *J* 13.3 and 7.5, $ArC\underline{H}_{2b}CHAr$), 2.68 (1H, ddd, *J* 16.5, 10.3 and 6.3, $ArC\underline{H}_{2a}CH_2N$), 2.53 – 2.39 (1H, m, $ArC\underline{H}_{2b}CH_2N$), 2.34 (3H, s, $ArCH_3$); δ_C (101 MHz) 160.8 (C), 148.05 (C), 147.0 (C), 143.1 (C), 140.2 (C), 137.5 (C), 129.55 (2 x ArCH), 127.6 (ArCH), 127.2 (2 x ArCH), 125.4 (ArCH), 111.4 (ArCH), 110.5 (ArCH), 107.9 (2 x ArCH), 99.1 (ArCH), 57.5 (NCH), 56.0 (OCH_3), 55.85 (OCH_3), 55.4 (2 x OCH_3), 44.7 (CH_2), 39.8 (CH_2), 27.1 (CH_2), 21.6 ($ArCH_3$); HRMS calculated for $C_{27}H_{31}NNaO_6S$ $[M+Na]^+$ 520.1770, found 520.1761

Method 2:

The sulfonamide **343** (894 mg, 1.799 mmol, 1.0 eq.) was dissolved in toluene (9.0 mL) under an atmosphere of nitrogen at 0 °C. To this was added *p*-toluenesulfonic acid (205 mg, 1.08 mmol, 0.6 eq.). The resulting solution was heated to 100 °C for 1 hour and then quenched with aqueous potassium carbonate (15 mL), extracted with dichloromethane (3 x 15 mL) and the combined organic extracts dried, filtered and evaporated to give *tetrahydroisoquinoline* **344** (745 mg, 83%) as a colourless glass. All data obtained were in accordance with those reported before.

(*E*)-*N*-(4,5-Dimethoxy-2-(4-methoxystyryl)phenethyl)-4-methylbenzenesulfonamide 345

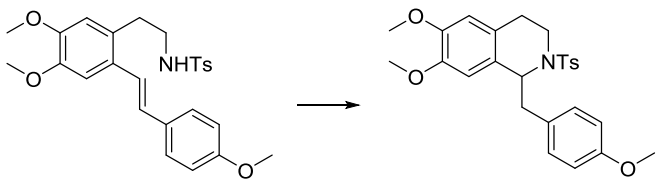


319 **345**

A solution of *N*-(2-bromo-4,5-dimethoxyphenethyl)-4-methylbenzenesulfonamide **319** (416 mg, 1.00 eq.) in ethanol/water (1:1, 4 mL) was treated with 2-(4-methoxyphenyl)vinylboronic acid (268 mg, 1.5 eq.), K_3PO_4 (426 mg, 2.0 eq.) and $Pd(dppf)Cl_2$.DCM (82 mg, 0.10 eq.) at 95 °C for 1.5 h according to General Procedure D. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give the unreacted starting material **319** (97 mg, 23%) and *sulfonamide* **345** (259 mg, 53%, 76% brsm) as

a colourless glass; δ_H (400 MHz) 7.64 (2H, d, *J* 8.2, 2 x ArH), 7.43 (2H, d, *J* 8.7, 2 x ArH), 7.16 (2H, d, *J* 8.1, 2 x ArH), 7.07 (1H, d, *J* 16.0, ArC<u>H</u>=CH), 7.04 (1H, s, ArH), 6.89 (2H, d, *J* 8.7, 2 x ArH), 6.79 (1H, d, *J* 15.9, ArCH=C<u>H</u>), 6.58 (1H, s, ArH), 4.73 (1H, t, *J* 6.1, NH), 3.91 (1H, s, $ArOCH_3$), 3.83 (3H, s, $ArOCH_3$), 3.82 (3H, s, $ArOCH_3$), 3.14 (2H, dd, *J* 13.8 and 6.8, NCH_2), 2.91 (2H, t, *J* 7.2, $ArCH_2$), 2.35 (3H, s, $ArCH_3$); δ_C (101 MHz) 159.4 (C), 148.7 (C), 148.2 (C), 143.4 (C), 137.0 (C), 130.4 (C), 129.7 (2 x ArCH), 129.2 (C), 128.9 (Ar<u>C</u>H=C), 128.1 (C), 127.8 (2 x ArCH), 127.1 (2 x ArCH), 123.2 (ArCH=C<u>H</u>), 114.3 (2 x ArCH), 113.2 (ArCH), 108.8 (ArCH), 56.1 ($ArOCH_3$), 56.1 ($ArOCH_3$), 55.4 ($ArOCH_3$), 44.0 (CH_2), 33.55 (CH_2), 21.55 ($ArCH_3$); HRMS (APCI) calculated for $C_{26}H_{29}NO_5S$ $[M]^+$ 467.1766, found 467.1766.

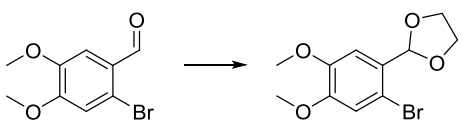
6,7-Dimethoxy-1-(4-methoxybenzyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline 346



345 **346**

The sulfonamide **345** (30 mg, 0.062 mmol, 1.0 eq.) was dissolved in toluene (0.3 mL) under an atmosphere of nitrogen. To this was added *p*-toluenesulfonic acid (7.1 mg, 0.037 mmol, 0.6 eq.). The resulting solution was stirred for 1 hour at 100 °C and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated to give *tetrahydroisoquinoline* **341** (28.5 mg, 95%) as a colourless oil; δ_H (400 MHz) 7.53 (2H, d, *J* 8.2, 2 x ArH), 7.13 (2H, d, *J* 8.1, 2 x ArH), 6.94 (1H, d, *J* 8.5, 2 x ArH), 6.77 (2H, d, *J* 8.6, 2 x ArH), 6.43 (1H, s, ArH), 6.11 (1H, s, ArH), 5.06 (1H, t, *J* 6.7, $ArCH_2C\underline{H}N$), 3.80 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.63 (3H, s, OCH_3), 3.63 – 3.61 (1H, m, NCH_{2a}) 3.43 – 3.35 (1H, m, NCH_{2b}), 3.13 (1H, dd, *J* 13.5 and 5.9, $ArC\underline{H}_{2a}CH$), 2.98 (1H, dd, *J* 13.5 and 7.6, $ArC\underline{H}_{2b}CH$), 2.62 (1H, ddd, *J* 16.2, 6.1 and 4.1, $ArC\underline{H}_{2a}CHN$), 2.44 (1H, app. dt, *J* 16.1 and 6.1, $ArC\underline{H}_{2b}CHN$), 2.35 (3H, s, $ArCH_3$); δ_C (101 MHz) 143.1 (C), 131.1 (2 x ArCH), 129.9 (C), 129.55 (2 x ArCH), 127.5 (C), 127.2 (2 x ArCH), 125.5 (C), 113.8 (2 x ArCH), 111.2 (ArCH), 110.4 (ArCH), 57.8 (CH), 55.9 (OCH_3), 55.8 (OCH_3), 55.4 (OCH_3), 43.55 (CH_2), 39.9 (CH_2), 27.0 (CH_2), 21.6 ($ArCH_3$); HRMS calculated for $C_{26}H_{29}NNaO_5S$ $[M+Na]^+$ 490.1664, found 490.1659

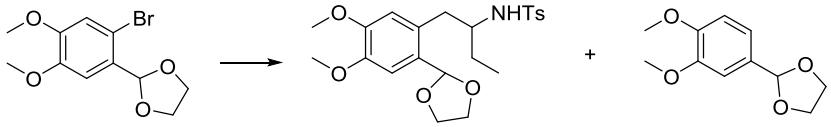
2-(2-Bromo-4,5-dimethoxyphenyl)-1,3-dioxolane[251] 347



347

A solution of 2-bromoveratraldehyde (25.0 g, 102 mmol, 1.0 eq.), ethylene glycol (35.4 g, 408 mmol, 4.0 eq.) and *p*-toluenesulfonic acid (1.95 g, 10.2 mmol, 0.1 eq.) in toluene (120 mL) was reflux for 24 hours and cooled to ambient temperature. The reaction mixture was then washed with saturated sodium bicarbonate (100 mL) and brine (100 mL), dried filtered and evaporated. The final product was purified by recrystallization from ethyl acetate/heptane to give *acetal* **347** (22.5 g, 76.3%) as a white solid; m.p. 104 – 107, lit.[252] m.p. 105 – 111 °C; ν_{max} 1597, 1264, 1209 (C-O); δ_H (400 MHz) 7.11 (1H, s, ArH), 7.01 (1H, s, ArH), 5.99 (1H, s, $ArCH(OCH_2)_2$), 4.22 – 4.11 (2H, m, 2 x OCH_{2a}), 4.10 – 4.01 (2H, m, 2 x OCH_{2b}), 3.88 (3H, s, OCH_3), 3.87 (3H, s, OCH_3).

N-(1-(2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl)butan-2-yl)-4-methylbenzenesulfonamide 348

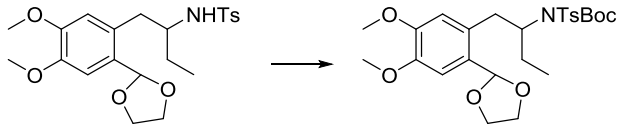


347 **348** **347a**

To a solution of 2-(2-bromo-4,5-dimethoxyphenyl)-1,3-dioxolane **347** (5.65 g, 19.55 mmol, 2.0 eq.) in tetrahydrofuran (80 mL) under an atmosphere of nitrogen at -78 °C was added n-butyllithium (2.4M, 8.33 mL, 20.0 mmol, 2.25 eq.) and the mixture stirred for 0.5 h. To the bright orange solution was then added solid magnesium bromide (3.68 g, 20.0 mmol, 2.25 eq.) and the resulting mixture stirred at 0 °C for 0.5 h and then cooled to -40 °C. Copper (I) iodide (253 mg, 1.333 mmol, 0.15 eq.) was then added and the reaction stirred for a further 0.5 h at -40 °C and then cooled to -78 °C. 2-Ethyl-1-tosylaziridine **154** (2.0 g, 8.89 mmol, 1.0 eq.) in tetrahydrofuran (20 mL) was then added, the solution stirred for 0.25 h at -78 °C and for a further 1 h at 0 °C. The reaction was quenched by aqueous ammonium chloride (40 mL) and the separated blue aqueous phase extracted with ethyl acetate (3 x 50 mL) and the combined organic extracts washed with brine (50 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 1:1) and recrystallization from ethyl acetate/heptane to give acetal impurity **347a** (2.20 g, 53%) and *sulfonamide* **348** (1.724 g, 45%) as a white solid; *sulfonamide* **348** m.p. 102 – 107 °C; ν_{max} 3236 (br, NH), 1324 (S=O), 1266 (C-O), 1160 (S=O); δ_H 7.21 (2H, d, *J* 8.2, 2 x ArH), 6.91 (2H, d, *J* 8.2, 2 x ArH), 6.90 (1H, s, ArH), 6.32 (1H, d, *J* 5.1, NH), 6.06 (1H, s, ArH), 5.76 (1H, s, $C\underline{H}(OCH_2)_2$), 4.30 – 4.21 (2H, m, $CH(OC\underline{H}_{2a})_2$), 4.14 – 4.06 (2H, m, $CH(OC\underline{H}_{2b})_2$), 3.90 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 3.15 – 3.11 (1H, m, NCH), 2.76 (1H, dd, *J* 14.2 and 11.1, $ArCH_{2a}$), 2.54 (1H, dd, *J* 14.2 and 3.9, $ArCH_{2b}$), 2.35 (3H, s, $ArCH_3$), 1.80 – 1.74 (2H, app. pent., $C\underline{H}_2CH_3$), 0.99 (3H, t, *J* 7.4,

$CH_2C\underline{H}_3$); δ_C 149.4 (C), 147.6 (C), 142.5 (C), 137.1 (C), 129.4 (C), 128.9 (2 x ArCH), 126.75 (2 x ArCH), 126.5 (C), 112.3 (ArCH), 109.65 (ArCH), 102.8 ($\underline{C}H(OCH_2)_2$), 65.4 (OCH_2), 65.3 (OCH_2), 57.0 (NCH), 55.9 (OCH_3), 55.2 (OCH_3), 34.5 (CH_2), 30.1 (CH_2), 21.5 ($ArCH_3$), 9.4 (CH_3); *acetal* **347a** δ_H 7.03 (2H, m, 2 x ArH), 6.87 – 6.84 (1H, d, *J* 8.0, ArH), 5.75 (1H, s, ArCH), 4.17 – 4.09 (2H, m, OCH_{2a}), 4.07 – 3.98 (2H, m, OCH_{2b}), 3.90 (3H, s, OCH_3), 3.88 (3H, s, OCH_3); δ_C 149.8 (C), 149.1 (C), 130.3 (C), 119.3 (ArCH), 110.8 (ArCH), 109.2 (ArCH), 103.7 ($\underline{C}H(OCH_2)_2$), 65.2 (2 x CH_2), 55.95 (CH_3), 55.85 (CH_3).

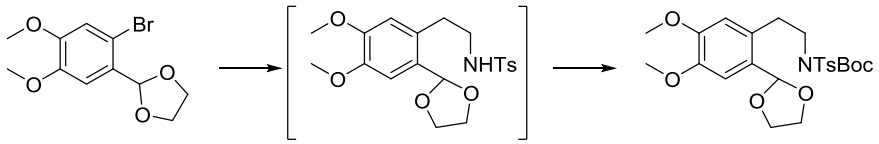
tert-Butyl (1-(2-(1,3-dioxolan-2-yl)-4,5-dimethoxyphenyl)butan-2-yl)(tosyl)carbamate 349



348 **349**

A solution of *N*-(1-(2-(1,3-dioxolan-2-yl)-4,5-dimethoxyphenyl)butan-2-yl)-4-methylbenzenesulfonamide **348** (1.62 g, 3.78 mmol, 1.0 eq.) in dichloromethane (75 mL) was treated with DMAP (92 mg, 0.756 mmol, 0.2 eq.) and Boc_2O (992 mg, 4.54 mmol, 1.2 eq.) according to General Procedure C. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give the *carbamate* **349** (1.375 g, 70%) as a white solid; m.p. 93 - 96 °C; ν_{max} 1722 (C=O), 1354 (S=O), 1269 (C-O), 1152 (S=O); δ_H (400 MHz) 7.29 (2H, br. d, *J* 6.0, 2 x ArH), 7.15 (1H, s, ArH), 7.06 (2H, d, *J* 8.0, 2 x ArH), 6.48 (1H,br s, ArH), 6.00 (1H, s, $ArC\underline{H}(OCH_2)_2$), 4.74 – 4.61 (1H, m, NCH), 4.22 – 4.13 (2H, m, $OC\underline{H}_{2a}C\underline{H}_{2a}O$), 4.08 – 4.01 (2H, m, $OC\underline{H}_{2b}C\underline{H}_{2b}O$), 3.93 (1H, s, $ArOCH_3$), 3.60 (1H, s, $ArOCH_3$), 3.26 (1H, dd, *J* 14.1 and 9.0, $ArCH_{2a}$), 3.18 (1H, dd, *J* 14.2 and 6.2, $ArCH_{2b}$), 2.13 – 1.99 (1H, m, $C\underline{H}_{2a}CH_3$), 1.80 – 1.68 (1H, m, $C\underline{H}_{2b}CH_3$), 1.43 (9H, s, $C(CH_3)_3$), 0.96 (1H, t, *J* 7.5, $CH_2C\underline{H}_3$); δ_C (101 MHz) 151.1 (C=O), 149.2 (C), 147.7 (C), 143.6 (C), 130.3 (C), 128.7 (2 x ArCH), 128.1 (C), 128.1 (2 x ArCH), 127.9 (C), 114.0 (ArCH), 109.3 (ArCH), 101.3 ($Ar\underline{C}H(OCH_2)_2$), 84.0 ($\underline{C}(CH_3)_3$), 65.2 ($O\underline{C}H_2\underline{C}H_2O$), 62.7 (CH), 35.1 ($CH_2$), 28.1 ($C(\underline{C}H_3)_3$), 26.3 ($CH_2$), 21.5 ($ArCH_3$), 11.5 ($CH_3$).

tert-Butyl (2-(1,3-dioxolan-2-yl)-4,5-dimethoxyphenethyl)(tosyl)carbamate 352

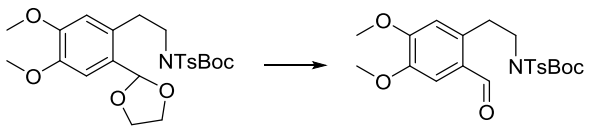


347 **351** **352**

To a solution of 2-(2-bromo-4,5-dimethoxyphenyl)-1,3-dioxolane **347** (6.46 g, 22.35 mmol, 2.0 eq.) in tetrahydrofuran (120 mL) under an atmosphere of nitrogen at -78 °C was added n-butyllithium (2.3M, 9.96 mL, 22.9 mmol, 2.05 eq.) and the mixture stirred for 0.5 h. To the bright orange solution was then

added solid magnesium bromide (4.32 g, 23.5 mmol, 2.1 eq.) and the resulting mixture stirred at 0 °C for 0.5 h and then cooled to -40 °C. Copper (I) iodide (638 mg, 3.35 mmol, 0.3 eq.) was then added and the reaction stirred for a further 0.5 h at -40 °C and then cooled to -78 °C. 1-Tosylaziridine **173** (2.20 g, 11.17 mmol, 1.0 eq.) in tetrahydrofuran (40 mL) was then added, the solution stirred for 0.25 h at -78 °C and for a further 1 h at 0 °C. The reaction was quenched by aqueous ammonium chloride (40 mL) and the separated blue aqueous phase extracted with ethyl acetate (3 x 70 mL) and the combined organic extracts washed with brine (80 mL), dried, filtered and evaporated. The crude material was purified by filtration through a plug of silica and was then redissolved in dichloromethane (100 mL) and treated with DMAP (273 mg, 2.23 mmol, 0.2 eq.) and Boc_2O (2.96 g, 13.41 mmol, 1.2 eq.) according to General Procedure C. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give the *carbamate* **352** (4.553 g, 80%) as a colourless glass; δ_H (400 MHz) 7.77 (2H, d, *J* 8.2, 2 x ArH), 7.28 (1H, d, *J* 8.1, 2 x ArH), 7.12 (1H, s, ArH), 6.76 (1H, s, ArH), 6.01 (1H, s, C<u>H</u>$(OCH_2)_2$), 4.19 (2H, t, *J* 6.9, OCH_{2a}), 4.06 (2H, t, *J* 7.1, OCH_{2b}), 4.05 – 3.99 (2H, br. m, NCH_2), 3.89 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.18 – 3.08 (2H, br. m, $ArCH_2$), 2.43 (3H, s, $ArCH_3$), 1.33 (9H, s, C(C<u>H</u>$_3)_3$); δ_C (101 MHz) 151.0 (C), 149.5 (C), 147.7 (C), 144.1 (C), 137.5 (C), 129.6 (C), 129.2 (ArCH), 127.8 (ArCH), 127.5 (C), 113.6 (ArCH), 109.6 (ArCH), 101.4 (C<u>H</u>$(OCH_2)_2$), 84.1 (<u>C</u>$(CH_3)_3$), 65.2 (2 x OCH_2) , 55.9 (2 x OCH_3), 48.4 (NCH_2), 33.1 ($ArCH_2$), 27.9 (C(<u>C</u>$H_3)_3$), 21.6 ($ArCH_3$).

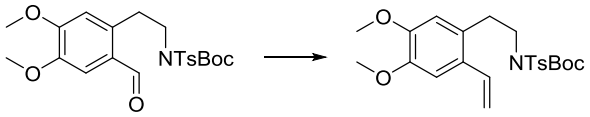
tert-Butyl (2-formyl-4,5-dimethoxyphenethyl)(tosyl)carbamate 353



352 **353**

To a solution of *tert*-butyl (1-(2-(1,3-dioxolan-2-yl)-4,5-dimethoxyphenyl)butan-2-yl)(tosyl)carbamate **352** (2.00 g, 3.94 mmol) in dichloromethane (50 mL) was added Amberlyst-15 (200 mg, 10% wt.) and the resulting mixture stirred vigorously for 16 hours at ambient temperature. The solution was then filtered, washed with aqueous sodium hydrogen carbonate (20 mL), dried, filtered and evaporated to give *aldehyde* **353** (1.63 g, 89%) as a colourless glass; δ_H (400 MHz) 10.27 (1H, s, CHO), 7.75 (2H, d, *J* 8.0, 2 x ArH), 7.40 (1H, s, ArH), 7.29 (2H, d, *J* 8.2, 2 x ArH), 6.84 (1H, s, ArH), 4.10 (2H, dd, *J* 15.1 and 8.0, NCH_2), 3.95 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.44 (2H, t, *J* 7.2, Ar<u>H</u>$_2CH_2N$), 2.43 (3H, s, $ArCH_3$), 1.27 (9H, s, $C(CH3)_3$); δ_C (101 MHz) 190.2 (CHO), 153.8 (C), 150.8 (C), 148.3 (C), 144.4 (C), 137.35 (C), 136.0 (C), 129.4 (2 x ArCH), 128.0 (2 x ArCH), 127.5 (C), 114.2 (ArCH), 111.9 (ArCH), 84.4 (<u>C</u>$(CH_3)_3$), 56.3 (OCH_3), 56.2 (OCH_3), 48.1 (CH_2), 32.2 (CH_2), 27.9 (C(<u>C</u>$H_3)_3$), 21.7 ($ArCH_3$).

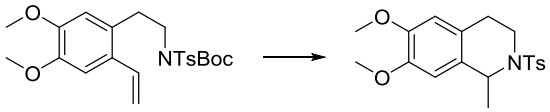
tert-Butyl (4,5-dimethoxy-2-vinylphenethyl)(tosyl)carbamate 354



353 **354**

A suspension of methyltriphenylphosphonium bromide (385 mg, 1.08 mmol, 1.25 eq.) was treated with n-butyllithium (1.6M in hexanes, 0.68 mL, 1.08 mmol, 1.25 eq.) and *tert*-butyl (2-formyl-4,5-dimethoxyphenethyl)(tosyl)carbamate **353** (400 mg, 0.863 mmol, 1.0 eq.) according to general procedure A2. The crude material was purified by column chromatography (petrol/diethyl ether 1:1) to give *alkene* **354** (358 mg, 90%) as a white solid; m.p. 86 – 89 °C; ν_{max} 1727 (C=O), 1351 (S=O), 1156 (S=O); δ_H (400 MHz) 7.75 (2H, d, *J* 8.4, 2 x ArH), 7.28 (2H, d, *J* 8.1, 2 x ArH), 7.07 (1H, dd, *J* 17.2 and 10.9, ArC<u>H</u>=CH_2), 7.04 (1H, s, ArH), 6.71 (1H, s, ArH), 5.59 (1H, dd, *J* 17.2, 1.1, ArCH=C<u>H_{2a}</u>), 5.26 (1H, dd, *J* 10.9 and 1.1, ArCH=C<u>H_{2b}</u>), 3.95 – 3.90 (2H, m, NCH_2), 3.90 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.10 – 3.08 (2H, m, NCH_2), 2.42 (3H, s, $ArCH_3$), 1.33 (9H, s, C(C<u>H_3</u>)$_3$); HRMS calculated for $C_{24}H_{31}NNaO_6S$ $[M+Na]^+$ 484.1770, found 484.1764.

6,7-Dimethoxy-1-methyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline[253] 355

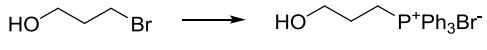


354 **355**

The sulfonamide **354** (69 mg, 0.150 mmol, 1.0 eq.) was dissolved in toluene (0.15 mL) under an atmosphere of nitrogen. To this was added *p*-toluenesulfonic acid (17 mg, 0.90 mmol, 0.6 eq.). The resulting solution was stirred for 1 hour at 100 °C and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The residue was purified by column chromatography (diethyl ether/petrol 1:1) to give *tetrahydroisoquinoline* **355** (19 mg, 35%) as a colourless glass; δ_H (400 MHz) 7.66 (1H, d, *J* 8.3, 2 x ArH), 7.20 (1H, d, *J* 8.0, 2 x ArH), 6.51 (1H, s, ArH), 6.44 (1H, s, ArH), 5.06 (1H, q, *J* 6.7, NCH), 3.88 (1H, ddd, *J* 14.1, 6.5 and 2.1, NCH_{2a}), 3.84 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.38 (1H, ddd, *J* 14.0,

11.6 and 4.0, NCH_{2b}), 2.63 (1H, ddd, *J* 17.0, 11.6 and 6.4, $ArCH_{2a}$), 2.50 (1H, ddd, *J* 16.8, 4.1 and 2.1, $ArCH_{2b}$), 2.37 (1H, s, $ArCH_3$), 1.45 (3H, d, *J* 6.8, $CHC\underline{H}_3$).

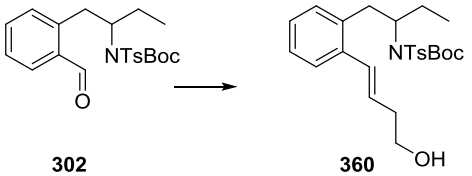
(3-Hydroxypropyl)triphenylphosphonium bromide[254] 359



359

A solution of 3-bromo-1-propanol (3.54 g, 25.47 mmol) and triphenylphosphine (6.68 g, 25.47 mmol) in toluene (75 mL) was heated at 111 °C for 24 hours.[255] The reaction mixture was allowed to cool to ambient temperature and the precipitate was collected by vacuum filtration, washed with toluene (2 x 50 mL), heptane (50 mL) and diethyl ether (50 mL) to yield *salt* **359** (7.09 g, 68%) as white powder, which was used without further purification.

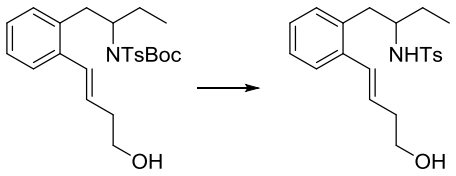
tert-Butyl (*E*)-(1-(2-(4-hydroxybut-1-en-1-yl)phenyl)butan-2-yl)(tosyl)carbamate 360



302 **360**

A suspension (3-hydroxypropyl)triphenylphosphonium bromide **359** (236 mg, 0.588 mmol, 1.4 eq.) was treated with n-butyllithium (1.6M in hexanes, 0.51 mL, 1.18 mmol, 2.8 eq.) and *tert*-butyl (1-(2-formylphenyl)butan-2-yl)(tosyl)carbamate **302** (181 mg, 0.420 mmol, 1.0 eq.) according to general procedure A2. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *alkene* **360** (82 mg, 41%) as a colourless glass, as a 1:5 mixture of *cis* and *trans* isomers; ν_{max} 3425 (OH), 1722 (C=O); *major (trans)-isomer* δ_H (400 MHz) 7.49 (1H, d, *J* 7.7, ArH), 7.28 (1H, d, *J* 6.2, ArH), 7.09 (6H, m, 6 x ArH), 6.85 (1H, d, *J* 15.5, ArC$\underline{H}$=CH), 6.09 (1H, dt, *J* 15.3 and 7.2, ArCH=C$\underline{H}$), 4.73 – 4.66 (1H, m, C$\underline{H}_2$OH), 3.79 – 3.75 (1H, m, NCH), 3.37 (1H, dd, *J* 13.8 and 9.3, $ArCH_{2a}$), 3.19 (1H, dd, *J* 13.8 and 6.3, $ArCH_{2b}$), 2.51 (2H, dd, *J* 7.1 and 6.3, CH=CHC$\underline{H}_2$), 2.36 (3H, s, $ArCH_3$), 2.12 – 1.99 (1H, m, C$\underline{H}_{2a}CH_3$), 1.76 (1H, ddq, *J* 6.5, 7.4 and 14.4, C$\underline{H}_{2b}CH_3$), 1.34 (9H, s, $C(CH_3)_3$), 0.98 (3H, t, *J* 7.5, $CH_2C\underline{H}_3$); δ_C (101 MHz) 150.8 (C=O), 143.45 (C), 137.8 (C), 137.6 (C), 136.1 (C), 131.2 (ArCH), 130.5 (ArC=$\underline{C}$), 130.0 (Ar$\underline{C}$=C), 129.0 (2 x ArCH), 128.0 (2 x ArCH), 127.5 (ArCH), 127.2 (ArCH), 126.7 (ArCH), 84.1 ($\underline{C}(CH_3)_3$), 62.1 (OCH_2), 61.3 (NCH), 37. 05 (CH_2), 37.1 (CH_2), 28.1 ($C(\underline{C}H_3)_3$), 26.3 (CH_2), 21.6 ($ArCH_3$), 11.7 (CH_3); HRMS (APCI) calculated for $C_{26}H_{34}NO_5S$ $[M-H]^-$ 472.2158, found 472.2158.

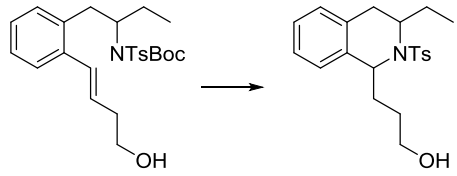
(*E*)-*N*-(1-(2-(4-Hydroxybut-1-en-1-yl)phenyl)butan-2-yl)-4-methylbenzenesulfonamide 361a



360 **361a**

The sulfonamide **360** (41 mg, 0.087 mmol, 1.0 eq.) was dissolved in dichloromethane (0.4 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (5.2 mg, 0.035 mmol, 0.4 eq.). The resulting solution was allowed to warm to ambient temperature and was stirred for 2 h and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give *sulfonamide* **361a** (19 mg, 59%) as a colourless glass and as a 10:1 mixture of *trans* and *cis* diastereoisomers; *major (trans)-diastereoisomer* δ_H (400 MHz) 7.47 (2H, d, *J* 8.2, 2 x ArH), 7.31 (1H, d, *J* 7.7, ArH), 7.18 – 7.13 (2H, m, 2 x ArH), 7.11 (2H, d, *J* 7.9, 2 x ArH), 7.09 – 7.03 (1H, m, ArH), 6.96 (1H, m, ArH), 6.72 (1H, d, *J* 15.6, ArC<u>H</u>=CH), 5.95 (1H, dd, *J* 8.2 and 7.2, ArCH=C<u>H</u>), 4.82 (1H, d, *J* 7.7, C<u>H</u>$_2$OH), 3.84 – 3.74 (1H, m, NCH), 2.86 (1H, dd, *J* 13.8 and 7.6, ArC<u>H</u>$_{2a}$), 2.72 (1H, dd, *J* 13.8 and 6.6, ArC<u>H</u>$_{2b}$), 2.50 (2H, q, *J* 6.4, CH=C<u>H</u>$_2$), 2.37 (3H, s, ArC<u>H</u>$_3$), 1.59 – 1.47 (1H, m, C<u>H</u>$_{2a}$CH$_3$), 1.42 (1H, m, C<u>H</u>$_{2b}$CH$_3$), 0.79 (3H, t, *J* 7.3, CH$_2$C<u>H</u>$_3$).

3-(3-Ethyl-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-1-ol 361

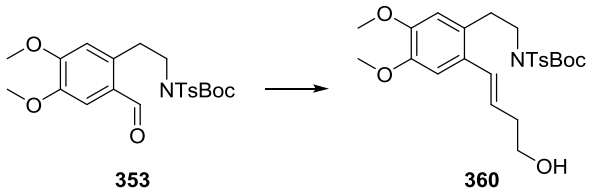


360 **361**

The sulfonamide **360** (41 mg, 0.087 mmol, 1.0 eq.) was dissolved in dichloromethane (0.4 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (5.2 mg, 0.035 mmol, 0.4 eq.). The resulting solution was heated to reflux for 4 h and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 2:1) to give *tetrahydroisoquinoline* **361** (13 mg, 40%) as a colourless glass and as a 20:1 mixture of *trans* and *cis*

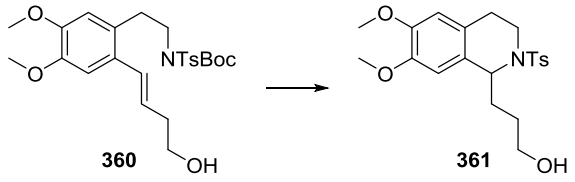
diastereoisomers; *major (cis)-diastereoisomer* δ_H (400 MHz) 7.40 (2H, d, *J* 8.2, 2 x ArCH), 7.06 – 7.00 (2H, m, 2 x ArH), 6.98 (2H, d, *J* 7.8, 2 x ArH), 6.89 (1H, d, *J* 7.1, ArH), 6.85 (1H, d, *J* 7.1, ArH), 4.87 (1H, dd, *J* 8.6 and 5.7, ArCHN), 3.81 – 3.66 (3H, m, OHC$\underline{H}_2$ and ArCH$_2$C$\underline{H}$N), 2.73 (1H, dd, *J* 15.9 and 7.2, ArCH$_{2a}$), 2.59 (1H, dd, *J* 15.8 and 8.3, ArCH$_{2b}$), 2.26 (3H, s, ArCH$_3$), 2.18 – 2.02 (1H, m, CH$_3$C$\underline{H}_{2a}$), 1.98 – 1.86 (2H, m, OHCH$_2$CH$_2$C$\underline{H}_2$), 1.85 – 1.77 (2H, m, OHCH$_2$C$\underline{H}_2$CH$_2$), 1.77 – 1.64 (1H, m, CH$_3$C$\underline{H}_{2b}$), 1.03 (1H, t, *J* 7.5, CH$_2$C$\underline{H}_3$); δ_C (101 MHz) 142.9 (C), 137.45 (C), 136.7 (C), 129.2 (2 x ArCH), 128.3 (ArCH), 127.3 (2 x ArCH), 127.1 (ArCH), 126.6 (ArCH), 126.2 (ArCH), 62.9 (OCH$_2$), 58.4 (ArCHN), 55.8 (CH$_2$N$\underline{C}$H), 33.8 (CH$_2$), 32.2 (CH$_2$), 31.5 (CH$_2$), 29.9 (CH$_2$), 21.5 (ArCH$_3$), 10.8 (CH$_3$).

tert-Butyl (*E*)-(2-(4-hydroxybut-1-en-1-yl)-4,5-dimethoxyphenethyl)(tosyl)carbamate 360



A suspension (3-hydroxypropyl)triphenylphosphonium bromide (856 mg, 2.13 mmol, 1.20 eq.) was treated with n-butyllithium (2.5M in hexanes, 1.97 mL, 4.4 mmol, 2.5 eq.) and *tert*-butyl (2-formyl-4,5-dimethoxyphenethyl)(tosyl)carbamate **353** (824 mg, 1.78 mmol, 1.0 eq.) according to general procedure A2. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *alkene* **360** (315 mg, 35%) as a colourless oil; ν_{max} 3390 (OH), 1728 (C=O); δ_H (400 MHz) 7.65 (1H, d, *J* 8.4, 2 x ArH), 7.13 (2H, d, *J* 8.3, 2 x ArH), 6.92 (1H, s, ArH), 6.83 (1H, s, ArH), 6.80 (1H, *J* 15.8, ArC$\underline{H}$=CH) 5.99 (1H, dt, *J* 15.6, 7.0, ArCH=C$\underline{H}$), 3.85 – 3.79 (2H, m, OCH$_2$), 3.80 (3H, s, OCH$_3$), 3.78 (3H, s, OCH$_2$), 3.05 – 2.99 (2H, m, NCH$_2$), 2.85 – 2.71 (2H, m, CH=CHC$\underline{H}_2$), 2.71 – 2.63 (1H, m, ArCH$_{2a}$), 2.46 (1H, dd, *J* 12.8 and 6.2, ArCH$_{2b}$), 2.36 (3H, s, ArCH$_3$), 1.26 (9H, s, C(CH$_3$)$_3$).

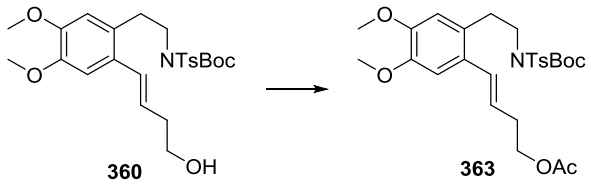
3-(6,7-Dimethoxy-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-1-ol 361



The alcohol **360** (18 mg, 0.36 mmol, 1.0 eq.) was dissolved in toluene (0.2 mL) under an atmosphere of nitrogen at 0 °C. To this was added *p*-toluenesulfonic acid (3.4 mg, 0.018 mmol, 0.5 eq.). The resulting solution was heated to 100 °C, stirred for 0.5 h and then quenched with aqueous potassium carbonate (2

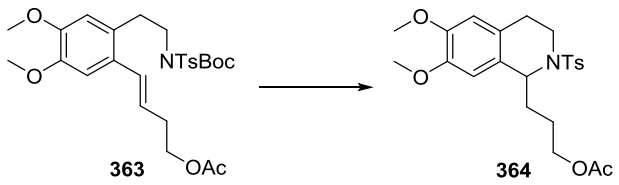
mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *tetrahydroisoquinoline* **361** (10 mg, 70%) as a colourless glass; ν_{max} 3412 (OH); δ_H 7.58 (2H, d, *J* 8.3, 2 x ArH), 7.10 (2H, d, *J* 8.2, 2 x ArH), 6.54 (1H, s, ArH), 6.32 (1H, s, ArH), 4.96 (1H, dd, *J* 7.8 and 6.1, NCH), 3.91 – 3.86 (1H, m, NCH_{2a}), 3.85 (3H, s, OCH_3), 3.82 – 3.77 (1H, m, OCH_{2a}), 3.76 (3H, s, OCH_3), 3.76 – 3.67 (1H, m, OCH_{2b}), 3.42 (1H, dt, *J* 14.5 and 8.5, NCH_{2b}), 2.39 (2H, dd, *J* 8.4 and 4.3, $ArCH_{2a}$), 2.32 (3H, s, $ArCH_3$), 1.90 – 1.83 (2H, m, CH_2), 1.83 – 1.76 (2H, m, CH_2); δ_C 150.1 (C=O), 147.9 (C), 147.6 (C), 143.0 (C), 138.0 (C), 129.3 (2 x ArCH), 128.8 (C), 127.0 (2 x ArCH), 124.6 (C), 111.4 (ArCH), 109.8 (ArCH), 62.7 (OCH_2), 56.2 (OCH_3), 56.1 (OCH_3), 55.85 (NCH), 38.6 (NCH_2), 33.9 (CH_2), 29.7 (CH_2), 25.65 (CH_2), 21.4 ($ArCH_3$).

(*E*)-4-(2-(2-((*N*-(*tert*-Butoxycarbonyl)-4-methylphenyl)sulfonamido)ethyl)-4,5-dimethoxyphenyl)but-3-en-1-yl acetate 363



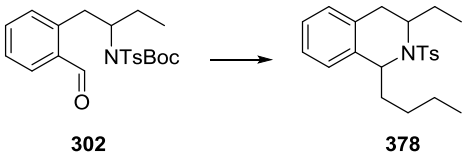
To a solution of *tert*-butyl (*E*)-(2-(4-hydroxybut-1-en-1-yl)-4,5-dimethoxyphenethyl)(tosyl)carbamate **360** (170 mg, 0.336 mmol, 1.0 eq.) in dichloromethane was added acetic anhydride (171 mg, 158 µl, 1.681 mmol, 5.0 eq.) and the mixture stirred overnight at ambient temperature. Aqueous sodium bicarbonate was added (5 mL) and the separated aqueous layer extracted with dichloromethane (3 x 5 mL). The combined organic mixtures were washed with aqueous sodium bicarbonate (10 mL) and brine (10 mL). The crude material was purified by column chromatography (petrol/ethyl acetate 3:2) to give *acetate* **363** (136 mg, 74%) as a colourless glass; δ_H (400 MHz) 7.67 (2H, d, *J* 8.3, 2 x ArH), 7.21 (2H, d, *J* 8.1, 2 x ArH), 6.90 (1H, s, ArH), 6.78 (1H, d, *J* 15.6, ArC<u>H</u>=CH), 6.62 (1H, s, ArH), 5.93 (1H, dt, *J* 15.5 and 7.0, ArCH=C<u>H</u>), 4.14 (1H, t, *J* 6.8, C<u>H</u>$_2$OAc), 3.86 – 3.80 (2H, m, NCH_2), 3.82 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.02 – 2.97 (2H, m, $ArCH_2$), 2.51 (1H, qd, *J* 6.7 and 0.9, CH=CHC<u>H</u>$_2$), 2.35 (3H, s, $OCOCH_3$), 2.27 (3H, s, $ArCH_3$), 1.25 (9H, s, $C(CH_3)_3$); δ_C 171.0 (O<u>C</u>OCH_3), 150.85 (<u>C</u>OO*t*-Bu), 148.6 (C), 148.0 (C), 144.1 (C), 137.5 (C), 129.4 (C), 129.2 (2 x ArCH), 129.0 (C), 127.9 (ArCH), 127.8 (2 x ArCH), 125.9 (ArCH), 113.4 (ArCH), 109.0 (ArCH), 84.1 (C), 63.9 (OCH_2), 56.0 (OCH_3), 55.9 (OCH_3), 55.9 (OCH_3), 47.7 (NCH_2), 33.8 (CH_2) 32.6 (CH_2), 27.8 (CH_3), 21.5 (CH_3).

3-(6,7-Dimethoxy-2-tosyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propyl acetate 364



The sulfonamide **363** (58 mg, 0.106 mmol, 1.0 eq.) was dissolved in toluene (0.2 mL) under an atmosphere of nitrogen at 0 °C. To this was added *p*-toluenesulfonic acid (10.1 mg, 0.053 mmol, 0.5 eq.). The resulting solution was heated to 100 °C, stirred for 0.5 h and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *tetrahydroisoquinoline* **364** (28 mg, 59%) as a colourless glass; ν_{max} 1752 (C=O); δ_H 7.57 (2H, d, *J* 8.3, 2 x ArH), 7.10 (2H, d, *J* 8.1, 2 x ArH), 6.52 (1H, s, ArH), 6.32 (1H, s, ArH), 4.92 (1H, dd, *J* 8.5 and 4.6, NCH), 4.18 (1H, ddd, *J* 11.0, 6.3 and 6.3, OCH_{2a}), 4.13 – 4.07 (1H, m, OCH_{2b}), 3.89 (1H, dt, *J* 14.5 and 4.5, NCH_{2a}), 3.85 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.40 (1H, dt, *J* 14.5 and 8.5, NCH_{2b}), 2.39 (2H, dd, *J* 8.4 and 4.4, $ArCH_2$), 2.32 (3H, s, $ArCH_3$), 2.04 (3H, s, $COOCH_3$), 1.88 – 1.84 (2H, m, CH_2), 1.82 – 1.73 (2H, m, CH_2); δ_C 171.1 (C=O), 147.95 (C), 147.6 (C), 143.0 (C), 138.0 (C), 129.3 (2 x ArCH), 128.5 (C), 127.0 (2 x ArCH), 124.7 (C), 111.5 (ArCH), 109.7 (ArCH), 63.9 (OCH_2), 56.05 (NCH), 55.9 (OCH_3), 55.9 (OCH_3), 38.6 (CH_2), 33.7 (CH_2), 25.75 (CH_2), 25.6 (CH_2), 21.4 (CH_3), 20.9 (CH_3); HRMS calculated for $C_{23}H_{29}NO_6S$ $[M+H]^+$ 447.1716, found 447.1719.

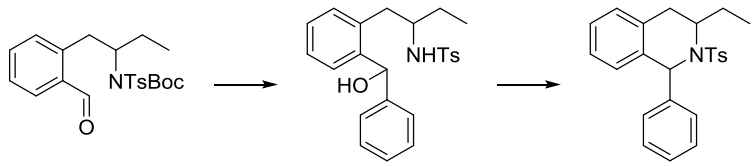
1-Butyl-3-ethyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 378



To a solution of *tert*-butyl (1-(2-formylphenyl)butan-2-yl)(tosyl)carbamate **302** (271 mg, 0.628 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) at -78 °C under an atmosphere of nitrogen was added butylmagnesium chloride (2M, 471 μl, 0.942 mmol, 1.5 eq.) and the mixture stirred for an hour. Aqueous ammonium chloride (5 mL) was added and the separated aqueous layer was extracted with ethyl acetate (3 x 5ml). The combined organic mixtures were washed with brine (10 mL), dried, filtered and evaporated. The crude material was dissolved in 1,2-dichloroethane (0.8 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (38 mg, 0.251 mmol, 0.4 eq.). The resulting solution was stirred for

5 minutes at 0 °C and then heated to 60 °C for 16 h. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/diethyl ether 6:1) to give *tetrahydroisoquinoline* **378** (49 mg, 21%); δ_H 7.32 (2H, d, *J* 8.3, 2 x ArH), 6.97 – 6.91 (1H, m, ArH), 6.89 (2H, d, *J* 8.0, 2 x ArH), 6.82 (1H, d, *J* 7.2, 2 x ArH), 6.75 (1H, d, *J* 7.2, ArH), 4.71 (1H, dd, *J* 8.6 and 6.4, 1-CH), 3.66 (1H, dddd, *J* 8.9, 8.7, 7.5 and 4.9, 3-CH), 2.67 (1H, dd, *J* 15.8 and 7.3, $ArCH_{2a}$), 2.52 (1H, dd, *J* 15.8 and 8.7, $ArCH_{2b}$), 2.19 (3H, s, $ArCH_3$), 2.06 – 2.03 (1H, m, CH_2), 1.79 – 1.75 (1H, m, CH_2), 1.64 – 1.48 (3H, m, CH_2), 1.37 – 1.30 (1H, m, CH_2), 1.32 – 1.25 (2H, m, CH_2), 0.96 (3H, t, *J* 7.5, CH_3), 0.84 (3H, t, *J* 7.2, CH_3); δ_C 142.5 (C), 137.7 (C), 136.5 (C), 132.7 (C), 129.0 (2 x ArCH), 128.0 (ArCH), 127.1 (2 x ArCH), 126.8 (ArCH), 126.5 (ArCH), 125.9 (ArCH), 58.7 (NCH), 55.6 (NCH), 36.7 (CH_2), 32.25 (CH_2), 31.4 (CH_2), 29.0 (CH_2), 22.5 (CH_2), 21.4 ($ArCH_3$), 14.05 (CH_3), 10.6 (CH_3).

3-Ethyl-1-phenyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 382

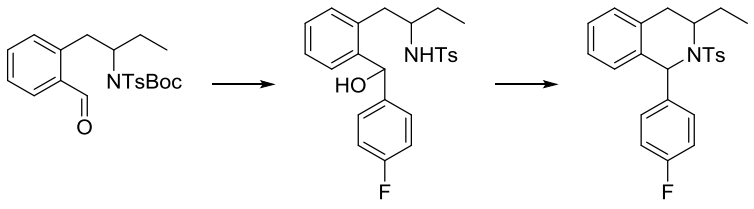


302 **383** **382**

To a solution of *tert*-butyl (1-(2-(1,3-dioxolan-2-yl)phenyl)butan-2-yl)(tosyl)carbamate **302** (50 mg, 0.116 mmol, 1.0 eq.) in tetrahydrofuran (2 mL) at -78 °C under an atmosphere of nitrogen was added phenylmagnesium chloride (2M, 122 μl, 0.244 mmol, 2.1 eq.) and the mixture stirred for 1 h. Aqueous ammonium chloride (5 mL) was added and the separated aqueous layer was extracted with ethyl acetate (3 x 5ml). The combined organic mixtures were washed with brine (5 mL), dried, filtered and evaporated. The crude material was dissolved in methanol (1.8 mL) and cooled to 0 °C. To this was added potassium carbonate (40 mg, 0.290 mmol, 2.5 eq.) and the resulting solution was stirred for 16 h at 60 °C. The reaction mixture was cooled to ambient temperature and partitioned between water (5 mL) and ethyl acetate (5 mL). The separated aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts washed with brine (10 mL), dried, filtered and evaporated. The crude material was dissolved in dichloromethane (1 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (7.0 mg, 0.046 mmol, 0.4 eq.) and the resulting solution was stirred for 0.5 h at 0 °C. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 6:1) to give *tetrahydroisoquinoline* **382** (36 mg, 79%) as a colourless glass, as a single diastereoisomer. A solid sample of the material was obtainer by vapour diffusion recrystallization from diethyl ether in a petroleum ether chamber; m.p. 118 –

121 °C; ν_{max} 3019, 2964, 1331 (S=O), 1155 (S=O); δ_H (400 MHz) 7.44 (2H, d, *J* 8.2, 2 x ArH), 7.28 – 7.24 (3H, m, 3 x ArH), 7.14 – 7.10 (2H, m, 2 x ArH), 7.00 (2H, d, *J* 8.0, 2 x ArH), 6.14 (1H, s, 1-CH), 4.00 – 3.92 (1H, m, 3-CH), 2.94 (1H, dd, *J* 16.2 and 4.5, $ArCH_{2a}$), 2.70 (2H, dd, *J* 16.3 and 6.7, $ArCH_{2b}$), 2.30 (3H, s, $ArCH_3$), 2.06 – 1.88 (1H, m, $C\underline{H}_{2a}CH_3$), 1.52 – 1.41 (1H, m, $C\underline{H}_{2b}CH_3$), 0.84 (3H, t, *J* 7.4, CH_3); δ_C (101 MHz) 142.3 (C), 141.7 (C), 139.7 (C), 136.0 (C), 132.8 (C), 129.1 (ArCH), 128.9 (2 x ArCH), 128.6 (2 x ArCH), 128.2 (ArCH), 128.0 (ArCH), 127.9 (ArCH), 127.1 (ArCH), 126.9 (ArCH), 126.75 (2 x ArCH), 126.4 (ArCH), 61.8 (1-CH), 56.2 (3-CH), 32.3 (CH_2), 26.35 (CH_2), 21.4 (CH_3), 11.3 (CH_3); HRMS (APCI) calculated for $C_{24}H_{25}NNaO_2S$ $[M+Na]^+$ 414.1504, found 414.1488.

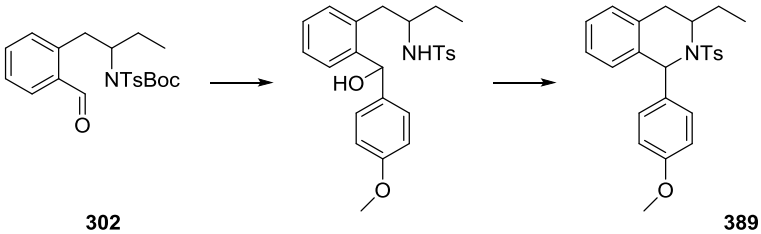
3-Ethyl-1-(4-fluorophenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline 386



302 **386**

To a solution of *tert*-butyl (1-(2-(1,3-dioxolan-2-yl)phenyl)butan-2-yl)(tosyl)carbamate **302** (57.6 mg, 0.134 mmol, 1.0 eq.) in tetrahydrofuran (2 mL) at -78 °C under an atmosphere of nitrogen was added 4-fluorophenylmagnesium bromide (1M, 140 µl, 0.140 mmol, 1.05 eq.) and the mixture stirred for 1 h. Aqueous ammonium chloride (2 mL) was added and the separated aqueous layer was extracted with ethyl acetate (3 x 5ml). The combined organic mixtures were washed with brine (5 mL), dried, filtered and evaporated. The crude material was dissolved in methanol (1 mL) and cooled to 0 °C. To this was added aqueous sodium hydroxide (50%, 0.1 mL) and the resulting solution was stirred for 2.5 h at 60 °C. The reaction mixture was cooled to ambient temperature and partitioned between water (5 mL) and ethyl acetate (5 mL). The separated aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts washed with brine (10 mL), dried, filtered and evaporated. The crude material was dissolved in dichloromethane (1 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (8.7 mg, 0.056 mmol, 0.4 eq.) and the resulting solution was stirred for 0.5 h at 0 °C. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 7:1) to give *tetrahydroisoquinoline* **386** (39 mg, 82%) as a white foam, as a single diastereoisomer; ν_{max} 3065, 2950, 1509, 1331 (S=O), 1161 (S=O); δ_H 7.55 (2H, d, *J* 8.4, 2 x ArH), 7.19 - 7.08 (6H, m, 6 x Ar), 7.00 - 6.91 (4H, m, 4 x ArH), 6.22 (1H, s, 1-CH), 3.81-3.73 (1H, m, 3-CH), 2.98 (1H, dd, *J* 15.7 and 4.9, $ArCH_{2a}$), 2.68 (2H, dd, *J* 15.9 and 6.8, $ArCH_{2b}$), 2.32 (3H, s, $ArCH_3$), 2.03 – 1.89 (1H, m, $C\underline{H}_{2a}CH_3$), 1.50 – 1.39 (1H, m, $C\underline{H}_{2b}CH_3$), 0.89 (3H, t, *J* 7.5, CH_3); HRMS (APCI) calculated for $C_{24}H_{26}FNNaO_3S$ $[M+Na]^+$ 450.1515, found 450.1517.

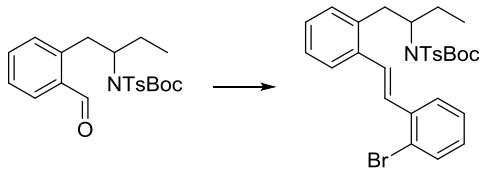
3-Ethyl-1-(4-methoxyphenyl)-2-tosyl-1,2,3,4-tetrahydroisoquinoline 389



302 **389**

To a solution of *tert*-butyl (1-(2-(1,3-dioxolan-2-yl)phenyl)butan-2-yl)(tosyl)carbamate **302** (54.0 mg, 0.125 mmol, 1.0 eq.) in tetrahydrofuran (2 mL) at -78 °C under an atmosphere of nitrogen was added 4-methoxyphenylmagnesium chloride (0.25M, 530 μl, 0.131 mmol, 1.05 eq.) and the mixture stirred for 1 h. Aqueous ammonium chloride (2 mL) was added and the separated aqueous layer was extracted with ethyl acetate (3 x 5ml). The combined organic mixtures were washed with brine (5 mL), dried, filtered and evaporated. The crude material was dissolved in methanol (1.5 mL) and cooled to 0 °C. To this was added aqueous sodium hydroxide (50%, 0.15 mL) and the resulting solution was stirred for 2 h at 70 °C. The reaction mixture was cooled to ambient temperature and partitioned between water (5 mL) and ethyl acetate (5 mL). The separated aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts washed with brine (10 mL), dried, filtered and evaporated. The crude material was dissolved in dichloromethane (1 mL) under an atmosphere of nitrogen and cooled to 0 °C. To this was added triflic acid (8.7 mg, 0.056 mmol, 0.4 eq.) and the resulting solution was stirred for 1 min. at 0 °C. The reaction mixture was quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 6:1) to give *tetrahydroisoquinoline* **389** (24 mg, 46%) as a white foam, as a single diastereoisomer; δ_H (400 MHz) 7.43 (2H, d, *J* 8.2, 2 x ArH), 7.16 (2H, d, *J* 8.5, 2 x ArH), 7.10 (1H, d, *J* 6.7, ArH), 7.04 – 6.96 (4H, m, 4 x ArH), 6.82 (2H, d, *J* 7.8, 2 x ArH), 6.79 (2H, d, *J* 8.6, 2 x ArH), 6.01 (1H, s, ArCHN), 3.78 (3H, s, $ArOCH_3$), 3.73 (1H, m, $NC\underline{H}CH_2$), 2.71 (1H, dd, *J* 15.4 and 6.8, $ArCH_{2a}$), 2.28 (3H, s, $ArCH_3$), 2.27 (1H, dd, *J* 15.4 and 8.8, $ArCH_{2b}$), 1.96 – 1.85 (1H, m, $C\underline{H}_{2a}CH_3$), 1.39 – 1.26 (1H, m, $C\underline{H}_{2a}CH_3$), 0.78 (3H, t, *J* 7.4, CH_3); δ_C (101 MHz) 158.85 (C), 142.7 (C), 136.4 (C), 135.5 (C), 134.3 (C), 132.7 (C), 129.2 (2 x ArCH), 129.1 (2 x ArCH), 128.1 (ArCH), 127.7 (ArCH), 127.4 (ArCH), 127.2 (2 x ArCH), 125.8 (ArCH), 113.5 (ArCH), 59.5 (ArCHN), 57.0 (NCH), 55.25 (OCH_3), 32.1 (CH_2), 31.5 (CH_2), 21.4 (CH3), 10.6 (CH_3); HRMS (APCI) calculated for $C_{25}H_{27}NNaO_3S$ $[M+Na]^+$ 444.1609, found 444.1619.

tert-Butyl (_E_)-(1-(2-(2-bromostyryl)phenyl)butan-2-yl)(tosyl)carbamate 396

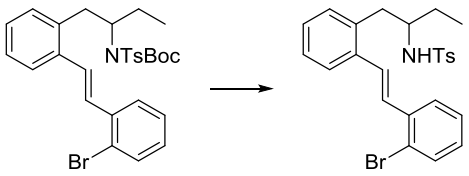


302 **396**

To a suspension of (2-bromo)benzylphosphonium bromide (1.66 g, 3.24 mmol, 1.2 eq.) in tetrahydrofuran (20 mL) at 0 °C was added solid potassium *tert*-butoxide (394 mg, 3.51 mmol, 1.3 eq.) portionwise, over five minutes. The reaction mixture was stirred for a further 0.5 h at 0 °C after which *tert*-butyl (1-(2-formylphenyl)butan-2-yl)(tosyl)carbamate **302** (1.17g, 2.70 mmol, 1.0 eq.) in tetrahydrofuran (15 mL) was added dropwise, over 5 minutes. The cooling bath was removed and the mixture was stirred at ambient temperature for 16 h. The reaction was quenched by addition of aqueous ammonium chloride (25 mL) and the separated aqueous layer extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine, dried, filtered and evaporated. The crude material was purified by column chromatography (dichloromethane) to give *alkene* **396** (1.244 g, 79%) as a colourless oil and as a 3:1 mixture of *trans* and *cis* isomers; ν_{max} 1725 (C=O), 1351 (S=O), 1152 (S=O); *major (trans)-isomer* δ_H (400 MHz) 7.79 (1H, dd, *J* 7.9 and 1.5, ArH), 7.71 (1H, d, *J* 7.7, ArH), 7.56 (1H, dd, *J* 8.0 and 1.1, ArH), 7.49 (1H, d, *J* 16.0, ArC<u>H</u>=CH), 7.36 (1H, d, *J* 16.0, ArCH=C<u>H</u>), 7.33 – 7.25 (3H, m, 3 x ArH), 7.22 – 7.18 (2H, m, 2 x ArH), 7.10 (2H, d, *J* 7.0, 2 x ArH), 7.12 – 7.03 (2H, m, 2 x ArH), 4.72 – 4.63 (1H, m, NCH), 3.47 (1H, dd, *J* 13.8 and 8.0, $ArCH_{2a}$), 3.29 (1H, dd, *J* 13.8 and 7.5, $ArCH_{2b}$), 2.37 (3H, s, $ArCH_3$), 2.17 – 2.00 (1H, m, $CH_3C\underline{H}_{2a}$), 1.77 – 1.64 (1H, m, $CH_3C\underline{H}_{2b}$), 1.34 (9H, s, $C(CH_3)_3$), 0.89 (3H, t, *J* 7.4, $C\underline{H}_3CH_2$); δ_C (101 MHz) 150.8 (C=O), 143.5 (C), 137.5 (C), 137.2 (C), 136.9 (C), 136.7 (C), 132.9 (ArCH), 131.3 (ArCH), 129.6 (ArCH), 128.9 (2 x ArCH), 128.8 (ArCH), 128.8 (ArCH), 128.1 (ArC=CH), 128.0 (2 x ArCH), 127.65 (ArCH), 127.3 (ArCH), 127.2 (ArCH), 126.35 (ArCH), 124.1 (C-Br), 84.0 ($\underline{C}(CH_3)_3$), 61.9 (NCH), 37.0 ($ArCH_2$), 27.9 ($C(\underline{C}H_3)_3$), 25.6 (CH_2), 21.5 ($ArCH_3$), 11.5 (CH_3); *minor (cis)-isomer* δ_H (400 MHz) 7.55 (2H, d, *J* 8.0, 2 x ArH), 7.01 (1H, d, *J* 7.6, ArH), 6.94 (1H, d, *J* 12.1, ArC<u>H</u>=CH), 6.89 – 6.65 (1H, m, ArH), 6.79 (1H, d, *J* 12.1, ArCH=C<u>H</u>), 4.80 – 4.70 (1H, m, NCH), 3.33 (1H, dd, *J* 14.0 and 9.2, $ArCH_{2a}$), 3.12 (1H, dd, *J* 13.9 and 6.2, $ArCH_{2b}$), 2.37 (3H, s, $ArCH_3$), 2.12 – 2.03 (1H, m, $CH_3C\underline{H}_{2a}$), 1.86 – 1.74 (1H, m, $CH_3C\underline{H}_{2b}$), 1.37 (9H, s, $C(CH_3)_3$), 1.00 (3H, t, *J* 7.5, $C\underline{H}_3CH_2$); δ_C (101 MHz) 143.3 (C), 137.8 (C), 137.4 (C), 137.3 (C), 136.3 (C), 132.5 (ArCH), 131.0 (ArCH), 130.9 (ArCH), 130.6 (ArCH), 130.0 (ArCH), 129.9 (ArCH), 128.6 (ArCH), 127.7 (ArCH), 126.8 (ArCH), 126.4 (ArCH), 124.1 (C-Br), 83.95 ($\underline{C}(CH_3)_3$), 61.5 (NCH), 36.8 ($ArCH_2$),

28.0 (C($\underline{C}H_3)_3$), 26.3 (CH_2), 22.7 ($ArCH_3$), 11.6 (CH_3); HRMS calculated for $C_{30}H_{34}BrNO_4S$ $[M+H]^+$ 583.1392, found 583.1393

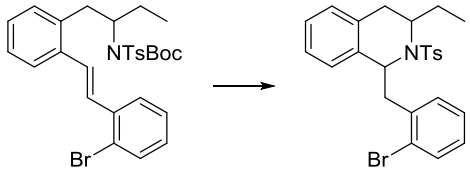
(*E*)-*N*-(1-(2-(2-Bromostyryl)phenyl)butan-2-yl)-4-methylbenzenesulfonamide 397



396 **397**

To a solution of *tert*-butyl (*E*)-(1-(2-(2-bromostyryl)phenyl)butan-2-yl)(tosyl)carbamate **396** (265 mg, 0.476 mmol, 1.0 eq.) in dichloromethane (5 mL) at 0 °C was added trifluoroacetic acid (367 µl, 4.76 mmol, 10.0 eq.) and the mixture allowed to stir at ambient temperature for 5 h. The reaction mixture was then concentrated and purified by column chromatography (petrol/diethyl ether 3:1) to give *sulfonamide* **397** (185 mg, 86%) as a colourless oil, as a 3:1 mixture of *trans* and *cis* isomers; ν_{max} 3279 (br, NH), 1325 (S=O), 1158 (S=O); *major (trans)-isomer* δ_H 7.76 (1H, dd, *J* 7.9 and 1.5, ArH), 7.58 (1H, d, *J* 8.3, ArH), 7.54 (1H, dd, *J* 8.0 and 1.2, ArH), 7.39 (2H, d, *J* 8.3, ArH), 7.30 (1H, d, *J* 16.1, ArC$\underline{H}$=CH), 7.20 (1H, d, *J* 16.0, ArCH=C$\underline{H}$), 7.16 – 7.14 (1H, m, ArH), 7.09 – 7.04 (3H, m, 3 x ArH), 6.99 – 6.94 (3H, m, ArH), 4.68 (1H, d, *J* 7.4, NH), 3.23 – 3.13 (1H, m, NCH), 3.07 (1H, dd, *J* 13.8 and 6.1, $ArCH_{2a}$), 2.70 (1H, dd, *J* 13.8 and 8.4, $ArCH_{2b}$), 2.26 (3H, s, $ArCH_3$), 1.48 – 1.33 (1H, m, $CH_3C\underline{H}_{2a}$), 1.33 – 1.20 (1H, m, $CH_3C\underline{H}_{2b}$), 0.60 (3H, t, *J* 7.4, CH_3); δ_C 142.95 (C), 137.2 (C), 137.1 (C), 136.2 (C), 135.9 (C), 133.0 (ArCH), 131.2 (ArCH), 129.5 (2 x ArCH), 129.0 (ArCH), 128.6 (ArCH), 127.9 (ArCH), 127.8 (ArCH), 127.3 (ArCH), 127.2 (ArCH), 127.0 (ArCH), 126.9 (2 x ArCH), 126.4 (ArCH), 124.1 (C-Br), 56.05 (NCH), 39.9 ($ArCH_2$), 27.0 (CH_2), 21.5 ($ArCH_3$), 9.7 (CH_3); *minor (cis)-isomer* δ_H 7.51 – 7.46 (3H, m, 3 x ArH), 7.30 – 7.26 (1H, m, ArH), 6.86 (3H, m, 3 x ArH), 6.75 (1H, dd, *J* 7.7 and 1.6, ArH), 6.62 (1H, d, *J* 12.1, ArC$\underline{H}$=C), 6.55 (1H, d, *J* 12.1, ArCH=C$\underline{H}$), 4.63 (1H, d, *J* 7.9, NH), 3.41 – 3.30 (1H, m, NCH), 2.71 (1H, dd, *J* 13.8 and 6.4, $ArCH_{2a}$), 2.56 (1H, dd, *J* 13.8 and 8.0, $ArCH_{2b}$), 2.30 (3H, s, $ArCH_3$), 1.48 – 1.36 (1H, m, $CH_3C\underline{H}_{2a}$), 1.32 – 1.23 (1H, m, $CH_3C\underline{H}_{2b}$), 0.70 (3H, t, *J* 7.4, CH_3); δ_C 143.1 (C), 137.9 (C), 137.0 (C), 136.1 (C), 135.9 (C), 132.7 (ArCH), 130.6 (ArCH), 130.5 (ArCH), 130.4 (ArCH), 129.95 (ArCH), 129.8 (ArCH), 129.5 (ArCH), 127.5 (ArCH), 126.8 (ArCH), 124.15 (C-Br), 55.8 (NCH), 39.1 ($ArCH_2$), 27.3 (CH_2), 21.5 ($ArCH_3$), 9.6 (CH_3); HRMS calculated for $C_{25}H_{26}BrNO_2S$ $[M]^+$ 483.0868, found 483.0875.

1-(2-Bromobenzyl)-3-ethyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline 398

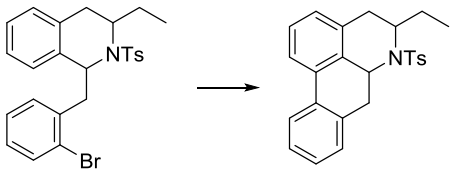


397 **398**

The sulfonamide **397** (147 mg, 0.311 mmol, 1.0 eq.) was dissolved in 1,2-dichloroethane (1.5 mL) under an atmosphere of nitrogen at 0 °C. To this was added triflic acid (18.1 mg, 0.125 mmol, 0.4 eq.). The resulting solution was heated to 60 °C, stirred for 7 h and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 3:1) to give *tetrahydroisoquinoline* **398** (103 mg, 70%) as a colourless glass, as a 9:1 mixture of *cis* and *trans* isomers; ν_{max} 3050, 3027, 2965, 2931, 2875, 1597, 1337 (S=O), 1160 (S=O); *major (cis)-isomer* δ_H 7.48 (1H, dd, *J* 8.0 and 1.1, ArH), 7.41 (2H, d, *J* 8.3, 2 x ArH), 7.19 (1H, td, *J* 7.4 and 1.2, ArH), 7.14 (1H, dd, *J* 7.6 and 1.8, ArH), 7.06 (1H, td, *J* 7.8 and 1.8, ArH), 7.01 (1H, td, *J* 7.4 and 1.1, ArH), 6.96 (2H, d, *J* 8.1, 2 x ArH), 6.93 (1H, d, *J* 7.4, ArH), 6.81 (1H, t, *J* 7.5, ArH), 6.37 (1H, d, *J* 7.5, ArH), 5.15 (1H, dd, *J* 8.8 and 6.7, 1-CH), 3.81 – 3.78 (1H, m, 3-CH), 3.32 (1H, dd, *J* 13.3 and 6.6, ArC$\underline{H}_{2a}$CHAr), 3.26 (1H, dd, *J* 13.3 and 8.9, ArC$\underline{H}_{2b}$CHAr), 2.89 (1H, dd, *J* 15.8 and 7.1, 4-C$\underline{H}_{2a}$), 2.81 (1H, dd, *J* 15.8 and 9.0, 4-C$\underline{H}_{2b}$), 2.30 – 2.19 (1H, m, $CH_3C\underline{H}_{2a}$), 2.24 (3H, s, $ArCH_3$), 1.93 – 1.83 (1H, m, $CH_3C\underline{H}_{2b}$), 1.10 (3H, t, *J* 7.5, CH_3); δ_C 142.8 (C), 137.55 (C), 136.5 (C), 135.85 (C), 133.1 (C), 132.8 (ArCH), 132.1 (ArCH), 129.2 (2 x ArCH), 128.4 (ArCH), 127.9 (ArCH), 127.4 (ArCH), 127.35 (2 x zArCH), 127.2 (ArCH), 126.9 (ArCH), 125.8 (ArCH), 125.35 (C-Br), 58.45 ($ArCH_2C\underline{H}Ar$), 56.0 ($ArCH_2C\underline{H}CH_2$), 43.2 ($ArC\underline{H}_2CHCH_2$), 32.5 ($Ar\underline{C}H_2CHAr$), 31.85 (CH_2), 21.4 ($ArCH_3$), 10.8 (CH_3); *minor (trans)-isomer* δ_H 7.49 (2H, d, *J* 8.3, 2 x ArH), 7.44 – 7.42 (1H, m, ArH), 7.14 (2H, m, 2 x ArH), 7.10 (2H, d, *J* 8.0, 2 x ArH), 7.08 – 7.04 (3H, m, 3 x ArH), 7.03 – 6.99 (1H, m, ArH), 6.70 (1H, d, *J* 7.5, ArH), 5.30 (1H, t, *J* 7.6, ArC$\underline{H}CH_2Ar$), 3.99 (1H, dddd, *J* 9.4, 7.8, 7.1 and 4.5, $ArCH_2C\underline{H}CH_2$), 3.49 (1H, dd, *J* 13.4 and 7.6, ArC$\underline{H}_{2a}$CHAr), 3.12 (1H, dd, *J* 13.4 and 7.7, ArC$\underline{H}_{2b}$CHAr), 3.02 (1H, dd, *J* 15.9 and 4.4, 1H, ArC$\underline{H}_{2a}CHCH_2$), 2.94 (1H, dd, *J* 15.9 and 7.1, ArC$\underline{H}_{2b}CHCH_2$), 2.36 (3H, s, $ArCH_3$), 1.93 – 1.82 (1H, m, $CH_3C\underline{H}_{2a}$), 1.39 – 1.36 (1H, m, $CH_3C\underline{H}_{2b}$), 0.84 (3H, t, *J* 7.4, CH_3); δ_C 137.7 (C), 136.0 (C), 134.0 (C), 132.75 (ArCH), 132.2 (ArCH), 129.4 (ArCH), 128.9 (ArCH), 128.2 (ArCH), 127.3 (ArCH), 127.2 (ArCH), 127.1 (ArCH), 126.1 (ArCH), 125.3 (C-Br), 59.4 ($ArCH_2C\underline{H}Ar$), 56.7 ($ArCH_2C\underline{H}CH_2$), 3.0 ($ArC\underline{H}_2CHCH_2$), 32.1 ($Ar\underline{C}H_2CHAr$), 26.4 (CH_2), 21.45 ($ArCH_3$), 11.5 (CH_3); HRMS calculated for

$C_{25}H_{26}BrNO_2S$ $[M]^+$ 483.0868, found 483.0860; LRMS m/z 483 ($[M]^+$, 70%), 232 ($[M\text{-}NHCOOMe]^+$, 3%).

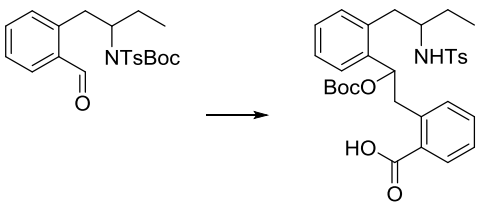
5-Ethyl-6-tosyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolone 399



398 **399**

To a solution of 1-(2-bromobenzyl)-3-ethyl-2-tosyl-1,2,3,4-tetrahydroisoquinoline **398** (75 mg, 0.155 mmol, 1.0 eq.) in dimethylacetamide (2 mL) was added palladium acetate (1.7 mg, 0.0077 mmol, 0.05 eq.), potassium carbonate (42.7 mg, 0.309 mg, 2.0 eq.) and tricyclohexylphosphine (5.4 mg, 0.0193 mmol, 0.125 eq.) and the resulting mixture heated to 130 °C for 16 h. The reaction was then cooled to ambient temperature and partitioned between ethyl acetate (10 mL) and water (5 mL). The separated organic phase was washed with water (4 x 5 mL), brine (5 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 1:3) to give *aporphine* **399** (42 mg, 67%) as a colourless glass; ν_{max} 3064, 3029, 2966, 2931, 2874, 1596 (S=O), 1338 (S=O); δ_H (400 MHz) 7.71 (1H, d, *J* 8.3, ArH), 7.65 (1H, d, *J* 7.7, ArH), 7.61 (2H, d, *J* 8.3, 2 x ArH), 7.51 (1H, d, *J* 7.8, ArH), 7.28 – 7.15 (3H, m, 3 x ArH), 7.13 (2H, d, *J* 8.5, 2 x ArH), 6.85 (1H, d, *J* 7.5, ArH), 4.67 (1H, dd, *J* 14.3 and 4.8, 6a-CH), 4.13 – 4.07 (1H, m, 5-CH), 3.38 (1H, dd, *J* 14.4 and 4.8, 7-CH_{2a}), 2.92 (1H, t, *J* 14.4, 7-CH_{2b}), 2.42 (1H, dd, *J* 15.6 and 1.7, 4-CH_{2a}), 2.33 – 2.29 (1H, m, 4-CH_{2b}), 2.27 (3H, s, $ArCH_3$), 1.52 – 1.40 (1H, m, $CH_3C\underline{H}_{2a}$), 1.32 – 1.28 (1H, m, $CH_3C\underline{H}_{2b}$), 0.92 (3H, t, *J* 7.4, CH_3); δ_C (101 MHz) 142.2 (C), 136.6 (C), 134.5 (C), 133.1 (C), 132.6 (C), 130.4 (C), 129.6 (C), 128.8 (2 x ArCH), 128.6 (ArCH), 127.7 (ArCH), 127.3 (ArCH), 127.1 (ArCH), 126.5 (ArCH), 126.35 (ArCH), 126.0 (2 x ArCH), 125.7 (ArCH), 122.7 (ArCH), 121.7 (ArCH), 52.25 (NCH), 51.05 (NCH), 38.4 (CH_2), 31.3 (CH_2), 26.1 (CH_2), 21.7 ($ArCH_3$), 9.9 (CH_3); HRMS calculated for $C_{25}H_{25}NO_2S$ $[M]^+$ 403.1606, found 403.1602.

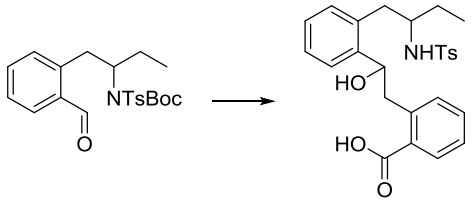
2-(2-((*tert*-Butoxycarbonyl)oxy)-2-(2-(2-((4-methylphenyl)sulfonamido)butyl)phenyl)ethyl) benzoic acid 407



302 **407**

To a solution of 2-methylbenzoic acid (207 mg, 1.52 mmol, 2.0 eq.) in tetrahydrofuran (3 mL) at -78 °C under an atmosphere of nitrogen was added butyllithium (2.35 M, 1.28 mL, 3.20 mmol, 4.2 eq.) dropwise over 0.5 h and the resulting deep red solution allowed to warm to -50 °C over 0.5 h. The reaction mixture was then cooled to -78 °C and cannulated to a -78 °C solution of *tert*-butyl (1-(2-formylphenyl)butan-2-yl)(tosyl)carbamate **302** (328 mg, 0.761 mmol, 1.0 eq.) in tetrahydrofuran (2 mL) until the red colour persisted for a period of several seconds. The reaction was quenched by aqueous ammonium chloride (5 mL) and ethyl acetate (5 mL) and the separated aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic mixtures were washed with brine (15 mL), dried, filtered and exaporated. The crude material was then dissolved in dichloromethane (5 mL) and trifluoroacetic acid (116 μl, 2.0 eq.) was added at 0 °C and the mixture allowed to warm to ambient temperature and stirred for 1.5 h. The mixture was then washed with aqueous sodium bicarbonate (5 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *sulfonamide* **407** (140 mg, 41%) as a viscous, colourless glass; δ_H (400 MHz) 8.14 (1H, d, *J* 7.7, ArH), 7.73 (1H, d, *J* 7.8, ArH), 7.57 (1H, td, *J* 7.5 and 1.0, ArH), 7.42 (2H, t, *J* 7.5, 2 x ArH), 7.31 (2H, br. d, *J* 8.8, 2 x ArH), 7.25 (1H, t, *J* 8.6, ArH), 7.11 – 7.07 (4H, s, 4 x ArH), 5.96 (1H, dd, *J* 12.4 and 2.7, ArC<u>H</u>OH), 4.58 (1H, dddd, *J* 5.0, 6.6, 8.2 and 9.8, NCH), 3.48 – 3.36 (2H, m, Ar_aCH_{2a} and Ar_bCH_{2a}), 3.24 – 3.14 (2H, m, Ar_aCH_{2b} and Ar_bCH_{2b}), 2.38 (3H, s, $ArCH_3$), 2.09 – 1.96 (1H, qdd, *J* 7.5, 8.2 and 14.4, C<u>H</u>$_{2a}CH_3$), 1.76 – 1.64 (1H, m, dqd, *J* 5.1, 7.5 and 14.6, C<u>H</u>$_{2a}CH_3$), 1.30 (9H, s, $C(CH_3)_3$), 0.87 (3H, t, *J* 7.3, CH_3); δ_C (101 MHz) 165.61 (C=O), 150.76 (C=O), 143.62 (C), 139.31 (C), 137.40 (C), 137.37 (C), 136.34 (C), 133.90 (ArCH), 131.42 (ArCH), 130.35 (ArCH), 129.02 (2 x ArCH), 128.94 (ArCH), 127.84 (2 x ArCH), 127.45 (ArCH), 127.41 (ArCH), 127.20 (ArCH), 125.14 (C), 84.28 (<u>C</u>$(CH_3)_3$), 76.46 (OCH), 62.06 (NCH), 36.27 ($ArCH_2$), 35.04 ($ArCH_2$), 27.9 ($C(\underline{C}H_3)_3$), 25.84 (CH_2), 21.52 ($ArCH_3$), 11.42 (CH_3).

2-(2-Hydroxy-2-(2-(2-((4-methylphenyl)sulfonamido)butyl)phenyl)ethyl)benzoic acid 408

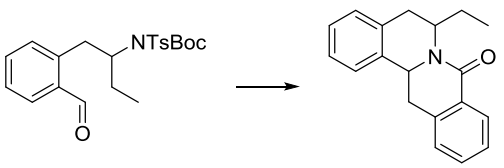


302 **408**

To a solution of 2-methylbenzoic acid (347 mg, 2.55 mmol, 1.1 eq.) in tetrahydrofuran (10 mL) at -78 °C under an atmosphere of nitrogen was added butyllithium (1.6 M, 3.5 mL, 5.56 mmol, 2.4 eq.) dropwise over 0.5 h and the resulting deep red solution allowed to warm to -20 °C over 0.5 h. The reaction mixture was then cooled to -78 °C and *tert*-butyl (1-(2-formylphenyl)butan-2-yl)(tosyl)carbamate **302** (1.00 g, 2.32 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) was added and the solution stirred for a further 0.5 h at -78 °C. The reaction was quenched by 10% aqueous sulfuric acid (5 mL) and ethyl acetate (5 mL) and the

separated aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic mixtures were washed with brine (15 mL), dried, filtered and exaporated. The crude material was then dissolved in dichloromethane (8 mL) and trifluoroacetic acid (1.6 mL) was added at 0 °C and the mixture allowed to warm to ambient temperature and stirred for 16 h. The mixture was then washed with aqueous sodium bicarbonate (5 mL), dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *alcohol* **408** (313 mg, 29%) as a yellow oil, as a 2:1 mixture of diastereoisomers; *major diastereoisomer* δ_H (400 MHz) 8.16 – 8.12 (1H, m, ArH), 7.60 – 7.55 (2H, m, 2 x ArH), 7.54 – 7.46 (3H, m, 3 x ArH), 7.47 – 7.40 (1H, m, ArH), 7.32 – 7.24 (2H, m, 2 x ArH), 7.21 – 7.18 (1H, m, ArH), 7.07 (2H, d, *J* 8.0, 2 x ArH), 5.67 (1H, dd, *J* 12.6 and 2.8, ArC$\underline{H}$(OH)), 5.25 (1H, d, *J* 8.2, NH), 3.34 (1H, dd and, *J* 17.6 and 12.6, ArC$\underline{H}_{2a}$CH(OH)), 3.33 (1H, m, NCH), 3.40 – 3.18 (1H, m, ArC$\underline{H}_{2b}$CH(OH)), 2.89 (1H, dd, *J* 14.1 and 6.1, ArC$\underline{H}_{2a}$CHN), 2.67 (1H, dd, *J* 14.2 and 8.3, ArC$\underline{H}_{2b}$CHN), 2.35 (3H, s, $ArCH_3$), 1.53 – 1.40 (1H, m, $CH_3C\underline{H}_{2a}$), 1.35 – 1.21 (1H, m, $CH_3C\underline{H}_{2b}$), 0.72 (3H, t, *J* 7.4, CH_3); δ_C (101 MHz) 165.4 (C=O), 143.0 (C), 139.15 (C), 138.0 (C), 136.8 (C), 135.45 (C), 134.0 (ArCH), 130.85 (ArCH), 130.4 (ArCH), 129.5 (2 x ArCH), 127.9 (ArCH), 127.5 (ArCH), 127.1 (ArCH), 127.1 (ArCH), 126.8 (2 x ArCH), 125.0 (ArCH), 76.8 (OCH), 57.1 (NCH), 38.2 ($ArCH_2$), 35.3 ($ArCH_2$), 27.0 (CH_2), 21.5 ($ArCH_3$), 10.0 (CH_3); *minor diastereoisomer* δ_H (400 MHz) 8.19 – 8.13 (1H, m, ArH), 7.60 – 7.55 (1H, m, ArH), 7.54 – 7.46 (2H, m, 2 x ArH), 7.47 – 7.40 (1H, m, ArH), 7.32 – 7.24 (2H, m, 2 x ArH), 7.20 (1H, m, ArH), 7.11 (2H, d, *J* 8.1, 2 x ArH), 7.08 – 7.05 (2H, m, 2 x ArH), 5.90 (1H, dd, *J* 12.4 and 2.8, ArC$\underline{H}$(OH)), 5.19 (1H, d, *J* 7.6, NH), 3.40 – 3.18 (2H, m, ArC$\underline{H}_{2a}$CH(OH) and NCH), 3.06 (1H, dd, *J* 14.0 and 5.7, ArC$\underline{H}_{2b}$CH(OH)), 3.02 – 2.91 (1H, m, ArC$\underline{H}_{2a}$CHN), 2.70 (1H, dd, *J* 14.5 and 8.5, ArC$\underline{H}_{2b}$CH), 2.35 (3H, s, $ArCH_3$), 1.53 – 1.40 (1H, m, $CH_3C\underline{H}_{2a}$), 1.35 – 1.21 (1H, m, $CH_3C\underline{H}_{2b}$), 0.64 (1H, t, *J* 7.4, CH_3); δ_C (101 MHz) 165.6 (C=O), 143.1 (C), 139.3 (C), 137.4 (C), 136.7 (C), 135.6 (C), 134.1 (ArCH), 131.2 (ArCH), 130.3 (ArCH), 128.7 (2 x ArCH), 127.9 (ArCH), 127.6 (ArCH), 127.3 (ArCH), 127.05 (ArCH), 126.9 (ArCH), 124.95 (ArCH), 76.6 (OCH), 56.4 (NCH), 39.1 ($ArCH_2$), 34.7 ($ArCH_2$), 26.85 (CH_2), 22.7 ($ArCH_3$), 9.8 (CH_3); HRMS calculated for $C_{26}H_{27}NNaO_4S$ [M-H_2O+Na]$^+$ 472.1559, found 472.1545.

6-Ethyl-5,6,13,13a-tetrahydro-8H-isoquinolino[3,2-a]isoquinolin-8-one 409

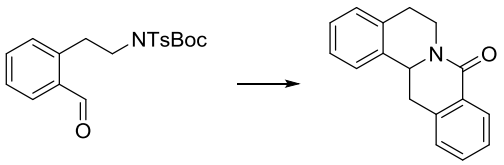


302 **409**

To a solution of 2-methylbenzoic acid (63 mg, 0.464 mmol, 2.0 eq.) in tetrahydrofuran (1 mL) at -78 °C under an atmosphere of nitrogen was added butyllithium (2.3 M, 0.40 mL, 0.92 mmol, 4.0 eq.) dropwise

over 0.5 h and the resulting deep red solution allowed to warm to -50 °C over 0.5 h. The reaction mixture was then cooled to -78 °C and cannulated to a -78 °C solution of *tert*-butyl (1-(2-formylphenyl)butan-2-yl)(tosyl)carbamate **302** (100 mg, 0.232 mmol, 1.0 eq.) in tetrahydrofuran (1 mL) until the red colour persisted for a period of several seconds. The reaction was quenched by aqueous ammonium chloride (2 mL) and ethyl acetate (3 mL) and the separated aqueous layer extracted with ethyl acetate (3 x 5 mL). The combined organic mixtures were washed with brine (10 mL), dried, filtered and exaporated. The crude material was then dissolved in toluene (2.3 mL) under an atmosphere of nitrogen at 0 °C. To this was added triflic acid (52 mg, 0.348 mmol, 1.0 eq.). The resulting solution was heated to 110 °C, stirred for 18 h and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *berberinone* **409** (39 mg, 65%) as a colourless glass, as a 4:1 mixture of *cis* and *trans* diastereoisomers. Vapour diffusion recrystallisation from diethyl ether/heptane gave *berberinone* **409** (29 mg, 45%) as colourless needles and as a single, *cis* diastereoisomer; m.p. 160-163; ν_{max} 3045, 2956, 1635 (C=O), 1400, 1307; *major (cis)-diastereoisomer* δ_H (400 MHz) 8.15 (1H, d, *J* 7.7, ArH), 7.47 (1H, t, *J* 7.4, ArH), 7.42 – 7.35 (2H, m, 2 x ArH), 7.35 – 7.28 (3H, m, 3 x ArH), 7.24 (1H, d, *J* 7.4, ArH), 4.89 (1H, dddd, *J* 8.4, 6.7 and 3.4 and 3.0, 6-CH), 4.76 (1H, dd, *J* 13.7 and 3.2, 13a-CH), 3.57 (1 H, dd, *J* 14.9 and 3.3, 13-CH_{2a}), 3.21 (1H, dd, *J* 14.8 and 13.8, 13-CH_{2b}), 2.98 (2H, app. d, *J* 3.3, 5-CH_2), 1.53 – 1.42 (1H, m, C$\underline{H}_{2a}CH_3$), 1.06 – 0.94 (1H, m, C$\underline{H}_{2b}CH_3$), 0.84 (3H, t, *J* 7.4, CH_3); δ_C (101 MHz) 164.8 (C=O), 136.8 (C), 135.5 (C), 135.5 (C), 131.7 (ArCH), 129.8 (C), 128.5 (ArCH), 128.3 (ArCH), 127.7 (ArCH), 127.4 (ArCH), 127.1 (ArCH), 126.8 (ArCH), 123.5 (ArCH), 52.6 (CH), 51.6 (CH), 32.6 (CH_2), 32.0 (CH_2), 27.05 ($ArCH_2$), 10.5 (CH_3); *minor (trans)-diastereoisomer* δ_H (400 MHz) 5.24 – 5.12 (1H, m, 6-CH), 3.03 (1H, d, *J* 13.6), 2.84 (1H, dd, *J* 15.9 and 1.8), 1.44 – 1.32 (1H, m, C$\underline{H}_{2a}CH_3$), 1.28 – 1.17 (1 H, m), 0.90 (2 H, t, *J* 7.4); only 6 distinct signals; HRMS (APCI) calculated for $C_{19}H_{19}NO$ $[M]^+$ 277.1467, found 277.1468.

5,6,13,13a-tetrahydro-8H-isoquinolino[3,2-a]isoquinolin-8-one 410

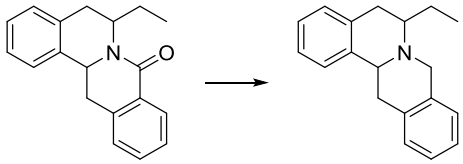


300b **410**

To a solution of 2-methylbenzoic acid (195 mg, 1.434 mmol, 2.0 eq.) in tetrahydrofuran (2 mL) at -78 °C under an atmosphere of nitrogen was added butyllithium (2.35 M, 1.22 mL, 2.87 mmol, 4.0 eq.) dropwise over 0.5 h and the resulting deep red solution allowed to warm to -50 °C over 0.5 h. The reaction mixture

was then cooled to -78 °C and cannulated to a -78 °C solution of tert-butyl (2-formylphenethyl)(tosyl)carbamate **300b** (289 mg, 0.717 mmol, 1.0 eq.) in tetrahydrofuran (2 mL) until the red colour persisted for a period of several seconds. The reaction was quenched by aqueous ammonium chloride (5 mL) and ethyl acetate (5 mL) and the separated aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic mixtures were washed with brine (15 mL), dried, filtered and exaporated. The crude material was then dissolved in toluene (3.5 mL) under an atmosphere of nitrogen at 0 °C. To this was added triflic acid (108 mg, 0.717 mmol, 1.0 eq.). The resulting solution was heated to 110 °C, stirred for 18 h and then quenched with aqueous potassium carbonate (2 mL), extracted with dichloromethane (3 x 5 mL) and the combined organic extracts dried, filtered and evaporated. The crude material was purified by column chromatography (petrol/ethyl acetate 1:1) to give *berberinone* **410** (136 mg, 76%) as an off-white solid; m.p. 172-174; ν_{max} 3028, 2930, 2886, 1637 (C=O), 1401, 1288; δ_H (400 MHz) 8.15 (1H, d, *J* 7.6, ArH), 7.46 (1H, td, *J* 7.4 and 1.1, ArH), 7.38 (1H, t, *J* 7.5, ArH), 7.31 – 7.20 (5H, m, 5 x ArH), 4.98 – 4.94 (2H, m, ArCHN and Ar$C\underline{H}_{2a}CH_2$), 3.25 (1H, dd, *J* 15.7 and 3.7, Ar$C\underline{H}_{2a}$CH), 3.09 – 2.94 (3H, m $ArCH_{2b}CH_2$ and NCH_2), 2.94 – 2.81 (1H, m, $ArCH_{2b}$CH); δ_C 164.7 (C=O), 137.5 (C), 136.1 (C), 135.2 (C), 131.9 (ArCH), 129.2 (C), 129.1 (ArCH), 128.7 (ArCH), 127.5 (ArCH), 127.0 (ArCH), 127.0 (ArCH), 126.9 (ArCH), 126.1 (ArCH), 55.35 (CH), 38.8 (CH_2), 38.0 (CH_2), 29.9 (CH_2); HRMS (APCI) calculated for $C_{17}H_{16}NO$ $[M+H]^+$ 250.1232, found 250.1221.

6-ethyl-5,8,13,13a-tetrahydro-6H-isoquinolino[3,2-a]isoquinoline 411

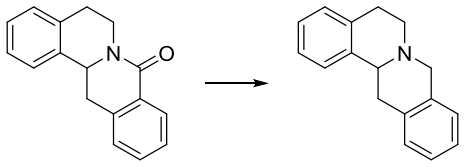


409 **411**

To a solution of 6-ethyl-5,6,13,13a-tetrahydro-8H-isoquinolino[3,2-a]isoquinolin-8-one **409** (17 mg, 0.0614 mmol, 1.0 eq.) in tetrahydrofuran (4 mL) was added lithium aluminium hydride (1M, 0.49 mL, 0.491 mmol, 8.0 eq.) and the resulting mixture heated to 70 °C for 0.5 h. The reaction was quenched according to General Procedure G and the crude material was purified by column chromatography (petrol/ethyl acetate 1:5) to give *berberine* **411** (10 mg, 62%) as a colourless oil, as a 4:1 mixture of *cis* and *trans* diastereoisomers; *major (cis)-diastereoisomer* δ_H (400 MHz) 7.27 (1H, d, *J* 7.5, ArH), 7.23 – 7.07 (7H, m, ArH), 4.33 (1H, d, *J* 14.7, 8-CH_{2a}), 3.78 (1H, dd, *J* 10.9 and 3.2, 13a-CH), 3.54 (1H, d, *J* 14.7, 8-CH_{2b}), 3.38 (1H, dd, *J* 16.2 and 3.3, 13-CH_{2a}), 2.99 (1H, dd, *J* 16.0 and 11.1, 13-CH_{2b}), 2.87 (1H, dd, *J* 15.9 and 10.4, 5-CH_{2a}), 2.80 (1H, dd, *J* 15.8 and 3.3, 5-CH_{2b}), 2.56 (1H, dddd, *J* 10.4, 7.2, 3.9 and 3.3, 6-CH), 1.97 (1H, dqd, *J* 14.8, 7.5 and 3.9, $C\underline{H}_{2a}CH_3$), 1.61 (1H, dqd, *J* 15.1, 7.5 and 7.2 $C\underline{H}_{2b}CH_3$), 1.03 (3H, t, *J* 7.5, CH_3); δ_C (101 MHz) 137.8 (C), 135.0 (C), 134.9 (C), 134.6 (C), 128.7 (ArCH), 128.6 (ArCH), 126.7 (ArCH), 126.3 (ArCH), 126.2 (ArCH), 126.1 (ArCH), 125.9 (ArCH), 125.5 (ArCH), 61.0

(CH), 59.7 (CH), 53.9 (CH_2), 37.8 (CH_2), 34.4 (CH_2), 25.8 (CH_2), 9.8 (CH_3); *minor (trans)-diastereoisomer* δ_H (400 MHz) 7.23 – 7.05 (8H, m, ArH), 4.19 (1H, d, *J* 15.1, 8-CH_{2a}), 3.99 (1H, dd, *J* 11.0 and 3.9, ArCHN), 3.88 (1H, d, *J* 15.2, 8-CH_{2b}), 3.26 (1H, dd, *J* 16.1 and 3.9, 5-CH_{2a}), 3.19 (1H, dd, *J* 15.9 and 4.6, 13-CH_{2a}), 3.07 (1H, dddd, *J* 7.8, 5.5, 3.9 and 2.9, 6-CH), 2.90 (1H, dd, *J* 16.1 and 11.1, 13-CH_{2b}), 2.79 (1H, dd, *J* 15.9 and 2.9, 5-CH_{2b}), 1.82 – 1.78 (1H, m, C$\underline{H}_{2a}CH_3$), 1.24 – 1.12 (1H, m, C$\underline{H}_{2b}CH_3$), 0.91 (3H, t, *J* 7.4, CH_3); δ_C (101 MHz) 138.4 (C), 135.1 (C), 134.7 (C), 133.3 (C), 129.75 (ArCH), 128.9 (ArCH), 126.4 (ArCH), 126.3 (ArCH), 126.3 (ArCH), 125.9 (2 x ArCH), 125.7 (ArCH), 58.3 (CH), 55.3 (CH), 53.95 (CH_2), 37.4 (CH_2), 33.1 (CH_2), 17.1 (CH_2), 11.7 (CH_3); HRMS (APCI) calculated for $C_{19}H_{22}N$ $[M+H]^+$ 264.1752, found 264.1743.

5,8,13,13a-Tetrahydro-6H-isoquinolino[3,2-a]isoquinoline 412



410 **412**

To a solution of 5,6,13,13a-tetrahydro-8H-isoquinolino[3,2-a]isoquinolin-8-one **410** (21 mg, 0.0843 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) was added lithium aluminium hydride (1M, 0.68 mL, 0.68 mmol, 8.0 eq.) and the resulting mixture heated to 70 °C for 0.25 h. The reaction was quenched according to General Procedure G and the crude material was purified by column chromatography (petrol/ethyl acetate 1:5) to give *berberine* **412** (18 mg, 62%) as an off-yellow solid; m.p. 78- 81; δ_H (400 MHz) 7.21 (1H, d, *J* 7.5, ArH) 7.17 – 7.02 (6H, m, 6 x ArH), 7.01 (1H, d, *J* 5.1, ArH), 3.96 (1H, d, *J* 14.9, $ArCH_{2a}N$), 3.68 (1H, d, *J* 15.6, $ArCH_{2b}N$), 3.65 – 3.60 (1H, m, 13a-CH), 3.31 (1H, dd, *J* 16.2 and 3.7, 13-CH), 3.13 (2H, m, 5-CH_{2a} and 6-CH_{2a}), 2.86 (1H, dd, *J* 16.0 and 11.6, 13-$ArCH_{2b}$), 2.69 (1H, dd, *J* 17.3 and 5.1 5-C$\underline{H}_{2b}$), 2.63 – 2.53 (1H, m, 6-CH_{2a}); δ_C (101 MHz) 138.1 (C), 134.7 (C), 134.6 (C), 134.6 (C), 129.0 (ArCH), 128.9 (ArCH), 126.4 (ArCH), 126.3 (ArCH), 126.3 (ArCH), 126.2 (ArCH), 126.0 (ArCH), 125.6 (ArCH), 60.0 (CH), 58.8 (CH_2), 51.4 (CH_2), 36.8 (CH_2), 29.7 (CH_2); HRMS (APCI) calculated for $C_{17}H_{18}N$ $[M+H]^+$ 236.1439, found 236.1434.

Hydrochloride salt was prepared by dissolving 5,8,13,13a-tetrahydro-6H-isoquinolino[3,2-a]isoquinoline **412** (10 mg) in methanol (0.1 mL) followed by addition of HCl (10 M, 11 μl, 2.5 eq.). The solvents were removed under reduced pressure and the material dried in a vacuum oven overnight to afford *salt* **412-HCl** (10 mg) as a white solid; m.p. 197 – 201 °C (lit. m.p.[256] 223 °C).

References

(1) Nyulászi, L. *Chem. Rev.* **2001**, *101*, 1229–1246.

(2) Hendrickson, J. B.; Spenger, R. E.; Sims, J. J. *Tetrahedron Lett.* **1961**, *2*, 477–480.

(3) Braye, E. H.; Hübel, W.; Caplier, I. *J. Am. Chem. Soc.* **1961**, *83*, 4406–4413.

(4) Barton, T. J.; Burns, G. T. *J. Am. Chem. Soc.* **1978**, *100*, 5246–5246.

(5) Katritzky, A. R. *J. Chem. Educ.* **1965**, *42*, 636.

(6) Campaigne, E. *J. Chem. Educ.* **1986**, *63*, 860.

(7) Perkin, W. H. *J. Chem. Soc.* **1870**, *23*, 368.

(8) Sequin-Frey, M. *J. Chem. Educ.* **1981**, *58*, 301.

(9) Anderson, T. *Ann. der Chemie und Pharm.* **1858**, *105*, 335–359.

(10) Shapiro, D. A.; Renock, S.; Arrington, E.; Chiodo, L. A.; Liu, L.-X.; Sibley, D. R.; Roth, B. L.; Mailman, R. *Neuropsychopharmacology* **2003**, *28*, 1400–1411.

(11) Brooks, M. Top 100 Selling Drugs of 2013 http://www.medscape.com/viewarticle/820011 (accessed Nov 4, 2014).

(12) Powell, D. Pacific yew, Taxus brevifolia (Taxales: Taxaceae) - 1359047 http://www.forestryimages.org/browse/detail.cfm?imgnum=1359047 (accessed Nov 4, 2014).

(13) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325–2327.

(14) Wall, M. E.; Wani, M. C. *Cancer Res.* **1995**, *55*, 753–760.

(15) Saville, M. W.; Lietzau, J.; Pluda, J. M.; Wilson, W. H.; Humphrey, R. W.; Feigel, E.; Steinberg, S. M.; Broder, S.; Yarchoan, R.; Odom, J.; Feuerstein, I. *Lancet* **1995**, *346*, 26–28.

(16) Nicolaou, K. C.; Hwang, C.-K.; Soresen, E. J.; Clairborne, C. F. *J. Chem. Soc. Chem. Commun.* **1992**, 1117.

(17) Fuchs, D. A.; Johnson, R. K. *Cancer Treat. Rep.* **1978**, *62*, 1219–1222.

(18) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. *J. Am. Chem. Soc.* **1994**, *116*, 1597–1598.

(19) Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. *J. Am. Chem. Soc.* **1994**, *116*, 1599–1600.

(20) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624–633.

(21) Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634–644.

(22) Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645–652.

(23) Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653–659.

(24) Heinig, U.; Scholz, S.; Jennewein, S. *Fungal Divers.* **2013**, *60*, 161–170.

(25) Expósito, O.; Bonfill, M.; Moyano, E.; Onrubia, M.; Mirjalili, M. H.; Cusidó, R. M.; Palazón, J. *Anticancer. Agents Med. Chem.* **2009**, *9*, 109–121.

(26) Okano, A.; Nakayama, A.; Schammel, A. W.; Boger, D. L. *J. Am. Chem. Soc.* **2014**, *136*, 13522–13525.

(27) Douglas, N. M.; Anstey, N. M.; Angus, B. J.; Nosten, F.; Price, R. N. *Lancet. Infect. Dis.* **2010**, *10*, 405–416.

(28) Miller, L. H.; Su, X. *Cell* **2011**, *146*, 855–858.

(29) Xiao, S.-H. *Acta Trop.* **2005**, *96*, 153–167.

(30) Ferreira, J. Artemisia annua http://en.wikipedia.org/wiki/File:Artemisia_annua.jpg (accessed Nov 4, 2014).

(31) Cumming, J. N.; Ploypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1996**, *37*, 253–297.

(32) Lapkin, A. A.; Peters, M.; Greiner, L.; Chemat, S.; Leonhard, K.; Liauw, M. A.; Leitner, W. *Green Chem.* **2010**, *12*, 241–251.

(33) Lapkin, A. A.; Plucinski, P. K.; Cutler, M. *J. Nat. Prod.* **2006**, *69*, 1653–1664.

(34) Barnes, K. I.; Chanda, P.; Ab Barnabas, G. *Malar. J.* **2009**, *8 Suppl 1*, S8.

(35) White, N. J. *Science* **2008**, *320*, 330–334.

(36) Hofmann, A. W. *Chem. Ber.* **1881**, *14*, 705–713.

(37) GRANDMONT, J.-P. Sarracenia Flava http://en.wikipedia.org/wiki/File:Sarracenia_Flava_JPG01.jpg (accessed Nov 4, 2014).

(38) Rujjanawate, C.; Kanjanapothi, D.; Panthong, A. *J. Ethnopharmacol.* **2003**, *89*, 91–95.

(39) Bandyopadhyay, R.; Frederickson, D. E.; McLaren, N. W.; Odvody, G. N.; Ryley, M. J. *Plant Dis.* **1998**, *82*, 356–367.

(40) Schardl, C. L.; Panaccione, D. G.; Tudzynski, P. *Alkaloids Chem. Biol.* **2006**, *63*, 45–86.

(41) Walkembach, J.; Brüss, M.; Urban, B. W.; Barann, M. *Br. J. Pharmacol.* **2005**, *146*, 543–552.

(42) Mulac, D.; Lepski, S.; Ebert, F.; Schwerdtle, T.; Humpf, H.-U. *J. Agric. Food Chem.* **2013**, *61*, 462–471.

(43) McKenzie, A. G. *Anaesthesia* **2000**, *55*, 551–556.

(44) Koniaris, L. G.; Zimmers, T. A.; Lubarsky, D. A.; Sheldon, J. P. *Lancet* **2005**, *365*, 1412–1414.

(45) Groner, J. I. *BMJ* **2002**, *325*, 1026–1028.

(46) Sawynok, J. *Can. J. Physiol. Pharmacol.* **1986**, *64*, 1–6.

(47) Raghavendra, T. *J. R. Soc. Med.* **2002**, *95*, 363–367.

(48) O'Donovan, D. G.; Horan, H. *J. Chem. Soc. C* **1968**, 2791.

(49) Deng, Y.; Maruyama, W.; Yamamura, H.; Kawai, M.; Dostert, P.; Naoi, M. *Anal. Chem.* **1996**, *68*, 2826–2831.

(50) Kobayashi, H.; Fukuhara, K.; Tada-Oikawa, S.; Yada, Y.; Hiraku, Y.; Murata, M.; Oikawa, S. *J. Neurochem.* **2009**, *108*, 397–407.

(51) Katz, Y.; Weizman, A.; Pick, C. G.; Pasternak, G. W.; Liu, L.; Fonia, O.; Gavish, M. *Brain Res.* **1994**, *646*, 235–241.

(52) Fodale, V.; Santamaria, L. B. *Eur. J. Anaesthesiol.* **2006**, *19*, 466.

(53) Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem.* **1987**, *30*, 1433–1454.

(54) Zara-Kaczian, E.; Gyorgy, L.; Deak, G.; Seregi, A.; Doda, M. *J. Med. Chem.* **1986**, *29*, 1189–1195.

(55) Keller, H. H.; Schaffner, R.; Carruba, M. O.; Burkard, W. P.; Pieri, M.; Bonetti, E. P.; Scherschlicht, R.; Da Prada, M.; Haefely, W. E. *Adv. Biochem. Psychopharmacol.* **1982**, *31*, 249–263.

(56) Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1979**, *18*, 1–24.

(57) Omer, O. L.; Díaz-Olivera, M.; Ismail, S. *Methods Find. Exp. Clin. Pharmacol.* **1984**, *6*, 147–151.

(58) Bischler, A.; Napieralski, B. *Chem. Ber.* **1893**, *26*, 1903–1908.

(59) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1956**, *78*, 2023–2025.

(60) Fodor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279–1300.

(61) Leonard, N. J.; Nommensen, E. W. *J. Am. Chem. Soc.* **1949**, *71*, 2808–2813.

(62) Ishikawa, T.; Shimooka, K.; Narioka, T.; Noguchi, S.; Saito, T.; Ishikawa, A.; Yamazaki, E.; Harayama, T.; Seki, H.; Yamaguchi, K. *J. Org. Chem.* **2000**, *65*, 9143–9151.

(63) Doi, S.; Shirai, N.; Sato, Y. *J. Chem. Soc. Perkin Trans. 1* **1997**, 2217–2222.

(64) Medley, J. W.; Movassaghi, M. *Org. Lett.* **2013**, *15*, 3614–3617.

(65) Awuah, E.; Capretta, A. *J. Org. Chem.* **2010**, *75*, 5627–5634.

(66) Meutermans, W. D. F.; Alewood, P. F. *Tetrahedron Lett.* **1995**, *36*, 7709–7712.

(67) Judeh, Z. M. A.; Ching, C. B.; Bu, J.; McCluskey, A. *Tetrahedron Lett.* **2002**, *43*, 5089–5091.

(68) Su, B.; Chen, F.; Wang, Q. *J. Org. Chem.* **2013**, *78*, 2775–2779.

(69) Geffe, M.; Opatz, T. *Org. Lett.* **2014**, *16*, 5282–5285.

(70) Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, *44*, 2030–2036.

(71) Bailey, P. D. *Tetrahedron Lett.* **1987**, *28*, 5181–5184.

(72) Stöckigt, J.; Zenk, M. H. *J. Chem. Soc. Chem. Commun.* **1977**, 646.

(73) Naoi, M.; Maruyama, W.; Nagy, G. M. *Neurotoxicology* **2004**, *25*, 193–204.

(74) Brown, R. T.; Smith, G. N.; Stapleford, K. S. J. *Tetrahedron Lett.* **1968**, *9*, 4349.

(75) Kutney, J. P. *Nat. Prod. Rep.* **1990**, *7*, 85.

(76) Brown, R. T.; Chapple, C. L. *J. Chem. Soc. Chem. Commun.* **1973**, 886b.

(77) Maresh, J. J.; Giddings, L.-A.; Friedrich, A.; Loris, E. A.; Panjikar, S.; Trout, B. L.; Stöckigt, J.; Peters, B.; O'Connor, S. E. *J. Am. Chem. Soc.* **2008**, *130*, 710–723.

(78) Dagani, R. *Chem. Eng. News Arch.* **2005**, *83*, 106.

(79) Ng, F. W.; Lin, H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9812–9824.

(80) Woodward, R. B.; Brehm, W. J.; Nelson, A. L. *J. Am. Chem. Soc.* **1947**, *69*, 2250–2250.

(81) Loegers, M.; Overman, L. E.; Welmaker, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 9139–9150.

(82) Soukasene, S.; Toft, D. J.; Moyer, T. J.; Lu, H.; Lee, H.-K.; Standley, S. M.; Cryns, V. L.; Stupp, S. I. *ACS Nano* **2011**, *5*, 9113–9121.

(83) Zhang, H.; Wang, X.; Dai, W.; Gemeinhart, R. A.; Zhang, Q.; Li, T. *Mol. Pharm.* **2014**, *11*, 226–233.

(84) Gobbi, P. G.; Broglia, C.; Merli, F.; Dell'Olio, M.; Stelitano, C.; Iannitto, E.; Federico, M.; Bertè, R.; Luisi, D.; Molica, S.; Cavalli, C.; Dezza, L.; Ascari, E. *Cancer* **2003**, *98*, 2393–2401.

(85) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535–545.

(86) Manabe, K.; Nobutou, D.; Kobayashi, S. *Bioorg. Med. Chem.* **2005**, *13*, 5154–5158.

(87) Vanden Eynden, M. J.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 5289–5291.

(88) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.

(89) Wee, A. G. H.; Yu, Q. *J. Org. Chem.* **2001**, *66*, 8935–8943.

(90) Herlé, B.; Wanner, M. J.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2011**, *76*, 8907–8912.

(91) Sewgobind, N. V; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405–6408.

(92) Mizuno, T.; Oonishi, Y.; Takimoto, M.; Sato, Y. *European J. Org. Chem.* **2011**, *2011*, 2606–2609.

(93) Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513–6556.

(94) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734.

(95) Overhand, M.; Hecht, S. M. *J. Org. Chem.* **1994**, *59*, 4721–4722.

(96) Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc. Chem. Commun.* **1977**, 233.

(97) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc. Chem. Commun.* **1976**, 736.

(98) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334.

(99) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5335–5340.

(100) Knight, D. W.; Redfern, A. L.; Gilmore, J. *Tetrahedron Lett.* **1998**, *39*, 8909–8910.

(101) Knight, D. W.; Redfern, A. L.; Gilmore, J. *Synlett* **1998**, *1998*, 731–732.

(102) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846–3852.

(103) Hultzsch, K. C. *Org. Biomol. Chem.* **2005**, *3*, 1819–1824.

(104) Johns, A. M.; Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9306–9307.

(105) Koller, J.; Bergman, R. G. *Organometallics* **2010**, *29*, 5946–5952.

(106) Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262–1284.

(107) Baeckvall, J. E. *Acc. Chem. Res.* **1983**, *16*, 335–342.

(108) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798–1799.

(109) Komeyama, K.; Kouya, Y.; Ohama, Y.; Takaki, K. *Chem. Commun.* **2011**, *47*, 5031–5033.

(110) Pawlikowski, A. V; Ellern, A.; Sadow, A. D. *Inorg. Chem.* **2009**, *48*, 8020–8029.

(111) Sarma, R.; Prajapati, D. *Chem. Commun.*. **2011**, *47*, 9525–9527.

(112) Hong, S.; Kawaoka, A. M.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 15878–15892.

(113) Manna, K.; Kruse, M. L.; Sadow, A. D. *ACS Catal.* **2011**, *1*, 1637–1642.

(114) Zhang, Y.; Yao, W.; Li, H.; Mu, Y. *Organometallics* **2012**, *31*, 4670–4679.

(115) Nixon, T. D.; Ward, B. D. *Chem. Commun.*. **2012**, *48*, 11790–11792.

(116) Gasc, M. B.; Lattes, A.; Perie, J. J. *Tetrahedron* **1983**, *39*, 703–731.

(117) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–704.

(118) Beck, J. F.; Samblanet, D. C.; Schmidt, J. A. R. *RSC Adv.* **2013**, *3*, 20708.

(119) Cooke, M. L.; Xu, K.; Breit, B. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 10876–10879.

(120) Brown, A. R.; Uyeda, C.; Brotherton, C. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 6747–6749.

(121) Subramanian, L. R.; Martínez, A. G.; Hanack, M.; Surya Prakash, G. K.; Hu, J. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd, 2001.

(122) Howells, R. D.; Mc Cown, J. D. *Chem. Rev.* **1977**, *77*, 69–92.

(123) Raamat, E.; Kaupmees, K.; Ovsjannikov, G.; Trummal, A.; Kütt, A.; Saame, J.; Koppel, I.; Kaljurand, I.; Lipping, L.; Rodima, T.; Pihl, V.; Koppel, I. A.; Leito, I. *J. Phys. Org. Chem.* **2013**, *26*, 162–170.

(124) Kamber, N. E.; Jeong, W.; Waymouth, R. M.; Pratt, R. C.; Lohmeijer, B. G. G.; Hedrick, J. L. *Chem. Rev.* **2007**, *107*, 5813–5840.

(125) Sawamoto, M.; Masuda, T.; Nishii, H.; Higashimura, T. *J. Polym. Sci. Polym. Lett. Ed.* **1975**, *13*, 279–282.

(126) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758.

(127) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2014**, *114*, 7317–7420.

(128) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471–1474.

(129) El-Taeb, G. M. M.; Evans, A. B.; Jones, S.; Knight, D. W. *Tetrahedron Lett.* **2001**, *42*, 5945–5948.

(130) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2006**, *47*, 2825–2828.

(131) Griffiths-Jones (née Haskins), C. M.; Knight, D. W. *Tetrahedron* **2010**, *66*, 4150–4166.

(132) Haskins, C. M.; Knight, D. W. *Chem. Commun.* **2002**, 2724–2725.

(133) Henderson, L.; Knight, D.; Williams, A. *Synlett* **2012**, *23*, 1667–1669.

(134) Haskins, C. M.; Knight, D. W. *Chem. Commun.*. **2005**, 3162–3164.

(135) Henderson, L.; Knight, D. W.; Williams, A. C. *Tetrahedron Lett.* **2012**, *53*, 4657–4660.

(136) Watanabe, H.; Uramoto, H.; Maeda-Hagiwara, M.; Kikuchi, T. *Arch. Int. Pharmacodyn. Thérapie* **1985**, *278*, 53–60.

(137) Surh, Y.-J.; Kim, H.-J. *Exp. Neurobiol.* **2010**, *19*, 63–70.

(138) Le, V. H.; Inai, M.; Williams, R. M.; Kan, T. *Nat. Prod. Rep.* **2014**.

(139) Michel, M. C.; Wetterauer, U.; Vogel, M.; de la Rosette, J. J. M. C. H. *Drug Saf.* **2008**, *31*, 505–514.

(140) Pelman, R. S.; Capo, J. P.; Forero-Schwanhaeuser, S. *Postgrad. Med.* **2008**, *120*, 85–91.

(141) Cioffi, A.; Italiano, A. *Expert Opin. Drug Metab. Toxicol.* **2012**, *8*, 113–122.

(142) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203.

(143) Shahzad, S. a; Wirth, T. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 2588–2591.

(144) Burk, M. J.; Lee, J. R.; Martinez, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 10847–10848.

(145) Cesati, R. R.; de Armas, J.; Hoveyda, A. H. *Org. Lett.* **2002**, *4*, 395–398.

(146) Dermer, O. C.; Ham, G. E. *Ethylenimine and Other Aziridines*; Elsevier, 1969; pp. 394–443.

(147) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258.

(148) Pellissier, H. *Tetrahedron* **2010**, *66*, 1509–1555.

(149) Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881–7929.

(150) Kozikowski, A. P.; Ishida, H.; Isobe, K. *J. Org. Chem.* **1979**, *44*, 2788–2790.

(151) Baldwin, J. E.; Spivey, A. C.; Schofield, C. J.; Sweeney, J. B. *Tetrahedron* **1993**, *49*, 6309–6330.

(152) Dunne, E. C.; Coyne, É. J.; Crowley, P. B.; Gilheany, D. G. *Tetrahedron Lett.* **2002**, *43*, 2449–2453.

(153) Berry, M. B.; Craig, D. *Synlett* **1992**, *1992*, 41–44.

(154) Vicario, J.; Badia, D.; Carrillo, L. *ARKIVOC* **2007**, *2007*, 304–311.

(155) Compain, P.; Goré, J.; Vatèle, J.-M. *Tetrahedron* **1996**, *52*, 10405–10416.

(156) Ye, W.; Leow, D.; Goh, S. L. M.; Tan, C.-T.; Chian, C.-H.; Tan, C.-H. *Tetrahedron Lett.* **2006**, *47*, 1007–1010.

(157) Daub, G. W.; Heerding, D. A.; Overman, L. E. *Tetrahedron* **1988**, *44*, 3919–3930.

(158) Marzorati, L.; Barazzone, G. C.; Bueno Filho, M. A.; Wladislaw, B.; Di Vitta, C. *Tetrahedron Lett.* **2007**, *48*, 6509–6513.

(159) Cunha, R. L. O. R.; Diego, D. G.; Simonelli, F.; Comasseto, J. V. *Tetrahedron Lett.* **2005**, *46*, 2539–2542.

(160) Fitremann, J.; Duréault, A.; Depezay, J.-C. *Tetrahedron Lett.* **1994**, *35*, 1201–1204.

(161) Akiyama, T.; Ishida, Y.; Kagoshima, H. *Tetrahedron Lett.* **1999**, *40*, 4219–4222.

(162) Nenajdenko, V. G.; Karpov, A. S.; Balenkova, E. S. *Tetrahedron: Asymmetry* **2001**, *12*, 2517–2527.

(163) Personal communications with Dr. J. Platts, Cardiff University.

(164) Brooner, R. E. M.; Widenhoefer, R. A. *Chem. Eur. J.* **2011**, *17*, 6170–6178.

(165) Hoye, T. R.; Hanson, P. R.; Vyvyan, J. R. *J. Org. Chem.* **1994**, *59*, 4096–4103.

(166) Hoye, T. R.; Zhao, H. *J. Org. Chem.* **2002**, *67*, 4014–4016.

(167) Ungemach, F.; Soerens, D.; Weber, R.; DiPierro, M.; Campos, O.; Mokry, P.; Cook, J. M.; Silverton, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6976–6984.

(168) Veitía, M. S.-I.; Brun, P. L.; Jorda, P.; Falguières, A.; Ferroud, C. *Tetrahedron: Asymmetry* **2009**, *20*, 2077–2089.

(169) Cantrill, A. A.; Osborn, H. M. I.; Sweeney, J. B. *Tetrahedron* **1998**, *54*, 2181–2208.

(170) Shen, L.; Yang, X.; Yang, B.; He, Q.; Hu, Y. *Eur. J. Med. Chem.* **2010**, *45*, 11–18.

(171) Smith, R. A.; White, R. L.; Krantz, A. *J. Med. Chem.* **1988**, *31*, 1558–1566.

(172) Collins, M.; Salouros, H.; Cawley, A. T.; Robertson, J.; Heagney, A. C.; Arenas-Queralt, A. *Rapid Commun. Mass Spectrom.* **2010**, *24*, 1653–1658.

(173) Kabalka, G. W.; Varma, R. S.; Gai, Y.-Z.; Baldwin, R. M. *Tetrahedron Lett.* **1986**, *27*, 3843–3844.

(174) Kabalka, G. W.; Laila, G. M. H.; Varma, R. S. *Tetrahedron* **1990**, *46*, 7443–7457.

(175) Fileti, E. E.; Chaban, V. V.; Prezhdo, O. V. *J. Phys. Chem. Lett.* **2014**, *5*, 3415–3420.

(176) Bauer, W.H.; Wiberley, S. E., *Borax to Boranes*; Advances in Chemistry; American Chemical Society: Washington, D.C., 1961; Vol. 32, pp. 115–126.

(177) Anderson, N. G. *Practical Process Research and Development – A Guide for Organic Chemists*; Academic Press, 2012; p. 488.

(178) Henderson, L.; Knight, D. W.; Rutkowski, P.; Williams, A. C. *Tetrahedron Lett.* **2012**, *53*, 4654–4656.

(179) Birkholz, M.-N.; Freixa, Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009**, *38*, 1099–1118.

(180) Manske, R. H. F.; Holmes, H. L. *The Alkaloids: Chemistry and Physiology V4: Chemistry and Physiology, Volume 4*; Academic Press, 1965; p. 356.

(181) Weber, M.; Breier, M.; Ko, D.; Thangaraj, N.; Marzan, D. E.; Swerdlow, N. R. *Psychopharmacology (Berl).* **2009**, *203*, 723–735.

(182) Cornforth, R. H.; Cornforth, J. W.; Popják, G. *Tetrahedron* **1962**, *18*, 1351–1354.

(183) Carme Pampín, M.; Estévez, J. C.; Estévez, R. J.; Maestro, M.; Castedo, L. *Tetrahedron* **2003**, *59*, 7231–7243.

(184) Williard, P. G.; Salvino, J. M. *J. Org. Chem.* **1993**, *58*, 1–3.

(185) *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd: Chichester, UK, 2001.

(186) Gu, P.; Kang, X.-Y.; Sun, J.; Wang, B.-J.; Yi, M.; Li, X.-Q.; Xue, P.; Li, R. *Org. Lett.* **2012**, *14*, 5796–5799.

(187) Lim, C.-K.; Kim, S.; Kwon, I. C.; Ahn, C.-H.; Park, S. Y. *Chem. Mater.* **2009**, *21*, 5819–5825.

(188) Zhao, Y.-M.; Gu, P.; Tu, Y.-Q.; Zhang, H.-J.; Zhang, Q.-W.; Fan, C.-A. *J. Org. Chem.* **2010**, *75*, 5289–5295.

(189) Sen, S. E.; Roach, S. L.; Boggs, J. K.; Ewing, G. J.; Magrath, J. *J. Org. Chem.* **1997**, *62*, 6684–6686.

(190) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700–3701.

(191) Ivanovska, N.; Hristova, M.; Philipov, S. *Int. J. Immunopharmacol.* **1999**, *21*, 337–347.

(192) Banning, J. W.; Salman, K. N.; Patil, P. N. *J. Nat. Prod.* **1982**, *45*, 168–177.

(193) Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Am. Chem. Soc.* **2004**, *126*, 187–193.

(194) Allin, S. M.; Gaskell, S. N.; Towler, J. M. R.; Page, P. C. B.; Saha, B.; McKenzie, M. J.; Martin, W. P. *J. Org. Chem.* **2007**, *72*, 8972–8975.

(195) Mastranzo, V. M.; Yuste, F.; Ortiz, B.; Sánchez-Obregón, R.; Toscano, R. A.; García Ruano, J. L. *J. Org. Chem.* **2011**, *76*, 5036–5041.

(196) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559.

(197) Kanemitsu, T.; Yamashita, Y.; Nagata, K.; Itoh, T. *Synlett* **2006**, 1595–1597.

(198) Wang, S.; Seto, C. T. *Org. Lett.* **2006**, *8*, 3979–3982.

(199) Mujahidin, D.; Doye, S. *European J. Org. Chem.* **2005**, *2005*, 2689–2693.

(200) Bracca, A. B. J.; Kaufman, T. S. *Tetrahedron* **2004**, *60*, 10575–10610.

(201) Ponzo, V. U.; Kaufman, T. S. *Tetrahedron Lett.* **1995**, *36*, 9105–9108.

(202) Dong, J.; Shi, X.-X.; Yan, J.-J.; Xing, J.; Zhang, Q.; Xiao, S. *European J. Org. Chem.* **2010**, *2010*, 6987–6992.

(203) Barbier, A. M.; Rumpf, P. *Bull. Soc. Chim. Fr.* **1953**, 293.

(204) Cheng, P.; Huang, N.; Jiang, Z.-Y.; Zhang, Q.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2475–2478.

(205) Berhal, F.; Wu, Z.; Zhang, Z.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2012**, *14*, 3308–3311.

(206) Hanna, J. N.; Ntie-Kang, F.; Kaiser, M.; Brun, R.; Efange, S. M. N. *RSC Adv.* **2014**, *4*, 22856.

(207) Morteza-Semnani, K.; Amin, G.; Shidfar, M. R.; Hadizadeh, H.; Shafiee, A. *Fitoterapia* **2003**, *74*, 493–496.

(208) Cortijo, J.; Villagrasa, V.; Pons, R.; Berto, L.; Martí-Cabrera, M.; Martinez-Losa, M.; Domenech, T.; Beleta, J.; Morcillo, E. J. *Br. J. Pharmacol.* **1999**, *127*, 1641–1651.

(209) Bhattacharya, S. K.; Bose, R.; Ghosh, P.; Tripathi, V. J.; Kay, A. B.; Dasgupta, B. *Psychopharmacology (Berl).* **1978**, *59*, 29–33.

(210) Gomberg, M.; Bachmann, W. E. *J. Am. Chem. Soc.* **1924**, *46*, 2339–2343.

(211) Cuny, G. D. *Tetrahedron Lett.* **2004**, *45*, 5167–5170.

(212) Zhao, Y.; Yan, D.; Wang, J.; Zhang, P.; Xiao, X. *J. Therm. Anal. Calorim.* **2009**, *102*, 49–55.

(213) Kuo, C.-L.; Chi, C.-W.; Liu, T.-Y. *Cancer Lett.* **2004**, *203*, 127–137.

(214) Tang, J.; Feng, Y.; Tsao, S.; Wang, N.; Curtain, R.; Wang, Y. *J. Ethnopharmacol.* **2009**, *126*, 5–17.

(215) Sun, Y.; Xun, K.; Wang, Y.; Chen, X. *Anticancer. Drugs* **2009**, *20*, 757–769.

(216) Zhou, L.; Yang, Y.; Wang, X.; Liu, S.; Shang, W.; Yuan, G.; Li, F.; Tang, J.; Chen, M.; Chen, J. *Metabolism.* **2007**, *56*, 405–412.

(217) Zhang, Y.; Li, X.; Zou, D.; Liu, W.; Yang, J.; Zhu, N.; Huo, L.; Wang, M.; Hong, J.; Wu, P.; Ren, G.; Ning, G. *J. Clin. Endocrinol. Metab.* **2013**.

(218) Zimmerman, H. E.; Kamath, A. P. *J. Am. Chem. Soc.* **1988**, *110*, 900–911.

(219) Rinehart, K. L.; Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Mascal, M.; Holt, T. G.; Shield, L. S.; Lafargue, F. *J. Am. Chem. Soc.* **1987**, *109*, 3378–3387.

(220) Weiberth, F. J.; Hall, S. S. *J. Org. Chem.* **1987**, *52*, 3901–3904.

(221) *Unpubl. results.*

(222) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; Butterworth Heinemann, 1997; p. 529.

(223) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(224) Harrowven, D. C.; Pascoe, D. D.; Guy, I. L. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 425–428.

(225) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; 1967; pp. 581–595.

(226) D'hooghe, M.; Kerkaert, I.; Rottiers, M.; De Kimpe, N. *Tetrahedron* **2004**, *60*, 3637–3641.

(227) Minakata, S.; Hotta, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2006**, *71*, 7471–7472.

(228) Barbasiewicz, M.; Michalak, M.; Grela, K. *Chemistry* **2012**, *18*, 14237–14241.

(229) Morrow, G. W.; Marks, T. M.; Sear, D. L. *Tetrahedron* **1995**, *51*, 10115–10124.

(230) Lin, M.-Y.; Das, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 9340–9341.

(231) Hopf, H.; Hucker, J.; Ernst, L. *European J. Org. Chem.* **2007**, *2007*, 1891–1904.

(232) Amsharov, K. Y.; Kabdulov, M. a.; Jansen, M. *European J. Org. Chem.* **2009**, 6328–6335.

(233) Qi, W.-Y.; Zhu, T.-S.; Xu, M.-H. *Org. Lett.* **2011**, *13*, 3410–3413.

(234) Shahzad, S. A.; Vivant, C.; Wirth, T. *Org. Lett.* **2010**, *12*, 1364–1367.

(235) Sawoo, S.; Srimani, D.; Dutta, P.; Lahiri, R.; Sarkar, A. *Tetrahedron* **2009**, *65*, 4367–4374.

(236) Rucker, M.; Brückner, R. *Tetrahedron Lett.* **1997**, *38*, 7353–7356.

(237) Tsuchida, S.; Kaneshige, A.; Ogata, T.; Baba, H.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3635–3638.

(238) Smith, P. A. S.; Budde, G. F.; Chou, S. S. P. *J. Org. Chem.* **1985**, *50*, 2062–2066.

(239) Izmer, V. V.; Lebedev, A. Y.; Nikulin, M. V.; Ryabov, A. N.; Asachenko, A. F.; Lygin, A. V.; Sorokin, D. A.; Voskoboynikov, A. Z. *Organometallics* **2006**, *25*, 1217–1229.

(240) Dai, Y.; Feng, X.; Liu, H.; Jiang, H.; Bao, M. *J. Org. Chem.* **2011**, *76*, 10068–10077.

(241) Pedrosa, R.; Andrés, C.; Iglesias, J. M. *J. Org. Chem.* **2001**, *66*, 243–250.

(242) Tummatorn, J.; Dudley, G. B. *Org. Lett.* **2011**, *13*, 1572–1575.

(243) Olivera, R.; SanMartin, R.; Domínguez, E.; Solans, X.; Urtiaga, M. K.; Arriortua, M. I. *J. Org. Chem.* **2000**, *65*, 6398–6411.

(244) Ueda, M.; Kawai, S.; Hayashi, M.; Naito, T.; Miyata, O. *J. Org. Chem.* **2010**, *75*, 914–921.

(245) Chandrasekhar, S.; Chandrashekar, G.; Reddy, M. S.; Srihari, P. *Org. Biomol. Chem.* **2006**, *4*, 1650–1652.

(246) Harada, R.; Nishida, N.; Uchiito, S.; Onozaki, Y.; Kurono, N.; Senboku, H.; Masao, T.; Ohkuma, T.; Orito, K. *European J. Org. Chem.* **2012**, *2012*, 366–379.

(247) Ito, K.; Tanaka, H.; Kayama, M. *Chem. Pharm. Bull.*. **1977**, *25*, 1249–1255.

(248) Milhazes, N.; Calheiros, R.; Marques, M. P. M.; Garrido, J.; Cordeiro, M. N. D. S.; Rodrigues, C.; Quinteira, S.; Novais, C.; Peixe, L.; Borges, F. *Bioorg. Med. Chem.* **2006**, *14*, 4078–4088.

(249) Ide, W. S.; Buck, J. S. *J. Am. Chem. Soc.* **1940**, *62*, 425–428.

(250) Kinderman, S. S.; Wekking, M. M. T.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 5519–5527.

(251) Charlton, J. L.; Alauddin, M. M. *J. Org. Chem.* **1986**, *51*, 3490–3493.

(252) Moody, C. J.; Warrellow, G. J. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2929.

(253) Barn, D. R.; Caulfield, W. L.; Cottney, J.; McGurk, K.; Morphy, J. R.; Rankovic, Z.; Roberts, B. *Bioorg. Med. Chem.* **2001**, *9*, 2609–2624.

(254) Maryanoff, B. E.; Reitz, A. B.; Duhl-Emswiler, B. A. *J. Am. Chem. Soc.* **1985**, *107*, 217–226.

(255) Riala, M.; Chronakis, N. *J. Org. Chem.* **2013**, *78*, 7701–7713.

(256) Chakravarti, S. N.; Haworth, R. D.; Perkin, W. H. *J. Chem. Soc.* **1927**, 2275.

Chapter 6: Appendix.

6.1 Publications

- Henderson, L.; Knight, D. W.; Rutkowski, P.; Williams, A. C. *Tetrahedron Lett.* **2012**, *53*, 4654–4656.