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# Investigations into the use of Ring Closing Metathesis to form 5-, 6-, 7- and 8-membered benzo-fused heterocylces

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# *Investigations into the use of Ring Closing Metathesis to form 5-, 6-, 7- and 8-membered benzo-fused heterocycles*

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*Supervised by Dr W.A.L. van Otterlo*
*Co-supervised by Prof C.B. de Koning*

*A dissertation submitted to the Faculty of Science, University of the Witwatersrand, in fulfillment of the requirements for the Degree of Master of Science*

*December 2005*

## *Declaration*

I declare that the work presented in this dissertation is my own, unaided work and was carried out under the supervision of Dr W.A.L. van Otterlo and Prof C.B. de Koning. It is being submitted for the Degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University.

_____

Jenny-Lee Panayides

December 2005

## *Abstract*

The first part of the dissertation involves the use of ring closing metathesis (RCM) and ruthenium mediated isomerisation-RCM tandem reactions to form a wide range of nitrogen-containing benzo-fused heterocycles. Those synthesized include the 6-membered isoquinolines, the 7-membered benzazepines and the 8-membered benzazocines. In order to put these compounds into perspective, a review of selected naturally occurring nitrogen-containing benzo-fused heterocycles is included along with some of their synthetic approaches. Of major significance is our utilization of the Wits methodology allowing one to access the 6-, 7- and 8-membered ring systems from a common synthetic intermediate. The 1,2,3,6-tetrahydro-2-benzazocines were all obtained after RCM in excellent yields (82-99%). We were also able to show that some ofthe protecting groups used were easily removed and that the ring could be hydrogenated after RCM to yield the 1,2,3,4,5,6-hexahydro-2-benzazocines. The isoquinolines were synthesized in 78% and 27% yield for the Ac- and Ts-protected compounds respectively, with no product isolated for the Boc- or $SO_2$Bn-protected compounds. These poor results, caused a change to our strategy and we then used a "combinatorial-type" approach for the synthesis of the 2,5-dihydro-1*H*-2-benzazepines and the 2,3-dihydro-1*H*-2-benzazepines with yield of 9, 47, 58 and 82% and 8, 26, 39 and 82% obtained respectively for the RCM reaction Futhermore, we attempted the synthesis of the substituted 4-phenyl isoquinolines and 5-phenyl benzazepines, but we found that the systems would not undergo RCM even at high temperatures and with large amounts of Grubbs II metathesis catalyst.

A short review is given in the second part of the dissertation concerning the naturally occurring and pharmaceutically useful indenols, indenones and indanones. It further highlights how our methodology was extended to include the synthesis of 4-isopropoxy-5-methoxy-1H-inden-1-ol (**X**), 4-isopropoxy-5-methoxy-1H-inden-1-one (**X**) and 4-isopropoxy-5-methoxy-1H-indanone (**X**) through the use of ruthenium-mediated isomerisation and RCM from a similar common intermediate. We have shown the synthesis of 3-substituted indenols, indenones and indanones using the same synthetic procedure, but by changing the reaction temperature during RCM. This dissertation also answers many of the questions posed during the post-doctoral work of Coyanis. Namely, we were able to support our proposed mechanism that the conversion of the unsubstituted indenol to the indenone was occurring via a

dehydrogenative-oxidation, through the use of $^{1}$H NMR studies that were coupled with an ICP-MS analysis. To the best of our knowledge, this is the first reported use of the Grubbs II catalyst (or its degradation products) in a tandem RCM-oxidation procedure by our group recently.

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*Of All The Things I Have Lost,*

*I Miss My Mind The Most…*

*~ Ozzy Osbourne ~*

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## *List of Abbreviations*

| | |
|---|---|
| AD | Alzheimer's disease |
| ADMET | acyclic diene metathesis polymerisation |
| $Boc_2O$ | di-*tert*-butyl-dicarbonate |
| CM | cross metathesis |
| CNS | central nervous system |
| Cox | cyclooxogenase enzyme |
| 3CP | 3C protease |
| DEAD | Diethyl azocarboxylate |
| DMAP | 4-(dimethylamino)pyridine |
| DMF | *N,N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| DNA | deoxyribonucleic acid |
| DNPH | 2.4-dinitrophenylhydrazine |
| ECA | ethacrynic acid |
| FGFr | fibroblast growth factor receptor |
| FTIR | Fourier Transform Infrared |
| Grubbs II catalyst | Grubbs catalyst $2^{nd}$ generation |
| HIV | human immunodeficiency virus |
| HMPA | hexamethyl phosphoric triamide |
| HRMS | high-resolution mass spectrometry |
| HRV | human rhinoviruses |
| ICP-MS | inductively coupled plasma mass spectrometry |
| IR | infrared |
| KHMDS | potassium hexamethyldisilazide |
| LHMDS | lithium hexamethyldisilazide |
| Leu | leucine |
| NHC | *N*-heterocyclic carbene |
| NMDA | *N*-methyl *D*-aspartate |
| NMR | nuclear magnetic resonance |
| NSAIDs | non-steroidal anti-inflammatory drugs |
| $Pd_2(dba)_3$ | tris(dibenzylideneacetone)dipalladium(0) |

| | |
|---|---|
| PDGFr | platelet derived growth factor receptor kinase |
| $Pd(PPh_3)_2$ | bis(triphenylphosphine)palladium(II) |
| *p*-TsOH | *p*-toluenesulfonic acid |
| RCM | ring closing metathesis |
| ROM | ring opening metathesis |
| ROMP | ring-opening metathesis polymerisation |
| rt | room temperature |
| Ru-isomerisation catalyst | carbonylchlorohydridotris(triphenylphosphine)-ruthenium (II) |
| TBS ether | tributylsilyl ether |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TK | tyrosine kinase |
| TLC | thin layer chromatography |
| top I | topoisomerase I |
| tosyl chloride | toluene-4-sulfonyl-chloride |
| Wits | University of the Witwatersrand |

# *Chapter 1:*

# *General Introduction and Literature Review*

# *Chapter 1: General Introduction and Literature Review*

## 1. General Explanation and Project Overview

Polyaromatic and heteroaromatic compounds, for instance, naphthalenes, isoquinolines, 4*H*- and 2*H*-chromenes, benzo[1,4]dioxins, benzo[*b*]furans and indenols are important structural motifs common to both natural products and a wide range of pharmaceuticals. They display a variety of biological activities, ranging from anti-microbials (such as anti-malarials) to anti-virals (such as anti-HIV drugs). These properties make them exciting targets for synthetic chemists, with consequently a wide range of syntheses reported, many of which are based on classical organic chemistry. However, these often have a number of drawbacks, including cost, scalability, low yields and problematic purifications. Thus, as part of our research program, a methodology study was undertaken by our research group to develop new reliable methods for the synthesis of these biological motifs, based on the use of ring closing metathesis (RCM) as the key step.[1-5]

Recent publications from our laboratories have shown that a ruthenium-mediated allyl isomerisation to the corresponding styrene and/or enol ether, complemented by ruthenium-mediated RCM can lead to a variety of ring systems, starting from the same precursor.[2,3,5] A large amount of the methodology developed in our laboratories that is related to this field has been in the formation of oxygen-containing benzo-fused heterocycles, with very little work done on the synthesis of the nitrogen-containing benzo-fused systems. The first part of this dissertation deals with an extension of our previously developed methodology to include the synthesis of a wide range of 6-, 7- and 8-membered nitrogen-containing benzo-fused heterocycles, employing both ruthenium-mediated allyl isomerisations and RCM.

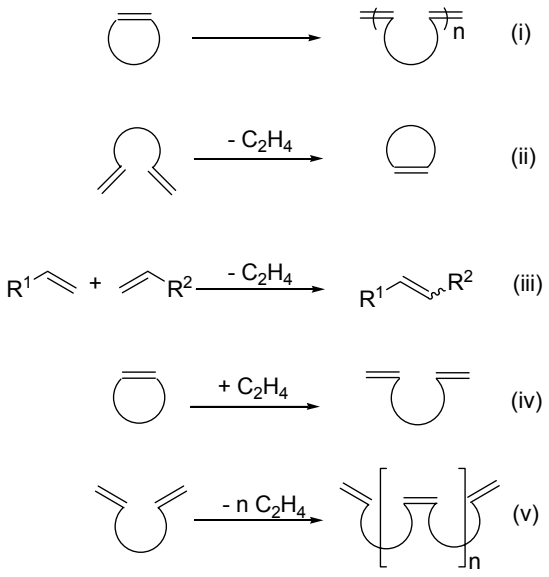
Various methods for the synthesis of indenols and indenones are also reported in the literature. The second part of this dissertation deals with the synthesis of a number of indenols, indenones and indanones utilizing similar isomerisation-RCM methodology to form these 5-membered ring systems. This section of the dissertation exploits the "non-metathetic behaviour"[6,7] of Grubbs second generation catalyst to synthesize indenones and indanones from indenols, via the tandem RCM-dehydrogenative oxidation reaction.[8]

## 2. Ring Closing Metathesis using Transition Metal Catalysts

Transition metals are becoming increasingly important in modern organic synthesis, often playing pivotal roles in the total synthesis of many natural products.[9] Of key importance in these syntheses is the efficient formation of the C=C bond and one of the most widespread and efficient ways of achieving this is through the use of olefin metathesis. It has become so important that Grubbs, Schrock and Chauvin received the Nobel Prize in Chemistry (2005) based on their contributions to this ever-expanding field.

Olefin metathesis is defined as a unique carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged in the presence of metal carbene complexes.[10,11] With the advent of efficient catalysts, olefin metathesis is quickly emerging as one of the most powerful strategies for carbon-carbon bond formation. The number of applications of this reaction has dramatically increased in the past few years. Of particular significance, this type of metathesis utilizes no additional reagents beyond a catalytic amount of metal carbene and the only other product from the reaction is, in most cases, a volatile olefin such as ethylene. RCM reactions are often simple, high yielding and friendly to the environment.[12]

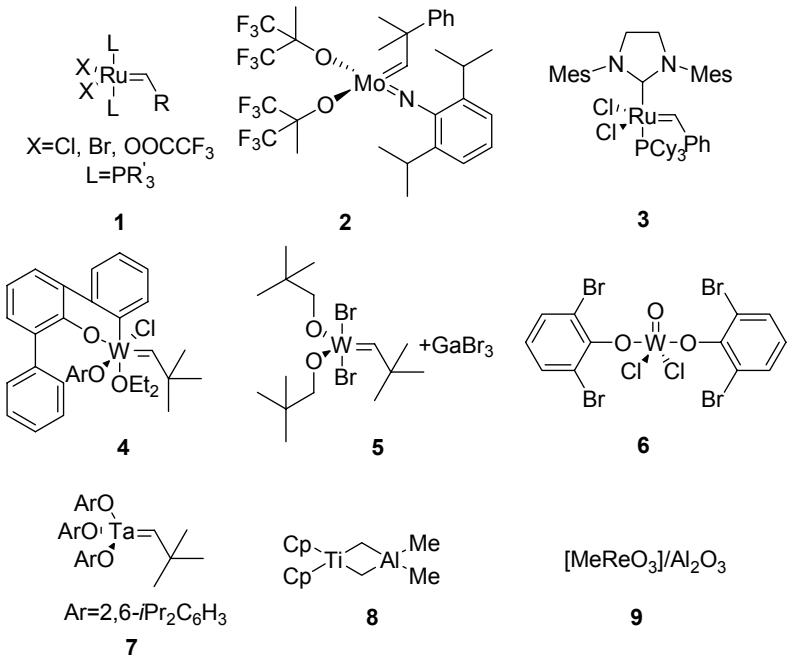
Olefin metathesis can be utilized in several closely related reaction types as outlined in **Scheme 1**: (i) ring-opening metathesis polymerization (ROMP), (ii) ring-closing metathesis (RCM), (iii) cross metathesis (CM), (iv) ring-opening metathesis (ROM) and (v) acyclic diene metathesis polymerisation (ADMET).[13-16] The major thrust of this dissertation deals with the application of ring closing metathesis to the synthesis of small benzo-fused molecules.




**Scheme 1** Different forms of olefin metathesis[13-16]

RCM has received a great deal of attention for the synthesis of medium or large sized rings from acyclic diene precursors. This intensive study is primarily due to the development of well-defined metathesis catalysts, which are tolerant to many functional groups, as well as reactive towards a diverse range of substrates.[12]

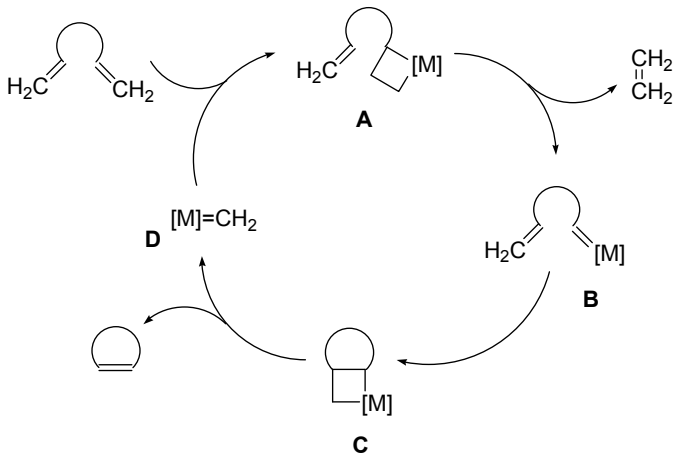
The disclosure by Grubbs that ruthenium carbene complexes of the general type **1 (Scheme 2)** are highly active single component catalysts for all types of alkene metathesis reactions denoted a real breakthrough and triggered an avalanche of interest in this transformation.[17-19] Their activity is usually lower than that of the other classical carbene, Schrock's molybdenum alkylidene **2**; however the "late" transition metal compounds of Grubbs show tolerance towards a wide array of functional groups and exhibit ease of handling as a result of reasonable stability against oxygen, water and minor impurities in solvents. This renders them as exceedingly practical tools for RCM type reactions.[20] **Scheme 2** displays a range of other catalysts and pre-catalysts that have also been shown to have metathetic capabilities.




**Scheme 2** Some typical metathesis catalysts and precatalysts[20]

The mechanism of RCM has been the subject of debate for several years and it was Chauvin, in 1971, who first proposed what is now the commonly accepted mechanism for this reaction.[13] It involves a sequence of formal [2+2] cycloadditions/cycloreversions, a series of alkene metal carbenes and metallacyclobutane intermediates such as those depicted in **Scheme 3**.[13,21]

However, it is important to note that this process is reversible. The forward reaction is entropically driven since it "cuts" one substrate into two products. However, the desired cycloalkene accumulates in the reaction mixture as one of the components is volatile (eg: ethene or propene), and hence, readily removed.[22]




**Scheme 3** Basic catalytic cycle of ring closing metathesis[13,21]

Grubbs introduced the first metathesis catalyst of the general formula $[(PR_3)_2X_2Ru{=}CHR]$, with the most prominent example of the first generation compounds being catalyst **10** (**Figure 1**). The replacement of one trialkylphosphane ligand by a *N*-heterocyclic carbene (NHC) has led to the new class of metathesis catalysts with the general formula $[(PR_3)(NHC)X_2RuCHR]$, which are even more active than the original complexes. The most representative of these second generation compounds is catalyst **11**.

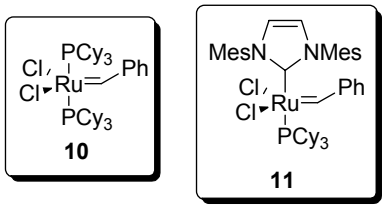
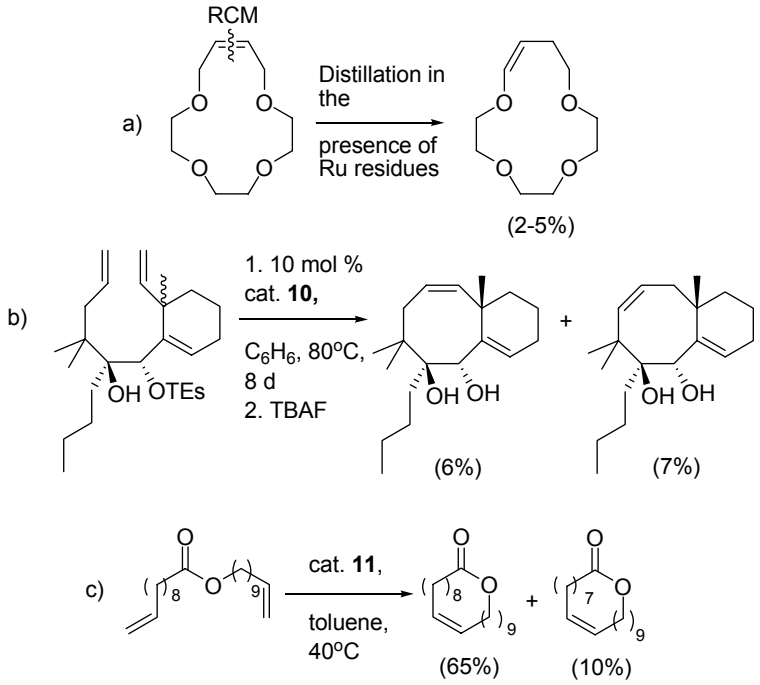



**Figure 1** Grubbs Metathesis Catalysts

## 3. Ruthenium Mediated Isomerisations

Several reports published over the last few years indicate that decomposition products of these ruthenium metathesis catalysts might be responsible for undesired side reactions, especially alkene isomerisation. Examples have been reported of an isomerisation subsequent to the metathesis step by Prunet and co-workers[23] (**Scheme 4a**) and Taylor and co-workers[24] (**Scheme 4b**), and prior to RCM by Fürstner *et al.*[25] (**Scheme 4c**).

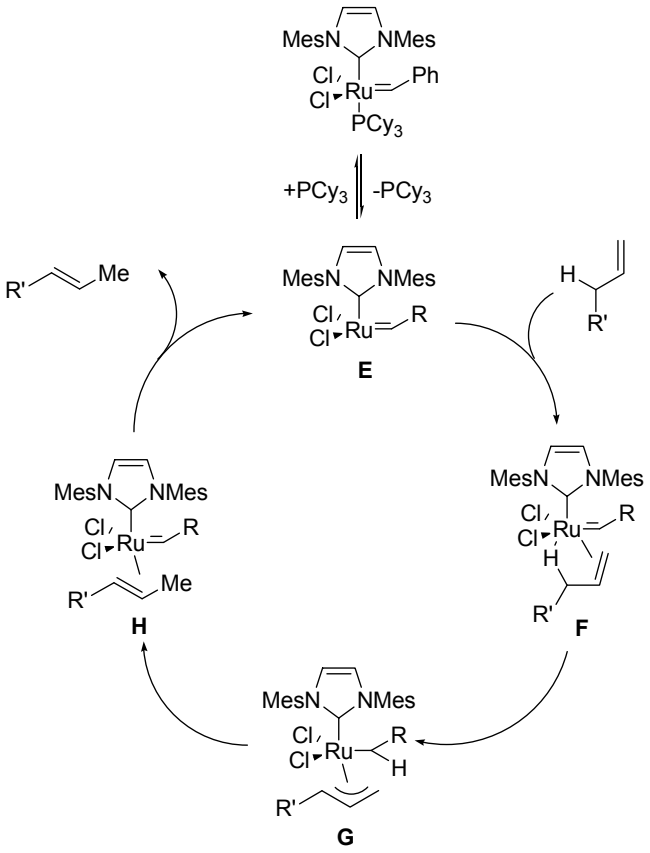



**Scheme 4** Examples of isomerisation reactions interfering with olefin metathesis[23-25]

It was stated, by Fürstner, that ruthenium hydride complexes are formed as by-products in some cases during the preparation of the second-generation metathesis catalysts.[26] If these are present as an impurity in the metathesis catalyst, they might be responsible for the observed isomerisation reactions. Alternatively, a ruthenium hydride species might be formed by decomposition of the ruthenium carbene species under the reaction conditions.[6]

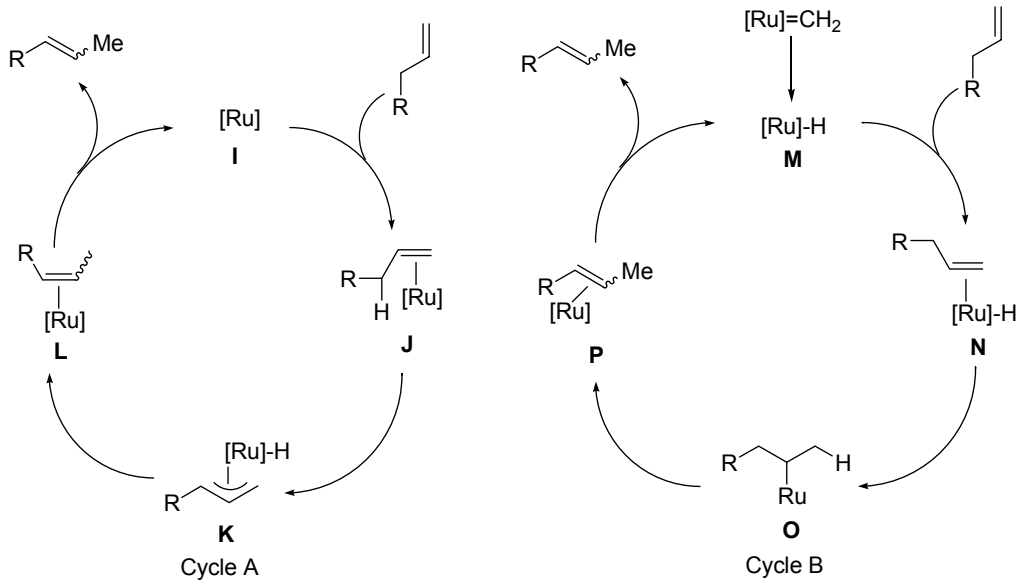
*3.1 Proposed Isomerization Mechanisms*

Other proposals have however been put forward to explain the formation of products resulting from double bond isomerisation. Nolan and co-workers[27] have investigated the competition of RCM and double bond isomerisation in some detail. Based on their experimental observations for an unsubstituted model system, the authors proposed a mechanism for the isomerisation process (**Scheme 5**) that involves coordination of the alkene to the 14-electron fragment **E** (from Grubbs second generation precatalyst). In the resulting π complex, **F**, an agostic interaction might facilitate deprotonation at the allylic position leading to a σ-alkyl/π-allyl complex **G**, which reacts to give the carbene complex **H**. Dissociation of the isomerised alkene regenerates the catalytically active species **E**.[6,27]




**Scheme 5** Proposed mechanism for alkene isomerisations via π-allyl complexes[6]

This mechanism is a modification of the π-allyl hydride mechanism (**Scheme 6**, cycle A), which is one of the two commonly proposed mechanisms for olefin isomerisation.[28] In the π-allyl hydride mechanism, an intermediate **K** is assumed to form that results from migration of the hydride from the allylic position of the alkene substrate to the metal centre. Reductive elimination gives the $\eta^2$ complex **L**, from which the substrate dissociates to regenerate the catalytically active species **I**. The second mechanism (**Scheme 6**, cycle B) is believed to occur via a hydrometalation/β-hydride elimination sequence, which requires the presence of a coordinatively unsaturated ruthenium hydride species **M**. Coordination of the alkene gives the π complex **N**, which undergoes a migratory insertion (hydrometalation) to give the σ-alkyl complex **O**. β-hydride elimination leads to the π complex **P**, from which the catalytically active species **M** is regenerated by dissociation of the isomerised alkene.[6]




**Scheme 6** Mechanistic proposals for double bond isomerisation in alkenes[6]

Cycle A: π-allyl hydride mechanism

Cycle B: hydrometalation/β-hydride elimination mechanism

Ruthenium-mediated catalysis has recently gained popularity for the isomerisation of terminal alkenes to internal alkenes, using the ruthenium isomerisation catalyst **12 (Figure 2)**. Krompiec *et al.*[29] has extensively investigated the use of this catalyst for propenyl ether synthesis by an isomerisation of the appropriately easy to synthesize allyl ethers. Their method shows an alternative to the use of bases, zeolites, supported metals and other transition metal complexes (rhodium, iridium, palladium, chromium, molybdenum, iron and platinum) for the isomerisation of these double bonds, that is both convenient and universal in use.

$[RuClH(CO)(PPh_3)_3]$
**12**

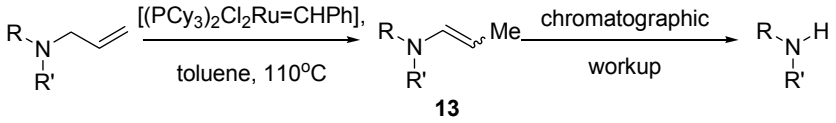
**Figure 2**

Krompiec *et al.*[30] has further highlighted the use of catalyst **12**, $[RuCl_2(PPh_3)_3]$ or $[RhH(CO(PPh_3)_3)]$ for the selective isomerisation of *N*-allylamides and *N*-allylamines. These types of enamines occupy a predominant place as intermediates in organic synthesis and in

the biological world, and as such there are many methods of enamine synthesis. Examples include: condensation of a secondary amine with a carbonyl compound,[31] hydroamination of alkynes,[32] methylenation of amides[33] and vinylamination.[34] An alternative method for the synthesis of enamines is the isomerisation of allyl amines using strong bases such as $^{t}$BuOK,[34] $^{n}$BuLi[35] or ruthenium,[36] rhodium[37] and iron[38] complexes. However, a number of these procedures have specific drawbacks, and the use of the mild conditions required by catalyst **12** are therefore favoured.

### *3.2 Ruthenium Catalyzed De-allylations*

In 2001 Alcaide *et al.*[7] reported a novel application of Grubbs first generation catalyst **10**, namely the first examples accounting for the catalytic deprotection of tertiary allylic amines by using reagents different from palladium catalysts.[39] The catalytic system directs the reaction towards the selective deprotection of allylamines, even in the presence of allylic ethers. This ruthenium promoted method is more convenient, chemoselective and operationally simple in comparison to the conventional palladium-catalyzed method. The current mechanistic hypothesis invokes a nitrogen-assisted ruthenium-catalyzed isomerisation, followed by hydrolysis of the enamine intermediate **13** (**Scheme 7**).[7]



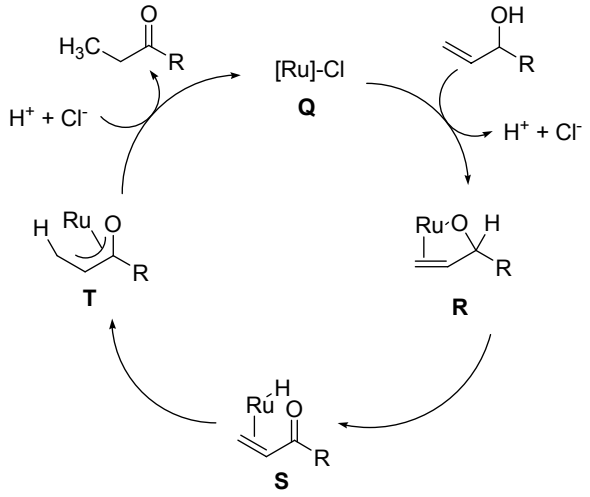

**Scheme 7** Grubbs carbene-catalysed deprotection of allylic amines[7]

The isomerisation of the *N*-allyl to *N*-propenyl amines is also the key step in the deprotection of amino groups that are protected as their *N*-allyl derivatives.[40] Krompiec[30] highlighted the use of catalyst **12** for these de-allylation deprotections.

### *3.3 Ruthenium Catalyzed Redox Isomerisations*

The isomerisation of allylic alcohols to ketones, often referred to as redox isomerisation, can be catalysed by ruthenium complexes, and examples of the use of Grubbs catalyst in this transformation have been published recently.[6] It is believed that the mechanism for this

transformation involves replacement of a ruthenium-bound chloride ion in **Q** by the allylic alcohol, giving intermediate **R**. β-Hydride elimination gives enone **S**, which is coordinated to a Ru-H species and undergoes subsequent migratory insertion into the Ru-H bond, leading to $\eta^3$ complex **T**. The complex **T** is cleaved from the metal by protonation to yield **Q** and the ketone (**Scheme 8**).[41]




**Scheme 8** Proposed mechanism for redox isomerisation of allylic alcohols to ketones[6]

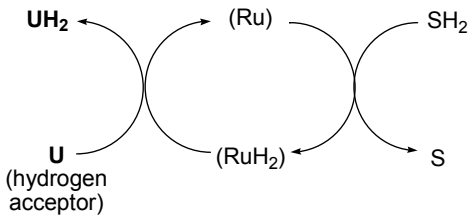
## 4. Ruthenium Mediated Oxidations

As mentioned in the previous section a number of other non-metathetic catalytic properties of the RCM catalysts have been noted, including isomerisation of alkenes pre-[25] or post-metathesis[42] Other examples includeatom transfer radical additions,[43] enol ester synthesis,[43] hydrogenation and dehydrogenative oxidations of alcohols.[44] A number of one-pot tandem RCM reactions have also been reported, including RCM-hydrogenation,[2,45] metathesis-dehydrogenation-hydro-genation,[44] RCM-Diels-Alder[46] and RCM-Pausen-Khand[47] reactions.

Recent work in our laboratories has noted a tandem ring closing metathesis-oxidation that results selectively in substituted indenols or indenones using only the Grubbs second generation catalyst **11**, and by varying the reaction conditions.[8] To the best of our knowledge formation of the latter indenone compounds construes the first observation of a one-pot tandem RCM-oxidation reaction mediated by a ruthenium-based metathesis catalyst.[8] A small amount of indanone was also noted during the abovementioned syntheses and further

investigation is required to clarify if this was due to the tandem ring closing metathesis-redox isomerisation reaction.[48]

The oxidizing ability of ruthenium is well documented and may be classified into two general categories, namely, dehydrogenative oxygenation, and oxidation with metal-oxo and metal-hydroperoxo species. The latter is well known in synthetic chemistry and will not be discussed.[49a] Dehydrogenative oxidation of organic substances with or without hydrogen acceptors is important from both biological and industrial aspects. Low-valent ruthenium complexes are excellent catalysts for the dehydrogenation of alcohols because of their low redox potential and affinity towards oxygen atoms.[49a] The basic concept of the catalytic dehydrogenative oxidation of alcohols is outlined in **Scheme 9** below. Oxidative addition of the low-valent ruthenium complex to the substrate and β-ruthenium hydride elimination produces the dehydrogenated compound and a ruthenium dihydride species, which react with a hydrogen acceptor **U** to afford hydrogenated product $\mathbf{UH_2}$ and a ruthenium complex catalyst to complete the cycle.[49a]




**Scheme 9** Catalytic Dehydrogenative Oxidation[49a]

It is also important to realize that ruthenium-mediated dehydrogenation of alcohols without hydrogen acceptors has also been reported; these include the use of the catalysts: $RuH_2(PPh_3)_4$, $Ru(OCOCF_3)_2(CO)(PPh_3)$ and $Ru_3(CO)_{12}/PPh_3$.[49a-d]

# *Chapter 2:*

# *Introduction to N-containing benzo-fused heterocycles*

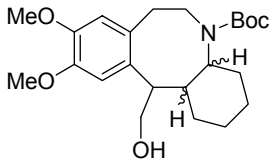
# *Chapter 2: Introduction to N-containing benzo-fused heterocycles*

As mentioned in **Chapter 1**, this dissertation deals primarily with the use of ring closing metathesis (RCM) in the formation of small benzo-fused molecules. The first part of the dissertation deals with the synthesis of a range of nitrogen-containing benzo-fused heterocycles. Thus, as an introduction to this work, the general 8-, 7- and 6-membered groups are outlined below. The commonly reported syntheses for the formation of these natural products, based on their skeletons, are also briefly outlined below.

## 1. Benzazocines (8-membered rings)

The benzazocines have been isolated from a wide number of sources, and it is hoped that their syntheses may provide useful routes to new and interesting types of narcotic antagonists.[50] New derivatives of benzazocines that have been synthesized show analgesic activity, affinity to the opiate receptor and potential antagonistic properties.[51] They are also found to be useful intermediates for the synthesis of a number of naturally occurring compounds, including the aziridine alkaloids, cyclazocine and its derivatives.

Members of the plant family Berberidaceae are known to contain a novel class of the isoindolobenzazocine alkaloid, magallanesine, isolated from *Berberis darwinii*. The unique framework of isoindolobenzazocine **14** contains the medium sized nitrogen-containing heterocyclic ring, which has generally proved the most difficult to prepare by conventional synthetic methods.[52] A number of other examples of the benzazocines and their derivatives will be described below.




**14**

**Figure 3**[52]

## *1.1 Cyclazocine and its Derivatives*

Cyclazocine (±)-**15** is a member of the 2,6-methano-3-benzazocine class of opioid receptor-interactive agents which contains a bridged 8-membered benzo-fused heterocyclic ring.[53-60] Numerous breakthroughs in understanding opioid receptor pharmacology (for example, the deduction of the multiple opioid receptor subtypes[61]) have been made in part through the study of cyclazocine and its enantiomers (-)-**16** and (+)-**17**.[53] In the 1960s and early 1970s, cyclazocine was evaluated in humans for analgesia and as a positive treatment in heroine addicts to prevent relapse.[53,60] Potent analgesia was observed in humans dosed with cyclazocine, and even after abrupt cyclazocine withdrawal, patients did not display drug-seeking behaviour.[60]

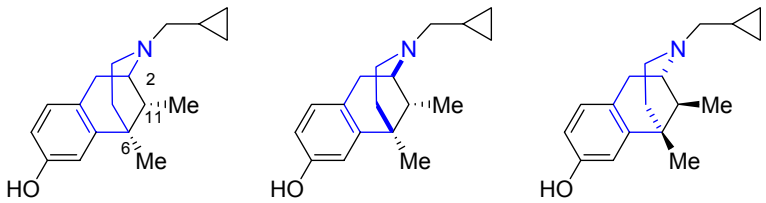



**Figure 4**[62]

The observations that cyclazocine produced opioid-induced analgesia in humans with a lower risk of dependency and displayed a milder withdrawal from morphine suggested that the agent might serve as a useful therapeutic for the treatment of heroine addiction.[63-65] Currently, cyclazocine is undergoing NIDA-sponsored evaluation for potential clinical utility as a treatment for cocaine abuse.[66] Results of this study so far do not support the use of cyclazocine for this indication; however, there was some suggestion that an analogue having a somewhat different opioid receptor profile might be useful.[62]

## *1.2 Aziridine Alkaloids*

In 1987, a new class of aziridine natural products, structurally similar to the mitomycins, was isolated from a culture broth of *Streptomyces sandaenis* by the Fujisawa Pharmaceutical Company.[67] The compounds were denoted FR-900482 **18** and FR-66979 **19** (**Figure 5**).

Compounds **18** and **19** exhibited potent antitumour activity against LX-1, MX-1, SC-6 and LC-6 carcinomas, as well as P-388 murine leukemia cells.[68] The triacetate derivative FR-973 **20** was three times more potent as an anticancer agent than **18** or **19**, in addition to being significantly less toxic.




**Figure 5** Aziridine Alkaloids[68]

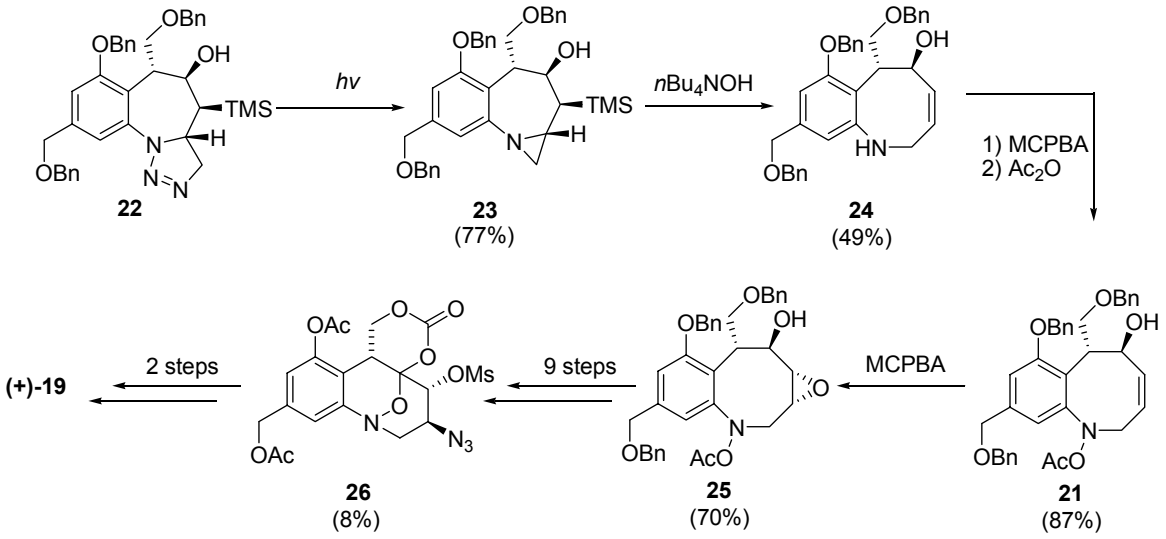
Due to the interconversion of **18** and **19** via simple chemical transformations,[69] the total synthesis of one can be treated as the formal synthesis of the other. Fukuyama *et al.*[70] accomplished the first total synthesis of racemic FR-900482 **18** in 1992, and since then another racemic synthesis was completed by Schkeryantz and Danishefsky[71] Enantioselective syntheses have also been completed by Terashima,[72] Williams,[69] Fukuyama[73] and Ciufolini;[74] with formal syntheses being reported by Rapaport[75] and Martin.[76]

There are three common approaches to the core of the natural product, two include nitroso- or nitrone-cycloadditions to access the 1,2-oxazine core and the oxidation of a pyrroloindole to form the aminoxyhemiketal group.[77] The final method involves the synthesis of an 8-membered benzazocine system followed by a late stage aminoxyhemiketal formation, and herein lies the interest in these synthetic targets to our group.

The diversity of the benzazocine approaches to aminoxyhemiketal core synthesis stems from the formation of the 8-membered ring via a number of different synthetic pathways, which are highlighted in detail below. The initial studies performed by Fukuyama proved to be a crucial development that resulted in a host of similar syntheses based upon intermediates related to functionalized benzazocine **21**.[70]

### *1.2.1 Homo-Brook Fragmentation to Benzazocines*

Photolysis of triazoline **22** generated aziridine **23** which underwent a novel base-induced homo-Brook fragmentation (**Scheme 10**). Deprotonation of the 8-C hydroxyl led to the formation of an oxysiletane ring, which fragmented to open the aziridine and form cyclooctenol **24**. The remainder of the synthesis is an extension of work previously performed by Fukuyama[70] Subsequent selective *N*-oxidation of **24** and *O*-acetylation proceeded in 87% yield, this was followed by epoxidation of olefin **21** from the less hindered face to obtain the oxirane **25** in 70% yield. Then epoxide **25** was opened using an azide, and a subsequent series of protections produced azidomesylate **26** in 8% yield. Overall the natural product **(+)-19** was synthesized in twenty-eight steps and in 0.2% yield.[74]

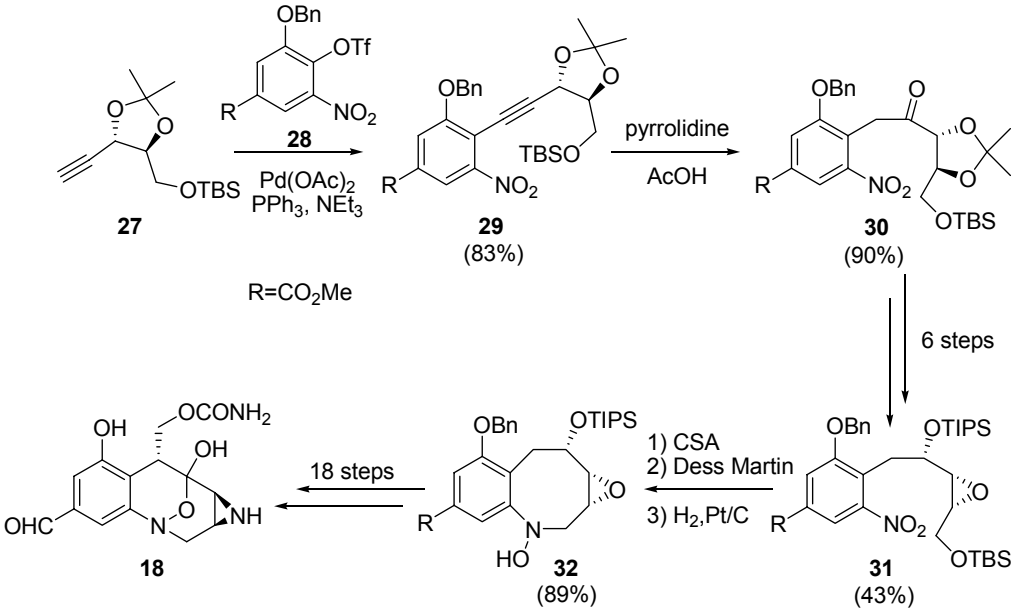



**Scheme 10** A segment of the Ciufolini Total Synthesis[74]

### *1.2.2 Aryl Nitro Cyclisation to Benzazocines*

The total synthesis of (±)-**18** demonstrated that a skeletally simple benzazocine could be converted into the natural product.[70] The synthesis of (+)-**18** by Fukuyama began with a Sonagashira coupling of acetylene **27** and aryl triflate **28** (**Scheme 11**).[73] Hydration of the triple bond proceeded regioselectively to ketone **30**. Six steps were required to form epoxide **31** from 1,3-dioxolane **30**. The TBS ether was selectively deprotonated, the resulting alcohol

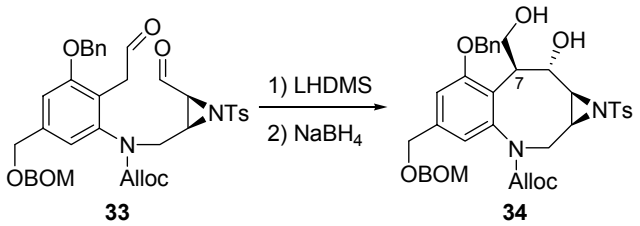
oxidized with the Dess-Martin periodinane, and the aryl nitro compound was hydrogenated over Pt/C to produce the *N*-hydroxybenzazocine **32** in 89% yield. Eighteen additional steps were used to transform **32** into (+)-**18** in 13% yield. Overall, **(+)-18** was synthesized in thirty-three steps in 1% yield.[77]




**Scheme 11** A segment of the Fukuyama Total Synthesis[73]

### *1.2.3 Aldol Cycloaddition to Benzazocines*

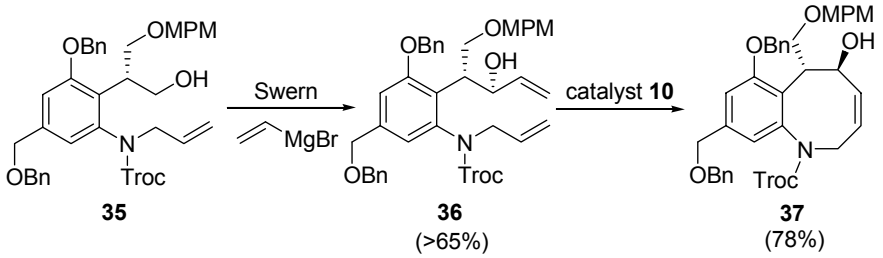
The first enantioselective total synthesis was completed by Terashima and co-workers in 1996.[72] The lengthy synthesis began with L-diethyl tartrate and hinged upon an intramolecular aldol reaction to form the 8-membered ring (**Scheme 12**).[78] Dialdehyde **33** was prepared in 37 steps from tartrate, was then treated with $LiN(SiMe_3)_2$ followed by sodium borohydride to afford diol **34** as the exclusive cyclized product in 48% overall yield. The corresponding acyclic diol was recovered in 33% yield. The remainder of the synthesis involved differential protections and oxidations of the primary and secondary alcohols as well as inversion of the 7-C stereogenic center.[77]




**Scheme 12** A segment of the Terashima Total Synthesis[78]

### *1.2.4 Ring Closing Metathesis to Benzazocines*

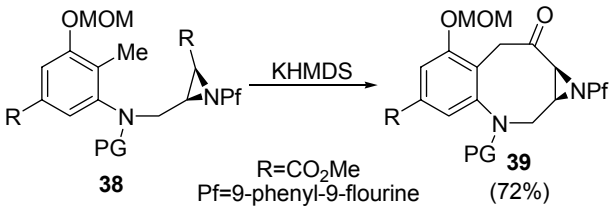
It was initially shown by Grubbs[79] that ring closing metathesis could be utilized for cyclization reactions yielding tetrahydrobenzazocine products and this was later implemented by Martin and co-workers.[75] After functional group manipulations to produce alcohol **35**, a tandem Swern oxidation-Grignard addition afforded diene **36** (**Scheme 13**). Subsequent RCM afforded benzazocine **37** in 78% yield.[75] Protection strategies were then employed to intersect with an intermediate in the Fukuyama synthesis.[70]




**Scheme 13** A segment of the Martin Formal Synthesis[75]

### *1.2.5 Epoxide Ring Opening to Benzazocines*

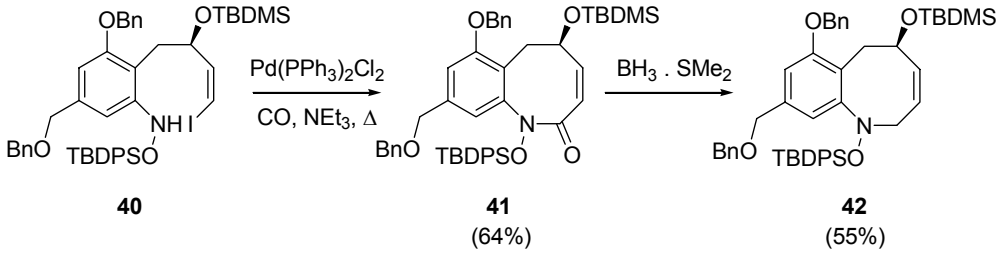
This synthesis was outlined by Rapaport and co-workers in 2003[76] and they found that lithiation of the ester **38** with KHMDS deprotonated the benzylic methyl group and the resulting carbanion attacked the methyl ester to form ketone **39** in 72% yield (**Scheme 14**). A series of steps similar to those found in the syntheses of Fukuyama[70] and Terashima[72] resulted in a formal synthesis of **20**.[77]




**Scheme 14** A segment of the Rapaport Formal Synthesis[76]

### *1.2.6 Pd-catalyzed Carbonylative Lactamization to Benzazocines*

The novel Pd-catalyzed carbonalative lactamization of **40** proceeded in 64% yield under one atmosphere of carbon monoxide and refluxing DMA to afford **41** (**Scheme 15**).[81] Subsequent reduction of lactam **41** with borane-methyl sulfide provided benzazocine **42** in 55% yield, without competitive hydroxyamine cleavage or 1,4-reduction.[77] While not a formal synthesis, it is anticipated that the strategy can be developed into an enantioselective synthesis of the natural product **20**, given the structural similarity to the Fukuyama[70] synthesis intermediates **21**.[77]

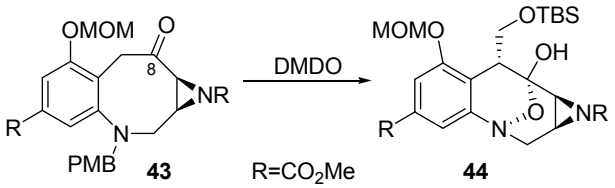



**Scheme 15** The Trost Synthetic Approach[81]

As can be seen by the syntheses outlined above, the current methods available for the synthesis of **18** provide intriguing avenues to the natural product. However, all the available syntheses are longer than twenty-five steps, highlighting the need for a more efficient synthesis of the benzazocine skeleton. Also, given the more pronounced and selective DNA cross-linking activity of FK-973 **20**, a synthesis allowing for generation of various analogues could provide more efficient anticancer agents.[77]

### *1.2.7 Reductive Amination-Highlighting a Use of Benzazocines in Natural Products*

Jimenez[80] established that pyrroloindoles could be oxidized by dimethydioxirane to yield the hemiketal core of the natural product. Recently Williams[69] demonstrated that oxidation of *p*-methoxybenzylamine **43** with dimethyldioxirane gave hydroxylamine that concomitantly extruded *p*-methoxybenzaldehyde (**Scheme 16**).[77] The single synthetic step oxidized and deprotected the amine and ultimately afforded the desired hemiketal core **44**, upon cyclization with the C8 carbonyl group.




**Scheme 16** A segment of the Williams Total Synthesis[69]

## 2. Benzazepines (7-membered rings)

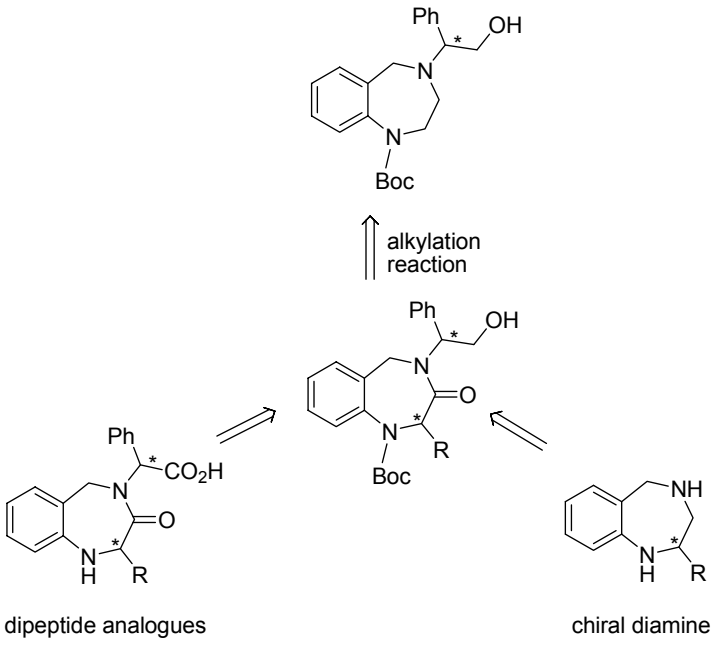
A number of categories of benzazepine compounds are known, each with unique biological activities. This section will highlight some of these groups and describe various syntheses.

### *2.1 1,4 Benzodiazepine Compounds*

1,4-Benzodiazepine compounds have been extensively investigated owing to their important biological properties, and in recent times their structure has been widely used as a "molecular scaffold".[82] Several of these nitrogen-containing heterocycles have been identified as anti-tumour, antibiotics (e.g. DC-81),[83] anti-HIV[84] and anti-thrombotic[85] agents, in addition to their well-known anxiolytic,[86] sedative,[87] and anti-convulsant[88] activities. A selected number of examples are highlighted in the chapter below to demonstrate the importance of *N*-containing 7-membered benzofused ring systems.

Because of both their structural motifs and physiochemical properties, this stucture has been considered among novel non-peptide peptidomimetics, as it can act as a mimic of peptide secondary structures (eg: γ- and β-turns).[85,89] As such, many stereocontrolled synthetic

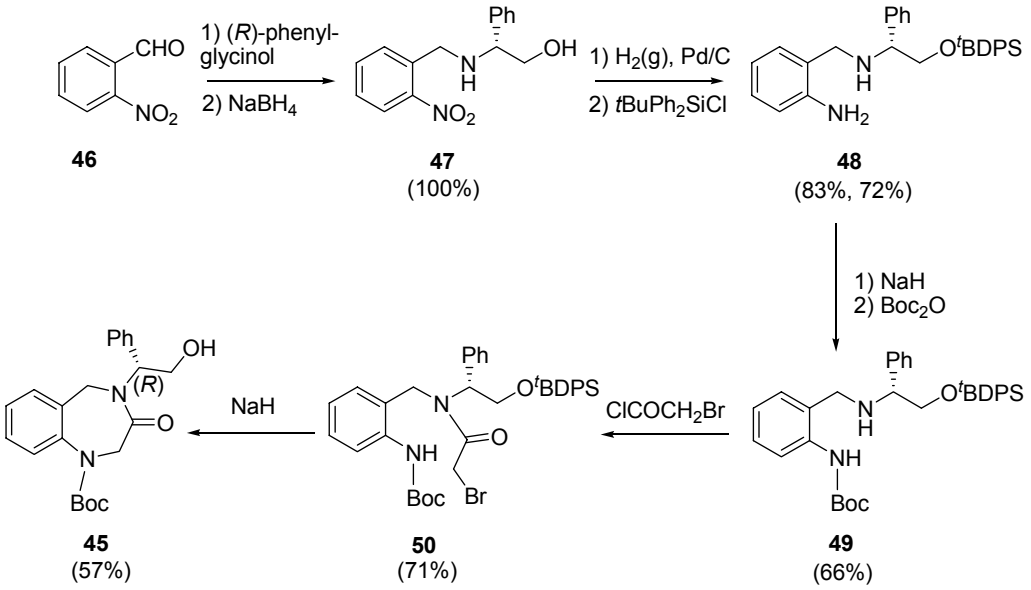
approaches to the 1,4-benzodiazepine compounds have been developed.[82] Among the most impotant strategies are the reductive cyclisation of amino aldehydes,[90] amino thioacetals,[91] cyclisation via isatoic anhydride by condensation with an amino acid derivative,[92] coupling of *N*-carboxy α-amino acid anhydrides with anthranilic acid derivatives,[93] condensation between 2-aminobenzophenone and α-substituted glycine derivatives[89a,94] and the use of a chiral auxillary attached to the 1,4-benzodiazepine structure.[92b,95,96] However, relatively little work has been done on the asymmetric synthesis of 2-substituted-1,4-benzodiazepines (**Scheme 17**).[97]




**Scheme 17** Access to 2-substituted 1,4-benzodiazepine[97]

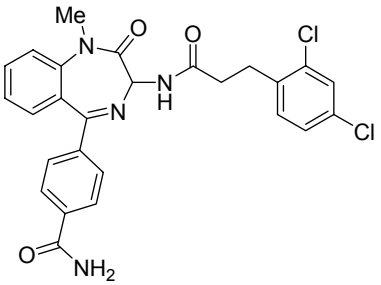
Cabedo *et al.*[82] have recently reported a novel route towards the asymmetric synthesis of 1,4–benzodiazepine core derivatives by preparing the enantiopure 1,4-benzodiazepine-3-one **45** from (*R*)-phenylglycinol (**Scheme 18**). This approach began with a reductive amination of aldehyde **46**, allowing the introduction of a chiral inductor giving amine **47**. The nitro group of **47** was then reduced in the presence of the chiral auxillary under standard hydrogenation conditions, without any cleavage of the auxillary yielding **48**. The lack of reactivity of the secondary benzyl derivatives of amino alcohols allows this transformation that was previously observed by Micouin and co-workers.[98]

The selective protection of the alcohol with $^{t}BuPh_2SiCl$ and the aromatic amine with $Boc_2O$ in the presence of sodium hydride afforded the secondary benzylamine **49**. Treatment of the resulting amine **49** with chloroacetyl bromide[99] gave the *N*-acylated derivative **50**. Subsequent treatment with sodium hydride in DMF facilitated an intramolecular cyclisation, and silyl group deprotection in a one-pot procedure. The seven-membered ring lactam **45** was obtained in a 16% overall yield from **46**.[82]




**Scheme 18** Synthesis of 1,4-benzodiazepine-3-one from (*R*)-phenylglycinol[82]

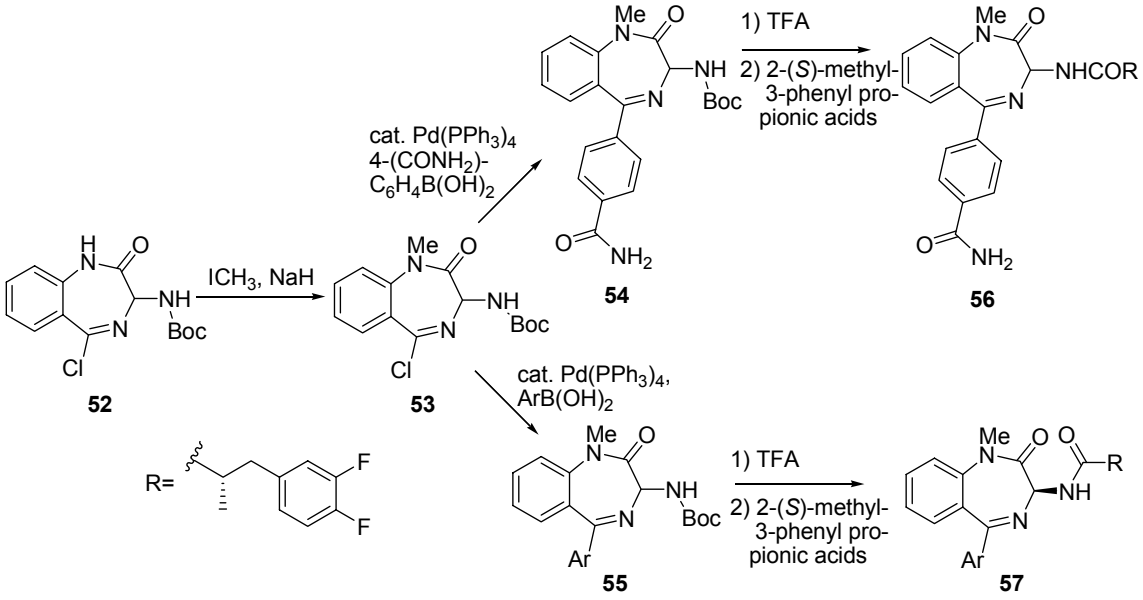
Alzheimer's disease (AD) is a commonly occurring neurodegenerative disease characterized by a progressive cognitive and memory decline. The neurodegeneration is thought to be due to the deposition and accumulation of amyloid (Aβ) peptides into extracellular proteinaceous plaques.[100] These Aβ peptides are produced by the sequential cleavage of membrane-bound amyloid-β precursor protein (βAPP) by two proteases known as β- and γ-secretases. The inhibition of either of these two proteases is a potential approach to treating AD as that would reduce the formation of Aβ peptides and consequently their aggregation into amyloid plaques. Investigations have been undertaken on a γ-secretase inhibitor discovery program to find an orally bioavailable, high potency compound.[101]



**51**

**Figure 6**[102]

A novel γ-secretase inhibitor **51**, shown in **Figure 6** above, has been identified. The original synthesis involved 16-steps,[102] which was not ideal for the preparation of analogues to investigate structure-activity relationships. A novel strategy describing the synthesis of 3-amino-1,4-benzodiazepines starting from chloroimidate **52** (**Scheme 19**) has been published,[103] which allows the convergent construction of structures such as compound **51** and **56-57** from a central intermediate.

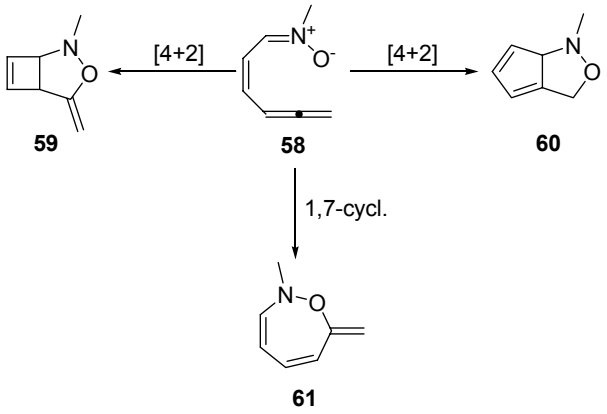


**Scheme 19** Synthesis of 3-amino-1,4-benzodiazepines from chloroimidate **52**[103]

The ring-forming processes of conjugated 1,3-dipoles are an important hetero-cyclisation method for the construction of five-membered ring-systems.[104] This methodology has

successfully been applied to the construction of seven-membered heterocycles, using conjugated nitriles, ylides, azomethine imines and nitrones.[105]

Conjugated nitrones of type **58** can undergo three different cyclisation processes: Two intramolecular [4+2] cycloadditions resulting in the formation of the bicyclic derivatives **59** and **60**, and a 1,7-ring-closure affording the *exo*-methyleneoxazepine **61** (**Scheme 20**).[106] It is hoped that this methodology for the formation of **61** may be extended to include the synthesis of the benzo-fused systems.




**Scheme 20** Cyclization processes of conjugated nitrones[106]

## *2.2 1,2-Dihydro[c]-benzazepine-3-one Compounds*

Despite the structural simplicity of the 1,2-dihydro[*c*]-benzazepine-3-one system **62** (**Figure 7**), which occurs as a substrate in a number of naturally occurring compounds,[107] there is no general synthetic approach for it's synthesis. Thus far only a few syntheses have been described, most having been elaborated for the synthesis of further annulated compounds, which frequently possess biological activity.[108]

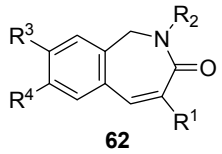
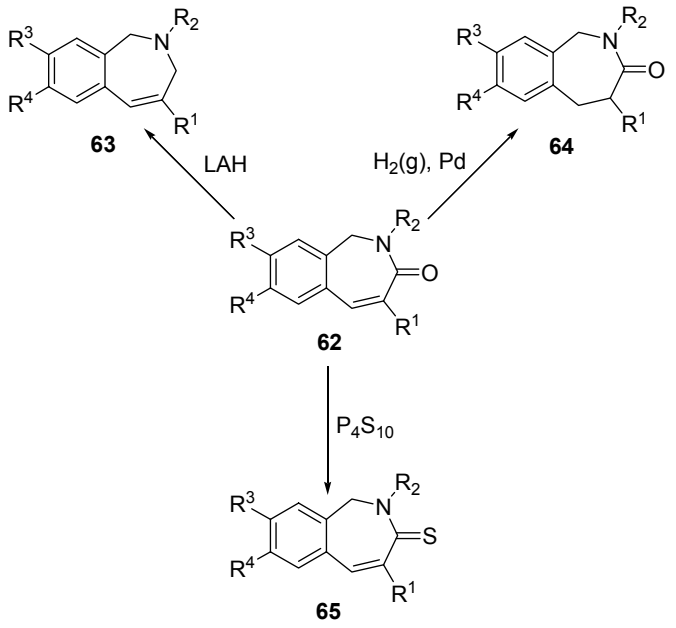



**Figure 7** The 1,2-dihydro[*c*]-benzazepine-3-one system[107]

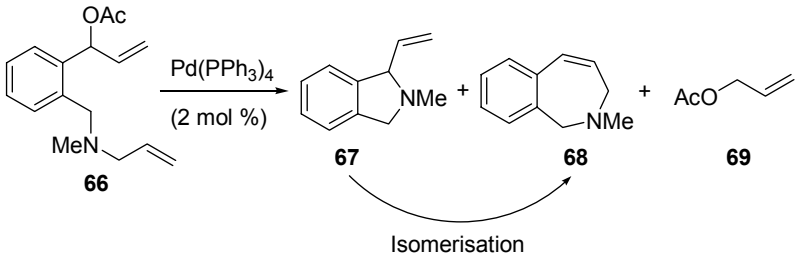
The kinetic stability, both thermal and chemical, of these heterocycles is usually high. No cleavage of the amide bonds has been reported under forced acidic or basic conditions.[106] The C=C and C=O groups can be reduced chemoselectively, depending on the reducing agent. Catalytic hydrogenation affords the tetrahydrobenzazepinone **64**, whereas treatment with lithium aluminium hydride yields the desired dihydroazepines **63** (**Scheme 21**). Thionation using phosphorus pentasulfide to afford thioketone **65** has also been reported.[106]




**Scheme 21** Reactivity of dihydrobenzazepin-3-ones[106]

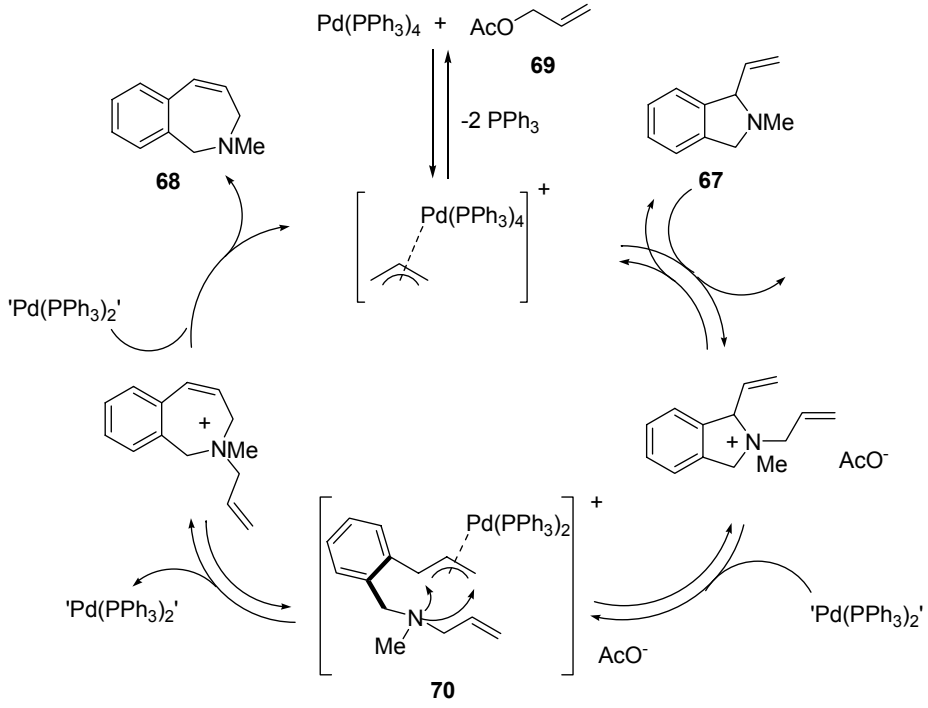
*2.3 2-Benzazepine Derivatives*

The synthesis of 2-benzazepine derivatives is also of importance as these compounds are shown to have potential biological activity, an example being an *N*-cyclopropylmethyl derivative of 2-benzazepine which displays a high CNS activity, with an eight fold increase of *in vivo* analgesic activity compared to morphine.[109] One of the methods for the synthesis of these derivatives is outlined in **Scheme 22** below. *N*-Methyl-*N*-allyl-2-(1-acetoxallyl)benzylamine **66** reacts in the presence of tetrakis(triphenylphosphine)palladium to give a mixture of isoindole **67**, 2-benzazepine **68** and allyl acetate **69** (**Scheme 22**). After almost all of **66** has reacted the isoindole **67** isomerizes to **68**.[110]




**Scheme 22** Reaction of **64** and $Pd(PPh_3)_4$[110]

A potential mechanistic pathway has been identified (**Scheme 23**).[110] The key intermediate, **70**, leads to benzazepine **68** *via* an intramolecular attack of the amino group in the position opposite to the $Pd(PPh_3)_2$ moiety with respect to the allyl fragment after a *syn-anti* isomerisation of the latter has taken place.[111]



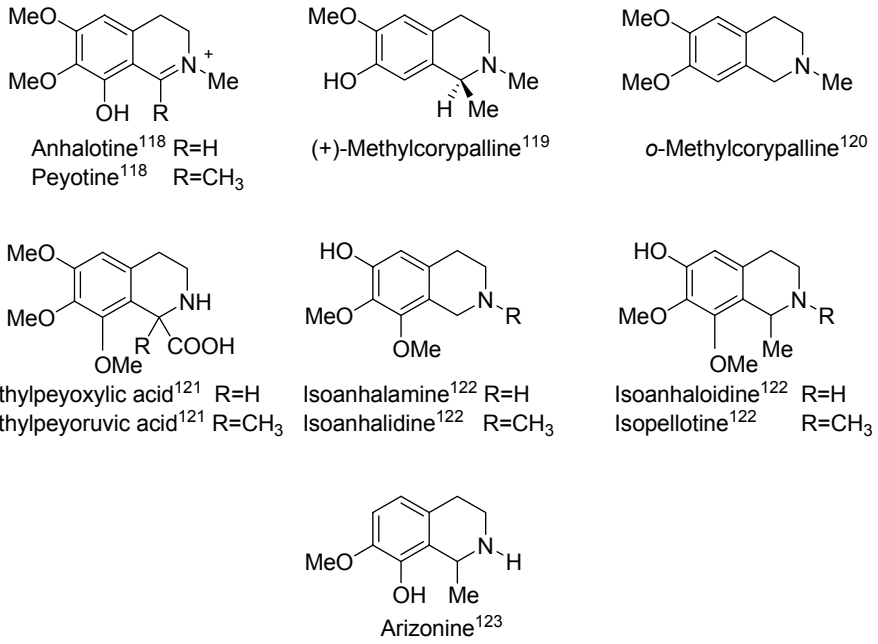

**Scheme 23** Reaction pathway for isomerization[110]

## 3. Isoquinolines and Related Compounds (6-membered rings)

The isoquinoline systems are well known and numerous reviews are available. The following sections serve to highlight the different classes of isoquinoline alkaloids that are applicable to our project.

### *3.1 The Simple Isoquinolines*

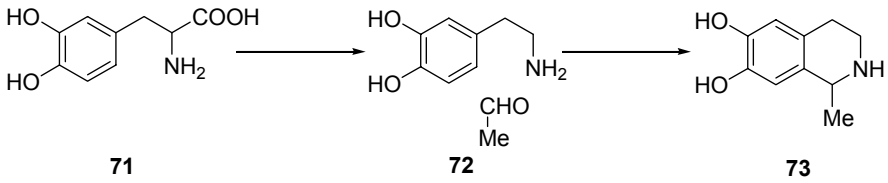
The chemistry, synthesis and biogenesis of peyote, *Lophophora Williamsii*, and other cactus alkaloids have been thoroughly reviewed.[112-116] New natural sources of simple isoquinoline alkaloids are the Euphorbiaceae and the Rhamnaceae. Some recently isolated alkaloids of interest are shown in **Scheme 24**.[117]




**Scheme 24** Recently Isolated Isoquinoline Alkaloids[117]

The simplest isoquinoline alkaloids that are found in plants are derivatives of the tetrahydroisoquinoline alkaloids, which contain oxygen substituents at positions 6 and 7, and occasionally at position 8. The most commonly seen oxygen substituents are hydroxyl and methoxy groups. The bases, which may be secondary or tertiary, often bear a methyl group at position 1.[124] They are thought to arise in nature from the condensation of β-

phenylethylamines with formaldehyde, acetaldehyde or their equivalents with the amines themselves generally derived from amino acids. This process is shown in **Scheme 25**, starting from dihydroxyphenylalanine **71**, which appears to be the fundamental building block from which all the bases of the isoquinoline series are derived.[124]



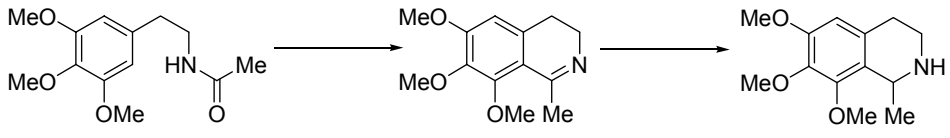

**71** **72** **73**

**Scheme 25** Formation of a Simple Isoquinoline[124]

3,4-Dihydroxytyramine **73** is one of the hypertensive agents of the common broom, *Cytisus scoparius*. Its structure is clear from its formation by decarboxylation of 3,4-dihydroxyphenylalanine **71**.[124]

### *3.1.1 The Anhalonium Bases*

The cactus *Anhalonium lewinii* contains a series of alkaloids, which are derivatives of mescaline. Spath confirmed their structure by synthesizing the tetrahydroquinoline **74** (**Scheme 26**), by Bischler-Napieralski cyclisation of *N*-acetylmescaline **75**, to yield dihydroiosquinoline **76**, which was then reduced to give **74**. *N*-methylation of **74** yielded the quarternary methiodide which was identical to the corresponding alkaloid derivatives, *O*-methyl-*O*-methylpellotine methiodide and *O*,*N*-dimethylanhalonidine methiodide.[124] The Bischler-Napieralski cyclisation is described in detail in *Section 3.5.2* below.

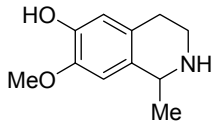



**75** **76** **74**

**Scheme 26** A Bischler-Napieralski Cyclisation to form tetrahydroisoquinolines[124]

### *3.1.2 Salsoline and Corypalline*

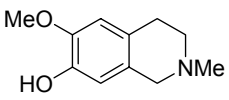
Salsoline **77** is found in *Salsola arbuscula* a desert plant, has a composition of $C_{11}H_{15}O_2N$, and contains a phenolic hydroxyl, a methoxy and an imino group.[124] The stucture of salsoline **77** has been determined by its synthesis from isovanillin. Salsoline **77** can be prepared using optically active immonium salts, by the Bischler-Napieralski route.




**77**

**Figure 8** Salsoline[124]

Corypalline **78** is isolated from *Corydalis pallida*, and is isomeric with salsoline **77**, also containing a phenolic hydroxyl and a methoxy group. However, it contains an *N*-methyl group and the *C*-methyl group is not present. The structure for the base was proven by its synthesis from vanillin.[124]

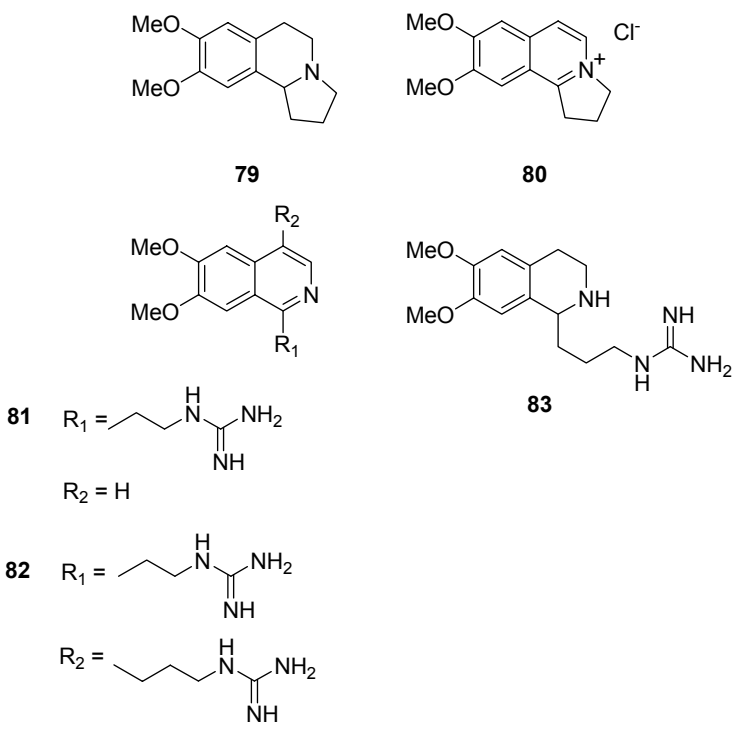



**78**

**Figure 9** Corypalline[124]

### *3.1.3 Crispine A-E*

*Carduus crispus L*. has been used in Chinese folk medicine for the treatment of colds, stomachache and rheumatism. The screening test for the inhibitory effect on the growth of some human cancer lines *in vitro* showed the extracts of *C. crispus* had significant effects on the cytotoxic activity. Phytochemical studies on the plant have led to the isolation of crispine A-E (**79-83** respectively).[125]

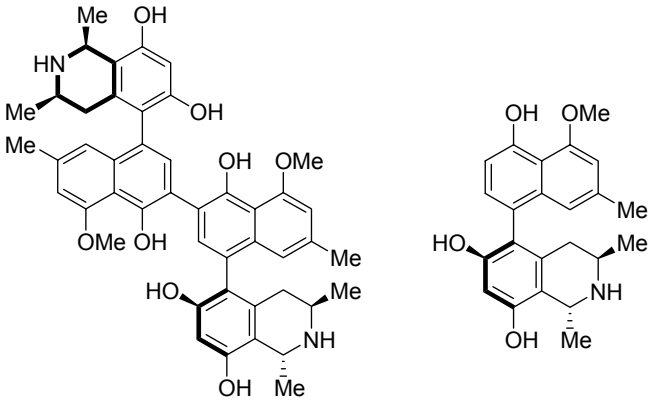



**Scheme 27** Structures of Compounds **79-83**[125]

Crispine A **79** and B **80** are alkaloids with a pyrrolo-[2,1-*a*]-isoquinoline skeleton and crispine C-E **81-83** are isoquinoline alkaloids with a guanidinyl group. Evaluation of the cytotoxic activity by the SRB method of all of these alkloids showed that compound **80** had some activity against certain human cancer lines.[125]

### *3.2 The Naphthylisoquinoline Alkaloids*

More complex compounds that contain the isoquinoline skeleton are the naphthylisoquinoline alkaloids such as michellamine A **84** and korupensamine A **85**, which show strong anti-malarial, anti-HIV1 and anti-HIV2 activities.[126] The michellamines A, B and C were isolated from *Ancistrocladius korupensis*.[127] It has been found that michellamine B inhibits the formation of syncytium, a primary route of cell to cell HIV transmission.[128] It has also been reported that the biological activities of the michellamines are primarily due to the heterocyclic portion of the tetrahydroisoquinoline unit.




Michellamine A **84** Korupensamine A **85**

**Figure 10** Naphthylisoquinoline Alkaloids

### *3.3 The 1- and 4-Substituted Tetrahydroisoquinolines*

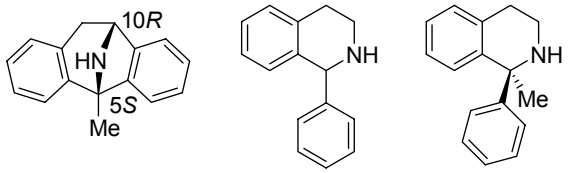
Over fifty anti-tumour and antibiotic natural products belonging to the tetrahydroisoquinoline family are known to date. Some of these are very potent cytotoxic agents and show a wide variety of other biological activities, such as anti-bacterial, anti-plasmoidal, and β-adrenergic receptor antagonism.[129]

#### *3.3.1 The 1-Substituted Tetrahydroisoquinolines*

The *N*-methyl *D*-aspartate (*NMDA*) receptor is a subtype of the excitatory amino acid receptors and has been implicated in a number of different physiological and pathological events in the brain. At present this site is a major target for the development of new drugs for the treatment of neuronal diseases, such as Alzheimer's disease and Parkinson's disease. *MK*-801 **86** is a well-known high-affinity ligand for the aforementioned binding site with a unique structure.[130] A select number of these potential drug compounds are described in this section.

In 1989 Gray *et al.*[131] reported new ligands for the binding site with the general structure **87,** a 1-substituted tetrahydroisoquinoline, however, it was found that these analogues had an affinity for the binding site that was three orders of magnitude less than *MK*-801. A few years later the research group at the Fujisawa Pharmaceutical Company presented the

tetrahydroisoquinoline **88** with a quarternary carbon atom at C-1 as a new and distinctly more potent ligand for the binding site as compared to **87**.[132]

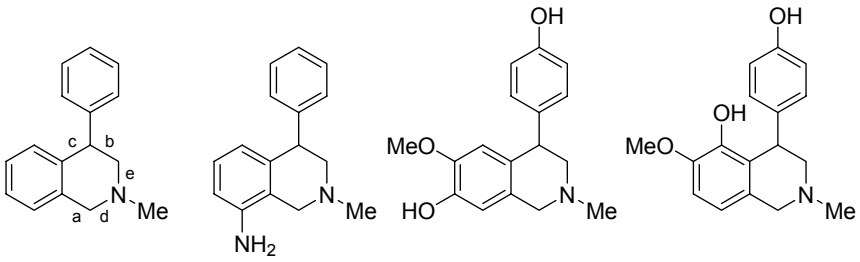



**86** **87** (*S*)-**88**

**Figure 11** Ligands for the PCP binding site[130]

### *3.3.2 The 4-Substituted Tetrahydroisoquinolines*

The 4-aryl-1,2,3,4-tetrahydroisoquinoline system **89** has attracted much attention over the past few years, owing to its physiological activities and its presence as the backbone in a number of natural products and pharmaceutical drugs.[133] These include nomifensine **90**[134] which inhibits dopamine and noradrenaline (re)uptake mechanisms, and infrequent phenolic Amaryllidaceae alkaloids, such as cherylline **91**,[135] isolated from *Crinum powelli*, and latifine **92**,[136] isolated from *Crinum latifolium*. This genus has been used in Vietnamese and Chinese traditional medicine as a rub and a tonic, for the treatment of allergic disorders and tumor diseases.




Basic Skeleton **89** Nomifensine **90** Cherylline **91** Latifine **92**

**Figure 12** 4-Aryl Tetrahydroisoquinolines[133]

Due to the increasing medicinal interest in this family of compounds, several syntheses of this skeleton have been published; they may be grouped according to the key bond formed (the bonds are labeled in **Figure 12** compound **89**):

- *Bond a* – formed by a Bischler-Napieralski reaction of *N*-formyl derivatives of phenethylamines or by cyclization of β-phenethylisocyanates,
- *Bond b* – formed by intramolecular Horner reaction,
- *Bond c* – achieved by several methods, including, photoinduced cyclization of *ortho*-halogenated *N*-acylbenzylamines, Friedel-Crafts type reactions, intramolecular coupling of quinoid intermediates, and palladium-catalyzed cylization of amide-enolates,
- *Bond d* – constructed by *N*-alkylation,
- *Bond e* – formed by *N*-alkylation.[133]

### *3.4 The Benzophenanthridines*

A number of more complex isoquinolines are also found in nature, for example, the Rutaceae are a common source of the benzophenanthridine alkaloids. Some relatively new benzophenanthridine alkaloids are outlined in **Figure 13** below.

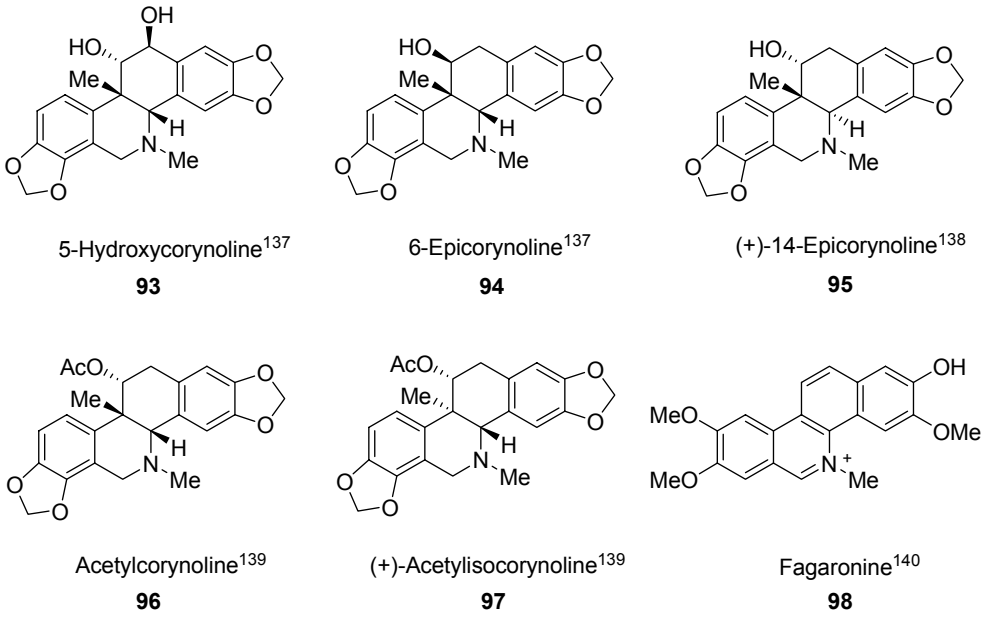



**Figure 13** Benzophenanthridine Alkaloids[137-140]

The most important benzophenanthridines, from a pharmacological standpoint, are nitidine[141] and fagaronine **98**.[142] Nitidine is active in the P388 lymphocytic test and is strongly cytotoxic.

Fagaronine **98** is as active as nitidine in the P388 system, but is devoid of cytotoxicity. Pre-clinical studies have been limited to nitidine.[143] The methoxy derivative of nitidine **99**, allonitidine **100**, and the tetramethoxy derivative **101**, are all active in the P388 test and the more resistant L1210 mouse leukemia test.[144] Compound **101** also shows curative activity against Lewis lung carcenoma (**Figure 14**).

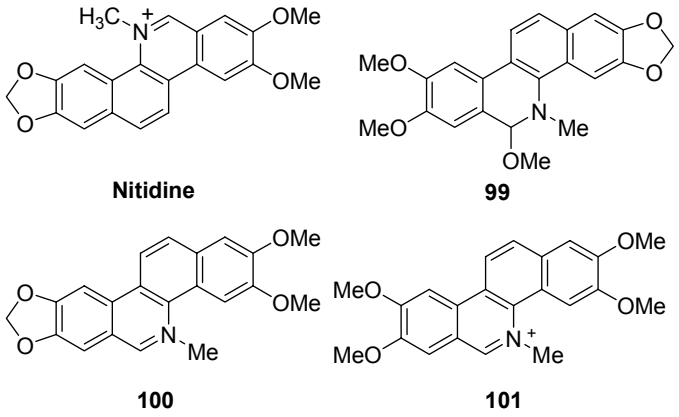
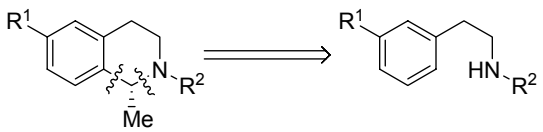



**Figure 14** Nitidine Derivatives[141]

## *3.5 Generally Reported Syntheses of the Isoquinolines, Dihydroisoquinolines and Tetrahydroisoquinolines*

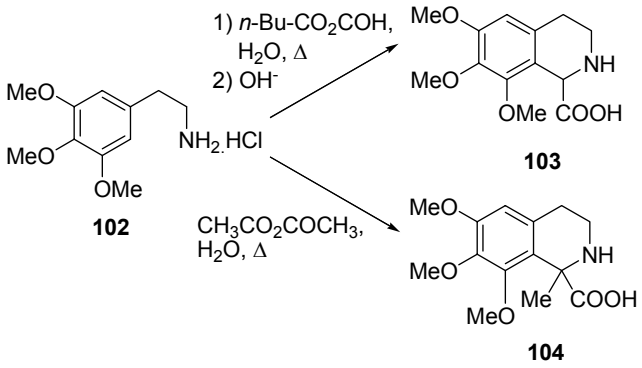
### *3.5.1 Pictet-Spengler Cyclisation*

The Pictet-Spengler cyclization has been used to prepare a variety of optically active tetrahydroisoquinolines, including salsoline **77** and salsolinol, as well as the alkaloids *O*-methylpeyoxylic and *O*-methylpeyoruvic acids from mescaline hydrochloride (**Scheme 28**).[129] It relies on the N/C1/Ar disconnection of the tetrahydroisoquinoline system.



**Scheme 28** General Disconnection using the Pictet-Spengler Cyclization[129]

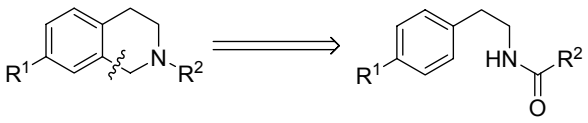
A study of the cyclization of Schiff bases under neutral or weakly acidic conditions has been undertaken[144] and it has shown that a phenolic group *ortho* or *para* to the cyclization site greatly facilitates the reaction (**Scheme 29**).[117]




**Scheme 29**[117]

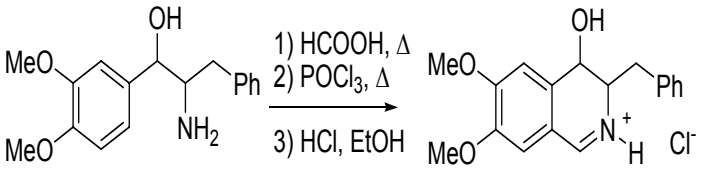
### *3.5.2 Bischler-Napieralski Cyclization*

Salsolidines can be prepared by the Bischler-Napieralski route, using optically active immonium salts.[124] The general disconnection for the Bischler-Napieralski route is shown in **Scheme 30**.




**Scheme 30** General Disconnection using the Bischler-Napieralski Route

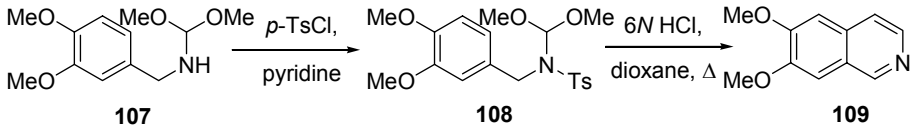
Another variation of the Bischler-Napieralski approach uses an amino alcohol **105**, which is then *N*-formylated and cyclized. The product is a 3-benzylisoquinoline derivative **106** as shown in **Scheme 31** below.[117]




**Scheme 31**[117]

### *3.5.3 Pomeranz-Fritsch Cyclization*

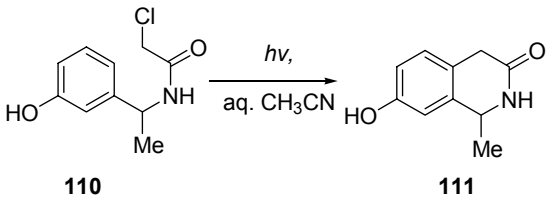
The Bobbit variation of the Pomeranz-Fritsch cyclization is an exceptionally useful approach to obtain the 4-hydroxytetrahydroisoquinolines.[117] Jackson and co-workers have worked out a superior method for the preparation of substituted isoquinolines, it involves the cyclization of acetal sulfonamides **108** under mildly acidic conditions (**Scheme 32**).[145]




**Scheme 32**[117]

### *3.5.4 Photocylization of N-Chloroacetylbenzylamines*

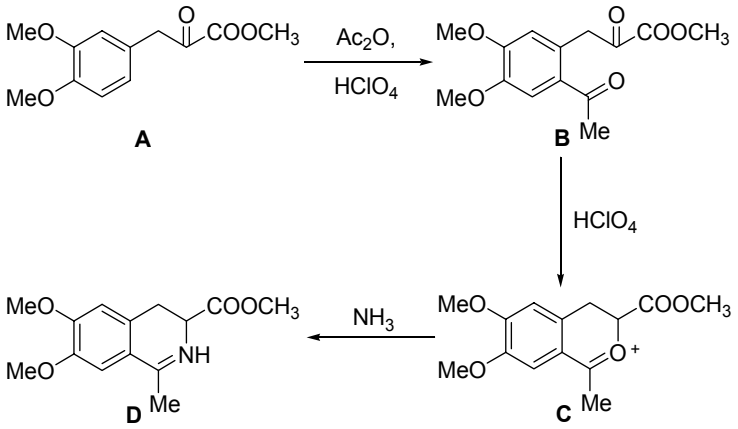
A novel route to isoquinoline derivatives involves irradiation of an *N*-chloroacetylbenzylamine **110** to afford an isoquinoline lactam **111** (**Scheme 33**).[146]




**Scheme 33**[117]

### *3.5.5 Amination of Benzopyrylium Salts*

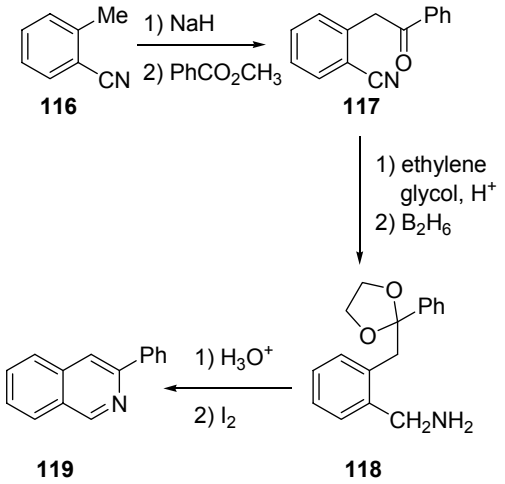
Acylation of 3,4-dimethoxyphenylpyruvic methyl ester **112** with acetic anhydride provides **113** followed by acid-catalyzed cyclization provides a benzopyrylium salt **114**. Further treatment with ammonia affords the dihydroisoquinoline derivative **115** in good yield (**Scheme 34**).[117]




**Scheme 34**[117]

### *3.5.6 Isoquinoline Synthesis via Ortho-Substituted Benzylamines*

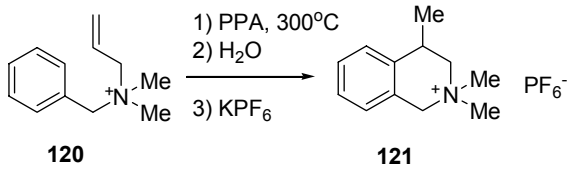
A synthesis of isoquinolines was developed that takes advantage of the fact that the *o*-tolunitrile carbanion **116** can be acetylated with an aromatic ester to afford **117**.[117] The overall yield from *o*-tolunitrile to isoquinoline **119** was 24% (**Scheme 35**).[147]




**Scheme 35**[147]

### *3.5.7 Cyclization of Aralkenyl-Substituted Quarternary Ammonium Salts*

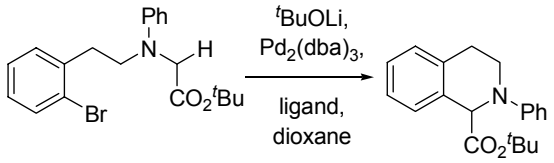
Quarternary ammonium salts **120** possessing both a β-alkenyl and a benzyl substituents cyclize in the presence of polyphosphoric acid to furnish tetrahydroisoquinoline salts **121** in respectable yields (**Scheme 36**).[148]




**Scheme 36**[148]

### *3.5.8 Palladium-Catalyzed Arylation*

The palladium-catalyzed enolate arylation of ketones is a useful tool for the synthesis of α-arylated carbonyl compounds. Gaertzen and Buchwald have reported the palladium-catalyzed intramolecular α-arylation of the related carbonyl compounds, the esters to synthesize a variety of fused bicyclic and tricyclic systems. When the ester **122** was treated with $^{t}$BuOLi, $Pd_2(dba)_3$ and a phosphine ligand in dioxane, it gave the tetrahydroisoquinoline carboxylic acid ester **123** in good yield (**Scheme 37**).[149]

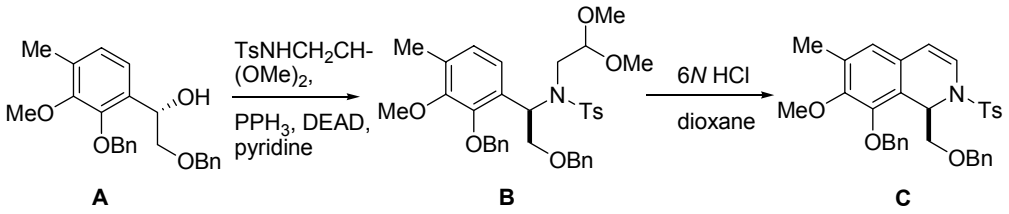



**122** **123**

**Scheme 37**[149]

### *3.5.9 Mitsunobu-Coupling Reaction*

Kaufman has used the Mitsunobu reaction for the synthesis of dihydroisoquinolines. Upon treatment of the secondary alcohol **124** with toluene *p*-sulfonamide, triphenylphosphine, DEAD and pyridine, the tosylaminoacetal **125** was obtained in 64% yield.[150] This compound was then cyclized using 6*N* HCl to obtain the tetrahydroisoquinoline **126** in 80% yield (**Scheme 38**).

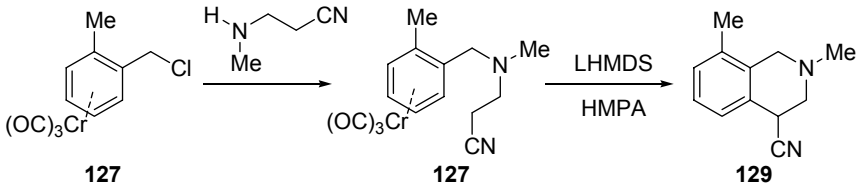



**A** **B** **C**

**Scheme 38**[150]

### *3.5.10 Chromium-Mediated Cyclization*

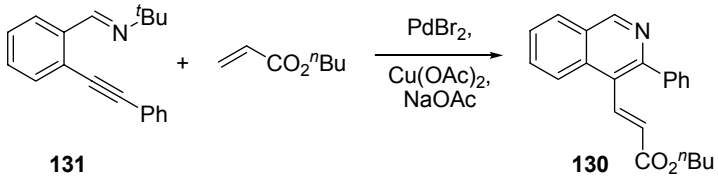
Using the inherent ability of nucleophiles to add to arene $Cr(CO)_3$ complexes, Yeh *et al.*[151] have reported the synthesis of tetrahydroisoquinolines. The addition of *N*-methyl-β-alaninenitrile to benzylchloride chromiumtricarbonyl complexes **127**, followed by the treatment of the arene-chromium tricarbonyl complex **128** with lithium-hexamethyldisilazide in hexamethylphosphoric triamide, gave the product of nucleophilic addition, **129** (**Scheme 39**).




**Scheme 39**[151]

### *3.5.11 Pd(II)-Catalyzed Cyclization*

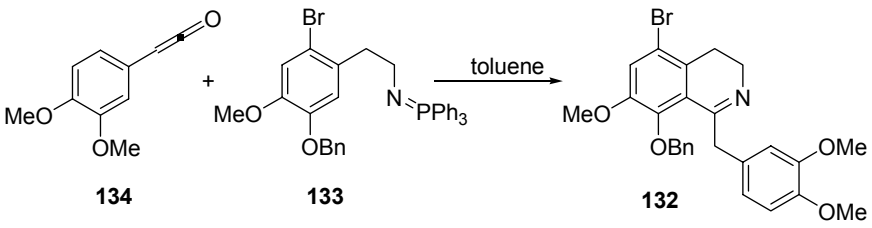
The Heck reaction and other palladium-catalyzed cylizations are well known methods for the preparation of cyclic systems. Recently, Huang and Larock described the synthesis of a number of different 4-arylisoquinolines **130** by the Pd(II)-catalyzed cyclization of substituted imines **131** followed by alkenylation.[152] An example of this is outlined in **Scheme 40** below.




**Scheme 40**[152]

### *3.5.12 Aza-Wittig Reaction*

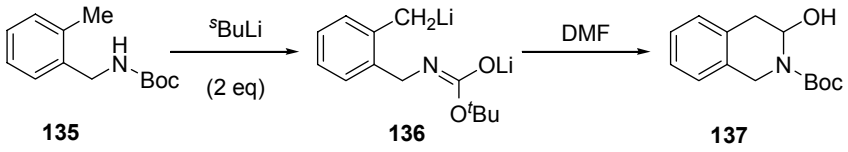
Even an intramolecular aza-Wittig reaction was used by Rodrigues *et al.*[153] to synthesize substituted 1-benzyl-3,4-dihydroisoquinolines **132** from phenethylimino-phosphoranes **133** with arylketenes **134** in good yields (**Scheme 41**).




**Scheme 41**[153]

### *3.5.13 Heteroatom-Directed Lateral Lithiation*

A number of heterocycle forming annelations based on heteroatom-facilitated lateral lithiation reactions have recently been reported and these procedures offer useful alternatives to the classical syntheses of isoquinoline derivatives **137**.[154] A synthesis of tetrahydroisoquinolines that was based on the lateral lithiation of *N*-(*tert*-butoxycarbonyl)-2-methylbenzylamine **135** is described in **Scheme 42** below. It provides routes to a variety of substituted dihydroisoquinolines, tetrahydroisoquinolines and the simple isoquinolines.[154]




**135** **136** **137**

**Scheme 42**[154]

## 4. The Wits RCM approach towards the synthesis of 6-, 7- and 8-membered benzo-fused heterocycles

Having looked at a number of different synthetic approaches to the benzazocines, benzazepines and isoquinolines, this section will now outline the Wits approach to these systems in detail. The Wits methodology encompasses the fact that the selective isomerisation of one or both double bonds in a certain substrates can sometimes facilitate the synthesis of various ring sizes from the same set of starting materials.[5]

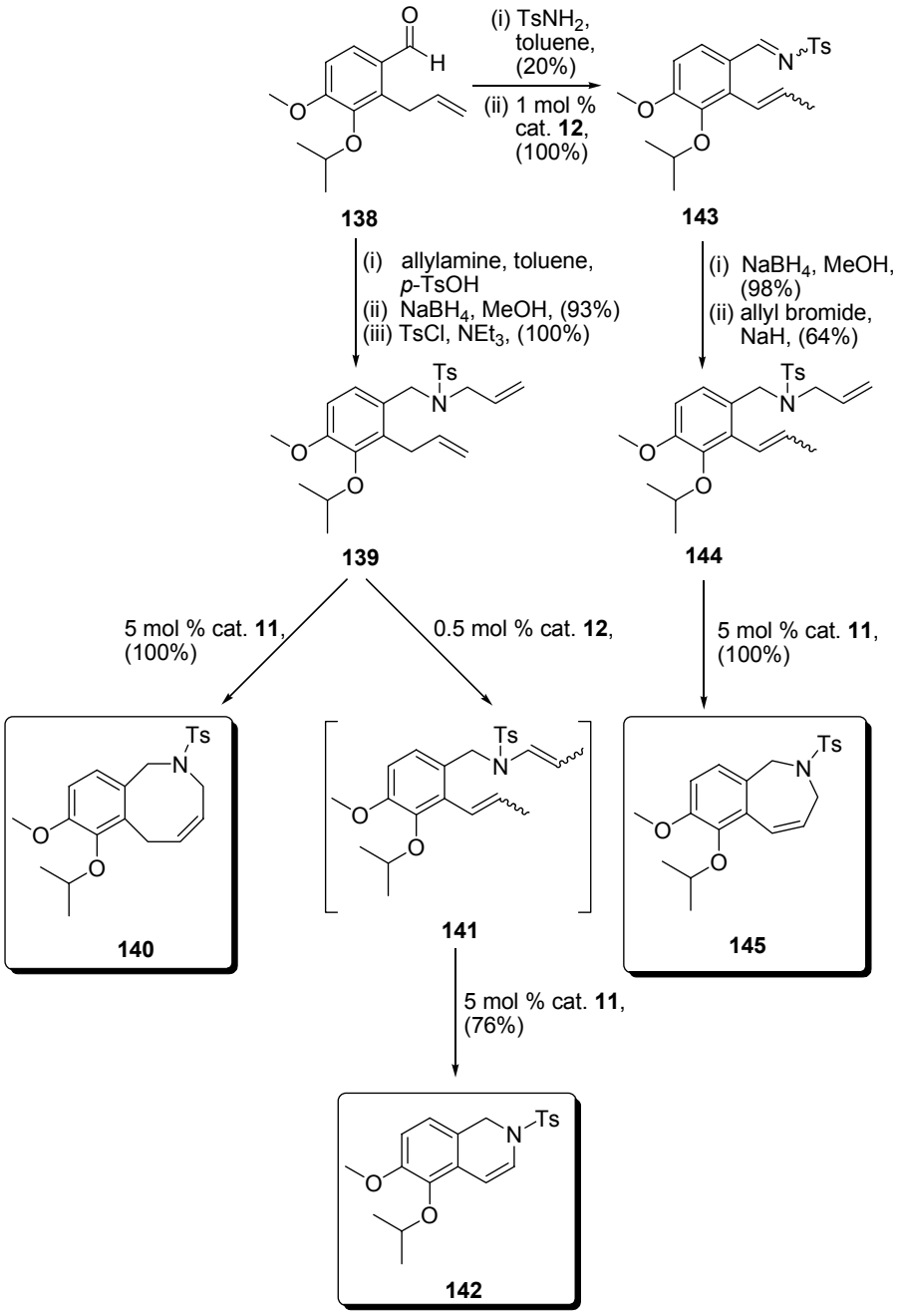
The Wits approach began with the synthesis of the common intermediate **138**, which was prepared according to the methodology published by Rousseau.[1] The common intermediate **138** then underwent a reductive amination and the amine formed was tosyl protected to give compound **139**. The protected amine was then subjected to standard methathesis conditions, using 5 mol % Grubbs II catalyst **11**, and the desired benzazocine **140** was obtained in quantitative yield.[129]

The 6-membered ring **142** was prepared by the isomerisation of both the allyl chains in the protected amine **139**, using Ru-isomerisation catalyst **12** giving intermediate **141,** before

RCM was performed. The desired compound **142** was obtained in 76% yield from the one-pot reaction.[129]

In order to access the benzazepine skeleton, a different approach was utilized. The common intermediate **138** was treated with tosyl amine yielding imine **143**. This was then subjected to a sodium borohydride reduction and the intermediate formed was subsequently allylated to give compound **144**. Amine **144** was then subjected to the RCM conditions, yielding the desired benzazepine **145** in quantitative yield.[129]

A general overview to the approach developed by Pathak is shown schematically in **Scheme 43** below.[129]

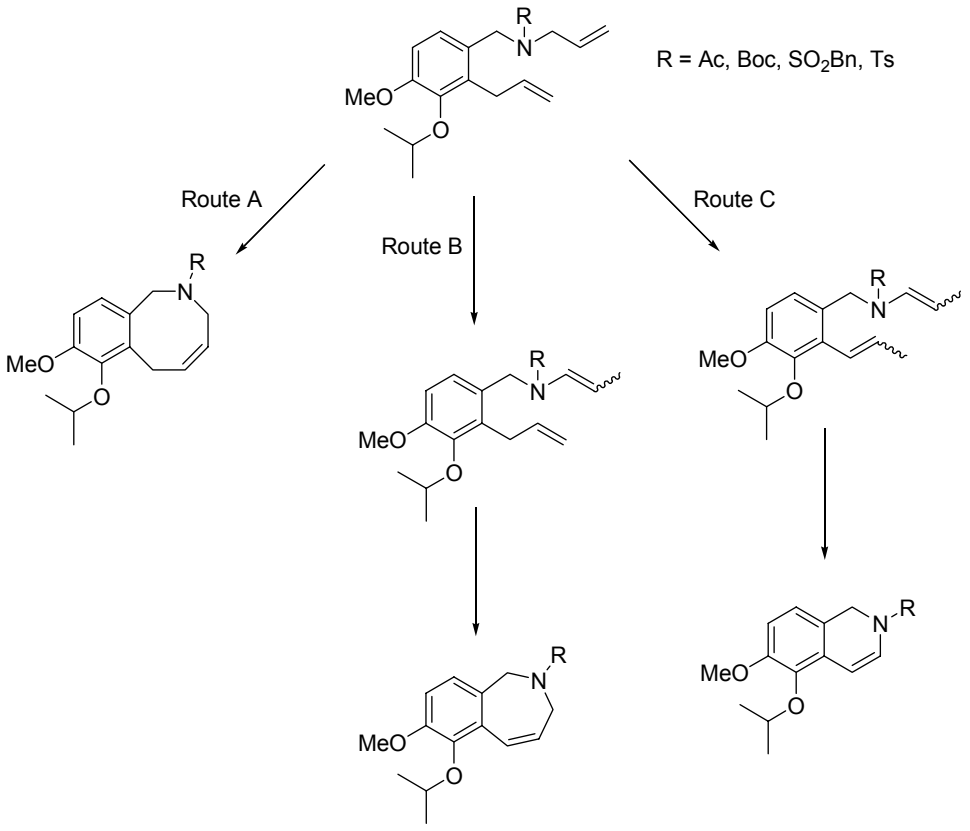



**Scheme 43** An outline of the Wits Approach to 6-, 7- and 8-membered benzo-fused heterocycles[5]

## 5. Aims of this Section

- To synthesize a range of benzazocines from the common synthetic precursor **138** using the ring closing metathesis strategy developed by Pathak[129] (*Route A*).

- To test the feasibility of deprotection reactions on the final 6-, 7- and 8-membered nitrogen-containing benzo-fused systems.
- To utilize ring closing metathesis to access a range of benzazepine systems from a common synthetic precursor (*Route B*).
- To investigate the possibility of selective isomerisations in our diene systems, using the ruthenium-based catalyst outlined by Krompiec[29] (catalyst **12**).
- To examine other diene systems to determine if with double allyl isomerisations it is possible to obtain isoquinoline analogues via ring closing metathesis (*Route C*).




**Scheme 44**

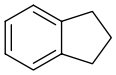
The results concerning our synthesis of the nitrogen-containing benzo-fused heterocycles are discussed in detail in **Chapter 4.**

# *Chapter 3:*

# *Introduction to the Indenols, Indenones and Indanones*

## *Chapter 3: Introduction to the Indenols, Indenones and Indanones*

In the previous chapter the importance of 6, 7 and 8 membered benzofused heterocyclic rings was described. In this chapter we will now introduce important 5 membered benzofused heterocycles, namely the indenols, indenones and indanones. The indan skeleton **146** (**Figure 15**) is ubiquitous in nature and examples are found in the indenol, indenone and indanone families.

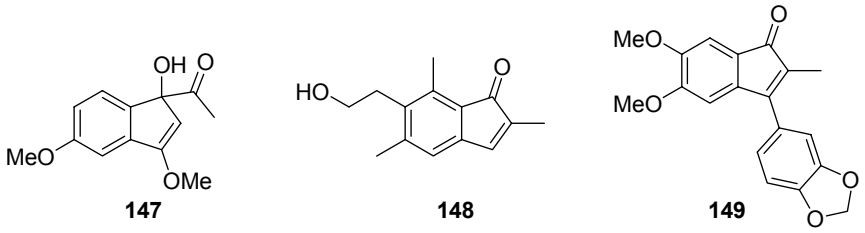


**X**

**Figure 15**

### 1. General explanation of Indenols, Indenones and Indanones

The general indene skeleton is a fairly common motif in natural and artificial compounds e.g. indenol **147**, isolated from the plant Adlay (*Coix lachryma-jobi* L. var. *ma-yuen* Stapf)[155] and indenone **148**, a synthetic derivative from the rhizomes of *Pteris wallichiana.*[156] Another example would be the neo-lignin **149** from the fruits of *Virola Sebifera* (**Figure 16**).[157] As a result, various methods for the synthesis of indenols[158] and indenones[159] have been recently reported in the literature.




**147** **148** **149**

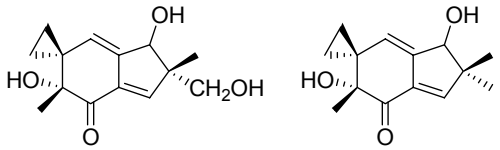
**Figure 16**[155-157]

## 2. Indenols

Indenols can be used as intermediates in the synthesis of organic compounds such as the chrysanthemates, which possess potent insecticidal properties.[160] Some indenols have also shown analgesic and myorelaxation activity.[161] They can be prepared by the reaction of *ortho*-manganated aryl ketones or benzaldehydes with alkynes.[162] A number of representative indenol examples and compounds related in structure will be described in the following sub-sections.

### *2.1 Illudin S and M*

In a report in the journal Nature in 1963 describing the isolation of an anti-tumor substance from *Lampteromyces japonicus* (synonymous with *O. illudens*), a bioluminescent mushroom,[163] it was stated that the mushroom was known in Japan for its toxicity, which had occasionally caused accidents due to its similarity in appearance to edible mushrooms.[164] A survey of wood-destroying fungi with anti-bacterial activity was carried out at the New York Botanical Garden in 1943, and *O. illudens* was found to inhibit the growth of *Staphlococcus aureus*.[165] Isolation of crystalline antibiotic substances illudin S **150** and illudin M **151** from culture liquids of the fungus was reported in 1950,[165] and elucidation of the structures was reported in 1963.[166] It was found to contain an indenol-like backbone. Although compounds **150** and **151** are not strictly indenols it can be postulated that they can be converted into their corresponding biological "relatives", the indenols (see section 4.1 for other examples as well as **Scheme 45**).




Illudin S **150** Illudin M **151**

**Figure 17**[164]

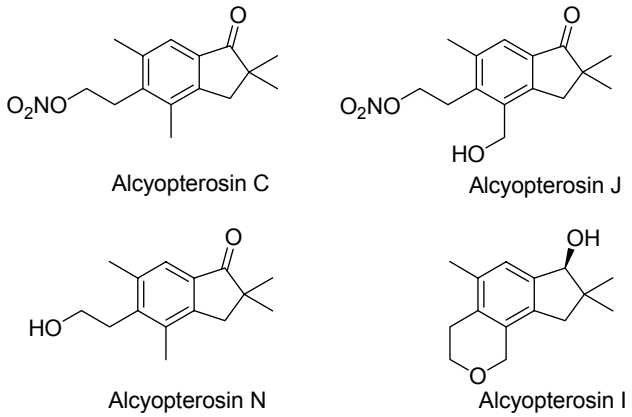
Illudin S **150** was also isolated from the mushroom *L. japonicus* by two groups in Japan and was found to be the toxic factor in the mushroom.[167] Illudins and certain derivatives have

been evaluated for anti-tumor activity and illudin M **151** significantly increased the life span of rats with Dunning leukemia.[164] Illudin S **150** and illudin M **151** are toxic to a wide range of tumor cells and normal cells after prolonged exposure, but show selective toxicity on short exposure for human myelocytic leukemia, and epidermoid, lung, ovarian, and breast carcinoma cells of various species of origin.[168]

Thus, illudins have the potential to be useful antitumour agents, however, because of their extreme toxicity and consequent low therapeutic index, there is scope for modified structures that may reduce cytotoxicity without compromising anti-tumour activity.[164]

### *2.2 Illudalane sesquiterpenoids*

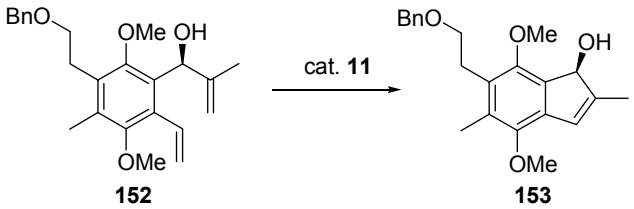
Illudalane sesquiterpenoids are not widely distributed in nature, and to date most of the compounds of this class have been isolated from ferns[169] and fungi.[170] It has been found that the soft coral *Alcyonium paessleri* from the South Georgia Islands is a rich source of aromatic sesquiterpinoids of the rare illudalane class.[171] Recently 15 novel illudulane sesquiterpinoids, alcyopterosins A-O were isolated, with eight of these containing nitrate ester groups.[171] These are the first nitrate esters to be reported as natural products, as well as the first illudalane sesquiterpinoids from the marine environment. These compounds contain both a modified indanol and various indanone backbones[171] (**Scheme 45**), with a full discussion of the indanone containing compounds following in *Section 4.4.*




**Scheme 45** Illudalane sesquiterpenoids[171]

### *2.3 Synthesis of Indenols by Ring Closing Metathesis*

Recent methods towards the synthesis of indenols include transition metal-catalyzed carbocyclisations utilizing nickel,[172] manganese,[173] cobalt[174] and palladium.[150b-d,175] The first reported use of RCM for the synthesis of an indenol was outlined by Clive and Yu[176] Their synthesis of (+)-puraquinonic acid included a ruthenium-mediated RCM to form substituted indenol **152** from diene **153** (**Scheme 46**).




**152** **153**

**Scheme 46** Synthesis of indenol using ring closing metathesis by Clive[176]

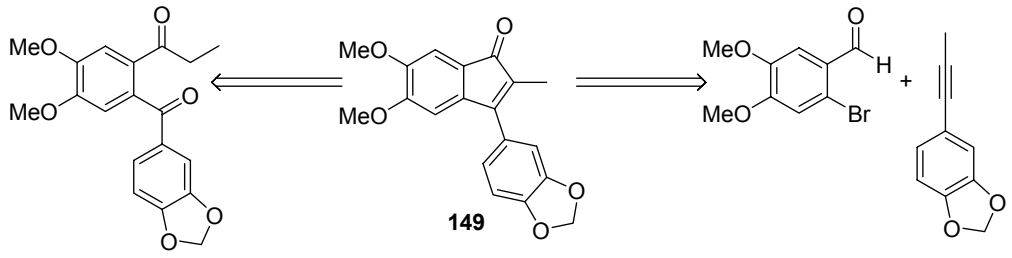
## 3. Indenones

Indenones have been used as fungicides, estrogen binding receptors, and fermentation activators.[165] They are also useful intermediates in the synthesis of a wide variety of natural products (eg: steroids or gibberellins).[165] They can be prepared by following traditional organic synthetic methods[177] or by metal-mediated reactions using carbonyl complexes (in these examples the carbonyl group comes from metal coordinated carbon monoxide).[160] Indenones, have also been synthesized by ruthenium-,[151c] palladium-[165] and rhodium-mediated cyclizations[151b] amongst others. A select number of examples will be described in the section below. Where applicable, synthetic approaches of interest to the indenone skeletons will also be described.

### *3.1 Indenone Based Lignans*

Compound **149** was isolated from the fruits of *Virola sibifera*.[149] This indenone has attracted much interest as it is the only 3-arylindenone to have been isolated from natural sources and thus represents a new class of lignans. It was reported recently that the 3-arylindenones display anti-tumour[178] and post coital contraceptive activity.[179]

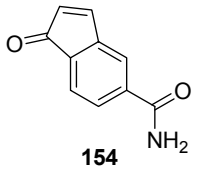
Two syntheses of indenone **149** have been investigated, the first based on a classical intramolecular aldol condensation,[149] and the second based on a new annulation procedure developed by Heck and Larock.[165,180] The retrosynthesis for these approaches are outlined in **Scheme 47** below.




**Scheme 47** Retrosynthetic analysis for indenone **149**[149]

*3.2 3CP Inhibitors*

The human rhinoviruses (HRV) are the primary cause of the common cold and belong to the Picornovirus family.[181] Picornoviruses have a single positive-stranded RNA genome that is translated into a 2000+ amino acid polyprotein. The 2A and 3C protease (3CP) processes this polyprotein into functional HRV viral proteins,[182] thus a synthesis of a series of inhibitors of 3CP could lead to a cure for the common cold. So far, the bicyclic indenone **154** has been found to be the most potent of the ketone derivatives, affording potent reversible inhibition of 3CP.[182]




**154**

**Figure 18**[182]

*3.3 FGFr and TK Inhibitors*

Fibroblast growth factor receptors (FGFr) belong to a family of transmembrane proteins that are involved in mitogenic signaling and the regulation of a number of cellular processes.[183]

The binding of the fibroblast growth factor to its receptor (FGFr) activates the cytosolic tyrosine kinase (TK) domain for substrate binding and phosphorylation.[184]

It has been suggested that loss of regulatory control of FGFr is linked to a number of disease states, including rheumatoid arthritis, angiogenesis, restenosis (following coronary angioplasty), and various kinds of cancers.[185,186] FGFr may stimulate production of plaminogen activator, mediating migration of tumor cells into normal tissues.[185] A number of 1-oxo-3-substituted-1*H*-indene-2-carboxamides **155-157** have been identified as potent inhibitors of TK activity. These compounds also exhibited selective inhibition of FGFr relative to platelet derived growth factor receptor kinase (PDGFr).[186]

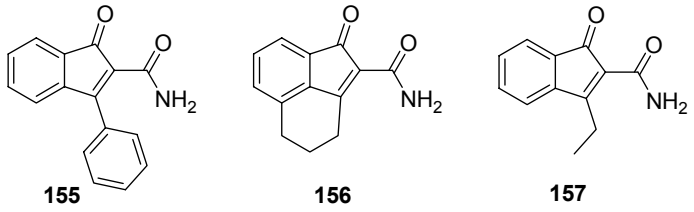
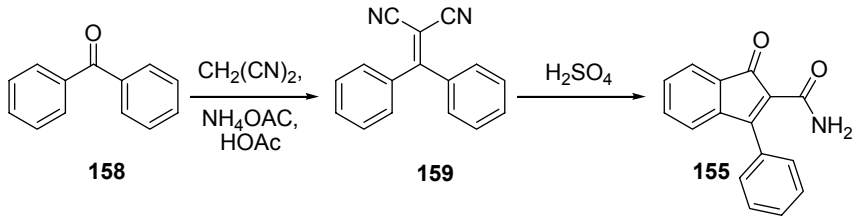


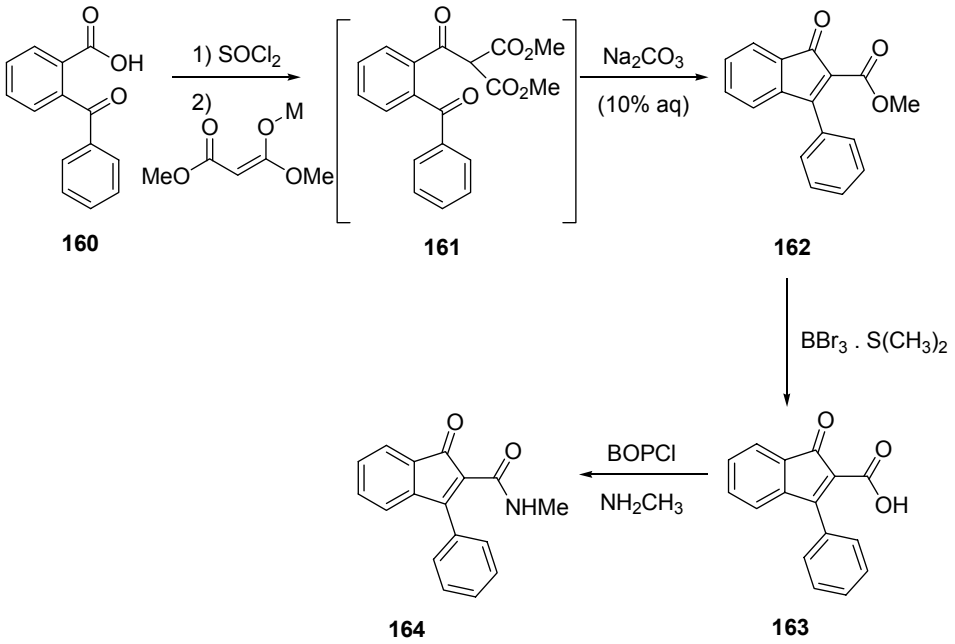

**Figure 19**[186]

The method used to prepare **155** is outlined in **Scheme 48** below. Benzophenone **158** was converted to the corresponding malonitrile **159** and this was then cyclized in sulfuric acid. The desired product was obtained in only 9% yield.[186] This method provides a direct route to 3-substituted analogues of **155**, but offers little flexibility of the carboxylic moiety.




**Scheme 48**[186]

Another route involved an intermediate reported by Burger and co-workers.[187] In this route 2-benzoylbenzoic acid **160** was converted to a diethyl malonate adduct **161** using thionyl chloride and potassium diethyl malonate (**Scheme 49**).[186]

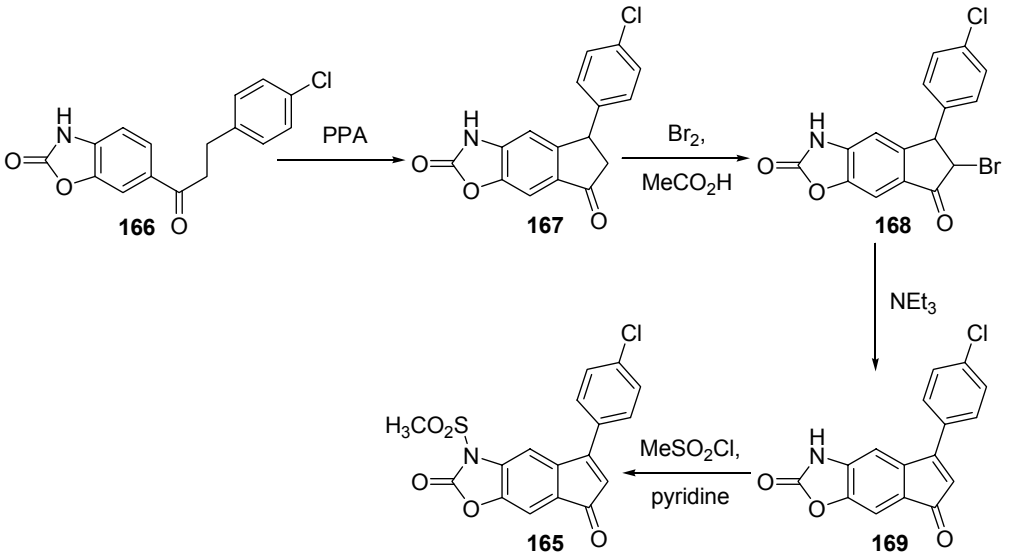



**Scheme 49**[186]

*3.4 COX-2 Inhibitors*

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen or inomethacin are widely used in the treatment of pain and inflammatory diseases.[188] Selective cyclooxogenase enzyme (COX-2) inhibitors could provide anti-inflammatory, analgesic and antipyretic drugs devoid of the unwanted side effects such as ulcers and renal failure associated with the classical nonselective NSAIDs.[189] Selective COX-2 inhibition could also be an important strategy to prevent or treat a number of cancers and to delay or slow the clinical expression of Alzheimer's disease.[190] Examples of this class of compounds include those with both the indenone and the indanone backbone.

Indenone **165** was synthesized by Chavatte *et al.* as outlined in **Scheme 50**.[188] Intramolecular cyclization of chalcone **166** was achieved by the treatment with polyphosphoric acid affording indanone **167** in 30% yield. The reaction of bromine in acetic acid-chloroform gave compound **168**, which was followed by debromination with triethylamine in acetone to yield compound **169**. Treatment of **169** with methanesulfonyl chloride in pyridine gave **165** in 76% yield.[188]




**Scheme 50** Synthesis of indenone **165** by Chavatte and co-workers[188]

## *3.5 Ethacrynic Acid Analogues*

Ethacrynic acid (ECA) **170** is a potent anti-gelling and anti-sickling agent, making ECA and its structural analogues useful therapeutic agents for the treatment of sickle cell anemia.[191] ECA however, may not be used due to its strong diuretic properties, and thus the analogues are important targets for synthesis. A number of structural analogues exist **171-174**, having both the indenone and the indanone moiety present (**Figure 20**).[191]

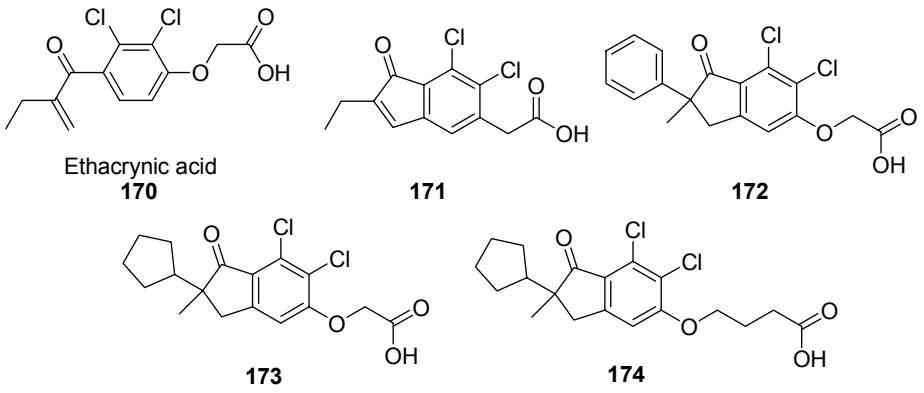



**Figure 20**[191]

### *3.6 Topoisomerase I inhibitors*

The indenoisoquinolines are a class of cytotoxic molecules that have been demonstrated to inhibit topoisomerase I (top I) by intercalating between DNA bases at the enzymes cleavage site.[192] This mechanism of action is identical to the natural product camptothecin **175** and its clinically useful derivative topotecan **176**.[192]

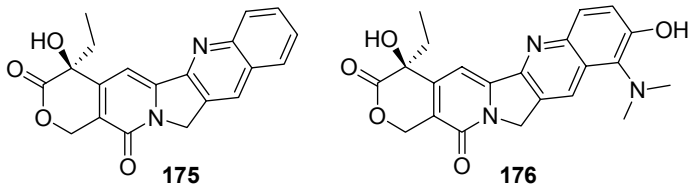



**Figure 21**[193]

Recently, a new class of indenoisoquinolines and dihydroindenoisoquinolines was synthesized by Morrell *et al.*[193] They possess a nitro substituent on the isoquinoline ring. The molecules have been tested for cytotoxicity in a 55 cell line screen and for top 1 inhibition. Results indicate that these substances are the most potent class of indenoisoquinolines synthesized to date.[193] Examples of these indenoisoquinolines (**177-179**) are outlined in **Figure 22** below.

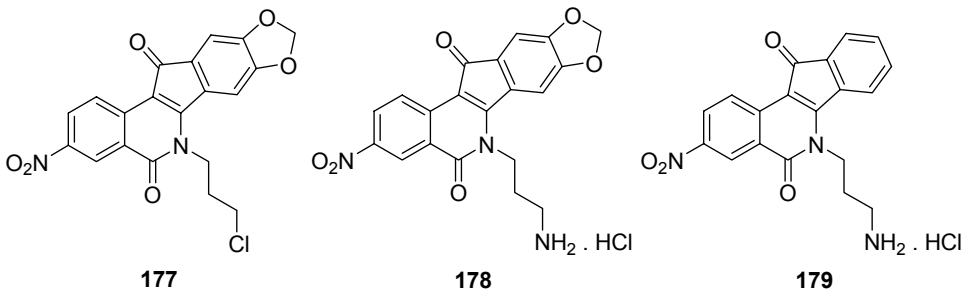


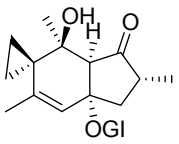

**Figure 22**[193]

## 4. Indanones

In this section a few examples of important indanone containing compounds will be described as well as some relevant synthetic approaches to them.

### *4.1 Ptaquiloside and the Pterosins*

A number of compounds related to the illudins have been isolated from *O. illudens* and other basidiomycetes.[194] Similar compounds have also been found in certain ferns, including the bracken, *Pteridium aquilinum*, which is a commercially important and widely distributed fern.[164] One bracken metabolite, ptaquiloside **180**, an indanone related structure, was found to be carcinogenic and to be a toxic factor responsible for acute cattle bracken poisoning.[195]



Ptaquiloside
**180**

**Figure 23**[164]

The related indanones are called pterosins and were reported to be cytotoxic and to possess antibacterial activity. The two most cytotoxic compounds were pterosin Z **181** and dehydropterosin B acetate **182**.[164] The chloroindantriols **183** and **184** derived from treatment of illudin M with dilute hydrochloric acid, were found to be comparable to the anticancer alkylating agent BCNU (**Figure 24**).[164] Thus, it appears that the indan-type structures are inherently somewhat cytotoxic.

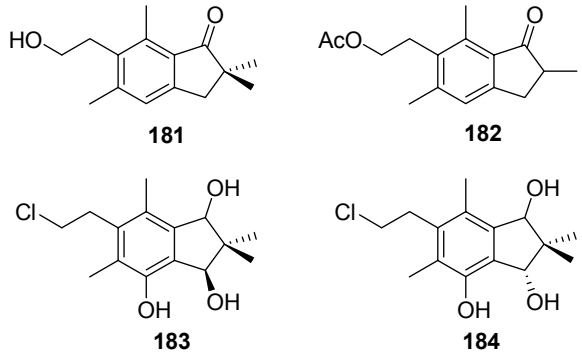



**Figure 24**[164]

The major pterosin found in bracken is pterosin B **185**. This compound may be an artifact formed by the decomposition of an unstable precursor, namely ptaquiloside **180**. Ptaquiloside readily loses a molecule of glucose giving an unstable dienone which reacts with water forming pterosin B **185** (**Figure 25**).[164]

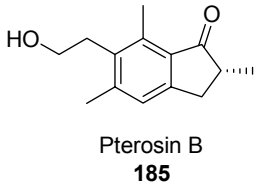
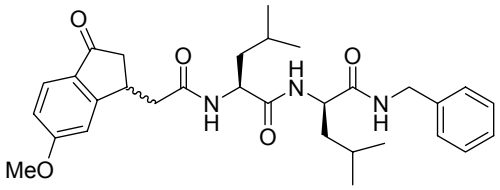



**Figure 25**[164]

*4.2 20S and 26S Proteasome Inhibitors*

The 26*S* proteasome is recognized as one of the central enzymes of nonlysosomal protein degradation.[196] This proteasomal protein degradation of key regulatory proteins, such as the cyclins and Iκ-B, has been identified as a mandatory step in controlling the respective signaling pathways for cell cycling and activation of NFκ-B.[197] Inhibiting the degradation of these important signal proteins may prove useful in controlling diseases, such as cancer and inflammation, that are driven by these cascades.[196] It has been reported that there exists a series of 5-methoxy-1-indanone-3-acetic acid based proteasome inhibitors that are highly selective for the chymotrypsin-like activity of the 20*S* proteasome. The structure of a representative example **186** of these novel proteasome inhibitors is shown in **Figure 26**.[196]



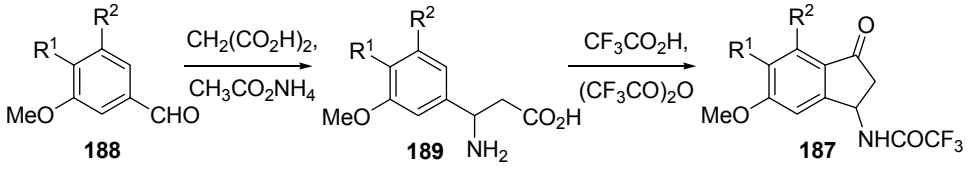

Indanone-Leu-d-Leu-benzamide

**186**

**Figure 26**[196]

*4.3 Aromatase Inhibitors*

The aromatase enzyme complex, responsible for the conversion of androgen to estrogen, is involved in reproduction, development, sexual differentiation, behavior, in some brain functions, as well as in the growth of hormone-dependent cancers (including some breast cancers).[198] Many inhibitors have already been studied; the first and second generation aromatase inhibitors are presently the major clinically available inhibitors. However, a third generation of potent non-steroidal aromatase inhibitors has been developed recently, and these include letrozole, vorozole and anastrozole.[199] These methoxy-3-trifluoroacetylaminoindan-1-ones **187** are prepared by a one-pot synthesis starting from methoxybenzaldehydes **188** via 3-amino-3-(methoxyphenyl)propionic acids **189** by means of refluxing trifluoroacetic acid and its anhydride (**Scheme 51**).[200]



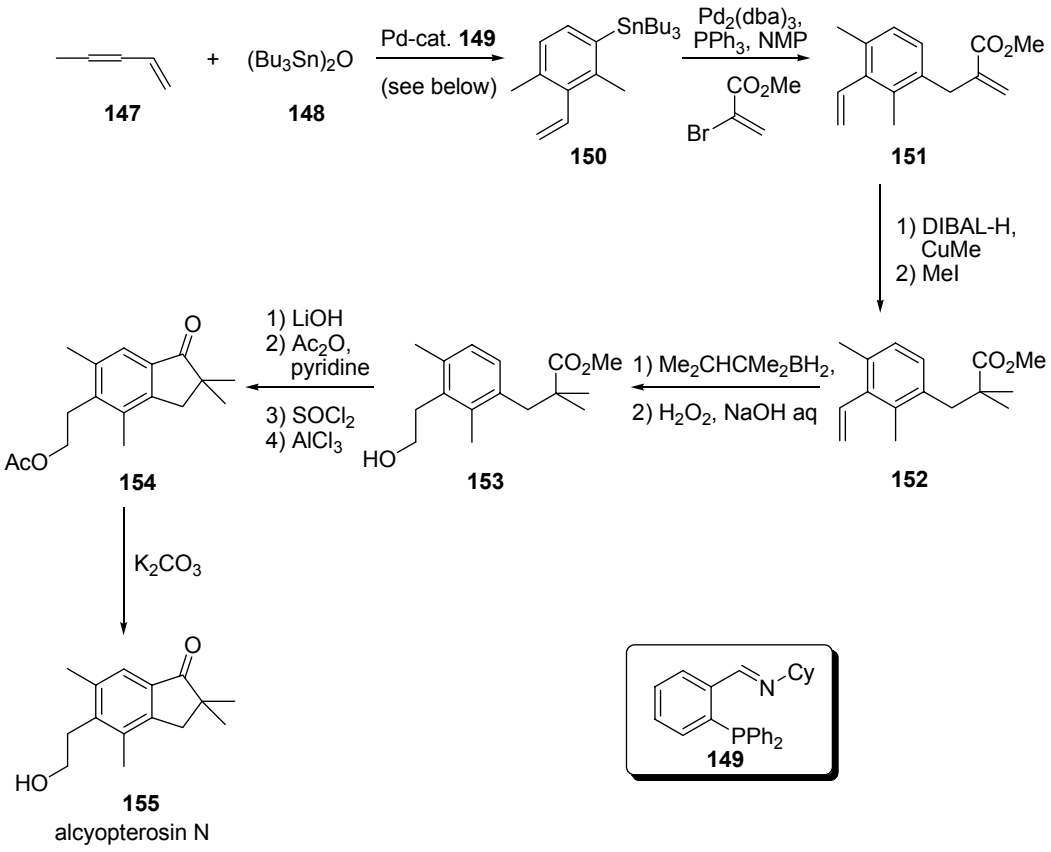

$R^1$=H, OMe, OMe and $R^2$=H, H, OMe

**Scheme 51**[200]

*4.4 Alcyopterosin N*

Alcyopterosin N **190** has recently been isolated from sub-Antarctic soft coral, *Alcyonium paessleri*, for background information refer to *Section 2.2* (Illudalane sesquiterpenoids).

Outlined in **Scheme 52** below is the synthesis of alcyopterosin N **190** using stannylative cycloaddition of enynes catalyzed by a palladium-iminophosphine.[201]




**Scheme 52** Synthesis of alcyopterosin N **171**[201]

## *4.5 Cyclooxogenase Inhibitors*

The cyclooxogenase enzyme exists in two forms,[202] a constitutive form COX-1, and an inducible form COX-2.[203] The COX-1 form is believed to be important in the maintenance of normal physiological functions, such as gastric cytoprotection and the COX-2 form can be induced by a wide variety of inflammatory mediators, and appears to play a major role in the production of prostglandins associated with inflammation responses.[203] Selective inhibition of COX-2 has useful anti-inflammatory therapeutic effects without the ulcerogenic side effects associated with the currently available nonsteroidal anti-inflammatory drugs, all of which inhibit both COX-1 and COX-2.[204] The aryl sulfonamide flosulide **199** is a potent and selective COX-2 inhibitor.[205] It has also been reported that the thioether analogue of flosulide,

L-745,337 **200**, is a potent and more selective COX-2 inhibitor, with superior pharmacokinetic and *in vivo* profiles.[203]

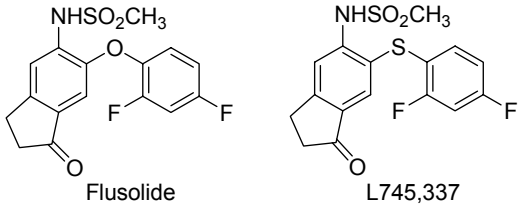


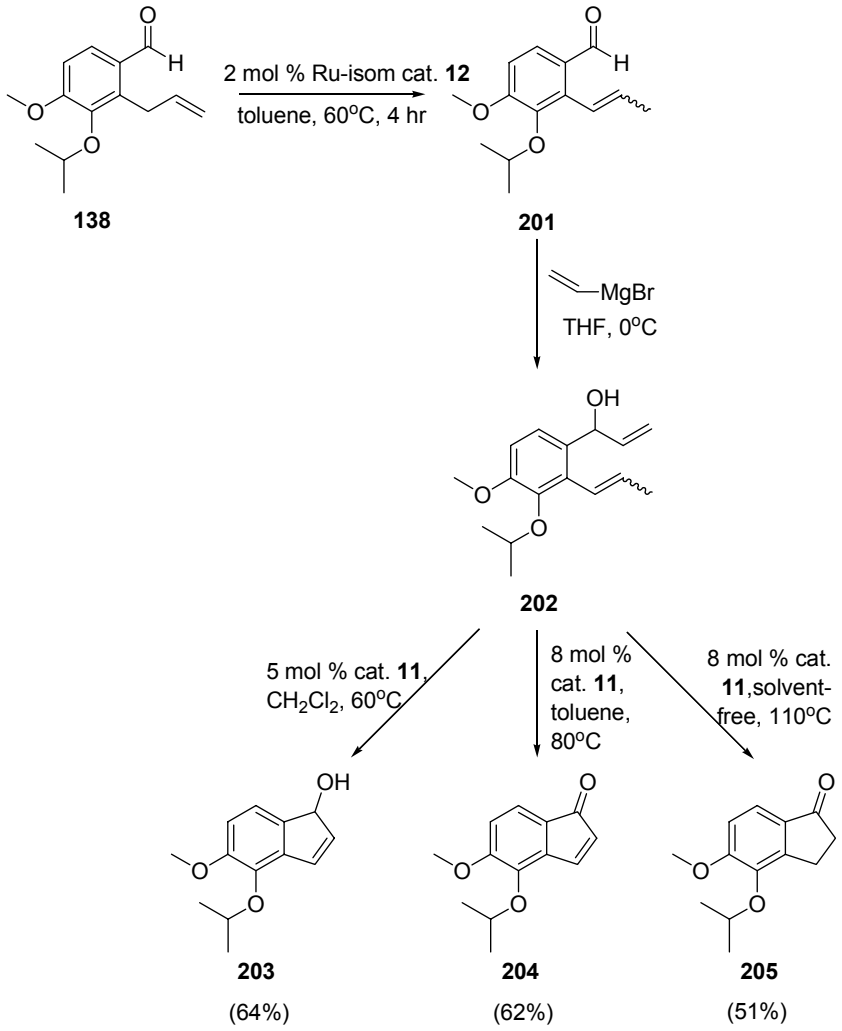

**Figure 27**[203]

## 5. The Wits RCM approach towards the synthesis of indenols, indenones and indanones[8]

In this approach, the readily available substituted benzaldehyde **138** was prepared according to the procedure outlined by Rousseau.[1] The benzaldehyde **138** was then treated with the Ru-isomerisation catalyst **12** and the isomerised product **201** was obtained. This was then subjected to a Grignard addition reaction,[206] affording the alcohol **202**. Standard RCM procedures were then employed for the synthesis of the indenol **203,** ustilising 5 mol % Grubbs II catalyst **11** in dichloromethane at 60$^{o}$C. The desired product, compound **203**, was isolated in 64% yield.

During the synthesis of the indenols, a small highly-fluorescent yellow spot was observed by thin layer chromatography that increased over time.[8] It was shown in the post-doctoral work of Coyanis,[48] that by optimizing the conditions for the indenol synthesis it was possible to isolate the corresponding indenone.[161] Coyanis found that longer reaction times and harsher conditions, i.e. toluene at 80$^{o}$C, utilising 8 mol % Grubbs II catalyst **11**, led to the synthesis of indenone **204** in 62% yield (**Scheme 53**).[158]

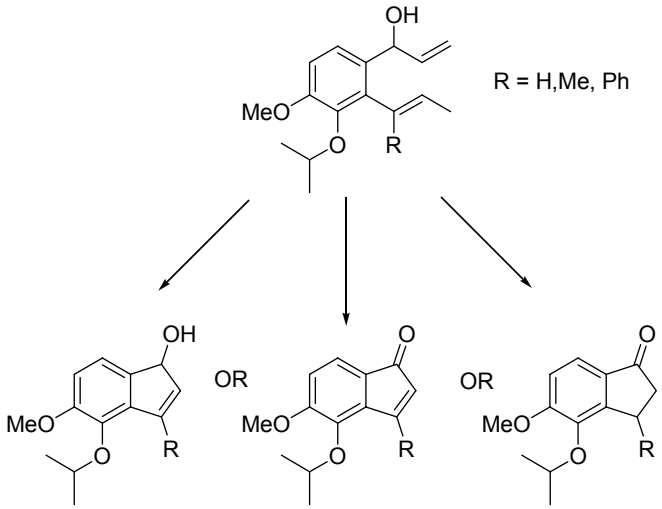
Quite serendipitously, the corresponding indanone **205** (**Scheme 53**) was isolated when the reaction mixture ran dry overnight. It was fully characterized and when the reaction was repeated, the indanone was found to form under exceptionally harsh conditions, namely solvent-free conditions at high temperatures and catalyst concentrations. The desired indanone **205** was isolated in 51% yield on the second attempt.




**Scheme 53 The Wits Approach**[158]

## 6. Aims of this Section

- To synthesize a range of substituted indenols, indenones and indanones from the common synthetic precursors (eg: compound **176**) using the previously developed methodology of Coyanis.[48]




**Scheme 54**

- To attempt to explain the role of ruthenium in indenol-indenone-indanone conversions via the implementation of a model $^{1}H$ NMR study, which would include control samples where ruthenium has been depleted.

Results pertaining to the synthetic study of the indenols, indenones and indanones are described in **Chapter 5.**

# *Chapter 4:*

# *Results and Discussion for the Synthesis of N-containing Benzo-fused Heterocycles*

# *Chapter 4: Results and Discussion for the Synthesis of N-containing benzo-fused heterocycles*

## 1. Introduction

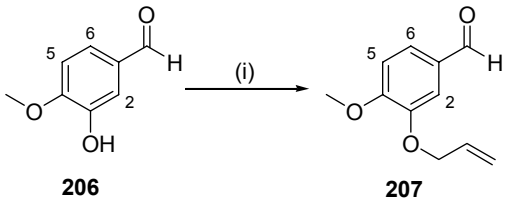
This chapter concerns our results on the preparation of the nitrogen-containing benzo-fused heterocycles. First, it will cover the synthesis of a number of common starting materials from a common intermediate. Then, the following sections will each deal with the individual synthesis of the 6-, 7- and 8-membered heterocyclic ring systems. Please refer to the experimental section (***Chapter 7***) for the detailed description of each synthetic step.

## 2. The 1-Propenyl System

### *2.1 Synthesis of Starting Materials*

A number of starting materials that were common to the synthesis of the 6-, 7- and 8-membered ring systems will be outlined in this section.

#### *2.1.1 O-Allylation of Isovanillin*

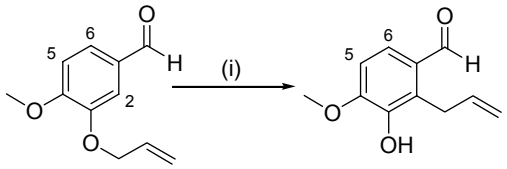



**Scheme 55** (i) 2.5eq, $K_2CO_3$, 2.5eq allyl bromide, DMF, 60$^{o}$C, 20 h

3-Allyloxy-4-methoxybenzaldehyde **207** was prepared according to the procedure outlined in Rousseau[1] which was developed in our laboratories a few years ago. This method involves the *O*-allylation of isovanillin **206**, with the phenol on isovanillin being deprotonated using potassium carbonate and then allyl bromide being added to facilitate the *O*-allylation. Rousseau obtained the desired product in 99% yield after 3-12 h. Our best yield to date is 99% after stirring for 20 h, which was obtained when the reaction was performed on

132mmol scale. 3-Allyloxy-4-methoxybenzaldehyde **207** was obtained as a bright yellow oil and its spectroscopic data corresponded closely with literature values.[1]

### *2.1.2 Claisen Rearrangement and Protection Reactions*




**Scheme 56** (i) commercial microwave, 100 sec or
(i) microwave reactor, 30 min, 200°C

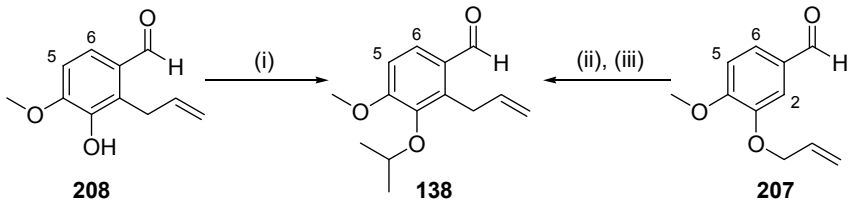
The Claisen rearrangement is known to proceed by means of a concerted, pericyclic [3,3] sigmatropic shift where a six-membered cyclic transition state in a chair conformation is preferred. Many different methods for achieving this rearrangement have been applied successfully[207] and include solvent-free high-temperature conditions as well as low-temperature conditions involving a Lewis acid catalyst such as $BF_3.OEt_2$.[208] Other examples have even used water as a catalyst.[209] Recently, the use of microwave irradiation to facilitate Claisen rearrangements has gained popularity.[210] Thus, we attempted the Claisen rearrangement of **207** by heating the compound under microwave irradiation, either in a commercial microwave or in the microwave reactor.

The commercial microwave oven was set to high power and **207** was heated in the Teflon container in short bursts (15, 15, 20 and 30 sec respectively with 5 min intervals in between each heating), the compound changed colour to brown and 2-allyl-3-hydroxy-4-methoxybenzaldehyde **208** was obtained in 100% yield. The compound was spectroscopically pure and no further purification was required.

We also attempted the Claisen rearrangement using the *Discovery* microwave reactor, setting the temperature to 200°C and performing the reaction in a sealed tube. This required much longer reaction times, with the best yield of 100% being obtained after 30 min. The desired product 2-allyl-3-hydroxy-4-methoxybenzaldehyde **208** was obtained as a viscous yellow oil

with no further purification being required. Even though this reaction required a longer period of time it was favoured over the use of the commercial microwave as it allowed for more controlled conditions that would be easily repeatable and ultimately safer (eg: pressure and temperature regulation, thus preventing runaway reactions).

The major advantage of using the microwave procedures for the Claisen rearrangement is that the product obtained was spectroscopically pure and limited the need for further purification. We observed that the reaction had occurred based on the spectroscopic data obtained as the $^{1}H$ NMR spectrum showed the disappearance of the peak at 7.41ppm for 2-H and the presence of a broad singlet for the OH peak at 5.86ppm. $^{13}C$ NMR spectroscopy showed the corresponding disappearance of the 2-C peak at 110.9ppm and a new peak in the 127-128ppm region that could correspond to the new quaternary carbon, as well as the presence of a new peak at 143.8ppm which corresponds to 3-C. The HRMS displayed a peak at 192.08046, which corresponds to the calculated value for $C_{11}H_{12}O_3$: 192.07864.

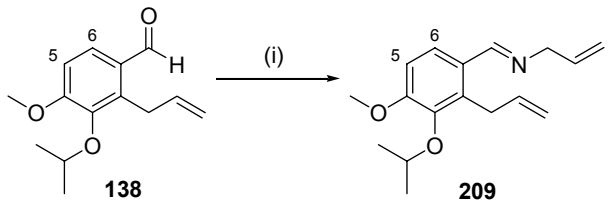



**Scheme 57** (i) 2.5eq $K_2CO_3$, 2.5eq isopropyl bromide, DMF, 60°C, 66 h or
(ii) DMF, 150-160°C, 64 h, (iii) 2.5eq $K_2CO_3$, 2.5eq isopropyl bromide, 60°C, 18 h

Two different approaches were used in the synthesis of 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **138** and they are outlined in **Scheme 57** above. The first of which employed the protection of 2-allyl-3-hydroxy-4-methoxybenzaldehyde **208**, with isopropyl bromide, and yielded the desired compound in 89% yield. The second of which required two steps from 3-allyloxy-4-methoxybenzaldehyde **207**, the Claisen rearrangement followed by the protection of the phenol with isopropyl bromide, as a one-pot reaction and gave the desired product in 75% yield over the two-steps.

In both instances, the product, 2-allyl-3-isopropoxy-4-methoxy-benzaldehyde **138**, was obtained as a bright yellow oil after chromatography. The spectroscopic data was in agreement with that reported in the literature.[1]

### *2.1.3 Imine Formation*

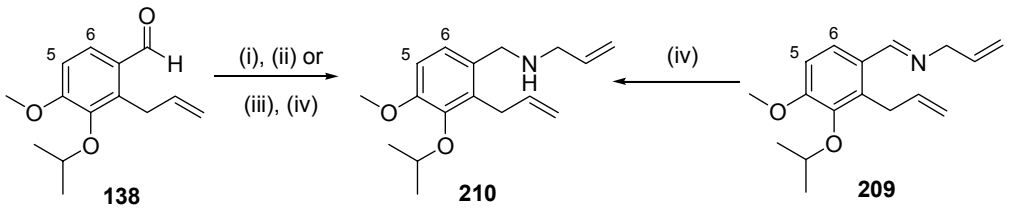



**Scheme 58** (i) 1.4eq allyl amine, rt, 3 h

2-Allyl-3-isopropoxy-4-methoxybenzaldehyde **138** was transferred directly to a round-bottomed flask and to this was added allyl amine; after which the solution was allowed to stir at rt under a nitrogen atmosphere for 3 h. Dry conditions were required for this reaction in order to prevent the reverse reaction from occurring, whereby water adds across the C=N bond and starting materials are obtained. The excess allyl amine was removed *in vacuo* and the *N*-[(*E*)-(2-allyl-3-isopropoxy-4-methoxy-phenyl)methylidene]-2-propen-1-amine **209** was obtained was a yellow oil that was spectroscopically pure and unexpectedly found to be exceptionally stable to air and moisture.

The product was identified by the characteristic loss of the aldehyde peak for 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **138** that was found as a singlet at 10.08ppm in the $^{1}H$ NMR spectrum and a peak at 191.1ppm in the $^{13}C$ NMR spectrum. The new imine proton and carbon signals were identified as the singlet at 8.44ppm in the $^{1}H$ NMR spectrum and at 160.4ppm in the $^{13}C$ NMR spectrum, with the characteristic C=N- stretch found at 1682cm$^{-1}$ in the FTIR spectrum. $^{15}N$ NMR spectroscopy was performed and it showed only one signal at –62.9ppm. In addition HRMS was performed on the compound and a peak was found at 272.17086, which corresponds to $M^{+}$ ($M^{+}$ for $C_{17}H_{23}NO_2$ is calculated as 273.17288, -1H 272.16505). Even though HRMS was not conclusive, all the other spectroscopic data was in agreement and this was deemed sufficient to continue with the next experiment.

### *2.1.4 Reductive Amination Reactions*




**Scheme 59** (i) 3eq allyl amine, 0.1eq *p*-TsOH, benzene, Dean-Stark, reflux, 18 h, (ii) $NaBH_4$, MeOH, 0°C, 1 h or (iii) 1.4eq allyl amine, rt, 24 h, (iv) 1.2eq $NaBH_4$, MeOH, 0°C, 1.5 h

Initially the reductive amination to form *N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-2-propen-1-amine **210** was performed according to the procedure outlined by Pathak and developed previously in our laboratories.[129] In this procedure 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **138**, allyl amine and the acid catalyst *p*-TsOH were dissolved in benzene and heated at reflux using a Dean-Stark head for 18 h, after which time the benzene was removed under reduced pressure, and the resulting mixture extracted with dichloromethane and saturated sodium bicarbonate solution. The residue was subsequently redissolved in methanol, cooled to 0°C, after which sodium borohydride was added and it was stirred at rt for 1 h. The desired compound **210** was then obtained in 90% yield over two steps after extraction.

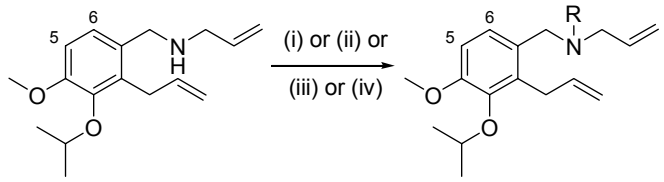
Although this method worked well, it was tedious to perform and we sought a simpler alternative. It was found that the imine **209** could be prepared under solvent-free conditions using only allyl amine at rt, as outlined in *Section 2.1.3* and **Scheme 58**. The imine was exceptionally stable and could then be used in the reduction outlined in **Scheme 59** (iv). The *N*-[(*E*)-(2-allyl-3-isopropoxy-4-methoxyphenyl)methylidene]-2-propen-1-amine **209** was then dissolved in methanol and cooled to 0°C before the addition of sodium borohydride. The solution was then stirred for 1.5 h, an extraction was performed and the solvent was removed *in vacuo*. The desired compound **210** was thereby obtained as a yellow oil in 81% yield.

Owing to the success of the imine reduction **209** we then attempted a one-pot reductive amination using our new procedure on aldehyde **138**. 2-Allyl-3-isopropoxy-4-

methoxybenzaldehyde **138** was stirred with allyl amine under solvent-free conditions for 24 h. Then the excess allyl amine was removed under reduced pressure and the residue was dissolved up in methanol. To the methanolic solution was then added sodium borohydride and it was stirred for 1.6 h at rt. After the workup the solvent was removed *in vacuo* and the amine **210** was obtained in 84% yield over the two steps.

The imine **209** product was identified as outlined in *Section 2.1.3* and the conversion of the imine to the desired amine **210** was followed to determine product formation. The characteristic changes that proved that the reduction had occurred were the disappearance of the N=CH peaks (singlet at 8.44ppm in the $^{1}H$ NMR spectrum and 160.4ppm in the $^{13}C$ NMR spectrum) and the appearance of new N-$CH_2$ (singlet at 3.69ppm in the $^{1}H$ NMR spectrum and 44.6ppm in the $^{13}C$ NMR spectrum) and NH (broad singlet at 1.42) peaks in the $^{1}H$ and $^{13}C$ NMR spectra respectively. All other spectroscopic data correlated to the reported values in the literature.[5]

### *2.1.5 Protection of the Amine*




**210** **139, 211-213**

**Scheme 60** (i) 1.5eq acetic anhydride, 2.5eq pyridine, rt, 3 h, or **211** R = Ac
(ii) 1.2eq $Boc_2O$, 0.1eq DMAP, THF, rt, 3 h, or **212** R = Boc
(iii) 2.5eq $NEt_3$, 1.1eq α-toluenesulfonyl chloride, $CH_2Cl_2$, rt, 3 h, or **213** R = $SO_2Bn$
(iv) 1.4eq $NEt_3$, 1.2eq tosyl chloride, $CH_2Cl_2$, 0$^{o}$C, 3.5 h **139** R = Ts

Originally four different protecting groups were chosen for use in this project. We hoped to compare how efficient they were as protecting groups, in particular to determine if they would remain in place during RCM, and whether or not they influenced the RCM reactions in any way. The reactivity with the different groups in place in order to determine if our procedures were applicable to a wide variety of substituents. Another reason for our choice of multiple protecting groups was to compare the ease with which the different protecting groups could

be removed in the final compounds in order to produce molecules that were similar in structure to a number of the natural products.

**Table 1** Yields for Protecting Group Additions

| | R | Yield (%) |
|---|---|---|
| **211** | Ac | 92 |
| **212** | Boc | 97 |
| **213** | $SO_2Bn$ | 62 |
| **139** | Ts | 94 |

The *N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-2-propen-1-amine **210** was dissolved in pyridine and this was cooled to 0$^{o}$C in an ice-water bath. Then a solution of acetic anhydride in pyridine was added dropwise to the amine, before the reaction mixture was allowed to warm to rt. The reaction mixture was subsequently stirred at rt for 3 h, before being subjected to workup. The resulting mixture was purified by column chromatography and *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)acetamide **211** was obtained as a yellow oil.

A solution of compound **210** in tetrahydrofuran was also prepared and to this solution was added $Boc_2O$ and DMAP. The reaction mixture was stirred at rt for 3 h, after which time the solvent was removed *in vacuo* and the residue was purified by chromatography. The Boc protected amine **212** was obtained as a pale yellow oil.

To prepare the benzyl sulfonyl protected amine **213**, compound **210** was dissolved in dichloromethane and to this solution was added triethylamine. The solution was then stirred for 15 min before the dropwise addition of a solution of α-toluenesulfonyl chloride in dichloromethane. The reaction mixture was stirred for 3 h at rt before the solvent was removed *in vacuo*. The residue was purified by chromatography to yield *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)phenylmethanesulfonamide **213** as a yellow oil.

Finally, to a stirred solution of compound **210** in dichloromethane at 0$^{o}$C, was added triethylamine and tosyl chloride. The reaction mixture was stirred for 4 h and the resulting mixture was subjected to an extraction before the solvent was removed *in vacuo*. The residue was purified by column chromatography and *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-

methoxybenzyl)-4-methylbenzenesulfonamide **139** was obtained in as a pale yellow oil that solidified on standing. The characterization of **139** by $^{1}H$ and $^{13}C$ NMR spectroscopy corresponded to the literature data,[129] with both the $^{1}H$ and $^{13}$NMR spectra providing evidence for the presence of the tosyl group. The signals due to the aromatic methyl group of the tosyl substituent were observed at 2.44ppm and two doublets due to the aromatic tosyl group were present at 7.32 and 7.73ppm, each with coupling constants of ~8.1Hz.

Since the three amine derivatives **211-213** were new compounds, they were characterised thoroughly by $^{1}H$ NMR, $^{13}C$ NMR and IR spectroscopic techniques. The thorough characterisation involved the use of HRMS that suggested that the expected compounds were obtained. A brief outline of the characteristic signals in the new compounds **211-213** are outlined in **Table 2** below.

**Table 2** Characteristic Spectroscopic Signals for the Protected Compounds

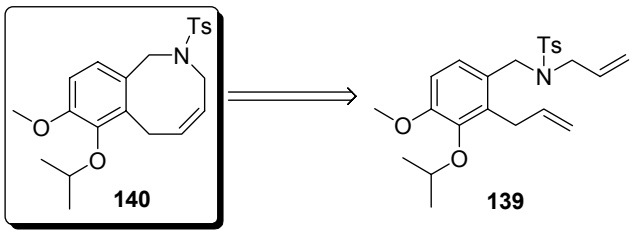
| | **$^{1}H$ NMR** | **$^{13}C$ NMR** |
|---|---|---|
| **211** | 2.05 and 2.14ppm ($CH_3$) | 21.4ppm ($CH_3$)<br>170.8 and 171.2ppm (C=O) |
| **212** | 1.46ppm [OC($CH_3$)$_3$] | 30.3ppm [OC($CH_3$)$_3$]<br>80.0ppm [O$C$($CH_3$)$_3$]<br>155.6ppm (C=O) |
| **213** | 4.25ppm ($SO_2CH_2Ar$)<br>7.38ppm ($SO_2CH_2$Ar-H) | 58.9ppm ($SO_2CH_2Ar$)<br>127.1, 128.6, 130.7ppm ($SO_2CH_2$Ar-C) |

**Table 2 contd.** Characteristic Spectroscopic Signals for the Protected Compounds

| | IR | HRMS |
|---|---|---|
| **211** | 1637cm$^{-1}$ (tertiary amide) | $C_{19}H_{27}NO_3$ Calculated: 317.19909<br>Found: 317.19972 |
| **212** | 1689cm$^{-1}$ (C=O stretch) | $C_{22}H_{33}NO_4$ Calculated: 375.24096<br>Found: 375.24500 |
| **213** | 671 and 750cm$^{-1}$ (5 adj Ar H)<br>1152cm$^{-1}$ ($SO_2$)<br>1273 and 1337cm$^{-1}$ ($SO_2$-N) | $C_{24}H_{31}NO_4S$ Calculated: 429.19738<br>Found: 429.19707 |

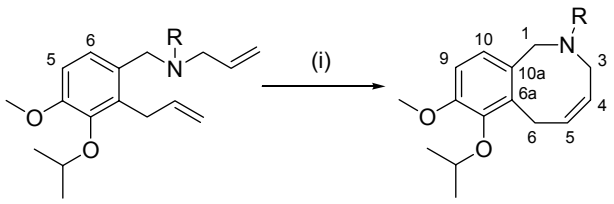
*2.2 Synthesis of Benzazocines (8-membered rings)*

At this point we decided it could be worthwhile to synthesize a range of protected benzazocines based on the RCM methodology outlined by Pathak[129] in which the tosyl-protected benzazocine **140** was prepared from the simple benzaldehyde **138**. As this method had not been used for the synthesis of any other protected benzazocines, we hoped to extend the methodology to include a wider range of protected compounds, and also to show its versatility in the synthesis of deprotected 1,2,3,6-tetrahydro-2-benzazocines and the hydrogenated 1,2,3,4,5,6-hexahydro-2-benzazocines. The general retrosynthesis for compound **140** is outlined in **Scheme 61** below.




**Scheme 61** Retrosynthesis for the Benzazocines

### *2.2.1 Ring Closing Metathesis to Form Benzazocines*




**139, 211-213** **140, 214-216**

**Scheme 62** (i) 5 mol % catalyst **11**, toluene, 60°C, 1 h

The general procedure employed for the synthesis of the benzazocines was to dissolve the diene **139**, **211-213** in distilled toluene and to heat the solution to 60°C. Then 5 mol % Grubbs II catalyst **11** was added and the reaction mixture was allowed to stir at 60°C for 1 h. After this time the solvent was removed *in vacuo* and the residue was purified by column chromatography to yield the corresponding benzazocine **140, 214-216**. The yields for the RCM reactions are shown in **Table 3** below along with a description of the product formed.

**Table 3** Yields and Products Formed by Ring Closing Metathesis

| | R | Yield | Product Formed |
|---|---|---|---|
| **214** | Ac | 82% | clear oil |
| **215** | Boc | 99% | clear oil |
| **216** | $SO_2Bn$ | 84% | white crystals |
| **140** | Ts | 98% | colourless crystals |

The formation of 1-[7-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocin-2(1*H*)-yl]-1-ethanone **214** was proven based on the spectroscopic data. The terminal alkene peaks present in the $^1$H NMR of the diene **211** disappeared, and these were replaced by a multiplet integrating for two protons at 5.86ppm. The three $CH_2$ peaks (dd at 3.51ppm integrating for 2H; two d at 3.85 and 4.17ppm, integrating for 1H each; and d at 4.64ppm, integrating for 2H) were present in the $^1$H NMR spectrum of **214**, allowing us to conclude that no isomerisation had occurred prior to RCM. The three $CH_2$ signals were also present in the $^{13}$C NMR spectrum at 24.7 and 25.3ppm, 44.1 and 45.4ppm and 50.9 and 52.8ppm (doubling due to rotamers). Both the methyl group (22.0 and 22.4ppm) and the carbonyl group (170.4 and 170.9ppm) showed

signals in the $^{13}C$ NMR spectrum, proving that the amine had not undergone a deprotection. All the signals are doubled up in both the $^{1}H$ and $^{13}C$ NMR spectra due to the presence of amide rotamers. The compound **214** was further analyzed by HRMS and a peak was found at 298.16371, which is characteristic of the product ($C_{17}H_{23}NO_3$ requires 289.16779).

The preparation of *tert*-butyl 7-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocine-2(1*H*)-carboxylate **215** was also confirmed from the supporting spectroscopic data. The CH=C$H_2$ protons in the $^{1}H$ NMR spectrum of the starting material **212** at 4.90-5.11ppm; were replaced by an alkene signal (multiplet) at 5.79ppm which integrated for 2H. The $CH_2$ signals showed small shifts, viz. 3.45 to 3.53ppm, 3.67 to 3.82 and 4.00ppm, 4.38 to 4.49ppm for the Ar$CH_2$C, N$CH_2$C and Ar$CH_2$N groups respectively. The nine methyl protons for the Boc protecting group were accounted for in the region of 1.38ppm. $^{13}C$ NMR spectral analysis of the molecule found two new signal regions present in the molecule (at 128.1 and 128.4ppm for 5-C and at 130.3 and 130.6ppm for 4-C, with doubling due to rotamers). This was coupled to the disappearance of the allylic alkene peaks in the starting material **212**, the CH=*C*$H_2$ peaks at 114.8 and 116.4ppm and the *C*H=$CH_2$ peaks at 133.7 and 136.2ppm. HRMS analysis of compound **215** found a peak at 347.20551, with the calculated value for $C_{20}H_{29}NO_4$ being 347.20966.

The RCM reaction to form 2-(benzylsulfonyl)-7-isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine **216** was also deemed a success based on the spectroscopic data. The $^{1}H$ NMR spectrum of the product **216** highlighted the formation of new peaks at 5.60 (1H, td, *J*=7.1 and 10.5Hz) and 6.06ppm (1H, td, *J*=7.3 and 10.3Hz), which correspond to positions 4-H and 5-H respectively. The simultaneous disappearance of the allylic alkene protons in the starting material **213** was noted (4.80 and 4.93, Ar$CH_2$CH=C$H_2$; 5.06, N$CH_2$CH=C$H_2$; 5.62, N$CH_2$C*H*=$CH_2$; 5.80ppm Ar$CH_2$C*H*=$CH_2$). $^{13}C$ NMR spectroscopic analysis showed the presence of the three $CH_2$ peaks at 26.8, 44.8, and 59.4ppm, concluding that no isomerisation had occurred before RCM. Two new signals were found at 125.6 and 135.4ppm, corresponding to 4-C and 5-C respectively. The compound **216** was further analyzed by HRMS and a peak was found at 401.16655, which corresponds to the molecular peak for $C_{22}H_{27}NO_4S$ at 401.16608.

The crystal structure was obtained for compound **216** and showed the formation of the 8-membered ring. The structure was found to have a buckeled ring (similar to the chair

conformation found in the 6-membered rings) with the double bond clearly in place. This is shown by the ORTEP diagram displayed in **Figure 28** below, with details outlined in **Appendix B**.

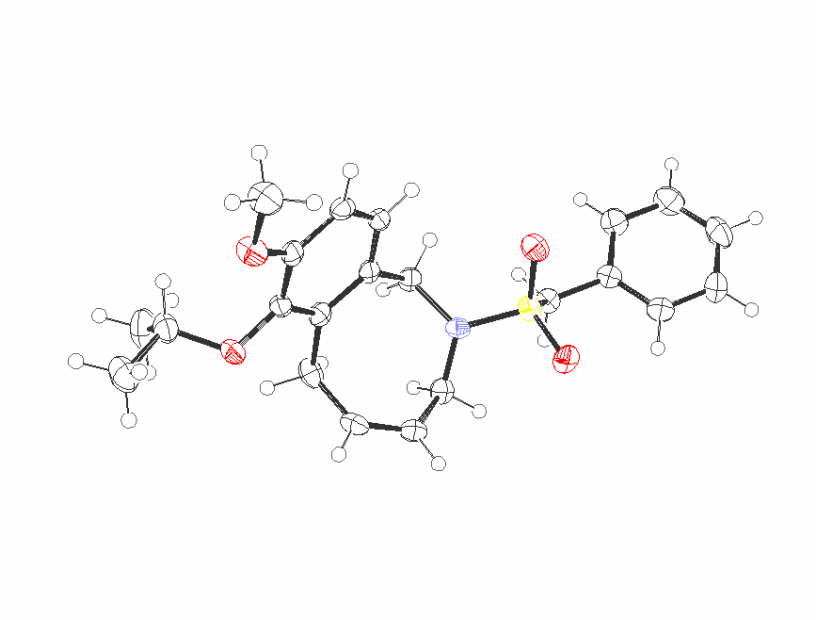
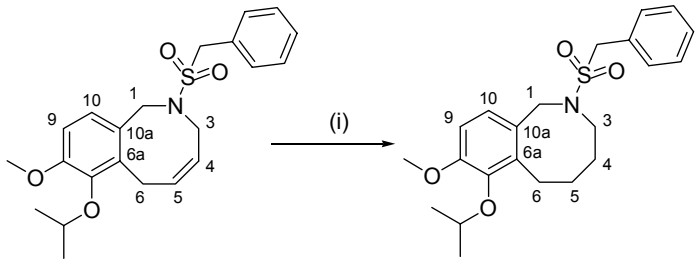


**Figure 28** ORTEP diagram of compound **216**
(showing the 50% probability thermal ellipsoids for all non-hydrogen atoms).

We also synthesized 7-isopropoxy-8-methoxy-2-[(4-methylphenyl)sulfonyl]-1,2,3,6-tetra-hydro-2-benzazocine **140** according to the procedure previously developed in our laboratories and reported by Pathak *et al.*[5] and found our NMR spectroscopic data agreed very well with that reported. IR and high-resolution mass spectroscopy were not performed as the compound had previously been synthesized in our laboratories.

### *2.2.2 Hydrogenation Reaction on Compound **216***

A hydrogenation reaction was performed on compound **216** in an attempted deprotection reaction. This procedure was employed as it was hoped that it would prove to be a simple method for the deprotection of the $SO_2Bn$ systems; other methods include the use of Raney nickel[211] and photolysis.[212] If the deprotection failed, we were hoping to be able to isolate and characterize the hydrogenated compound, thus proving that the systems could be hydrogenated if need be.




**216** **217**

**Scheme 63** (i) 10% Pd/C, 5 atm $H_2$, EtOH, rt, 18 h

The 2-(benzylsulfonyl)-7-isopropoxy-8-methoxy-1,2,3,4-tetrahydro-2-benzazocine **216** was dissolved in absolute ethanol through the use of sonnication. To the emulsion was added 10% Pd/C and the solution was subjected to hydrogenation in an autoclave at 5 atm $H_2$ for 18 h. The reaction mixture was then filtered, rinsed with $CH_2Cl_2$, the solvent was removed *in vacuo* and the solid collected was recrystallised from EtOAc-Hexane to yield 2-(benzylsulfonyl)-7-isopropoxy-8-methoxy-1,2,3,4,5,6-hexahydro-2-benzazocine **217** as colourless crystals in 98% yield. None of the deprotected amine was observed.

The product **217** was identified by the characteristic loss of the alkene protons and the appearance of two new $CH_2$ groups in both the $^1H$ and $^{13}C$ spectra. $^1H$ NMR spectroscopy showed the loss of the alkene peaks at 5.60 (1H, td, *J*=7.1 and 10.5Hz, 4-H) and 6.06ppm (1H, td, *J*=7.3 and 10.3Hz, 5-H) and the appearance of new $CH_2$ peaks at 1.51 (2H, m, 4-H) and 1.66ppm (2H, m, 5-H). $^{13}C$ NMR spectroscopy showed the loss of the alkene peaks at 125.6 (4-C) and 135.4ppm (5-C) and the appearance of new $CH_2$ peaks at 24.0 (5-C*) and 29.3ppm (4-C[1]). The success of the reaction was further shown by the loss of the C=C isolated stretch at 1691cm$^{-1}$ in the IR spectrum. HRMS analysis found a peak at 403.18176, which corresponds to the calculated peak for $C_{22}H_{29}NO_4S$ at 403.18173.

The structure of the hydrogenated compound **217** was confirmed by a single-crystal X-ray structure. The structure was exceptionally interesting as it showed the presence of two distinctly different and completely unsymmetrical molecules in the unit cell. The ORTEP diagram is shown in **Figure 29** below (further information may be found in **Appendix B**).

[1] These two assignments may be interchanged as no C-H correlated spectrum was run that would identify them unambiguously.

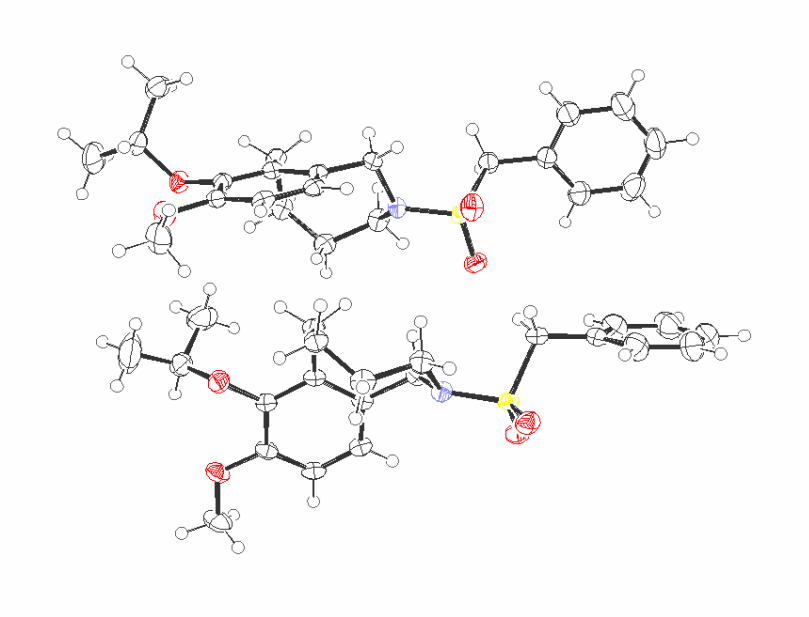
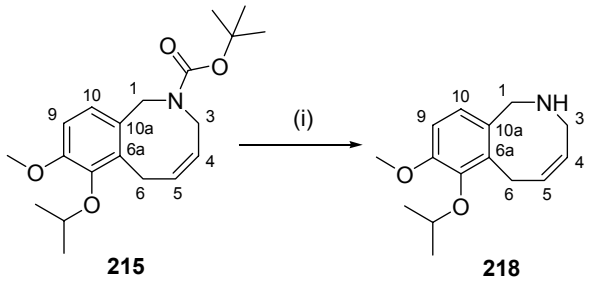


**Figure 29** ORTEP diagram of compound **217**
(showing the 50% probability thermal ellipsoids for all non-hydrogen atoms

### *2.2.3 Deprotection Reaction of compound **215***

With the deprotection of the $SO_2Bn$ protected amine **216** having failed we wanted to attempt the deprotection reaction on another one of our amine protected benzazocine systems. Considering that Boc deprotections are relatively simple to perform and due to the complexity of the Boc protected NMR spectra (due to the presence of amide rotamers), we decided to attempt the deprotection reaction on benzazocine **215**.




**215** **218**

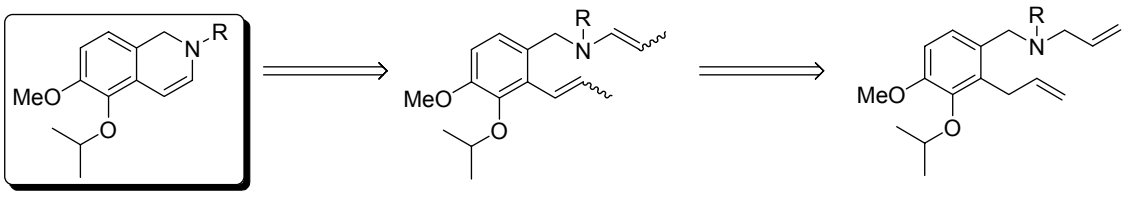
**Scheme 64** (i) 1.5eq trifluoroacetic acid, $CH_2Cl_2$, rt, 1 h

A solution was prepared of the *tert*-butyl 7-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocine-2(1*H*)-carboxylate **215** in $CH_2Cl_2$ and to this solution was added trifluoroacetic acid. The reaction mixture was then left to stir at rt for 1 h, before being diluted with water and EtOAc. The mixture was then neutralized and extracted before the solvent was removed *in vacuo*. A dark orange semi-solid was obtained that was essentially pure by spectroscopy and no further purification was performed. 7-Isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine **218** was thus obtained in 99% yield. This result is indeed promising as it confirms that if we want to perform further *N*-alkylations on systems like **215** the Boc-protection group is readily removed.

As this was a new compound, characterisation involved NMR and IR spectroscopy as well as high-resolution mass spectroscopy. The $^{1}H$ NMR spectrum highlighted the loss of the Boc protecting group by the lack of nine protons at 1.38ppm as well as by the presence of a new singlet at 8.84ppm for the NH. The $^{13}C$ NMR spectrum also showed the loss of the Boc group by the lack of the peaks at 28.4 [OC($CH_3$)$_3$] and 79.4 and 79.5 ppm [O$C$($CH_3$)$_3$]. HRMS confirmed the formation of 7-isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine **218** by a peak at 247.15654 which corresponds to the peak for $C_{15}H_{21}NO_2$ (calculated to be present at 247.15723).

### *2.3 Synthesis of Isoquinolines (6-membered rings)*

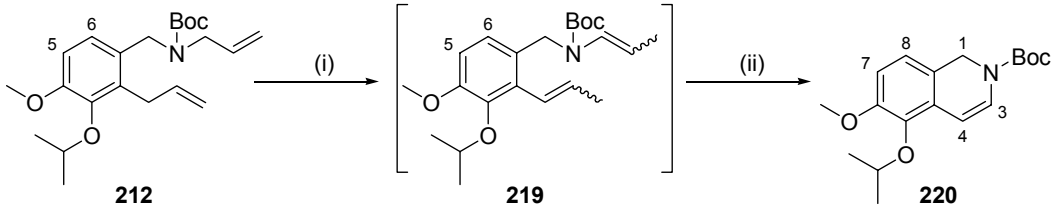
It had been previously shown in our laboratories that by treating diene **139** with 0.5 mol % catalyst **12** at 110$^{o}$C for 2 h followed by RCM using Grubbs II catalyst **11**, the 1,2-dihydroisoquinoline ring system **142** was obtained, which alludes to the isomerisation of both double bonds. The general retrosynthesis illustrating our approach to the isoquinolines is shown below in **Scheme 65**




R = Ac, Boc, $SO_2Bn$, Ts

**Scheme 65** Retrosynthesis for the Isoquinolines

We decided to investigate this process, consisting of isomerisation followed by RCM, further by including the presence of other protecting groups. We initially tried the one-pot isomerisation-RCM procedure outlined by Pathak[129] on our Ac-, Boc- and $SO_2Bn$- protected compounds (**211**, **212** and **213** respectively). This procedure failed dismally with the products from the reactions being mixtures that were largely inseparable and generally unidentifiable.



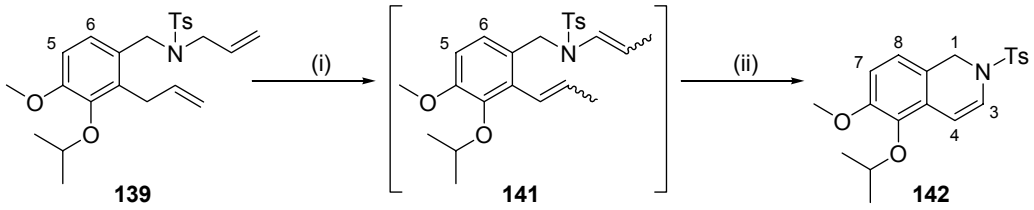

**212** **219** **220**

**Scheme 66** (i) 1 mol % catalyst **12**, toluene, 110°C, 2 h,
(ii) 5 mol % catalyst **11**, toluene, 110°C, 2 h

The only reaction that gave any identifiable product was with the use of the Boc protected compound **212**, from which we were only able to isolate 10% of the desired product 2-acetyl-5-isopropoxy-6-methoxy-1,2-dihydroisoquinoline **220**. The procedure used for this reaction was to dissolve the amine **212** in distilled toluene, to heat the solution to 110°C and then to add 1 mol % Ru-isomerisation catalyst **12**. The reaction mixture was then stirred for 2 h before the addition of 5 mol % of Grubbs II catalyst **11**. The reaction mixture was then stirred for a further 2 h, the solvent was removed *in vacuo* and the residue was purified by chromatography.

The formation of product **220** was indicated by the loss of both the alkene protons in the $^1$H NMR spectrum of the starting material, as well as by the appearance of methyl groups in the spectrum of the isomerised intermediate. The presence of the double bond in the ring was shown by the multiplet at 5.83-5.91ppm, which was assigned as 4-H, and the multiplet at 7.24-7.28ppm, which was assigned, as 3-H. The peak for the $CH_2$ group was present in the multiplet between 4.47 and 4.77ppm. The spectral analysis of this compound was particularly problematic due to the presence of amide rotamers and the excessive broadening of the peaks due to the Boc protecting group. No variable temperature NMR was available to us that would have aided with this problem and insufficient material was recovered in order to perform the deprotection reaction that would simplify the spectra.

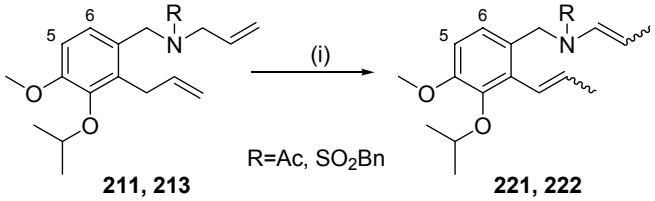
We then decided to proceed by repeating the experiment outlined by Pathak[129] (namely the tosyl protected compound **139**) to confirm that there were no problems with our setup and experimental technique.




**Scheme 67** (i) 5.5 mol % catalyst **12**, toluene, 110$^o$C, 4 h,
(ii) 5 mol % catalyst **11**, toluene , 110$^o$C, 21 h

The *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-4-methylbenzenesulfonamide **139** was dissolved in distilled toluene and the solution was degassed. Then 0.5 mol % Ru-isomerisation catalyst **12** was added and the reaction mixture was stirred for 2 h at 110-120$^o$C. After this time $^1$H NMR spectroscopy showed no isomerisation had occurred so a further 5 mol % isomerisation catalyst was added and the reaction mixture was stirred for a further 2 h. After this additional time $^1$H NMR spectroscopy showed total isomerisation of both of the double bonds. Grubbs II catalyst **11** (5 mol %) was then added and the reaction mixture was allowed to stir for 21 h at 110$^o$C. After cooling the reaction mixture to rt and removing the solvent *in vacuo*, the resulting residue was purified by column chromatography to yield the desired product 5-isopropoxy-6-methoxy-2-[(4-methylphenyl)sulfonyl]-1,2-dihydroisoquino-

line **142** in a poor 27% yield. This result was compared to that of Pathak[129] and she obtained the product in 76% yield; the difference in yield was upsetting and led us to the decision that we should isolate the products directly after isomerisation in order to confirm the formation of the bis-isomerised compound and to hopefully improve the yield of the subsequent RCM.

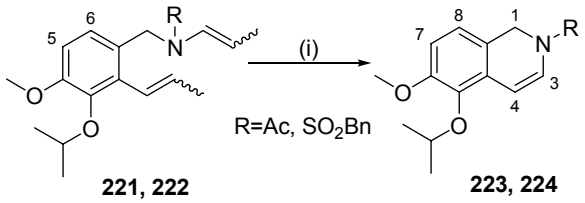



**Scheme 68** (i) 5 mol % catalyst 12, toluene, 100-110°C, 19 h

This was then initially attempted for the *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-acetamide **211** and for the *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-phenylmethanesulfonamide **213**. In both instances, the amine **211** or **213** was dissolved in distilled toluene and degassed. The solution was then heated to 100-110°C before the addition of 5 mol % of the Ru-isomerisation catalyst **12**. The reaction mixture was then stirred for 19 h, the solvent was removed *in vacuo* and the residue was purified by column chromatography. *N*-[3-Isopropoxy-4-methoxy-2-(1-propenyl)benzyl]-*N*-(1-propenyl)acetamide **221** and *N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl](phenyl)-*N*-(1-propenyl)methanesulfonamide **222** were obtained in yields of 94% and 87% respectively.

Compound **221** was characterized by the loss of the "terminal methylene signals" and terminal alkene peaks of the starting material in the $^{1}H$ and $^{13}C$ NMR spectra, as well as the corresponding loss of the terminal $RHC=CH_2$ stretches in the FTIR spectrum. The product **221** showed significant splitting of the signals due to the presence of amide rotamers in both the $^{1}H$ and $^{13}C$ NMR spectra. The signals for the methyl groups were found at 1.59 and 1.65ppm as well as at 1.91-1.95 and 2.04-2.07ppm in the $^{1}H$ NMR spectrum. The corresponding signals were present at 15.3 and 15.5ppm for $NCH=CHCH_3$ and at 19.0 and 19.1ppm for $ArCH=CHCH_3$ in the $^{13}C$ NMR spectrum. The FTIR spectrum showed a signal at 1645cm$^{-1}$ which was due to either the tertiary amide or the C=C conjugated with C=O. Finally, the compound was analysed by HRMS and the molecular ion was found at 317.19862 ($C_{19}H_{27}NO_3$ requires 317.19909).

In the same manner, product **222** was identified by the characteristic loss of the terminal alkene and $CH_2$ peaks in both the $^1H$ and $^{13}C$ NMR spectra, coupled with the presence of two new methyl group peaks. These were found at 1.52 and 1.85ppm in the $^1H$ NMR spectrum and at 15.2 and 19.0ppm in the $^{13}C$ NMR spectrum. The structure of **225** was further confirmed by HRMS where a peak was found at 429.19830 that corresponded to the required molecular ion peak at 429.19738 for $C_{24}H_{31}NO_4S$.



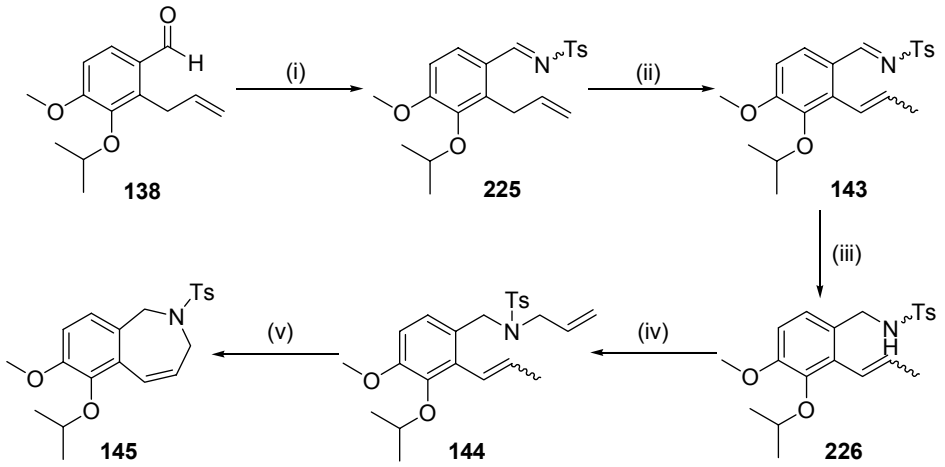

**Scheme 69** (i) 5 mol % catalyst 11, toluene, 110$^o$C, 3 h

Knowing that there were no problems with the isomerisation step of the reaction, we were then able to move on to the metathesis reaction. Both compounds **221** and **222** were then dissolved in toluene and heated to 110$^o$C before the addition of 5 mol % Grubbs II catalyst **11**. The reaction mixture was then stirred for 3 h, before it was cooled to rt, the solvent was removed *in vacuo* and the resulting residue was purified by column chromatography. 2-Acetyl-5-isopropoxy-6-methoxy-1,2-dihydroisoquin-oline **223** was obtained as a clear oil in 78% yield, but unfortunately, in the other reaction none of the desired 2-(benzylsulfonyl)-5-isopropoxy-6-methoxy-1,2-dihydroisoquinoline **224** was obtained.

2-Acetyl-5-isopropoxy-6-methoxy-1,2-dihydroisoquinoline **223** was identified by the characteristic loss of the methyl signals and the shift of the alkene signals in both the $^1H$ and the $^{13}C$ NMR spectra. The FTIR spectrum for the product highlighted a peak at 669cm$^{-1}$ for a *cis* alkene and a peak at 1625cm$^{-1}$ which was due to the conjugated C=C and C=O. The $^1H$ NMR spectrum displayed the signals for 4-H at 6.17 and 6.20ppm and the signals for 3-H at 7.27 and 7.37ppm. The $^{13}C$ NMR spectrum showed the peaks for 4-C at 105.3 and 105.6ppm and the peaks for 3-C at 125.4 and 125.8ppm. HRMS analysis of the compound showed a peak at 261.13696, which corresponds to that for $C_{15}H_{19}NO_3$ at 261.13649.

The poor yields for the formation of 2-acetyl-5-isopropoxyx-6-methoxy-1,2-dihydroisoquinoline **223** in 10% yield and for the formation of 5-isopropoxy-6-methoxy-2-[(4-methylphenyl)sulfonyl]-1,2-dihydroisoquinoline **142** in 27% yield, as well as the lack of product formation for 2-(benzylsulfonyl)-5-isopropoxy-6-methoxy-1,2-dihydroisoquinoline **220**, may be attributed to the steric hindrance caused by the bulky protections group. This may be preventing the ruthenium metal carbene from attaching to the site, thus preventing metathesis from occurring. The poor yields are also highlighted by the formation of a number of de-allylated by-products that were isolated and characterized. They are discussed fully in *Section 2.5* below.

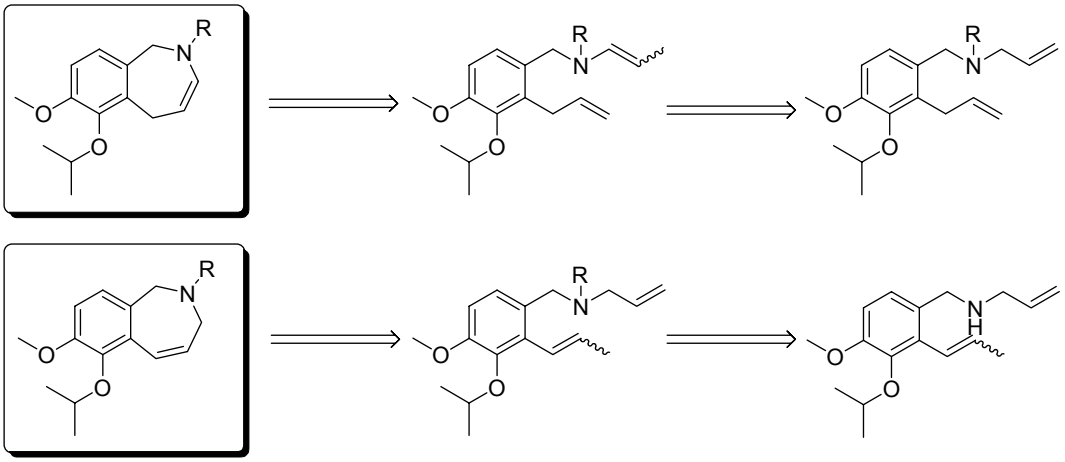
*2.4 Synthesis of Benzazepines (7-membered rings)*




**Scheme 70** (i) $TsNH_2$, toluene, 110°C, 20%, (ii) 1 mol % catalyst **12**, toluene, 90°C, 2 h, 100%, (iii) $NaBH_4$, MeOH, 0°C, 30 min, 98%, (iv) allyl bromide, NaH, THF, rt, 6 h, 64%, (v) 5 mol % Grubbs II catalyst **11**, toluene, 60°C, 2 h, 100%

Previously the tosyl-protected 7-membered benzo-fused ring had been prepared in our group by a conversion of benzaldehyde **138** into the *N*-tosyl-protected imine **225** followed by the isomerisation of the terminal alkene, which led to the formation of the thermodynamically more stable styrene-type system **143**. At this point the *N*-tosylimine **143** was reduced with sodium borohydride in methanol at 0°C to afford the amine **226** in 98% yield. The resultant amine **226** was then alkylated with allyl bromide in the presence of sodium hydride to give the *N*-allylated compound **144** in reasonable yield. Finally the precursor **144** was subjected to

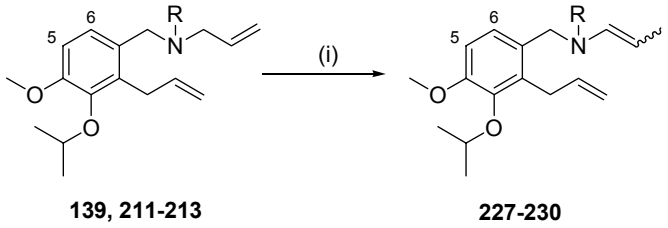
metathesis conditions and gave the expected product, 2,3-dihydro-*1H*-2-benzazepine **145** in quantitative yield.



**Scheme 71** Retrosyntheses to the Benzazepine Ring systems

Alluding from this we decided to test whether we could selectively isomerise only one of the double bonds in our diene systems **139**, **211-213** using the Ru-isomerisation catalyst **12**, in order to access the benzazepine ring systems via a shorter route. In addition this could grant us access to the 7-membered systems where the double bond was in either of the two positions selectively, namely the 2,5-dihydro-2-benzazepines and the 2,3-dihydro-2-benzazepines. Our approach is illustrated by the retrosyntheses in **Scheme 71** above.

### *2.4.1 Preparation of 2,5-dihydro-1H-2-benzazepines*




**139, 211-213** **227-230**

**Scheme 72** (i) Ru-isomerisation catalyst **12**, toluene, 80$^{o}$C, 20 h

Initially, we attempted the isomerisations by employing a combinatorial approach. We set up the Carousel reactor with twelve reactions, thus each of the four protected amines had three

reaction vessels, with 0.5 mol %, 1 mol % and 2 mol % of the Ru-isomerisation catalyst **12** respectively. The results of the reactions are outlined in **Table 4** below. Each of the protected amines was dissolved in distilled toluene and the solution was degassed for 5 min using $N_2$. Then Ru-isomerisation catalyst **12** was added and the solutions were heated to 80$^{o}$C for 20 h (the temperature of 80$^{o}$C was chosen to avoid double isomerisation that was shown to occur at 110$^{o}$C). After this time they were allowed to cool to rt, the solvent was removed *in vacuo* and the residues were then subjected to column chromatography. Initial determination of the products was by NMR spectroscopy, but this was subsequently supported by IR and HRMS spectroscopy.

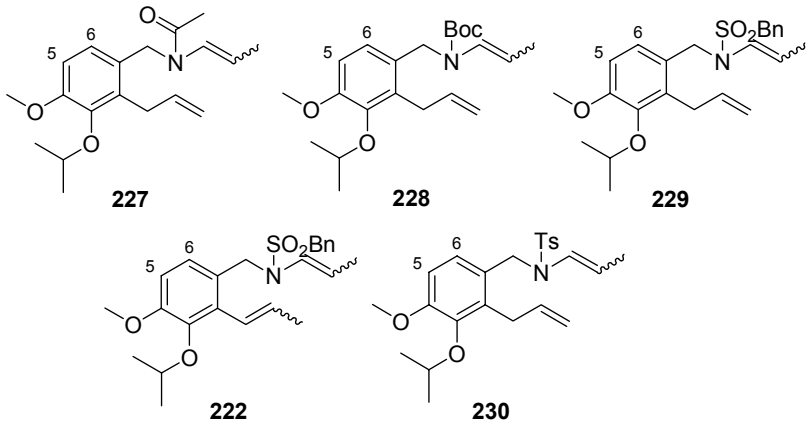



**Figure 27** Diagrammatic Representation of Products Formed

**Table 4** Results of Isomerisation Reactions

| R | Catalyst 12 | Product Formed | Yield |
|---|---|---|---|
| Ac | 0.5 mol % | **227** | 44% |
| Ac | 1 mol % | **227** | 77% |
| Ac | 2 mol % | **227** | 60% |
| Boc | 0.5 mol % | **SM** | - |
| Boc | 1 mol % | **228** | 80% |
| Boc | 2 mol % | **228** | 70% |
| $SO_2Bn$ | 0.5 mol % | **SM** | - |
| $SO_2Bn$ | 1 mol % | **229** | 90% |
| $SO_2Bn$ | 2 mol % | **222 + 229** | inseperable mixture |

**Table 4 contd.** Results of Isomerisation Reactions

| R | Catalyst 12 | Product Formed | Yield |
|---|---|---|---|
| Ts | 0.5 mol % | **SM** | - |
| Ts | 1 mol % | **SM + 230** | 26% (58% SM recovered) |
| Ts | 2 mol % | **SM + 230** | 57% (14% SM recovered) |

As can be seen from **Table 4** above, the *N*-allyl chain shows the greater tendency for isomerisation and is thus favoured for all the protected amines. The best yields were obtained for 1 mol % isomerisation catalyst **12** for all of the compounds except the tosyl protected amine **139**, where 2 mol % **12** was favoured.

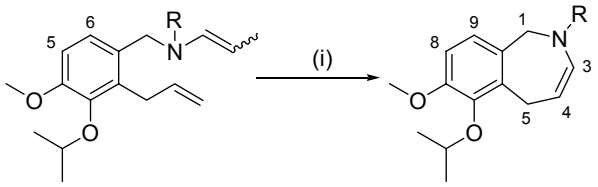
*N*-(2-Allyl-3-isopropoxy-4-methoxybenzyl)-*N*-(1-propenyl)acetamide **227** was fully characterized through the use of HRMS, NMR and IR spectroscopy. $^{1}$H NMR spectroscopy showed the presence of a multiplet at 1.63ppm for the methyl group and also showed signals for both of the alkene protons; a multiplet at 5.91 for NCH=C*H* and a doublet at 7.35ppm for NC*H*=CH. We were able to identify which of the double bonds isomerised based on the $^{13}$C NMR spectrum because of the large differences in the $^{13}$C NMR for the different $CH_2$ groups. Our assignments were then supported by CH and COSY spectra. In the starting material **211**, the N*C*$H_2$C group had signals at 48.1 and 49.2ppm and the Ar*C*$H_2$C group showed peaks at 30.0 and 30.5ppm. In the product **227**, the signals at 48.1 and 49.2ppm had disappeared and the signal at 30.2 and 30.4ppm was present, allowing us to conclude that the *N*-allyl chain had isomerised. The Ar$CH_2$N signals remained unchanged and new methyl signals were found at 15.3 and 15.5ppm for the CH=CH*C*$H_3$ group. The product **227** was then analyzed by HRMS and a peak was found at 317.19916, which corresponds to the molecular peak for $C_{19}H_{27}NO_3$ at 317.19903.

The same process of analysis was applied to the other new compounds **228-230**. They were fully analyzed base on NMR and IR spectroscopy. HRMS confirmed the molecular ions for the products were present. The characteristic peaks in the new compounds are outlined briefly in **Table 5** below. Two new methyl groups were found in both the $^{1}$H and the $^{13}$C NMR

spectra for **222**, allowing us to conclude that both the double bonds had isomerised (see *Section 2.3* above).

**Table 5** Characteristic Signals for Compounds **228-230**

| Compound | $^{1}$H NMR | $^{13}$C NMR | HRMS |
|---|---|---|---|
| **228** | 1.49ppm $CH_3$ | 15.3ppm $CH_3$ | $C_{22}H_{33}NO_4$ |
| | | 104.2ppm CH=*C*HCH$_3$ | Calculated: 375.24096 |
| | | 124.7ppm *C*H=CHCH$_3$ | Found: 375.24162 |
| **229** | 1.53ppm $CH_3$ | 15.2ppm $CH_3$ | $C_{24}H_{31}NO_4S$ |
| | | 107.0ppm CH=*C*HCH$_3$ | Calculated: 429.19738 |
| | | 135.8ppm *C*H=CHCH$_3$ | Found: 429.19812 |
| **230** | 2.44ppm $CH_3$ | 21.5ppm $CH_3$ | $C_{24}H_{31}NO_4S$ |
| | | 137.1ppm *C*H=CHCH$_3$ | Calculated: 429.19738 |
| | | | Found: 429.19760 |




**227-230** **231-234**

**Scheme 73** (i) Grubbs II catalyst **11**, toluene, 60$^{o}$C, 19-25 h

Having successfully prepared the isomerised dienes **227-230** we were finally in a position to subject them to the metathesis conditions. RCM was performed on the compounds by preparing a solution of the diene **227-230** in distilled toluene and then heating the solution to 60$^{o}$C before the addition of Grubbs II catalyst **11**. After 19-25 h the solutions were allowed to cool to rt, the solvent was removed *in vacuo* and the resulting residues were subjected to column chromatography. The yields of the benzazepines **231-234** are outlined in **Table 6** below.

**Table 6** Yields for RCM Reactions to form **231-234**

| Compound | R | Grubbs II catalyst 11 | Temp | Time | Yield |
|---|---|---|---|---|---|
| **231** | Ac[2] | 10 mol % | 80°C | 25 h | 9% |
| **232** | Boc | 5 mol % | 60°C | 24 h | 82% |
| **233** | $SO_2Bn$ | 5 mol % | 60°C | 19 h | 58% |
| **234** | Ts | 5 mol % | 60°C | 25 h | 47% |

We were able to confirm the formation of the 7-membered ring by the disappearance of the signals for the methyl group and terminal alkene group in the starting materials. This was further supported by the presence of two new alkene peaks (that had different shifts to the original alkene values). HRMS confirmed that the expected molecular ion was present in all the newly prepared compounds **231-234**. This procedure of identification is explained below for the conversion of compound **228** to **232** (where R=Boc).

The $CH_3$ peak at 1.49ppm and the terminal alkene peaks at 4.93 and 5.03ppm which were present in the $^1$H NMR spectrum of the starting material **228** had disappeared after the reaction. The $^1$H NMR spectrum of the product **232** showed new alkene signals at 5.87-5.93ppm (4-H) and 6.72-6.75ppm (3-H and Ar-H), which had a significantly shifted from those of the starting material **228**: 5.89ppm (1H, dq, C*H*=$CH_2$) and 6.63ppm (1H, d, NCH=C). This was supported by the corresponding disappearance of the $CH_3$ peak at 15.3ppm and the terminal alkene peak at 115.2ppm in the $^{13}$C NMR spectrum of the starting material **228**. The $^{13}$C NMR spectrum for *tert*-butyl 6-isopropoxy-7-methoxy-1,5-dihydro-2*H*-2-benzazepine-2-carboxylate **232** showed the alkene protons were present at 104.2ppm (4-C) and 124.7ppm (3-C). These assignments were confirmed by COSY and CH correlated spectra. Product formation was further supported by the HRMS spectra, which found a peak at 333.19534 ($C_{19}H_{27}NO_4$ requires 333.19401). The identical method of identification was employed for the assignment of the other ring-closed compounds **231**, **233** and **234**. The characteristic peaks used in these assignments are outlined in **Table 7** below.

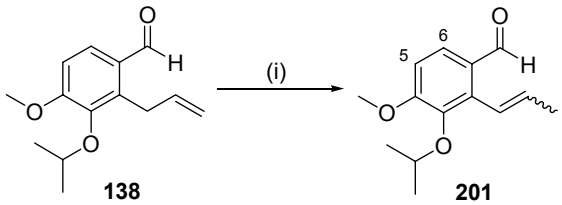
[2] Having attempted the reaction with 5 mol % Grubbs II catalyst 11 at 60°C and having isolated no product, we retried the experiment with 10 mol % Grubbs II catalyst 11 at 80°C. The desired product was obtained, but in poor yield.

**Table 7** Characteristic Signals used for Identification of Benzazepines **231**, **233**, **234**

| Compound | R | $^{1}$H NMR | $^{13}$C NMR | HRMS |
|---|---|---|---|---|
| **231** | Ac | 6.36ppm 4-H<br>7.57ppm 3-H | 113.7ppm 4-C<br>135.7ppm 3-C | $C_{16}H_{21}NO_3$<br>Calculated: 275.15214<br>Found: 275.15020 |
| **233** | $SO_2Bn$ | 5.79-6.01ppm 4-H<br>6.32ppm 3-H | 115.3ppm 4-C<br>137.1ppm 3-C | Insufficient Material |
| **234** | Ts | 5.90-6.02ppm 4-H<br>6.21ppm 3-H | 124.9ppm 4-C<br>132.6ppm 3-C | Insufficient Material |

### *2.4.2 Preparation of 2,3-dihydro-1H-2-benzazepines*

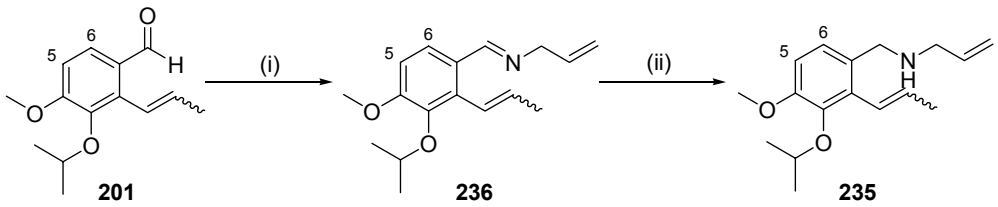
Accepting that we had synthesized the one type of benzazepine, we were hopeful that by changing the order of our synthetic steps we would be able to afford the benzazepines with the double bond in the 4-position. The substituted benzaldehyde **138** (**Scheme 74**) was used as the starting material for this synthetic strategy, and the initial step was to isomerise the allyl bond. This isomerisation step had been previously attempted in our laboratories using various isomerisation methods, including the use of potassium *tert*-butoxide and palladium (II) chloride. However, Coyanis[48] found the Ru-isomerisation catalyst **12** to be the most effective. Following this route, the reductive amination was performed and the subsequent free amine **235** was protected with each of the four protecting groups earmarked for this methodological study. This then set the scene for us to perform the metathesis reaction in order to obtain the 2,3-dihydro-2-benzazepine series. This method was a favoured alternative to that of Pathak (*Section 2.3* **Scheme 72**) as it would ultimately allow a wide variety of different benzazepines to be synthesized from a common intermediate.[1]




**Scheme 74** (i) 2 mol % catalyst **12**, toluene, 80°C, 23 h

The previously prepared benzaldehyde **138** was dissolved in toluene and the solution was heated to 80°C before the addition of the Ru-isomerisation catalyst **12**. The reaction mixture was then stirred for 23 h; after this time $^1$H NMR spectroscopy showed partial isomerisation, so a further 2 mol % Ru-isomerisation catalyst **12** was added. After the reaction mixture was stirred for a further 23 h, the solvent was removed *in vacuo* and the remaining residue was purified by column chromatography. 3-Isopropoxy-4-methoxy-2-(1-propenyl)benzaldehyde **201** was obtained as a yellow-brown oil that solidified on standing in 92% yield.

The formation of 3-isopropoxy-4-methoxy-2-(1-propenyl)benzaldehyde **201** was proven by the loss of the allyl alkene protons and the presence of a new methyl group and new alkene protons in the $^1$H NMR spectrum. The signals for these were found at 1.98ppm ($CH_3$), 5.80-6.09ppm (ArCH=C*H*$CH_3$) and 6.59-6.73ppm (ArC*H*=$CHCH_3$) respectively, with mixtures of *E/Z* isomers being present in each of the alkene regions. The corresponding changes were observed in the $^{13}$C NMR spectrum, a new methyl peak was found at 19.0ppm and new alkene peaks were found at 125.2ppm (ArCH=*C*$HCH_3$) and 136.1ppm (Ar*C*H=$CHCH_3$). All of the other signals in the proton and carbon spectra corresponded to those described by Coyanis.[48]

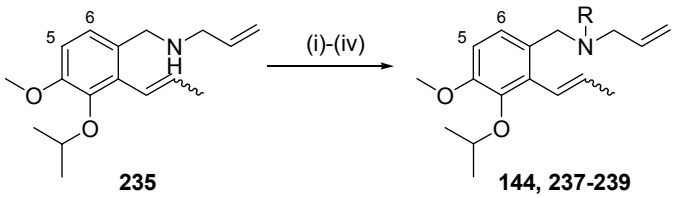



**Scheme 75** (i) 1.4eq allyl amine, rt, 22 h, (ii) 1.2eq $NaBH_4$, MeOH, 0°C, 2 h

The *N*-{[3-isopropoxy-4-methoxy-2-(1-propenyl)phenyl]methylidene}-2-propen-1-amine **236** was prepared according to the procedure outlined in *Section 2.1.3* above. The 3-isopropoxy-4-

methoxy-2-(1-propenyl)benzaldehyde **201** was stirred with allyl amine for 22 h at rt. Then the excess allyl amine was removed *in vacuo* and the product was isolated as a yellow-orange oil in 100% without the need for further purification. The product was identified by the obvious loss of the aldehyde peak in both the $^{1}H$ and $^{13}C$ NMR spectra. The allyl chain was clearly observed in the $^{1}H$ NMR spectrum by the presence of the $CH_2$ group at 4.20ppm, the CH=C$H_2$ at 5.12-5.23ppm and the CH=C$H_2$ at 5.72ppm. The imine formation was proven by the presence of the ArCH=N peak at 8.41ppm in the $^{1}H$ NMR spectrum. Similarly, the $CH_2$ peak was found at 63.5 and 63.7ppm and the CH=$CH_2$ peak was found at 115.7ppm in the $^{13}C$ NMR spectrum. Also, the $CH$=$CH_2$ signal was present at 134.0ppm and the ArCH=N peak was present at 161.8ppm. The HRMS of the compound identified the molecular ion at 273.17290 with the expected molecular ion having been calculated to be at 273.17288 (for $C_{17}H_{23}NO_2$). In addition FTIR confirmed the presence of the imine through the imine H stretch at 3617cm$^{-1}$.

Step (ii) in **Scheme 75** above, outlines the reduction of the imine to form *N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]-2-propen-1-amine **235**. The imine **236** was dissolved in methanol and the solution was cooled to 0$^{o}$C in an ice-water bath. To the methanolic solution was then added sodium borohydride and the reaction mixture was stirred at 0$^{o}$C for 2 h. After this time the excess sodium borohydride was destroyed and the residue was extracted. The desired product **235** was then obtained as a yellow oil in 82% yield, with no further purification required. The product **235** was identified by the characteristic loss of the N=CH peak in both the proton and the $^{13}C$ spectra and by the presence of the new $CH_2$ singlet in the proton spectrum at 3.73ppm. This was further supported by the presence of a $CH_2$ peak in the carbon spectrum at 51.0ppm and by the broad singlet integrating for one proton at 1.68ppm that we identified as the NH peak in the $^{1}H$ NMR spectrum. FTIR spectroscopy highlighted both the $NCH_2$ stretch at 2838cm$^{-1}$ as well as the NH band at 3666cm$^{-1}$. HRMS analysis of the compound showed a peak at 275.19120, with $C_{17}H_{25}NO_2$ having a calculated molecular ion of 275.18853.




**Scheme 76** (i) 1.5eq acetic anhydride, 2.5eq pyridine, rt, 3 h or **237** R = Ac
(ii) 1.2eq $Boc_2O$, 0.1eq DMAP, THF, rt, 3 h or **238** R = Boc
(iii) 2.5eq $NEt_3$, 1.1eq α-toluenesulfonyl chloride, $CH_2Cl_2$, rt, 18 h or **239** R = $SO_2Bn$
(iv) 1.4eq $NEt_3$, 1.2eq tosyl chloride, $CH_2Cl_2$, $0^oC$-rt, 3 h **144** R = Ts

At this point the amine nitrogen needed to be protected. Again, for this section of the project, the same four protecting groups were chosen. The protection reactions followed the same general procedures as those outlined in the sections above. The yields obtained for the protection reactions are outlined in **Table 8** below.

**Table 8** Yields for Protecting Group Additions

| Compound | R | Yield (%) |
|---|---|---|
| **237** | Ac | 72 |
| **238** | Boc | 86 |
| **239** | $SO_2Bn$ | 29 |
| **144** | Ts | 77 |

A solution was prepared of *N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]-2-propen-1-amine **235** and distilled pyridine, which was cooled to $0^oC$. To this was then added dropwise a solution of acetic anhydride in pyridine, which was then left to stir at rt for 3 h. After purification the desired compound was obtained as a clear oil, with the residue further purified by column chromatography. The NMR spectra obtained were exceptionally complex due to the presence of amide rotamers as well as the *E/Z* isomers.The product, *N*-allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]ac-etamide **237**, was identified by the presence of two new singlets at 2.08 and 2.13ppm in the $^1H$ NMR spectrum, which corresponded to those expected for the acetyl group. This was also confirmed in the $^{13}C$ NMR spectrum by the presence of the new $CH_3$ peaks at 21.4 and 21.5ppm, as well as the carbonyl peaks at 170.7 and 171.0ppm. Further support for the protection was found in the FTIR spectrum, with the

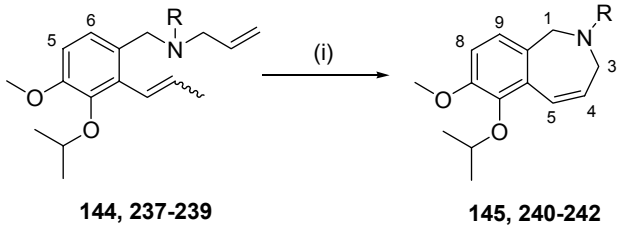
signal at 1630cm$^{-1}$ that may have been due to a tertiary amide. The compound was also analyzed by HRMS, which confirmed the presence of the molecular ion peak at 317.19985 ($C_{19}H_{27}NO_3$ requires 317.19909).

The second protection was performed as follows; starting material **235** was dissolved in tetrahydrofuran and to this was added $Boc_2O$. After a few minutes of stirring, the DMAP was added and the reaction mixture was then stirred for a further 3 h. After this time the solvent was removed *in vacuo* and the residue was purified by column chromatography. The desired compound, *tert*-butyl allyl[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]carbamate **238**, was obtained as a pale yellow oil in 86% yield. Characterization of the product found a singlet at 1.53ppm in the proton NMR spectrum for $OC(CH_3)_2$. The $^{13}C$ NMR spectrum showed new peaks at 28.4 and 79.5ppm for the $OC(CH_3)_3$ and $OC(CH_3)_3$ peaks respectively. The characteristic carbonyl peak was also present at 155.6ppm in the $^{13}C$ NMR spectrum. HRMS revealed the molecular ion at 375.23970, which correlates to the peak for $C_{22}H_{33}NO_4$ at 375.24096.

The amine **235** was dissolved in dichloromethane and to this solution was added triethylamine. After a few minutes of stirring, the α-toluenesulfonyl chloride-dichloromethane solution was added dropwise and a white gas was evolved that was probably hydrochloric acid gas. The reaction mixture was stirred overnight and the solvent was then removed *in vacuo*. The crude mixture was further purified by column chromatography to yield *N*-allyl-*N*-(3-isopropoxy-4-methoxy-2-(1-propenyl)-benzyl]phenylmethanesulfonamide **239** as a yellow oil. The protecting group was identified in the NMR spectra and this confirmed the reaction had occurred. In the $^1H$ NMR spectrum, the $CH_2$ peak was observed at 4.23 ppm and the five phenyl protons were found at 7.35-7.36ppm. The $^{13}C$ NMR spectrum displayed the $CH_2$ peak at 59.4ppm, the phenyl protons at 128.6, 129.2 and 130.8ppm and the quarternary phenyl carbon at 132.9ppm. FTIR spectroscopy was useful in identifying the $SO_2$-N- stretches at 1150 and 1334cm$^{-1}$, while the HRMS showed the molecular ion to be at 429.19619 (calculated as 429.19738 for $C_{24}H_{31}NO_4S$).

Lastly compound **235** was dissolved in dichloromethane and then cooled to 0$^o$C, before the addition of triethylamine and tosyl chloride. The reaction mixture was then stirred for 3 h before extraction. The desired product, *N*-allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)-benzyl]-4-methylbenzenesulfonamide **144**, was obtained as a cream-white solid after

chromatography. All of the spectroscopic data correlated well to that of Pathak,[129] however, our melting point was found to be 62-64°C (Pathak quoted 81-82°C). This value was significantly different, thus FTIR and HRMS spectroscopic analyses were performed on the compound as well. The FTIR spectrum showed the $SO_2$-N- stretches as 1339 and 1522cm$^{-1}$ and HRMS found the molecular ion to be at 429.19780 (calculated for $C_{24}H_{31}NO_4S$: 429.19738). We concluded from this supporting information that we had in fact synthesized the desired compound **144**.




**144, 237-239** **145, 240-242**

**Scheme 77** (i) catalyst **11**, toluene, 60-80°C, 18-21 h

Having our desired dienes in hand, we were then able to proceed to the RCM step. Considering our previous success, we were hopeful of our product formation and we thus employed similar conditions to those used in the synthesis of the 8-membered ring systems. The general procedure employed was to dissolve the protected amine **144, 237-239** in distilled toluene and to heat the solution to 60-80°C. Grubbs II metathesis catalyst **11** was then added and the reaction mixtures were stirred for 18-21 h. After this time the solvent was removed *in vacuo* and the residue was purified by column chromatography. The yields for the metathesis reactions to obtain benzazepines **145**, **240-242** are shown in **Table 9** below.

**Table 9** Yields for RCM reactions to form **145**, **240-242**

| Compound | R | Grubbs II catalyst (11) | Temperature | Time | Yield |
|---|---|---|---|---|---|
| **240** | Ac[3] | 10 mol % | 80°C | 21 h | 8% |
| **241** | Boc | 5 mol % | 60°C | 18 h | 26% |
| **242** | $SO_2Bn$‡ | 10 mol % | 80°C | 21 h | 39% |
| **145** | Ts | 5 mol % | 60°C | 19.5 h | 82% |

[3] These reactions were initially attempted with 5 mol % catalyst **11** at 60°C, but they gave poor yields, thus they were repeated using the conditions outlined in the table.

All of the spectra were consequently compared to those of the 2,5-dihydro-1*H*-2-benzazepines in order to determine if isomerisation of the double bond had occurred. It was found that none of the compounds were in fact identical, and we were thus able to confirm that no isomerisation had occurred post-metathesis. All of the compounds discussed below showed the three $CH_2$ signals for the benzazepine ring in both the $^1H$ and $^{13}C$ spectra, proving that no isomerisation had occurred pre-metathesis.

The formation of 2-acetyl-6-isopropoxy-7-methoxy-2,3-dihydro-1*H*-2-benzazepine **240** was highlighted by the loss of the methyl group and terminal alkene signals in both the $^1H$ and $^{13}C$ NMR spectra. The $^1H$ NMR spectrum also showed the presence of the alkene protons, a signal at 6.36ppm for 4-H, and a doublet at 7.57ppm for 5-H. In the $^{13}C$ NMR spectrum, peaks were found for 4-C at 126.1ppm and for 5-C at 135.7ppm.

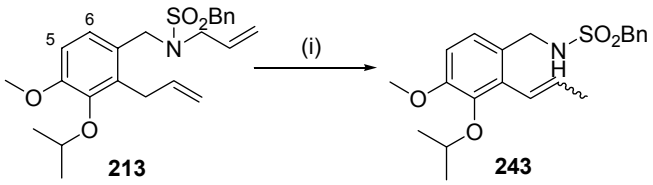
The 2-(benzylsulfonyl)-6-isopropoxy-7-methoxy-2,3-dihydro-1*H*-2-benzazepine **242** was shown to have been formed by the lack of a $CH_3$ signal and the lack of the terminal alkene peaks that were present in the starting material 194. The $^1H$ NMR spectrum had peaks at 5.76 and 6.92-6.99ppm for 4-H and 5-H respectively. The $^{13}C$ NMR spectra showed signals at 125.3ppm (4-C) and 128.9ppm (5-C), which were different from those for the alkene protons of the starting diene **239**. HRMS was then performed and a peak was found at 387.14958, which corresponds to that expected for $C_{21}H_{25}NO_4S$, namely 387.15043.

The formation of 6-isopropoxy-7-methoxy-2-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1*H*-2-benzazepine **145** was highlighted by the presence of the peaks for 4-H (5.86ppm) and 5-H (6.68ppm) in the $^1H$ NMR spectrum, and those for 4-C (130.0ppm) and 5-C (132.2ppm) in the $^{13}C$ NMR spectrum (the carbon assignments are interchangeable as no CH correlated spectrum was run as this is not a new compound for our laboratories). Our spectroscopic data correlated well to that outlined by Pathak.[129] However, our melting point, which was found to be 147-149$^oC$, could not be compared to Pathak as the compound that they isolated was an oil. This again prompted us to analyze the compound further by HRMS in order to confirm the product formation. HRMS for $C_{21}H_{25}NO_4S$ required that the molecular ion be at 387.15043 and we found a peak at 387.14872, confirming the formation of 6-isopropoxy-7-methoxy-2-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1*H*-2-benzazepine **145**.

## *2.5 De-allylated Compounds*

While attempting the isomerisations on our diene systems to form the isoquinoline structures a few other compounds were isolated. These compounds showed that *N*-de-allylation was occurring when a large amount of the Ru-isomerisation catalyst was added and the reactions were performed at elevated temperatures. The catalytic deprotection of tertiary allylic amines is well known in the presence of palladium catalysts.[39]

Knowing that these de-allylation reactions were occurring we decided to investigate the exact conditions that allowed these products to form. These types of de-allylation reactions were originally shown to occur in the presence of Grubbs first generation catalyst **10** by Alcaide and Almendros,[7] but to the best of our knowledge this is the first reported de-allylation reaction using catalyst **12**. Background information on the proposed mechanism of this reaction has already been outlined in **Chapter 1**.




**213** **243**

**Scheme 78** (i) 5 mol % catalyst **12**, 135-140°C, 19 h

Our initial attempts at the isomerisation of *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)phenylmethanesulfonamide **213** used mild conditions, but when these failed we opted for very harsh conditions to see if we could force the isomerisation to occur. What we found instead was that de-allylation had occurred to form *N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl](phenyl)methanesulfonamide **243** presumably via the isomerised alkene **238**. This discovery encouraged us to repeat the reaction to determine the optimal conditions for de-allylation reaction to occur on this system. We found that when **213** was mixed with the Ru-isomerisation catalyst **12** under solvent-free conditions, and the reaction mixture was heated to 135-140°C for 19 h, the product isolated after chromatography was **243**. The yield for the de-allylation reaction was 56% and the product, **243**, was found to be cream-coloured crystals with a melting point of 127-130°C.

The product **243** was identified by the characteristic loss of the allyl alkene protons. Two peaks were found at 1.49 and 1.88ppm in the $^{1}H$ NMR spectrum that were assigned as the methyl group (mixture of *E/Z* isomers). The corresponding methyl peaks were shown in the $^{13}C$ NMR spectrum at 15.2 and 19.2ppm. A broad singlet was observed in the proton spectrum at 1.60ppm that was identified as the NH peak based on the disappearance of the signal after a $D_2O$ wash and an NH bend was observed in the FTIR spectrum at 1481$cm^{-1}$. Subsequent HRMS analysis found a molecular ion peak at 389.16542, which correlates to that for $C_{21}H_{27}NO_4S$ at 389.16608. After recrystallisation, a single-crystal X-ray structure was obtained that proved the structure we proposed for compound **243**. It is shown schematically by the ORTEP diagram illustrated in **Figure 31** below.

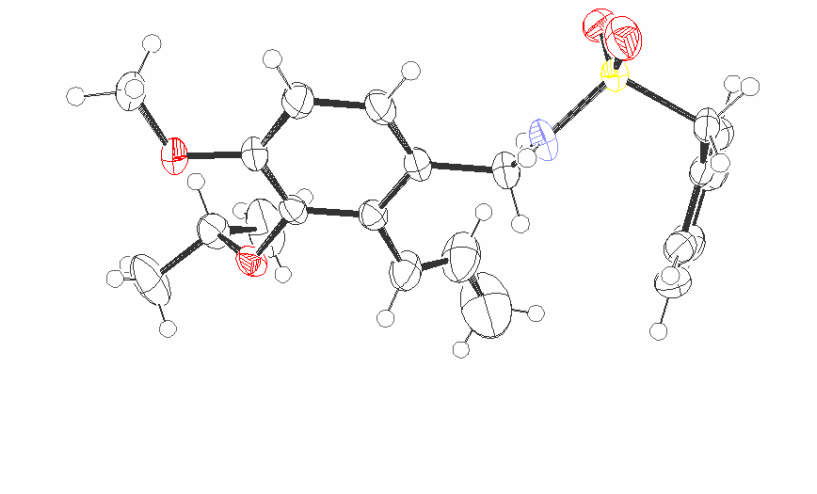
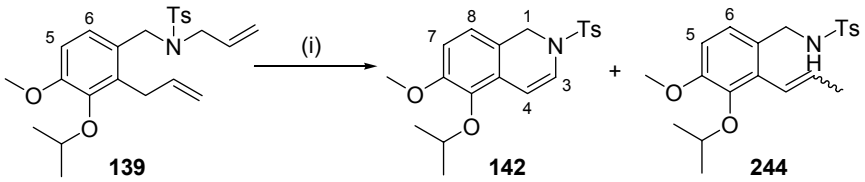


**Figure 31** ORTEP diagram of compound **243**
(showing the 50% probability thermal ellipsoids for all non-hydrogen atoms).



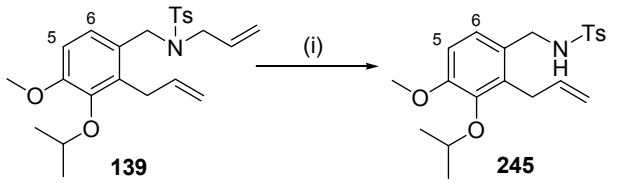

**139** **142** **244**

**Scheme 79** (i) 0.5+5 mol % catalyst **12**, toluene, 110-115°C, 2+2 h, followed by 5 mol % catalyst **11**, 110°C, 21 h

As described in the section on 6-membered ring formations above, *Section 2.3*, when attempting the isomerisation reactions at high temperatures and with large amounts of the Ru-isomerisation catalyst **12** present, de-allylated compounds were found. The desired isoquinoline **142** was obtained in 21% yield along with the de-allylated product, *N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]-4-methylbenzenesulfon-amide **244**, in 27% yield.

De-allylated compound **244** was obtained as a yellow solid with a melting point of 129-135°C. It was identified by the characteristic loss of the alkene protons from the allyl chain and the presence of a new NH peak in the NMR spectra. The $^{1}$H NMR spectrum showed a new methyl group at 1.77ppm along with the two shifted alkene protons at 5.96 and 6.21ppm, which showed that isomerisation of the double bond had occurred. The NH proton was identified as the peak at 4.48ppm by the corresponding lack of signal in the CH correlated spectrum. The methyl group was observed at 19.1ppm in the $^{13}$C spectrum, along with the two alkene peaks at 124.2 and 132.6ppm. The loss of the allyl chain was supported by the HRMS spectrum that found a peak at 389.16367, the corresponding molecular ion for $C_{21}H_{27}NO_4S$ would have been at 389.16608.

Both the formation of compound **243** and **244** highlight that the *N*-allyl chain selectively isomerises before the aromatic-allyl chain. This is supported by the initial isomerisation reactions that were performed under combinatorial conditions in order to synthesise the 2,5-dihydro-1*H*-2-benzazepines (*Section 2.4.*1 above*)*.




**Scheme 80** (i) 5 mol % catalyst **12**, toluene, 105°C, 18 h

Having isolated compound **244** from our reaction mixture, we attempted to synthesize it directly in order to determine the exact conditions required. The *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-4-methylbenzenesulfonamide **139** was dissolved in distilled toluene, the solution was degassed with $N_2$ and then heated to 105°C. To the solution was then added 5 mol % of the Ru-isomerisation catalyst **12** and it was stirred for 18 h. After this time the solution was allowed to cool to rt, the solvent was removed *in vacuo* and the resulting residue was purified by column chromatography. We did not isolate **244**, but instead obtained *N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-4-methylbenzenesulfonamide **245**, in which the aryl allyl group had not isomerised, in 51% yield as a pale yellow oil that solidified on standing.

Compound **245** was identified by the loss of the *N*-allyl peaks (both alkene and $CH_2$) in the NMR spectra. The $^1$H NMR spectrum had a doublet at 3.38ppm for the $CH_2$ group and a multiplet at 5.81-5.83ppm for the C*H*=$CH_2$ proton. The terminal alkene protons were observed at 4.74ppm and 4.93ppm for *trans* and *cis* positions respectively. The multiplet at 4.49-4.54ppm also integrated for the NH proton (as well as for O*C*H$(CH_3)_2$). The corresponding signals were observed in the $^{13}$C NMR spectrum at 30.5ppm ($CH_2$), 115.2ppm (CH=*C*$H_2$) and 137.1ppm (*C*H=$CH_2$). Both the FTIR and HRMS spectra also supported the formation of this product. FTIR showed at peak at 3019cm$^{-1}$, which may be due to a terminal alkene, and HRMS found a molecular ion peak at 389.16714 ($C_{21}H_{27}NO_4S$ requires 389.16608).

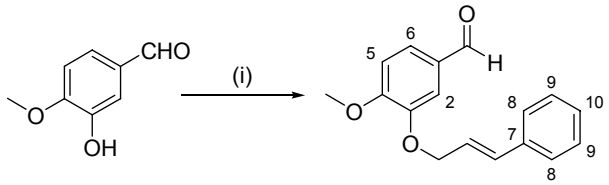
As yet we have no concrete evidence to explain the difference in product formed via the seemingly similar reaction conditions. We believe that further investigation into this result is required, but due to the time limitations it could not be accomplished during the duration of this project.

## 3. The 1-Phenyl-1-Propenyl Substituted System

### *3.1 Synthesis of Phenyl-Substituted Starting Materials*

#### *3.1.1 O-Cinnamyl Addition to Isovanillin*

Having had a fair amount of success when using our unsubstituted allylated systems we then decided to continue our methodology study with a more complex range of phenyl-substituted allyl systems. These are based on the addition of the cinnamyl group instead of the allyl chain in the initial protection reactions.

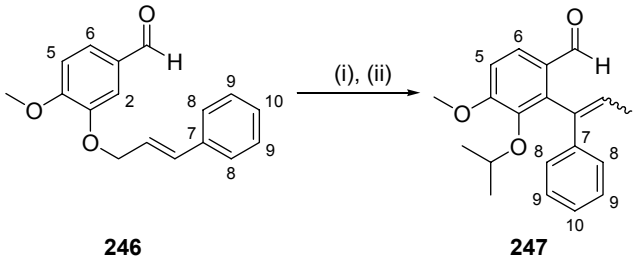



**206** **246**

**Scheme 81** (i) 2.5eq $K_2CO_3$, 2.5eq cinnamyl bromide, 60°C, 23 h

Initially, a solution was prepared of potassium carbonate in DMF and it was then heated to 60°C, before the addition of isovanillin. To the reaction mixture was then added the cinnamyl bromide, and it was stirred at 60°C for 23 h. The desired product, 4-methoxy-3-{[(2*E*)-3-phenyl-2-propenyl]oxy}benzaldehyde **246** was obtained after chromatography as a pale yellow semi-solid in 100% yield, which was an improvement on that obtained by Rousseau[1] (85%). The preparation of the product was confirmed by the new phenyl protons, alkene protons and the new $CH_2$ group observed in both the proton and carbon NMR spectra. In the $^1$H NMR spectrum, the $OCH_2$ peak was observed at 4.83ppm, the one alkene proton was found at 6.45ppm and the other one was present at 6.76ppm. The five new phenyl protons were found in the multiplet from 7.25 to 7.48ppm. Similarly, the corresponding peaks were observed in the $^{13}$C NMR spectrum. The peaks observed at 69.6ppm, 123.5ppm, 126.7ppm, 128.0ppm, 128.5ppm and 134.0ppm were assigned as being $OCH_2$, 10-C, 8-C, $OCH_2CH$=CH, 9-C and $OCH_2CH$=*C*H respectively. These correlated well to those observed by Rousseau[1] and no further analyses were performed.

### *3.1.2 Claisen Rearrangement and Protection*

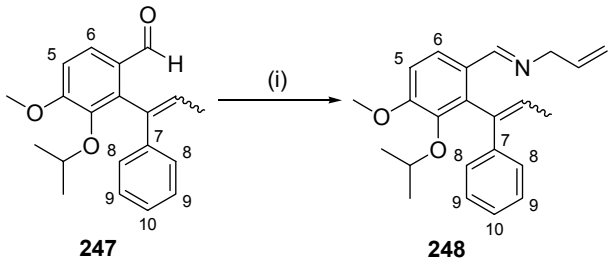



**246** **247**

**Scheme 82** (i) DMF, 160-165°C, 44 h,
(ii) 2.5eq $K_2CO_3$, 2.5eq isopropyl bromide, DMF, 60°C, 44 h

We then attempted the Claisen rearrangement on 4-methoxy-3-[(3-phenyl-2-propenyl)oxy]benzaldehyde **246**. As Rousseau had obtained the styrene product in only 51% yield using the conventional methodology,[1] we decided to try out our microwave based method. However, this failed to give us any of the desired product **247** and we instead only obtained the Claisen-Cope product. This reaction is discussed in detail in *Section 3.4* below. We thus returned to the conventional method employed by Rousseau and prepared a solution of benzaldehyde **246** in dimethylformamide, which was then heated to 160-165°C for 44 h. After this time, the solution was allowed to cool to 60°C, before the addition of the potassium carbonate and the isopropyl bromide. The reaction mixture was then stirred at 60°C for a further 44 h, before it was subjected to the workup and the residue was purified by chromatography. The 3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzaldehyde **247** was obtained as a purple oil in 50% yield. The NMR data correlated well to that reported by Rousseau[1] and the yields were also similar.

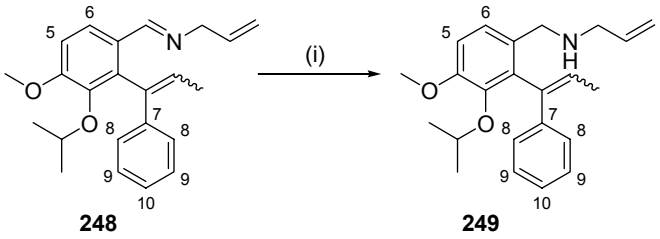
### *3.1.3 Reductive Amination Reactions*




**Scheme 83** (i) 1.4eq allyl amine, rt, 24 h

Having the desired aldehyde in our hands, we were then able to continue our synthesis by performing the same reductive amination on it. The aldehyde **247** was thus stirred with allyl amine at rt for 24 h. After this time the excess allyl amine was removed *in vacuo* and the desired product, *N*-{(*E*)-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)phenyl]methyl-idene}-2-propen-1-amine **248**, was obtained as an orange oil in 100% yield. The compound was judged clean by spectroscopy and no further purification was required. We were initially surprised at the product formation, as Pathak had not managed to synthesize compound **248** during the course of her research in our laboratories. This result was thus very exciting and prompted our further investigation into this area.

The imine **248** was characterized fully as it was a new compound for our laboratories. The FTIR spectrum showed the presence of a C=N stretch at 1678cm$^{-1}$, and the NMR spectra showed the disappearance of the aldehyde peak. The new peaks observed in the $^{1}$H NMR spectrum were a singlet at 8.13ppm for the CH=N proton and those for the allyl chain, at 4.06-4.08, 5.04-5.15 and 5.88-5.99ppm ($NCH_2$, CH=C$H_2$ and C$H$=$CH_2$ respectively). These peaks were also found in the $^{13}$C NMR spectrum at 63.4 ($NCH_2$), 115.7 (CH=$CH_2$), 136.3 ($C$H=$CH_2$) and 161.2ppm (CH=N). The preparation of imine **248** was also confirmed by HRMS, in which a molecular ion peak was found at 349.20968, which correlates well to that for $C_{23}H_{27}NO_2$ at 349.20418.

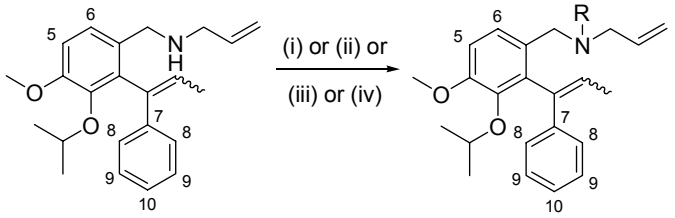



**Scheme 84** (i) 1.2eq sodium borohydride, MeOH, 0°C-rt, 2.5 h

The *N*-{(*E*)-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)phenyl]methylidene}-2-propen-1-amine **248** was dissolved in methanol (to which one drop of distilled water was added to catalyse the reaction) and the solution was cooled to 0°C. Then sodium borohydride was added and the reaction mixture was left to stir for 2.5 h at 0°C-rt. After this time the excess sodium borohydride was destroyed and the reaction mixture was extracted. The *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-benzyl]-2-propen-1-amine **249** was obtained after workup as a dark yellow oil that was judged pure by spectroscopy in quantitative yield.

Product **249** was identified by the characteristic loss of the CH=N peak in both the $^{1}H$ and $^{13}C$ NMR spectra. A singlet was observed at 1.42ppm in the $^{1}H$ NMR spectrum that was assigned as the NH proton. A doublet was also observed at 3.46ppm in the $^{1}H$ NMR spectrum that was found to be the new $CH_2$ group and this was also observed in the $^{13}C$ NMR spectrum as peaks at 50.3 and 50.7ppm. The reduction was further confirmed by the presence of the NH stretches at 1595 and 3494$cm^{-1}$ in the FTIR spectrum as well as the confirmation of the molecular ion peak at 351.21969 ($C_{23}H_{29}NO_2$ requires 351.21983) in the HRMS spectrum.

### *3.1.4 Protection of the Amine*




**249** **250-253**

**Scheme 85** (i) 1.5eq acetic anhydride, 2.5eq pyridine, rt, 3 h, or R = Ac **250**
(ii) 1.2eq $Boc_2O$, 0.1eq DMAP, THF, rt, 2.3 h, or R = Boc **251**
(iii) 2.5eq $NEt_3$, 1.1eq α-toluenesulfonyl chloride, $CH_2Cl_2$, rt, 4 h, or R = $SO_2Bn$ **252**
(iv) 1.4eq $NEt_3$, 1.2eq tosyl chloride, $CH_2Cl_2$, $0^oC$-rt, 3 h R = Ts **253**

The four different protecting groups highlighted for use in this MSc project were again used in the protection of the amine. The yields for the protection reactions employed to form compounds **250-253** are outlined in **Table 10** below.

**Table 10** Yields for the Protection Reactions to form **206-209**

| Compound | R | Yield (%) |
|---|---|---|
| **250** | Ac | 66 |
| **251** | Boc | 92 |
| **251** | $SO_2Bn$ | 45 |
| **253** | Ts | 71 |

As before a solution was prepared of *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-benzyl]-2-propen-1-amine **249** and pyridine, which was then cooled to $0^oC$. To this was then added dropwise a solution of acetic anhydride and pyridine. The reaction mixture was then stirred at $0^oC$-rt for 3 h. After this time the reaction mixture was purified by extraction and the desired product, *N*-allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]acet-amide **250**, was obtained as a dark yellow oil. The product was identified by the characteristic loss of the NH peak and the formation of a new singlet at 3.93ppm for the methyl group in the $^1H$ NMR spectrum. This was coupled to the presence of new peaks at 21.2ppm for the methyl group and 170.9 and 171.1 for the carbonyl group in the $^{13}C$ NMR spectrum. FTIR

spectroscopy showed the presence of the C-O stretch at 1216cm$^{-1}$ and the corresponding loss of the NH stretches. Also, HRMS analysis of the compound found a peak at 393.23103, which corresponds nicely to that for $C_{25}H_{31}NO_3$ at 393.23039.

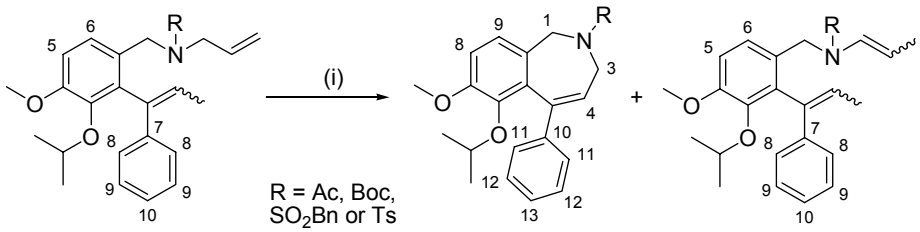
Amine **249** was dissolved in tetrahydrofuran and to this solution was added $Boc_2O$. It was then stirred for 5 min before the addition of DMAP and the reaction mixture was then stirred for a further 2.3 h at rt before the solvent was removed *in vacuo*. The desired product, *tert*-butyl allyl[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-carbamate **251**, was isolated after chromatography as a purple oil. Compound **251** was shown to have formed by the presence of the new $OC(CH_3)_3$ singlets at 1.39 and 1.44ppm, as well as by the characteristic loss of the NH peak in the $^1$H NMR spectrum. The $^{13}$C NMR spectrum showed the presence of three new signals, 27.7 and 28.3ppm for $OC(CH_3)_3$, 79.6ppm for $OC(CH_3)_3$ and 155.9ppm for the C=O group. A C-O stretch was observed in the FTIR spectrum at 1216cm$^{-1}$. Furthermore, HRMS analysis was performed on the compound with the peak expected for $C_{28}H_{37}NO_4$ predicted to be at 451.27226 and with the molecular ion peak observed at 451.27299.

Compound **249** was dissolved in dichloromethane, with triethylamine being added to the mixture and allowed to stir for 15 min, before the dropwise addition of the α-toluenesulfonyl chloride-dichloromethane solution. The reaction mixture was then stirred for 4 h at rt, before the solvent was removed *in vacuo* and the resulting residue was purified by column chromatography. *N*-Allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]phenylmethanesulfonamide **252** was obtained as an orange solid with a melting point of 105-108$^o$C after purification. The formation of **252** was identified by the characteristic loss of the amine proton signal in the $^1$H NMR spectrum and the presence of new signals at 4.11-4.24 and 7.14-7.28ppm, for the $CH_2$ group and the five benzyl protons respectively. This data was supplemented by the observation of new peaks in the $^{13}$C NMR spectrum at 59.1ppm ($CH_2$), 127.5, 128.3, 130.6 and 132.7ppm (benzyl carbons). The FTIR spectrum also showed the presence of the protecting group by the peaks at 1151 and 1337cm$^{-1}$ for $SO_2$-N stretches and deformations. HRMS required a peak at 505.22868 for $C_{30}H_{35}NO_4S$ and the molecular ion was present at 505.22896.

Lastly, compound **249** was dissolved in dichloromethane and the solution was cooled to 0$^o$C. To this solution was then added triethylamine and tosyl chloride, subsequently the reaction

mixture was stirred at 0°C-rt for 3 h. After this time the reaction mixture was quenched, extracted, and the resulting residue was purified by column chromatography. The desired product *N*-allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-4-methylbenzenesulfonamide **253** was obtained as a pale pink oil that solidified on standing and had a melting point of 110-113°C. The product **253** was identified by the loss of the amine proton in the $^{1}H$ NMR spectrum as well as by the presence of the characteristic tosyl peaks, namely, a singlet for the $TsCH_3$ at 2.40ppm, a multiplet at 7.15-7.30 and a doublet at 7.55ppm for the two different aromatic regions. This was further confirmed by the presence of the new $TsCH_3$ peak at 21.5ppm and the characteristic aromatic peaks for a tosyl group at 127.2 and 129.5ppm in the $^{13}C$ NMR spectrum. The FTIR supported the other evidence for the product formation by the signals at 1163 and 1338$cm^{-1}$, which are $SO_2$-N stretches. Finally, HRMS analysis of the compound gave a peak at 505.22896, with a peak for $C_{30}H_{35}NO_4S$ required at 505.22868.

### *3.2 Phenyl-Substituted Benzazepines (7-membered rings)*




**Scheme 86** (i) 8 mol % catalyst **11**,[4] toluene, 80°C, 2.5h

Having our required diene systems **250-253** in hand, we were then able to continue with the desired RCM step to form the benzazepine rings. Similar conditions were employed for each RCM attempt and the conditions are outlined in **Table 11** below.

[4] Initially the RCM was attempted using the conditions developed for the simple 8-membered rings, namely 5 mol % Grubbs II, 60°C for 1 h (increased to overnight), but no consumption of starting material was observed. Thus, we reattempted the reaction at elevated temperatures and with more Grubbs II catalyst.

**Table 11** Conditions for RCM Reactions

| Expected Product | R | Time | Product Formed |
|---|---|---|---|
| **254** | Ac | 2.5 h | **214** (32%) |
| **255** | Boc | 22 h | Product peaks found by HRMS but NMR spectra uninterperable |
| **256** | $SO_2Bn$ | 22 h | |
| **257** | Ts | 22 h | |

A solution was prepared from *N*-allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]acetamide **250** and distilled toluene, which was degassed using nitrogen for 10 min. This was then heated to 80°C, 8 mol % Grubbs II catalyst **11** was added and the reaction mixture was stirred for 2.5 h. After this time there was total consumption of the starting material by thin layer chromatography so the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo*. The resulting residue was then purified by column chromatography and analyzed by NMR spectroscopy. None of the desired product was formed, but the isomerised diene **258** was isolated instead in 32% yield (this compound is fully characterized in *Section 3.3* below). This result was depressing, but not totally unexpected, as the system we were attempting the metathesis on is exceptionally hindered, with the phenyl group actually locking into certain conformations due to the lack of free rotation about the C-C bond because of steric hindrance (observed as doubling of the isopropyl and phenyl peaks in NMR spectra of starting materials **250-253**). The isomerisations too, were not unexpected, as the isomerising ability of the Grubbs II catalyst **11**'s degradation products has been well documented over the past few years.[23-26] This is explained in detail in **Chapter 1**, *Section 3* above.

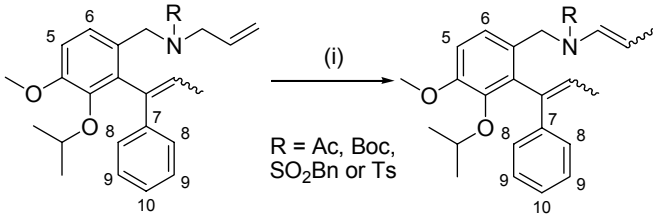
For the attempted RCM on compounds **251-253**, the protected amines were dissolved in distilled toluene and the solution was heated to 80°C, before the addition of 8 mol % Grubbs II catalyst **11**. The reaction mixtures were then stirred for 22 h, before the solvent was removed *in vacuo* and the resulting residues were purified by column chromatography. The NMR spectra for all of the products were complex, with mixtures of isomers, amide rotamers and splitting occurring due to the lack of free rotation of the phenyl ring. The presence of the desired benzazepines **255-257** were thus not confirmed satisfactorily by NMR spectroscopy due to the complexity of the spectra, but the desired molecular ions were however observed in

the HRMS spectra. This itself does not confirm the formation of the products, but it may suggest that trace amounts of the desired compounds are forming. There exists the possibility that by changing the conditions to higher temperatures and more catalyst, one may drive the reaction to afford the desired benzazepines, but we felt that the steric hindrances to the Ru-carbene attachment step may be too great to obtain reasonable yields of the desired products. No further attempts were thus made to cyclise these dienes during the course of this project.

## *3.3 Phenyl Substituted Isoquinolines (6-membered rings)*

### *3.3.1 Isomerisation Reactions*

Having isolated the isomerised diene, **258**, from our reaction mixture for the attempted synthesis of **254**, we were excited about the possibility that isomerisation reactions were possible for the dienes **250-253**. We had initially decided to attempt the isomerisations using the Ru-isomerisation catalyst **12** developed by Krompiec *et al.*[29,30] and even after the isolation of **258** using Grubbs II catalyst **11**, decided to pursue our initial route. It was favoured over attempting the isomerisations with Grubbs II catalyst **11** as the Ru-isomerisation catalyst **12** is far more selective in that there is no possibility of metathesis occurring.




**Scheme 87** (i) 2 mol % catalyst **12**, toluene, 90°C, 18-21 h

The general procedure used for the isomerisation reactions was to dissolve the protected amines **250-253** in distilled toluene and to heat the resulting solution to 90°C. Then 2 mol % of the Ru-isomerisation catalyst **12** was added and the reaction mixture was stirred for 18-21 h, before the removal of the solvent *in vacuo* and the purification of the residue by column chromatography. The yields for the formation of products **258-261** are outlined in **Table 12** below.

**Table 12** Yields for Isomerisation Reactions

| Compound | R | Time | Yield (%) |
|---|---|---|---|
| **258** | Ac | 21 h | 82 |
| **259** | Boc | 17.5 h | 96 |
| **260** | $SO_2Bn$ | 27 h | 90 |
| **261** | Ts | 26 h | 82 |

The formation of *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-*N*-(1-propenyl)acetamide **258** was shown by the characteristic loss of the terminal allyl alkene protons and the $CH_2$ group in both the proton and the carbon NMR spectra. This was coupled to the presence of a new methyl peak at 1.70ppm, as well as the shift of the two alkene protons to 4.69 and 7.17-7.29ppm, in the $^1$H NMR spectrum. The same new peaks were observed in the $^{13}$C NMR spectrum, with the methyl group at 16.0 and 16.1ppm; and the alkenes at 109.0ppm and 125.9 and 126.0ppm. The HRMS spectrum required the peak for $C_{25}H_{31}NO_3$ to be at 393.23039, and a molecular ion was found at 393.23162.

The exact same procedure was used to determine whether the isomerised dienes **259-261** had formed. The characteristic signals used to determine that these compounds had formed are outlined in **Table 13** below.

**Table 13** Characteristic Peaks used to Identify Compounds **259-261**

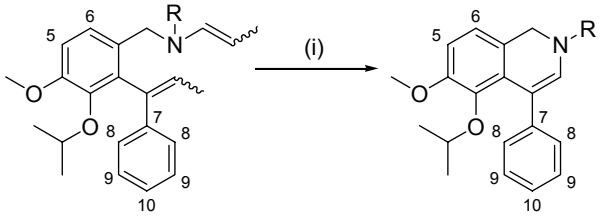
| | R | $^1$H NMR (ppm) | $^{13}$C NMR (ppm) | HRMS |
|---|---|---|---|---|
| **259** | Boc | 1.23-1.60ppm ($CH_3$) | 16.0 ($CH_3$) | $C_{28}H_{37}NO_4$ |
| | | 3.97-4.50 (NCH=C*H*) | 104.1 (NCH=*C*H) | Calculated: 451.27226 |
| | | 7.09-7.26 (NC*H*=CH) | 136.2 (N*C*H=CH) | Found: 451.27373 |
| **260** | $SO_2Bn$ | 1.44 and 1.51 ($CH_3$) | 15.9 ($CH_3$) | $C_{30}H_{35}NO_4S$ |
| | | 4.39 (NCH=C*H*) | 107.0 (NCH=*C*H) | Calculated: 505.22868 |
| | | 6.28-6.33 (NC*H*=CH) | 125.4 (N*C*H=CH) | Found: 505.22717 |

**Table 13 contd.** Characteristic Peaks used to Identify Compounds **259-261**

| R | $^1$H NMR (ppm) | $^{13}$C NMR (ppm) | HRMS |
|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **261** | Ts | 1.65 ($CH_3$) | 16.0 ($CH_3$) | $C_{30}H_{35}NO_4S$ |
| | | 4.45 (NCH=C*H*) | 107.9 (NCH=*C*H) | Calculated: 505.22868 |
| | | 6.52 (NC*H*=CH) | 125.6/7 (N*C*H=CH) | Found: 505.22739 |

### *3.3.2 Ring Closing Metathesis*




**258-261** **262-265**

**Scheme 88** (i) 8 mol % catalyst **11**, toluene, 80°C, 18-24 h

Having our required diene systems **258-261** in hand, we were then able to continue with the metathesis step to form the isoquinoline skeletons. Similar conditions were employed in each of RCM reactions and differences are outlined in **Table 14** below. The general procedure used was to dissolve the diene **258-261** in distilled toluene and to heat the solution to 80°C before the addition of 8 mol % Grubbs II catalyst **11**. The reaction mixtures were then stirred for 18-24 h, the solvent was removed *in vacuo* and the resulting residues were purified by column chromatography.

**Table 14** Conditions for RCM reactions

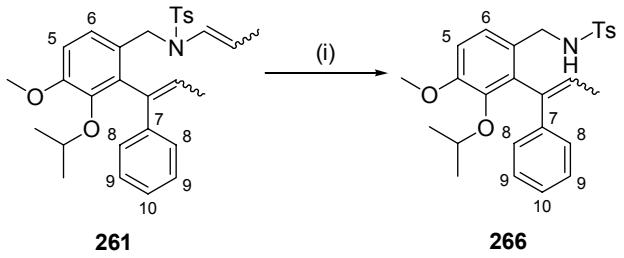
| Expected Product | R | Time | Compound Isolated |
|---|---|---|---|
| **262** | Ac | 18 h | Starting Material (69%) |
| **263** | Boc | 19.5 h | Starting Material (100%) |
| **264** | $SO_2Bn$ | 23 h | Starting Material (79%) |
| **265** | Ts | 24 h | Starting Material (39%) |

In all of the cases, even after long periods of time only starting material was recovered. This was a little bit disappointing, as HRMS did indicate the presence of trace amounts of the desired products **262-265**. However, this was not concrete evidence to prove that the reaction had occurred. We think that the bulky phenyl group is preventing the Ru-carbene complex

from metathesizing the double bonds, thus preventing the desired reaction from occurring. One way of trying to prove this would be to include very small protecting groups on both the oxygen and nitrogen atoms, hopefully releasing some of the bulk and allowing the reaction to occur. Due to the time restraints on this project, we were unable to test this theory, but hopefully it may be attempted in the future.

### *3.3.3 De-allylated Compound*

When increasing the amount of Grubbs II catalyst **11** used to 10 mol % for the metathesis reaction outlined in *Section 3.3.2* above, we isolated a de-allylated compound, *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-4-methyl-*N*-(1-propenyl)benzenesulfonamide **266**, after 17 h at 80°C. Compound **266** was obtained as a white semi-solid in 32% yield after column chromatography. This reaction was not surprising, considering the literature precedent[6,26] and our isolation of the de-allylated materials outlined in *Section 2.5*.

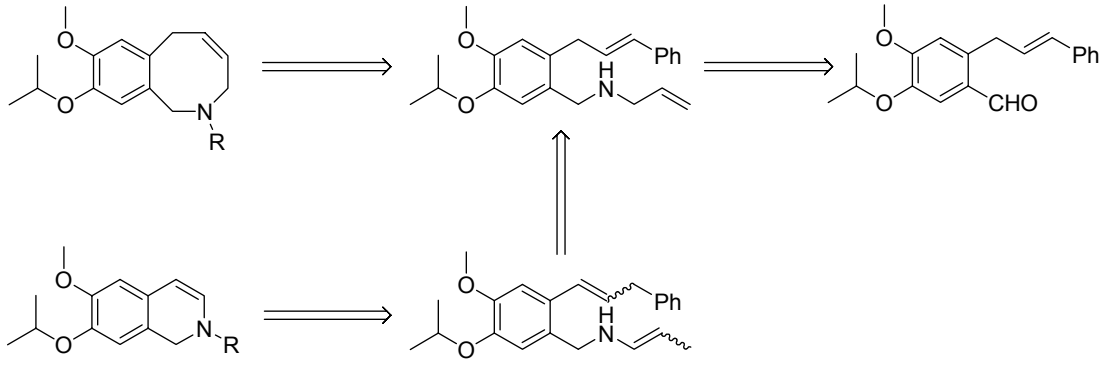



**261** **266**

**Scheme 89** (i) 10 mol % catalyst 11, toluene, 80°C, 17 h

Compound **266** had a melting point of 125-128°C. The compound **266** was identified by the loss of the methyl group and the two alkene protons that were present in $^{1}H$ and $^{13}C$ NMR spectra of the starting material **261**. $^{1}H$ NMR spectroscopy showed the presence of a broad singlet at 4.11-4.15ppm that was due to the NH proton. A HRMS analysis of the product found a peak at 465.19540 and $C_{27}H_{31}NO_4S$ required a molecular ion value of 465.19738.

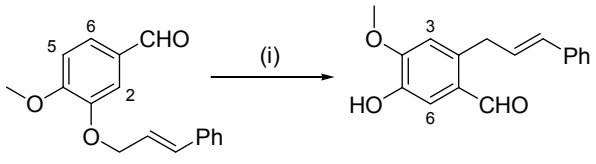
## *3.4 The Cope Products*




**Scheme 90** General Retrosynthesis for Heterocycles with a Substitution Pattern commonly seen in natural products.

The isolation of the product **267** (**Scheme 91**) that had undergone a Claisen rearrangement followed by the Cope rearrangement when performing the reaction under microwave conditions (*Section 3.1.2*) led us to the synthesis of another group of heterocycles. Although the proposed metathesis step was not particularly atom economical due to the loss of a phenyl group, we continued with this route as we already had the compounds in hand and we simply wanted to test the methodology to see if it could be applied to the new substitution pattern. This was important as it led us to a number of benzazocines with the same substitution pattern as the natural products outlined in **Chapter 2**. In future a new method will need to be developed to access the substitution pattern and to maintain the viability of the route, ie: to be atom economical. The general retrosynthesis for the heterocycles with the "natural" substitution pattern is outlined in **Scheme 90** above.

### *3.4.1 Claisen-Cope Rearrangement and Protection Reaction*

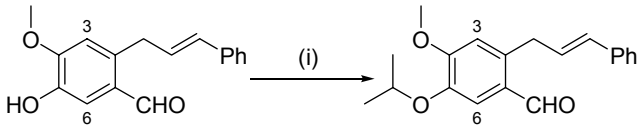



**246** **267**

**Scheme 91** (i) microwave reaction, 200°C, 50W, 150psi max, 5 min run, 5 min hold

Initially the Claisen-Cope rearrangements were performed by placing the 4-methoxy-3-{(2*E*)-3-phenyl-2-propenyl]oxy}benzaldehyde **246** neat in the sealed tube for the microwave

reactor. The program was then run with the temperature at 200°C and with a run time of 5 min and a hold time of 5 min. This yielded the desired product, 5-hydroxy-4-methoxy-2-[(1*E*)-3-phenyl-2-propenyl]benzaldehyde **267**, as a dark brown oil with no further purification required, in 100% yield (**Scheme 91**). The product was identified by the characteristic loss of the aromatic peak for 2-H in the $^{1}$H NMR of the starting material (at 7.25-7.48ppm) and the presence of a new OH signal in the $^{1}$H NMR spectrum of the product (as a broad singlet at 1.57ppm). The corresponding results were observed in the $^{13}$C NMR spectrum.

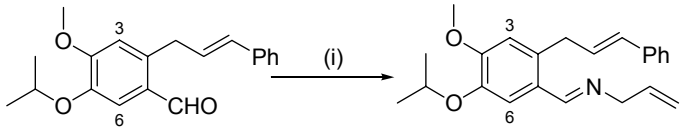



**267** **268**

**Scheme 92** (i) 2.5eq $K_2CO_3$, 2.5eq isopropyl bromide, DMF, 60°C, 19 h

The substituted benzaldehyde **267** was then dissolved in DMF and the solution was heated to 60°C. The potassium carbonate was then added and stirred until a suspension formed, before the addition of the isopropyl bromide. The reaction mixture was then stirred for 19 h, subjected to a workup and the residue was purified by column chromatography. The desired product, 5-isopropoxy-4-methoxy-2-[(1*E*)-3-phenyl-2-propenyl]benzaldehyde **268**, was obtained as a dark yellow oil in 76% yield (**Scheme 92**). It was identified by the characteristic loss of the phenol proton and by the presence of the new isopropyl peaks, a doublet at 1.39ppm for OCH(C*H*$_3$)$_2$ and a septet at 4.62ppm for OC*H*(CH$_3$)$_2$, in the $^{1}$H NMR spectrum. The presence of the isopropyl group was also noted in the $^{13}$C NMR spectrum where the OCH(*C*H$_3$)$_2$ peak was found at 21.9ppm and the O*C*H(CH$_3$)$_2$ peak was found at 71.5ppm. HRMS for $C_{20}H_{22}O_3$ required a peak at 310.15689, and analysis of the product found the molecular ion peak to be at 310.15830.

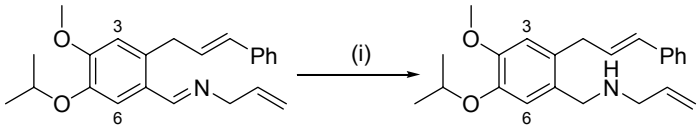
### *3.4.2 Reductive Amination Reactions*




**268** **269**

**Scheme 93** (i) 1.4eq allyl amine, rt, 21.5 h

The precursor **268** was subsequently stirred with allyl amine for 21.5 h at rt. After this time the excess allyl amine was removed *in vacuo*. The desired product, *N*-((*E*)-{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]phenyl}methylidene)-2-propen-1-amine **269**, was obtained as a yellow oil in 100% yield and no further purification was required. The product **269** was identified by the characteristic loss of the aldehyde peak in both the $^{1}H$ and $^{13}C$ NMR spectra. The $^{1}H$ NMR spectrum showed a peak at 8.52ppm for the CH=N proton. It also highlighted the presence of the allyl chain by the signals at 4.22, 5.06-5.22 and 5.98-6.10ppm, which are assigned as $CH_2$, CH=C*H*$_2$ and C*H*=$CH_2$ respectively. The corresponding peaks were observed in the $^{13}C$ NMR spectrum, with the peak for CH=N at 159.5ppm and the peak for the allyl $CH_2$ at 63.7ppm. We also observed the terminal alkene peaks at 115.7ppm for the CH=*C*$H_2$ carbon and at 136.3ppm for the *C*H=$CH_2$ carbon. The FTIR spectrum supported this assignment by the presence of the C=N stretch at 1646cm$^{-1}$. Analysis by HRMS found the molecular ion to be at 349.20344 ($C_{23}H_{27}NO_2$ requires 349.20418).



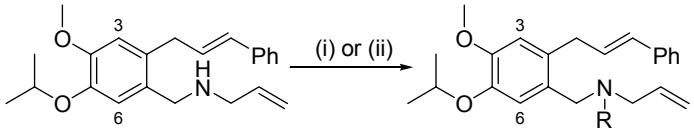

**269** **270**

**Scheme 94** (i) 1.2eq $NaBH_4$, MeOH, 0$^{o}$C-rt, 4.5 h

Imine **269** was next dissolved in methanol and cooled to 0$^{o}$C. Then sodium borohydride was added and the reaction mixture was left to stir at 0$^{o}$C-rt for 4.5 h. After this time the excess sodium borohydride was destroyed, the mixture was extracted and the solvent was removed *in vacuo*. The reduced *N*-{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]benzyl}-2-propen-1-amine **270** was obtained as a dark yellow oil in 75% yield, with no further purification being required. The product was identified by the characteristic loss of the CH=N

peaks in the $^{1}H$ and $^{13}C$ NMR spectra. The FTIR spectrum highlighted the reduction by the presence of the NH stretch at 3618cm$^{-1}$. The new NH signal was shown as a broad singlet at 1.58ppm, with the new $CH_2$ group shown as a singlet at 3.73ppm in the $^{1}H$ NMR spectrum. The corresponding $CH_2$ signal was observed in the $^{13}C$ NMR spectrum at 50.2ppm. In addition, the HRMS analysis found a peak at 351.21926, with $C_{23}H_{29}NO_2$ requiring the molecular ion be found at 351.21983.

### *3.4.3 Protection Reactions*




**270** **271-272**

**Scheme 95** (i) 1.2eq $Boc_2O$, 0.1eq DMAP, THF, rt, 3 h, or R = Boc **271**
(ii) 1.4eq $NEt_3$, 1.2eq tosyl chloride, $CH_2Cl_2$, 0$^{o}$C-rt, 2.5 h R = Ts **272**

Due to the time constraints in this project only two of the four protecting used previously were used for these reactions. The Boc group was chosen as it is relatively simple to remove and the tosyl group was chosen as all the products tend to be solids (useful for running single-crystal X-ray structures). The reactions were performed on compound **270** and the yields for the products **271-272** are outlined in **Table 15** below.

**Table 15** Yields for the Protection Reactions

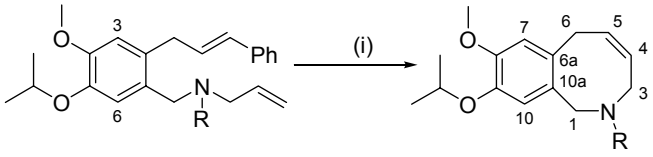
| Compound | R | Yield (%) |
|---|---|---|
| **271** | Boc | 79 |
| **272** | Ts | 72 |

The *N*-{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]benzyl}-2-propen-1-amine **270** was dissolved in distilled tetrahydrofuran and to this solution was added $Boc_2O$. After stirring the solution for 5 min, DMAP was added. The reaction mixture was then stirred at rt for 3 h and after this time the solvent was removed *in vacuo*. The residue was then purified by column chromatography and the desired product, *tert*-butyl allyl{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]benzyl}carbamate **271**, was obtained as a yellow oil. The product

was identified by the characteristic loss of the NH peaks in the $^{1}$H NMR and FTIR spectra. The $^{1}$H NMR spectrum showed the presence of the two new singlets at 1.45 and 1.48ppm for the $OC(CH_3)_3$ methyl groups (two signals occur due to the amide rotamers). The corresponding peaks were observed in the $^{13}$C NMR spectrum at 28.4ppm and 79.7ppm, for $OC(CH_3)_3$ and $OC(CH_3)_3$ respectively. The HRMS spectrum showed a peak at 451.27205, which correlates well to the peak at 451.27226 for $C_{28}H_{37}NO_4$.

In addition, compound **270** was dissolved in dichloromethane and the solution was cooled to 0$^{o}$C. Then triethylamine was added and the solution was stirred for 5 min before the addition of the tosyl chloride. The reaction mixture was then stirred at 0$^{o}$C-rt for 2.5 h, before the reaction mixture was quenched, extracted and the solvent removed *in vacuo*. The resulting residue was then purified by chromatography to obtain *N*-allyl-*N*-{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]benzyl}-4-methylbenzenesulfon-amide **272** as a yellow oil that solidified on standing (melting point 79-82$^{o}$C). This product was identified by the disappearance of the NH stretch on the FTIR spectrum and by the loss of the NH peak on the $^{1}$H NMR spectrum. Several new peaks were observed in the $^{1}$H NMR spectrum for the tosyl group, namely, a $TsCH_3$ singlet at 2.43ppm and two different groups of TsH, a multiplet at 7.20-7.31ppm and doublet at 7.73ppm (*J*=8.1Hz). The characteristic peaks for the tosyl group were also observed in the $^{13}$C NMR spectrum. The methyl group was found at 21.5ppm, the aromatic groups at 127.3 and 128.5/129.7ppm and the quaternary carbons at 132.6 and 143.2ppm.

### *3.4.4 Ring Closing Metathesis to form Compounds **273** and **274***




**271-272** **273-274**

**Scheme 96** (i) 5 mol % catalyst **11**, toluene, 60$^{o}$C, 20-22.5 h

For both of the protected amines **271** and **272** the reaction was set up according to the procedure used for the synthesis of the benzazocines described in *Section 2.2.1* above. The general procedure involved dissolving the amines **271-272** in distilled toluene and heating the solutions to 60$^{o}$C before the addition of 5 mol % Grubbs II catalyst **11**. The reaction mixtures were then stirred for 20-22.5 h before the solvent was removed *in vacuo*. The resulting residues were then purified by column chromatography and the desired compounds **273-274** were obtained as outlined in **Table 16** below.

**Table 16** Yields for Ring Closing Metathesis Reactions

| Compound | R | Time | Yield (%) | Compound Detection By |
|---|---|---|---|---|
| **273** | Boc | 22.5 h | (73) | HRMS |
| **274** | Ts | 20 h | (39) | $^{1}$H NMR |

As shown in **Table 16** above, the formation of *tert*-butyl 9-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocine-2(1*H*)-carboxylate **273** could not be determined by NMR spectroscopy due to severe peak broadening (possibly due to amide rotamers). However, the compound was detected by HRMS, with the peak found at 347.20925 and with $C_{20}H_{29}NO_4$ requiring a peak at 347.20966. This is not sufficient evidence on its own to prove the formation of the product exclusively and that is why a tentative yield is given in brackets.

A similar problem arose for the preparation of 9-isopropoxy-8-methoxy-2-[(4-methylphenyl)sulfonyl]-1,2,3,6-tetrahydro-2-benzazocine **274**, whereby the product formation could only be shown by $^{1}$H NMR spectroscopy. The product formation was identified by the characteristic loss of the phenyl protons, as well as the loss of the terminal alkene peaks. Three signals were observed in the $^{1}$H NMR spectrum for the $CH_2$ groups. They were found at 3.41 ($ArCH_2C$), 3.73-3.77 ($NCH_2C$) and 4.22ppm ($ArCH_2N$), which confirms that no isomerisation occurred prior to RCM and thus the presence of the eight membered ring. The alkene peaks were observed at 5.41-5.58ppm and 5.84ppm and they were assigned as $NCH_2CH$=CH and $NCH_2CH$=C*H* respectively.

This brought to an end our attempted syntheses of the 6,7 and 8 membered nitrogen-containing benzo-fused heterocycles. The conclusion and future work for this section will be discussed in **Chapter 6**.

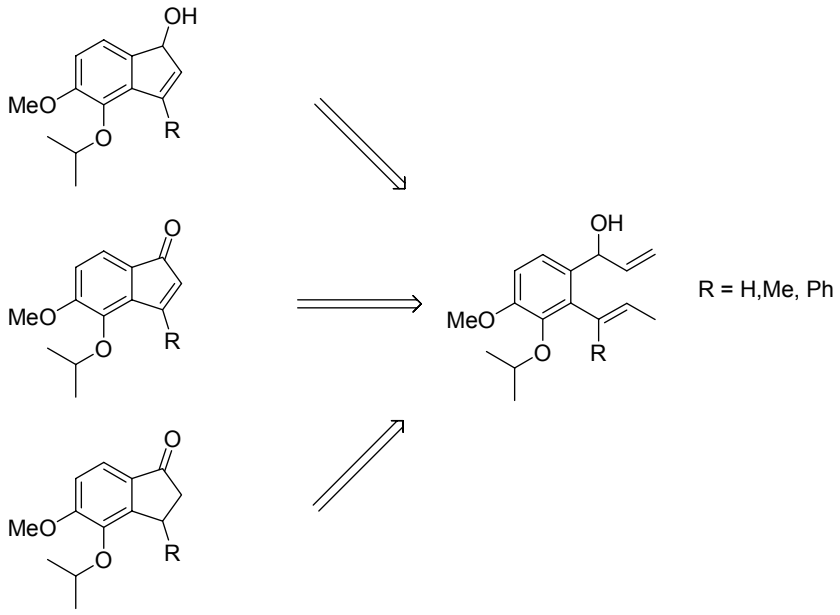
# *Chapter 5:*

# *Results and Discussion for the Synthesis of Indenols, Indenones and Indanones*

# *Chapter 5: Results and Discussion for the Synthesis of Indenols, Indenones and Indanones*

## 1. Introduction

As described in the introduction, during the post-doctoral project of Coyanis[48] a number of different indenones were isolated from the reaction mixtures for the formation of the indenols using ring closing metathesis (RCM). This observation led us to the investigation of the oxidizing potential of Grubbs II catalyst **11** (or its degradation products). To the best of our knowledge this result is the first example of the Grubbs' catalysts showing catalytic oxidizing ability.[7]




**Scheme 97** General retrosynthesis for the synthesis of indenols, indenones and indanones.

The serendipitous isolation of an unsubstituted indanone **205** also required further investigation in order to determine if the methodology could be applied to a number of different substrates. In addition we also hoped to tell if the conversion was due to the well-known redox-isomerisation mechanism.

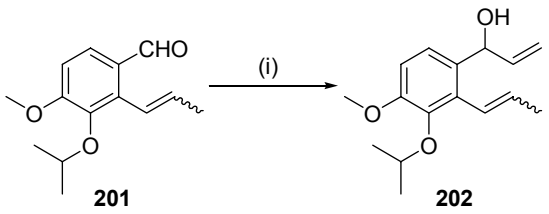
This part of the project thus aims to answer a number of questions posed by the work of Coyanis and initially necessitated the preparation of several compounds synthesized

previously.[48] This chapter first covers the synthesis of a number of common starting materials and then the following sections each deal with the synthesis of the indenols, indenones and indanones with various substituents on the 5-membered ring. Please refer to the experimental section (***Chapter 7***) for the detailed description of each synthetic step.

## 2. The 1-Propenyl System

### *2.1 Synthesis of the Starting Material*

Compound **201** was synthesized according to the methodology outlined by Coyanis.[48] The synthesis is described in detail in the experimental section and has already been discussed in *Section 2.4.2* in **Chapter 4**.



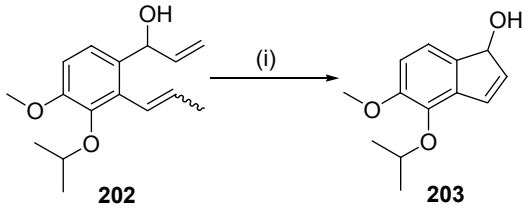

**Scheme 98** (i) 5eq vinyl magnesium bromide, THF, -60$^{o}$C, 18 h

A solution was prepared of 3-isopropoxy-4-methoxy-2-(1-propenyl)benzaldehyde **201** in distilled tetrahydrofuran and the solution was cooled to –60$^{o}$C. To this was then added vinyl magnesium bromide and the solution was stirred for 18 h at -60$^{o}$C. After this time the reaction mixture was warmed to rt and then extracted. The residue obtained was then subjected to column chromatography. The desired product, 1-[3-isopropoxy-4-methoxy-2-(1-propenyl)phenyl]-2-propen-1-ol **202**, was obtained as a yellow oil in 88% yield.

The product **202** was analyzed by $^{1}$H and $^{13}$C NMR spectroscopy and the spectra were found to correlate well to those of Coyanis.[48] A large amount of Grignard reagent was required as the solution we had was quite old and may have become contaminated with trace amounts of moisture, thus this value is not representative of that for a new bottle of Grignard reagent. A more representative value would be the 1.2eq used by Coyanis to obtain the desired product in a yield of 99%.[48]

*2.2 Synthesis of Indenol **203***

Coyanis[48] isolated the indenol **203** in 64% yield, by RCM of diene **202** after optimization, and we repeated the reaction in the hopes that we would be able to improve the moderate yield.

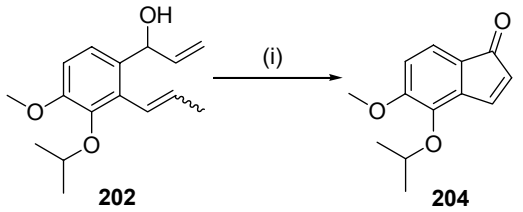



**Scheme 99** (i) 5 mol % catalyst **11**, $CH_2Cl_2$, rt, 3 h

The diene **202** was thus dissolved in distilled dichloromethane and the solution was degassed using nitrogen for 15 min. Then Grubbs II catalyst **11** was added and the reaction mixture was stirred at rt for 3 h. After this time the solvent was removed *in vacuo* and the resulting residue was purified by column chromatography. The desired product, 4-isopropoxy-5-methoxy-1*H*-inden-1-ol **203**, was obtained as a dark yellow oil in a considerably improved 87% yield. A spectroscopic analysis of the compound correlated well to that of Coyanis[48] and the product was thus shown to have formed.

*2.3 Synthesis of Indenone **204***

Coyanis obtained the desired indenone **204** in 62% yield after 8 mol % catalyst **11** was added to a solution of compound **202** in toluene (80°C for 2 h). We hoped that we would be able to obtain the desired product **204** using less catalyst at lower temperatures, thus we developed the procedure outlined in **Scheme 100** below.

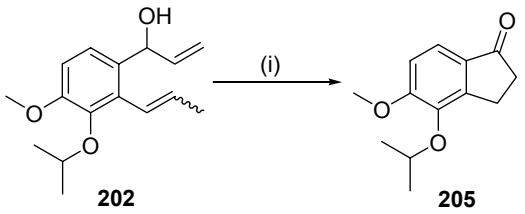



**Scheme 100** (i) 5 mol % catalyst **11**, toluene, 60°C, 17 h

The 1-[3-isopropoxy-4-methoxy-2-(1-propenyl)phenyl]-2-propen-1-ol **202** was dissolved in distilled toluene and the solution was heated to 60°C. Then Grubbs II catalyst **11** was added and the reaction mixture was stirred for 17 h. After this time the solvent was removed *in vacuo* and the residue obtained was purified by column chromatography. The desired product, 4-isopropoxy-5-methoxy-1*H*-inden-1-one **204**, was obtained as a bright yellow oil in only 45% yield. Product formation was proven by a comparison of our NMR spectroscopic data with that obtained by Coyanis.[48] We were only able to show that the reaction was occurring due to the dehydrogenative-oxidation of the indenol after completing our $^{1}$H NMR study. This is discussed in detail in **Section 5** below.

### *2.4 Synthesis of Indanone **205***

Coyanis[48] had only isolated the indanone **205** by chance from precursor **202** (in 51% yield when the reaction mixture ran dry over night) and had never aimed to synthesize it specifically. We wanted to develop a method for the synthesis of this indanone directly, with the aim that our method could then be used for the synthesis of a number of other indanones.




**Scheme 101** (i) 8 mol % catalyst **11**, toluene, 80°C, 22 h

We started by dissolving compound **202** in distilled toluene and subsequently heated the solution to 80°C. This was then followed by the addition of Grubbs II catalyst **11**. The reaction mixture was then stirred for 22 h, the solvent was removed *in vacuo* and the resulting black residue was purified by column chromatography. From the column, we were able to isolate the desired product, 4-isopropoxy-5-methoxy-1-indanone **205**, as a pale orange oil, that solidified on standing, in 89% yield, as well as a small amount of the indenone **204** (11% yield relative to starting material). The product obtained was positively identified by a comparison of our spectroscopic data with that obtained by Coyanis.[48] It is postulated that the

conversion of the indenol to indanone was occurring via a RCM-redox-isomerisation reaction. As mentioned in the introduction the redox isomeriszation is a known reaction mediated by ruthenium-based metathesis catalysts.[6] In addition we determined the melting point of indanone **205** to be 52-55°C.

The formation of the indanone **205** was further confirmed by the single crystal X-ray structure that we were able to obtain. It is shown schematically in **Figure 32** below as an ORTEP diagram.

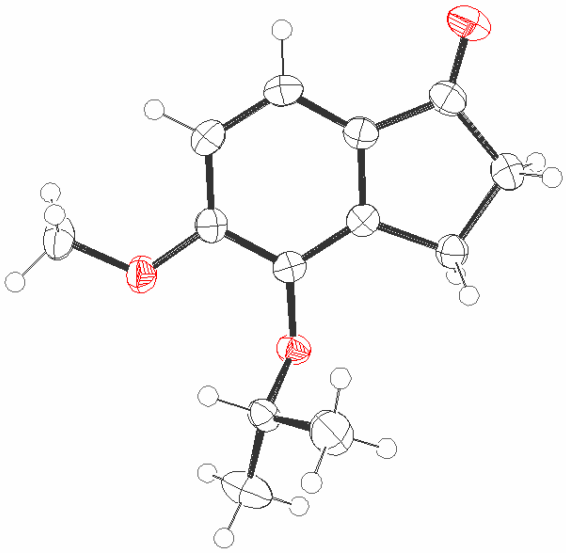
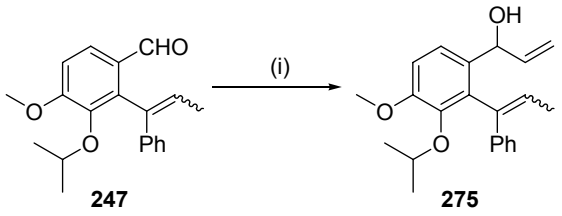


**Figure 32** Ortep diagram of compound **205**
(showing the 50% probability thermal ellipsoids for all non-hydrogen atoms).

## 3. The 1-Phenyl-1-Propenyl-Substituted System

### *3.1 Synthesis of the Starting Material*

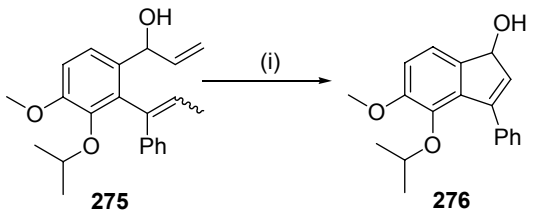
Compound **247** was synthesised according to the procedure described by Rousseau.[1] The synthesis is described in detail in the experimental section and is further discussed in *Section 3.1.2* in **Chapter 4.**




**Scheme 102** (i) 10eq, vinyl magnesium bromide, THF, -60°C, 22 h

The 3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzaldehyde **247** was dissolved in distilled THF and the solution was cooled to –60°C. Then vinyl magnesium bromide was added and the reaction mixture was left to stir for a further 22 h at -60°C. After this time the reaction mixture was extracted and the residue obtained was subjected to column chromatography. 1-[3-Isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)phenyl]-2-propen-1-ol **275** was subsequently obtained as a dark red-purple oil in 46% yield. The product was characterized by $^{1}H$ and $^{13}C$ NMR spectroscopy and the data was found to correlate well to that obtained by Coyanis.[48] Again as the Grignard was old, a more representative value would be the 1.2eq used by Coyanis (0°C) to obtain the desired product in 73% yield.[48]

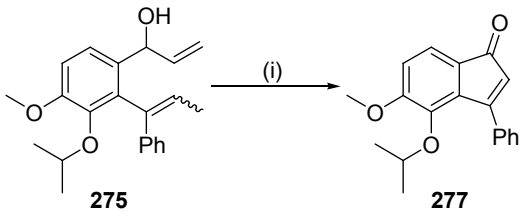
*3.2 Synthesis of the Indenol **276***




**Scheme 103** (i) 5 mol % catalyst **11**, $CH_2Cl_2$, rt, 17 h

A solution was prepared of compound **275** in distilled dichloromethane and to this was then added Grubbs II catalyst **11**. The reaction mixture was then stirred at rt for 17 h, before the solvent was removed *in vacuo* and the resulting residue was purified by column chromatography. The desired product, 4-isopropoxy-5-methoxy-3-phenyl-1*H*-inden-1-ol **276**, was obtained as a cream-coloured solid in 49% yield along with the indenone **277** (24% yield relative to the starting material). Indenol **276** had a melting point of 56-59°C and the spectroscopic data compared well to that of the compound isolated by Coyanis.[48]

*3.3 Synthesis of the Indenone **277***




**Scheme 104** (i) 8 mol % catalyst **11**, toluene, 80$^{o}$C, 17 h

Compound **275** was dissolved in toluene and the solution was heated to 80$^{o}$C before the addition of Grubbs II catalyst **11**. The reaction mixture was then stirred for 17 h, the solvent was removed *in vacuo* and the resulting residue was purified by column chromatography. This time the desired product, 4-isopropoxy-5-methoxy-3-phenyl-1*H*-inden-1-one **277** was obtained as a bright-orange semi-solid in 69% yield. The melting point for the indenone **277** was found to be 63-68$^{o}$C and a spectroscopic analysis of the compound in conjunction with a comparison of Coyanis' data led us to conclude that we had in fact prepared the correct compound.

Coyanis[48] had obtained the same product in 82% yield when the reaction was set up using 8 mol % catalyst **11** at 110$^{o}$C for 12 h. Our milder conditions did not provide a good enough yield and we expect that in the future this may be optimized by performing the reaction at a lower temperature, eg: 60-80$^{o}$C with 5 mol % catalyst **11**.

We were further able to isolate crystals of good enough quality to be used for a single crystal X-ray diffraction on the compound. From this we confirmed the formation of our product **277**. This is outlined by the ORTEP diagram shown in **Figure 33** below.

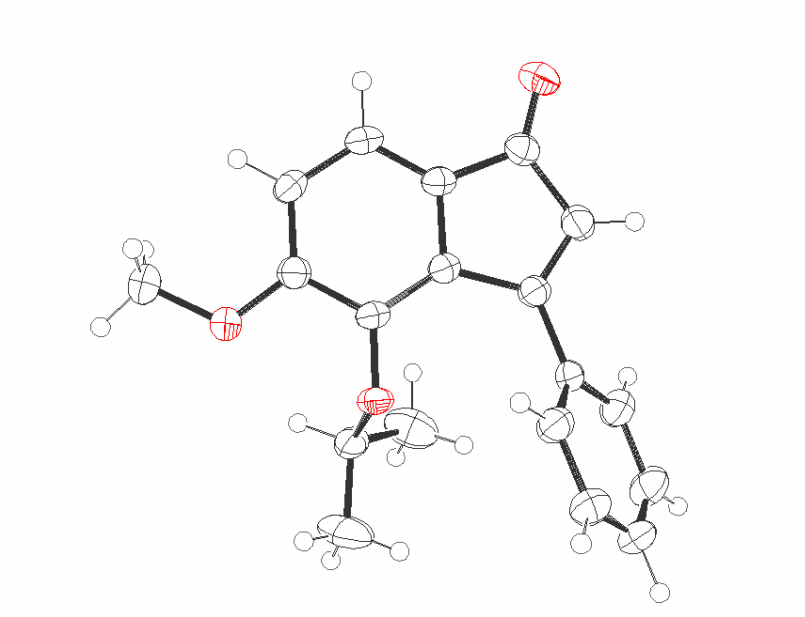
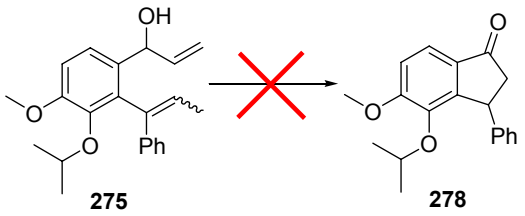


**Figure 33 ORTEP** diagram of compound **277**
(showing the 50% probability thermal ellipsoids for all non-hydrogen atoms).

## *3.4 Attempted Synthesis of the Indanone*




**Scheme 105** Synthesis of Indanone **278**

Numerous attempts were made for the synthesis of indanone **278** through the use of RCM, with all of them failing in one respect or another. A summary of the reagents and conditions used for these attempts are outlined in **Table 17** below.

**Table 17** Conditions for Attempted RCM reactions

| Grubbs II catalyst 11 (mol %) | Temperature | Time | Product Formed |
|---|---|---|---|
| 8 | 80°C | 18 h | Indenone **277** |
| 8 | 110°C | 17 h | Indenone **277** |
| 8 | 110°C | 45 h | Indenone **277** |

The one other procedure that was not attempted due to the time constraints of the project was the addition of 10 mol % Grubbs catalyst **11** and the heating of the mixture under solvent-free conditions to high temperatures, but we do not feel that the probability of this yielding product is good, as with the other reactions not even as trace of the desired indanone was seen.

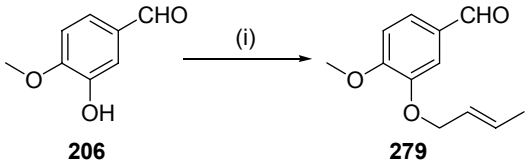
We propose that the reason that no reaction is occurring on this system is not due to the lack of metathesis occurring (as it has been proven to work on these types of systems by the formation of the indenols and the indenones), but rather to the inability of the subsequent redox-isomerisation reaction to occur. This may be due to the fact that the indenol alkene is resonance stabilized through both of the phenyl rings (as it is in the α-position to each of the systems). There is generally no indenol isolated as it then undergoes the proposed facile dehydrogenative-oxidation reaction to form the thermodynamically favoured indenone **277**, rather than the indanone.

### 4. The 1-Methyl-2-Propenyl Substituted System

In order for us to obtain the methyl substituted systems that we wanted to prepare, we needed to begin our synthesis with the crotyl addition to the phenol in isovanillin **206**. This was subsequently subjected to the Claisen rearrangement and isomerised before reaction with the Grignard reagent, thus setting us up for the metathesis reactions.

## *4.1 Synthesis of Starting Materials*

### *4.1.1 O-Crotylation of Isovanillin*

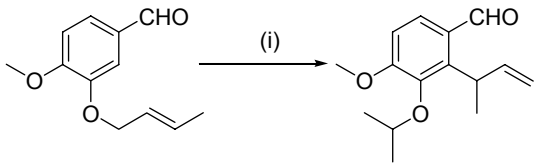



**206** **279**

**Scheme 106** (i) 2.5eq crotyl bromide, 2.5eq $K_2CO_3$, DMF, 60°C, 22 h

A suspension was made of the potassium carbonate and *N,N*-dimethylformamide and this was then heated to 60°C and stirred for 15 min. After this time the isovanillin **206** was added and the solution went bright yellow before the addition of the crotyl bromide. The reaction mixture was then stirred for 22 h, subjected to the workup procedure and subsequently purified by column chromatography. The desired product, 3-[(2*E*)-2-butenyloxy]-4-methoxybenzaldehyde **279** was then obtained as a bright yellow oil in 99% yield. The product was analyzed by $^{1}H$ and $^{13}C$ NMR spectroscopy and the data was found to correlate well to the results obtained by Rousseau,[1] with an improved yield noted (Rousseau obtained the product in 90% yield).

### *4.1.2 Claisen Rearrangement and Protection Reaction*




**279** **280**

**Scheme 107** (i) DMF, 180°C, 44 h,
(ii) 2.5eq $K_2CO_3$, 2.5eq isopropyl bromide, DMF, 60°C, 18 h

A solution was prepared from 3-[(2*E*)-2-butenyloxy]-4-methoxybenzaldehyde **279** in DMF and it was heated to 180°C for 44 h. After this time the solution was cooled to 60°C and to it was added the potassium carbonate and isopropyl bromide. The reaction mixture was then

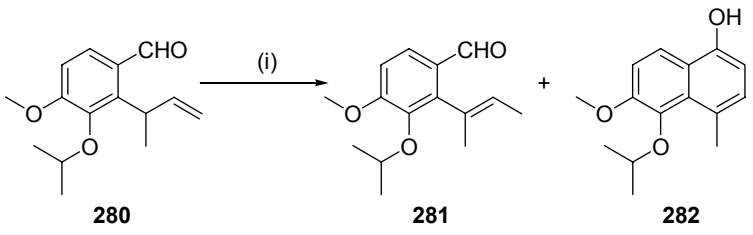
stirred for a further 18 h, subjected to the workup and purified by column chromatography. 3-Isopropoxy-4-methoxy-2-(1-methyl-2-propenyl)benzaldehyde **280** was subsequently obtained as a bright orange oil in 73% yield. The compound was then analyzed by NMR spectroscopy and it was found that the data we obtained was in excellent agreement with that reported by Rousseau.[1] Surprisingly our yield also showed a marked improvement on that obtained by Rousseau (62%).

### *4.1.3 Isomerisation Reactions for Compound **280***

We initially attempted the isomerisation of compound **280** through the use of potassium *tert*-butoxide as Coyanis had reported numerous difficulties with the isomerisation when using the Ru-isomerisation catalyst **12**. These attempts by Coyanis[48] are summarized in **Table 18** below.

**Table 18** Isomerisation Attempts by Coyanis[48]

| Attempt | Catalyst 12 (mol %) | Solvent | Temperature | Time | Product Obtained |
|---|---|---|---|---|---|
| 1 | 1 | toluene | 90°C | 26 h | **SM 280** |
| 2 | 1.2 | toluene | 110°C | 38 h | **SM 280** |
| 3 | 1.4 | toluene | 110°C | 15 h | **SM 280** |
| 4 | 2 | toluene | 110°C | 48 h | **SM 280** |




**Scheme 108** (i) 1.1eq KO$^t$Bu, DMF, 60°C, 1 h

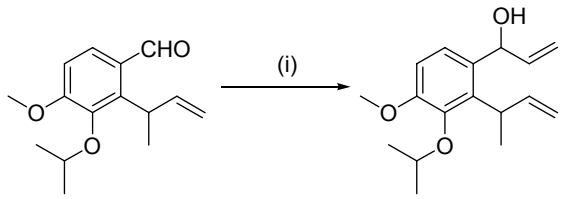
We attempted the isomerisation of 3-isopropoxy-4-methoxy-2-(1-methyl-2-propenyl)benzaldehyde **280** by dissolving the compound in DMF and stirring it in the presence of potassium *tert*-butoxide for 1 h at 60°C. After various extractions, the residue was purified by column chromatography and two products were obtained from the reaction. The

desired product, 3-isopropoxy-4-methoxy-2-[(1*E*)-1-methyl-1-propenyl]benzaldehyde **281**, was obtained as an orange oil in only 8% yield and was found to be the minor product of the reaction. The predominant product isolated from the reaction was the naphthol, 5-isopropoxy-6-methoxy-4-methyl-1-naphthol **282**. It was obtained as an orange-brown oil in only 12% yield.

Compound **281** was identified by the characteristic loss of the terminal alkene protons and the subsequent formation of the methyl group, observed in both the $^{1}H$ and $^{13}C$ NMR spectra. The data obtained for compound **281** correlated well to that quoted by Coyanis[48] and supported our assignment of the product. Compound **282** was identified by presence of the new hydroxyl and methyl groups as well as by the presence of the extra aromatic protons. Rousseau[1] had previously reported this result for similar systems and our observations corresponded to those reported, thus supporting our assignment of the product.

### *4.1.4 Grignard Addition to Compound **280***

Considering the problem of the exceptionally poor yield obtained for the isomerisation of compound **280** to compound **281**, we decided to change the order of the reactions, with the hope that this would then lead to better yields.




**280** **283**

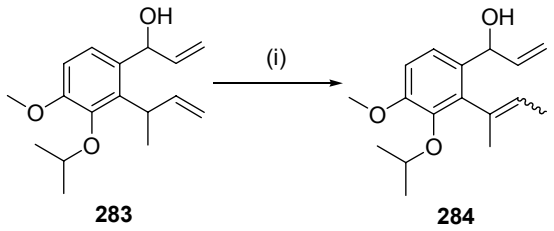
**Scheme 109** (i) 10eq vinyl magnesium bromide, THF, -60$^{o}$C, 18 h

Having the 3-isopropoxy-4-methoxy-2-(1-methyl-2-propenyl)benzaldehyde **280** in hand, we decided to try the Grignard addition directly to the unisomerised aldehyde **280**. The aldehyde **280** was dissolved in distilled tetrahydrofuran and the solution was cooled to –60$^{o}$C before the addition of the vinyl magnesium bromide. The reaction mixture was then stirred for 18 h, subjected to the workup procedure and purified by column chromatography. The desired product, 1-[3-isopropoxy-4-methoxy-2-(1-methyl-2-propenyl)phenyl]-2-propen-1-ol **283**, was

obtained as a yellow oil in 72% yield. The formation of the product was shown through the use of NMR spectroscopy. Our $^{1}H$ and $^{13}C$ NMR spectral data was compared to that of Coyanis,[48] and there was found to be an excellent correlation. Thus we were able to show that the product had formed.

### *4.1.5 Isomerisation Reaction to form Compound **284***

Having obtained the product **283** in good yield, we then attempted the isomerisation on the alkene. We did not attempt the isomerisation using the Ru-isomerisation catalyst **12** as we envisaged that we would encounter similar problems to those observed by Coyanis[48] for the transformation **280** to **281**. We were also hopeful that this reaction would proceed in better yield, as no possibility existed for the formation of the naphthol **282** when compound **283** was exposed to potassium *tert*-butoxide.

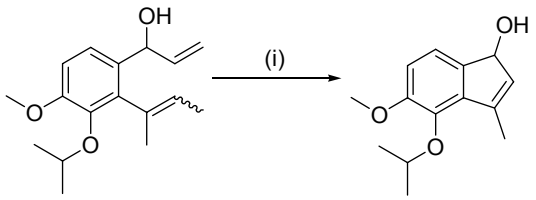



**Scheme 110** (i) 1.3eq KO$^{t}$Bu, DMF, rt, 15 min

The 1-[3-isopropoxy-4-methoxy-2-(1-methyl-2-propenyl)phenyl]-2-propen-1-ol **283** was dissolved in DMF and to this solution was added sublimed potassium *tert*-butoxide. The reaction mixture was stirred at rt for 15 min, the reaction mixture was then extracted and the resulting residue was purified by column chromatography. The desired product, 1-[3-isopropoxy-4-methoxy-2-(1-methyl-1-propenyl)phenyl]-2-propen-1-ol **284**, was obtained as a yellow oil in 76% yield. The spectroscopic data obtained for the product was compared to that of Coyanis[48] (the product was prepared by the conversion of compound **281** to compound **284**) and the details were found to be almost identical. It was thus shown that the product had in fact formed. Of interest to us was that NMR spectroscopy indicated a complex mixture of *E/Z* isomers.

Based on the good yields for the Grignard reaction of compound **280** to compound **283** and the isomerisation reaction of compound **283** to compound **284**, this synthetic strategy was used for all further reactions performed on this system.

### *4.2 Synthesis of Indenol **285***

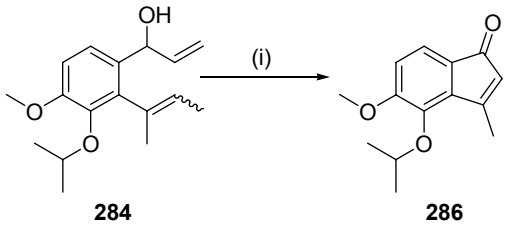



**284** **285**

**Scheme 111** (i) 5 mol % catalyst **11**, $CH_2Cl_2$, rt, 1 h

Precursor **284** was dissolved in distilled dichloromethane and the solution was degassed for 10 min using nitrogen. Then the Grubbs II catalyst **11** was added and the solution was stirred for 1 h at rt. After this time the solvent was removed *in vacuo* and the residue was purified by column chromatography. Satisfyingly, the desired product, 4-isopropoxy-5-methoxy-3-methyl-1*H*-inden-1-ol **285**, was obtained as a bright yellow oil in 57% yield. The yield we obtained was comparable to the 64% obtained by Coyanis[48] after 2 h. Our NMR spectroscopic data for indenol **285** was found to correlate perfectly to that reported by Coyanis and we were able to conclude that we had formed the product.

### *4.3 Synthesis of Indenone **286***

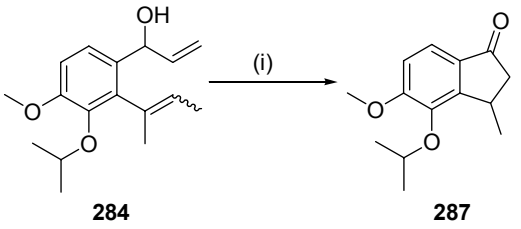



**284** **286**

**Scheme 112** (i) 8 mol % catalyst **11**, toluene, 80°C, 16 h

For this reaction a solution was prepared of compound **284** in distilled toluene, which was subsequently heated to 80°C before the addition of the Grubbs II catalyst **11**. The reaction mixture was stirred for 16 h, the solvent was removed *in vacuo* and the residue was purified by column chromatography. 4-Isopropoxy-5-methoxy-3-methyl-1*H*-inden-1-one **286** was obtained as a dark yellow semi-solid in 42% yield, with indenol **285** isolated in 23% yield (relative to the starting material). Indenone **286** was positively identified by the comparison of our $^{1}$H and $^{13}$C NMR spectra with those reported by Coyanis.[48]

### *4.4 Synthesis of Indanone **287***




**284** **287**

**Scheme 113** (i) 5 mol % catalyst **11**, 110-170°C, 18 h

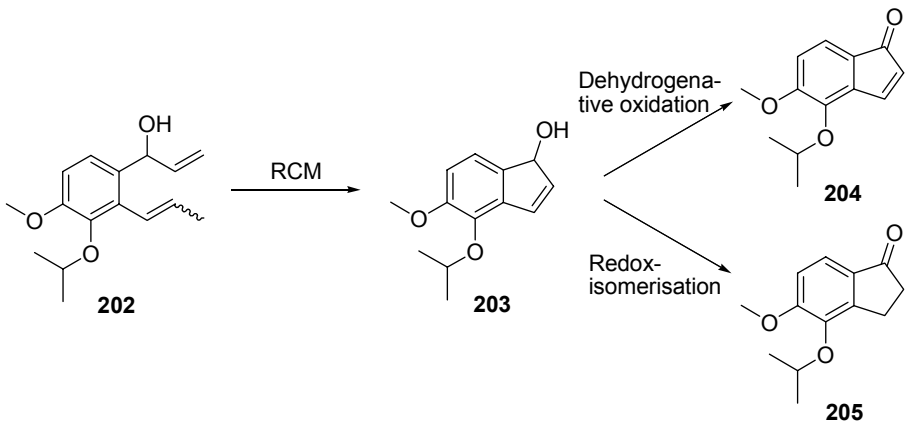
Compound **284** was transferred to our reaction vessel as a solution in dichloromethane, which was subsequently degassed using nitrogen for 10 min. After this time Grubbs II catalyst **11** was added and the solution was heated to 110°C, with the subsequent loss of the dichloromethane to leave a solvent-free reaction mixture. This solventless mixture was then stirred at 160-170°C for 18 h and the resulting residue was purified by column chromatography. The desired indanone, 4-isopropoxy-5-methoxy-3-methyl-1-indanone **287**, was obtained as a dark yellow oil in a poor 18% yield. A small amount of indenone **286** was also isolated in 7% yield. As the indanone **287** was a novel compound for our laboratories, it was fully characterized by HRMS, NMR and FTIR spectroscopy.

The formation of indanone **287** was shown by the C=O signals in the FTIR spectrum at 1217 and 1699cm$^{-1}$. $^{1}$H NMR spectroscopy highlighted the indanone ring by the presence of the methyl group as a doublet at 1.27ppm, the $CH_2$ group by the two of double doublets at 2.25 and 2.91ppm and by the doublet of quartets for the C*H*$CH_3$ proton. Similarly, the $^{13}$C NMR spectrum had the methyl peak at 20.6ppm, the $CHCH_3$ peak at 31.5ppm, the $CH_2$ peak at

45.9ppm and lastly, the C=O peak at 205.2ppm. HRMS analysis of the product presented the molecular ion peak at 234.12130, with the peak for $C_{14}H_{18}O_3$ expected at 234.12559.

## 5. NMR Experiments to Probe the Mechanism of Indenone/Indanone Formation

During the post-doctoral work of Coyanis[48] the question was posed as to why the indenones are found in the reaction mixtures for the formation of the indenols. A large part of the work performed in this section was done in order to postulate a mechanism for this process and to subsequently support our observation that the reactions were occurring due to the oxidizing ability of the Grubbs II metathesis catalyst **11** (or its degradation products) to effect the dehydrogenation of the indenols to the indenones.




**Scheme 114**

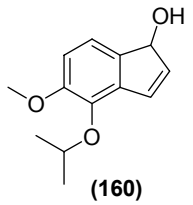
Before we could even begin to postulate a mechanism for the suspected conversion of the indenols to indenones we needed to prove that the ruthenium present in the Grubbs II metathesis catalyst **11** or its degradation products was in fact causing the conversion. In order to show that ruthenium was playing a pivotal role in the conversion it was necessary for us to have a ruthenium depleted "control system". The preparation of this ruthenium depleted system is discussed in detail in *Section 5.1* below.

Once we had this control in hand, we were hoping to proceed to our $^1$H NMR/ICP-MS study of the conversion reactions. We were planning on completing a comparative analysis of the conversion of indenol to indenone/indanone wherein we were hoping to compare the

ruthenium depleted sample with other samples that contained fresh Grubbs II catalyst **11**, Grubbs II catalyst **11**'s degradative products and alternative ruthenium source, eg: ruthenium chloride. The $^{1}$H NMR/ICP-MS studies of the conversion reaction are outlined in detail in *Section 5.2* below.

## *5.1 Ruthenium Removal*

Our initial attempts at the ruthenium removal in our systems centered on the removal of ruthenium from previously synthesized indenol **203** (**Figure 34**). We were hoping that by removing the ruthenium we could monitor the difference between the ruthenium-free sample and the original sample upon heating. A number of different methods have recently been reported for the removal of the ruthenium byproducts of the Grubbs metathesis catalysts.




**(160)**

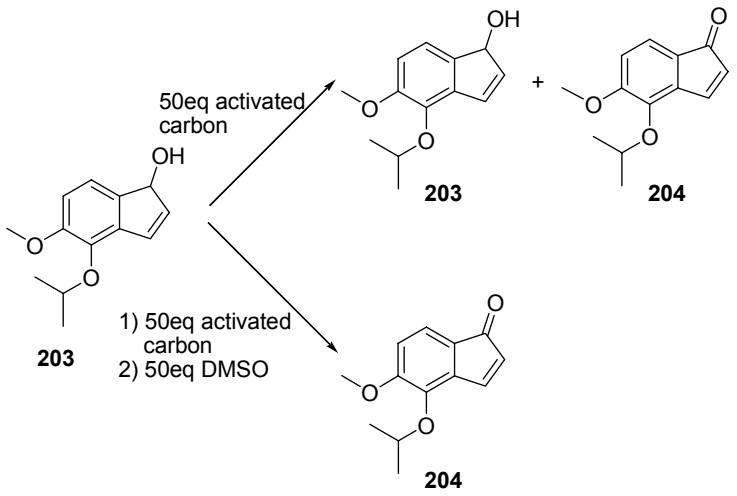
**Figure 34**

The Grubbs[213] method involves conversion of the ruthenium byproducts into water-soluble ruthenium phosphine complexes, using the quite expensive tris(hydroxymethyl)phosphine. The Paquette group[214] utilized the oxidation of the ruthenium species with $Pb(OAc)_4$. However this method has a significant drawback in the introduction of a toxic reagent. Georg *et al.*[215] have reported the removal of the ruthenium byproducts using the inexpensive reagents triphenylphosphine oxide ($Ph_3P$=O) or dimethyl sulfoxide (DMSO). Their procedure involves the treatment of the crude reaction mixtures with $Ph_3P$=O or DMSO followed by filtration through silica gel or column chromatography with silica gel.[215]

Also Dixneuf and co-workers[216] used carbon black to clean up the ionic liquid after ring closing metathesis reactions for the purpose of recycling the ionic liquid. Optimized conditions of these methods allowed for the reduction of ruthenium levels down to approximately 1-2μg per 5 mg of product.[216] Cho and Kim.[217] have recently reported a method where crude RCM product was adsorbed onto silica gel and filtered through a silica

gel pad, the filtrate was treated with activated carbon and the resulting residue further purified by silica gel chromatography. Using the optimized conditions, the residual ruthenium levels were reduced to 0.06-0.53μg per 5 mg of product, without a detectable loss of product.[217]

We initially decided to try a mixture of both the Georg[215] and Cho[217] approaches. We dissolved our indenol **203** in a solution of 10% EtOAc-Hexane and the solution was then stirred with 50eq of activated carbon (relative to the amount of catalyst **11**) at rt for 4 h. After this time the solution was filtered through celite and the solvent was removed *in vacuo*. The resulting residue was then dissolved in distilled dichloromethane and 50eq of DMSO (relative to the amount of catalyst **11**) was added. The reaction mixture was then stirred at rt for 18 h. After this time the solvent was removed *in vacuo* and the resulting residue was purified by column chromatography, a yellow oil being obtained.

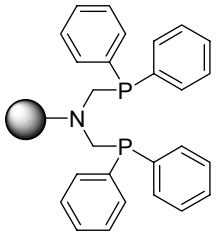



**Scheme 115** Overview of Ruthenium Removal Procedure Attempted

This oil was then analyzed and it was found to contain only indenone **204**. Thus the procedure was repeated and stopped after treatment with activated carbon; the oil obtained here was then analyzed and found to contain a mixture of indenol **203** and indenone **204**. Based on either acid-catalysed conversion in the presence of activated carbon or the fact that the DMSO was apparently oxidizing our indenols, neither of these routes were deemed suitable. Thus, we reverted back to the literature.

During the course of the project, Breinbauer and co-workers[218] published their results on the preparation of an efficient and inexpensive scavenger resin for Grubbs catalysts. They introduced the resin bound phosphine **288** (**Figure 35**) as a readily accessible chelate P-ligand for the design of immobilized transition metal catalysts in organic synthesis, which can be stored at rt under air for more than six months without the formation of P(V)-species. They proposed three different ways of using the resin bound phosphine **288**, firstly on its own, showing 90% ruthenium removal, secondly, compound **288** and silica, giving ruthenium removal of 94% or thirdly the use of compound **288** in conjunction with activated carbon, that gave a 96% ruthenium removal.[218]

We then wished to attempt the Breinbauer resin bound phosphine **288** on our system, but found that we could not obtain the necessary chemicals in our country in order to synthesize it. Thankfully, Professor Breinbauer[5] was kind enough to send some of their polymer bound resin **288** for use on our system.




**288**

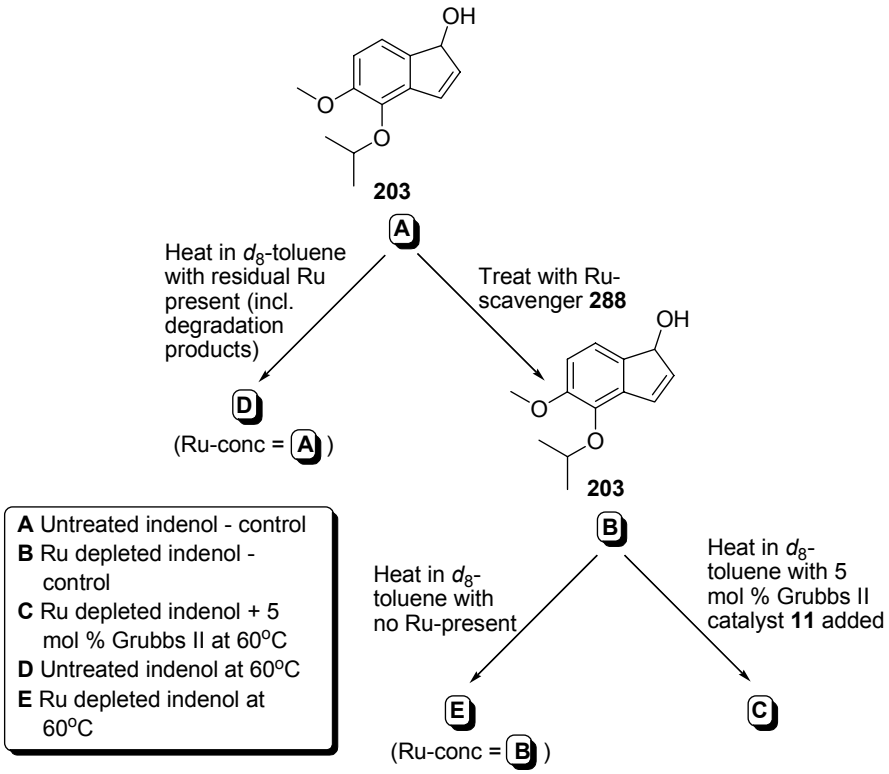
**Figure 35**[218]

We thus proceeded to dissolve indenol **203** in distilled dichloromethane and to degas the solution using nitrogen for 30 min. Then 5eq of the Ru-scavenger **288,** relative to the amount of Grubbs II catalyst **11,** was added to the reaction mixture and it was stirred at rt for 17 h. After this time the bright white "beads" of the scavenger had turned to a greenish grey-brown. The Ru-scavenger **288** was then filtered off through a celite pad, rinsed and the solvent was removed *in vacuo*. The indenol **203** was subsequently recovered in almost quantitative yield and was retained for the NMR spectroscopy study.

[5] Max-Planck-Institute for Molecular Physiology and Fachbereich Chemie, University Dortmund

## *5.2 $^1$H NMR Spectroscopic Studies of the Conversion of the Indenol to Indenone/Indanone*

Having a ruthenium-depleated indenol **203** sample in hand,[6] we then proceeded to our $^1$H NMR spectroscopic studies. The general procedure for the preparation of the NMR samples was to prepare the samples in the NMR tubes and to degas them for 15 min using argon. The NMR tubes to be heated were then submerged approximately 3cm deep in a pre-heated oil bath, with the samples to be run at rt having been stored in the same room on the counter top. The samples were analyzed in 1 h intervals (unless stated otherwise), with the samples being removed from the heat and then running the NMR spectra immediately. The general overview for the NMR spectroscopy/ICP-MS studies are outlined schematically in **Scheme 116** below.




**Scheme 116** Overview of the NMR/ICP-MS Study

The use of the general procedure outlined above allows us to draw numerous conclusions due to the presence of the two controls that are included in the method (**A** and **B**). If no conversion

[6] The ruthenium free indenol sample was obtained by purification of a previously synthesized indenol **203** sample using the procedure outlined in *Section 5.1* above (employing the Breinbauer scavenger **288**). We outline how the samples for the $^1$H NMR analysis were tested for ruthenium removal using ICP-MS in *Section 5.3* below.

of indenol **203** to indenone **204** occurs in sample **E** we can safely say that the lack of ruthenium prevents the conversion from occurring. If the conversion of indenol **203** to indenone **204** occurs in sample **D**, we can conclude that the Grubbs II catalyst **11** degradation products help catalyze the reaction. Also, if the conversion of indenol **203** to indenone **204** occurs in **C** we can assume that the reaction is ruthenium catalyzed and suggest that it is due to Grubbs II catalyst **11** or its degradation products. Showing that the conversion of **203** to **204** is ruthenium catalyzed supports our theory that the indenol to indenone conversion is a *ruthenium catalyzed* dehydrogenative oxidation. Ratios quoted in this section are for indenol:indenone:indanone; with $^{1}$H NMR spectra run at time zero for all compounds and found to be pure indenol **203**. The ratios reported are estimated by inspection of the $^{1}$H NMR spectra.

Case Study 1

The first of the NMR spectroscopy/ICP-MS studies was performed exactly as outlined in **Scheme 116** above. The three tubes that were heated, namely **C-1**, **D-1** and **E-1** were placed in an oil bath set to 60$^{o}$C. The $^{1}$H NMR spectra were run in intervals of 45 min and the results obtained for the $^{1}$H NMR spectra are outlined in **Table 19** below.

**Table 19** Results for $^{1}$H NMR Spectra used in Case Study 1

| Tube | Ru-content | Temp | Time (min) | Product[a] |
|---|---|---|---|---|
| **A-1** | Residual | rt | 80 | Indenol |
| | | | 145 | Indenol |
| | | | 210 | Indenol |
| | | | 1180 | Indenol |
| **B-1** | Ru-depleted | rt | 80 | Indenol |
| | | | 145 | Indenol |
| | | | 210 | Indenol |
| | | | 1180 | Indenol |

[a] ratios = indenol:indenone:indanone

**Table 19 contd.** Results for $^{1}$H NMR Spectra used in Case Study 1

| Tube | Ru-content | Temp | Time (min) | Product[a] |
|---|---|---|---|---|
| **C-1** | Ru-depleted + 5 mol % cat. 11 | 60°C | 80 | Indenol (trace Indenone) |
| | | | 145 | Indenol (trace Indenone and Indanone) |
| | | | 210 | 3:2:1 |
| | | | 1180 | 3:5:1 |
| **D-1** | Residual | 60°C | 80 | Indenol |
| | | | 145 | Indenol |
| | | | 210 | Indenol |
| | | | 1180 | Indenol |
| **E-1** | Ru-depleted | 60°C | 80 | Indenol |
| | | | 145 | Indenol |
| | | | 210 | Indenol |
| | | | 1180 | Indenol |

[a] ratios = indenol:indenone:indanone

As can be seen from **Table 19** above, the reaction mixture in NMR tube **C-1** shows a conversion of the indenol to a mixture of the indenone and indanone. This result is as would be expected, as the addition of 5 mol % Grubbs II catalyst **11** greatly increases the amount of ruthenium present. This result alludes that the reaction is ruthenium catalyzed but cannot confirm it as none of the other reaction tubes showed any significant change. The next step in our quest for information was to either increase the concentration or to increase the reaction temperature as in our next case study.

Case Study 2

In this case study we decided to increase the temperature to see if we could force the reaction to occur in the tubes **C-2**, **D-2** and **E-2**. The next of the NMR spectroscopy/ICP-MS studies was again performed as outlined in **Scheme 116** above and the three tubes that were heated, namely **C-2**, **D-2** and **E-2**, were placed in an oil bath set to 100°C. The $^{1}$H NMR spectra were run in intervals of 45 min and the results obtained for the $^{1}$H NMR spectra are outlined in **Table 20** below.

**Table 20** Results for $^{1}$H NMR Spectra used in Case Study 2

| Tube | Ru-content | Temp | Time (min) | Product[a] |
|---|---|---|---|---|
| **A-2** | Residual | rt | 1328 | Indenol |
| | | | 6173 | Indenol |
| **B-2** | Ru-depleted | rt | 1328 | Indenol |
| | Ru-depleted + 5 | | 6173 | Indenol |
| **C-2** | mol % cat. 11 | 100$^{o}$C | 101 | 5:1:5 |
| | | | 180 | 2:2:9 |
| | | | 259 | 1:2:9 |
| | | | 355 | 1:2:9.5 |
| | | | 1400 | 1:2:10 |
| | | | 1680 | 0.5:2.5:10.5 |
| **D-2** | Residual | 100$^{o}$C | 101 | Indenol |
| | | | 180 | Indenol |
| | | | 259 | Indenol |
| | | | 355 | Indenol |
| | | | 1400 | 0.8:13:0 |
| | | | 1680 | 0.9:12.5:0 |
| **E-2** | Ru-depleted | 100$^{o}$C | 101 | Indenol |
| | | | 180 | Indenol |
| | | | 259 | Indenol |
| | | | 355 | Indenol |
| | | | 1400 | Indenol |
| | | | 1680 | Indenol |

[a] ratios = indenol:indenone:indanone

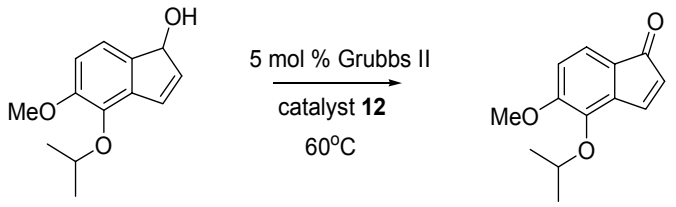
As can be seen from **Table 20** above, the tube **C-2** clearly showed a conversion of the indenol to a mixture of indenone and indanone. As suspected at the outset of the study, the indanone formation was favoured at this high temperature. Again, all that the results from tube **C-2** showed, was that the conversion was occurring in the presence of the Ru-catalyst **11**, and thus that the conversion was ruthenium catalyzed.

However, this study differs significantly from case study 1 in that the tube containing the residual ruthenium (tube **D-2**) also showed a small amount of conversion. What is interesting to note is that tube **D-2** only showed the conversion of indenol to indenone and that none of the indanone was detected. This further supports our proposal that the conversion is a ruthenium catalyzed dehydrogenative-oxidation, as well as suggesting that this reaction occurs preferentially to the redox-isomerisation under residual ruthenium concentrations.

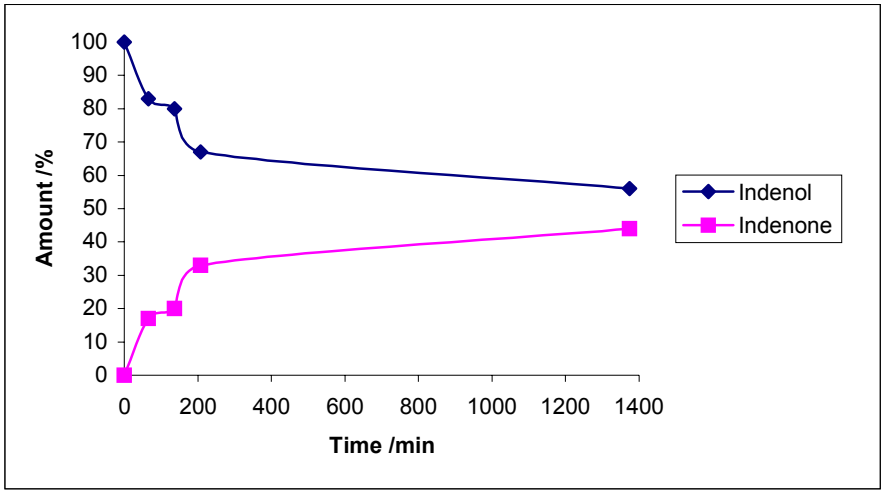
The reason that tube **C-2** shows more of the indanone than **C-1** (produced by the well know redox-isomerisation) could be due to the significantly higher temperature employed for the reaction. At this temperature, the indenol to indanone conversion is occurring more rapidly, to the detriment of the indenol to indenone transformation. In addition the higher concentration of Grubbs II catalyst **11** in **C-2** could explain why there is more indanone present than in **D-2**.

Case Study 3:

The next of the NMR spectroscopy/ICP-MS studies was performed under similar conditions to those outlined in **Scheme 116** above for tube **C-3**. Tube **C-3** contained the "ruthenium depleted" indenol **203** to which 5 mol % Grubbs II catalyst **11** had been added as it showed the most significant changes in the previous case studies. Tube **C-3** was then heated at 60°C. The data obtained is shown graphically in **Graph 1** below; note that no indanone **205** was detected under the reaction conditions.




**Scheme 117**




**Graph 1** Graphical Representation of Case Study 3

(% Amount is given based on the NMR spectrum integration)

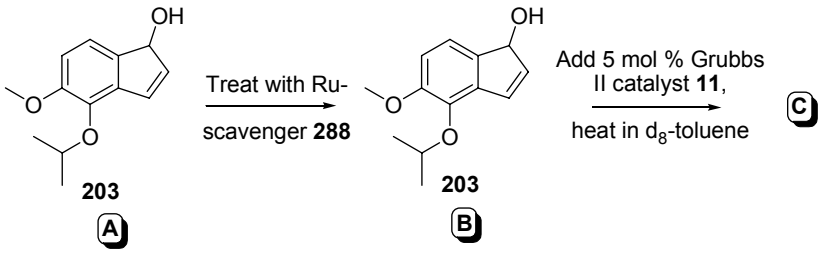
As can be seen for **Graph 1** above, at time zero the solution contained only indenol and no indenone **204**, as would be expected. The graph then shows how over time the concentration of the indenol **203** decreases and at the same time the indenone **204** concentration increases. Both of the curves tend to a point where they may intersect at an equilibrium; however, due to the time limits on this study, was not observed.

The graph clearly shows that as the concentration of the indenol **203** is decreasing, the concentration of the indenone **204** is increasing by the same factor, thus highlighting the clear correlation of the two compounds. This was then the final evidence we required to support our theory that the indenol is converting to the indenone by a dehydrogenative oxidation reaction.

### *5.3 ICP-MS Study to Determine Ruthenium Removal*

After performing the ruthenium removal using the Breinbauer[218] scavenger, we needed a way of testing that we had in fact formed our required "ruthenium depleted" indenol **203**. We then decided to utilize the procedure used by Georg *et al.,*[215] whereby they used ICP-MS to determine the ruthenium concentration in their samples after removal using their procedure. We assigned total ruthenium removal to be a value of less than 0.5 μg Ru/5mg of indenol sample.

Selected samples from the $^1$H NMR case studies 1 and 2 were analyzed by ICP-MS. The standard curve plotted for our investigation is shown in Appendix C. Based on **Scheme 116**, samples **A**, **B** and **C** were initially analyzed in order to determine the ruthenium removal capabilities of the scavenger **288**. As you may recall, sample **A** contained the untreated indenol **203**, sample **B** contained the indenol after treatment with the scavenger and sample **C** contained the treated indenol + 5 mol % Grubbs II catalyst **11**. The reaction order is shown in **Scheme 118** below.




**Scheme 118** Samples Used for ICP-MS Analysis

Our ICP-MS determination found the following values:

- Sample **A-1** contained 4.000μg Ru/5mg indenol sample
- Sample **B-1** contained 0.108μg Ru/5mg indenol sample
- Sample **C-1** contained 21.736μg Ru/5mg indenol sample

These values show a 97% reduction in the ruthenium levels from sample **A-1** to **B-1** (ie: after treatment with scavenger **288**) and a 20 126% increase in the ruthenium levels after the addition of the Grubbs II catalyst **11**. Having satisfied ourselves that the scavenger **288** was working, we then decided to analyze our samples from the second case study.

The samples that were analyzed from case study 2 were **A-2**, **B-2**, **C-2** and **E-2**. We included sample **E-2** in this study as a control to confirm that our ICP-MS analysis was correct. Our analysis found:

- Sample **A-2** contained 0.766μg Ru/5mg sample
- Sample **B-2** contained 0.160μg Ru/5mg sample
- Sample **C-2** contained 3.029μg Ru/5mg sample
- Sample **E-2** contained 0.160μg Ru/5mg sample

This data highlights a 79% reduction in the ruthenium levels going from sample **A-2** to sample **B-2**. After the addition of Grubbs II catalyst **11** to sample **B-2**, sample **C-2** showed a 1893% increase in the ruthenium levels. The control, sample **E-2**, showed the exact same level of ruthenium as sample **B-2**. This is as would be expected and confirms that there were no errors that occurred under reaction conditions or through the analysis.

This analysis thus allows us to conclude that our samples used after ruthenium removal using the Breinbauer scavenger **288** were acceptably termed "ruthenium depleted". In addition, we now have qualitative evidence for the conversion of the indenol **203** to the indenone **204** and the indanone **205**, supporting our proposal that the reactions occur as dehydrogenative oxidation and redox isomerisation respectively.

# *Chapter 6:*

# *Conclusion and Future Work*

# *Chapter 6: Conclusion and Future Work*

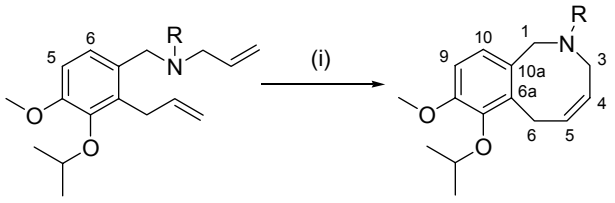
## 1. Summaries and Conclusion

The aims of this project were discussed and listed at the end of **Chapters 2** and **3**. The main aims will be discussed in turn, thus giving an idea of the success of the project.

### *1.1 Synthesis of N-containing benzo-fused heterocycles*

- *To synthesize a range of benzazocines from the common synthetic precursor **138** using the ring closing metathesis strategy developed by Pathak.*[129].

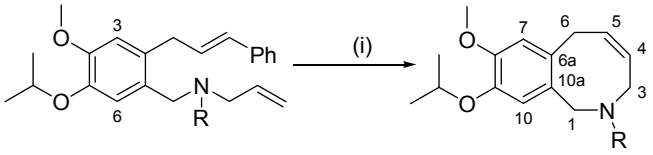
This aim was fulfilled as we were able to synthesize four different protected 8-membered benzo-fused benzazocines based on the methodology developed by Pathak.[129] The 1-[7-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocin-2(1*H*)-yl]-1-ethanone **214** was obtained from the corresponding diene in 82% yield as a clear oil. The *tert*-butyl 7-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocine-2(1*H*)-carboxy-late **215** was formed in 99% yield and the 2-(benzylsulfonyl)-7-isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine **216** was found in 84% yield. Finally, the 7-isopropoxy-8-methoxy-2-[(4-methylphenyl)sulfonyl]-1,2,3,6-tetrahydro-2-benzazocine **140** was obtained in 98% yield after RCM.




**Scheme 119**

Having isolated the Claisen-Cope product **267** when attempting the Claisen rearrangement of the cinnamyl containing aldehyde **246**, we then continued our investigation into other benzazocines, by including the new substitution pattern on the benzene ring in this study. This was very important for us to do, as the substitution pattern obtained by the Cope

rearrangement is the same as that found in many of the natural products outlined in **Chapter 2**. We then took our protected aldehyde **268**, performed the reductive amination on it to obtain the amine **270**, and accomplished the protection reactions (Boc and Ts groups were used) and finally attempted the RCM. From the RCM we were able to isolate *ter*t-butyl 9-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocine-2(1*H*)-carboxylate **273** in 73% yield and 9-isopropoxy-8-me-thoxy-2-[(4-methylphenyl)sulfonyl]-1,2,3,6-tetrahydro-2-benzazocine **274** in 39% yield.

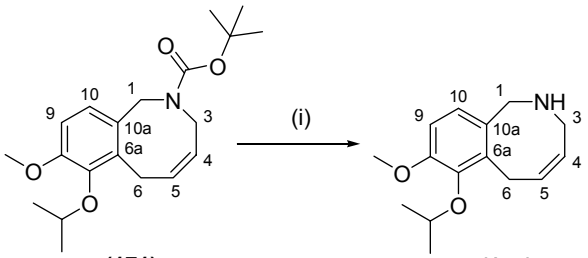



**227-228** **229-230**

**Scheme 120**

- *Test the feasibility of deprotection reactions on the final 6-,7- and 8-membered nitrogen containing benzo-fused systems.*

Due to the time constraints of the project, we were only able to test the deprotection reactions on the benzazocine systems. We were unable to deprotect compound **216** using the hydrogenation procedure with palladium on carbon, but we did show that this procedure hydrogenated the alkene in the 8-membered ring in excellent yield (98%). Our second attempt, at the Boc deprotection of compound **215** gave the desired 7-isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine **218** in 99% yield from the corresponding precursor.

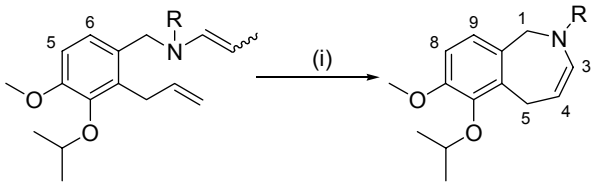



**(171)** **(174)**

**Scheme 121**

- *Utilize ring closing metathesis to access a range of benzazepine systems from a common synthetic precursor.*

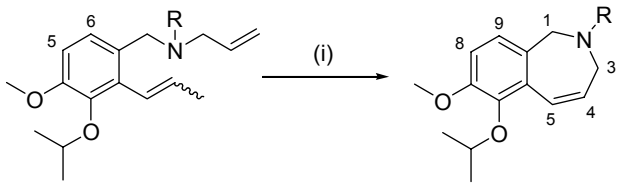
Two different approaches were utilized for the formation of the 7-membered benzazepines. The first of which allowed us to access the 2,5-dihydro-1*H*-2-benzazepines via the common intermediate **210**, of which we protected the amine with our four protecting groups, isomerised the diene and performed the ring closing metathesis. We obtained the 2-acetyl-6-isopropoxy-7-methoxy-2,5-dihydro-1*H*-2-benzazepine **231** in 9% yield, the *tert*-butyl 6-isopropoxy-7-methoxy-1,5-dihydro-2*H*-2-benzazepine-2-carboxylate **232** in 82% yield, the 2-(benzylsulfonyl)-6-isopropoxy-7-methoxy-2,5-dihydro-1*H*-2-benzazepine **233** in 58% yield and the 6-isopropoxy-7-methoxy-2-[(4-methylphenyl)sulfonyl]-2,5-dihydro-1*H*-2-benzazepine **234** in 47% yield after RCM from their respective diene precursors.




**183-186** **187-190**

**Scheme 122**

The second approach allowed us access to the 2,3-dihydro-1*H*-2-benzazepines by starting from the common intermediate **235**, performing the protection reactions and finally completing the RCM reaction. The 2-acetyl-6-isopropoxy-7-methoxy-2,3-dihydro-1*H*-2-benzazepine **240** was obtained in 8% yield, the *tert*-butyl 6-isopropoxy-7-methoxy-1,3-dihydro-2*H*-2-benzazepine-2-carboxylate **241** was obtained in 26% yield, the 2-(benzylsulfonyl)-6-isopropoxy-7-methoxy-2,3-dihydro-1*H*-2-benzazepine **242** in 39% yield and 6-isopropoxy-7-methoxy-2-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1*H*-2-benzazepine **145** in 82% yield after RCM.




**106, 193-195** **107, 196-198**

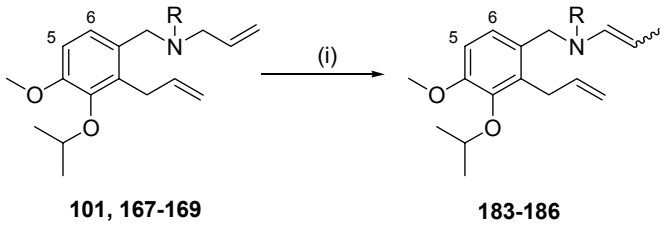
**Scheme 123**

Having had limited success with the formation of our allyl based benzazepines. We attempted the synthesis of 5-phenyl-2-benzazepines by changing our initial chain in the starting materials to the cinnamyl group. Using this, we were then able to synthesize the common intermediate, *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-2-propen-1-amine **249**. Amine **249** was then used in the four protection reactions and the products were then subjected to the RCM conditions. After RCM, we obtained 32% yield of *N*-allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]acetamide **250**. For the other three protecting groups, we were only able to observe molecular ion peaks in the HRMS, but we were not able to isolate and fully characterize the compounds.

- *Investigate the possibility of selective isomerisations in our diene systems, using the ruthenium-based catalyst outlined by Krompiec[29] (catalyst **12**).*

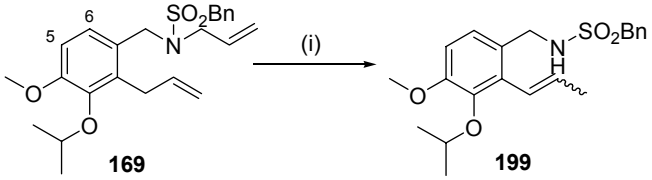
After numerous problems with our synthesis of the isoquinoline based systems, we attempted a range of different conditions to isomerise the protected dienes. Our initial investigation showed that both of the double bonds in the diene systems could be isomerised by the use of 5 mol % of the Ru-isomerisation catalyst **12** at a high temperature (100-110$^{o}$C).

We found that 1 mol % of the Ru-isomerisation catalyst **12** was the optimal amount of catalyst to use for the isomerisation of only one of the double bonds in the diene with a temperature of 80$^{o}$C giving the most favourable results. We were able to confirm that the *N*-allyl chain had selectively isomerised by $^{13}$C NMR spectroscopy (**Scheme 124**).




**Scheme 124**

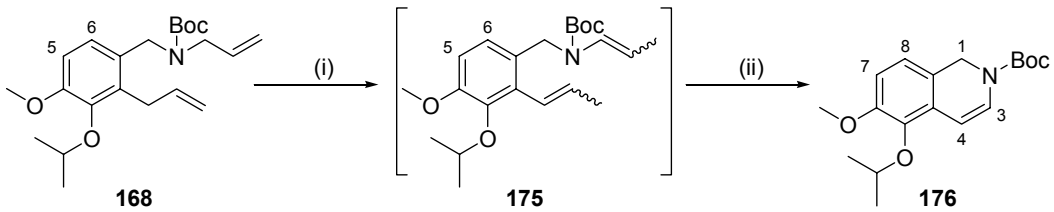
While attempting the isomerisations on our diene systems we found that de-allylation of the *N*-allyl chain was occurring when large quantities of the Ru-isomerisation catalyst **12** (5-10 mol %) and high temperatures (110-140$^{o}$C) were used. These types of de-allylation reactions were shown to occur in the presence of Grubbs first generation catalyst by Alcaide,[7] but to the best of our knowledge this is the first reported use of catalyst **12** for these reactions.




**Scheme 125**

- *Examine other diene systems to determine if with double allyl isomerisations it is possible to obtain isoquinoline analogues via ring closing metathesis.*

We performed double isomerisations on the diene systems **139, 211-213** as outlined above, but we only obtained poor yields of the products, if we managed to isolate them at all. We prepared the Boc-protected isoquinoline **220** in only 10% yield and the Ts-protected isoquinoline **142** in 27% yield, using the one-pot reaction procedure. Having had so many problems with the one-pot isomerisation-RCM reaction, we decided to isolate the isomerized intermediate and were subsequently able to isolate 2-acetyl-5-isopropoxy-6-methoxy-1,2-dihydroisoquinoline **223** in 78% yield after RCM. However, none of the $SO_2Bn$-protected isoquinoline **224** was obtained.



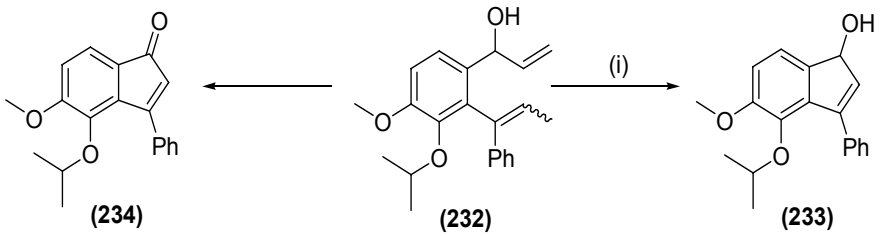

**Scheme 126**

We then attempted the synthesis of the 4-phenyl substituted isoquinolines by taking the protected compounds obtained from the common intermediate **249** and subjecting them to the Ru-isomerisation catalyst **12**. We were able to isolate the isomerised compounds in excellent yield. Having these in hand, we then attempted the RCM on them, but in all instances only the starting materials were isolated. Due to the time constraints of the project we were unfortunately unable to continue our investigation into the lack of formation of the desired isoquinolines.

*1.2 Synthesis of Indenols, Indenones and Indanones.*

- *Synthesize a range of indenols, indenones and indanones from common synthetic precursors (eg. Compound **202**) using the previously developed methodology of Coyanis*.[48]

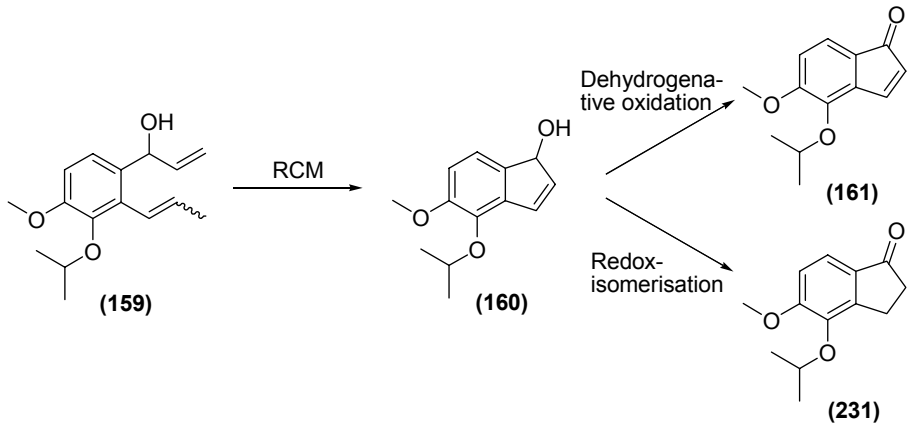
We prepared 1-[3-isopropoxy-4-methoxy-2-(1-propenyl)phenyl]-2-propen-1-ol **202** using established methodology and used it for the synthesis of 1-[3-isopropoxy-4-me-thoxy-2-(1-phenyl-1-propenyl)phenyl]-2-propen-1-ol **275** and 1-[3-isopropoxy-4-methoxy-2-(1-methyl-1-propenyl)phenyl]-2-propen-1-ol **284**. Each of the desired indan compounds was obtained using the same RCM methodology, with the procedures differing only in the reaction temperature. The indenols **203**, **276** and **285** were prepared at rt and were obtained in yields of 87%, 49% and 57% respectively. The indenones **204**, **277** and **286** were synthesized at 60-80$^{o}$C and were obtained in yields of 45%, 69% and 42% respectively. The unsubstituted indanone **231** was prepared at 80$^{o}$C using 8 mol % Grubbs II catalyst **11** in 89% yield. Unfortunately we were unable to prepare the phenyl-substituted indanone **278** even after numerous attempts. Finally the methyl-substituted indanone **287** was obtained in 18% yield after 18 h at 110-170$^{o}$C using 5 mol % Grubbs II catalyst **11**.




**Scheme 127**

- *Attempt to explain the role of ruthenium in indenol-indenone-indanone conversions via the implementation of a model $^{1}H$ NMR study which would include control standardss where ruthenium has been depleted.*

The unsubstituted indenone compounds were isolated from the reaction mixtures for the preparation of the unsubstituted indenols by Coyanis.[48] We hoped to be able to hypothesize as to why they were present and support our ideas through the use of NMR spectroscopy studies. We monitored the conversion of the indenol **203** to the indenone **204** and indanone **205** through the use of $^{1}H$ NMR spectroscopy studies.




**Scheme 128**

We compared the reactions containing residual ruthenium from the RCM reactions after column chromatography, those with 5 mol % Grubbs II catalyst **11** added and in samples where the ruthenium had been removed using a scavenger **288**. We found that the sample with the added Grubbs catalyst in showed the most efficient conversion of indenol **203** to indenone

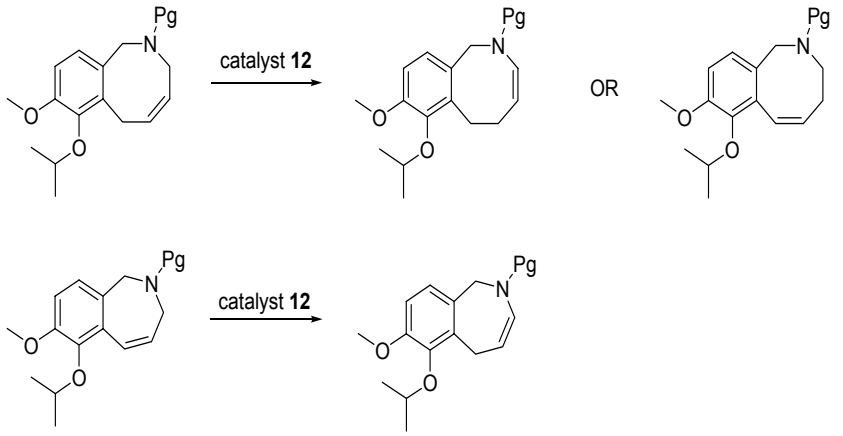
**204** at 60-80$^{o}$C and demonstrated almost exclusive conversion to indanone **205** at 100$^{o}$C. The sample where the ruthenium had been removed with the scavenger showed no conversion at all, independent of the temperature, and the sample with the residual ruthenium showed conversion of indenol **203** to indenone **204** at 100$^{o}$C after 1400 min.

The final study on the conversion in the presence of Grubbs II catalyst found that the indenol **203** converted exclusively to the indenone **204** at lower temperatures. These results support our suggestion that the conversion of indenol **203** to indenone **204** is a ruthenium catalysed dehydrogenative oxidation, whereas the conversion of indenol to indanone occurs via the well known redox isomerisation reaction. To the best of our knowledge, this is the first ever reported use of the Grubbs II catalyst **11** or its degradative products for a tandem RCM-oxidation reaction.

## 2. Future Work

Having completed the full methodology study for the nitrogen-containing benzo-fused heterocycles, we can now extend it to include a substitution pattern that mirrors the one found in the natural products. Hopefully, this will then allow us to synthesize a range of different compounds, which may then be used in biological testing for various diseases.

The first key aspect of future work should be to fully investigate the possibility of performing internal isomerisations of the alkene double bond in both the benzazocines and the benzazepines (**Scheme 129**) using the ruthenium isomerisation catalyst **12** as well as other isomerisation methods. An area of particular interest will be to see if it is possible to access both isomers from the isomerisation of benzazocines, and whether or not you can access each of the isomers selectively.

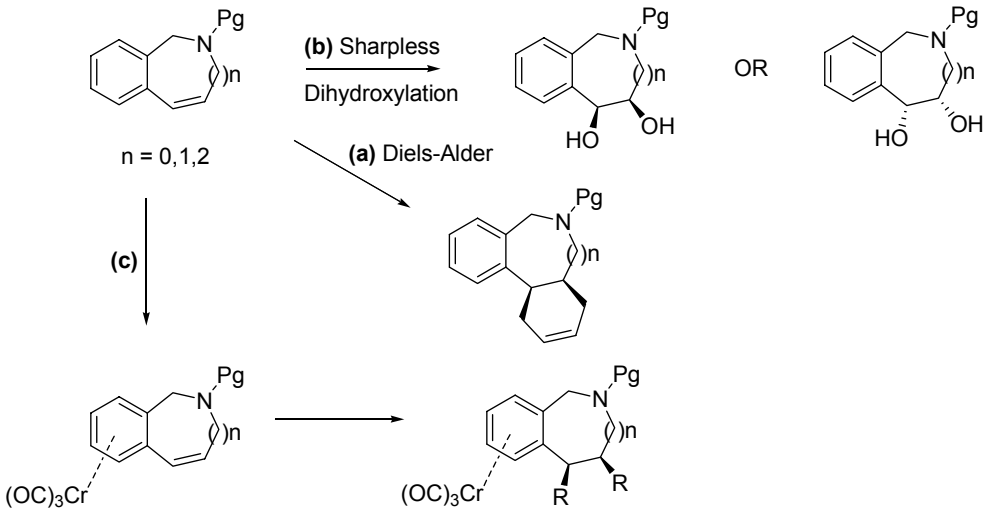



**Scheme 129**

Internal isomerisation of the alkene is of great importance as it allows a far greater scope for functionalisation. An isomerised benzazocine can potentially be functionalized at the 3, 4, 5 and 6 positions and benzazepines at the 3, 4 and 5 positions.

Functionalisation of the ring alkene is the second key aspect of any future work on this project. A few of the possible routes of functionalisation include epoxidation, aminohydroxylation and oxymercuration. An interesting route would be to utilize the alkene in Diels-Alder type reactions, thereby gaining access to tricyclic molecules, and potentially polycyclic molecules depending on the diene used [**Scheme 130 (a)**].

Potentially the most interesting aspect of functionalisation would be to look at performing asymmetric Sharpless dihydroxylations thereby giving access to the possibility of stereoselective functionalistions [(**Scheme 130 (b)**]. An alternative approach to asymmetric synthesis could be to form arene $Cr(CO)_3$ complexes prior to attempting any functionalisation of the alkene, thereby effectively masking the one face of the molecule from attack [(**Scheme 130 (c)**].




**Scheme 130**

A long term goal would no doubt be to synthesize a library of isoquinolines, benzazepines and benzazocines for the purpose of investigating their pharmacological activities, through biological studies.

# *Chapter 7:*

# *Experimental Procedures*

# *Chapter 7: Experimental Procedures*

## 1. General Details

### *1.1 Purification of Solvents and Reagents*

All solvents used for reactions and preparative chromatography were distilled prior to use. Solvents used in reactions were pre-dried in their reagent bottles and then distilled over the appropriate drying mediums under a nitrogen atmosphere.

- Tetrahydrofuran and diethyl ether were distilled from sodium metal wire and benzophenone.
- Benzene and toluene were distilled from sodium metal lumps.
- Acetonitrile, dichloromethane, *N,N*-dimethylformamide (stored over 4Å molecular sieves after distillation), methanol and triethylamine were distilled from calcium hydride.
- Acetic anhydride was distilled from 4Å molecular sieves.
- Pyridine was distilled from potassium hydroxide.

Chloroform was dried by passing it through basic alumina (Merck aluminium oxide, basic, activity grade I). Potassium *tert*-butoxide was resublimed under high vacuum immediately before use. Tosyl chloride was purified according to Perrin[219] before use and stored in a dessicator until required. It was purified by dissolving (10g) in the minimum volume $CH_2Cl_2$ (~25cm$^3$), filtered, and diluted with five volumes of hexane (5×25cm$^3$) to precipitate the impurities. The solution was then filtered and concentrated to 40cm$^3$ by evaporation. White crystals precipitated out on standing (*m.p*. was in agreement with the literature value of 67-69$^o$C).

Grubbs II catalyst **11** and the Ru-isomerisation catalyst **12** were stored in Schlenk tubes under argon. The procedure for storing the catalysts was to place the Schlenk tubes under vacuum and then under argon four to five times to ensure that the systems were free from air and they were then stored in the dark.

### *1.2 Experimental Techniques*

All reactions were performed under an inert atmosphere (either nitrogen or argon) using a standard manifold line and connected to a vacuum pump. The nitrogen and argon were dehydrated by bubbling the gas through sulfuric acid, and then neutralizing by passing through sodium hydroxide pellets. The vessels were flame-dried while under vacuum and were then allowed to cool to room temperature under the inert atmosphere.

### *1.3 General Procedures*

Concentration or evaporation *in vacuo* refers to the removal of solvent under reduced pressure (approximately 20mmHg, 40-50$^{o}$C) on a rotary evaporator and final drying on an oil pump (approximately 1-2mmHg) at room temperature. Items dried under "high vacuum" were also dried using an oil pump (approximately 1-2mmHg).

Yields are calculated from the immediate synthetic precursor, unless otherwise specified.

### *1.4 Chromatographic Separations*

Macherey-Nagel Silica gel 60 (particle size 0.063-0.200mm) was used as the adsorbent for conventional preparative chromatography, with a silica to compound ratio of 30:1. The silica was packed into a suitable column, the product was loaded onto the silica surface and covered in acid washed sea sand. The elution process was performed using the indicated solvent mixtures and was usually performed under standard air pump pressure conditions.

The $R_f$ values quoted are those obtained from thin layer chromatography on aluminium-backed Macherey-Nagel ALUGRAM Sil G/$UV_{254}$ plates pre-coated with 0.25mm silica gel 60 or Aldrich TLC plates, silica gel on aluminum. Spray reagents were used on thin layer chromatography plates for the detection of compounds that were not highly UV active. General reagents used include acidic vanillin, basic $KMnO_4$, acidic ceric ammonium sulfate and acidic anisaldehyde. Acidic DNPH was used for the detection of ketones and aldehydes specifically.

### *1.5 Spectroscopic and Physical Data*

Sanyo EM-590 manufactured the commercial microwave oven used in certain reactions. The microwave reactor referred to is the CEM Discovery and operating conditions employed for the reactions are outlined in the experimental procedures.

The Carousel reactor employed for certain reaction sequences was manufactured by Radleys Discovery Technologies and is sold as the Carousel Reaction Station.

All melting points were obtained on a Reichert hot-stage microscope and are uncorrected.

Infrared spectra were obtained either on a Bruker Vector 22 spectrometer, or on a Varian 800FT-IR spectrometer (Scimitar Series). Liquids were run as thin films between sodium chloride plates, while solids were run as solutions in chloroform between sodium chloride plates. The absorptions are reported on the wavenumber ($cm^{-1}$) scale in the 600-3500$cm^{-1}$ range. The signals are reported: value (assignment).

Hydrogen nuclear magnetic resonance ($^{1}H$ NMR) spectra were recorded on Bruker AC-200, Bruker Advance-300 and Bruker DRX 400 spectrometers at 200.13, 300.13 and 400.13MHz respectively using standard pulse sequences. The probe temperature for all experiments was 300±1K. All spectra were recorded in deuterated chloroform ($CDCl_3$) in 5mm NMR tubes unless otherwise specified. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane as the internal standard. The $^{1}H$ NMR chemical shifts are reported: value (number of hydrogens, description of signal, coupling constants in hertz (Hz) where applicable, assignment). Abbreviations used: s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, sept=septet, m=multiplet and b=broad.

Decoupled carbon nuclear magnetic resonance ($^{13}C$ NMR) spectra were recorded on Bruker Advance-300 and Bruker DRX 400 spectrometers at 75 and 100MHz respectively Chemical shifts are reported on the δ scale relative to the central signal of deuterated chloroform taken as δ 77.00. The $^{13}C$ NMR chemical shifts are reported: value (assignment). The $^{1}H$ and $^{13}C$ NMR spectroscopic assignments with the same superscript are interchangeable. DEPT, CH-

correlated and COSY spectra were routinely used for the complete assignment of NMR signals.

High-resolution mass spectra were recorded on a VG7-SEQ Double Focussing Mass Spectrometer at 70eV and 200μA. The polarity was positive, ionization employed was EI, with a resolution of 3000, a mass range of 3000amu (8kV) and a scan rate of 5secs/decade. Data are quoted: *m/z* value (relative abundance).

Microwave digestion of samples for ICP-MS analysis was performed using the Anton Paar Multiwave 3000 (microwave sample preparation platform system). ICP-MS results were detected using the Spectro Mass-2000 with the SpecPure Multielement Standards (group 4 elements) being used for the preparation of our standard curves.

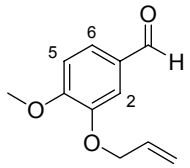
Crystal structure intensity data were collected on a Bruker SMART 1K CCD area diffractometer with graphite monochromated Mo $K_\alpha$ radiation (50kV, 30mA). The collection method involved ω-scans of width 0.3°. Data reduction was carried out using the program *SAINT*+.[220] The crystal structure was solved by direct methods using *SHELXTL.*[221] Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on $F^2$ using *SHELXTL.*[221] Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using *SHELXTL,*[221] *PLATON*[222] and *Mercury*.[223]

### *1.6 Nomenclature and Numbering of Compounds*

The compounds prepared during the course of this project are named in the following experimental sections according to systematic nomenclature. However, the numbering system used to illustrate the diagrams of these compounds is one adopted for convenience and is not meant to reflect the systematic numbering of these compounds.

## 2. Experimental Procedures: *N*-containing benzo-fused heterocycles

### *2.1 Preparation of 3-allyloxy-4-methoxybenzaldehyde **207***

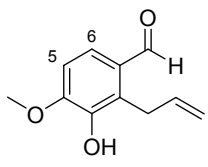



**207**

Potassium carbonate (2.5eq, 329mmol, 45.6g) was added to DMF (250cm$^3$) and the solution was heated to 60$^o$C for 20 min. Isovanillin (1eq, 132mmol, 20.1g) was added to the solution along with allyl bromide (2.5eq, 329mmol, 28.6cm$^3$) and the mixture changed colour from milky white to yellow. The reaction mixture was then stirred at 60$^o$C under an Ar atmosphere for 20 h. After this time it was cooled to rt and the inorganic solids were filtered off through a celite pad. The solvent was then removed *in vacuo* to yield a yellow-orange oil. The crude mixture was purified by column chromatography (10-30% EtOAc-Hexane) and the product was obtained as a bright yellow oil (25.1g, 99% yield). Spectroscopic data was in agreement with that of Rousseau.[1]

***R*$_f$** = 0.50 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, CDCl$_3$)** 3.96 (1H, s, $OCH_3$), 4.67 (2H, d, *J*=5.4Hz, $OCH_2$), 5.31-5.48 (2H, m, $OCH_2CH=CH_2$), 6.05-6.15 (1H, m, $OCH_2CH=CH_2$), 6.99 (1H, d, *J*=8.2Hz, 5-H), 7.41 (1H, d, *J*=1.7Hz, 2-H), 7.46 (1H, dd, *J*=1.7 and 8.2Hz, 6-H), 9.84 (1H, s, CHO); **$\delta_C$ (50 MHz, CDCl$_3$)** 56.1 ($OCH_3$), 69.7 ($OCH_2$), 110.6 (5-C), 110.9 (2-C), 118.6 ($OCH_2CH=CH_2$), 126.8 (6-C), 130.0 (1-C), 132.4 ($OCH_2CH=CH_2$), 148.5 (4-C$^a$), 154.8 (3-C$^a$), 190.8 (CHO).

### *2.2 Preparation of 2-allyl-3-hydroxy-4-methoxybenzaldehyde **208***




**208**

Method A:

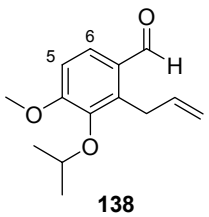
3-Allyloxy-4-methoxybenzaldehyde **207** (5.26mmol, 1.01g) was transferred directly to a round bottom flask and placed inside the Teflon container. The commercial microwave was set to high power and the Claisen rearrangement was affected by microwaving in short bursts (15, 15, 20 and 30 sec respectively with 5 min intervals in between each heating). After this time a colour change was observed from the yellow oil to a brown oil. This was found to be the product and no further purification was required (1.01g, 100% yield).

Method B:

3-Allyloxy-4-methoxybenzaldehyde **207** (31.3mmol, 6.01g) was placed neat in a sealed tube for the microwave reactor. The program was set up with the power output at 50W, the temperature at 200°C, the maximum allowable pressure at 150psi with no cooling and continuous stirring. The run time was set to 5 min with hold times of 5, 5 and 20 min respectively or 10 and then 20 min respectively with cool down times of 5-10 min between each interval. The progress of the Claisen rearrangement was monitored at each interval by 200MHz $^1$H NMR spectroscopy. After the 30 min in total it was found that the reaction had gone to completion and the compound was spectroscopically pure. The product was obtained as a viscous yellow brown oil and no further purification was required (6.01g, 100% yield).

***R*$_f$** = 0.41 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 1281 (-OH bending), 1492 (Ar ring), 1579 (Ar ring), 1603 (Ar ring), 1726 (saturated aldehyde), 2931 (CHO), 3020 (Ar H), 3541 (-OH stretch); **$\delta_H$ (300 MHz, CDCl$_3$)** 3.88 (2H, d, *J*=5.9Hz, $CH_2$), 3.97 (3H, s, $OCH_3$), 4.96-5.03 (2H, m, CH=C*H*$_2$), 5.86 (1H, s, OH), 6.03 (1H, tdd, *J*=6.0, 10.6 and 16.6Hz, C*H*=$CH_2$), 6.88 (1H, d, *J*=8.5Hz, 5-H), 7.44 (1H, d, *J*=8.5Hz, 6-H), 10.07 (1H, s, CHO); **$\delta_C$ (50 MHz, CDCl$_3$)** 28.4 ($CH_2$), 56.1 ($OCH_3$), 108.1 (5-C), 115.3 (CH=*C*H$_2$), 125.4 (6-C), 127.5 (*C*H=CH$_2$[a]), 128.2 (2-C[a]), 136.2 (1-C), 143.8 (3-C), 150.7 (4-C), 191.4 (CHO); **MS *m/z*** 192 ($M^+$, 90%), 77 (29), 91 (15), 103 (22), 131 (19), 136 (18), 143 (25), 149 (19), 159 (31), 162 (18), 177 (100), 192 (90), 193 (23), ***HRMS*** calculated for $C_{11}H_{12}O_3$: 192.07864, found: 192.08046.

*2.3 Preparation of 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **138***



**138**

Method A:

The Claisen rearrangement was affected upon the heating of 3-allyloxy-4-methoxybenzaldehyde **207** (75.6mmol, 14.6g), which had been dissolved in DMF (145cm$^3$) to 150-160°C under an Ar atmosphere for 64 h. The reaction mixture was then cooled to 60°C before the addition of the isopropyl bromide (2.5eq, 189mmol, 17.7cm$^3$) and potassium carbonate (2.5eq, 189mmol, 26.2g). The reaction mixture was left to stir at 60°C for 18 hours and was then cooled to rt before the inorganic solids were filtered off through a celite plug. The solvent was removed *in vacuo* to yield a dark brown oil which was purified by column chromatography

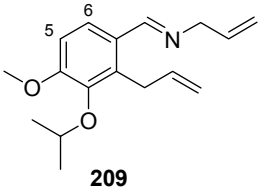
(5-10% EtOAc-Hexane). The product was obtained as a bright yellow oil (13.4g, 75% over 2 steps).

Method B:

3-Allyloxy-4-methoxybenzaldehyde **207** (1eq, 41.8mmol, 8.02g) was placed neat in a sealed tube for the microwave reactor. The program was set up with the power output at 50W, the temperature at 200°C, the maximum allowable pressure at 150psi with no cooling and continuous stirring. The run time was set to 5 min with hold times of 5, 5 and 20 min respectively or 10 and then 20 min respectively with cool down times of 5-10 min between each interval. 200MHz $^1$H NMR spectroscopy monitored the progress of the Claisen rearrangement at each interval. After the 30 min in total it was found that the reaction had gone to completion and was relatively clean so the phenol **208** was dissolved in DMF (80cm$^3$) and heated to 60°C before the addition of the potassium carbonate (2.5eq, 103mmol, 14.2g) and isopropyl bromide (2.5eq, 103mmol, 9.70cm$^3$). The reaction mixture was left to stir at 60°C under an Ar atmosphere for 66 h after which time it was allowed to cool to rt. The inorganic solids were filtered off through a celite pad and the solvent was removed *in vacuo*. The dark brown oil was purified by column chromatography (5-10% EtOAc-Hexane) to yield the product as a bright yellow oil (8.56g, 89% yield over 2 steps). The spectroscopic results correlated well to that obtained by Pathak[129] and no further analysis was required.

***R*$_f$** = 0.65 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.28 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 3.90 (5H, m, OCH$_3$ and CH$_2$), 4.51 [1H, sept, *J*=6.2, OC*H*(CH$_3$)$_2$], 4.97 (2H, two dd, *J*=1.6, 13.7 and 18.8Hz, CH=C*H*$_2$), 6.00 (1H, m, C*H*=CH$_2$), 6.90 (1H, d, *J*=8.6Hz, 5-H), 7.64 (1H, d, *J*=8.6Hz, 6-H), 10.08 (1H, s, CHO); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.8 [OCH(*C*H$_3$)$_2$], 29.0 (CH$_2$), 55.7 (OCH$_3$), 74.9 [O*C*H(CH$_3$)$_2$], 109.6 (5-C), 115.6 (CH=*C*H$_2$), 128.0 (1-C), 128.0 (6-C), 136.4 (2-C[a]), 137.1 (*C*H=CH$_2$[a]), 144.9 (3-C), 157.6 (4-C), 191.1 (CHO).

## *2.4 Preparation of N-[(E)-(2-allyl-3-isopropoxy-4-methoxyphenyl)methylidene]-2-propen-1-amine **209***



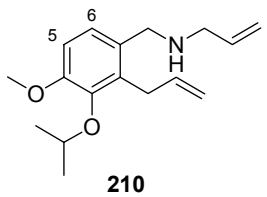
**209**

2-Allyl-3-isopropoxy-4-methoxybenzaldehyde **138** (7.98 mmol, 1.87g) was transferred directly to a round-bottomed flask and to this was added allyl amine (1.4eq, 11.2mmol, 0.900cm$^3$). The reaction

mixture was placed under a $N_2$ atmosphere and was allowed to stir at rt for 3 h. After this period of time the excess allyl amine was removed *in vacuo* to yield a yellow oil. The product was essentially pure by $^1$H NMR spectroscopy and no further purification was required (2.42g, 99% yield).

***R*$_f$** = 0.63 (30% EtOAc-Hexane); **vmax/cm$^{-1}$ (NaCl plate)** 734 (alkanes), 926 (C=$CH_2$), 1383 (C-$OCH_3$), 1591 (Ar ring), 1637 (diene), 1682 (C=N-), 2841 (N-$CH_2$), 3020 (C=CH stretch); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.27 [6H, d, *J*=6.1Hz, OCH(C*H*$_3$)$_2$], 3.69 (2H, dd, *J*=1.7 and 3.8Hz, Ar-$CH_2$), 3.86 (3H, s, $OCH_3$), 4.21 (2H, dd, *J*=1.3 and 5.6Hz, N-$CH_2$), 4.49 [1H, sept, *J*=6.2Hz, OC*H*(CH$_3$)$_2$], 5.00-5.24 (4H, m, $NCH_2CH=CH_2$ and $ArCH_2CH=CH_2$), 5.90-6.09 (2H, m, $NCH_2CH=CH_2$ and $ArCH_2CH=CH_2$), 6.83 (1H, d, *J*=8.7Hz, 5-H), 7.73 (1H, d, *J*=8.7Hz, 6-H), 8.44 (1H, s, N=CH); **$\delta_C$ (100.6 MHz, $CDCl_3$)** 22.6 and 22.7 [OCH(*C*H$_3$)$_2$], 30.7 ($ArCH_2$), 55.6 ($OCH_3$), 63.7 ($NCH_2$), 74.4 [O*C*H(CH$_3$)$_2$], 109.9 (5-C), 114.6 ($NCH_2CH=CH_2$[a]), 115.8 ($ArCH_2CH=CH_2$[a]), 124.1 (6-C), 131.7 (1-C), 132.5 ($NCH_2CH=CH_2$), 136.9 (2-C), 137.5 ($ArCH_2CH=CH_2$), 145.0 (3-C), 151.8 (4-C), 160.4 (N=CH); **$\delta_N$** (40.6MHz, $CDCl_3$) –62.9; **MS *m/z*** 272 ($M^+$, 67%) 39 (23), 41 (61), 43 (28), 115 (39), 143 (86), 144 (20), 160 (21), 161 (25), 174 (31), 175 (75), 176 (91), 177 (24), 190 (30), 216 (42), 218 (100), 230 (98), 231 (68), 232 (23), 258 (32), 272 (67), 273 (26), 274 (25), ***HRMS*** calculated for $C_{17}H_{23}NO_2$: 273.17288, found: 272.17086.

### *2.5 Preparation of N-(2-allyl-3-isopropoxy-4-methoxybenzyl)-2-propen-1-amine **210***



**210**

Method A:

2-Allyl-3-isopropoxy-4-methoxybenzaldehyde **138** (29.9 mmol, 7.01g) was transferred directly to a round-bottomed flask and to this was added allyl amine (1.4eq, 41.9mmol, 3.20cm$^3$). The reaction mixture was placed under an Ar atmosphere and was allowed to stir at rt for 24 h. After this period of time the excess allyl amine and water were removed *in vacuo* to yield an orange oil, which was pure by $^1$H NMR spectroscopy. The imine was then dissolved in MeOH (70cm$^3$) and cooled to 0$^o$C in an ice-water bath. To this methanolic solution was added sodium borohydride (1.2eq, 35.9mmol, 1.37g) and the solution was allowed to stir for 1 h 40 min. After this time the remaining sodium borohydride was destroyed by the addition of water (100cm$^3$) and then 1M HCl solution (until the pH was ~7).

The MeOH was removed under reduced pressure, to yield a yellow oil on the aqueous layer. This was then extracted with EtOAc (3×100cm$^3$) and the combined organics were dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to yield an oil that was purified by column chromatography (5-50% EtOAc-Hexane). The product was obtained as an orange oil (6.95g, 84% yield over 2 steps).

Method B:

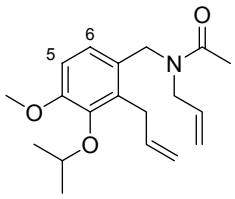
2-Allyl-3-isopropoxy-4-methoxybenzaldehyde **138** (12.8mmol, 3.00g), allyl amine (3eq, 38.4mmol, 2.88cm$^3$) and the acid catalyst *p*-TsOH (0.1eq, 1.28mmol, 0.252g) were dissolved in benzene (150cm$^3$). The system was placed under a $N_2$ atmosphere and was heated at reflux using a Dean-Stark head for 18 h. After this time the benzene was evaporated under reduced pressure, the resulting material was diluted with $CH_2Cl_2$ (100cm$^3$) and was then extracted with saturated $NaHCO_3$ (100cm$^3$). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to yield the imine in pure form. The residue was then dissolved in MeOH (30cm$^3$) and cooled to 0$^o$C in an ice-water bath. To this methanolic solution was added sodium borohydride (1.2eq, 15.4mmol, 0.589g) along with a drop of water and the mixture was stirred for 1 h. On completion of the reaction the excess sodium borohydride was destroyed using water (20cm$^3$) and 1M HCl. The pH was corrected to ~7 using saturated $NaHCO_3$. The MeOH was removed under reduced pressure and the remaining residue (in the aqueous layer) was extracted with EtOAc (3×20cm$^3$). The combined organics were then dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to yield the product as a yellow-orange oil (3.18g, 90% yield over 2 steps).

Method C:

The *N*-[(*E*)-(2-allyl-3-isopropoxy-4-methoxyphenyl)methylidene]-2-propen-1-amine **209** (3.70mmol, 1.01g) was dissolved in MeOH (10cm$^3$) and cooled to 0$^o$C in an ice-water bath before the addition of the sodium borohydride (1.2eq, 4.44mmol, 0.167g). The solution was allowed to stir for 1 h 30 min before the addition of water (10cm$^3$) and then 1M HCl solution (until the pH was ~7). The MeOH was removed under reduced pressure to yield a yellow oil on the aqueous layer. This was then extracted with EtOAc (2×25cm$^3$) and the combined organics were dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to yield the product as a yellow oil (0.828g, 81%).

***R*$_f$** = 0.41 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.26 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 1.42 (1H, s, NH), 3.26 (2H, td, *J*=1.2 and 5.9Hz, ArC$H_2^a$), 3.54 (2H, td, *J*=1.4 and 5.7Hz, NHC$H_2^a$CH), 3.69 (2H, s, ArC$H_2$NH), 3.81 (3H, s, $OCH_3$), 4.51 [1H, sept, *J*=6.2Hz, OC*H*(CH$_3$)$_2$], 4.88-4.99 (2H, m, ArCH$_2$CH=C$H_2$), 5.14 (2H, two dd, *J*=1.5, 13.7 and 11.5Hz, NHCH$_2$CH=C$H_2$), 5.88-5.99 (2H, m, ArCH$_2$C*H*=CH$_2$ and NHCH$_2$C*H*=CH$_2$), 6.75 (1H, d, *J*=8.4Hz, 5-H), 7.01 (1H, d, *J*=8.4Hz, 6-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.5 [OCH(*C*H$_3$)$_2$], 29.5 (ArCH$_2$), 44.6 (ArCH$_2$NH), 55.5 ($OCH_3$), 63.6 (NH*C*H$_2$CH=CH$_2$), 74.6 [O*C*H(CH$_3$)$_2$], 110.2 (5-C), 115.7 and 115.8 (ArCH$_2$CH=*C*H$_2$ and NHCH$_2$CH=*C*H$_2$), 123.0 (6-C), 127.9 (1-C), 133.6 (2-C), 136.2 (NHCH$_2$*C*H=CH$_2$), 137.1 (ArCH$_2$*C*H=CH$_2$), 144.4 (3-C), 154.6 (4-C). The spectroscopic results correlated well to that obtained by Pathak[129] and no further analyses were required.

### *2.6 Preparation of N-allyl-N-(2-allyl-3-isopropoxy-4-methoxybenzyl)acetamide **211***



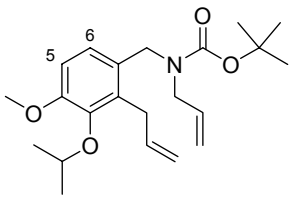

**211**

A solution was prepared of *N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-2-propen-1-amine **210** (5.47mmol, 1.51g) in pyridine (5.47mmol, 0.450cm$^3$) and it was cooled to 0$^o$C in an ice-water bath. To this was added dropwise a solution of acetic anhydride (1.5eq, 8.20mmol, 0.800cm$^3$) in pyridine (1.5eq, 8.20mmol, 0.650cm$^3$). The ice-water bath was then removed and the reaction mixture was stirred at rt under an Ar atmosphere for 3 h. After this time EtOAc (15cm$^3$) was added and the reaction mixture was then extracted with brine (3×10cm$^3$). The combined aqueous layers were then extracted with $CH_2Cl_2$ (3×10cm$^3$). The organic layers were then combined and washed with a saturated ammonium chloride solution that had been basified to pH 10 with 25% ammonia solution (15cm$^3$). The combined organic portions were then dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by column chromatography (10-30% EtOAc-Hexane) to yield the desired product as a yellow oil (1.59g, 92%).

***R*$_f$** = 0.22 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 992 ($R_2C=CH_2$), 1520 (Ar ring), 1637 (tertiary amide), 2838 ($OCH_3$), 2981 ($CH_2$), 3022 (C=CH$_2$ stretch); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.26 [6H, dd, *J*=4.8 and 6.1Hz, OCH(C*H*$_3$)$_2$], 2.05 and 2.14 [3H, two s, $CH_3$], 3.44 (2H, d, *J*=5.5Hz, ArC*H*$_2$CH=CH$_2$), 3.71 (1H, d, *J*=4.8Hz, NC*H*$_2$CH=CH$_2^a$), 3.82 (3H, d, *J*=4.8Hz, $OCH_3$), 3.98 (1H, d, *J*=5.9Hz, NC*H*$_2$CH=CH$_2^a$), 4.40 (1H, s, ArC*H*$_2$N$^b$), 4.52 [1H,

sept, *J*=6.2Hz, OC*H*($CH_3$)$_2$], 4.57 (1H, s, ArC$H_2$N[b]), 4.82-5.21 (4H, m, ArC$H_2$CH=C$H_2$ and NC$H_2$CH=C$H_2$), 5.74-5.90 (2H, m, ArC$H_2$C*H*=C$H_2$ and NC$H_2$C*H*=C$H_2$), 6.75-6.82 (2H, m, 5-H and 6-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.4 (*C*$H_3$), 22.6 [OCH(*C*$H_3$)$_2$], 30.0 and 30.5 (Ar*C*$H_2$CH=$CH_2$), 45.1 (Ar$CH_2$N), 48.1 and 49.2 (N*C*$H_2$CH=$CH_2$), 55.5 (O$CH_3$), 74.5 and 74.6 [O*C*H($CH_3$)$_2$], 110.0 and 110.1 (5-C), 114.7 and 115.1 (NC$H_2$CH=*C*$H_2$), 116.5 and 117.3 (Ar$CH_2$CH=*C*$H_2$), 119.9 (6-C), 123.4 (1-C), 127.5 and 128.2 (2-C), 132.6 and 133.1 (NC$H_2$*C*H=$CH_2$), 135.8 and 136.5 (Ar$CH_2$*C*H=$CH_2$), 145.22 and 145.4 (3-C[c]), 152.1 (4-C[c]), 170.8 and 171.2 (C=O); **MS *m/z*** 317 ($M^+$, 30%) 43 (24), 115 (20), 143 (40), 145 (23), 161 (28), 174 (27), 176 (100), 177 (35), 192 (53), 218 (41), 234 (24), 317 (30), ***HRMS*** calculated for $C_{22}H_{33}NO_4$: 317.19909, found: 317.19972.

### *2.7 Preparation of tert-butyl allyl(2-allyl-3-isopropoxy-4-methoxybenzyl)- carbamate **212***



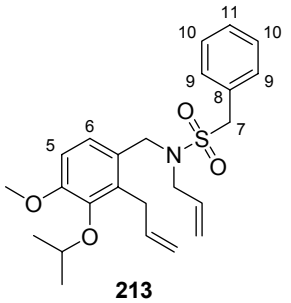

**212**

The *N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-2-propen-1-amine **210** (5.47mmol, 1.51g) was dissolved in THF (150$cm^3$) and to this solution was added $Boc_2O$ (1.2eq, 6.56mmol, 1.55ml). The solution was stirred for 5 min before the addition of the DMAP (0.1eq, 0.547mmol, 0.0669g). The reaction mixture was allowed to stir at rt under an Ar atmosphere for 3 h after which time the solvent was removed *in vacuo*. The orange oil was purified by column chromatography (5-10% EtOAc-Hexane) to yield the desired product as a pale yellow oil (1.99g, 97%).

***$R_f$*** = 0.80 (30% EtOAc-Hexane); **νmax/$cm^{-1}$ (NaCl plate)** 738 ($CH_2$ rock), 909 ($R_2C$=$CH_2$), 1463 ($CH_2$), 1514 (Ar ring), 1689 (C=O stretch), 2932 and 2978 ($CH_2$ stretching); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.26 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 1.46 [9H, d, *J*=3.7Hz, OC(C*H*$_3$)$_3$], 3.45 (2H, d, *J*=5.6Hz, ArC*H*$_2$CH=$CH_2$), 3.67 (2H, broad s, NC*H*$_2$CH=$CH_2$), 3.82 (3H, s, $OCH_3$), 4.38 (2H, broad s, Ar$CH_2$N), 4.51 [1H, sept, *J*=6.2Hz, OC*H*($CH_3$)$_2$], 4.90-5.11 (4H, m, ArC$H_2$CH=C*H*$_2$ and NC$H_2$CH=C*H*$_2$), 5.72 (1H, s, NC$H_2$C*H*=$CH_2$), 5.87 (1H, ddt, *J*=5.7, 10.7 and 15.9Hz, ArC$H_2$C*H*=$CH_2$), 6.75 (1H, d, *J*=8.5Hz, 5-H), 6.83 (1H, d, *J*=8.5Hz, 6-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 28.3 [OCH(*C*$H_3$)$_2$], 30.3 [OC(*C*$H_3$)$_3$], 46.6 (Ar*C*$H_2$CH=$CH_2$), 48.2 (N*C*$H_2$CH=$CH_2$), 55.5 ($OCH_3$), 74.4 [O*C*H($CH_3$)$_2$], 80.0 [O*C*($CH_3$)$_3$], 109.9 (5-C), 114.8 (NC$H_2$CH=*C*$H_2$[a]), 116.4 (Ar$CH_2$CH=*C*$H_2$[a]), 122.8 (6-C), 124.6 (1-C[b]), 128.9 (2-C[b]), 133.7 (NC$H_2$*C*H=$CH_2$), 136.2 (Ar$CH_2$*C*H=$CH_2$), 145.1 (3-C), 151.8 (4-C), 155.6 (C=O); **MS *m/z***

375 ($M^+$, 15%) 41 (40), 57 (73), 70 (72), 115 (15), 117 (15), 143 (38), 144 (18), 145 (15), 160 (20), 162 (28), 175 (32), 176 (100), 177 (36), 236 (25), 278 (32), 319 (21), 375 (15), ***HRMS*** calculated for $C_{22}H_{33}NO_4$: 375.24096, found: 375.2450.

*2.8 Preparation of N-allyl-N-(2-allyl-3-isopropoxy-4-methoxybenzyl)phenyl-methanesulfonamide **213***

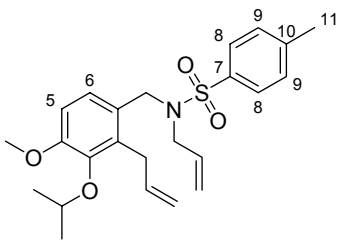


**213**

The *N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-2-propen-1-amine **210** (2.82mmol, 0.779g) was dissolved in $CH_2Cl_2$ (8$cm^3$) and stirred for 5 min under an Ar atmosphere. To this was added $NEt_3$ (2.5eq, 7.05mmol, 1.00$cm^3$) and the reaction mixture was stirred at rt for a further 15 min before the dropwise addition of the α-toluenesulfonyl chloride (1.1eq, 3.10mmol, 0.593g) which had been dissolved in $CH_2Cl_2$ (4$cm^3$). The reaction mixture was stirred for 3 h at rt and then the solvent was removed *in vacuo*. The residue was purified by column chromatography (5% EtOAc-Hexane) to yield the product as a yellow oil (0.710g, 62%).

***R_f*** = 0.35 (30% EtOAc-Hexane); **$\nu_{max}$/$cm^{-1}$ (NaCl plate)** 671 and 750 (5 adj Ar H), 1152 ($SO_2$), 1216 (CO-$CH_3$), 1273 and 1337 ($SO_2$-N), 1487 (Ar ring), 1594 (Ar ring), 2838 ($OCH_3$), 2978 (N-$CH_2$), 3022 (C=$CH_2$ stretch); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.23 [6H, d, *J*=6.2Hz, $OCH(CH_3)_2$], 3.41 (2H, d, *J*=5.7Hz, $ArCH_2$[a]), 3.64 (2H, d, *J*=6.6Hz, $NHCH_2CH$[a]), 3.80 (3H, s, $OCH_3$), 4.07 (2H, s, $ArCH_2NH$), 4.25 (2H, s, $SO_2CH_2$), 4.48 [1H, sept, *J*=6.2Hz, $OCH(CH_3)_2$], 4.80 (1H, dd, *J*=1.7 and 17.2Hz, $ArCH_2CH=CH_2$[b]), 4.93 (1H, dd, *J*=1.6 and 10.2Hz, $ArCH_2CH=CH_2$[b]), 5.02 and 5.08 (2H, two d, *J*=5.7Hz, $NHCH_2CH=CH_2$), 5.62 (1H, tdd, *J*=6.7, 10.1 and 16.8Hz, $NHCH_2CH=CH_2$), 5.80 (1H, ddt, *J*=5.7 and 10.9Hz, $ArCH_2CH=CH_2$), 6.76 (1H, d, *J*=8.5Hz, 5-H), 7.04 (1H, d, *J*=8.5Hz, 6-H), 7.35-7.40 (5H, m, $SO_2$BnH); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.4 [$OCH(CH_3)_2$], 30.0 ($ArCH_2$), 48.1 ($ArCH_2NH$), 50.0 ($NHCH_2CH$), 55.5 ($OCH_3$), 58.9 ($SO_2CH_2$), 74.4 [$OCH(CH_3)_2$], 110.0 (5-C), 115.0 ($NHCH_2CH=CH_2$), 119.0 ($ArCH_2CH=CH_2$), 123.8 (6-C), 127.1 (11-C), 128.6 (10-C), 129.0 (1-C), 130.7 (9-C), 132.2 ($NHCH_2CH=CH_2$[c]), 132.8 ($SO_2CH_2PhC$[c]), 136.3 ($ArCH_2CH=CH_2$), 144.9 (3-C), 152.2 (4-C); **MS *m/z*** 429 ($M^+$, 28%) 41 (10), 91 (80), 144 (10), 160 (11), 161 (12), 176 (100), 232 (32), 274 (11), 429 (28), ***HRMS*** calculated for $C_{24}H_{31}NO_4S$: 429.19738, found: 429.19707.

*2.9 Preparation of N-allyl-N-(2-allyl-3-isopropoxy-4-methoxybenzyl)-4-methylbenzenesulfonamide **139***

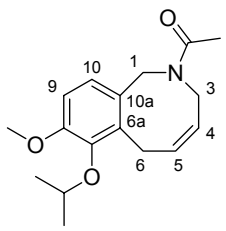



**139**

To a stirred solution of *N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-2-propen-1-amine **210** (1.45 mmol, 0.409g) in $CH_2Cl_2$ (20cm$^3$) was added $NEt_3$ (1.4eq, 2.03mmol, 0.300 cm$^3$) and previously recrystallised tosyl chloride (1.2eq, 1.74mmol, 0.333g) at 0$^o$C under a $N_2$ atmosphere. The reaction mixture was allowed to stir at 0$^o$C for 3.5 h and then at rt for 40 min. Afterwards the reaction mixture was diluted with water (20cm$^3$) and then $CH_2Cl_2$ (20cm$^3$) was added. The combined organics were washed with water (2×20cm$^3$) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by column chromatography (20% EtOAc-Hexane). The product was obtained as a pale yellow oil that solidified on standing (0.666g, 94%), with spectroscopic data that correlated well to that reported by Pathak[129].

***R**$_f$* = 0.70 (30% EtOAc-Hexane); ***m.p.*** 46-52$^o$C; **$\delta_H$ (300 MHz, $CDCl_3$)** 1.25 [6H, d, *J*=6.1Hz, OCH(C*H*$_3$)$_2$], 2.44 (3H, s, $CH_3$), 3.50 (2H, d, *J*=5.5Hz, Ar$CH_2$), 3.70 (2H, d, *J*=6.3Hz, NHC*H*$_2$CH), 3.82 (3H, s, $OCH_3$), 4.25 (2H, s, ArC*H*$_2$N), 4.49 [1H, sept, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 4.82-4.98 (4H, m, Ar$CH_2$CH=C*H*$_2$ and NH$CH_2$CH=C*H*$_2$), 5.43 (1H, tdd, *J*=6.4, 10.2 and 12.7Hz, NH$CH_2$C*H*=$CH_2$), 5.87 (1H, ddt, *J*=5.6 and 10.7Hz, Ar$CH_2$C*H*=$CH_2$), 6.73 (1H, d, *J*=8.5Hz, 5-H), 6.98 (1H, d, *J*=8.5Hz, 6-H), 7.32 (2H, d, *J*=8.1Hz, 9-H), 7.73 (2H, d, *J*=8.2Hz, 8-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.5 ($CH_3$), 22.5 [OCH(*C*H$_3$)$_2$], 30.1 (Ar*C*H$_2$CH=$CH_2$), 48.3 (Ar$CH_2$N), 49.7 (NH*C*H$_2$CH=$CH_2$), 55.5 ($OCH_3$), 74.5 [O*C*H($CH_3$)$_2$], 109.9 (5-C), 115.0 (NHCH$_2$CH=*C*H$_2$), 118.6 (Ar$CH_2$CH=*C*H$_2$), 124.3 (6-C), 126.7 (1-C), 127.4 (8-C), 129.7 (9-C), 132.6 and 132.8 (NH$CH_2$*C*H=$CH_2$ and 2-C), 136.5 and 137.0 (7-C and Ar$CH_2$*C*H=$CH_2$), 143.2 (10-C), 145.1 (3-C), 152.3 (4-C).

*2.10 Preparation of 1-[7-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocin-2(1H)-yl]-1-ethanone **214***

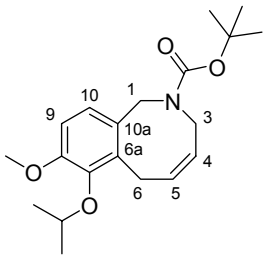



**214**

A solution was prepared from *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-acetamide **211** (0.288mmol, 0.0914g) and distilled toluene (10cm$^3$), which was degassed using $N_2$ for 20 min. Then the solution was heated to 60$^o$C before the addition of Grubbs II catalyst **11** (0.05eq, 0.0144mmol, 0.0133g). The reaction mixture was stirred at 60$^o$C under an Ar atmosphere for 1 h. After this time the solvent was removed *in vacuo* to yield a dark brown oil that was purified by column chromatography (5-10% EtOAc-Hexane). The product was obtained as a clear oil (0.0682g, 82%), showing evidence of rotamers due to the amide functionality.

***R**$_f$* = 0.05 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 672 (alkene), 734 (alkane), 1216 (C-O), 1378 and 1427 (alkane), 1522 (Ar H), 1631 (tertiary amide), 2248 (-N-CO), 2837 and 2898 ($OCH_3$), 2982 ($CH_2$ stretch), 3022 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.27 [6H, d, *J*=6.2Hz, $OCH(CH_3)_2$], 2.00 and 2.09 (3H, two s, $CH_3$), 3.49 and 3.53 (2H, two d, *J*=7.5Hz, 6-H), 3.82 (3H, d, *J*=4.5Hz, $OCH_3$), 3.85 (1H, d, *J*=5.9Hz, 3-H$^a$), 4.17 (1H, d, *J*=4.7Hz, 3-H$^a$), 4.48 [1H, sept, *J*=6.2Hz, $OCH(CH_3)_2$], 4.64 (2H, d, *J*=27.4Hz, 1-H), 5.71-6.01 (2H, m, 4-H and 5-H), 6.71 and 6.82 (1H, two dd, *J*=1.6 and 8.3Hz, 9-H), 6.82 and 7.00 (1H, two d, *J*=8.3Hz, 10-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.0 and 22.4 ($CH_3$), 22.5 and 22.6 [$OCH(CH_3)_2$], 24.7 and 25.3 (6-C), 44.1 and 45.4 (3-C), 50.9 and 52.8 (1-C), 55.5 and 55.6 ($OCH_3$), 74.4 and 74.8 [$OCH(CH_3)_2$], 109.5 and 109.7 (9-C), 123.7 and 125.5 (10-C), 126.9 and 127.6 (5-C), 128.6 and 128.2 (10a-C), 129.3 (4-C$^a$), 132.2 and 132.6 (6a-C), 133.1 (4-C$^a$), 144.2 and 145.0 (7-C), 152.6 and 152.7 (8-C), 170.4 and 170.9 (C=O); **MS *m/z*** 289 ($M^+$, 100%) 43 (64), 73 (46), 115 (41), 143 (97), 157 (58), 164 (41), 173 (74), 176 (68), 177 (45), 188 (96), 189 (50), 204 (50), 289 (100), ***HRMS*** calculated for $C_{17}H_{23}NO_3$; 289.16779, found: 289.16371.

*2.11 Preparation of tert-butyl 7-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocine-2(1H)-carboxylate **215***

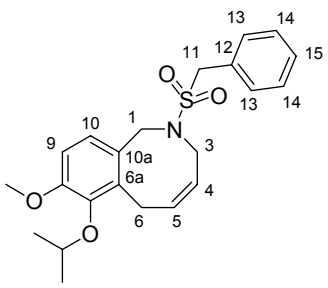



**215**

A solution was prepared of *tert*-butyl allyl(2-allyl-3-isopropoxy-4-methoxybenzyl) carbamate **212** (1.07mmol, 0.402g) and toluene (40cm$^3$). This was degassed using $N_2$ for 15 min and the solution was then heated to 60$^o$C, before the addition of Grubbs II catalyst **11** (0.05eq, 0.0533mmol, 0.0508g). The reaction mixture was allowed to stir at 60$^o$C under an Ar atmosphere for 1 h. After this time the solvent was removed *in vacuo* to yield a black oil that was then purified by column chromatography (5% EtOAc-Hexane). The desired product was obtained as a clear oil (0.366g, 99%). NMR spectroscopy shows the product as a mixture of amide rotamers.

***R**$_f$* = 0.63 (20% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 653 (alkene), 1376 (C(CH$_3$)$_3$), 1464 (alkane), 1514 (Ar H), 1682 (tertiary amide), 2254 (-NCO), 2931 (CH$_2$ stretch), 2976 (-CO-CH$_3$), 3085 (Ar H); **$\delta_H$ (300 MHz, CDCl$_3$)** 1.27 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 1.34 and 1.42 [9H, two s, OC(CH$_3$)$_3$], 3.51-3.56 (2H, m, 6-H), 3.81-3.84 (4H, m, OCH$_3$ and one of 3-H), 4.00 (1H, d, *J*=4.4 Hz, one of 3-H), 4.47-4.54 [3H, m, OC*H*(CH$_3$)$_2$ and 1-H], 5.81-83 (2H, m, 4-H and 5-H), 6.69 (1H, t, *J*=7.3Hz, 9-H), 6.83-6.97 (1H, m, 10-H); **$\delta_C$ (50 MHz, CDCl$_3$)** 22.5 and 22.6 [OCH(*C*H$_3$)$_2$], 25.2 and 25.3 (6-C), 28.4 [OC(*C*H$_3$)$_3$], 44.5 and 44.9 (3-C), 51.7 (1-C), 55.6 (OCH$_3$), 74.5 and 74.6 [O*C*H(CH$_3$)$_2$], 79.4 and 79.5 [O*C*(CH$_3$)$_3$], 109.2 and 109.6 (9-C), 124.5 and 125.2 (10-C), 128.1 and 128.4 (5-C), 129.4 (10a-C), 130.3 and 130.6 (4-C), 132.9 and 133.2 (6a-C), 144.4 (7-C), 152.2 and 152.4 (8-C), 155.5 (C=O); **MS *m/z*** 347 (M$^+$, 44%) 41 (27), 57 (100), 137 (30), 143 (50), 175 (37), 187 (27), 188 (67), 204 (22), 249 (20), 290 (66), 291 (51), 347 (44), ***HRMS*** calculated for $C_{20}H_{29}NO_4$; 347.20966, found: 347.20551.

*2.12 Preparation of 2-(benzylsulfonyl)-7-isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine **216***

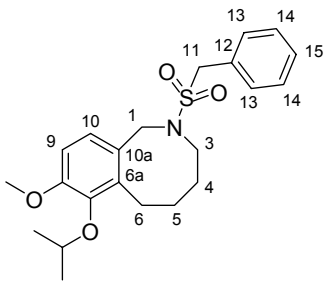



**216**

The *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxy-benzyl)phenylmethanesulfonamide **213** (0.466 mmol, 0.205g) was dissolved in toluene (20cm$^3$) and the solution was degassed using $N_2$ for 15 min. The solution was then heated to 60$^o$C before the addition of Grubbs II catalyst **11** (0.05eq, 0.0233mmol, 0.0194g). The reaction mixture was stirred at 60$^o$C under an Ar atmosphere for 1 h. After this time the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo*. The crude compound was purified by column chromatography (10% EtOAc-Hexane) to yield white crystals (0.157g, 84%).

***R**$_f$* = 0.49 (30% EtOAc-Hexane); ***m.p.*** 119-122$^o$C; **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 670 and 767 (5 adj Ar H), 1141 (-N-$SO_2$), 1333 (-N-$SO_2$), 1372 (alkane), 1463 (alkane), 1647 and 1691 (C=C isolated), 2977 (-CO-$CH_3$), 3023 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.28 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 3.63 (2H, d, *J*=7.3Hz, Ar$CH_2$C$^a$), 3.83-3.86 (7H, m, OC*H*$_3$, Ar$CH_2$N$^a$, N$CH_2$C$^a$), 4.48-4.56 [3H, m, OC*H*(C$H_3$)$_2$, $SO_2CH_2$Ar], 5.60 (1H, td, *J*=7.1 and 10.5Hz, 4-H), 6.06 (1H, td, *J*=7.3 and 10.3Hz, 5-H), 6.75 (1H, d, *J*=8.3Hz, 9-H), 6.98 (1h, d, *J*=8.3Hz, 10-H), 7.23-7.26 (2H, m, 14-H), 7.30-7.32 (3H, m, 13-H, 15-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.6 [OCH(*C*H$_3$)$_2$], 26.8 (6-C), 44.8 (3-C), 52.8 ($SO_2CH_2$Ar), 55.6 (OC$H_3$), 59.4 (1-C), 74.6 [O*C*H(CH$_3$)$_2$], 109.8 (10-C), 125.6 (4-C), 126.0 (9-C), 127.7 (6a-C), 128.3 (14-C), 128.5 (14-C), 129.1 (10a-C), 130.7 (13-C, 15-C), 134.4 (12-C), 135.4 (5-C), 144.5 (7-C), 152.8 (8-C); **MS *m/z*** 401 (M$^+$, 47%) 91 (88), 128 (13), 137 (13), 143 (17), 175 (20), 176 (13), 179 (11), 188 (16), 204 (100), 205 (13), 246 (15), 252 (16), 253 (15), 265 (19), 284 (70), 285 (14), 401 (47), 402 (13), ***HRMS*** calculated for $C_{22}H_{27}NO_4S$; 401.16608, found: 401.16655.

*2.13 Preparation of 2-(benzylsulfonyl)-7-isopropoxy-8-methoxy-1,2,3,4,5,6-hexahydro-2-benzazocine **217***

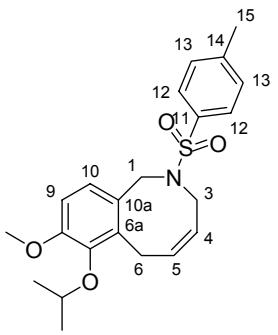



**217**

The 2-(benzylsulfonyl)-7-isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine **216** (0.275 mmol, 0.109g) was dissolved in absolute ethanol (10cm$^3$) by sonnication. To the emulsion was added 10% Pd/C (0.15g/mmol, 0.0430g) and this mixture was subjected to hydrogenation in an autoclave at 5 atm $H_2$ for 18 h. The reaction mixture was then filtered through celite and rinsed with $CH_2Cl_2$ (3×50cm$^3$). The solvent was then removed *in vacuo* to yield a cream-white solid. This was then recrystallised by dissolving the compound in the minimum amount of EtOAc and then adding Hexane dropwise to the solution until it became cloudy. The solution was then left to stand overnight and the recrystallised material was collected by filtering off the solvent. The pure product was obtained as colourless crystals (0.108g, 98%).

***R*$_f$** = 0.54 (30% EtOAc-Hexane); ***m.p.*** 141-147$^o$C; **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (5 adj Ar H), 736 (alkane-$CH_2$ rock), 774 (5 adj Ar H), 850 (2 adj Ar H), 1149 (-N-$SO_2$), 1332 (-N-$SO_2$), 1425 (alkane), 2977 (-CO-$CH_3$); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.25 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 1.51-1.52 (2H, m, 4-H), 1.66-1.68 (2H, m, 5-H), 2.87-2.91 (2H, m, 6-H), 3.09-3.12 (2H, m, 3-H), 3.82 (3H, s, $OCH_3$), 4.18 (2H, s, 1-H), 4.22 (2H, s, $SO_2CH_2Ar$), 4.53 [1H, sept, *J*=6.2Hz, OC*H*(CH$_3$)$_2$], 6.73 (1H, d, *J*=8.4Hz, 9-H), 6.94 (1H, d, *J*=8.4Hz, 10-H), 7.35-7.37 (5H, m, 13-H, 14-H and 15-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.6 [OCH(*C*H$_3$)$_2$], 24.0 (5-C$^a$), 27.9 (6-C$^a$), 29.3 (4-C$^a$), 46.9 (3-C), 49.7 (11-C), 55.5 ($OCH_3$), 58.7 (1-C), 74.3 [O*C*H(CH$_3$)$_2$], 110.0 (9-C), 125.6 (10-C), 128.1 (6a-C), 128.5 (15-C), 128.7 (13-C), 129.5 (10a-C), 130.7 (14-C), 135.4 (12-C), 144.3 (7-C), 152.6 (8-C); **MS *m/z*** 403 (M$^+$, 36%) 28 (19), 30 (13), 65 (10), 91 (100), 92 (10), 120 (17), 160 (12), 176 (21), 177 (22), 178 (17), 190 (13), 205 (20), 206 (71), 253 (19), 361 (28), ***HRMS*** calculated for $C_{22}H_{29}NO_4S$; 403.18173, found: 403.18176.

*2.14 Preparation of 7-isopropoxy-8-methoxy-2-[(4-methylphenyl)sulfonyl]-1,2,3,6-tetrahydro-2-benzazocine **140***

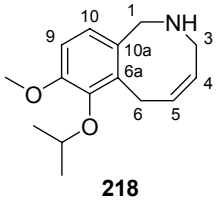



**140**

The *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-4-methylbenzenesulfonamide **139** (0.364mmol, 0.156g) was dissolved in toluene (15cm$^3$) and the solution was degassed using $N_2$ for 20 min. Then the solution was heated to 60$^o$C and Grubbs II catalyst **11** (0.05eq, 0.0182mmol, 0.0161g) was added. The reaction mixture was left to stir at 60$^o$C under an Ar atmosphere for 1 h and then the solvent was removed *in vacuo* to yield a black-green oil. This was then purified by column chromatography (5-10% EtOAc-Hexane) and the product was obtained as a pale yellow oil (0.139g, 95%). NMR spectroscopic data was found to correspond to that reported by Pathak[129].

***R**$_f$* = 0.59 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.23 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 2.40 (3H, s, $CH_3$), 3.54 (2H, d, *J*=6.7Hz, 6-H), 3.75 (2H, d, *J*=6.7Hz, 3-H), 3.82 (3H, s, $OCH_3$), 4.41 [1H, sept, *J*=6.2Hz, OC*H*(CH$_3$)$_2$], 4.47 (2H, s, 1-H), 5.45 (1H, td, *J*=6.7 and 11.1Hz, 4-H), 5.79 (1H, td, *J*=6.7 and 11.2Hz, 5-H), 6.71 (1H, d, *J*=8.4Hz, 9-H), 6.89 (1H, d, *J*=8.4Hz, 10-H), 7.23 (2H, d, *J*=8.1Hz, 13-H), 7.62 (2H, d, *J*=8.3Hz, 12-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.5 (15-C), 22.5 [OCH(*C*H$_3$)$_2$], 26.5 (6-C), 43.3 (3-C), 50.8 (1-C), 55.6 ($OCH_3$), 74.8 [O*C*H(CH$_3$)$_2$], 110.0 (9-C), 124.5 (10-C$^a$), 125.4 (5-C$^a$), 127.3 (12-C), 127.7 (10a-C), 129.4 (13-C), 133.2 (4-C$^b$), 133.4 (6a-C$^b$), 136.9 (11-C), 143.0 (14-C), 144.3 (7-C), 152.9 (8-C).

*2.15 Preparation of 7-isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine **218***



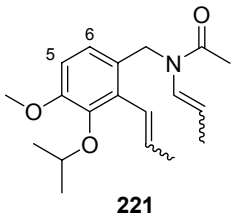

**218**

The *tert*-butyl 7-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocine-2(1*H*)-carboxylate **215** (0.300mmol, 0.104g) was dissolved in $CH_2Cl_2$ (2cm$^3$) and to this solution was added triflouroacetic acid (1.5eq, 0.450mmol, 0.0350cm$^3$). The reaction mixture was allowed to stir at rt under an Ar atmosphere for 1 h, after which time the solution had gone dark brown. To the reaction mixture was added distilled water (2cm$^3$) and the solution was diluted with EtOAc (2cm$^3$). It was then neutralised using a saturated solution of $NaHCO_3$ and 10 % aqueous acetic acid. The organic layer was kept aside and the aqueous layer was extracted with EtOAc

($3\times10cm^3$). The combined organics were then dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to yield a dark orange semi-solid (0.0731g, 99%) which was essentially pure by $^1H$ NMR spectroscopy and no further purification was required.

***R*$_f$** = 0.05 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (RHC=CHR), 1440 ($CH_2$ deformations), 1520 (NH), 1603 (Ar ring), 1674 (isolated C=C), 2976 (-$CH_2$ stretch), 3020 (Ar H), 3618 (NH); **$\delta_H$ (400 MHz, $CDCl_3$)** 1.17 [6H, d, *J*=6.1Hz, OCH(C$H_3$)$_2$], 3.17 (2H, d, *J*=7.8Hz, 6-H), 3.66 (2H, s, 3-H), 3.76 (3H, s, $OCH_3$), 4.21 (2H, s, 1-H), 4.34 [1H, sept, *J*=6.2Hz, OC*H*($CH_3$)$_2$], 5.50 (1H, dd, *J*=8.0 and 18.9Hz, 4-H), 6.13 (1H, td, *J*=4.1 and 8.7Hz, 5-H), 6.76 (1H, d, *J*=8.4Hz, 9-H), 7.00 (1H, d, *J*=8.4Hz, 10-H), 8.84 (1H, s, NH); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.5 [OCH(*C*$H_3$)$_2$], 29.1 (6-C), 36.8 (3-C), 45.3 (1-C), 55.6 ($OCH_3$), 75.2 [O*C*H($CH_3$)$_2$], 111.2 (9-C), 117.7 (10-C), 121.6 (5-C), 127.0 (10a-C), 133.4 (4-C), 140.1 (6a-C), 144.6 (7-C), 154.2 (8-C); **MS *m/z*** 247 ($M^+$, 68%) 51 (23), 77 (19), 91 (15), 115 (31), 137 (24), 143 (39), 144 (18), 145 (19), 161 (28), 162 (25), 173 (26), 174 (23), 175 (35), 176 (60), 177 (20), 179 (21), 187 (18), 188 (43), 189 (15), 190 (32), 204 (100), 205 (21), 247 (68), ***HRMS*** calculated for $C_{15}H_{21}NO_2$; 247.15723, found: 247.15654.

### *2.16 Preparation of N-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]-N-(1-propenyl)-acetamide **221***



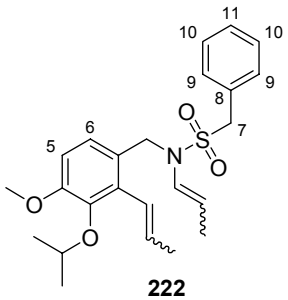

**221**

The *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)acetamide **211** (0.956mmol, 0.303g) was dissolved up in toluene ($30cm^3$) and the solution was degassed for 15 min using $N_2$. Then Ru-isomerisation catalyst **12** (0.05eq, 0.0478mmol, 0.0450g) was added and the reaction mixture was heated to 105$^o$C under an Ar atmosphere for 18.5 h. The progress of the reaction was monitored by $^1H$ NMR spectroscopy and the reaction mixture was allowed to cool to rt. The solvent was removed *in vacuo* to yield a dark brown-black oil which was purified by column chromatography (5-15% EtOAc-Hexane) to yield the desired product as a yellow oil (0.285g, 94%).

***R*$_f$** = 0.42 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 773 (C-H), 930 (RCH=CHR), 1216 (C-O), 1481 (Ar ring), 1645 (tertiary amide/ C=C conj with C=O), 2977 ($CH_3$), 3019 (C=$CH_2$ str); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.22-1.24 [6H, m, OCH(C$H_3$)$_2$], 1.59 (1.9H, d, *J*=6.6Hz, $CH_3^a$),

1.65 (1.2H, d, *J*=6.6Hz, $CH_3$[a]), 1.91-1.95 (2.6H, m, $CH_3$[b]), 2.04-2.07 (2.2H, m and s, $CH_3$[b] and $COCH_3$[c]), 2.30 (1.6H, s, $COCH_3$[c]), 3.80 (3H, d, *J*=6.3Hz, $OCH_3$), 4.33-4.35 [1H, m, $OCH(CH_3)_2$], 4.65 and 4.81 (2H, two s, $ArCH_2N$), 4.74-4.76 (1H, m, NCH=C*H*$CH_3$), 5.94-5.97 (1H, m, ArCH=C*H*$CH_3$), 6.41-6.47 (1.5H, m, 5-H and NC*H*=$CHCH_3$[d]), 6.64-6.73 (2H, m, 6-H and ArC*H*=$CHCH_3$), 7.31-7.36 (1H, m, NC*H*=$CHCH_3$[d]); **$\delta_C$ (50 MHz, $CDCl_3$)** 15.3 and 15.5 (NCH=CH*C*$H_3$), 19.0 and 19.1 (ArCH=CH*C*$H_3$), 22.1 and 22.2 ($COCH_3$), 22.4 and 22.5 [$OCH(CH_3)_2$], 44.8 ($ArCH_2N$), 55.6 ($OCH_3$), 75.0 and 75.1 [$OCH(CH_3)_2$], 106.9 (NCH=*C*$HCH_3$), 109.0 (5-C), 119.9 (6-C), 120.8 (2-C), 124.3 and 124.7 (ArCH=*C*$HCH_3$), 126.3 and 126.9 (1-C), 128.0 (Ar*C*H=$CHCH_3$), 132.2 and 132.5 (N*C*H=$CHCH_3$), 144.7 and 145.0 (3-C), 151.6 and 152.0 (4-C), 169.1 and 169.4 (C=O); **MS *m/z*** 317 ($M^+$, 29%) 43 (10), 115 (8), 117 (22), 145 (29), 162 (14), 175 (18), 176 (12), 177 (100), 178 (15), 219 (14), 261 (19), 317 (29), ***HRMS*** calculated for $C_{19}H_{27}NO_3$; 317.19909, found: 317.19862.

### *2.17 Preparation of N-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl](phenyl)-N-(1-propenyl)methanesulfonamide **222***



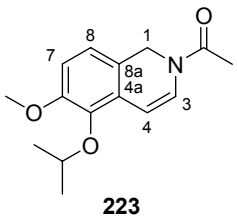

**222**

The *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxy-benzyl)phenyl-methanesulfonamide **213** (0.707mmol, 0.304g) was dissolved in distilled toluene (30$cm^3$) and the solution was degassed using $N_2$ for 15 min. Then the Ru-isomerisation catalyst **12** (0.05eq, 0.0354mmol, 0.0326g) was added and the reaction mixture was allowed to stir at 90-100$^o$C under an Ar atmosphere for 18.5 h. A crude $^1$H NMR spectrum showed that isomerisation of the double bonds had occurred and so the solvent was removed *in vacuo* to yield a dark brown-black oil. This was then purified by column chromatography (5-10% EtOAc-Hexane) to yield the product as a pale yellow oil (0.265g, 87%).

***$R_f$*** = 0.73 (30% EtOAc-Hexane); **$\nu_{max}$/$cm^{-1}$ (NaCl plate)** 669 (5 adj Ar H), 772 (C-H), 1047 (C-O), 1216 (-CO-$CH_3$), 1354 ($SO_2$-N), 1426 and 1521 (Ar ring), 2400 ($OCH_3$), 2977 (N-$CH_2$), 3020 (C=CH str); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.19 [6H, d, *J*=6.1Hz, $OCH(CH_3)_2$], 1.52 (4H, dd, *J*=1.3 and 6.6Hz, $CH_3$), 1.85 (3H, dd, *J*=1.5 and 6.5Hz, $CH_3$), 3.77 (3H, d, *J*=4.4Hz, $OCH_3$), 4.07 (2H, s, $ArCH_2N$), 4.42-4.44 [5H, m, $OCH(CH_3)_2$, $SO_2CH_2Ar$ and NCH=C*H*$CH_3$], 5.45 (1H, dq, *J*=6.5 and 15.9Hz, NC*H*=$CHCH_3$[a]), 6.33 (2H, ddd, *J*=1.3, 15.1

and 17.6Hz, ArCH=C*H*$CH_3$[a] and ArC*H*=$CHCH_3$), 6.74 (1H, dd, *J*=8.6 and 17.3Hz, 5-H, mixture of isomers), 7.01 (1H, dd, *J*=8.9 and 11.5Hz, 6-H, mixture of isomers), 7.39-7.40 (5H, m, 9-H, 10-H, 11-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 15.2 (NCH=CH*C*$H_3$), 19.0 (ArCH=CH*C*$H_3$), 22.4 [OCH(*C*$H_3$)$_2$], 48.5 (Ar*C*$H_2$N), 55.5 ($OCH_3$), 58.5 ($SO_2$*C*$H_2$Ar), 75.0 [O*C*H($CH_3$)$_2$], 106.9 (NCH=*C*$HCH_3$), 110.6 (5-C), 121.6 (6-C), 124.1 (2-C), 124.6 (ArCH=*C*$HCH_3$), 126.0 (11-C), 128.7 (1-C), 128.8 (10-C), 129.6 (Ar*C*H=$CHCH_3$), 131.0 (9-C), 131.8 (8-C), 131.9 (N*C*H=$CHCH_3$), 144.3 (3-C), 151.7 (4-C); **MS *m/z*** 429 ($M^+$, 1%) 41 (5), 91 (49), 115 (7), 117 (18), 131 (5), 145 (20), 161 (8), 175 (10), 176 (8), 177 (100), 178 (12), 216 (13), 219 (38), 220 (6), 233 (5), 274 (17), 373 (30), 374 (7), ***HRMS*** calculated for $C_{24}H_{31}NO_4S$; 429.19738, found: 429.19830.

### *2.18 Preparation of 2-acetyl-5-isopropoxy-6-methoxy-1,2-dihydroisoquinoline **223***



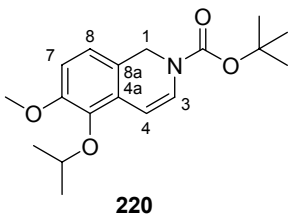

**223**

The *N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]-*N*-(1-propenyl)acetamide **221** (0.321mmol, 0.102g) was dissolved in pre-distilled toluene (8$cm^3$) and degassed using $N_2$ for 15 min. After this time the solution was heated to 110°C before the addition of Grubbs II catalyst **11** (0.05eq, 0.0161mmol, 0.0139g). The reaction mixture was then left to stir at 110°C under an Ar atmosphere for 3 h. The reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo* to yield a brown-black oil. This was then purified by column chromatography (5-30% EtOAc-Hexane) to yield the desired product as a clear oil (0.0655g, 78%). NMR spectroscopy highlighted the presence of amide rotamers.

***$R_f$*** = 0.32 (30% EtOAc-Hexane); **$\nu_{max}$/$cm^{-1}$ (NaCl plate)** 669 (RHC=CHR *cis*), 879 (2 adj Ar C-H), 1216 (-C-O), 1386 (-$COCH_3$), 1440 and 1462 ($CH_2$ deformations), 1625 (C=C conj with C=O or Ar ring), 1661 (tertiary amide), 2839 (N-$CH_2$-), 2938 ($CH_2$ str), 3018 (C=CH); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.29 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 2.21 and 2.25 (3H, two s, $CH_3$, major and minor respectively), 3.81 (3H, s, $OCH_3$), 4.23 [1H, sept, *J*=6.2Hz, OC*H*($CH_3$)$_2$], 4.73 and 4.84 (2H, two s, Ar$CH_2$N, minor and major respectively), 6.17 and 6.20 (1H, d, *J*=8.0Hz, 4-H, major and minor respectively), 6.72 and 6.77 (2H, two d, *J*=8.2Hz, 7-H and 8-H), 7.26 and 7.27 (1H, two d, *J*=10.1Hz, 3-H, minor and major respectively); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.3 ($CH_3$), 22.1 and 22.5 [OCH(*C*$H_3$)$_2$], 43.8 (Ar$CH_2$N), 55.8 ($OCH_3$), 75.4 and

75.5 [O*C*H(CH$_3$)$_2$], 105.3 and 105.6 (4-C), 110.4 and 110.9 (7-C), 120.3 and 120.8 (8-C), 122.7 (4a-C), 125.0 (8a-C), 125.4 and 125.8 (3-C), 141.6 and 142.6 (5-C), 152.2 and 152.6 (6-C), 168.4 (C=O); **MS *m/z*** 261 ($M^+$, 52%) 43 (11), 131 (23), 145 (14), 146 (8), 160 (19), 161 (15), 175 (42), 176 (100), 177 (29), 217 (8), 218 (18), 219 (28), 226 (8), 261 (52), 262 (10), 265 (22), 269 (9), ***HRMS*** calculated for $C_{15}H_{19}NO_3$; 261.13649, found: 261.13696.

*2.19 Preparation of tert-butyl 5-isopropoxy-6-methoxy-2(1H)-isoquinolinecarboxylate **220***

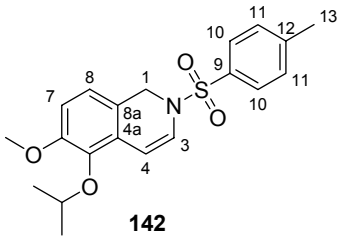



**220**

A solution was prepared from *tert*-butyl allyl(2-allyl-3-isopropoxy-4-methoxybenzyl) carbamate **212** (0.411mmol, 0.154g) and pre-distilled toluene (13cm$^3$). The solution was degassed using $N_2$ for 15 min and then the solution was heated to 110$^o$C under an Ar atmosphere. Then the Ru-isomerisation catalyst **12** (0.01eq, 0.00411mmol, 0.0042g) was added and the reaction mixture was allowed to stir for 2 h. After this time Grubbs II catalyst **11** (0.05eq, 0.021mmol, 0.018g) was added and the reaction mixture was stirred at 110$^o$C under an Ar atmosphere for 2 h. The reaction mixture was cooled to rt and the solvent was removed *in vacuo* to yield a brown-black oil. This was then purified by column chromatography (5% EtOAc-Hexane) to yield the product as a clear oil (0.0134g, 10%).

***R$_f$*** = 0.61 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (RHC=CHR), 850 (2 adj. Ar H), 1216 (C-O), 1370 (alkane), 1440 (alkane), 1479 (Ar ring), 1601 (Ar ring), 1666 (C=C aryl conj), 1693 (tertiary amide), 2839 (-OCH$_3$), 2937 (C-H), 2978 (CH$_2$), 3019 (Ar H); **$\delta_H$ (300 MHz, CDCl$_3$)** 1.24-1.42 [15H, m, OC(C*H*$_3$)$_3$ and OCH(C*H*)$_{32}$], 3.80-3.83 (3H, m, OCH$_3$), 4.47-4.77 [3H, m, OC*H*(CH$_3$)$_2$ and ArCH$_2$N], 5.83-5.91 (1H, m, 4-H), 6.69-6.97 (2H, m, 7-H and 8-H), 7.24-7.28 (1H, m, 3-H). Insufficient material remained after FITR for $^{13}$C and HRMS analysis.

## *2.20 Preparation of 5-isopropoxy-6-methoxy-2-[(4-methylphenyl)sulfonyl]-1,2-dihydroisoquinoline **142***

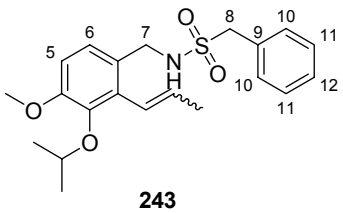



**142**

The *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxy-benzyl)-4-methyl benzenesulfonamide **139** (0.249 mmol, 0.107g) was dissolved up in distilled toluene (10cm$^3$) and the solution was degassed for 15 min using $N_2$. To this solution was added the Ru-isomerisation catalyst **12** (0.005eq, 0.00125mmol, 0.0031g). The reaction mixture was heated to 110-120$^o$C for 2 h. After this time $^1$H NMR spectroscopy showed no isomerisation of the double bonds. A further 5 mol % of the Ru-isomerisation catalyst **12** (0.05eq, 0.0125mmol, 0.0137g) was added and the reaction mixture was stirred at 115$^o$C under a $N_2$ atmosphere for 2 h. The $^1$H NMR spectrum showed isomerisation of both of the double bonds. The reaction mixture was then allowed to cool to rt and the solvent was removed *in vacuo* to yield a dark brown-black oil. The crude isomerised diene was then dissolved in distilled toluene (10cm$^3$) and the solution was heated to 110$^o$C under an Ar atmosphere. Then Grubbs II catalyst **11** (0.05eq, 0.0125mmol, 0.0119g) was added and the reaction mixture was left to stir for 2 h. After this time $^1$H NMR spectroscopy showed no ring closing metathesis had occurred so a further 5 mol % Grubbs II catalyst **11** (0.05eq, 0.0125mmol, 0.0124g) was added. The reaction mixture was then left to stir at 110$^o$C under an Ar atmosphere for 21 h. After this time the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo*. The compound was then purified by column chromatography (5-20% EtOAc-Hexane). The desired product was obtained as a cream oil **142** (0.0115g, 21%) along with de-allylated starting material **200** as a yellow solid (0.0258g, 27%). NMR spectroscopic data compared well with that observed by Pathak[129].

***R**$_f$* = 0.57 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, CDCl$_3$)** 1.21-1.26 [6H, m, OCH(C*H*$_3$)$_2$], 2.38 (3H, s, TsCH$_3$), 3.78 (3H, s, OCH$_3$), 4.35 [1H, sept, *J*=6.3Hz, OC*H*(CH$_3$)$_2$], 4.48 (2H, s, ArCH$_2$N), 6.21 (1H, d, *J*=7.9Hz, 7-H), 6.64-6.66 (2H, m, 3-H and 4-H), 6.74 (1H, d, *J*=7.9Hz, 8-H), 7.24-7.27 (2H, m, 11-H), 7.68 (2H, d, *J*=8.3Hz, 10-H); **$\delta_C$ (50 MHz, CDCl$_3$)** 21.5 (TsCH$_3$), 22.5 [OCH(*C*H$_3$)$_2$], 46.9 (ArCH$_2$N), 55.8 (OCH$_3$), 75.3 [O*C*H(CH$_3$)$_2$], 106.3 (4-C), 110.7 (7-C), 120.5 (8-C), 120.8 (4a-C), 125.4 (8a-C$^a$), 126.2 (3-C), 126.9 (9-C$^a$), 127.2 (10-C), 128.8 (12-C$^a$), 129.7 (11-C), 143.9 (5-C), 152.5 (6-C).

*2.21 Preparation of N-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl](phenyl)-methanesulfonamide **243***

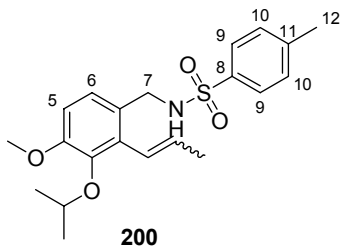


**243**

The *N*-Allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl) phenylmethanesulfonamide **213** (0.344 mmol, 0.148g) was transferred to the flask using a minimum volume of $Et_2O$ and the reaction mixture was heated to 80°C under a $N_2$ atmosphere to remove the solvent. The Ru-isomerisation catalyst **12** (0.05eq, 0.0172mmol, 0.0164g) was then added and the reaction mixture was further heated to 135-140°C and allowed to stir for 19 h under $N_2$. The dark brown oil was left to cool to rt and the crude product was purified by column chromatography (5-15% EtOAc-Hexane). The solvent was removed *in vacuo* to yield the product as cream coloured crystals (0.0754g, 56%).

***R*$_f$** = 0.55 (30% EtOAc-Hexane); ***m.p.*** 127-130°C; **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (CH rock), 775 (CH out of plane deformations), 1153 (-$SO_2$-N-), 1331 ($SO_2$), 1380 ($C(CH_3)_2$), 1438 (conj Ar ring), 1481 (NH bend), 1573 (conj Ar ring), 2977 ($CH_2$ or $CH_3$ stretch), 3020 (NH stretch or C=CH); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.22 [6H, d, *J*=6.2Hz, $OCH(CH_3)_2$], 1.49 (0.6H, dd, *J*=1.6 and 6.9Hz, $C=CHCH_3^a$), 1.60 (1H, s, NH, confirmed by $D_2O$ wash), 1.88 (2.3H, dd, *J*=1.6 and 6.5Hz, $C=CHCH_3^a$), 3.83 (3H, s, $OCH_3$), 4.09-4.20 (4H, m, $ArCH_2N$ and $SO_2CH_2Ar$), 4.32-4.35 [1H, m, $OCH(CH_3)_2$], 6.02-6.04 (1H, m, $ArCH=CHCH_3$), 6.29-6.34 (1H, m, $ArCH=CHCH_3$), 6.76 (1H, d, *J*=8.4Hz, 5-H), 7.00 (1H, d, *J*=8.5Hz, 6-H), 7.33-7.35 (5H, m, 10-H, 11-H, 12-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 15.2 and 19.2 ($CH_3$), 22.5 [$OCH(CH_3)_2$], 45.5 and 45.7 (7-C), 55.7 ($OCH_3$), 59.4 (8-C), 75.2 [$OCH(CH_3)_2$], 110.3 and 110.6 (5-C), 124.4 ($ArCH=CHCH_3$), 124.7 (6-C), 127.2 (2-C), 128.7 (11-C), 129.2 (1-C), 130.2 (9-C), 130.6 (10-C), 132.9 ($ArCH=CHCH_3$), 145.3 (3-C), 153.1 (4-C); **MS *m/z*** 389 ($M^+$, 11%), 40 (12), 41 (18), 43 (19), 54 (14), 56 (15), 69 (38), 91 (55), 130 (13), 175 (16), 176 (19), 192 (100), 193 (12), 219 (45), 220 (25), 234 (38), ***HRMS*** calculated for $C_{21}H_{27}NO_4S$: 389.16608, found: 389.16542.

*2.22 Preparation of N-{3-isopropoxy-4-methoxy-2-[(1E)-1-propenyl]benzyl}-4-methylbenzenesulfonamide **200***



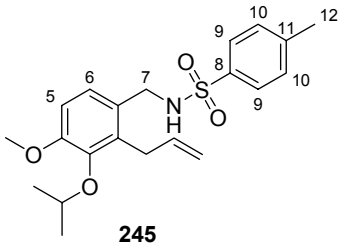

**200**

The *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxy-benzyl)-4-methyl benzenesulfonamide **139** (0.249 mmol, 0.107g) was dissolved up in distilled toluene (10cm$^3$) and the solution was degassed for 15 min using $N_2$. To this solution was added the Ru-isomerisation catalyst **12** (0.005eq, 0.00125mmol, 0.0031g) and the reaction mixture was heated to 110-120$^o$C for 2 h. After this time $^1$H NMR spectroscopy showed no isomerisation of the double bonds. A further 5 mol % of the Ru-isomerisation catalyst **12** (0.05eq, 0.0125mmol, 0.0137g) was added and the reaction mixture was stirred at 115$^o$C under a $N_2$ atmosphere for 2 h. The $^1$H NMR spectrum showed isomerisation of both of the double bonds. The reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo* to yield a dark brown-black oil. The crude isomerised diene was then dissolved in distilled toluene (10cm$^3$) and the solution was heated to 110$^o$C under an Ar atmosphere. Then Grubbs II catalyst **11** (0.05eq, 0.0125mmol, 0.0119g) was added and the reaction mixture was left to stir for 2 h. After this time $^1$H NMR spectroscopy showed no ring closing metathesis had occurred so a further 5 mol % Grubbs II **11** (0.05eq, 0.0125mmol, 0.0124g) was added. The reaction mixture was then left to stir at 110$^o$C under an Ar atmosphere for 21 h. After this time the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo*. The compound was then purified by column chromatography (5-20% EtOAc-Hexane). The ring-closed product was obtained as a cream oil **142** (0.0115g, 21%) along with de-allylated starting material **200** as a yellow solid (0.0258g, 27%).

***R*$_f$** = 0.45 (30% EtOAc-Hexane); ***m.p.*** 129-135$^o$C; **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 814 (2 adj Ar H), 917 (RHC=CHR *trans*), 1160 (-$SO_2$-N-), 1330 (-$SO_2$-N-), 1383 (alkane), 1440 (alkane), 1465 (CH deformations), 1580 (NH), 1636 (C=C aryl conj), 2839 (-$OCH_3$), 2977 (-$CH_2$ or –$CH_3$ stretching), 3019 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.19 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 1.77 (3H, dd, *J*=1.5 and 6.5Hz, CH=CHC*H*$_3$), 2.43 (3H, s, Ts$CH_3$), 3.78 (3H, s, $OCH_3$), 4.07 (2H, d, *J*=5.8Hz, Ar$CH_2$N), 4.28 [1H, sept, *J*=6.1Hz, OC*H*(C$H_3$)$_2$], 4.48 (1H, t, *J*=5.7Hz, NH, peak not present in CH correlated spectrum), 5.96 (1H, qd, *J*=6.5 and 16.0Hz, CH=C*H*$CH_3$), 6.21 (1H, dd, *J*=1.5 and 16.1Hz, ArC*H*=CH$CH_3$), 6.65 (1H, d, *J*=8.4Hz, 5-H), 6.83 (1H, d,

*J*=8.4Hz, 6-H), 7.29 (2H, d, *J*=8.1Hz, 10-H), 7.73 (2H, d, *J*=8.2Hz, 9-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 19.1 (CH=CH*C*$H_3$), 21.5 (12-C), 22.5 [OCH(*C*$H_3$)$_2$], 45.5 (Ar$CH_2$N), 55.7 ($OCH_3$), 75.2 [O*C*H($CH_3$)$_2$], 110.3 (5-C), 124.2 (Ar*C*H=CH$CH_3$), 124.9 (6-C), 126.2 (2-C), 127.2 (9-C), 129.6 (10-C), 132.6 (ArCH=*C*H$CH_3$), 132.9 (1-C), 136.8 (8-C), 143.3 (11-C), 145.1 (3-C), 153.0 (4-C); **MS *m/z*** 389 ($M^+$, 8%), 43 (15), 65 (5), 69 (28), 91 (15), 131 (14), 160 (5), 161 (13), 163 (5), 175 (23), 176 (25), 177 (9), 190 (9), 191 (7), 192 (100), 193 (13), 219 (33), 234 (62), 235 (10), 264 (7), 389 (8), ***HRMS*** calculated for $C_{21}H_{27}NO_4S$: 389.16608, found: 389.16367.

## *2.23 Preparation of N-(2-allyl-3-isopropoxy-4-methoxybenzyl)-4-methylbenzene-sulfonamide **245***



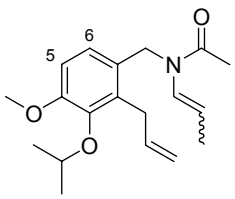

**245**

The *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxy-benzyl)-4-methylbenzenesulfon-amide **139** (0.705mmol, 0.303g) was dissolved in toluene (30$cm^3$) and the solution was degassed using $N_2$ for 15 min. After this time the Ru-isomerisation catalyst **12** (0.05eq, 0.0353mmol, 0.0356g) was added and the reaction mixture was heated to 105$^o$C. The reaction mixture was allowed to stir under an Ar atmosphere for 18 h and the solvent was removed *in vacuo* to yield a dark brown-black oil. The crude mixture was purified by column chromatography (5% EtOAc-Hexane) to yield the desired product as a pale yellow oil that solidified on standing (0.139g, 51%) as well as some of the unreacted diene **139** (0.0625g, 21% recovery).

***$R_f$*** = 0.51 (30% EtOAc-Hexane); ***m.p.*** 83-85$^o$C; **$\nu_{max}$/$cm^{-1}$ (NaCl plate)** 706 (alkane), 814 (2 adj Ar H), 1160 (-$SO_2$-N-), 1328 (-$SO_2$-N-), 1383 (alkane), 1439 (alkane), 1465 (CH deformations), 1488 and 1580 (-NH), 1637 (C=C aryl conj), 2839 (-$OCH_3$), 2938 (-$CH_3$), 2977 (Ar H), 3019 (C=$CH_2$); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.21 [6H, two d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 2.44 (3H, s, Ts$CH_3$), 3.38 (2H, d, *J*=5.7Hz, ArC*H*$_2$C), 3.81 (3H, s, $OCH_3$), 4.01 (2H, d, *J*=5.9Hz, Ar$CH_2$N), 4.49-4.54 [2H, m, OC*H*($CH_3$)$_2$ and NH], 4.74 (1H, dd, *J*=1.6 and 17.2Hz, CH=C*H*$_2$ *trans*), 4.93 (1H, dd, *J*=1.5 and 10.2Hz, CH=C*H*$_2$ *cis*), 5.81-5.83 (1H, m, C*H*=$CH_2$), 6.68 (1H, d, *J*=8.5Hz, 5-H), 6.86 (1H, d, *J*=8.5Hz, 6-H), 7.31 (2H, d, *J*=8.0Hz, 10-H), 7.74 (2H, d, *J*=8.2Hz, 9-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.5 (12-C), 22.6 [OCH(*C*$H_3$)$_2$], 30.5

(Ar*C*$H_2$C), 55.5 ($OCH_3$), 74.6 [O*C*H($CH_3$)$_2$], 110.1 (5-C), 115.2 (CH=*C*$H_2$), 124.2 (2-C), 124.7 (6-C), 127.2 (9-C), 129.6 (10-C), 132.6 (1-C), 136.7 (8-C), 137.1 (*C*H=$CH_2$), 143.4 (11-C), 145.2 (3-C), 152.7 (4-C); **MS *m/z*** 389 ($M^+$, 37%), 65 (6), 91 (23), 115 (9), 117 (5), 143 (10), 144 (13), 145 (8), 155 (10), 161 (23), 162 (8), 163 (9), 164 (10), 175 (20), 176 (100), 177 (19), 184 (10), 190 (13), 191 (18), 192 (75), 193 (10), 234 (27), 389 (37), 390 (10), ***HRMS*** calculated for $C_{21}H_{27}NO_4S$: 389.16608, found: 389.16714.

## *2.24 Preparation of N-(2-allyl-3-isopropoxy-4-methoxybenzyl)-N-(1-propenyl) acetamide **227***



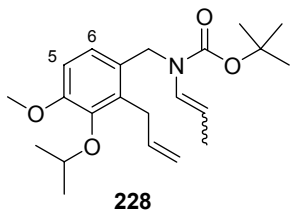

**227**

The reaction was set up in the Carousel Reactor and the reaction tube was evacuated and placed under Ar three times before beginning. The *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)acetamide **211** (0.648mmol, 0.206g) was dissolved in toluene (20$cm^3$) and the solution was degassed for 5 min using $N_2$. The solution was then heated to 80$^o$C before the addition of the Ru-isomerisation catalyst **12** (0.01eq, 0.00648mmol, 0.0064g). The reaction mixture was allowed to stir at 80$^o$C under an Ar atmosphere for a further 20 h. After this time the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo* to yield a yellow-brown oil that was purified by column chromatography (5-15% EtOAc-Hexane). The desired product was obtained as a pale yellow oil (0.159g, 77%).

***R*$_f$** = 0.49 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 774 (alkane), 929 and 1047 (RCH=$CH_2$), 1216 (C-O), 1486 (alkane), 1522 (Ar ring), 1645 (tertiary amide), ~3000 weak (-CO-$CH_3$), 3019 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.26 [6H, m, OCH(C*H*$_3$)$_2$], 1.61-1.66 (3H, m, CH=CHC*H*$_3$), 2.04 and 2.30 (3H, two s, $COCH_3$), 3.50-3.52 (2H, m, Ar$CH_2$C), 3.80 (3H, d, *J*=7.6Hz, $OCH_3$), 4.51-5.08 [5H, m, OC*H*($CH_3$)$_2$, Ar$CH_2$N and CH=C*H*$_2$ (*cis* and *trans*)], 5.90-5.92 (1H, m, N-CH=C*H*), 6.53-6.73 (3H, m, C*H*=$CH_2$, 5-H and 6-H), 7.35 (1H, d, *J*=14.5Hz, NC*H*=CH); **$\delta_C$ (50 MHz, $CDCl_3$)** 15.3 and 15.5 (CH=CHC*H*$_3$), 22.2 ($COCH_3$), 22.6 [OCH(*C*H$_3$)$_2$], 30.2 and 30.4 (Ar*C*$H_2$C), 44.8 and 48.2 (Ar$CH_2$N), 55.5 ($OCH_3$), 74.5 and 75.0 [O*C*H($CH_3$)$_2$], 106.9 and 109.0 (CH=*C*$H_2$ *cis*), 110.3 and 110.5 (5-C), 115.2 (CH=*C*$H_2$ *trans*), 119.5 and 120.1 (6-C), 126.2 (N*C*H=CH), 126.9 and 127.6 (), 128.0 (1-C), 128.4 (*C*H=$CH_2$), 130.2 and 130.9 (2-C), 135.7 and 136.0 (NCH=*C*HCH$_3$), 145.2 (3-C), 151.4 and

151.8 (4-C), 169.0 and 169.6 (C=O); **MS *m/z*** 317 ($M^+$, 20%) 43 (13), 91 (9), 115 (16), 117 (31), 144 (8), 145 (33), 161 (15), 175 (13), 176 (46), 177 (100), 178 (4), 214 (10), 218 (8), 219 (10), 265 (9), 275 (12), 317 (20), ***HRMS*** calculated for $C_{19}H_{27}NO_3$: 317.19909, found: 317.19916.

## *2.25 Preparation of tert-butyl 2-allyl-3-isopropoxy-4-methoxybenzyl(1-pro-penyl)-carbamate **228***



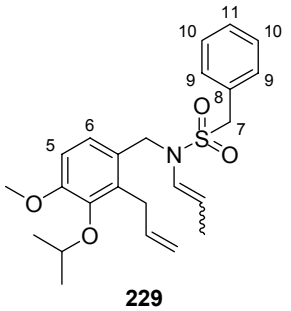

**228**

The reaction was set up in the Carousel Reactor and the reaction tube was evacuated and placed under Ar three times before beginning. The *tert*-butyl allyl(2-allyl-3-isopropoxy-4-methoxybenzyl)carbamate **212** (0.537mmol, 0.202g) was dissolved in toluene (20$cm^3$) and the solution was degassed using $N_2$ for 5 min. The solution was then heated to 80$^oC$ before the addition of the Ru-isomerisation catalyst **12** (0.01eq, 0.00537mmol, 0.0054g). Then the reaction mixture was allowed to stir at 80$^oC$ under an Ar atmosphere for 20 h. After this time the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo* to yield a yellow-brown oil. The crude oil was then purified by column chromatography (5% EtOAc-Hexane) and the product was obtained as a pale yellow oil (0.161g, 80%).

***R_f*** = 0.77 (30% EtOAc-Hexane); **$\nu_{max}$/$cm^{-1}$ (NaCl plate)** 774 (alkane), 929 ($RCH=CH_2$), 1216 (C-O), 1376 and 1403 [$-C(CH_3)_3$], 1482 (alkane), 1665 (tertiary amide), 1693 (-C=C-N-), 2978 ($-CH_3$), 3020 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.25 [6H, dd, *J*=6.3 and 8.7Hz, $OCH(CH_3)_2$], 1.40-1.61 [12H, m, $OC(CH_3)_3$ and $CH_3$], 3.50 (2H, d, *J*=5.6Hz, $ArCH_2C$), 3.80 (3H, s, $OCH_3$), 4.34-4.59 [3H, m, $ArCH_2N$, $OCH(CH_3)_2$ and $CH=CHCH_3$], 4.93 (1H, d, *J*=17.1Hz, $CH=CH_2$), 5.03 (1H, dd, *J*=1.5 and 10.1Hz, $CH=CH_2$), 5.89 (1H, dq, *J*=5.7 and 10.6Hz, $CH=CH_2$), 6.63 (1H, d, *J*=8.4Hz, NCH=C), 6.73 (1H, d, *J*=8.4Hz, 6-H), 6.97 (1H, d, *J*=8.4Hz, 5-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 15.3 ($CH_3$), 22.5 [$OC(CH_3)_3$], 28.2 [$OCH(CH_3)_2$], 30.3 ($ArCH_2C$), 45.4 ($ArCH_2N$), 55.5 ($OCH_3$), 74.5 [$OCH(CH_3)_2$], 75.0 [$OC(CH_3)_3$], 104.2 ($CH=CHCH_3$), 110.1 or 110.5 (5-C), 115.2 ($CH=CH_2$), 119.6 (6-C), 124.7 (NCH=C), 128.0 (2-C), 132.1 (1-C), 135.9 ($CH=CH_2$), 145.0 (3-C), 151.3 (4-C[a]), 151.5 (C=O[a]); **MS *m/z*** 375 ($M^+$, 2%) 41 (10), 57 (43), 117 (13), 145 (17), 175 (8), 176 (27), 177 (100), 178 (14), 219

(34), 234 (9), 235 (9), 263 (19), 319 (12), 333 (21), ***HRMS*** calculated for $C_{22}H_{33}NO_4$: 375.24096, found: 375.24162.

*2.26 Preparation of N-(2-allyl-3-isopropoxy-4-methoxybenzyl)(phenyl)-N-(1-propenyl)-methanesulfonamide **229***

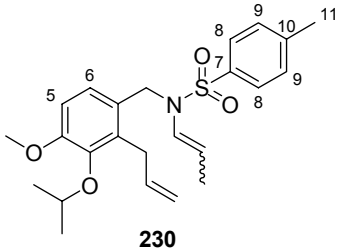



**229**

The reaction was set up in the Carousel Reactor, with the reaction tube evacuated and placed under Ar three times before beginning. Then the *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)phenylmethanesulfonamide **213** (0.488mmol, 0.210g) was dissolved in toluene (20cm$^3$) and the solution was degassed using $N_2$ for 5 min. The solution was then heated to 80$^o$C before the addition of the Ru-isomerisation catalyst **12** (0.01eq, 0.00488mmol, 0.0048g). The reaction mixture was then stirred at 80$^o$C under an Ar atmosphere for 20 h, after which time the solvent was removed *in vacuo* to yield a pale brown oil. The crude mixture was then purified by column chromatography (5% EtOAc-Hexane) to yield the desired product as a pale yellow oil (0.188g, 90%).

***R**$_f$* = 0.71 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (5 adj Ar H), 756 (5 adj Ar H), 929 (RCH=$CH_2$), 1154 (-N-$SO_2$), 1355 (-N-$SO_2$), 1663 (C=C-N-), 2978 (CO-$CH_3$), 3021 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.21 [6H, dd, *J*=6.2 and 9.9Hz, OCH(C*H*$_3$)$_2$], 1.53 (3H, dt, *J*=1.3 and 6.7Hz, $CH_3$), 3.28 (2H, d, *J*=5.8Hz, Ar$CH_2$C), 3.76 and 3.77 (3H, two s, $OCH_3$), 4.07 (2H, br s, Ar$CH_2$N), 4.37-4.46 [4H, m, Ar$CH_2SO_2$, OC*H*(C$H_3$)$_2$ and NCH=C*H*], 4.74 (1H, dd, *J*=1.6 and 17.2Hz, CH=C$H_2$ *cis*)and 4.94 (1H, dd, *J*=1.5 and 10.2Hz, CH=C$H_2$ *trans*), 5.45-5.73 (1H, m, NC*H*=CH), 6.30-6.44 (1H, m, Ar$CH_2$C*H*=CH), 6.72 (1H, d, *J*=8.6Hz, 5-H), 6.96 (1H, two d, *J*=8.6Hz, 6-H), 7.38-7.39 (5H, m, Ph-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 15.2 ($CH_3$), 22.5 [OCH(*C*H$_3$)$_2$], 30.1 (Ar*C*H$_2$C), 48.0 (Ar$CH_2$N), 55.5 ($OCH_3$), 58.5 (Ar$CH_2SO_2$), 74.5 [O*C*H(CH$_3$)$_2$], 107.0 (N-CH=*C*H), 110.2 (5-C), 115.2 (CH=*C*H$_2$), 121.0 (6-C), 124.6 and 126.8 (Ar$CH_2$*C*H=C), 128.4 (11-C), 128.8 (2-C), 128.9 (10-C), 130.3 (1-C), 131.9 (9-C), 135.8 (N*C*H=CH), 144.7 (3-C), 151.6 (4-C); **MS *m/z*** 429 (M$^+$, 1%) 91 (35), 115 (5), 117 (14), 145 (16), 161 (5), 175 (6), 176 (12), 177 (100), 178 (13), 216 (4), 219 (29), 220 (4), 232 (5), 274 (15), 344 (4), 373 (10), 387 (15), 388 (4), ***HRMS*** calculated for $C_{24}H_{31}NO_4S$: 429.19738, found: 429.19812.

*2.27 Preparation of N-(2-allyl-3-isopropoxy-4-methoxybenzyl)-4-methyl-N-(1-propenyl)-benzenesulfonamide **230***

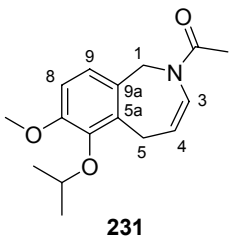



**230**

The reaction was set up in the Carousel Reactor with the reaction tube evacuated and placed under Ar three times before beginning. The *N*-allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-4-methylbenzenesulfonamide **139** (0.482mmol, 0.207g) was then dissolved in toluene (20cm$^3$) and the solution was degassed using $N_2$ for 5 min. The solution was heated to 80$^o$C before the addition of the Ru-isomerisation catalyst **12** (0.01eq, 0.00482mmol, 0.0048g), and it was then allowed to stir under an Ar atmosphere for 20 h. The reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo* to yield a yellow oil. The mixture was purified by column chromatography (5-10% EtOAc-Hexane) to give recovered starting material (0.120g, 58% recovery) and the desired product as a pale yellow oil (0.0532g, 26%).

***R**$_f$* = 0.46 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 815 (2 adj Ar H), 916 and 993 (RCH=$CH_2$), 1159 and 1342 (-N-$SO_2$), 1580 (Ar ring), 1638 (isolated C=C), 2839 (-$OCH_3$), 2871 (-$CH_3$), 2977 (-CO-$CH_3$), 3013 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.22-1.26 [9H, m, OCH(C*H*$_3$)$_2$ and $CH_3$], 2.44 (3H, d, *J*=3.1Hz, Ts$CH_3$), 3.38 (2H, dd, *J*=1.6 and 4.2Hz, Ar$CH_2$C), 3.79 (3H, d, *J*=3.2Hz, $OCH_3$), 4.01 (2H, d, *J*=5.9Hz, Ar$CH_2$N), 4.47-4.50 [2H, m, OC*H*(C$H_3$)$_2$ and NCH=C*H*C$H_3$], 4.74 (1H, dd, *J*=1.7 and 17.2Hz, CH=C$H_2$ *trans*), 4.93 (1H, dd, *J*=1.6 and 10.2Hz, CH=C$H_2$ *cis*), 5.82-6.21 (1H, m, NC*H*=CH), 6.69 (1H, d, *J*=8.4Hz, 5-H), 6.86 (1H, d, *J*=8.4Hz, 6-H), 7.31 (2H, d, *J*=8.1Hz, 9-H), 7.75 (2H, d, *J*=8.2Hz, 8-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.5 ($CH_3$), 22.6 [OCH(*C*H$_3$)$_2$], 30.5 (Ar*C*H$_2$C), 45.0 (Ar$CH_2$N), 55.5 ($OCH_3$), 74.6 [O*C*H(C$H_3$)$_2$], 110.1 (5-C), 115.2 (CH=*C*H$_2$), 124.7 (6-C), 127.2 (8-C), 127.3 (2-C), 129.6 (9-C), 132.6 (1-C), 136.7 (7-C), 137.1 (N-*C*H=CH), 143.4 (10-C), 145.2 (3-C), 152.7 (4-C), no peak observed for NCH=*C*HCH$_3$ in the $^{13}$C NMR spectrum; **MS *m/z*** 429 (M$^+$, 0.6%) 91 (24), 115 (11), 143 (12), 144 (18), 145 (9), 155 (10), 161 (26), 162 (9), 163 (8), 175 (18), 176 (100), 177 (22), 184 (9), 190 (12), 191 (17), 192 (50), 234 (10), 389 (38), 390 (9), ***HRMS*** calculated for $C_{24}H_{31}NO_4S$: 429.19738, found: 429.19760.

*2.28 Preparation of 2-acetyl-6-isopropoxy-7-methoxy-2,5-dihydro-1H-2-benzaze-pine* ***231***

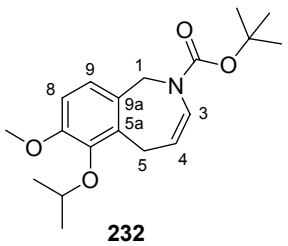



**231**

The *N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-*N*-(1-propenyl)aceta-mide **227** (0.0189mmol, 0.0600g) was dissolved up in toluene (6cm$^3$) and the solution was heated to 80$^o$C before the addition of the Grubbs II catalyst **11** (0.1eq, 0.0189mmol, 0.0164g). Then the reaction mixture was allowed to stir at 80$^o$C under an Ar atmosphere for 25 h, after which time thin layer chromatography showed no further change and so the solvent was removed *in vacuo* to yield a dark brown-black oil. This was then purified by column chromatography (5-10% EtOAc-Hexane) to yield the desired product as an orange resin (0.0061g, 12%).

***R**$_f$* = 0.24 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (RHC=CHR *cis*), 849 (2 adj. Ar H), 1216 (C-O), 1373 ($CH_3$ symmetrical deformation), 2839 (-$OCH_3$), 2896 (-$CH_2$ or -$CH_3$ stretch), 3020 (Ar H); **$\delta_H$ (300 MHz, CDCl$_3$)** 1.28-1.30 [6H, m, OCH(C*H*$_3$)$_2$], 1.54 (3H, s, Ar$CH_2$C), 2.44 (3H, s, $CH_3$), 3.85 (3H, s, $OCH_3$), 4.49 [1H, sept, *J*=6.1Hz, OC*H*($CH_3$)$_2$], 5.30 (3H, s, Ar$CH_2$N), 6.36 (1H, d, *J*=12.5Hz, 4-H), 6.93 (1H, d, *J*=8.3Hz, 8-H), 7.16 (1H, d, *J*=8.2Hz, 9-H), 7.57 (1H, d, *J*=12.5Hz, 3-H); **$\delta_C$ (50 MHz, CDCl$_3$)** 22.6 [OCH(*C*$H_3$)$_2$], 26.9 ($CH_3$), 29.7 (Ar*C*$H_2$C), 44.9 (Ar$CH_2$N), 55.9 ($OCH_3$), 76.4 [O*C*H($CH_3$)$_2$], 113.7 (4-C), 123.6 (8-C), 126.1 (9-C), 135.7 (3-C), 168.2 (C=O), no quarternary carbons were observed on the $^{13}$C NMR spectrum; **MS *m/z*** 275 (M$^+$, 11%), 41 (10), 43 (28), 143 (12), 160 (16), 161 (20), 162 (15), 163 (26), 174 (11), 175 (44), 176 (45), 177 (38), 190 (18), 204 (100), 205 (70), 206 (11), 232 (10), 247 (25), 275 (11), 289 (40), ***HRMS*** calculated for $C_{16}H_{21}NO_3$: 275.15214, found: 275.15020.

*2.29 Preparation of tert-butyl 6-isopropoxy-7-methoxy-1,5-dihydro-2H-2-benza-zepine-2-carboxylate* ***232***



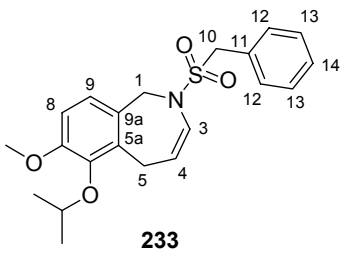

**232**

*tert*-Butyl 2-allyl-3-isopropoxy-4-methoxybenzyl(1-propenyl)-carbamate **228** (0.553mmol, 0.208g) was dissolved in toluene (20cm$^3$) and the solution was heated to 60$^o$C before the addition of Grubbs II catalyst **11** (0.05eq, 0.0277mmol, 0.0272g). Then the reaction mixture was allowed to stir at 60$^o$C under an Ar

atmosphere for 24 h. After this time the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo*. The dark brown oil was then purified by column chromatography (5% EtOAc-Hexane) and the desired product was obtained as a pale yellow oil (0.151g, 82%).

***R_f*** = 0.71 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 743 ($CH_2$ rocking), 851 (2 adj Ar H), 1216 (C-O), 1370 ($CH_3$ symmetrical deformation), 1455 (alkane), 1482 (Ar ring), 1575 (Ar ring), 1600 (ar ring), 1694 (C-O tertiary amide), 1665 (C=C isolated), 2733 (N-$CH_2$), 2839 (-$OCH_3$), 2937 (-$CH_2$ or –$CH_3$ stretches), 3019 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.23-1.25 [6H, m, OCH(C*H*$_3$)$_2$], 1.40-1.57 [9H, m, OC($CH_3$)$_3$], 1.92 (2H, d, *J*=5.9Hz, Ar$CH_2$C), 3.80 (3H, s, $OCH_3$), 4.34-4.85 [5H, m, OC*H*($CH_3$)$_2$, Ar$CH_2$C and Ar$CH_2$N], 5.87-5.93 (1H, broad m, 4-H), 6.43 (1H, d, *J*=16.1Hz, 8-H), 6.72-6.75 (2H, m, 9-H and 3-H), peak broadening occurred in the spectrum due to the presence of the amide rotamers; **$\delta_C$ (50 MHz, $CDCl_3$)** 22.5 [OCH(*C*H$_3$)$_2$], 28.3 [OC(*C*H$_3$)$_3$], 45.8 (Ar*C*H$_2$C), 55.7 ($OCH_3$), 60.4 (Ar$CH_2$N), 75.0 [O*C*H(CH$_3$)$_2$], 80.8 [O*C*(CH$_3$)$_3$], 104.2 (4-C), 110.5 (8-C), 120.3 (9-C), 124.7 (3-C), 131.9 (5a-C[a]), 132.1 (9a-C[a]), 151.5 (C=O), two of the quarternary carbons were not observed in the $^{13}$C NMR spectrum; **MS *m/z*** 333 ($M^+$, 1%) 57 (93), 69 (14), 117 (13), 145 (20), 156 (14), 175 (29), 176 (25), 177 (100), 178 (18), 180 (11), 193 (11), 205 (10), 219 (49), 221 (16), 263 (60), 319 (25), ***HRMS*** calculated for $C_{19}H_{27}NO_4$: 333.19401, found: 333.19534.

*2.30 Preparation of 2-(benzylsulfonyl)-6-isopropoxy-7-methoxy-2,5-dihydro-1H-2-benzazepine **233***

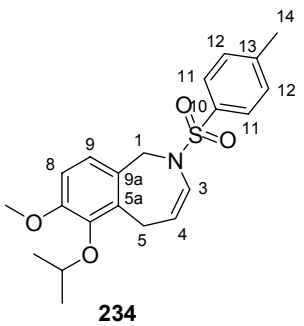



**233**

The *N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-(phenyl)-*N*-(1-propenyl)methanesulfonamide **229** (0.169mmol, 0.0726g) was dissolved in toluene (7cm$^3$) and the solution was heated to 60$^o$C before the addition of the Grubbs II catalyst **11** (0.05eq, 0.00846mmol, 0.0083g). The reaction mixture was allowed to stir at 60$^o$C under an Ar atmosphere for 18.5 h, after this time thin layer chromatography showed no further change so the solvent was removed *in vacuo*. Then the dark brown oil was purified by column chromatography (5-10% EtOAc-Hexane) to yield a white solid (0.0380g, 58%).

***R*$_f$** = 0.43 (30% EtOAc-Hexane); ***m.p.*** 124-127°C; **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 626 (RHC=CHR *cis*), 850 (2 adj Ar H), 1335 (-$SO_2$-N-), 1477 (Ar ring), 1601 (Ar ring), 2897 (-$OCH_3$), 2929 (-$CH_2$ or -$CH_3$ stretches), 3020 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.24 [6H, dd, *J*=6.3 and 8.9Hz, OCH(C$H_3$)$_2$], 1.87 (1.5H, d, *J*=6.4Hz, Ar$CH_2$C$^a$), 3.46 (0.9H, d, *J*=5.5Hz, Ar$CH_2$C$^a$), 3.82 (3H, s, $OCH_3$), 4.09-4.18 (4.5H, m, Ar$CH_2$N), 4.30-4.40 (1.7H, m, Ar$CH_2SO_2$$^b$), 4.52 [0.5H, sept, *J*=6.3Hz, OC*H*(C$H_3$)$_2$], 4.82-4.96 (1H, m, Ar$CH_2SO_2$$^b$), 5.79-6.01 (1H, m, 4-H), 6.32 (0.5H, d, *J*=16.1Hz, 3-H), 6.76 (1H, dd, *J*=2.5 and 8.3Hz, 8-H), 7.00 (1H, dd, *J*=2.7 and 8.4Hz, 9-H), 7.23-7.34 (5H, m, 12-H, 13-H and 14-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 19.2 (Ar*C*$H_2$C$^c$), 22.5 and 22.6 [OCH(*C*$H_3$)$_2$], 30.6 (Ar*C*$H_2$C$^c$), 45.1 and 45.6 (Ar$CH_2$N), 55.6 and 55.7 ($OCH_3$), 59.2 and 59.3 (Ar$CH_2SO_2$), 74.6 and 75.2 [O*C*H(C$H_3$)$_2$], 110.2 and 110.3 (8-C), 115.3 (NCH=*C*H), 124.4 (9-C$^a$), 124.6 (14-C$^a$), 128.6 and 128.7 (13-C), 129.3 (5a-C), 130.6 (12-C), 132.4 (11-C), 132.8 and 132.9 (9a-C), 137.1 (N*C*H=CH), 145.3 (6-C), 152.7 and 153.1 (7-C). Insufficient material remained for us to perform HRMS after NMR and FTIR spectroscopy.

### *2.31 Preparation of 6-isopropoxy-7-methoxy-2-[(4-methylphenyl)sulfonyl]-2,5-dihydro-1H-2-benzazepine **234***



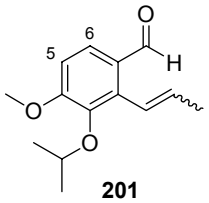

**234**

The *N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-4-methyl-*N*-(1-propenyl)benzenesulfonamide **230** (0.0294mmol, 0.0126g) was dissolved in toluene (10cm$^3$) and the solution was heated to 60°C. Then the Grubbs II catalyst **11** (0.5eq, 0.0149mmol, 0.0170g) was added and the reaction mixture was allowed to stir under an Ar atmosphere for 25 h. After this time no further change was observed by thin layer chromatography and the solvent was removed *in vacuo* to yield a dark brown oil. The crude mixture was purified by column chromatography (5% EtOAc-Hexane) to give the desired product as a pale yellow resin (0.0053g, 47%).

***R*$_f$** = 0.45 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (RHC=CHR, *cis*), 784 (2 adj Ar H), 1160(-$SO_2$-N-), 1334 (-$SO_2$-N-), 1599 (Ar ring), 2977 (-$CH_2$ or –$CH_3$ stretches), 3020 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.19 [6H, d, *J*=6.2Hz, OCH(C$H_3$)$_2$], 1.77 (2H, dd, *J*=1.4 and 6.5Hz, Ar$CH_2$C), 2.43 (3H, s, $CH_3$), 3.79 (3H, s, $OCH_3$), 4.07-4.09 (2H, m, Ar$CH_2$N), 4.27

[1H, sept, *J*=6.1Hz, OC*H*$(CH_3)_2$], 5.90-6.02 (1H, m, 4-H), 6.21 (1H, dd, *J*=1.4 and 16.1Hz, 3-H), 6.65 (1H, d, *J*=8.4Hz, 8-H), 6.83 (1H, d, *J*=8.4Hz, 9-H), 7.30 (2H, d, *J*=8.1Hz, 12-H), 7.73 (2H, d, *J*=8.1Hz, 11-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 19.1 ($CH_3$), 22.5 [OCH($CH_3$)$_2$], 29.7 (Ar$CH_2$C), 45.6 (Ar$CH_2$N), 55.7 ($OCH_3$), 75.2 [O*C*H$(CH_3)_2$], 110.3 (8-C), 124.2 (9-C), 124.9 (4-C), 126.2 (5a-C), 127.2 (11-C), 129.6 (12-C), 132.6 (3-C), 133.0 (9a-C), 136.9 (10-C), 143.4 (6-C), 145.1 (13-C), 153.0 (7-C). Insufficient material remained for us to perform a HRMS analysis after NMR and FTIR spectroscopy were completed.

### *2.32 Preparation of 3-isopropoxy-4-methoxy-2-(1-propenyl)benzaldehyde **201***



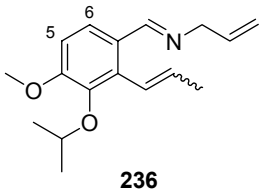

**201**

The 2-allyl-3-isopropoxy-4-methoxybenzaldehyde **138** (4.30mmol, 1.01g) was dissolved in toluene (100cm$^3$) and the solution was heated to 80$^o$C. Then the Ru-isomerisation catalyst **12** (0.02eq, 0.0861mmol, 0.0890g) was added and the reaction mixture was left to stir under an Ar atmosphere for 23 h. The reaction mixture was then allowed to cool to rt and the solvent was removed *in vacuo* to yield a brown oil, $^1$H NMR spectroscopy of the crude mixture showed only partial isomerisation, so the oil was redissolved in toluene (50cm$^3$) and the solution was again heated to 80$^o$C. Additional Ru-isomerisation catalyst **12** (0.02eq, 0.0861mmol, 0.0827g) was added and the reaction mixture was left to stir under an Ar atmosphere for a further 22.5 h. After this time the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo*, $^1$H NMR spectroscopy showed total isomerisation. The dark brown oil was then purified by column chromatography (5-10% EtOAc-Hexane) to yield a yellow-brown oil that crystallised on standing (0.924g, 92%). A mixture of *E/Z* isomers was observed by NMR spectroscopy, and the spectroscopic data was found to correlate well to that reported by Coyanis[206].

***$R_f$*** = 0.66 (30% EtOAc-Hexane); ***m.p.*** 37-40$^o$C; **$\delta_H$ (300 MHz, $CDCl_3$)** 1.27 [6H, d, *J*=6.2Hz, OCH(C$H_3$)$_2$], 1.98 (3H, dd, *J*=1.7 and 6.6 Hz, $CH_3$), 3.91 (3H, s, $OCH_3$), 4.42 [1H, sept, *J*=6.2Hz, OC*H*$(CH_3)_2$], 5.80 and 6.03-6.09 (1H, m, ArCH=C*H*$CH_3$, mixture of E/Z isomers), 6.59-6.60 and 6.73 (1H, m, ArC*H*=C$HCH_3$, mixture of *E/Z* isomers), 6.91 (1H, d, *J*=8.7Hz, 5-H), 7.69 (1H, d, *J*=8.7Hz, 6-H), 10.00 and 10.05 (1H, two s, CHO, mixture of *E/Z* isomers); **$\delta_C$ (50 MHz, $CDCl_3$)** 19.0 ($CH_3$), 22.5 [OCH($CH_3$)$_2$], 55.8 ($OCH_3$), 75.3

[O*C*H($CH_3$)$_2$], 110.3 (5-C), 122.5 (2-C), 123.0 (6-C), 125.2 (ArCH=*C*HCH$_3$), 128.3 (1-C), 136.1 (Ar*C*H=CHCH$_3$), 144.2 (3-C), 157.1 (4-C), 191.6 (CHO).

*2.33 Preparation of N-{[3-isopropoxy-4-methoxy-2-(1-propenyl)phenyl]methyl-idene}-2-propen-1-amine **236***

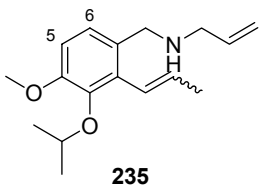



**236**

The 3-isopropoxy-4-methoxy-2-(1-propenyl)benzalde-hyde **201** (0.436mmol, 0.102g) was placed in a flask that was under an Ar atmosphere and to this was added allyl amine (1.4eq, 0.611mmol, 0.0500cm$^3$). The mixture was then allowed to stir at rt for 22 h. After this time the excess allyl amine was removed *in vacuo* to yield a yellow-orange oil. The product was essentially pure by $^1$H NMR spectroscopy and no further purification was required (0.119g, 100%). A mixture of *E/Z* isomers was observed by NMR spectroscopy.

***R**$_f$* = 0.67 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 929 (RCH=CH$_2$), 2977 ($CH_3$), 3019 (Ar H), 3617 (imine H); **$\delta_H$ (300 MHz, CDCl$_3$)** 1.22-1.28 [6H, m, OCH(C*H*$_3$)$_2$], 1.94 (3H, dd, *J*=1.2 and 5.6Hz, $CH_3$), 3.86 (3H, s, $OCH_3$), 4.20 (2H, dd, *J*=1.2 and 5.6Hz, NC*H*$_2$C), 4.38 [1H, sept, *J*=6.1Hz, OC*H*($CH_3$)$_2$], 5.12-5.23 (2H, m, CH=C*H*$_2$), 5.72 (1H, qd, *J*=6.6 and 15.9Hz, C*H*=CH$_2$), 5.88-6.11 (1H, m, ArCH=C*H*CH$_3$), 6.60 (1H, dd, *J*=1.5 and 16.0 Hz, ArC*H*=CHCH$_3$), 6.84 (1H, d, *J*=8.7Hz, 5-H), 7.71 (1H, d, *J*=8.6Hz, 6-H), 8.41 (1H, s, ArCH=N); **$\delta_C$ (50 MHz, CDCl$_3$)** 19.0 ($CH_3$), 22.5 and 22.6 [OCH(*C*H$_3$)$_2$], 55.6 and 55.7 ($OCH_3$), 63.5 and 63.7 (N*C*H$_2$C), 74.7 and 75.1 [O*C*H($CH_3$)$_2$], 110.7 (5-C), 115.7 (CH=*C*H$_2$), 123.0 (2-C), 123.3 (6-C), 124.3 (ArCH=*C*HCH$_3$), 134.0 (*C*H=CH$_2$), 134.8 (1-C), 136.3 (Ar*C*H=CHCH$_3$), 144.2 (3-C), 154.3 (4-C) 161.8 (ArCH=N); **MS *m/z*** 273 (M$^+$, 4%), 39 (7), 41 (11), 43 (8), 65 (7), 77 (9), 91 (10), 103 (8), 147 (5), 149 (7), 160 (5), 162 (5), 163 (6), 164 (10), 174 (6), 175 (10), 176 (8), 177 (100), 178 (12), 192 (22), 193 (21), 216 (21), 220 (7), 234 (37), 235 (7), 258 (26), 259 (6), 274 (5), ***HRMS*** calculated for $C_{17}H_{23}NO_2$: 273.17288, found: 273.17290.

*2.34 Preparation of N-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]-2-propen-1-amine* ***235***




**235**

Method A:

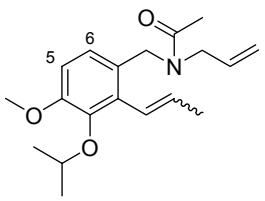
The *N*-{[3-isopropoxy-4-methoxy-2-(1-propenyl)-phenyl]methylidene}-2-propen-1-amine **236** (0.436 mmol, 0.110g) was dissolved in MeOH (1cm$^3$) and the solution was cooled to 0$^o$C in an ice-water bath. To this methanolic solution was added sodium borohydride (1.2eq, 0.523mmol, 0.0206g), and the reaction mixture was left to stir at 0$^o$C under an Ar atmosphere for 2 h. After this time distilled water was added to destroy the excess sodium borohydride and the pH was neutralised using 1M HCl and saturated $NaHCO_3$ solutions. The MeOH was removed on the rotary evaporator and the remaining aqueous layer was extracted with EtOAc (3×5cm$^3$). The combined organics were then dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to yield a yellow oil (0.0985g, 82%), which was spectroscopically pure and required no further purification.

Method B:

The 3-isopropoxy-4-methoxy-2-(1-propenyl)benzaldehyde **201** (1.13mmol, 0.268g) was transferred to a flask using the minimum amount of $Et_2O$ and this was then removed under vacuum. To the aldehyde was then added allyl amine (1.4eq, 1.58mmol, 0.115cm$^3$) and the reaction mixture was allowed to stir at rt under an Ar atmosphere for 18 h. After which time a small amount was removed and analysed by $^1$H NMR spectroscopy. It was found that pure imine formation had occurred so the imine was dissolved in MeOH (3cm$^3$) and the solution was cooled to 0$^o$C in an ice-water bath. This was followed by the addition of sodium borohydride (1.2eq, 1.36mmol, 0.528g). The reaction mixture was stirred under an Ar atmosphere and was allowed to warm to rt from 0$^o$C over a period of 3.5 h. After this time distilled water was added to destroy the excess sodium borohydride and the pH was neutralised using 1M HCl and saturated $NaHCO_3$ solutions. The MeOH was removed on the rotary evaporator to yield a milky aqueous solution. This was then extracted with EtOAc (3×10cm$^3$) and the combined organics were dried over anhydrous $MgSO_4$. The solution was filtered through cotton wool and the solvent was removed *in vacuo*. The desired product was obtained as an essentially pure yellow oil and no further purification was required (0.277g, 89%).

***$R_f$*** = 0.28 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 805 (2 adj Ar H), 994 (RCH=$CH_2$), 1381 and 1439 (alkane), 2838 (-N-$CH_2$-), 2936 (-$OCH_3$), 2977 (-$CH_3$), 3011 (Ar H), 3080 (C=$CH_2$), 3666 (-NH); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.23 [6H, d, *J*=6.2Hz, OCH($CH_3$)$_2$], 1.68 (1H, broad s, NH), 1.90 (3H, dd, *J*=1.5 and 6.5Hz, $CH_3$), 3.24 (2H, d, *J*=6.0Hz, N$CH_2$C), 3.73 (2H, s, Ar$CH_2$NH), 3.81 (3H, s, $OCH_3$), 4.32 [1H, sept, *J*=6.2Hz, O$CH$($CH_3$)$_2$], 5.10-5.18 (2H, m, CH=C$H_2$), 5.92 (1H, tdd, *J*=6.0, 10.2 and 16.3Hz, C$H$=$CH_2$), 6.14 (1H, qd, *J*=6.5 and 15.9Hz, ArCH=C$H$$CH_3$), 6.43 (1H, dd, *J*=1.5 and 16.0Hz, Ar$CH$=$CHCH_3$), 6.73 (1H, d, *J*=8.4Hz, 5-H), 6.99 (1H, d, *J*=8.4Hz, 6-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 19.2 ($CH_3$), 22.5 [OCH($CH_3$)$_2$], 51.0 ($ArCH_2N$), 51.8 (N$CH_2$C), 55.7 ($OCH_3$), 75.0 [O$CH$($CH_3$)$_2$], 110.1 (5-C), 115.9 (CH=$CH_2$), 124.4 (6-C[a]), 124.9 (1-C[a]), 130.8 (2-C[b]), 131.7 (ArCH=$CHCH_3$[b]), 132.8 (Ar$CH$=$CHCH_3$[b]), 136.9 ($CH$=$CH_2$), 145.0 (3-C), 152.2 (4-C); **MS *m/z*** 275 ($M^+$, 12%), 41 (52), 43 (22), 117 (22), 145 (24), 161 (51), 163 (21), 175 (55), 176 (58), 177 (55), 178 (28), 190 (37), 192 (41), 216 (44), 218 (31), 232 (100), 233 (36), 234 (20), ***HRMS*** calculated for $C_{17}H_{25}NO_2$: 275.18853, found: 275.19120.

## *2.35 Preparation of N-allyl-N-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]-acetamide **237***

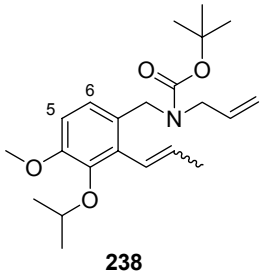



**237**

A solution was prepared of *N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]-2-propen-1-amine **235** (0.740mmol, 0.204g) and distilled pyridine (1eq, 0.740mmol, 0.060cm$^3$) and it was cooled to 0$^o$C in an ice-water bath. To this was added dropwise a solution of pre-distilled acetic anhydride (1.5eq, 1.11mmol, 0.110cm$^3$) in pyridine (1.5eq, 1.11mmol, 0.100cm$^3$). Then the ice-water bath was removed and the reaction mixture was stirred at rt under an Ar atmosphere for 3 h. After this time the reaction mixture was diluted with EtOAc (5cm$^3$) and stirred for 5 min. Then the organic layer was extracted with brine (3×10cm$^3$). The combined aqueous layers were then extracted with $CH_2Cl_2$ (3×10cm$^3$). Then the organic layers were combined and extracted with saturated $NH_4Cl$ that was basified to pH 11 with a 25 % ammonia solution (40cm$^3$). The combined organics were then dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to yield a pale yellow oil. The crude compound was then purified by column chromatography (5-10% EtOAc-Hexane) to yield the desired product as a clear oil (0.168g, 72%). Amide rotamers were observed in both the $^1$H and $^{13}$C NMR spectra.

***R**f* = 0.24 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 772 (alkane), 929 (RCH=$CH_2$), 1216 (C-O), 1478 (alkane), 1522 (Ar ring), 1630 (tertiary amide or C=C aryl conj), 3019 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.21-1.25 [6H, m, OCH(C*H*$_3$)$_2$], 1.86-1.92 (3H, m, $CH_3$), 2.08 and 2.13 (3H, two s, $COCH_3$), 3.69 (1H, d, *J*=4.7Hz, NC*H*$_2$CH$^a$), 3.81 and 3.83 (3H, two s, $OCH_3$), 3.96 (1H, d, *J*=5.8Hz, NC*H*$_2$CH$^a$), 4.27-4.36 [1H, m, OC*H*(CH$_3$)$_2$], 4.23 and 4.62 (2H, two s, ArCH$_2$N), 5.04-5.18 (2H, m, CH=C*H*$_2$), 5.60-6.04 (2H, m, C*H*=CH$_2$ and ArCH=C*H*), 6.29 and 6.34 (1H, two d, *J*=1.9, ArC*H*=CH), 6.71-6.87 (2H, m, 5-H and 6-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 19.0 and 19.1 ($CH_3$), 21.4 and 21.5 ($COCH_3$), 22.4 and 22.5 [OCH(*C*H$_3$)$_2$], 45.6 and 47.9 (ArCH$_2$N), 49.1 and 49.3 (N*C*H$_2$C), 55.7 ($OCH_3$), 75.0 and 75.1 [O*C*H(CH$_3$)$_2$], 110.2 and 110.4 (5-C), 116.5 and 117.2 (CH=*C*H$_2$), 120.8 (6-C), 123.6 (CH=*C*HCH$_3$), 124.2 and 124.6 (1-C$^b$), 126.7 and 127.4 (2-C$^b$), 132.1 and 132.4 (Ar*C*H=CH), 133.1 and 133.2 (*C*H=CHCH$_3$), 144.8 and 145.2 (3-C), 152.2 and 152.3 (4-C), 170.7 and 171.0 (C=O); **MS *m/z*** 317 ($M^+$, 72%), 41 (15), 43 (21), 115 (11), 117 (13), 146 (13), 161 (30), 175 (100), 176 (80), 177 (31), 193 (86), 193.5 (40), 218 (24), 220 (15), 232 (30), 234 (22), 235 (11), 274 (19), 176 (21), 302 (10), 317(72), 318 (16), ***HRMS*** calculated for $C_{19}H_{27}NO_3$: 317.19909, found: 317.19985.

### *2.36 Preparation of tert-butyl allyl[3-isopropoxy-4-methoxy-2-(1-propenyl)-benzyl]carbamate **238***



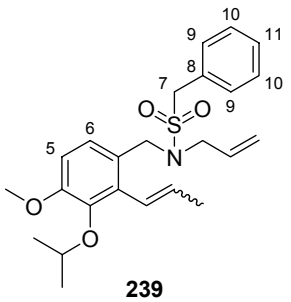

**238**

The *N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)-benzyl]-2-propen-1-amine **235** (1.00mmol, 0.277g) was dissolved in pre-distilled THF (28cm$^3$) and to this was added $Boc_2O$ (1.2eq, 1.21mmol, 0.290cm$^3$). The solution was then stirred for 5 min before the addition of DMAP (0.1eq, 0.100mmol, 0.0160g). Then the reaction mixture was allowed to stir at rt under an Ar atmosphere for 3 h. After this time the solvent was removed *in vacuo* and the residue was purified by column chromatography (5% EtOAc-Hexane). The desired product was obtained as a pale yellow oil (0.324g, 86%). A mixture of *E/Z* isomers was observed in the spectra.

***R**f* = 0.76 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 756 ($CH_2$), 843 (2 adj Ar H), 927 (RCH=$CH_2$), 1119 (C-O), 1371 (-$COCH_3$), 1459 (alkane), 1479 and 1574 (Ar ring), 1678

(tertiary amide or isolated C=C), 2839 (-$OCH_3$), 2936 (-$CH_3$), 2980 (-$CH_2$), 3018 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.22 [6H, d, *J*=6.2Hz, OCH($CH_3$)$_2$], 1.53 [9H, s, OC($CH_3$)$_3$], 1.88 (3H, d, *J*=6.1Hz, $CH_3$), 3.62-3.74 (2H, m, N$CH_2$C), 3.81 (3H, s, $OCH_3$), 4.32 [1H, sept, *J*=6.2Hz, OC*H*($CH_3$)$_2$], 4.43 (2H, s, Ar$CH_2$N), 5.04 (2H, t, *J*=14.4Hz, CH=C$H_2$), 5.70-5.96 (2H, m, C*H*=$CH_2$ and ArCH=C*H*), 6.34 (1H, dd, *J*=1.4 and 16.0Hz, ArC*H*=CH), 6.74 (1H, d, *J*=8.5Hz, 5-H), 6.86 (1H, d, *J*=8.5Hz, 6-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 19.1 ($CH_3$), 22.5 [OCH(*C*$H_3$)$_2$], 28.4 [OC(*C*$H_3$)$_3$], 47.0 (Ar$CH_2$N), 48.2 (N*C*$H_2$CH), 55.7 ($OCH_3$), 74.9 [O*C*H($CH_3$)$_2$], 79.5 [O*C*($CH_3$)$_3$], 110.1 (5-C), 116.1 (CH=*C*$H_2$), 123.3 (2-C), 124.6 (ArCH=*C*H), 132.0 (Ar*C*H=CH), 133.8 (*C*H=$CH_2$), 144.9 (3-C), 146.7 (4-C), 155.6 (C=O), no peaks were observed in the $^{13}$C NMR spectrum for 1-C and 6-C; **MS *m/z*** 375 ($M^+$, 4%), 41 (28), 57 (100), 70 (26), 161 (16), 175 (67), 176 (33), 177 (24), 232 (34 ), 234 (19), 274 (82), 275 (17), 276 (15), 318 (15), 319 (71), ***HRMS*** calculated for $C_{22}H_{33}NO_4$: 375.24096, found: 375.23970.

### *2.37 Preparation of N-allyl-N-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]-phenylmethanesulfonamide **239***



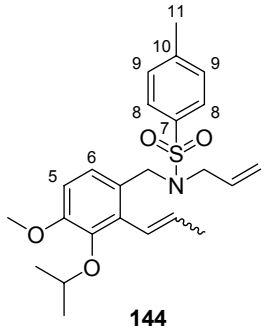

**239**

The *N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)-benzyl]-2-propen-1-amine **235** (0.746mmol, 0.205g) was dissolved in predistilled $CH_2Cl_2$ (2cm$^3$); to this was added $NEt_3$ (2.5eq, 1.86mmol, 0.260cm$^3$) and the solution was allowed to stir at rt for 15 min. Then the α-toluenesulfonyl chloride (1.1eq, 0.821mmol, 0.159g) was dissolved in $CH_2Cl_2$ (2cm$^3$) and the mixture was added dropwise to the amine solution, a cloudy white gas evolved during the addition. Then the reaction mixture was stirred at rt under an Ar atmosphere for 18 h, before the solvent was removed *in vacuo* to yield a pink-orange oil that solidified on standing. The crude mixture was then purified by column chromatography (5-20% EtOAc-Hexane) to yield the desired product as a yellow oil (0.0927g, 29%). Mixtures of *E/Z* isomers were observed in the spectra.

***R**$_f$* = 0.63 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (alkane), 930 (RCH=$CH_2$), 1150 (-$SO_2$-N-), 1334 (-$SO_2$-N-), 1439 (alkane), 1481 (-$CH_2$), 2977 ($CH_3$), 3020 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.21 [6H, d, *J*=6.2Hz, OCH(*C*$H_3$)$_2$], 1.88 (3H, d, *J*=6.4Hz, $CH_3$), 3.55

(2H, d, *J*=6.5Hz, NC*H*$_2$C), 3.81 (3H, s, OCH$_3$), 4.14 (2H, s, ArCH$_2$N), 4.23 (2H, s, ArCH$_2$SO$_2$), 4.31 [1H, sept, *J*=6.2Hz, OC*H*(CH$_3$)$_2$], 5.01-5.12 (2H, m, CH=C*H*$_2$), 5.55-5.81 (2H, m, C*H*=CH$_2$ and ArCH=C*H*), 6.34 (1H, d, *J*=16.1Hz, ArC*H*=CH), 6.76 (1H, d, *J*=8.5Hz, 5-H), 7.08 (1H, d, *J*=8.5Hz, 6-H), 7.35-7.36 (5H, m, 9-H, 10-H and 11-H); **$\delta_C$ (50 MHz, CDCl$_3$)** 19.1 (CH$_3$), 22.5 [OCH(*C*H$_3$)$_2$], 48.2 (ArCH$_2$N), 49.8 (N*C*H$_2$C), 55.7 (OCH$_3$), 59.4 (ArCH$_2$SO$_2$), 75.0 [O*C*H(CH$_3$)$_2$], 110.3 (5-C), 119.0 (CH=*C*H$_2$), 124.5 (6-C[a]), 124.8 (1-C[a]), 126.3 (2-C[a]), 128.6 (10-C and CH=*C*HCH$_3$), 129.2 (11-C), 130.8 (9-C), 132.4 (Ar*C*H=CH), 132.9 (8-C), 133.2 (*C*H=CH$_2$), 144.7 (3-C), 152.5 (4-C); **MS *m/z*** 429 (M$^+$, 7%), 41 (6), 91 (49), 117 (7), 145 (6), 161 (6), 176 (13), 177 (13), 178 (5), 216 (17), 232 (70), 233 (10), 274 (100), 275 (20), 429 (8), ***HRMS*** calculated for $C_{24}H_{31}NO_4S$: 429.19738, found: 429.19619.

## *2.38 Preparation of N-allyl-N-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]-4-methyl-benzenesulfonamide **144***



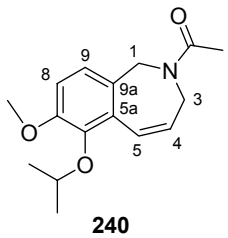

**144**

The *N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)-benzyl]-2-propen-1-amine **235** (1.68mmol, 0.463g) was dissolved in pre-distilled CH$_2$Cl$_2$ (5cm$^3$) and then cooled to 0$^o$C in an ice-water bath. To this solution was added NEt$_3$ (1.4eq, 2.35mmol, 0.350cm$^3$) and it was stirred for 5 min before the addition of the tosyl chloride (1.2eq, 2.02mmol, 0.391g). The reaction mixture was allowed to stir at 0$^o$C-rt for 3 h, after this time distilled water (5cm$^3$) was added and the aqueous layer was extracted with CH$_2$Cl$_2$ (5cm$^3$). The combined organics were then extracted with distilled water (2×5cm$^3$) and were dried over anhydrous MgSO$_4$. The solvent was then removed *in vacuo* to yield a dark yellow-orange oil that solidified on standing. The crude mixture was then purified by column chromatography (5-10% EtOAc-Hexane) to yield the desired product as a cream-white solid (0.553g, 77%), with NMR spectroscopy showing a mixture of *E/Z* isomers.

***R$_f$*** = 0.70 (30% EtOAc-Hexane); ***m.p.*** 62-64$^o$C; **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 772 (CH$_2$), 929 (RCH=CH$_2$), 1159 (-SO$_2$-N-), 1339 (-SO$_2$-N-), 1522 (Ar H), 2977 (-CH$_3$), 3020 (Ar H); **$\delta_H$ (300 MHz, CDCl$_3$)** 1.23 [6H, two d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 1.86 (3H, dd, *J*=1.5 and 6.5Hz, CH$_3$), 2.44 (3H, s, TsCH$_3$), 3.66 (2H, d, *J*=6.4Hz, NC*H*$_2$C), 3.81 (3H, s, OCH$_3$), 4.09-4.30 [1H, m, OC*H*(CH$_3$)$_2$], 4.26 and 4.33 (2H, two s, ArCH$_2$N), 4.85-4.96 (2H, m, CH=C*H*$_2$), 5.42

(1H, tdd, *J*=6.4, 10.1 and 16.7Hz, C*H*=$CH_2$), 5.92 (1H, qd, *J*=6.6 and 16.0Hz, CH=C*H*$CH_3$), 6.36 (1H, dd. *J*=1.5 and 16.0Hz, ArC*H*=CH), 6.73 (1H, d, *J*=8.5Hz, 5-H), 7.02 (1H, d, *J*=8.5Hz, 6-H), 7.31 (2H, d, *J*=8.1Hz, 9-H), 7.73 (2H, d, *J*=8.2Hz, 8-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 19.0 ($CH_3$), 21.5 ($TsCH_3$), 22.4 and 22.5 [$OCH(CH_3)_2$], 48.2 and 48.3 ($ArCH_2N$), 49.5 and 49.7 ($NCH_2C$), 55.5 and 55.7 ($OCH_3$), 74.5 and 75.0 [$OCH(CH_3)_2$], 109.8 and 110.1 (5-C), 115.0 (CH=$CH_2$), 118.5 (6-C), 124.5 (1-C), 126.0 (2-C), 126.7 (*C*H-$CH_3$), 127.3 (8-C), 129.6 (9-C), 132.4 (Ar*C*H=CH), 133.5 (*C*H=$CH_2$), 137.3 (7-C), 143.1 (10-C), 144.7 and 145.0 (3-C), 152.5 (4-C); **MS *m/z*** 429 ($M^+$, 3%), 41 (8), 91 (14), 117 (9), 145 (9), 161 (11), 176 (22), 177 (13), 215 (20), 220 (6), 224 (6), 232 (56), 233 (9), 274 (100), 275 (18), ***HRMS*** calculated for $C_{24}H_{31}NO_4S$: 429.19738, found: 429.19780.

### *2.39 Preparation of 2-acetyl-6-isopropoxy-7-methoxy-2,3-dihydro-1H-2-benzazepine **240***

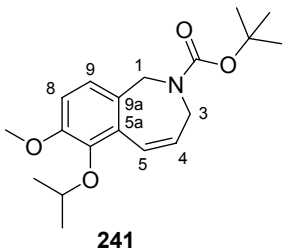



**240**

The *N*-allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)-benzyl]acetamide **237** (0.266mmol, 0.0845g) was dissolved up in distilled toluene (8.5$cm^3$) and the resulting solution was heated to 80°C. To the solution was then added Grubbs II catalyst **11** (0.1eq, 0.0266mmol, 0.0229g). The reaction mixture was then allowed to stir at 80°C under an Ar atmosphere for 21 h. After this time the solvent was removed *in vacuo* to yield a dark brown residue that was then purified by column chromatography (5-15% EtOAc-Hexane). The desired compound was obtained as a white solid (0.0054g, 8%).

***$R_f$*** = 0.51 (30% EtOAc-Hexane); ***m.p.*** >230°C; **$\nu_{max}$/$cm^{-1}$ (NaCl plate)** 669 (RHC=CHR, *cis*), 850 (2 adj Ar H), 1215 (C-O), 1370 ($CH_3$ symmetrical deformation), 1477 ($CH_2$ or $CH_3$ CH deformations), 1677 (C=C aryl conj or tertiary amide), 2897 (-$OCH_3$), 2938 (-$CH_2$ or –$CH_3$ stretch), 3019 (Ar H).; **$\delta_H$ (300 MHz, $CDCl_3$)** 1.29 [6H, d, *J*=6.2Hz, $OCH(CH_3)_2$], 2.44 (3H, s, $CH_3$), 3.85 (3H, s, $OCH_3$), 4.49 [1H, sept, *J*=6.1Hz, $OCH(CH_3)_2$], 6.36 (1H, d, *J*=12.5Hz,, ArCH=C*H*), 6.93 (1H, d, *J*=8.3Hz, 8-H), 7.16 (1H, d, *J*=8.3Hz, 9-H), 7.57 (1H, d, *J*=12.5Hz, ArC*H*=CH); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.6 [$OCH(CH_3)_2$], 26.9 ($CH_3$), 29.7 ($ArCH_2N^a$), 44.9 ($NCH_2CH^a$), 55.9 ($OCH_3$), 76.3 [$OCH(CH_3)_2$], 113.7 (8-C), 123.5 (9-C), 126.1 (4-C), 129.6 (9a-C), 130.1 (5a-C), 135.7 (5-C), 145.9 (6-C), 152.7 (7-C), 168.2 (C=O). Insufficient material remained after NMR and FTIR spectroscopy to perform the HRMS analysis.

*2.40 Preparation of tert-butyl 6-isopropoxy-7-methoxy-1,3-dihydro-2H-2-benzazepine-2-carboxylate **241***

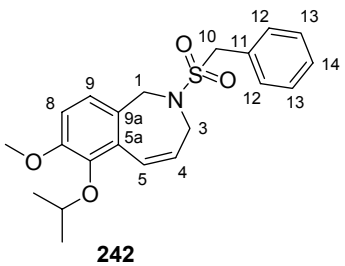



**241**

The *tert*-butyl allyl[3-isopropoxy-4-methoxy-2-(1-propenyl)-benzyl]carbamate **241** (0.268mmol, 0.101g) was dissolved in pre-distilled toluene (10cm$^3$) and the solution was heated to 60$^o$C. Then Grubbs II catalyst **11** (0.05eq, 0.0134mmol, 0.0117g) was added and the reaction mixture was allowed to stir at 60$^o$C under an Ar atmosphere for 18 h. The solvent was then removed *in vacuo* to yield a brown-black oil, that was then purified by column chromatography (5% EtOAc-Hexane). The product was obtained as a pale yellow oil (0.0235, 26%). Severe peak broadening occurred in the $^1$H NMR spectrum, which made the assignments extremely difficult.

***R**$_f$* = 0.74 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 668 (RHC=CHR, *cis*), 852 (2 adj Ar H), 1216 (C-O), 1369 ($CH_3$ symmetrical deformation), 1440 ($CH_2$ or $CH_3$ deformations), C=C aryl conj. Or tertiary amide), 2855 (-$OCH_3$), 2929 ($CH_2$ or $CH_3$ stretch), 3017 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.22-1.52 [15H, m, OC(C*H*$_3$)$_3$ and OCH(C*H*$_3$)$_2$], 3.80-3.86 (5H, m, $OCH_3$ and $NCH_2C$), 4.25-4.77 [3H, m, $OCH(CH_3)_2$ and Ar $CH_2N$], 5.87-5.89 (1H, m, 4-H), 6.31-6.39 (1H, m, 8-H), 6.69-7.09 (1H, m, 5-H and 9-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.6 [$OCH(CH_3)_2$], 29.7 [OC(*C*H$_3$)$_3$], 47.8 ($ArCH_2N$), 55.8 ($OCH_3$[a]), 55.9 ($NCH_2C$[a]), 75.2 [O*C*H(CH$_3$)$_2$], 83.5 [OC(*C*H$_3$)$_3$], 110.3 (8-C), 113.3 (9-C), 122.5 (4-C), 124.7 (9a-C), 124.9 (5a-C), 126.7 (5-C), 132.0 (6-C), 134.5 (7-C), 163.2 (C=O). Insufficient material remained after NMR and FTIR spectroscopy to perform the HRMS analysis.

*2.41 Preparation of 2-(benzylsulfonyl)-6-isopropoxy-7-methoxy-2,3-dihydro-1H-2-benzazepine **242***



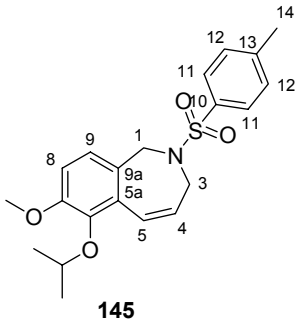

**242**

*N*-Allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-pro-penyl)benzyl]phenylmethanesulfonamide **239** (0.122mmol, 0.0526g) was dissolved in pre-distilled toluene (5cm$^3$) and the solution was heated to 80$^o$C. To this solution was added Grubbs II catalyst **11** (0.1eq, 0.0122mmol, 0.0107g) and it

was allowed to stir at 80°C under an Ar atmosphere for 21 h. After this time the solvent was removed *in vacuo* to yield a dark brown resin that was purified by column chromatography (5% EtOAc-Hexane). The desired product was obtained as a yellow oil (0.0184g, 39%).

***R*$_f$** = 0.49 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (RHC=CHR, *cis*), 743 (5 adj Ar H), 879 (2 adj Ar H), 1150 (-$SO_2$-N-), 1354 (-$SO_2$-N-), 1456 ($CH_2$ or $CH_3$ deformations), 1490 (Ar ring), 1575 (Ar ring), 1598 (Ar ring), 1666 (C=C aryl conj), 2931 ($CH_3$ or $CH_2$ stretch), 3020 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.28 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 3.79 (2H, s, NC*H*$_2$C), 3.84 (3H, s, $OCH_3$), 4.09-4.11 (2H, m, $ArCH_2N$), 4.33 (2H, s, $ArCH_2SO_2$), 4.46 [1H, sept, *J*=6.2Hz, OC*H*(CH$_3$)$_2$], 5.76 (1H, td, *J*=3.9 and 12.6Hz, ArC*H*=CH), 6.78 (1H, d, *J*=8.2Hz, 8-H), 6.92-6.99 (2H, m, $NCH_2C$*H*=CH and 9-H), 7.16-7.29 (5H, m, 12-H, 13-H and 14-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.5 [OCH(*C*H$_3$)$_2$], 50.7 (N*C*H$_2$C), 51.7 ($ArCH_2N$), 55.8 ($OCH_3$), 58.6 ($ArCH_2SO_2$), 75.5 [O*C*H(CH$_3$)$_2$], 111.0 (8-C), 122.9 (9a-C), 123.5 (9-C), 124.2 (5a-C), 125.3 (4-C), 128.3 (14-C), 128.5 (13-C), 128.9 (5-C), 129.7 (11-C), 130.6 (12-C), 145.3 (6-C), 152.8 (7-C); **MS *m/z*** 387 ($M^+$, 28%), 41 (6), 43 (7), 65 (10), 91 (100), 92 (10), 103 (7), 131 (6), 146 (5), 147 90, 161 (13), 162 (9), 163 (67), 164 (8), 174 (11), 175 (8), 176 (5), 189 (42), 190 (49), 191 (7), 204 (8), 205 (20), 232 (8), 280 (6), 359 (11), 387 (28), 388 (6), 401 (9), ***HRMS*** calculated for $C_{21}H_{25}NO_4S$: 387.15043, found: 387.14958.

*2.42 Preparation of 6-isopropoxy-7-methoxy-2-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1H-2-benzazepine **145***

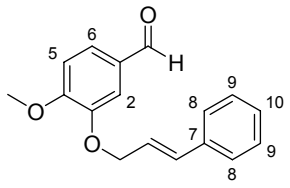



**145**

The *N*-allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-pro-penyl)benzyl]-4-methylbenzenesulfonamide **144** (0.471mmol, 0.203g) was dissolved up in pre-distilled toluene (20cm$^3$) and the solution was heated to 60°C. Then the Grubbs II catalyst **11** (0.05eq, 0.0236mmol, 0.0206g) was added and the reaction mixture was stirred at 60°C under an Ar atmosphere for 19.5 h. After this time the reaction mixture was cooled to rt and the solvent was removed *in vacuo* to yield a dark brown oil. The crude mixture was purified by column chromatography (5-10% EtOAc-Hexane) to obtain the desired product as a pale yellow oil that solidified on standing (0.149g, 82%).

***R**f* = 0.54 (30% EtOAc-Hexane); ***m.p.*** 147-149°C; **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (RCH=CHR, *cis*), 747 ($CH_2$ rocking), 813 (2 adj Ar H), 1157 (-$SO_2$-N-), 1342 (-$SO_2$-N-), 1440 ($CH_2$ or $CH_3$ defromations), 1490 (Ar ring), 1577 (Ar ring), 1599 (Ar ring), 1670 (C=C aryl conj), 2840 (-$OCH_3$), 2939 ($CH_3$ or $CH_2$ stretch), 3020 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.22 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 2.41 (3H, s, Ts$CH_3$), 3.14-3.17 (2H, m, NC*H*$_2$C), 3.85 (3H, s, $OCH_3$), 4.15 (2H, s, Ar$CH_2$N), 4.42 [1H, sept, *J*=6.2Hz, OC*H*(C$H_3$)$_2$], 5.86 (1H, td, *J*=7.8 and 11.2Hz, ArCH=C*H*), 6.68 (1H, d, *J*=11.2Hz, ArC*H*=CH), 6.89 (1H, d, *J*=8.5Hz, 8-H), 7.27 (2H, d, *J*=7.9Hz, 12-H), 7.37 (1H, d, *J*=8.5Hz, 9-H), 7.66 (2H, d, *J*=8.3Hz, 11-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.5 ($CH_3$[a]), 22.5 [OCH(*C*H$_3$)$_2$], 28.6 ($CH_3$[a]), 43.5 (N*C*H$_2$C), 49.7 (Ar$CH_2$N), 55.8 ($OCH_3$), 75.0 [O*C*H(C$H_3$)$_2$], 111.9 (8-C), 126.6 (9-C[b]), 127.1 (11-C), 127.8 (9a-C[b]), 128.2 (5a-C[b]), 129.6 (12-C), 130.0 (4-C[b]), 132.2 (5-C[b]), 136.7 (10-C), 143.0 (13-C), 144.1 (6-C), 152.1 (7-C); **MS *m/z*** 387 ($M^+$, 3%), 91 (26), 115 (18), 143 (14), 144 (15), 161 (20), 175 (24), 176 (63), 177 (11), 189 (12), 203 (12), 204 (66), 205 (10), 246 (100), 247 (19), 401 (28), ***HRMS*** calculated for $C_{21}H_{25}NO_4S$: 387.15043, found: 387.14872.

### *2.43 Preparation of 4-methoxy-3-{[(2E)-3-phenyl-2-propenyl]oxy}benzaldehyde **246***



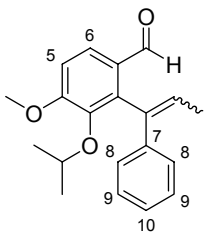

**246**

Distilled and dried DMF (30cm$^3$) and potassium carbonate (2.5eq, 49.3mmol, 6.90g) were stirred at rt until a cream suspension formed and the solution was then heated to 60°C. Then isovanillin **206** (19.7mmol, 3.02g) was added and the reaction mixture changed colour to bright yellow. The cinnamyl bromide (2.5eq, 49.3mmol, 9.73g) was added and the reaction mixture was stirred at 60°C under an Ar atmosphere for 23 h. After this time the reaction mixture was allowed to cool to rt and the inorganic solids were filtered off through a celite plug, which was rinsed with $CH_2Cl_2$ (50cm$^3$). The solvent was removed *in vacuo* to yield a yellow-orange oil that was then purified by column chromatography (10-30% EtOAc-Hexane). The desired product was obtained as a pale yellow semi-solid (5.29g, 100%). Spectroscopic data was in agreement with that reported by Rousseau.[1]

***R**f* = 0.45 (30% EtOAc-Hexane); ***m.p.*** 67-69°C after recrystallisation (the product was dissolved in the minimum amount of $Et_2O$ possible and Hexane was added dropwise until the solution became cloudy); **$\delta_H$ (300 MHz, $CDCl_3$)** 3.97 (3H, s, $OCH_3$), 4.83 (2H, dd, *J*=0.7 and

6.0Hz, $OCH_2$), 6.45 (1H, td, *J*=6.0 and 15.9Hz, $OCH_2CH$=CH), 6.76 (1H, d, *J*=16.0Hz, $OCH_2CH$=C*H*), 7.00 (1H, d, *J*=8.6Hz, 5-H), 7.25-7.48 (7H, m, 2-H, 5-H and 8-H, 9-H and 10-H), 9.85 (1H, s, CHO); **$\delta_C$ (50 MHz, $CDCl_3$)** 56.2 ($OCH_3$), 69.6 ($OCH_2$), 110.7 (5-C), 110.9 (2-C), 123.5 (10-C), 126.7 (8-C), 126.8 (6-C), 128.0 ($OCH_2$*C*H=CH), 128.5 (9-C), 130.0 (1-C), 134.0 ($OCH_2CH$=*C*H), 136.2 (7-C), 148.6 (3-C), 154.8 (4-C), 190.8 (CHO).

### *2.44 Preparation of 3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-benzalde-hyde **247***

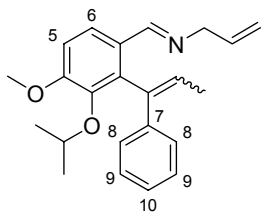



**247**

The Claisen rearrangement was effected by heating the 4-methoxy-3-{[(2*E*)-3-phenyl-2-propenyl]oxy}benzaldehyde **246** (9.52mmol, 2.55g) in distilled DMF (20$cm^3$) to 160-165$^oC$ for 44 h under an Ar atmosphere. Then the reaction mixture was cooled to 60$^oC$ before the addition of the potassium carbonate (2.5eq, 23.8mmol, 3.29g). The reaction mixture was then stirred until a cream suspension formed, then the isopropyl bromide (2.5eq, 23.8mmol, 2.25$cm^3$) was added. The reaction mixture was allowed to stir at 60$^oC$ under an Ar atmosphere for a further 44 h. After this time the reaction mixture was allowed to cool to rt and the inorganic solids were filtered off through a celite plug. The celite was then rinsed with both EtOAc (100$cm^3$) and $CH_2Cl_2$ (100$cm^3$) to ensure no product was trapped in the solids. Then the solvent was removed on the rotary evaporator (70$^oC$) and the remaining DMF was distilled off under high vacuum using a standard oil bath. The remaining dark red residue was then purified by column chromatography (5% EtOAc-Hexane). The desired compound was obtained as a purple oil (1.47g, 50%). Our NMR data was found to correlate well with that reported by Rousseau.[1]

***$R_f$*** = 0.64 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 0.98 and 1.11 [6H, two d, *J*=6.2Hz, $OCH(CH_3)_2$], 1.63 (3H, d, *J*=7.0Hz, $CH_3$), 3.92 (3H, s, $OCH_3$), 4.36 [1H, sept, *J*=6.2Hz, $OCH(CH_3)_2$], 6.51 (1H, q, *J*=7.0Hz, C=C*H*$CH_3$), 7.01 (1H, d, *J*=8.6Hz, 5-H), 7.18-7.28 (5H, m, Ph H), 7.83 (1H, d, *J*=8.6Hz, 6-H), 9.83 (1H, s, CHO); **$\delta_C$ (50 MHz, $CDCl_3$)** 16.1 ($CH_3$), 22.4 [$OCH(CH_3)_2$], 55.7 ($OCH_3$), 74.9 [$OCH(CH_3)_2$], 111.0 (5-C), 123.8 (10-C), 126.0 (8-C), 126.9 (6-C), 127.3 (C=*C*H$CH_3$), 128.3 (9-C), 129.1 (1-C), 134.5 (*C*=C$HCH_3$), 138.1 (7-C), 141.6 (2-C), 144.4 (4-C), 158.4 (3-C), 191.8 (CHO).

*2.45 Preparation of N-{(E)-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-phenyl]-methylidene}-2-propen-1-amine* ***248***

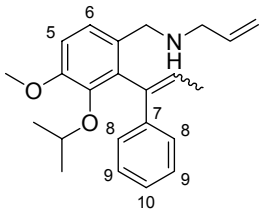



**248**

The 3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-benzaldehyde **247** (0.661mmol, 0.205g) was transferred to the reaction flask using the minimum amount of $Et_2O$ and this was removed *in vacuo*. Then allyl amine (1.4eq, 0.925mmol, 0.100cm$^3$) was added and the mixture was allowed to stir at rt under an Ar atmosphere for 24 h. After this time the excess allyl amine was removed *in vacuo* and the desired product was obtained as an orange oil (0.231g, 100%). No further purification was required as the compound was spectroscopically pure.

***R**$_f$* = 0.13 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 771 (5 adj Ar H), 929 (RCH=$CH_2$), 1381 and 1431 (alkane), 1518 and 1588 (Ar ring), 1639 (C=C isolated), 1678 (C=N), 2840 (-$OCH_3$), 2902 (-$CH_2$), 2980 (-$CH_3$), 3022 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 0.97 and 1.09 [6H, two d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 1.59 (3H, d, *J*=7.0Hz, $CH_3$), 3.87 (3H, s, $OCH_3$), 4.06-4.08 (2H, m, $NCH_2$), 4.32 [1H, sept, *J*=6.1Hz, OC*H*$(CH_3)_2$], 5.04-5.15 (2H, m, CH=C*H*$_2$), 5.88-5.99 (1H, m, C*H*=$CH_2$[a]), 6.34-6.44 (1H, m, C=C*H*$CH_3$[a]), 6.96 (1H, d, *J*=8.7Hz, 5-H), 7.17-7.31 (5H, m, 8-H, 9-H and 10-H), 7.88 (1H, d, *J*=8.7Hz, 6-H), 8.13 (1H, s, CH=N); **$\delta_C$ (50 MHz, $CDCl_3$)** 16.0 ($CH_3$), 22.1 and 22.4 [OCH(*C*$H_3)_2$], 55.6 ($OCH_3$), 63.4 ($NCH_2$), 74.6 [O*C*H$(CH_3)_2$], 111.3 (5-C), 115.7 (CH=*C*$H_2$), 122.1 (6-C), 126.0 (8-C), 126.5 (C=*C*H$CH_3$), 126.7 (10-C), 128.2 (9-C), 128.5 (2-C), 131.0 (1-C), 135.4 (*C*=CH$CH_3$), 136.3 (*C*H=$CH_2$), 141.8 (7-C), 144.1 (3-C), 155.2 (4-C), 161.2 (CH=N); **MS *m/z*** 349 ($M^+$, 9%), 28 (8), 69 (100), 100 (9), 119 (8), 131 (43), 219 (91), 220 (9), 236 (9), 250 (9), 251 (9), 254 (9), 264 (24), 292 (18), 334 (56), 335 (12), 349 (9), ***HRMS*** calculated for $C_{23}H_{27}NO_2$: 349.20418, found: 349.20968.

*2.46 Preparation of N-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-2-propen-1-amine **249***




**249**

Method A:

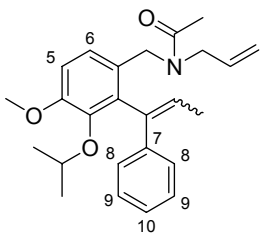
The *N*-{(*E*)-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)phe-nyl]methylidene}-2-propen-1-amine **248** (0.612mmol, 0.214g) was dissolved in MeOH (2cm$^3$) and 1 drop of distilled water was added. The methanolic solution was then cooled to 0$^o$C in an ice-water bath and to this was added sodium borohydride (1.2eq, 0.735mmol, 0.299g). The reaction mixture was allowed to stir at 0$^o$C-rt for 2.5 h. After this time the excess sodium borohydride was destroyed by the dropwise addition of distilled water and 1M HCl until the reaction mixture was neutral. The MeOH was then removed on the rotary evaporator and a yellow oil was found on top of the aqueous layer. Then EtOAc (10cm$^3$) was added to dissolve the compound and the aqueous layer was extracted with EtOAc (3×10cm$^3$). The combined organics were dried over anhydrous $MgSO_4$, filtered and the solvent was removed in vacuo to yield the product as a dark yellow oil (0.214g, 100%), with no further purification being required.

Method B:

The 3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzaldehyde **247** (1.77mmol, 0.550g) was transferred to a flask using $Et_2O$ which was then removed under vacuum. To the aldehyde was then added allyl amine (1.4eq, 2.50mmol, 0.200cm$^3$) and the reaction mixture was allowed to stir at rt under an Ar atmosphere for 21 h. After which time a small amount was removed and analysed by $^1$H NMR spectroscopy. It was found that pure imine formation had occurred so the imine was dissolved in MeOH (5.5cm$^3$) and the solution was cooled to 0$^o$C in an ice-water bath. This was followed by the addition of sodium borohydride (1.2eq, 2.12mmol, 0.0805g). The reaction mixture was then left to stir under an Ar atmosphere at 0$^o$C for 2 h. After this time distilled water was added to destroy the excess sodium borohydride and the pH was neutralised using 1M HCl and saturated $NaHCO_3$ solutions. The reaction mixture was then extracted with $CH_2Cl_2$ (10cm$^3$) and EtOAc (3×10cm$^3$) and the combined organics were dried over anhydrous $MgSO_4$. The solution was filtered through cotton wool and the solvent was removed *in vacuo*. The desired product was obtained as an essentially pure orange oil and no further purification was required (0.620g, 100%).

***R*$_f$** = 0.25 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 752 (5 adj Ar H), 927 (RCH=$CH_2$), 1377 and 1439 (alkane), 1595 (NH), 1646 (C=C isolated), 2837 ($OCH_3$), 2937 (-$CH_2$), 2978 (-$CH_3$), 3019 (Ar H), 3494 (N-H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.04 and 1.13 [6H, two d, *J*=6.1Hz, OCH(C*H*$_3$)$_2$], 1.36 and 1.64 (3H, two d, *J*=6.1 and 6.9Hz respectively, $CH_3$), 1.42 (1H, s, NH), 3.02-3.04 (2H, m, NC*H*$_2$CH), 3.46 (2H, d, *J*=2.1Hz, $ArCH_2N$), 3.84 (3H, s, $OCH_3$), 4.27 [1H, sept, *J*=6.2Hz, OC*H*(CH$_3$)$_2$], 4.96-5.06 (2H, m, CH=C*H*$_2$), 5.69-5.82 (1H, m, C*H*=$CH_2$), 6.41 (1H, q, *J*=6.9Hz, C=C*H*$CH_3$), 6.88 (1H, d, *J*=8.4Hz, 5-H), 7.12-7.36 (6H, m, 6-H, 8-H, 9-H and 10-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 16.1 ($CH_3$), 22.4 and 22.7 [OCH(*C*H$_3$)$_2$], 50.3 and 50.7 ($ArCH_2N$), 51.7 and 52.0 (N*C*H$_2$CH), 55.5 and 56.1 ($OCH_3$), 74.7 [O*C*H(CH$_3$)$_2$], 110.8 (5-C), 114.0 (2-C[a]), 115.6 (CH=*C*H$_2$), 115.9 (C=*C*HCH$_3$[a]), 124.1 (6-C[b]), 125.3 (1-C[b]), 125.9 and 126.1 (8-C), 126.6 (10-C[b]), 128.2 and 128.5 (9-C), 133.4 (*C*H=$CH_2$), 136.8 and 136.9 (*C*=$CHCH_3$), 141.4 (7-C), 144.8 (3-C), 152.3 (4-C); **MS *m/z*** 351 ($M^+$, 8%), 28 (88), 32 (14), 69 (100), 131 (18), 161 (5), 219 (30), 220 (5), 252 (17), 253 (7), 264 (6), 294 (4), 310 (9), 351 (8), ***HRMS*** calculated for $C_{23}H_{29}NO_2$: 351.21983, found: 351.21969.

### *2.47 Preparation of N-allyl-N-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-benzyl]-acetamide **250***

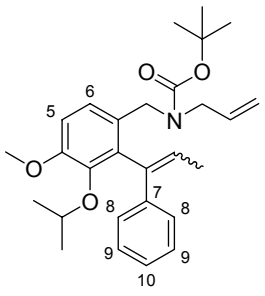



**250**

A solution was prepared of *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-2-propen-1-amine **249** (1.43mmol, 0.504g) and distilled pyridine (1eq, 1.43mmol, 0.120cm$^3$), which was then cooled to 0$^o$C in an ice-water bath. To this was added dropwise a solution of pre-distilled acetic anhydride (1.5eq, 2.15mmol, 0.200cm$^3$) and distilled pyridine (1.5eq, 2.15mmol, 0.190cm$^3$). Then the ice-water bath was removed and the reaction mixture was stirred at rt for 3 h. Thin layer chromatography indicated that the reaction had gone to completion so the reaction mixture was diluted with EtOAc (15cm$^3$) and allowed to stir for 5 min. Then the organic mixture was extracted with brine (3×20cm$^3$). The combined aqueous layers were then extracted with $CH_2Cl_2$ (3×20cm$^3$). The combined organics were then washed with a saturated $NH_4Cl$ solution that had been basified to pH 11 using a 25% ammonia solution (50cm$^3$). The combined organics were then dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to yield an orange oil. This was then purified by column chromatography (10-40% EtOAc-Hexane) to yield the desired product as a dark yellow oil (0.373g, 66%).

***R**f* = 0.22 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 698 (alkane), 772 (5 adj Ar H), 985 ($RCH=CH_2$), 1216 (C-O), 1382 and 1436 (alkane), 1480 and 1575 (Ar ring), 1631 (tertiary amide or isolated C=C), 2839 ($-OCH_3$), 2936 ($-CH_3$), 3018 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.01-1.14 [6H, m, $OCH(CH_3)_2$], 1.65 (3H, dd, *J*=4.1 and 6.9Hz, $CH_3$), 1.95 and 1.99 (3H, two s, $COCH_3$), 3.85 (3H, d, *J*=4.5Hz, $OCH_3$), 3.93 (2H, d, *J*=6.0Hz, $NCH_2CH$), 4.06 and 4.14 (2H, two s, $ArCH_2N$), 4.20-4.40 [1H, m, $OCH(CH_3)_2$], 4.88-5.05 (2H, m, $CH=CH_2$), 5.45-5.73 (1H, m, $CH=CH_2$), 6.42 (1H, m, $C=CHCH_3$), 6.83-6.97 (2H, m, 5-H and 6-H), 7.14-7.27 (5H, m, 8-H, 9-H and 10-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 15.9 and 16.0 ($CH_3$), 21.2 ($COCH_3$), 22.5 and 22.6 [$OCH(CH_3)_2$], 45.3 ($ArCH_2N^a$), 48.1 ($NCH_2C$), 48.5 ($ArCH_2N^a$), 55.5 ($OCH_3$), 74.8 and 74.9 [$OCH(CH_3)_2$], 110.9 and 111.0 (5-C), 116.3 and 117.4 ($CH=CH_2$), 119.9 and 123.0 (6-C), 125.2 ($C=CHCH_3$), 125.5 and 125.7 (8-C), 126.5 (2-C$^b$), 126.9 (10-C$^b$), 127.4 (1-C$^b$), 128.1 and 128.3 (9-C), 132.5 and 132.8 ($CH=CH_2^c$), 135.9 and 136.3 ($C=CHCH_3^c$), 140.2 and 140.7 (7-C), 144.7 and 145.3 (3-C), 152.4 and 152.5 (4-C), 170.9 and 171.1 (C=O); **MS *m/z*** 393 ($M^+$, 33%), 41 (40), 43 (17), 45 (10), 55 (15), 56 (14), 57 (36), 69 (10), 220 (18), 225 (13), 237 (17), 251 (47), 252 (100), 253 (38), 268 (18), 294 (17), 322 (10), 365 (23), 393 (33), 394 (11), ***HRMS*** calculated for $C_{25}H_{31}NO_3$: 393.23039, found: 393.23103.

### *2.48 Preparation of tert-butyl allyl[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-benzyl]carbamate **251***

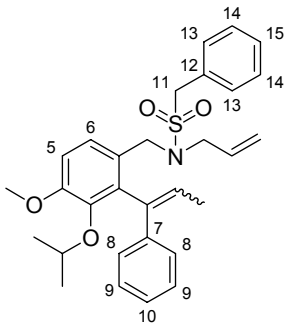



**251**

The *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-pro-penyl)benzyl]-2-propen-1-amine **249** (1.42mmol, 0.500g) was dissolved in pre-distilled THF (50cm$^3$). To this was added $Boc_2O$ (1.2 eq, 1.71mmol, 0.400cm$^3$) and the solution was stirred for 5 min before the addition of the DMAP (0.1eq, 0.142mmol, 0.0177g). The reaction mixture was allowed to stir at rt under an Ar atmosphere for 2.25 h. After this time the solvent was removed *in vacuo* to yield a purple oil. The crude mixture was then purified by column chromatography (5-10% EtOAc-Hexane) to yield the desired compound as a purple oil (0.592g, 92%). Peak broadening was observed in the $^1$H NMR spectra due to amide rotamers.

***R**f* = 0.76 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (5 adj Ar H), 1216 (C-O), 1404 (alkane), 1478 (Ar ring), 1693 (tertiary amide), 3019 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.00 and 1.10 [6H, two d, *J*=5.7Hz, OCH($CH_3$)$_2$], 1.39 and 1.44 [9H, two s, OC($CH_3$)$_3$], 1.63 (3H, d, *J*=6.7Hz, $CH_3$), 3.47-3.80 (2H, m, $NCH_2C$), 3.84 (3H, s, $OCH_3$), 4.02-4.20 (2H, $ArCH_2N$), 4.27 [1H, sept, *J*=6.2Hz, OC*H*($CH_3$)$_2$], 4.81-5.00 (2H, m, CH=C$H_2$), 5.58-5.68 (1H, m, C*H*=$CH_2$), 6.37 (1H, q. *J*=6.8Hz, C=C*H*$CH_3$), 6.82-6.95 (2H, m, 5-H and 6-H), 7.15-7.26 (5H, m, 8-H, 9-H and 10-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 15.8 and 15.9 ($CH_3$), 22.5 and 22.6 [OCH(*C*$H_3$)$_2$], 27.7 and 28.3 [OC(*C*$H_3$)$_3$], 46.4 and 46.9 ($ArCH_2N$), 48.9 ($NCH_2C$), 55.5 ($OCH_3$), 74.7 [O*C*H($CH_3$)$_2$], 79.6 [O*C*($CH_3$)$_3$], 110.8 (2-C[a]), 111.1 (5-C[a]), 116.1 and 116.9 (CH=*C*$H_2$), 120.5 (6-C[b]), 122.0 (1-C[b]), 125.0 and 125.2 (C=*C*H$CH_3$), 125.7 and 126.6 (8-C), 127.7 (10-C), 128.2 and 129.2 (9-C), 133.5 (*C*H=$CH_2$), 136.4 (*C*=$CHCH_3$), 140.9 (7-C), 144.8 (3-C), 152.1 (4-C), 155.9 (C=O); **MS *m/z*** 451 ($M^+$, 13%), 41 (10), 57 (18), 70 (11), 225 (11), 237 (12), 239 (10), 251 (46), 252 (100), 253 (29), 254 (10), 292 (5), 293 (8), 294 (55), 296 (21), 297 (14), 308 (7), 350 (14), 351 (6), 395 (11), 451 (13), 452 (5), ***HRMS*** calculated for $C_{28}H_{37}NO_4$: 451.27226, found: 451.27299.

### *2.49 Preparation of N-allyl-N-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-benzyl]-phenylmethanesulfonamide **252***

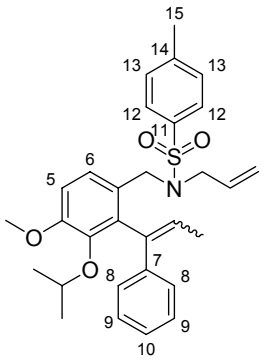



**252**

The *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-2-propen-1-amine **249** (1.34mmol, 0.470g) was dissolved in pre-distilled $CH_2Cl_2$ (5cm$^3$). Then $NEt_3$ (2.5eq, 3.34mmol, 0.500cm$^3$) was added and the reaction mixture was allowed to stir for 15 min before the dropwise addition of the α-toluenesulfonyl chloride (1.1eq, 1.47mmol, 0.284g), which had been dissolved up in $CH_2Cl_2$ (2cm$^3$). During the addition a white gas was liberated. The reaction mixture was allowed to stir at rt under an Ar atmosphere for 4 h, after which time the colour had changed from yellow to dark orange. The solvent was removed *in vacuo* to yield a yellow oil with crystals in it. The mixture was then purified by column chromatography (5-15% EtOAc-Hexane) to give the product as an orange solid (0.302g, 45%).

***$R_f$*** = 0.63 (30% EtOAc-Hexane); ***m.p.*** 105-108°C; **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (5 adj Ar H), 702 (alkane), 765 (5 adj Ar H), 999 (RCH=$CH_2$), 1151 (-$SO_2$-N-), 1337 (-$SO_2$-N-), 1377 and 1442 (alkane), 1482 (Ar ring), 1694 (C=C), 2977 (-$CH_3$), 3020 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.00 and 1.08 [6H, two d, *J*=6.1Hz, OCH(C*H*$_3$)$_2$], 1.49 (3H, d, *J*=7.0Hz, $CH_3$), 3.59 (2H, t, *J*=7.4Hz, $NCH_2C$), 3.73 (2H, two s, $ArCH_2N$), 3.83 (3H, s, $OCH_3$), 4.11-4.24 [3H, m, $ArCH_2SO_2$ and OC*H*(CH$_3$)$_2$], 4.92-5.01 (2H, m, CH=C*H*$_2$), 5.41-5.55 (1H, m, C*H*=$CH_2$), 6.32 (1H, q, *J*=7.0Hz, C=C*H*CH$_3$), 6.90 (1H, d, *J*=8.6Hz, 5-H), 7.14-7.28 (11H, m, 6-H, 8-H, 9-H, 10-H, 13-H, 14-H and 15-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 16.0 ($CH_3$), 22.4 and 22.6 [OCH(*C*H$_3$)$_2$], 48.3 ($ArCH_2N$), 50.1 ($NCH_2C$), 55.5 ($OCH_3$), 59.1 ($ArCH_2SO_2$), 74.7 and 74.8 [O*C*H(CH$_3$)$_2$], 111.2 (5-C), 119.2 (CH=*C*H$_2$), 122.7 (6-C), 125.6 (C=*C*HCH$_3$), 125.7 (8-C[a]), 126.7 (1-C and 2-C), 127.5 (15-C[b]), 128.3 (14-C[a]), 128.5 (9-C[a]), 129.0 (10-C[b]), 130.6 (13-C), 132.3 (*C*H=CH$_2$[c]), 132.7 (12-C[c]), 136.0 (C=*C*HCH$_3$[c]), 140.8 (7-C), 144.5 (3-C), 152.4 (4-C); **MS *m/z*** 505 ($M^+$, 19%), 41 (79), 42 (78), 53 (63), 56 (66), 60 (53), 69 (76), 70 (35), 84 (31), 85 (30), 91 (55), 129 (32), 254 (62), 255 (39), 256 (76), 308 (49), 350 (100), 351 (28), ***HRMS*** calculated for $C_{30}H_{35}NO_4S$: 505.22868, found: 505.22896.

## *2.50 Preparation of N-allyl-N-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-benzyl]-4-methylbenzenesulfonamide **253***

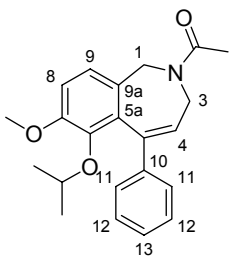



**253**

The tosyl chloride was purified according to Perrin[219] before use. The *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-2-propen-1-amine **249** (1.38mmol, 0.484g) was dissolved in distilled $CH_2Cl_2$ (5cm$^3$) and the solution was cooled to 0°C in an ice-water bath. To this solution was added $NEt_3$ (1.4eq, 1.93mmol, 0.270cm$^3$) and it was allowed to stir for 5 min before the addition of the tosyl chloride (1.2eq, 1.65mmol, 0.312g). The reaction mixture was then allowed to stir at 0°C under an Ar atmosphere for 2 h and then at rt for a further 1 h. After this time distilled water (5cm$^3$) was added and the aqueous layer was extracted with $CH_2Cl_2$ (5cm$^3$). The combined organics were then extracted with distilled water (2×5cm$^3$) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to yield a yellow-orange oil that solidified on standing. The crude compound was then purified by column chromatography (5-15% EtOAc-Hexane) to yield a pale pink oil that solidified on stading (0.493g, 71%).

***$R_f$*** = 0.68 (30% EtOAc-Hexane); ***m.p.*** 110-103°C; **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 671 and 771 (5 adj Ar H), 929 (RCH=$CH_2$), 1163 and 1338 (-$SO_2$-N-), 1430 (alkane), 1481 (Ar ring), 1601 (C=C), 2832 (-$OCH_3$), 2981 (-$CH_3$), 3022 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.00 and 1.10 [6H, two d, *J*=6.2Hz, OCH($CH_3$)$_2$], 1.60 (3H, d, *J*=6.8Hz, $CH_3$), 2.40 (3H, s, Ts$CH_3$), 3.68-3.71 (2H, m, $NCH_2$C), 3.85 (3H, s, $OCH_3$), 4.02 and 4.08 (2H, two s, Ar$CH_2$N), 4.25 [1H, sept, *J*=6.1Hz, OC*H*($CH_3$)$_2$], 4.79-4.87 (2H, m, CH=C$H_2$), 5.30-5.44 (1H, m, C*H*=$CH_2$), 6.33 (1H, q, *J*=6.9Hz, C=C*H*$CH_3$), 6.92 (1H, d, *J*=8.6Hz, 5-H), 7.15-7.30 (8H, m, 6-H, 8-H, 9-H, 10-H and 13-H), 7.55 (2H, d, *J*=8.2Hz, 12-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 16.0 ($CH_3$), 21.5 (Ts$CH_3$), 22.4 and 22.6 [OCH(*C*$H_3$)$_2$], 47.9 (Ar$CH_2$N), 50.6 (N*C*$H_2$C), 55.5 ($OCH_3$), 74.7 [O*C*H($CH_3$)$_2$], 111.0 (5-C), 118.8 (CH=*C*$H_2$), 122.6 (6-C), 125.5 (C=*C*H$CH_3$), 125.8 (8-C), 126.6 (2-C[a]), 127.2 (12-C), 127.6 (10-C), 128.2 (9-C), 129.2 (1-C[a]), 129.5 (13-C), 132.1 (*C*H=$CH_2$), 136.1 (*C*=CH$CH_3$), 137.1 (11-C[b]), 140.7 (7-C[b]), 143.0 (14-C[b]), 144.6 (3-C), 152.4 (4-C); **MS *m/z*** 505 ($M^+$, 7%), 41 (50), 42 (37), 55 (31), 56 (27), 69 (80), 72 (21), 81 (37), 91 (22), 251 (20), 252 (69), 253 (32), 294 (23), 308 (34), 350 (100), 351 (26), ***HRMS*** calculated for $C_{30}H_{35}NO_4S$: 505.22868, found: 505.22896.

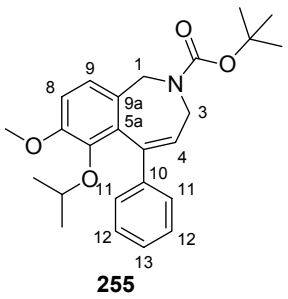
## *2.51 Attempted synthesis of 2-acetyl-6-isopropoxy-7-methoxy-5-phenyl-2,3-dihydro-1H-2-benzazepine **254***



**254**

A solution was prepared from *N*-allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]acetamide **250** (0.404mmol, 0.159g) and pre-distilled toluene (15cm$^3$) and this was degassed using $N_2$ for 10 min. Then the Grubbs II catalyst **11** (0.08eq, 0.0323mmol, 0.0282g) was added and the reaction mixture was heated to 80°C under an Ar atmosphere for 2.5 h. After this time thin layer chromatography confirmed that all the starting material had been consumed, so the solvent was removed *in vacuo* to yield a dark brown oil that was then purified by column chromatography (5-15% EtOAc-Hexane). NMR spectroscopy confirmed the formation of the isomerised diene *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-*N*-(1-propenyl)acetamide **258** (0.0513g, 32%).

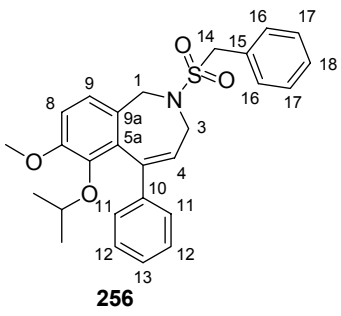
*2.52 Attempted synthesis of tert-butyl 6-isopropoxy-7-methoxy-5-phenyl-1,3-dihydro-2H-2-bezazepine-2-carboxylate **255***




**255**

The *tert*-butyl allyl[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]carbamate **251** (0.459 mmol, 0.208g) was dissolved in pre-distilled toluene (20cm$^3$) and this solution was degassed using $N_2$ for 10 min. To this solution was added Grubbs II catalyst **11** (0.08eq, 0.0368mmol, 0.0313g) and the reaction mixture was heated to 80$^o$C for 22 h. After this time the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo* to yield a dark brown oil. This was then purified by column chromatography (5-10% EtOAc-Hexane) to obtain a pale yellow-brown oil (0.062g). We could not use NMR spectroscopy to determine if product formation had occurred due to the peak broadening because of the amide rotamers. HRMS found a peak at 410.38540, which may have been the M+1H peak, but this is inconclusive evidence for product formation.

*2.53 Attempted synthesis of 6-isopropoxy-7-methoxy-5-phenyl-2-[(phenylsulfonyl)-methyl]-2,3-dihydro-1H-2-benzazepine **256***

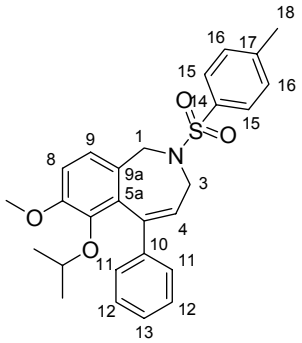



**256**

The *N*-allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]phenylmethanesul-fonamide **252** (0.185mmol, 0.0934g) was dissolved in pre-distilled toluene (10cm$^3$) and the solution was degassed using $N_2$ for 10 min. Then the Grubbs II catalyst **11** (0.05eq, 0.00924mmol, 0.0083g) was added and the reaction mixture was allowed to stir at 60$^o$C under an Ar atmosphere for 23 h. After this time the reaction mixture was cooled to rt and the solvent was removed *in vacuo* to yield a dark brown-black oil. The crude mixture was then purified by column chromatography (5-20% EtOAc-Hexane) to yield pale yellow semi-solid (0.0114g). The NMR spectra were very complex and could not be used for identification purposes. HRMS found the molecular ion at 463.18040 as required, however, this is not sufficient evidence for product formation.

**MS *m/z*** 463 ($M^+$, 1%), 41 (10), 43 (12), 91 (100), 100 (21), 137 (12), 163 (12), 175 (26), 176 (14), 189 (13), 204 (38), 220 (10), 246 (10), 252 (15), 268 (13), 310 (15), 401 (41), 402 (10), ***HRMS*** calculated for $C_{27}H_{29}NO_4S$: 463.18173, found: 463.18040.

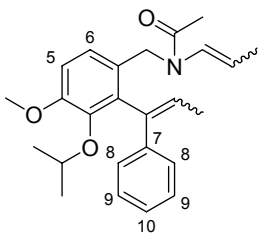
## *2.54 Attempted synthesis of 6-isopropoxy-7-methoxy-2-[(4-methylphenyl)sulfonyl]-5-phenyl-2,3-dihydro-1H-2-benzazepine **257***




**257**

*N*-Allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-4-methyl-benzenesulfonamide **253** (0.304mmol, 0.154g) was dissolved up in pre-distilled toluene (15cm$^3$) and the solution was degassed using $N_2$ for 10 min. Then Grubbs II catalyst **11** (0.08eq, 0.0243mmol, 0.0219g) was added and the solution was heated to 80$^o$C for 22 h. After this time the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo* to yield a brown-black oil. This was then purified by column chromatography (5-20% EtOAc-Hexane). HRMS found peaks in the region for the six-membered ring (449.1661) and for the seven-membered ring (463.18137), but the NMR spectra were uninterperable.

## *2.55 Preparation of N-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-N-(1-propenyl)acetamide **258***



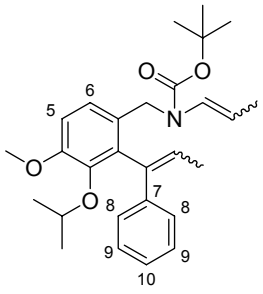

**258**

The *N*-allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-benzyl]acetamide **250** (0.265mmol, 0.104g) was dissolved in toluene (10cm$^3$). The solution was then heated to 90$^o$C before the addition of the Ru-isomerisation catalyst **12** (0.02eq, 0.00530mmol, 0.0053g). The reaction mixture was then stirred at 90$^o$C under an Ar atmosphere for 21 h. The isomerisation was confirmed by $^1$H NMR spectroscopy, the reaction mixture was cooled to rt and the solvent was removed *in vacuo*. The crude mixture was then purified by column chromatography (5-10% EtOAc-Hexane) to yield the desired product as a yellow oil (0.0852g, 82%).

***R_f*** = 0.48 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (alkane), 772 (5 adj Ar H), 1216 (C-O), 1379 and 1410 (alkanes), 1645 (tertiary amide or isolated C=C), 3019 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.03-1.17 [6H, m, OCH($CH_3$)$_2$], 1.51 and 1.59 (3H, two d, *J*=6.6Hz,

C=CHC*H*$_3$), 1.70 (3H, d, *J*=7.0Hz, $CH_3$), 1.91 and 2.22 (3H, two s, $COCH_3$), 3.82 and 3.85 (3H, two s, $OCH_3$), 4.13-4.91 [3H, m, $ArCH_2N$ and OC*H*$(CH_3)_2$], 4.69 (1H, qd, *J*=6.6 and 13.4Hz, CH=C*H*$CH_3$), 6.40-6.50 (1H, m, C=C*H*$CH_3$), 6.70 (1H, dd, *J*=5.7 and 8.4Hz, 5-H), 6.85 (1H, t, *J*=8.6Hz, 6-H), 7.17-7.29 (6H, m, NC*H*=CH, 8-H, 9-H and 10-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 15.3 and 15.4 (C=CH*C*$H_3$), 16.0 and 16.1 ($CH_3$), 21.9 and 22.2 (CO*C*$H_3$), 22.5 and 22.7 [OCH(*C*$H_3)_2$], 44.7 and 47.8 ($ArCH_2N$), 55.5 ($OCH_3$), 74.8 and 75.0 [O*C*H$(CH_3)_2$], 109.0 (NCH=*C*H$CH_3$), 111.1 (6-C), 119.7 and 120.6 (5-C), 125.4 (ArC=*C*H$CH_3$), 125.5 and 125.6 (8-C), 125.9 and 126.0 (N*C*H=CH), 126.7 and 126.8 (10-C), 127.9 and 128.3 (9-C), 132.0 and 132.6 (2-C[a]), 135.8 and 136.3 (1-C[a]), 140.2 and 140.7 (7-C), 144.9 and 145.3 (3-C), 152.0 and 152.4 (4-C), 169.1 and 169.5 (C=O); **MS *m/z*** 393 ($M^+$, 60%), 91 (16), 115 (12), 129 (15), 165 (22), 176 (13), 179 (19), 192 (11), 194 (10), 220 (10), 221 (18), 252 (38), 253 (100), 337 (20), 393 (60), 394 (17), ***HRMS*** calculated for $C_{25}H_{31}NO_3$: 393.23039, found: 393.23162.

## *2.56 Preparation of tert-butyl 3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-benzyl(1-propenyl)carbamate **259***



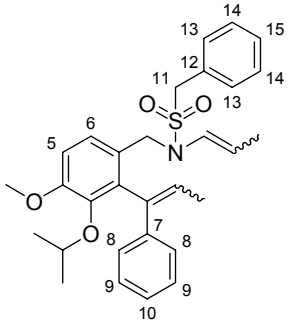

**259**

The *tert*-butyl allyl[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]carbamate **251** (0.338mmol, 0.152g) was dissolved in toluene (15cm$^3$) and the solution was heated to 90$^o$C. Then the Ru-isomerisation catalyst **12** (0.02eq, 0.00675mmol, 0.0065g) was added and the reaction mixture was stirred at 90$^o$C under an Ar atmosphere for 17.5 h. After this time a small amount was removed for $^1$H NMR spectroscopy, which showed complete isomerisation of the double bond. Thus the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo*. The crude mixture was purified by column chromatography (5% EtOAc-Hexane) to yield the desired compound as a dark pink-purple oil (0.147g, 96%).

***R*$_f$** = 0.80 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (5adj Ar H), 876 (2 adj Ar H), 1218 (C-O), 1423 (alkane), 1479 and 1520 (Ar ring), 1682 (tertiary amide), 2978 (-$CH_3$), 3020 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.00-1.13 [6H, m, OCH(C*H*$_3)_2$], 1.23-1.60 [12H, m, OC(C*H*$_3)_3$ and CH=CHC*H*$_3$], 1.69 (3H, d, *J*=6.0Hz, C=CHC*H*$_3$), 3.83 (3H, s, $OCH_3$), 3.97-4.50 [4H, m, $ArCH_2N$, OC*H*$(CH_3)_2$ and NCH=C*H*], 6.40-6.44 (1H, m, C=C*H*$CH_3$), 6.67-6.71

(1H, m, 5-H), 6.84-6.98 (1H, m, 6-H), 7.09-7.26 (6H, m, NC*H*=C, 8-H, 9-H and 10-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 16.0 (CH=CH*C*$H_3$), 16.1 (C=CH*C*$H_3$), 22.5 and 22.7 [OCH(*C*$H_3$)$_2$], 28.2 and 28.3 [OC(*C*$H_3$)$_3$], 46.2 (Ar$CH_2$N), 55.4 and 55.5 ($OCH_3$), 74.8 [O*C*H($CH_3$)$_2$], 80.7 [O*C*($CH_3$)$_3$], 104.1 (NCH=*C*H), 110.8 and 111.0 (5-C), 119.4 (6-C[a]), 120.1 (2-C[a]), 124.9 (C=*C*H$CH_3$), 125.9 (8-C[b]), 126.7 (1-C[b]), 127.8 (10-C[c]), 128.3 (9-C[c]), 129.3 (*C*=CH$CH_3$), 136.2 (N*C*H=CH), 140.7 (7-C), 144.9 (3-C), 151.9 (4-C), 153.6 (C=O); **MS *m/z*** 451 ($M^+$, 3%), 57 (64), 70 (8), 91 (9), 115 (5), 130 (8), 165 (9), 175 (6), 178 (7), 221 (9), 237 (8), 252 (47), 253 (100), 254 (19), 280 (7), 292 (9), 295 (37), 297 (38), 308 (5), 322 (7), 339 (70), 340 (15), 350 (9), 395 (39), 396 (10), ***HRMS*** calculated for $C_{28}H_{37}NO_4$: 451.27226, found: 451.27373.

### *2.57 Preparation of N-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-(phenyl)-N-(1-propenyl)methanesulfonamide **260***



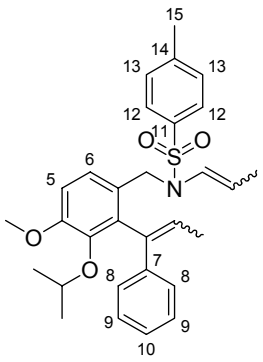

**260**

The *N*-allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]phenylmethanesulfonamide **252** (0.277mmol, 0.141g) was dissolved up in toluene (14$cm^3$) and the solution was heated to 90$^o$C before the addition of the Ru-isomerisation catalyst **12** (0.02eq, 0.00554mmol, 0.0052g). Then the reaction mixture was left to stir at 90$^o$C under an Ar atmosphere for 27 h, after which time $^1$H NMR spectroscopy showed total isomerisation of the double bond. The reaction mixture was thus allowed to cool to rt and the solvent was removed *in vacuo*. Then the crude compound was purified by column chromatography (5-10% EtOAc-Hexane) to yield the desired product as a bright yellow semi-solid (0.127g, 90%).

***$R_f$*** = 0.76 (30% EtOAc-Hexane); ***m.p.*** 92-95$^o$C; **$\nu_{max}$/$cm^{-1}$ (NaCl plate)** 744 (5 adj Ar H), 1154 and 1354 (-$SO_2$-N-), 1382 (alkane), 1479 (-$CH_3$ or –$CH_2$ deformations), 2979 (-$CH_3$ or –$CH_2$); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.00 and 1.07 [6H, two d, *J*=6.1Hz, OCH(C*H*$_3$)$_2$], 1.25-1.27 (3H, m, C=CHC*H*$_3$), 1.44 and 1.51 (3H, two d, *J*=6.6 and 6.9Hz respectively, CH=CHC*H*$_3$), 3.70 (3H, s, $OCH_3$), 3.77-3.83 (2H, m, Ar$CH_2$N), 4.08-4.22 [3H, m, OC*H*($CH_3$)$_2$ and Ar$CH_2SO_2$], 4.39 (1H, dt, *J*=6.7 and 13.3Hz, NCH=C*H*), 6.28-6.33 (2H, m, NC*H*=CH and C=C*H*$CH_3$), 6.85 (1H, d, *J*=8.6Hz, 5-H), 7.06 (1H, d, *J*=8.6Hz, 6-H), 7.14-7.28 (10H, 8-H, 9-H, 10-H, 13-H, 14-H and 15-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 15.0 (C=CH*C*$H_3$), 15.9

(CH=CH*C*$H_3$), 22.4 and 22.7 [OCH(*C*$H_3$)$_2$], 48.1 (Ar$CH_2$N), 55.5 ($OCH_3$), 58.3 (Ar$CH_2SO_2$), 74.8 [O*C*H($CH_3$)$_2$], 107.0 (NCH=*C*H), 111.2 (5-C), 121.3 (6-C), 125.4 (N*C*H=CH[a]), 125.8 (8-C), 126.2 (C=C*H*$CH_3$[a]), 126.7 (15-C[b]), 128.3 (9-C[c]), 128.6 (14-C[c]), 128.7 (10-C[b]), 130.7 (13-C), 131.9 (12-C), 135.8 (*C*=CH$CH_3$), 140.4 (7-C), 144.5 (3-C), 152.2 (4-C); **MS *m/z*** 505 ($M^+$, 2%), 41 (8), 43 (7), 91 (83), 92 (7), 129 (7), 165 (9), 175 (7), 221 (10), 237 (8), 251 (19), 252 (38), 253 (100), 254 (19), 268 (23), 292 (12), 294 (16), 295 (27), 296 (8), 308 (15), 310 (26), 350 (69), 351 (17), 449 (41), 450 (12), ***HRMS*** calculated for $C_{30}H_{35}NO_4S$: 505.22868, found: 505.22717.

## *2.58 Preparation of N-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-4-methyl-N-(1-propenyl)benzenesulfonamide **261***



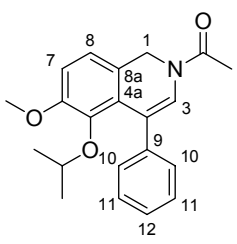

**261**

*N*-Allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-pro-penyl)benzyl]-4-methyl-benzenesulfonamide **253** (0.398mmol, 0.201g) was dissolved in toluene (20$cm^3$) and the solution was heated to 90°C before the addition of the Ru-isomerisation catalyst **12** (0.02eq, 0.00796mmol, 0.0085g). The reaction mixture was stirred at 90°C under an Ar atmosphere for 26 h. After this time $^1$H NMR spectroscopy showed only starting material was present, additional Ru-isomerisation catalyst (0.02eq, 0.00796mmol, 0.0079g) was added and the reaction mixture was stirred at 90°C for a further 18 h. Following this $^1$H NMR spectroscopy still highlighted the presence of some unreacted starting material, thus the reaction mixture was heated to 100°C and Ru-isomerisation catalyst (0.02eq, 0.00796mmol, 0.0085g) was added. The reaction mixture was stirred at 100°C for a further 21 h. After this time $^1$H NMR spectroscopy showed complete isomerisation of the double bond, so the reaction mixture was allowed to cool to rt and the solvent was removed *in vacuo* to yield a brown oil. The oil was then purified by column chromatography (5% EtOAc-Hexane) and the desired compound was obtained as a orange-pink solid (0.165g, 82%).

***$R_f$*** = 0.72 (30% EtOAc-Hexane); ***m.p.*** 124-127°C; **$\nu_{max}$/$cm^{-1}$ (NaCl plate)** 743 (5 adj Ar H), 1165 and 1382 (-$SO_2$-N-), 1479 (-$CH_2$ or –$CH_3$ deformations), 2980 (-$CH_2$ or –$CH_3$); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.04 and 1.12 [6H, two d, *J*=6.1Hz, OCH(C*H*$_3$)$_2$], 1.49 (3H, d, *J*=6.5Hz, C=CHC*H*$_3$), 1.65 (3H, d, *J*=6.9Hz, CH=CHC*H*$_3$), 2.39 (3H, s, Ts$CH_3$), 3.84 (3H, s, $OCH_3$), 4.03 (2H, s, Ar$CH_2$N), 4.25 [1H, sept, *J*=6.0Hz, OC*H*(C$H_3$)$_2$], 4.45 (1H, dt, *J*=6.5 and 13.3Hz,

CH=C*H*CH$_3$), 6.38 (1H, q, *J*=6.9Hz, C=C*H*CH$_3$), 6.52 (1H, d, *J*=14.0Hz, NC*H*=CH), 6.88 (1H, d, *J*=8.6Hz, 5-H), 7.13-7.26 (8H, m, 6-H, 8-H, 9-H, 10-H and 13-H), 7.46 (2H, d, *J*=8.1Hz, 12-H); **$\delta_C$ (50 MHz, CDCl$_3$)** 15.1 (C=CH*C*H$_3$), 16.0 (CH=CH*C*H$_3$), 21.5 (TsCH$_3$), 22.4 and 22.7 [OCH(*C*H$_3$)$_2$], 47.3 (ArCH$_2$N), 55.5 (OCH$_3$), 74.9 [O*C*H(CH$_3$)$_2$], 107.9 (CH=*C*HCH$_3$), 111.1 (5-C), 121.5 (6-C), 124.7 (C=*C*HCH$_3$), 125.6 and 125.7 (N*C*H=CH), 125.8 (8-C), 126.7 (2-C$^a$), 126.8 and 126.9 (12-C), 127.1 (1-C$^a$), 128.3 and 128.4 (9-C), 129.4 and 129.6 (13-C), 131.9 (*C*=CHCH$_3$), 135.9 and 136.6 (11-C), 140.6 and 140.8 (7-C), 143.1 and 143.3 (14-C), 144.7 and 144.8 (3-C), 152.2 and 153.1 (4-C); **MS *m/z*** 505 (M$^+$, 1%), 58 (8), 91 (31), 129 (10), 165 (10), 175 (9), 178 (8), 221 (12), 237 (8), 251 (20), 252 (33), 253 (100), 254 (19), 293 (10), 294 (14), 295 (24), 309 (10), 350 (71), 351 (19), 449 (44), 450 (12), ***HRMS*** calculated for $C_{30}H_{35}NO_4S$: 505.22868, found: 505.22739.

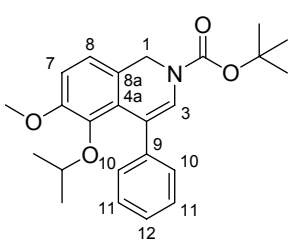
## *2.59 Attempted synthesis of 2-acetyl-5-isopropoxy-6-methoxy-4-phenyl-1,2-dihydroisoquinoline **262***



**262**

A solution was prepared of *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-*N*-(1-propenyl])acetamide **258** (0.101mmol, 0.0398g) in distilled toluene (5cm$^3$). The solution was then heated to 80$^o$C before the addition of Grubbs II catalyst **11** (0.08eq, 0.00809mmol, 0.0069g). The reaction mixture was then allowed to stir at 80$^o$C under an Ar atmosphere for 18 h. After this time the solvent was removed *in vacuo* and the crude reaction mixture was purified by column chromatography (5% EtOAc-Hexane). The reaction yielded no product (trace amounts were detected by HRMS, peak found at 337.16737) and starting material was recovered (0.0274g, 69% recovery).

## *2.60 Attempted synthesis of tert-butyl 5-isopropoxy-6-methoxy-4-phenyl-2(1H)-isoquinoline carboxylate **263***

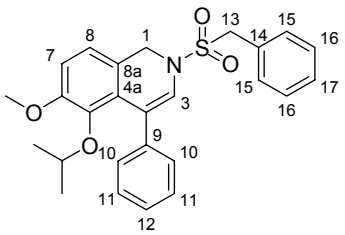


**263**

A solution was prepared of *tert*-butyl 3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl(1-propenyl)-carbamate **259** (0.258mmol, 0.116g) in distilled toluene (10cm$^3$) and it was heated to 80$^o$C. Then Grubbs II catalyst **11** (0.08eq,

0.0206mmol, 0.0180g) was added and the reaction mixture was stirred at 80°C under an Ar atmosphere for 19.5 h. After this time the solvent was removed *in vacuo* to yield a dark brown oil that was purified by column chromatography (5% EtOAc-Hexane). None of the desired product was isolated (trace amounts detected by HRMS, peak found at 395.20854), only starting material was recovered (0.116g, 100% recovery).

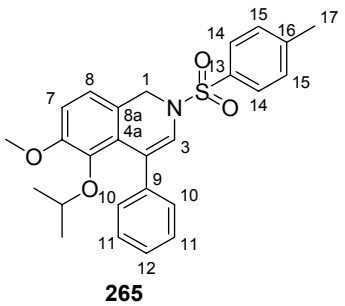
### *2.61 Attempted synthesis of 2-(benzylsulfonyl)-5-isopropoxy-6-methoxy-4-phenyl-1,2-dihydroisoquinoline **264***




**264**

The *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-benzyl](phenyl)-*N*-(1-propenyl)methanesulfonamide **260** (0.136mmol, 0.0689g) was dissolved in distilled toluene (7cm$^3$) and the solution was heated to 80°C. Then Grubbs II catalyst **11** (0.08eq, 0.0109mmol, 0.0105g) was added and the reaction mixture was stirred at 80°C under an Ar atmosphere for 23 h. After this time thin layer chromatography indicated no change so the solvent was removed *in vacuo* and the crude mixture was purified by column chromatography (5% EtOAc-Hexane). No ring-closed product was isolated (trace amounts determined by HRMS, peak found at 449.16631), only starting material was recovered (0.0544g, 79% recovered).

### *2.62 Attempted synthesis of 5-isopropoxy-6-methoxy-2-[(4-methylphenyl)sulfonyl]-4-phenyl-1,2-dihydroisoquinoline **265***




**265**

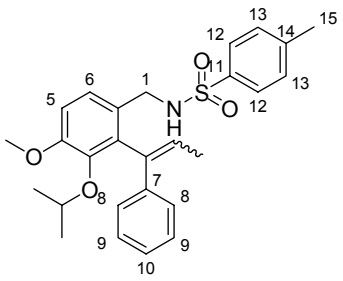
Attempt 1:

*N*-[3-Isopropoxy-4-methoxy-2-(1-phenyl-1-pro-penyl)benzyl]-4-methyl-*N*-(1-propenyl)benzene-sulfonamide **261** (0.209mmol, 0.106g) was dissolved up in distilled toluene (10cm$^3$). The solution was heated to 80°C before the addition of the Grubbs II catalyst **11** (0.08eq, 0.0167mmol, 0.0142g). Then the reaction mixture was allowed to stir at 80°C under an Ar atmosphere for 24 h. After this time thin layer chromatography showed no further change so the solvent was removed *in vacuo* to yield a dark brown oil that was

purified by column chromatography (5% EtOAc-Hexane). None of the desired product was isolated but starting material was recovered (0.0813g, 39% recovered).

Attempt 2:

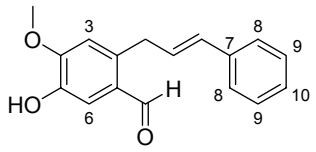
A solution was prepared of *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-4-methyl-*N*-(1-propenyl)benzenesulfonamide **261** (0.0613mmol, 0.0310g) in distilled toluene (2cm$^3$) and it was heated to 80$^o$C. Then Grubbs II catalyst **11** (0.1eq, 0.00490mmol, 0.0054g) was added and the reaction mixture was allowed to stir at 80$^o$C under an Ar atmosphere for 17 h. After this time thin layer chromatography showed no further change so the solvent was removed *in vacuo*. The crude reaction mixture was purified by column chromatography (5-10% EtOAc-Hexane) to yield the de-allylated product, *N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-4-methylbenzenesulfonamide **266**, as a white semi-solid (0.0092g, 32%).




**266**

***R**$_f$* = 0.45 (30% EtOAc-Hexane); ***m.p.*** 125-128$^o$C; **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 690 (5 adj Ar H), 837 ( 2 adj Ar H), 1158 (-$SO_2$-N-), 1400 (-$SO_2$-N-), 1462 ($CH_2$ or $CH_3$ deformations), 1562 (NH), 1605 (Ar ring), 2992 ($CH_2$ or $CH_3$ stretch), 3064 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.00 and 1.09 [6H, two d, *J*=6.1Hz, OCH(C*H*$_3$)$_2$], 1.55 (3H, d, *J*=6.9Hz, $CH_3$), 2.41 (3H, s, Ts$CH_3$), 3.70-3.85 (5H, m, $OCH_3$ and Ar$CH_2$N), 4.11-4.15 (1H, broad m, NH), 4.23 [1H, sept, *J*=6.1Hz, OC*H*(CH$_3$)$_2$], 6.24 (1H, q, *J*=6.9Hz, C=C*H*CH$_3$), 6.84 (1H, d, *J*=8.4Hz, 5-H), 7.05-7.08 (3H, m, 6-H and 9-H), 7.18-7.21 (5H, m, 8-H, 10-H and 13-H), 7.51 (2H, d, *J*=8.1Hz, 12-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 16.1 ($CH_3$), 21.5 (Ts$CH_3$), 22.4 and 22.7 [OCH(*C*H$_3$)$_2$], 45.0 (Ar$CH_2$N), 55.6 ($OCH_3$), 74.9 [O*C*H(CH$_3$)$_2$], 111.1 (5-C), 124.7 (6-C), 125.7 (8-C), 125.9 (2-C$^a$), 126.9 (1-C$^a$), 127.1 (12-C), 127.6 (10-C), 128.4 (9-C), 129.4 (13-C), 133.4 (C=*C*HCH$_3$), 136.0 (*C*=CHCH$_3$), 136.7 (11-C), 140.9 (7-C), 143.1 (14-C), 144.9 (3-C), 153.1 (4-C); **MS *m/z*** 465 (M$^+$, 4%) 43 (6), 91 (16), 115 (5), 152 (5), 165 (10), 178 (7), 191 (6), 219 (7), 220 (6), 221 (7), 224 (9), 237 (14), 236 (6), 237 (7), 239 (10), 251 (27), 252 (60), 253 (35), 254 (6), 266 (6), 268 (62), 269 (12), 294 (5), 295 (6), 310 (100), 311 (22), 337 (5), 393 (15), 394 (5), 465 (4), ***HRMS*** calculated for $C_{27}H_{31}NO_4S$: 465.19738, found: 465.19540.

*2.63 Preparation of 5-hydroxy-4-methoxy-2-[(1E)-3-phenyl-2-propenyl]-benzaldehyde **267***

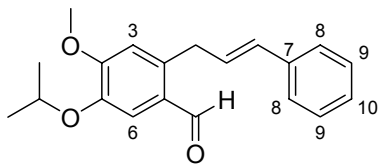


**267**

The Cope rearrangement was effected by placing the 4-methoxy-3-{[(2*E*)-3-phenyl-2-propenyl]oxy}benzaldehyde **246** (0.939mmol, 0.249g) neat in the sealed tube for the microwave reactor. The program was set up with the power output at 50W, the temperature at 200°C, the maximum allowable pressure at 150psi with no cooling and continuous stirring. The run time was set to 5 min with a hold time of 5 min. This yielded the desired compound as a dark brown oil that was spectroscopically pure and no further purification was required (0.249g, 100%).

***R**f* = 0.61 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 699 (5 adj Ar H), 844 (2 adj Ar H), 1267 (-OH), 1508 (Ar ring), 1595 (Ar ring), 2565 (CHO), 2983 ($CH_2$ or $CH_3$ stretch), 3064 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.57 (1H, s, OH), 3.91-3.92 (2H, m, $CH_2$), 3.96 (3H, s, $OCH_3$), 6.32-6.37 (2H, m, C*H*=CHPh and CH=C*H*Ph), 6.77 (1H, s, 3-H), 7.19-7.45 (5H, m, Ph H), 7.43 (1H, s, 6-H), 10.15 (1H, s, CHO); **$\delta_C$ (50 MHz, $CDCl_3$)** 35.0 ($CH_2$), 55.9 ($OCH_3$), 113.3 (3-C), 115.5 (6-C), 125.7 (8-C0, 125.8 (1-C[a]), 125.9 (10-C[a]), 128.1 (9-C), 128.7 (*C*H=CHPh[b]), 131.2 (CH=*C*HPh[b]), 136.9 (2-C), 137.4 (7-C), 145.9 (5-C), 155.0 (4-C), 189.9 (C=O).

*2.64 Preparation of 5-isopropoxy-4-methoxy-2-[(1E)-3-phenyl-2-propenyl]-benzaldehyde **268***



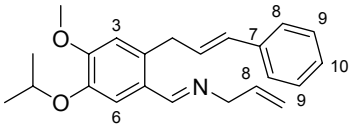
**268**

The 4-methoxy-3-{[(2*E*)-3-phenyl-2-propenyl]-oxy}benzaldehyde **246** (9.35mmol, 2.51g) was placed in a sealed tube for the microwave reactor in 0.250g batches and the Cope rearrangement was performed under solvent free conditions. The program was set up with the power output at 50W, the temperature at 200°C, the maximum allowable pressure at 150psi with no cooling and continuous stirring. The run time was set to 5 min with a hold time of 5 min for each of the 0.250g batches of aldehyde. All the Cope products were combined in a round bottomed flask and were dissolved in DMF (25cm$^3$). The solution was placed under an Ar atmosphere and then heated to 60°C. The $K_2CO_3$ (2.5eq, 23.4mmol, 3.24g) was added and the

solution was stirred until a suspension formed. Then isopropyl bromide (2.5eq, 23.4mmol, 2.20cm$^3$) was added and the reaction mixture was allowed to stir at 60$^o$C under an Ar atmosphere for 19 h. After this time the reaction mixture was cooled to rt and the inorganic solids were filtered off through a celite pad which was rinsed with $CH_2Cl_2$ (50cm$^3$). The solvent was then removed on the rotary evaporator (75$^o$C) and dried *in vacuo*. The crude mixture was then purified by column chromatography (5-10% EtOAc-Hexane) to obtain the desired product as a dark yellow oil (2.20g, 76%).

***R**$_f$* = 0.63 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (alkane), 772 (5 adj Ar H), 878 (isolated Ar H), 929 (trans RCH=CHR), 1216 (C-O), 1423 (alkane), 1510 and 1594 (Ar ring), 1679 (aryl conj C=C), 2978 (-$CH_2$ or –$CH_3$), 3020 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.39 [6H, d, *J*=6.1Hz, OCH(C*H*$_3$)$_2$], 3.90-3.92 (5H, m, $CH_2$ and $OCH_3$), 4.62 [1H, sept, *J*=6.1Hz, OC*H*(CH$_3$)$_2$], 6.38-6.39 (2H, m, C*H*=CHPh and CH=C*H*Ph), 6.77 (1H, s, 3-H), 7.16-7.32 (5H, m, 8-H, 9-H and 10-H), 7.42 (1H, s, 6-H), 10.20 (1H, s, CHO); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.9 [OCH(*C*H$_3$)$_2$], 35.0 ($CH_2$), 56.1 ($OCH_3$), 71.5 [O*C*H(CH$_3$)$_2$], 113.5 (3-C), 115.6 (6-C), 126.1 (8-C), 126.8 (1-C$^a$), 127.3 (10-C$^a$), 128.5 (9-C), 128.8 (*C*H=CHPh$^b$), 131.4 (CH=*C*HPh$^b$), 137.1 (2-C), 137.6 (7-C), 146.1 (5-C), 155.2 (4-C), 190.1 (CHO); **MS *m/z*** 310 (M$^+$, 46%), 91 (23), 136 (33), 151 (12), 152 (16), 163 (82), 164 (12), 177 (100), 178 (15), 219 (54), 239 (18), 268 (50), 310 (46), 311 (10), ***HRMS*** calculated for $C_{20}H_{22}O_3$: 310.15689, found: 310.15830.

### *2.65 Preparation of N-((E)-{5-isopropoxy-4-methoxy-2-[(2E)-3-phenyl-2-propenyl]phenyl}methylidene)-2-propen-1-amine **269***

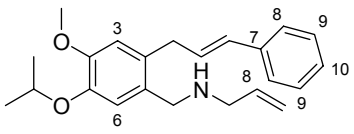



**269**

The 5-isopropoxy-4-methoxy-2-[(1*E*)-3-phenyl-2-propenyl]-benzaldehyde **268** (6.41mmol, 1.99g) was transferred to the reaction flask using the minimum amount of $Et_2O$ and the solvent was removed under high vacuum. To the aldehyde was then added allyl amine (1.4eq, 8.97mmol, 0.700cm$^3$) and the reaction mixture was stirred at rt under an Ar atmosphere for 21.5 h. After this time the excess allyl amine was removed under high vacuum and imine formation was confirmed by $^1$H NMR spectroscopy. The product was obtained as a yellow oil and no further purification was required (2.24g, 100%).

***R*$_f$** = 0.63 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (alkane), 772 (5 adj Ar H), 927 (isolated Ar H), 967 (C=C *trans*), 1216 (C-O), 1508 and 1598 (alkane), 1645 (C=N-), 1677 (aryl conj C=C), 2980 (-$CH_2$ or –$CH_3$), 3019 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.37 [6H, *J*=5.9Hz, OCH($CH_3$)$_2$], 3.71 (2H, *J*=2.4Hz, Ar$CH_2$C), 3.86 (3H, s, $OCH_3$), 4.22 (2H, d, *J*=5.4Hz, N$CH_2$C), 4.65 [1H, sept, *J*=5.9Hz, OC*H*($CH_3$)$_2$], 5.06-5.22 (2H, m, CH=C$H_2$), 5.98-6.10 (1H, m, C*H*=$CH_2$), 6.31-6.32 (2H, m, C*H*=CHPh and CH=C*H*Ph), 6.70 (1H, s, 3-H), 7.17-7.33 (5H, m, 8-H, 9-H and 10-H), 7.59 (1H, s, 6-H), 8.52 (1H, s, N=CH); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.0 [OCH(*C*$H_3$)$_2$], 35.4 (Ar*C*$H_2$C), 55.9 ($OCH_3$), 63.7 (N*C*$H_2$C), 71.3 [O*C*H($CH_3$)$_2$], 113.2 (3-C), 113.6 (6-C), 115.7 (CH=*C*$H_2$), 126.1 (8-C), 126.7 (1-C), 127.1 (10-C), 128.6 (9-C), 129.3 (*C*H=CHPh), 130.9 (CH=*C*HPh), 133.1 (2-C), 136.3 (*C*H=$CH_2$), 137.3 (7-C), 146.1 (5-C), 152.3 (4-C), 159.5 (N=CH); **MS *m/z*** 349 ($M^+$, 18%), 41 (28), 43 (22), 91 (46), 115 (17), 136 (35), 151 (21), 152 (23), 164 (85), 165 (20), 177 (100), 178 (20), 190 (15), 216 (31), 219 (45), 231 (18), 239 (16), 251 (20), 252 (17), 258 (50), 268 (44), 310 (37), 348 (25), 349 (18), ***HRMS*** calculated for $C_{23}H_{27}NO_2$: 349.20418, found: 349.20344.

### *2.66 Preparation of N-{5-isopropoxy-4-methoxy-2-[(2E)-3-phenyl-2-propenyl]-benzyl}-2-propen-1-amine **270***

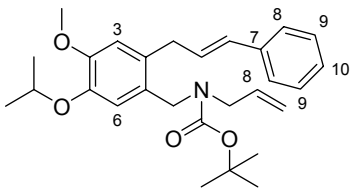



**270**

The *N*-((*E*)-{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]phenyl}methylidene)-2-propen-1-amine **269** (6.26 mmol, 2.19g) was dissolved in MeOH (200cm$^3$) and cooled to 0$^o$C in an ice-water bath. Then sodium borohydride (1.2eq, 7.52mmol, 0.294g) was added and the reaction mixture was allowed to stir at 0$^o$C-rt under an Ar atmosphere for 4.5 h. After this time thin layer chromatography showed no further change so distilled water (200cm$^3$) was added to the reaction mixture. The pH was then neutralised using 1M HCl and saturated $NaHCO_3$ solutions. The solvent was removed *in vacuo* before the aqueous layer was extracted with $CH_2Cl_2$ (4×100cm$^3$). The combined organics were then extracted with distilled water (200cm$^3$) and dried over anhydrous $MgSO_4$. The solvent was then removed *in vacuo* to give the desired product as a dark yellow oil (1.66g, 75%).

***R**f* = 0.43 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (alkane), 772 (5 adj Ar H), 929 (isolated Ar H), 1216 (C-O), 1513 (Ar ring), 2978 (-$CH_2$ or –$CH_3$), 3019 (Ar H), 3618 (-NH); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.36 [6H, d, *J*=6.0Hz, OCH(C*H*$_3$)$_2$], 1.58 (1H, br s, NH), 3.25-3.28 (2H, m, NC$H_2$C), 3.55 (2H, s, ArC$H_2$C), 3.73 (2H, s, ArC$H_2$N), 3.82 (3H, s, O$CH_3$), 4.53 [1H, sept, *J*=6.0Hz, OC*H*(C$H_3$)$_2$], 5.07-5.20 (2H, m, CH=C$H_2$), 5.85-5.98 (1H, m, C*H*=$CH_2$), 6.32-6.35 (2H, m, C*H*=CHPh and CH=C*H*Ph), 6.74 (1H, s, 3-C), 6.93 (1H, s, 6-C), 7.18-7.34 (5H, m, 8-H, 9-H and 10-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.0 [OCH(*C*H$_3$)$_2$], 35.8 (Ar*C*H$_2$C), 50.2 (ArC$H_2$N), 51.9 (N*C*H$_2$C), 56.1 (O$CH_3$), 71.6 [O*C*H(CH$_3$)$_2$], 114.0 (3-C), 115.9 (CH=*C*H$_2$), 117.7 (6-C), 125.9 (2-C[a]), 126.0 (8-C), 127.0 (10-C), 127.9 (1-C[a]), 128.4 (9-C), 129.6 (*C*H=CHPh), 130.5 (CH=*C*HPh), 136.8 (*C*H=CH$_2$), 137.4 (7-C), 145.6 (5-C), 149.5 (4-C); **MS *m/z*** 351 (M$^+$, 18%), 41 (11), 69 (8), 91 (25), 161 (24), 165 (9), 175 (8), 176 (8), 191 (7), 204 (11), 219 (12), 220 (7), 221 (9), 237 (12), 251 (14), 252 (100), 253 (22), 261 (8), 294 (33), 295 (8), 310 (9), 351 (18), ***HRMS*** calculated for $C_{23}H_{29}NO_2$: 351.21983, found: 351.21926.

## *2.67 Preparation of tert-butyl allyl{5-isopropoxy-4-methoxy-2-[(2E)-3-phenyl-2-propenyl]-benzyl}carbamate **271***



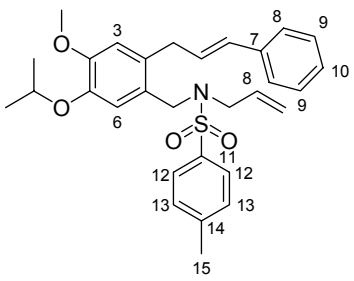

**271**

The *N*-{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]benzyl}-2-propen-1-amine **270** (1.47mmol, 0.517g) was dissolved in freshly distilled THF (50cm$^3$). To this solution was added $Boc_2O$ (1.2eq, 1.76mmol, 0.400cm$^3$) and it was stirred for 5 min. Then DMAP (0.1eq, 0.147mmol, 0.0180g) was added and the reaction mixture was left to stir at rt under an Ar atmosphere for 3 h. After this time thin layer chromatography showed consumption of the starting material so the solvent was removed *in vacuo* to yield an orange oil. This was then purified by column chromatography (5-10% EtOAc-Hexane) to obtain the desired product as a yellow oil (0.525g, 79%).

***R**f* = 0.74 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.35 [6H, d, *J*=6.1Hz, OCH(C*H*$_3$)$_2$], 1.45 and 1.48 [9H, two s, OC(C*H*$_3$)$_3$], 3.47 (2H, d, *J*=3.7Hz, ArC$H_2$C[a]), 3.53-3.76 (2H, m, NC$H_2$C[a]), 3.93 (3H, s, O$CH_3$), 4.43-4.49 [3H, m, ArC$H_2$N and OC*H*(C$H_3$)$_2$], 5.02-5.10 (2H, m, CH=C$H_2$), 5.71-5.73 (1H, br m, C*H*=$CH_2$), 6.25-6.30 (1H, m, CH=C*H*Ph[b]), 6.75 (1H, d,

*J*=10.9Hz, C*H*=CHPh[b]), 7.16-7.33 (7H, m, 3-H, 6-H, 8-H, 9-H and 10-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.1 [OCH($CH_3$)$_2$], 28.4 [OC($CH_3$)$_3$], 35.6 (Ar$CH_2$C), 46.2 (Ar$CH_2$N), 48.0 (N$CH_2$C), 56.1 ($OCH_3$), 71.6 [O*C*H($CH_3$)$_2$], 79.7 [O*C*($CH_3$)$_3$], 109.9 (3-C), 114.0 (CH=*C*$H_2$), 116.4 (6-C), 126.0 (8-C), 127.0 (10-C), 127.8 (2-C[c]), 128.3 (1-C[c]), 128.4 (9-C), 128.6 (*C*H=CHPh[d]), 130.6 (CH=*C*HPh[d]), 133.7 (*C*H=$CH_2$), 137.4 (7-C), 145.6 (5-C), 149.6 (4-C), 155.5 (C=O); **MS *m/z*** 451 ($M^+$, 22%), 57 (37), 70 (25), 91 (37), 161 (26), 162 (9), 170 (9), 237 (8), 239 (57), 240 (12), 251 (24), 252 (100), 253 (26), 281 (83), 282 (20), 293 (9), 294 (42), 295 (17), 395 (14), 451 (22), ***HRMS*** calculated for $C_{28}H_{37}NO_4$: 451.27226, found: 451.27205.

*2.68 Preparation of N-allyl-N-{5-isopropoxy-4-methoxy-2-[(2E)-3-phenyl-2-propenyl]benzyl}-4-methylbenzenesulfonamide **272***



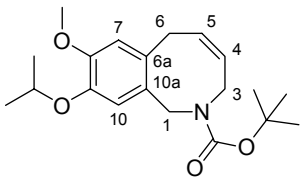
**272**

*N*-{5-Isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]-benzyl}-2-propen-1-amine **270** (1.43mmol, 0.503g) was dissolved in $CH_2Cl_2$ (25cm$^3$) and the solution was cooled to 0$^o$C in an ice-water bath. $NEt_3$ (1.4eq, 2.00mmol, 0.300cm$^3$) was then added and the reaction mixture was allowed to stir for 5 min before the addition of the tosyl chloride (1.2eq, 1.72mmol, 0.331g). The reaction mixture was then stirred at 0$^o$C-rt for 2.5 h, before being diluted with distilled water (25cm$^3$). The aqueous layer was then extracted with $CH_2Cl_2$ (25cm$^3$), then the organic layers were combined and extracted with distilled water (2×25cm$^3$) before being dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to yield a dark orange oil that was then purified by column chromatography (5-10%EtOAc-Hexane). The desired compound was obtained as a yellow oil that solidified on standing (0.521g, 72%).

***$R_f$*** = 0.60 (30% EtOAc-Hexane); ***m.p.*** 79-82$^o$C; **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 742 (5 adj Ar H), 815 (2 dj Ar H), 934 (RCH=$CH_2$), 968 (RCH=$CH_2$), 1160 (-$SO_2$-N-), 1275 (C=C isolated), 1343 (-$SO_2$-N-), 1447 ($CH_2$ or $CH_3$ deformations), 1513 (Ar ring), 1599 (Ar ring), 2936 ($CH_2$ or $CH_3$ stretch), 3013 (ArH); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.32 [6H, d, *J*=6.1Hz, OCH(C$H_3$)$_2$], 2.43 (3H, s, Ts$CH_3$), 3.48 (2H, d, *J*=5.2Hz, Ar$CH_2$C), 3.70-3.74 (2H, m, N$CH_2$C), 3.83 (3H, s, $OCH_3$), 4.28-4.42 [3H, m, Ar$CH_2$N and OC*H*($CH_3$)$_2$], 4.84-5.00 (2H, m, CH=C$H_2$), 5.41-5.52

(1H, m, C*H*=$CH_2$), 6.25-6.35 (2H, m, C*H*=CHPh and CH=C*H*Ph), 6.70 (1H, s, 3-H), 6.81 (1H, s, 6-H), 7.20-7.31 (7H, m, 8-H, 9-H, 10-H and 13-H), 7.73 (2H, d, *J*=8.1Hz, 12-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.5 ($TsCH_3$), 22.1 [$OCH(CH_3)_2$], 35.5 ($ArCH_2C$), 47.8 ($ArCH_2N$), 49.5 ($NCH_2C$), 56.0 ($OCH_3$), 71.5 [$OCH(CH_3)_2$], 113.9 (3-C), 117.3 ($CH=CH_2$), 118.7 (6-C), 125.4 (2-C[a]), 126.1 (8-C), 127.1 (10-C), 127.3 (12-C), 128.3 (1-C[a]), 128.5 (13-C), 129.7 (13-C), 130.8 (*C*H=CHPh), 131.4 (CH=*C*HPh), 132.6 (11-C), 137.0 ($CH=CH_2$), 137.4 (7-C), 143.2 (14-C), 145.6 (5-C), 149.9 (4-C).

## *2.69 Preparation of tert-butyl 9-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocine-2(1H)-carboxylate **273***



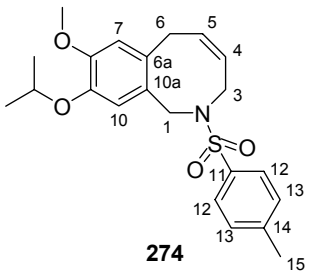

**273**

The *tert*-butyl allyl{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]benzyl}-carbamate **271** (0.476 mmol, 0.215g) was dissolved in distilled toluene (20$cm^3$) and the solution was heated to 60°C. Then Grubbs II catalyst **11** (0.05eq, 0.0238mmol, 0.0237g) was added and the reaction mixture was stirred at 60°C under an Ar atmosphere for 22.5 h. After this time the reaction mixture was cooled to rt and the solvent was removed *in vacuo* to yield a dark brown oil. This was then purified by column chromatography (5% EtOAc-Hexane) to obtain the desired compound as a viscous yellow oil (0.121g, 73%). Peak broadening was observed in the $^1$H NMR spectrum due to the Boc protecting group and further structural determination would require the removal of the Boc protecting group, however, due to the time constraints on this project it was not possible.

***$R_f$*** = 0.58 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.26-1.55 [15H, m, $OCH(CH_3)_2$ and $OC(CH_3)_3$], 3.36 (2H, d, *J*=7.8Hz, $ArCH_2C$), 3.83-3.85 (4H, m, $OCH_3$ and one of $NCH_2CH^a$), 4.05 (1H, d, *J*=4.9Hz, one of $NCH_2CH^a$), 4.44-4.53 [3H, m, $ArCH_2N$ and $OCH(CH_3)_2$], 5.65-5.91 (1H, m, 4-H), 6.64-6.83 (1H, m, 5-H), 7.26-7.30 (2H, m, 7-H and 10-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.1 and 22.2 [$OCH(CH_3)_2$], 28.4 [$OC(CH_3)_3$], 32.6 and 33.0 ($ArCH_2C$), 45.0 and 45.3 ($NCH_2CH$), 51.6 ($ArCH_2N$), 56.0 ($OCH_3$), 71.4 and 71.9 [$OCH(CH_3)_2$], 79.6 [$OC(CH_3)_3$], 113.9 and 114.3 (7-C), 118.3 and 118.5 (10-C), 126.0 and 126.3 (6a-C), 127.5 and 127.9 (5-C), 128.4 and 128.5 (10a-C), 129.1 and 130.6 (4-C), 131.2 and 131.5 (9-C), 145.0 (8-C), 149.5 (C=O); **MS *m/z*** 347 ($M^+$, 100%), 57 (91), 77 (10), 115 (13), 137 (41), 143

(15), 161 (12), 162 (10), 174 (10), 175 (95), 176 (34), 179 (33), 187 (25), 188 (51), 189 (16), 204 (28), 205 (10), 246 (18), 248 (21), 249 (28), 290 (71), 291 (52), 347 (100), 348 (23), ***HRMS*** calculated for $C_{20}H_{29}NO_4$: 347.20966, found: 347.20925.

*2.70 Preparation of 9-isopropoxy-8-methoxy-2-[(4-methylphenyl)sulfonyl]-1,2,3,6-tetrahydro-2-benzazocine **274***



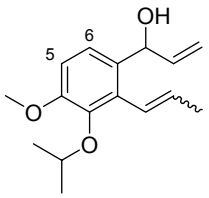
**274**

The *N*-allyl-*N*-{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]benzyl}-4-methylbenzenesulfon-amide **272** (0.411 mmol, 0.208g) was dissolved in distilled toluene (20cm$^3$) and the solution was heated to 60$^o$C before the addition of Grubbs II catalyst **11** (0.05eq, 0.0206mmol, 0.0176g). The reaction mixture was then stirred at 60$^o$C under an Ar atmosphere for 20 h. After this time the solvent was removed *in vacuo* and the crude mixture was purified by column chromatography (5-10% EtOAc-Hexane) to give the desired compound as a milky yellow oil (0.0649g, 39%) as well as a dimer of the starting material.

***R**$_f$* = 0.40 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 669 (RHC=CHR, *cis*), 761 (5 adj Ar H), 850 (2 adj Ar H), 1158 (-$SO_2$-N-), 1334 (-$SO_2$-N-), 1517 (Ar ring), 1600 (Ar ring), 2898 (-$OCH_3$), 2937 ($CH_2$ or $CH_3$ stretch), 3020 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.33 and 1.39 [6H, two d, *J*=6.1Hz, OCH(C*H*$_3$)$_2$], 2.41 (3H, s, Ts$CH_3$), 3.41 (2H, d, *J*=6.3Hz, Ar$CH_2$C), 3.73-3.77 (2H, m, N$CH_2$C), 3.83 (3H, s, $OCH_3$), 4.22 (2H, s, Ar$CH_2$N), 4.39-4.47 [1H, m, OC*H*(CH$_3$)$_2$], 5.41-5.58 (1H, m, NCH$_2$C*H*=CH), 5.76-5.84 (1H, m, ArCH$_2$C*H*=CH), 6.61 (1H, s, 7-H), 6.70 (1H, s, 10-H), 7.21-7.27 (2H, m, 13-H), 7.65 (2H, d, *J*=8.2Hz, 12-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.5 ($CH_3$), 22.1 [OCH(*C*H$_3$)$_2$], 34.3 (6-C), 43.3 (3-C), 50.5 (1-C), 56.0 ($OCH_3$), 71.6 [O*C*H(CH$_3$)$_2$], 113.9 (7-C$^a$), 118.1 (10-C$^a$), 124.0 (5-C), 127.2 (12-C), 128.9 (6a-C), 129.5 (13-C), 131.1 (10a-C), 133.3 (4-C), 136.8 (11-C), 143.0 (14-C), 145.9 (9-C), 150.1 (8-C).

## 3. Experimental Procedures: Indenols, Indenones and Indanones

### *3.1 Preparation of 1-[3-isopropoxy-4-methoxy-2-(1-propenyl)phenyl]-2-propen-1-ol* ***202***

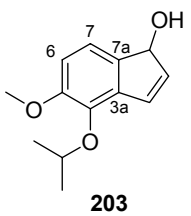



**202**

A solution was prepared of 3-isopropoxy-4-methoxy-2-(1-propenyl)benzaldehyde **201** (3.22mmol, 0.755g) in freshly distilled THF (100cm$^3$) and this reaction was placed in an acetone bath that was cooled to –60$^o$C using the cryostat. To the cooled solution was added vinyl magnesium bromide (5eq[7], 16.1mmol, 2.20cm$^3$). The reaction mixture was then stirred at –60$^o$C under an Ar atmosphere for 18 h. Then the reaction mixture was allowed to warm to rt before the addition of distilled water (50cm$^3$). The THF was then removed on the rotary evaporator and the remaining aqueous layer was extracted with EtOAc (3×10cm$^3$). The combined organics were then dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The crude mixture was then purified by column chromatography (5-10% EtOAc-Hexane) to yield the desired compound as a yellow oil (0.742g, 88%). Our NMR spectroscopic data was found to correlate well to that reported by Coyanis.[206]

***R**$_f$* = 0.54 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.23 [6H, dd, *J*=1.8 and 6.2Hz, OCH(C*H*$_3$)$_2$], 1.90 (3H, d, *J*=6.5Hz, $CH_3$), 3.81 (3H, s, $OCH_3$), 4.32 [1H, sept, *J*=6.2Hz, OC*H*(CH$_3$)$_2$], 5.17-5.32 (2H, m, CH=C*H*$_2$), 5.44 (1H, s, C*H*-OH), 5.94-6.12 (2H, m, C*H*=CH$_2$ and CH=C*H*CH$_3$), 6.45 (1H, d, J=16.0Hz, C*H*=CHCH$_3$), 6.80 (1H, d, *J*=8.6Hz, 5-H), 7.13 (1H, d, *J*=8.6Hz, 6-H), the OH peak was not observed on the $^1$NMR spectrum; **$\delta_C$ (50 MHz, $CDCl_3$)** 19.0 ($CH_3$), 22.5 [OCH(*C*H$_3$)$_2$], 55.7 ($OCH_3$), 71.2 (CH-OH), 75.1 [O*C*H(CH$_3$)$_2$], 110.6 (5-C), 114.3 (CH=*C*H$_2$), 122.0 (6-C), 124.6 (CH=*C*HCH$_3$), 129.6 (2-C), 132.2 (*C*H=CHCH$_3$), 133.1 (1-C), 140.4 (*C*H=CH$_2$), 144.6 (3-C), 152.4 (4-C).

### *3.2 Preparation of 4-isopropoxy-5-methoxy-1H-inden-1-ol* ***203***




**203**

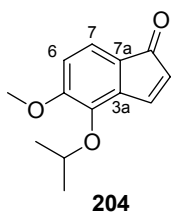
The 1-[3-isopropoxy-4-methoxy-2-(1-propenyl)phenyl]-2-propen-1-ol **202** (1.00mmol, 0.263g) was dissolved in pre-distilled $CH_2Cl_2$ (25cm$^3$) and the solution was degassed for 15 min using $N_2$. The Grubbs II catalyst **11** (0.05eq, 0.0501mmol, 0.0430g) was then added and the

[*] Our Grignard reagent stock was quite old and may have been contaminated with trace amounts of water, thus this value of 5 eq is not a representative amount for a good reagent.

reaction mixture was allowed to stir at rt under an Ar atmosphere for 3 h. After this time the solvent was removed *in vacuo* to yield a brown oil that was then purified by column chromatography (5-10% EtOAc-Hexane). The desired product was obtained as a dark yellow oil (0.191g, 87%), with similar NMR data to that reported by Coyanis.[206]

***R*$_f$** = 0.31 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.29 [6H, dd, *J*=5.1 and 5.8Hz, OCH(C*H*$_3$)$_2$], 3.84 (3H, s, OCH$_3$), 4.37 [1H, sept, *J*=6.2Hz, OC*H*(CH$_3$)$_2$], 5.15 (1H, d, *J*=8.6Hz, C*H*-OH), 6.32 (1H, dd, *J*=1.8 and 5.7Hz, CHC*H*=CHAr), 6.71 (1H, d, *J*=7.9Hz, 6-H), 6.82 (1H, d, *J*=5.7Hz, CHCH=C*H*Ar), 7.16 (1H, d, *J*=7.9Hz, 7-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.6 [OCH(*C*H$_3$)$_2$], 56.1 (OCH$_3$), 75.6 [O*C*H(CH$_3$)$_2$], 77.4 (CH-OH), 109.7 (6-C), 118.7 (7-C), 129.6 (2-C), 136.7 (7a-C), 137.5 (3-C), 138.5 (3a-C), 140.6 (4-C), 153.6 (5-C).

### *3.3 Preparation of 4-isopropoxy-5-methoxy-1H-inden-1-one **204***

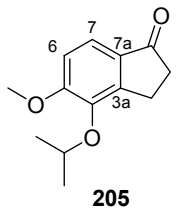


**204**

The 1-[3-isopropoxy-4-methoxy-2-(1-propenyl)phenyl]-2-pro-pen-1-ol **202** (0.412mmol, 0.108g) was dissolved in pre-distilled toluene (10cm$^3$) and the solution was heated to 60$^o$C before the addition of Grubbs II catalyst **11** (0.05eq, 0.0206mmol, 0.0180g). The reaction mixture was subsequently stirred at 60$^o$C under an Ar atmosphere for 17 h. After this time the solvent was removed *in vacuo* to yield a dark brown oil. The crude mixture was then purified by column chromatography (5% EtOAc-Hexane) to give the desired product as a bright yellow oil (0.0400g, 45%). Our NMR spectroscopic data correlated to that obtained by Coyanis.[206]

***R*$_f$** = 0.58 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.28 [6H, two d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 3.87 (3H, s, OCH$_3$), 4.39-4.48 [1H, m, OC*H*(CH$_3$)$_2$], 5.85 (1H, d, *J*=6.1Hz, 6-H), 6.60 (1H, d, *J*=7.7Hz, 7-H), 7.08 (1H, d, *J*=8.3Hz, 2-H), 7.65 (1H, d, *J*=8.4Hz, 3-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.9 and 23.2 [OCH(*C*H$_3$)$_2$], 56.3 (OCH$_3$), 76.0 [O*C*H(CH$_3$)$_2$], 113.4 (6-C), 119.7 (3a-C), 120.6 (7-C), 128.7 (7a-C), 131.7 (2-C), 143.1 (3-C), 149.1 (4-C), 158.9 (5-C), 196.1 (C=O)..

### *3.4 Preparation of 4-isopropoxy-5-methoxy-1-indanone **205***




**205**

The 1-[3-isopropoxy-4-methoxy-2-(1-propenyl)phenyl]-2-propen-1-ol **202** (0.755mmol, 0.198g) was dissolved in pre-distilled toluene (20cm$^3$) and the solution was heated to 80$^o$C. Then Grubbs II catalyst **11** (0.08eq, 0.0604mmol, 0.0518g) was added and the reaction mixture was allowed to stir at 80$^o$C under an Ar atmosphere for 22 h. After this time the solvent was removed *in vacuo* to give a brown-black oil that was then purified by column chromatography (5-10% EtOAc-Hexane). The desired product was obtained as a pale orange oil that solidified on standing (0.147g, 89%) as well as a small amount of 4-isopropoxy-5-methoxy-1*H*-inden-1-one **204** (0.0276g, 17% relative to starting material). The NMR spectroscopic data was compared to that of Coyanis[206] and found to be in excellent agreement.

***R*$_f$** = 0.45 (30% EtOAc-Hexane); ***m.p.*** 52-55$^o$C; **$\delta_H$ (300 MHz, CDCl$_3$)** 1.32 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 2.66 (2H, dd, *J*=5.2 and 6.7Hz, ArCH$_2$), 3.05-3.09 (2H, m, COCH$_2$), 3.93 (3H, s, OCH$_3$), 4.54 [1H, sept, *J*=6.1Hz, OC*H*(CH$_3$)$_2$], 6.96 (1H, d, *J*=8.4Hz, 6-H), 7.51 (1H, d, *J*=8.3Hz, 7-H); **$\delta_C$ (50 MHz, CDCl$_3$)** 22.7 [OCH(*C*H$_3$)$_2$], 22.9 (ArCH$_2$), 36.4 (CO*C*H$_2$), 56.1 (OCH$_3$), 74.7 [O*C*H(CH$_3$)$_2$], 112.2 (6-C), 119.8 (7-C), 131.1 (3a-C), 143.5 (7a-C), 149.1 (4-C), 157.9 (5-C), 205.7 (C=O).

### *3.5 Ruthenium Removal, NMR experiments and ICP-MS testing*

#### *3.5.1 Ruthenium Removal*

Attempt 1:

The indenol **203** (0.112g, with 0.0322g of Grubbs II catalyst **11** present from the RCM reaction) was dissolved in 10% EtOAc-Hexane (15cm$^3$) and the solution was placed in the reaction vessel under a $N_2$ atmosphere. To the solution was then added Activated Carbon, Darco G-60, 100 mesh (50eq relative to Grubbs II catalyst **11**, 1.62g) and it was left to stir at rt for 4 h. After this time the solution was filtered through a celite pad and rinsed with 5% EtOAc-Hexane (200cm$^3$) and then 10% EtOAc-Hexane (150cm$^3$). The solvent was removed *in vacuo* to yield a yellow oil (0.0823g). The oil was then dissolved in distilled $CH_2Cl_2$ (200cm$^3$) and to the solution was added DMSO (50eq relative to Grubbs II catalyst **11**, 1.91mmol, 0.140cm$^3$). The reaction mixture was then left to stir at rt under a $N_2$ atmosphere

overnight. The solvent was then removed *in vacuo* to yield a yellow oil that was purified by column chromatography (10% EtOAc-Hexane). A bright yellow oil was then obtained off of the column (0.0047g). The oil obtained was analysed by $^1$H NMR spectroscopy and it was found to contain a only the pure indenone **204**.

As the mass obtained after columning was so low, it appeared as though a large amount of the indenol may have been trapped in the activated carbon, thus it was rewashed with 10-40% EtOAc-Hexane (4×100cm$^3$) and $CH_2Cl_2$ (100cm$^3$). After the solvent was removed in vacuo more of the yellow oil was isolated (0.0605g). Thus this oil had not been subjected to treatment with DMSO. The oil obtained was then analysed by $^1$H NMR spectroscopy and it was found to contain a mixture of indenol **203** and indenone **204**.

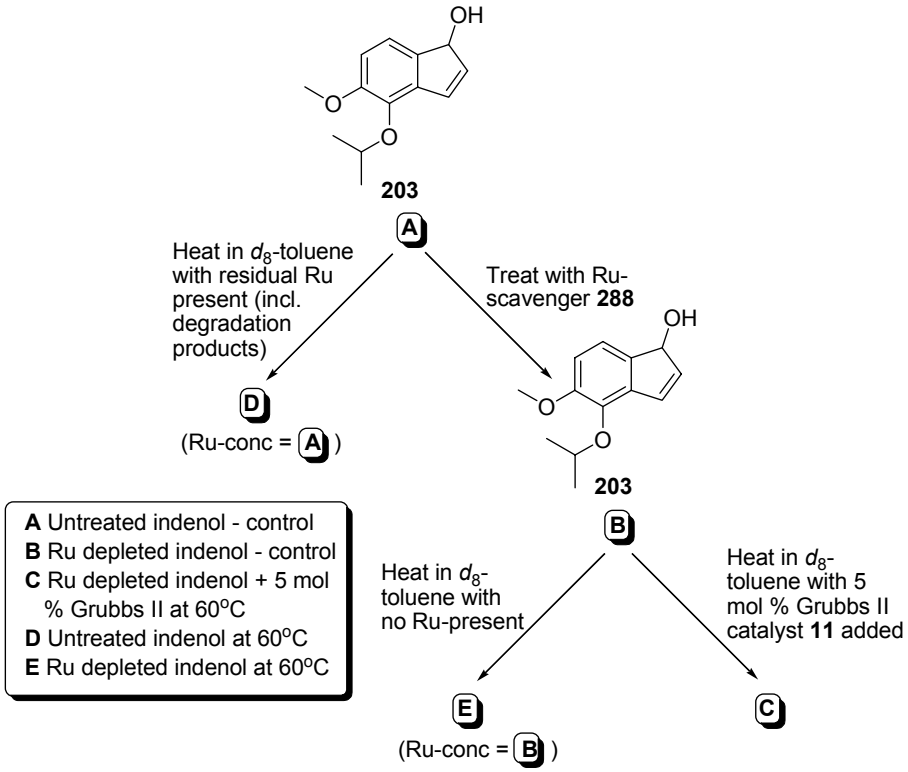
Attempt 2:

The indenol **203** (0.485mmol, 0.107g) was dissolved in distilled $CH_2Cl_2$ (10cm$^3$) and the solution was then degassed for 30 min using $N_2$. Then the Ru-scavenger (0.77mmol/g, 5eq relative to Grubbs II catalyst **11** present in the indenol sample, 0.0162g) was added and the reaction mixture was left to stir for 17 h at rt under an Ar atmosphere. After this time the white "beads" of the Ru-scavenger had changed colour from bright white to grey-brown. The Ru-scavenger was then filtered off through a celite pad, which was subsequently rinsed with $CH_2Cl_2$ (50cm$^3$). The solvent was then removed *in vacuo* to yield a bright yellow semi-solid. The percentage recovery of the indenol **203** was found to be 99.7%.

### *3.5.2 $^1$H NMR Spectroscopy Experiments*

General Procedure:

Indenol **203** was used as prepared in *Section 3.2* above for the samples containing residual ruthenium (NMR tubes **A** and **D**). Indenol **203** was subjected to the ruthenium removal process outlined in *Section 3.5.1* above for use in the ruthenium-depleted samples, (NMR tubes **B**, **C** and **E**). To the ruthenium depleted indenol **203** (in NMR tube **C**) was added a further 5 mol % Grubbs II catalyst **11**.




Each of the samples **A**-**E** above, were dissolved in $d_8$-toluene and the resulting solutions were then degassed using Ar for 2 min. The NMR tubes **C**, **D** and **E** were then each submerged approximately 3cm deep in an oil bath that had previously been heated to 60°C in *Case Study 1* (or 100°C in *Case Study 2*). NMR tubes **A** and **B** were kept at rt for the duration of the study. The NMR tubes were removed from the heat and the samples were run on the 300MHz NMR spectrometer in 45 min to 1 h intervals. Ratios of indenol **203** : indenone **204** : indanone **205** reported are calculated based on their relative intensities in the $^1$H NMR spectra. For final data analysis please refer to the ***Results and Discussion***, ***Chapter 5***, *Section 5.2*, **Tables 19-20** and **Graph 1**.

### *3.5.3 ICP-MS Testing*

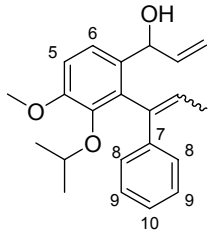
The general procedure used for our ICP analysis of the indenol **203** follows that of Georg and co-workers.[215] Samples were accurately weighed (0.0200-0.0300mg) and then digested with 6*N* nitric acid (6cm$^3$). We employed microwave digestion, with the program set at a power output of 1200W, a ramp time of 15 min and a hold time of 30 min, with no cooling. The system was then set to hold, with cooling, for 20 min. After this time the resulting residue was

diluted to a total volume of 25cm$^3$ using deionised water, and the samples were stored in the refrigerator until required.

Our standard curve was prepared through the use of the SpecPure Multielement Standards for the Group 4 Elements. The stock solution was prepared as a 10ppm solution. The standard curve and the supporting information on the instruments may be found in **Appendix C.** We then analysed our previously prepared samples by a comparison of our data to that obtained for the standard curve. The results we obtained are discussed fully in the ***Results and Discussion***, ***Chapter 5***, *Section 5.3*.

### *3.6 Preparation of 1-{3-isopropoxy-4-methoxy-2-[(1E)-1-phenyl-1-propenyl]-phenyl}-2-propen-1-ol **275***

The 3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)-benzaldehyde **247** (1.96mmol, 0.607g) was dissolved in pre-distilled THF (80cm$^3$) and the solution was cooled to –60$^o$C in an acetone bath using the cryostat. Then vinyl magnesium bromide (10eq[8], 19.6mmol, 2.60cm$^3$) was added and the reaction mixture was allowed to stir at –60$^o$C under an Ar atmosphere for 22 h. After this time the reaction mixture was allowed to warm to rt and distilled water (50cm$^3$) was added. The reaction mixture was neutralised using aqueous 1M HCl and the solvent was then removed on the rotary evaporator. The remaining aqueous layer was extracted with $CH_2Cl_2$ (4×50cm$^3$). The combined organics were then dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to yield a purple oil. This was then purified by column chromatography (5% EtOAc-Hexane) and the product was obtained as a dark red-purple oil (0.307g, 46%). NMR spectroscopic data correlated well to that obtained by Coyanis.[206]



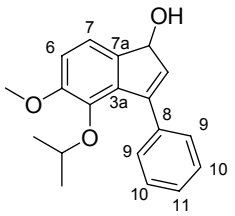
**275**

***R**f* = 0.56 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.00 and 1.13 [6H, two d, *J*=6.1Hz, OCH(C*H*$_3$)$_2$], 1.56-1.59 (3H, m, $CH_3$), 3.85 (3H, s, $OCH_3$), 4.26 [1H, sept, *J*=6.1Hz, OC*H*(CH$_3$)$_2$], 5.07-5.30 (3H, m, C*H*-OH and CH=C*H*$_2$), 5.93 (1H, ddd, *J*=5.6, 10.2 and 17.0Hz, C*H*=CH$_2$), 6.45 (1H, q, *J*=6.9Hz, C=C*H*CH$_3$), 6.96 (1H, d, *J*=8.6Hz, 5-H), 7.18-7.33 (6H, m, 6-H, 8-H, 9-H and 10-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 16.3 ($CH_3$), 22.4 and 22.7

[8] Our Grignard reagent stock was quite old and may have been contaminated with trace amounts of water, thus this value of 10 eq is not a representative amount for a good reagent.

[OCH($CH_3$)$_2$], 55.6 ($OCH_3$), 71.2 (CH-OH), 74.7 [O*C*H($CH_3$)$_2$], 111.6 (5-C), 113.9 (CH=*C*H$_2$), 122.0 (6-C), 125.9 (8-C), 126.1 (C=*C*HCH$_3$[a]), 126.8 (2-C[a]), 128.1 (10-C[a]), 128.4 (9-C), 134.3 (1-C[b]), 136.0 (*C*=CHCH$_3$[b]), 140.2 (*C*H=CH$_2$), 141.4 (7-C), 144.3 (3-C), 152.8 (4-C).

### *3.7 Preparation of 4-isopropoxy-5-methoxy-3-phenyl-1H-inden-1-ol **276***

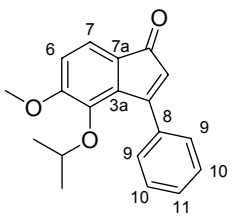


**276**

A solution was prepared of 1-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)phenyl]-2-propen-1-ol **275** (0.227 mmol, 0.0769g) in distilled $CH_2Cl_2$ (8cm$^3$) and to this was added Grubbs II catalyst **11** (0.05eq, 0.0114mol, 0.0107g). Then the reaction mixture was stirred at rt under an Ar atmosphere for 17 h. After this time the solvent was removed *in vacuo* to yield a dark brown oil that was then purified by column chromatography (5% EtOAc-Hexane). The desired compound was obtained as a cream solid (0.0328g, 49%) as well as 4-isopropoxy-5-methoxy-3-phenyl-1*H*-inden-1-one (**277**) (0.0150g, 24% relative to starting material). The NMR spectroscopic data correlated well to that obtained by Coyanis.[206]

***R*$_f$** = 0.39 (30% EtOAc-Hexane); ***m.p.*** 56-59$^o$C; **$\delta_H$ (300 MHz, $CDCl_3$)** 0.68 and 0.74 [6H, two d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 1.62 (1H, br s, OH), 3.84 (3H, s, $OCH_3$), 3.92-3.98 [1H, m, OC*H*($CH_3$)$_2$], 5.19 (1H, d, *J*=1.2Hz, C*H*-OH), 6.25 (1H, d, *J*=2.1Hz, CH=CPh), 6.78 (1H, d, *J*=8.0Hz, 6-H), 7.23-7.53 (5H, m, 7-H, 8-H, 9-H and 10-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.3 and 21.4 [OCH(*C*H$_3$)$_2$], 56.0 ($OCH_3$), 75.7 (CH-OH[a]), 75.8 [O*C*H($CH_3$)$_2$[a]], 109.6 (6-C), 111.9 (2-C), 118.9 (7-C), 127.4 (9-C), 127.5 (11-C[b]), 128.5 (3a-C[b]), 128.9 (10-C), 136.2 (7a-C), 139.9 (8-C[c]), 141.5 (3-C[c]), 146.2 (4-C), 154.6 (5-C).

### *3.8 Preparation of 4-isopropoxy-5-methoxy-3-phenyl-1H-inden-1-one 277*



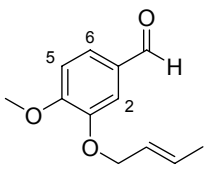
**277**

A solution was prepared of 1-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)phenyl]-2-propen-1-ol **275** (0.302 mmol, 0.102g) in distilled toluene (10cm$^3$). The solution was heated to 80$^o$C before the addition of Grubbs II catalyst **11** (0.08eq, 0.0241mmol, 0.0218g). The reaction mixture was allowed to stir at 80$^o$C under an Ar atmosphere

for 17 h. After this time the reaction mixture was cooled to rt and the solvent was removed *in vacuo*. The dark brown oil obtained was then purified by column chromatography (5% EtOAc-Hexane) and the desired compound was found as a bright-orange semi-solid (0.0615g, 69%). The NMR spectroscopic data was compared to that of Coyanis[206] and found to be in excellent agreement.

***R_f*** = 0.31 (30% EtOAc-Hexane); ***m.p.*** 63-68°C; **$\delta_H$ (300 MHz, $CDCl_3$)** 0.87 [6H, d, *J*=6.1Hz, $OCH(CH_3)_2$], 3.98 (3H, s, $OCH_3$), 4.12-4.16 [1H, s, C*H*=CPh), 6.78 (1H, d, *J*=7.9Hz, 6-H), 6.95-7.59 (6H, m, 7-H and Ph-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.5 [$OCH(CH_3)_2$], 56.1 ($OCH_3$), 76.3 [$OCH(CH_3)_2$], 110.0 (6-C), 119.4 (7-C[a]), 126.6 (*C*H=CPh[a]), 127.6 (9-C), 128.3 (10-C), 129.5 (11-C), 130.0 (3a-C), 134.4 (7a-C), 140.4 (8-C), 142.2 (4-C), 159.7 (3-C), 163.1 (5-C), 195.4 (C=O).

### *3.9 Preparation of 3-[(2E)-2-butenyloxy]-4-methoxybenzaldehyde **279***

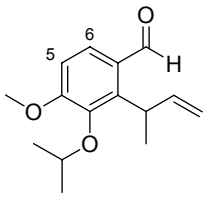



**279**

Potassium carbonate (2.5eq, 83.6mmol, 11.6g) and DMF (65$cm^3$) were heated to 60°C and left to stir for 15 min under an Ar atmosphere. After this time the isovanillin **206** (33.4mmol, 5.09g) was added and the solution turned bright yellow. To this solution was then added crotyl bromide (2.5eq, 83.6mmol, 8.60$cm^3$) and the mixture changed to a biscuit colour with the evolution of a cloudy white gas. The reaction mixture was then stirred at 60°C under an Ar atmosphere for 22 h. After this time the inorganic solids were filtered off through a celite pad and the solvent was removed on the rotary evaporator (75°C) and then under high vacuum. The crude mixture was then purified by column chromatography (5-20% EtOAc-Hexane) to yield the product as a bright yellow oil (6.83g, 99%), with similar NMR data to that reported by Rousseau.[1]

***R_f*** = 0.54 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.76 (3H, dd, *J*=0.9 and 6.1Hz, $CH_3$), 3.96 (3H, s, $OCH_3$), 4.58 and 4.73 (2H, two d, *J*=5.9 and 5.3Hz respectively, $OCH_2$), 5.73-5.96 (2H, m, C*H*=$CHCH_3$ and CH=C*H*$CH_3$), 6.98 (1H, d, *J*=8.2Hz, 5-H), 7.42-7.47 (1H, m, 6-H), 9.84 (1H, s, CHO); **$\delta_C$ (50 MHz, $CDCl_3$)** 17.8 ($CH_3$), 56.1 ($OCH_3$), 69.5 ($OCH_2$), 110.5 (2-C and 5-C), 125.3 (6-C), 126.6 (CH=*C*$HCH_3$), 129.9 (1-C), 131.5 (*C*H=$CHCH_3$), 148.6 (3-C), 154.7 (4-C), 190.8 (CHO).

### *3.10 Preparation of 3-isopropoxy-4-methoxy-2-(1-methyl-2-propenyl)benzaldehyde **280***

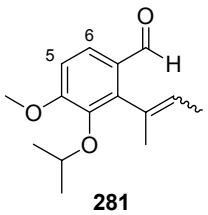


**280**

The 3-[(2*E*)-2-butenyloxy]-4-methoxybenzaldehyde **279** (24.3mmol, 5.01g) was dissolved in DMF (50cm$^3$) and the solution was heated to 180$^o$C under an Ar atmosphere for 44 h. After this time the reaction mixture was cooled to 60$^o$C before the addition of the potassium carbonate (2.5eq, 60.7mmol, 8.37g) and the isopropyl bromide (2.5eq, 60.7mmol, 5.70cm$^3$). The reaction mixture was then allowed to stir at 60$^o$C under an Ar atmosphere for a further 18 h. Then the reaction mixture was allowed to cool to rt and the inorganic salts were filtered off through a celite plug that was rinsed with $CH_2Cl_2$ (100cm$^3$). A brown oil was then obtained by removing the solvents *in vacuo* (the rotary evaporator was set to 75$^o$C), and this was then purified by column chromatography (5% EtOAc-Hexane). The desired product was obtained as a bright orange oil (4.39g, 73%), with similar NMR spectroscopic data to that reported by Coyanis.[206]

***R*$_f$** = 0.70 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.29 [6H, dd, *J*=6.2 and 17.2Hz, OCH(C*H*$_3$)$_2$], 1.50 (3H, d, *J*=7.4Hz, $CH_3$), 3.91 (3H, s, $OCH_3$), 4.46-4.59 [2H, m, OC*H*(CH$_3$)$_2$ and ArC*H*(CH$_3$)C], 4.99-5.03 (2H, m, CH=C*H*$_2$), 6.23 (1H, ddd, *J*=3.8, 10.6 and 17.4Hz, C*H*=CH$_2$), 6.88 (1H, d, *J*=8.6Hz, 5-H), 7.75 (1H, d, *J*=8.7Hz, 6-H), 10.33 (1H, s, CHO); **$\delta_C$ (50 MHz, $CDCl_3$)** 21.2 ($CH_3$), 22.4 and 22.6 [OCH(*C*H$_3$)$_2$], 33.2 (Ar*C*H(CH$_3$)C), 55.7 ($OCH_3$), 74.9 [O*C*H(CH$_3$)$_2$], 109.8 (5-C), 113.7 (CH=*C*H$_2$), 125.9 (6-C), 128.5 (1-C), 142.2 (2-C), 143.4 (*C*H=CH$_2$), 144.1 (3-C), 157.4 (4-C), 191.3 (CHO).

### *3.11 Preparation of 3-isopropoxy-4-methoxy-2-[(1E)-1-methyl-1-propenyl]-benzaldehyde **281***

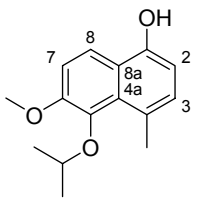


**281**

The 3-isopropoxy-4-methoxy-2-(1-methyl-2-propenyl)ben-zaldehyde **280** (2.02mmol, 0.502g) was dissolved up in DMF (25cm$^3$) and then potassium *tert*-butoxide (1.1eq, 2.22mmol, 0.251g) was added. The solution was then heated to 60$^o$C and allowed to stir under an Ar atmosphere for 1 h. Distilled water (20cm$^3$) was then added and the reaction mixture was stirred for 5 min. The pH was then neutralised using 1M aqueous HCl and saturated $NaHCO_3$ solutions. The solvent was removed on the rotary evaporator and the

remaining aqueous layer was extracted with EtOAc (3×50cm$^3$). The combined organics were then dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude mixture was purified by column chromatography (5-10% EtOAc-Hexane) to yield the desired product as a orange oil (0.0377g, 8%). However, a second predominant product (orange-brown oil) was recovered and this was found to be 5-isopropoxy-6-methoxy-4-methyl-1-naphthol **282** (0.0601g, 12% relative to starting material). Our spectroscopic data correlated well to that reported by Coyanis.[206]

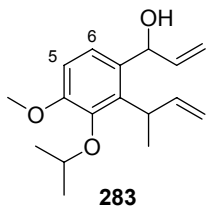
***R**$_f$* = 0.81 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.24 [6H, two dd, *J*=6.1Hz, OCH(C*H*$_3$)$_2$, 1.42 and 1.82 (3H, two d, *J*6.8Hz, $CH_3$), 2.04 (3H, two s, $CH_3$), 3.91 (3H, two s, $OCH_3$), 4.36-4.45 [1H, m, OC*H*$(CH_3)_3$], 5.41 and 5.79 (1H, two q, C=C*H*$CH_3$), 6.92 (1H, dd, *J*=6.5Hz and *J*8.4Hz, 6H), 7.72 (1H, dd, *J*=8.7Hz and 11.3 Hz, 5-H), 9.91 (1H, two s, CHO); **$\delta_C$ (50 MHz, $CDCl_3$)** 13.7 and 18.0 (C=CH*C*H$_3$), 15.3 [C(*C*H$_3$)CH], 22.6 and 22.7 [OCH(*C*H$_3$)$_2$], 55.8 ($OCH_3$), 75.3 and 75.4 [O*C*H$(CH_3)_2$], 110.4 and 110.5 (5-C), 124.0 and 124.1 (6-C), 125.5 (C=*C*HCH$_3$[a]), 127.0 and 128.0 (1-C), 128.5 (C=*C*HCH$_3$[a]), 130.5 and 130.8 (*C*=CHCH$_3$), 140.9 (2-C[b]), 143.9 and 144.9 (3-C[b]), 157.6 and 158.2 (4-C), 191.8 and 192.0 (C=O).



**282**

*5-isopropoxy-6-methoxy-4-methyl-1-naphthol **282**:* ***R**$_f$* = 0.61 (30% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 809 (2 adj Ar H), 1485 (Ar ring), 1590 (Ar ring), 1636 (Ar ring), 2843 (-$OCH_3$), 2938 ($CH_2$ or $CH_3$ stretch), 3017 (Ar H), 3255 (-OH); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.22-1.27 [6H, m, OCH(C*H*$_3$)$_2$], 1.60-1.77 (3H, m, $CH_3$), 3.82-3.95 (3H, m, $OCH_3$), 4.73-4.80 (1H, m, OC*H*$(CH_3)_2$], 5.32 (1H, broad m, OH), 6.24-6.27 (1H, m, 2-H), 6.93-7.03 (2H, m, 3-H and 7-H), 7.87-7.99 (1H, m, 8-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 22.4 and 22.6 [OCH(*C*H$_3$)$_2$], 30.7 ($CH_3$), 55.8 ($OCH_3$), 74.3 [O*C*H$(CH_3)_2$], 111.6 (2-C), 123.0 (8-C), 125.8 (7-C), 127.1 (4-C), 139.0 (8a-C[a]), 142.4 (4a-C[a]), 149.9 (6-C[b]), 151.8 (5-C[b]), 152.9 (3-C), 155.4 (1-C); **MS *m/z*** 246 ($M^+$, 34%) 41 (12), 43 (13), 77 (15), 83 (11), 103 (11), 115 (18), 131 926), 159 (15), 160 (13), 161 (12), 165 (11), 175 (21), 184 (23), 187 (15), 189 (62), 202 (100), 203 (46), 204 (84), 205 (28), 246 (34), 262 (18), ***HRMS*** calculated for $C_{15}H_{18}O_3$: 246.12559, found: 246.12414.

### *3.12 Preparation of 1-[3-isopropoxy-4-methoxy-2-(1-methyl-2-propenyl)phenyl]-2-propen-1-ol **283***



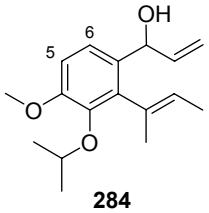

**283**

The 3-isopropoxy-4-methoxy-2-(1-methyl-2-propenyl)-benzaldehyde **280** (8.06mmol, 2.00g) was dissolved in distilled THF (200cm$^3$) and the solution was cooled to –60$^o$C in an acetone bath using a cryostat. To this solution was added vinyl magnesium bromide (10eq[9], 80.6mmol, 10.8cm$^3$) and the reaction mixture was allowed to stir at –60$^o$C under an Ar atmosphere for 18 h. Then the reaction mixture was allowed to warm to rt before the addition of distilled water (200cm$^3$). The pH was then neutralised using 1M aqueous HCl and the solvent was remove *in vacuo*. The remaining aqueous layer was then extracted with EtOAc (3×150cm$^3$). The combined organics were then dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude mixture was then purified by column chromatography (5-10% EtOAc-Hexane) to give the desired product as a yellow oil (1.61g, 72%). NMR spectroscopic data correlated well with that reported by Coyanis.[206]

***R*$_f$** = 0.64 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.27 [6H, dd, *J*=6.2Hz and 14.8Hz, OCH(C*H*$_3$)$_2$], 1.43 (3H, two d, *J*=7.3Hz, $CH_3$), 3.82 (3H, s, $OCH_3$), 4.41-4.54 [1H, m, OC*H*(CH$_3$)$_2$], 4.95-5.38 (4H, m, CH=C*H*$_2$ and CH=C*H*$_2$), 5.56 (1H, s, C*H*OH), 5.96-6.30 (2H, m, C*H*=CH$_2$ and C*H*=CH$_2$), 6.81 (1H, dd, *J*=3.5 and 8.6Hz, 6-H), 7.10 (1H, dd, *J*=6.1Hz and 8.5Hz, 5-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 19.3 and 20.0 ($CH_3$), 22.6 and 22.7 [OCH(*C*H$_3$)$_2$], 33.5 and 33.7 (*C*CH$_3$-CH=), 55.6 ($OCH_3$), 69.8 and 69.9 (CH-OH), 74.4 and 74.5 [O*C*H(CH$_3$)$_2$], 110.6 and 110.7 (5-C), 112.9, 113.5 and 114.0 (CH=*C*CH$_2$ and CH=*C*H$_2$), 123.5 and 123.9 (6-C), 134.4 and 134.5 (2-C), 137.4 and 137.6 (1-C), 140.3 and 140.4 (*C*HOH-CH=), 143.7 and 143.9 (*C*H=CH$_2$), 144.0 and 144.2 (3-C), 152.0 and 152.2 (4-C).

[9] Our Grignard reagent stock was quite old and may have been contaminated with trace amounts of water, thus this value of 10 eq is not a representative amount for a good reagent.

### *3.13 Preparation of 1-{3-isopropoxy-4-methoxy-2-[(1E)-1-methyl-1-propenyl]-phenyl}-2-propen-1-ol **284***

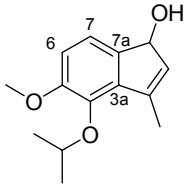


**284**

The 1-[3-isopropoxy-4-methoxy-2-(1-methyl-2-propenyl)-phenyl]-2-propen-1-ol **283** (1.47mmol, 0.406g) was dissolved up in DMF (15cm$^3$). To this was added sublimed potassium *tert*-butoxide (1.3eq, 1.91mmol, 0.217g) and the reaction mixture was stirred at rt under an Ar atmosphere for 15 min. After this time distilled water (15cm$^3$) was added and the pH was neutralised using 1M aqueous HCl. The solvent was removed *in vacuo* and then the remaining aqueous layer was extracted with EtOAc (3x15cm$^3$). The combined organics were then extracted with distilled water (3×100cm$^3$) and a small amount of brine. They were then dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to yield a bright yellow oil. This was purified by column chromatography (5% EtOAc-Hexane) with the desired product being obtained as a yellow oil (0.306g, 76%).The NMR data we obtained was similar to that reported by Coyanis.[206]

***R**f* = 0.36 (30% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.15-1.49 [6H, m, OCH(C*H*$_3$)$_2$], 1.77-1.90 (3H, m, $CH_3$), 3.82 (3H, s, $OCH_3$), 4.32-4.54 [1H, m, OC*H*(CH$_3$)$_2$], 4.95-5.64 (4H, m, C*H*-OH, CH=C*H*$_2$ and C=C*H*CH$_3$), 5.93-6.10 (1H, m, C*H*=CH$_2$), 6.79-6.88 (1H, m, 5-H), 7.08-7.20 (1H, m, 6-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 13.4 and 13.5 ($CH_3$), 15.5 and 15.7 [OCH(*C*H$_3$)$_2$], 17.9 ($CH_3$), 19.3 and 19.9 [OCH(*C*H$_3$)$_2$], 22.6 and 22.7 [OCH(*C*H$_3$)$_2$], 24.5 ($CH_3$), 55.5 and 55.6 ($OCH_3$), 69.8, 69.9, 70.8, 71.0, 71.3, 71.5 and 71.6 (CH-OH), 74.5, 75.0 and 75.4 [O*C*H(CH$_3$)$_2$], 110.7, 110.8, 110.9 and 111.0 (5-C), 112.8, 113.5, 113.7, 113.9 and 114.0 (CH=*C*H$_2$), 121.4, 121.8, 121.9, 122.0 and 123.5 (6-C), 123.8 (2-C), 124.5 and 125.4 (C=*C*HCH$_3$), 132.5, 132.9, 133.0, 133.1 and 133.5 (1-C), 134.4, 136.1 and 137.6 (*C*=CHCH$_3$), 140.3, 140.4, 140.7 and 141.1 (*C*H=CH$_2$), 143.6 and 143.9 (3-C), 152.2 and 152.3 (4-C).

### *3.14 Preparation of 4-isopropoxy-5-methoxy-3-methyl-1H-inden-1-ol **285***



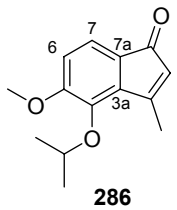
**285**

The 1-{3-isopropoxy-4-methoxy-2-[(1*E*)-1-methyl-1-pro-penyl]phenyl}-2-propen-1-ol **284** (0.374mmol, 0.103g) was dissolved in distilled $CH_2Cl_2$ (10cm$^3$) and the solution was degassed using $N_2$ for 10 min. Then

Grubbs II catalyst **11** (0.05eq, 0.0187mmol, 0.0160g) was added and the solution was stirred at rt under an Ar atmosphere for 1 h, after which time the solvent was removed *in vacuo* to give a dark brown oil. This was purified by column chromatography (5-10% EtOAc-Hexane) to give the desired product as a bright yellow oil (0.0496g, 57%), confirmed by an NMR comparison to the data of Coyanis.[206]

***R*$_f$** = 0.23 (20% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.26 [6H, dd, *J*=6.2 and 16.3Hz, OCH(C*H*$_3$)$_2$], 1.77 (1H, br s, OH), 2.23 (3H, t, *J*=1.5Hz, $CH_3$), 3.82 (3H, s, $OCH_3$), 4.63 [1H, sept, *J*=6.2Hz, OC*H*(CH$_3$)$_2$], 4.99 (1H, s, C*H*-OH), 5.93 (1H, s, C*H*=CCH$_3$), 6.68 (1H, d, *J*=7.9Hz, 6-H), 7.10 (1H, d, *J*=7.9Hz, 7-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 16.5 ($CH_3$), 22.3 and 22.5 [OCH(*C*H$_3$)$_2$], 56.0 ($OCH_3$), 74.2 [O*C*H(CH$_3$)$_2$[a]], 75.4 (CH-OH[a]), 109.8 (6-C), 118.1 (*C*H=CCH$_3$[b]), 133.4 (7-C[b]), 136.5 (3a-C[c]), 140.1 (7a-C[c]), 141.3 (3-C[c]), 141.6 (4-C), 153.6 (5-C).

### *3.15 Preparation of 4-isopropoxy-5-methoxy-3-methyl-1H-inden-1-one **286***

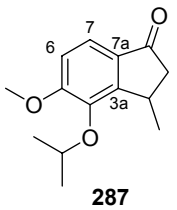


**286**

The 1-{3-isopropoxy-4-methoxy-2-[(1*E*)-1-methyl-1-pro-penyl]phenyl}-2-propen-1-ol **284** (0.326mmol, 0.0900g) was dissolved in distilled toluene (9cm$^3$) and the solution was heated to 80$^o$C before the addition of Grubbs II catalyst **11** (0.08eq, 0.0260mmol, 0.0226g). The reaction mixture was allowed to stir at 80$^o$C under an Ar atmosphere for 16 h. After this time the solvent was removed *in vacuo* to give a dark brown oil that was then purified by column chromatography (5-10% EtOAc-Hexane). The desired product was obtained as a dark yellow semi-solid (0.0316g, 42%) and a small amount of 4-isopropoxy-5-methoxy-3-methyl-1*H*-inden-1-ol **285** (0.0316g, 23% relative to the starting material) was isolated. NMR spectroscopic data correlated well to that reported by Coyanis.[206]

***R*$_f$** = 0.48 (20% EtOAc-Hexane); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.30 [6H, d, *J*=6.2Hz, OCH(C*H*$_3$)$_2$], 2.39 (3H, s, $CH_3$), 3.86 (3H, s, $OCH_3$), 4.72 [1H, sept, *J*=6.2Hz, OC*H*(CH$_3$)$_2$], 5.61 (1H, s, C*H*=CCH$_3$), 6.61 (1H, d, *J*=7.8Hz, 6-H), 7.12 (1H, d, *J*=7.8Hz, 7-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 17.9 ($CH_3$), 22.5 [OCH(*C*H$_3$)$_2$], 56.0 ($OCH_3$), 74.7 [O*C*H(CH$_3$)$_2$], 110.1 (6-C), 118.1 (7-C), 125.5 (*C*H=CCH$_3$), 125.9 (7a-C), 136.7 (3a-C), 141.9 (4-C), 158.5 (5-C), 162.1 (3-C), 196.4 (C=O).

### *3.16 Preparation of 4-isopropoxy-5-methoxy-3-methyl-1-indanone **287***




**287**

The 1-{3-isopropoxy-4-methoxy-2-[(1*E*)-1-methyl-1-pro-penyl]phenyl}-2-propen-1-ol **284** (0.288mmol, 0.0795g) was transferred to the round bottomed flask using $CH_2Cl_2$ ($8cm^3$) and then the solution was degassed using $N_2$ for 11 min. After this time Grubbs II catalyst **11** (0.05eq, 0.0144mmol, 0.0130g) was added and the solution was heated to 110°C (all the $CH_2Cl_2$ evaporated off over time). Then the solventless reaction mixture was allowed to stir at 110-170°C under an Ar atmosphere for 18 h. After this time the residue was purified by column chromatography (5-10% EtOAc-Hexane) to yield the desired compound as a dark yellow oil (0.0124g, 18%) and a trace amount of 4-isopropoxy-5-methoxy-3-methyl-1*H*-inden-1-one **286** (0.0049g, 7% relative to starting material).

***R_f*** = 0.34 (20% EtOAc-Hexane); **$\nu_{max}$/cm$^{-1}$ (NaCl plate)** 753 (alkane), 1217 (-C-O), 1335 (-$COCH_3$), 1379 and 1437 (alkane), 1490 and 1594 (Ar ring), 1699 (aryl C=O), 2882 (-$OCH_3$), 2981 (-$CH_2$ or –$CH_3$), 3019 (Ar H); **$\delta_H$ (300 MHz, $CDCl_3$)** 1.27 (3H, d, *J*=6.1Hz, $CH_3$), 1.39 [6H, dd, *J*=6.6 and 17.5Hz, OCH($CH_3$)$_2$], 2.25 (1H, dd, *J*=2.6 and 19.0Hz, 2-H$^a$), 2.91 (1H, dd, *J*=7.7 and 19.0Hz, 2-H$^a$), 3.51(1H, dp, *J*=2.5 and 7.2Hz, 3-H), 3.83-3.94 (3H, m, $OCH_3$), 4.58 [1H, sept, *J*=6.1Hz, OC*H*($CH_3$)$_2$], 6.96 (1H, d, *J*=8.4Hz, 6-H), 7.49 (1H, d, *J*=8.3Hz, 7-H); **$\delta_C$ (50 MHz, $CDCl_3$)** 20.6 ($CH_3$), 22.6 and 22.7 [OCH(*C*$H_3$)$_2$], 31.5 (3-C), 45.9 (2-C), 56.1 ($OCH_3$), 75.6 [O*C*H($CH_3$)$_2$], 112.3 (6-C), 119.6 (7-C), 130.6 (7a-C), 143.7 (3a-C), 153.1 (4-C), 158.3 (5-C), 205.2 (C=O); **MS *m/z*** 234 ($M^+$, 21%), 41 (11), 43 (14), 69 (100), 77 (8), 91 (8), 131 (18), 132 (15), 177 (57), 178 (8), 190 (9), 191 (7), 192 (64), 219 (80), 220 (28), 234 (21), 263 (9), 264 (7), ***HRMS*** calculated for $C_{14}H_{18}O_3$: 234.12559, found: 234.12130.

# *Chapter 8:*

# *References*

# *Chapter 8: References*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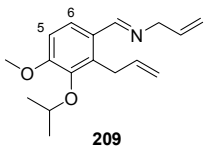
# *Appendices*

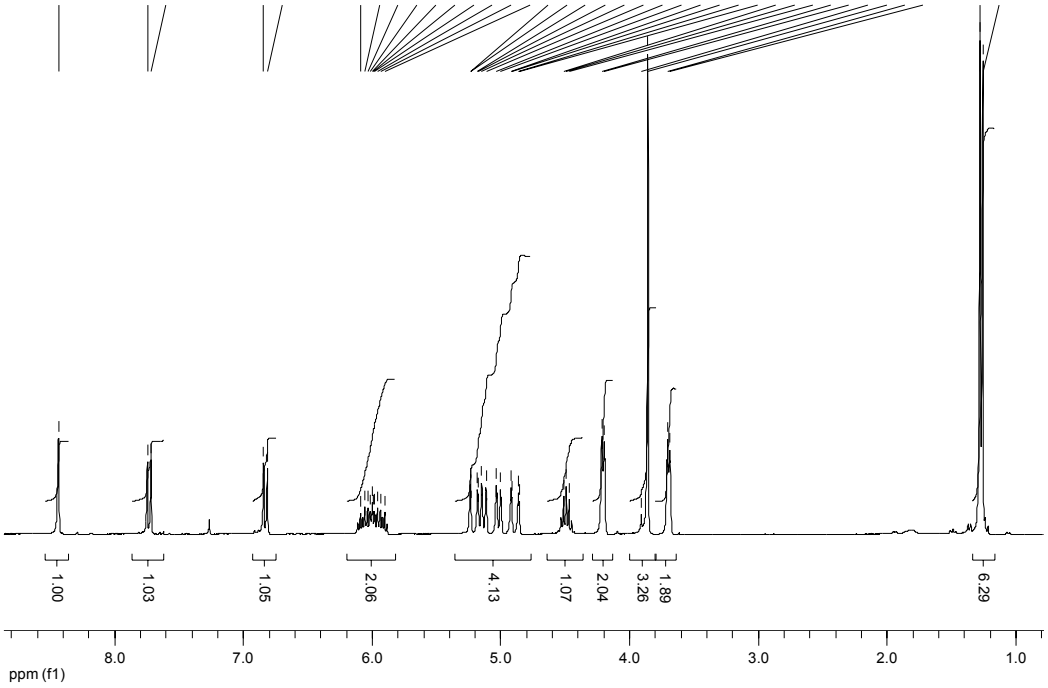
# *Appendix A:*

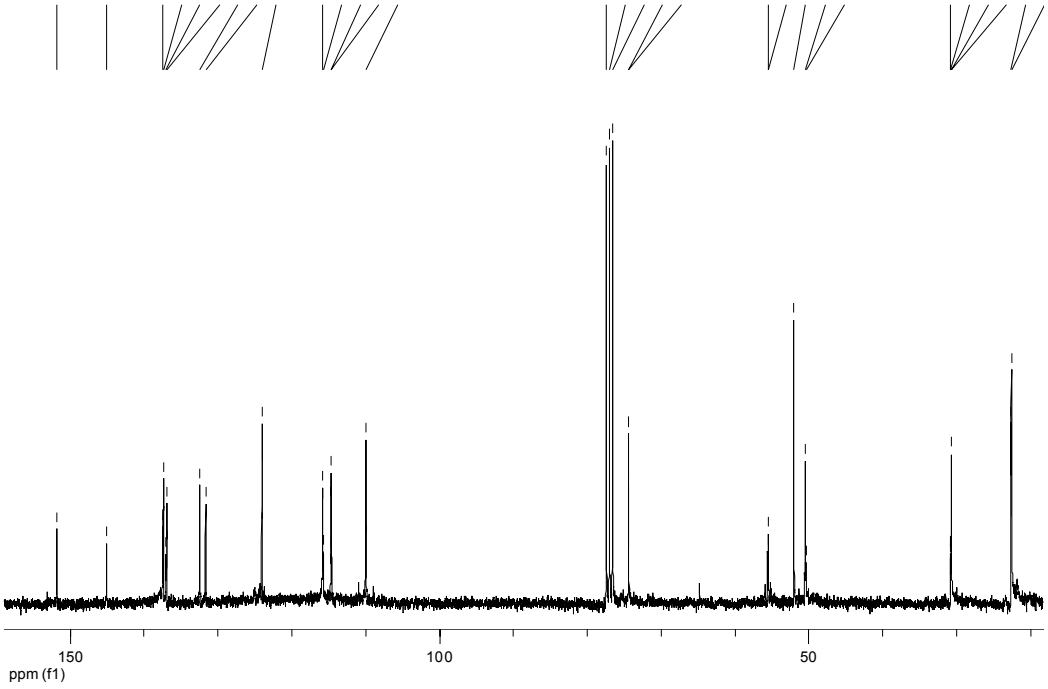
# *Selected NMR Spectra*

**_N_-[(_E_)-(2-Allyl-3-isopropoxy-4-methoxyphenyl)methylidine]-2-propen-1-amine 209**

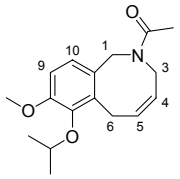



**209**



**1-[7-Isopropoxy-8-methoxy-3,6-dihydro-2-benzazocin-2(1*H*)-yl]-1-ethanone 214**

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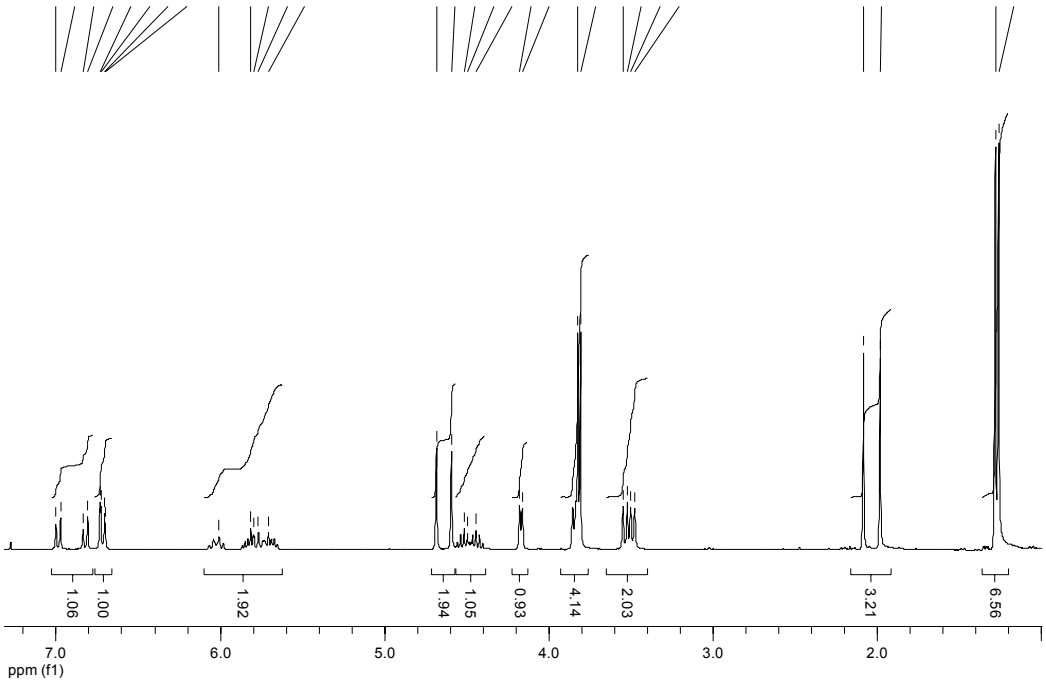
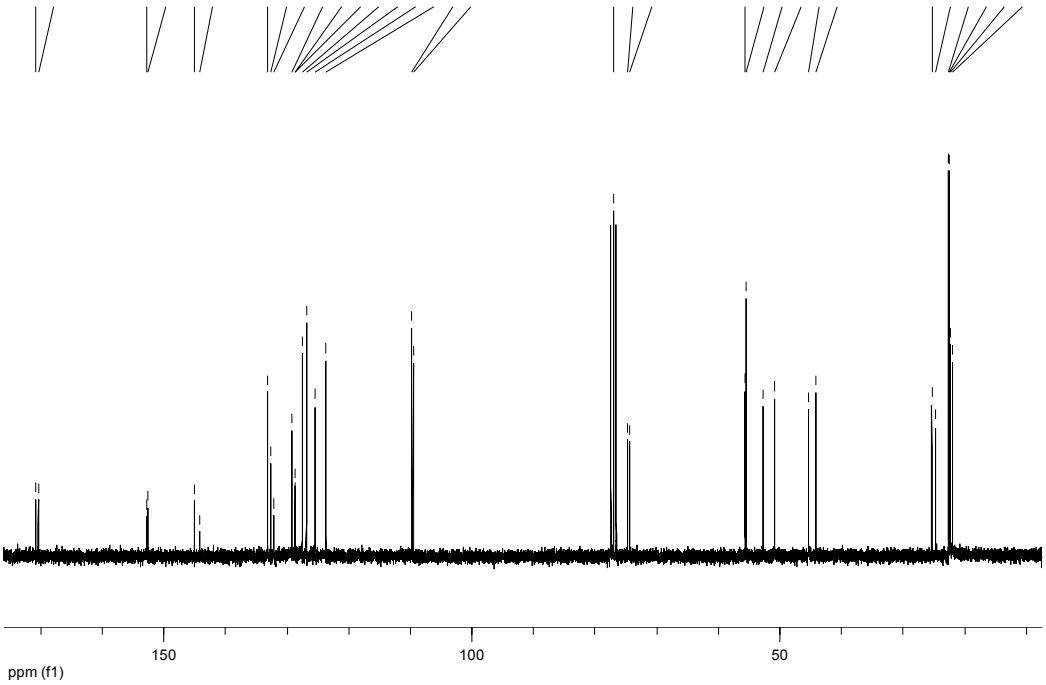
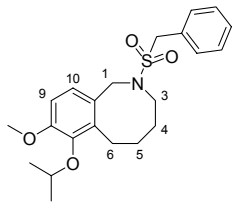


**2-(Benzylsulfonyl)-7-isopropoxy-8-methoxy-1,2,3,45,6-hexahydro-2-benzazocine 217**

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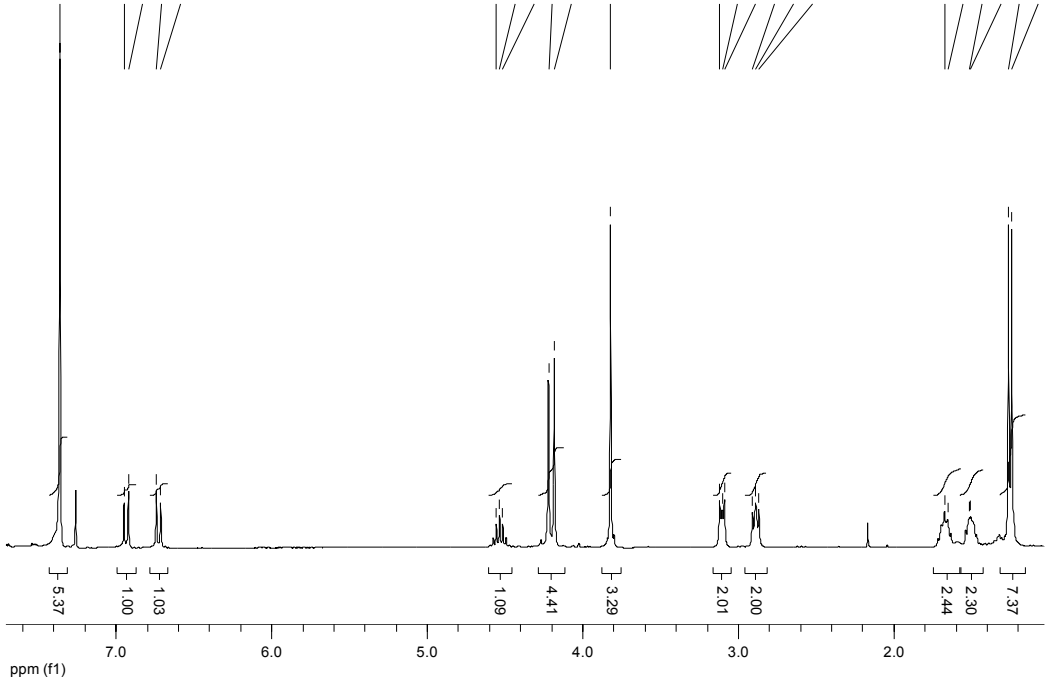
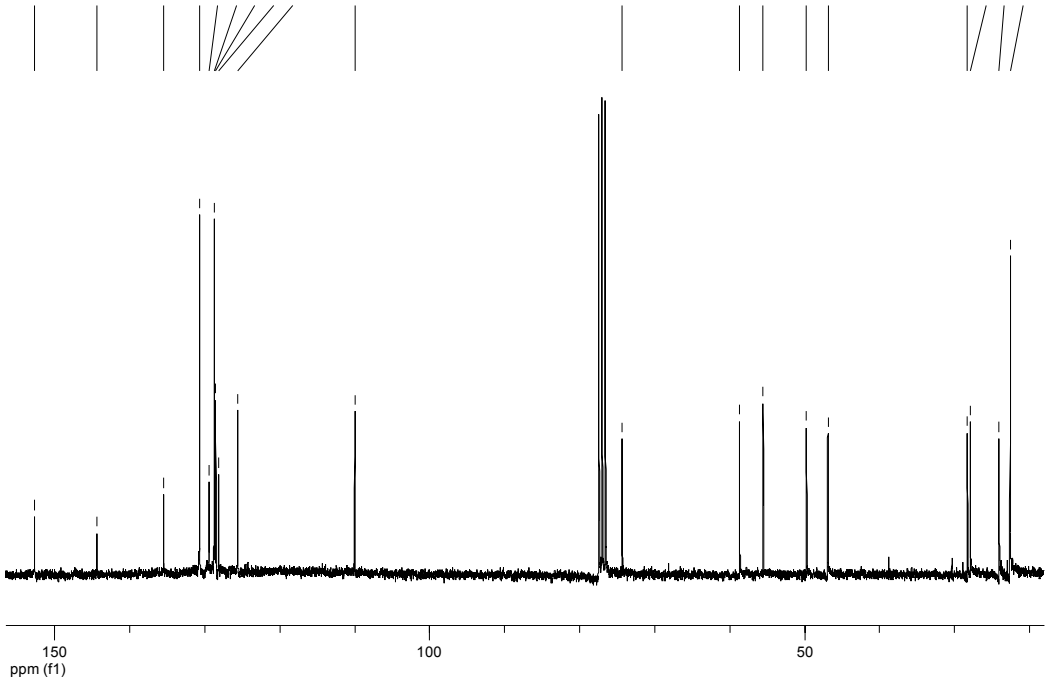
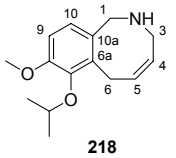


**7-Isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine 218**

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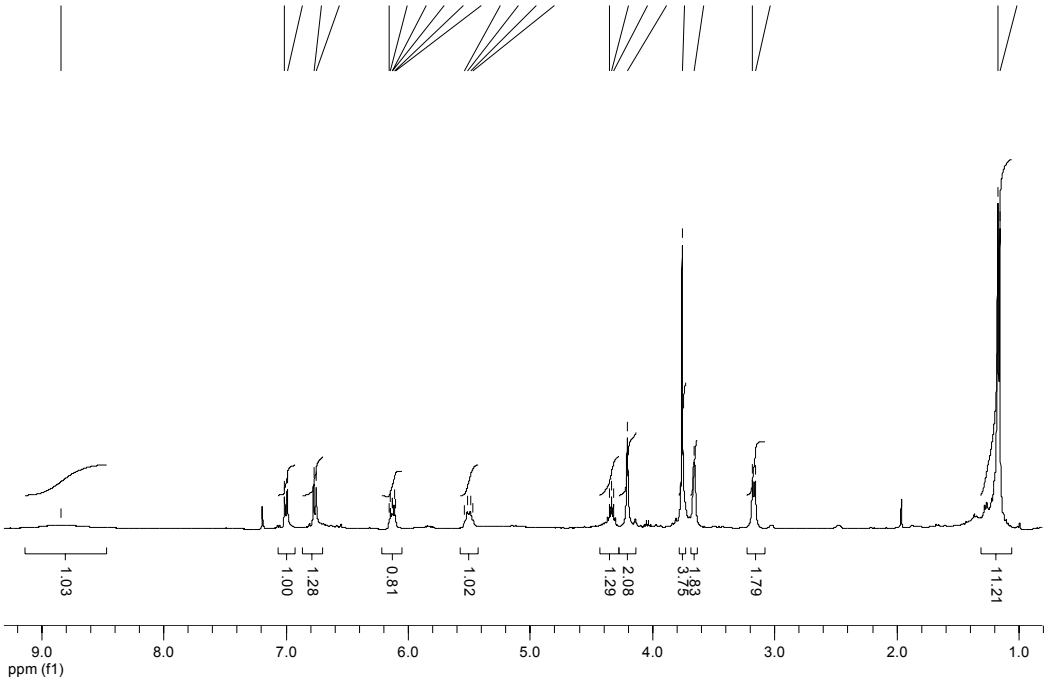
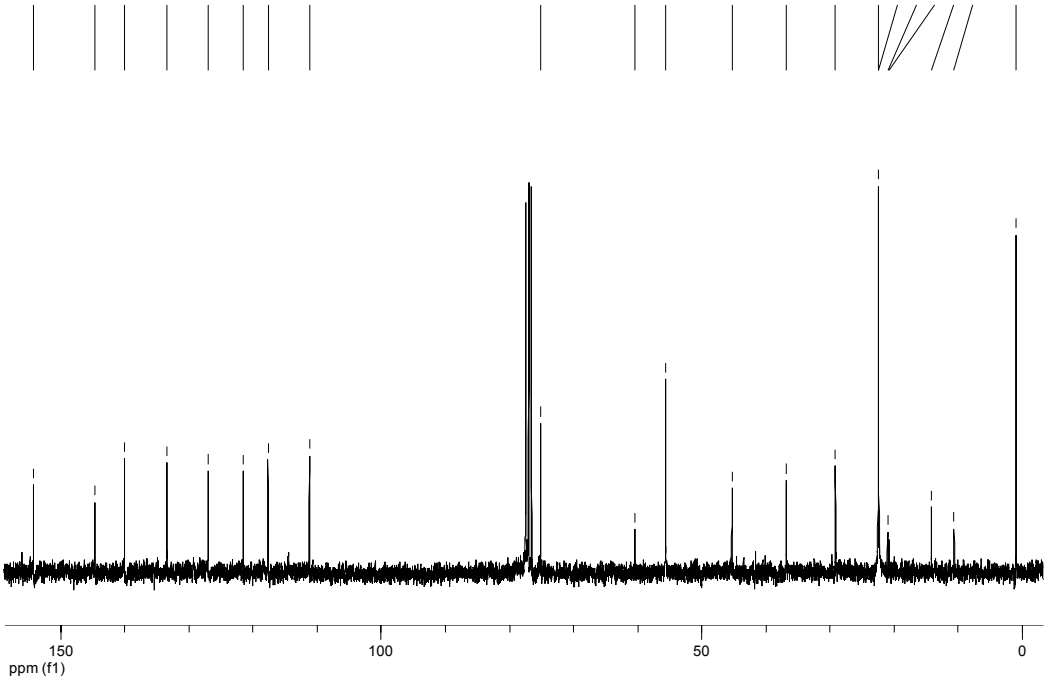
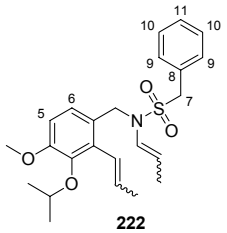


## *N*-(1-propenyl)methansulfonamide 222

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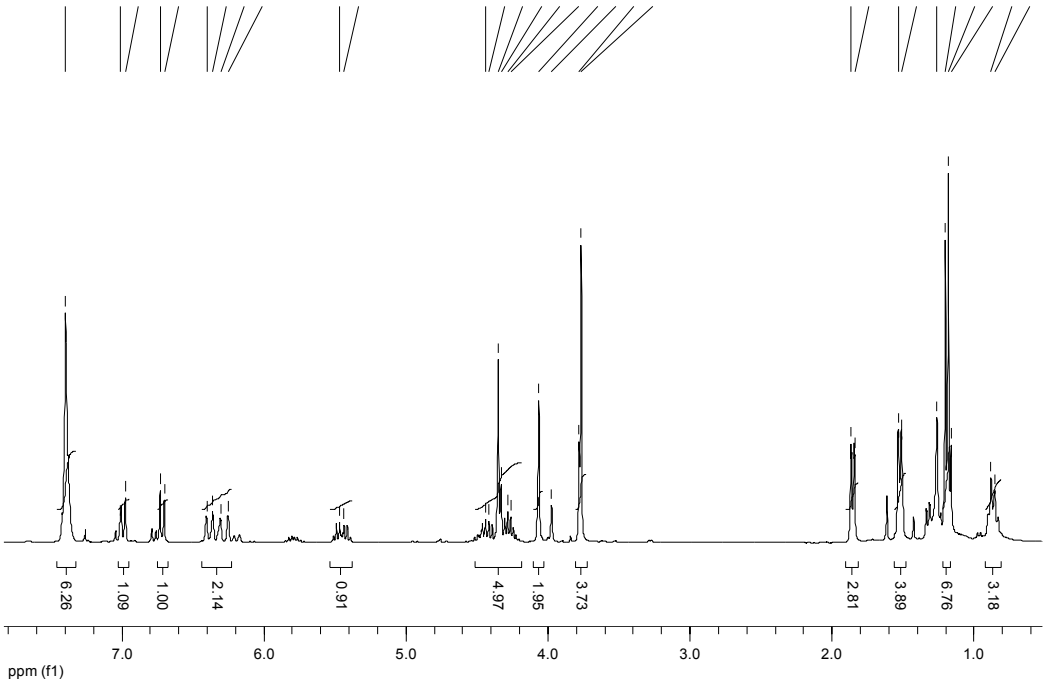
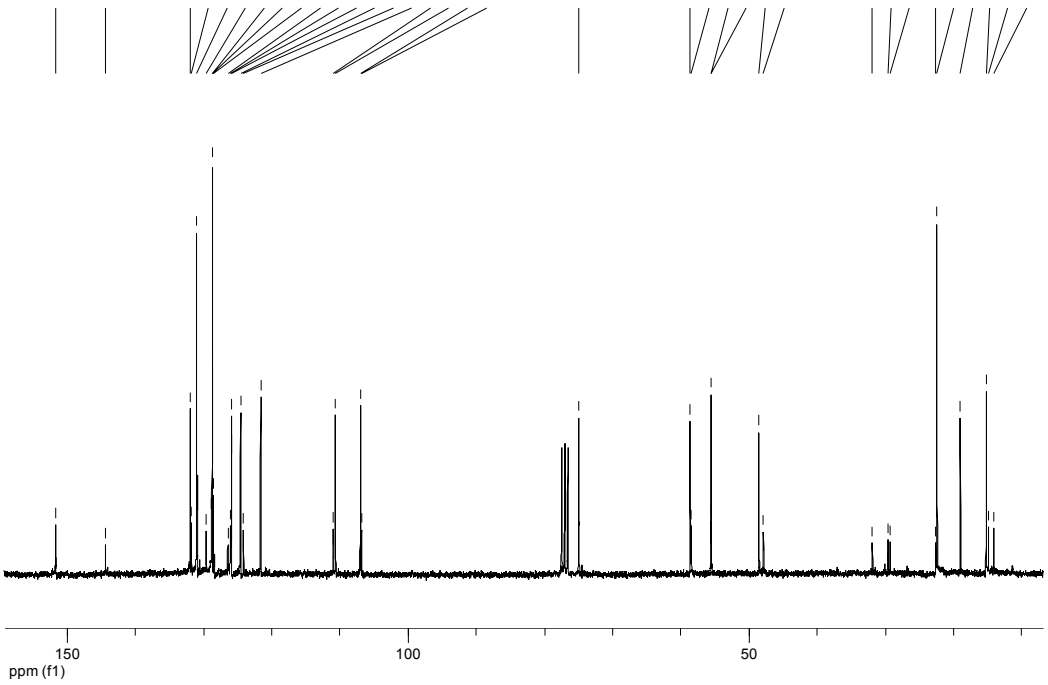
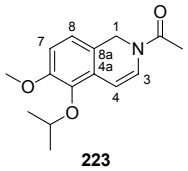


**2-Acetyl-5-isopropoxy-6-methoxy-1,2-dihydroisoquinoline 223**



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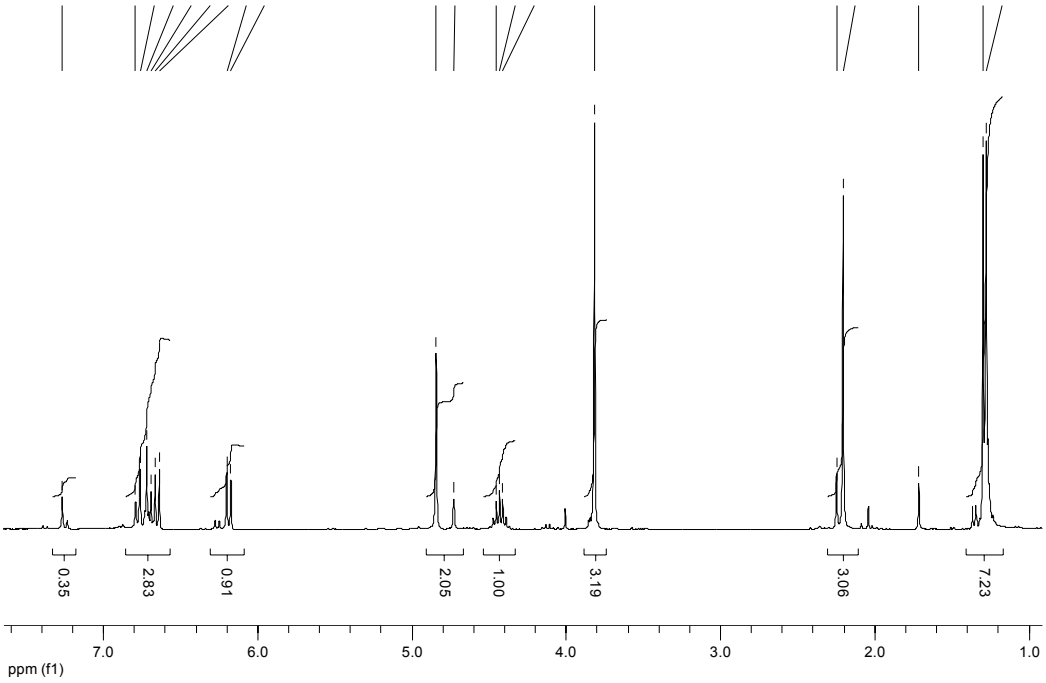
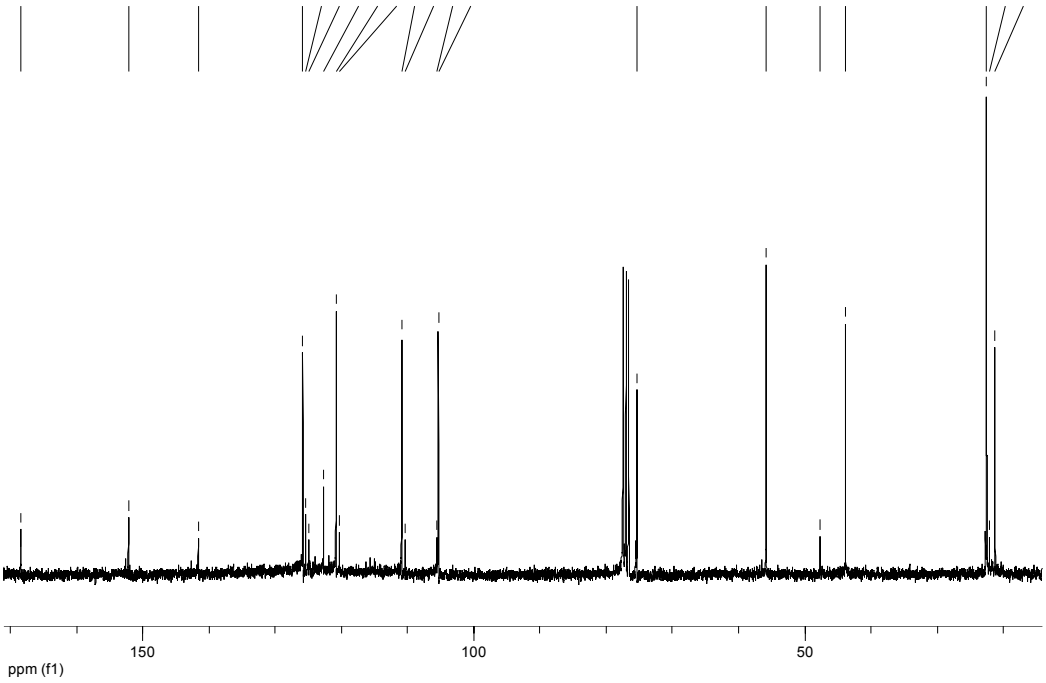
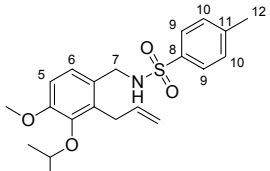
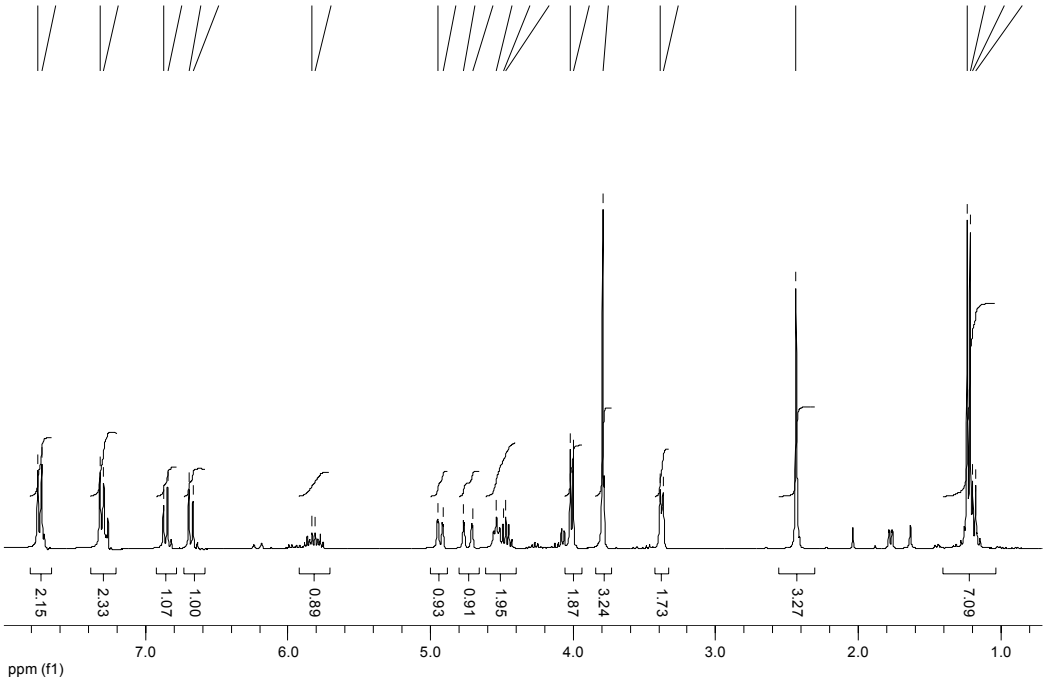


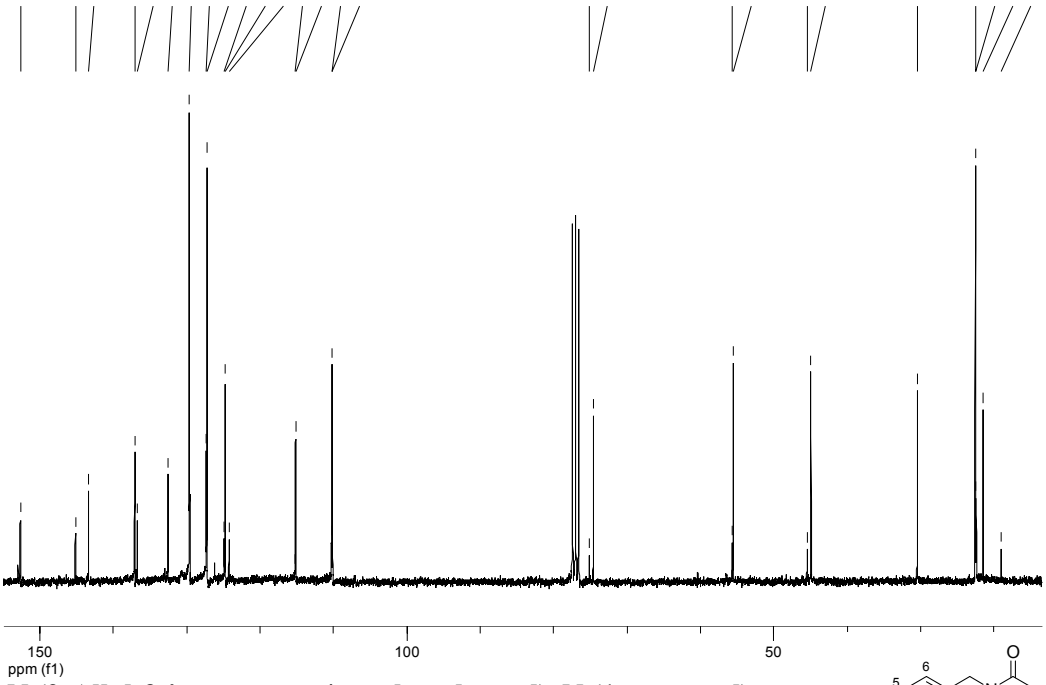




***N*-(2-Allyl-3-isopropoxy-4-methoxybenzyl)-4-methylbenzene-**

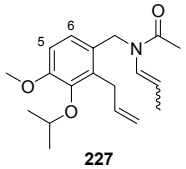


**sulfonamide 244**

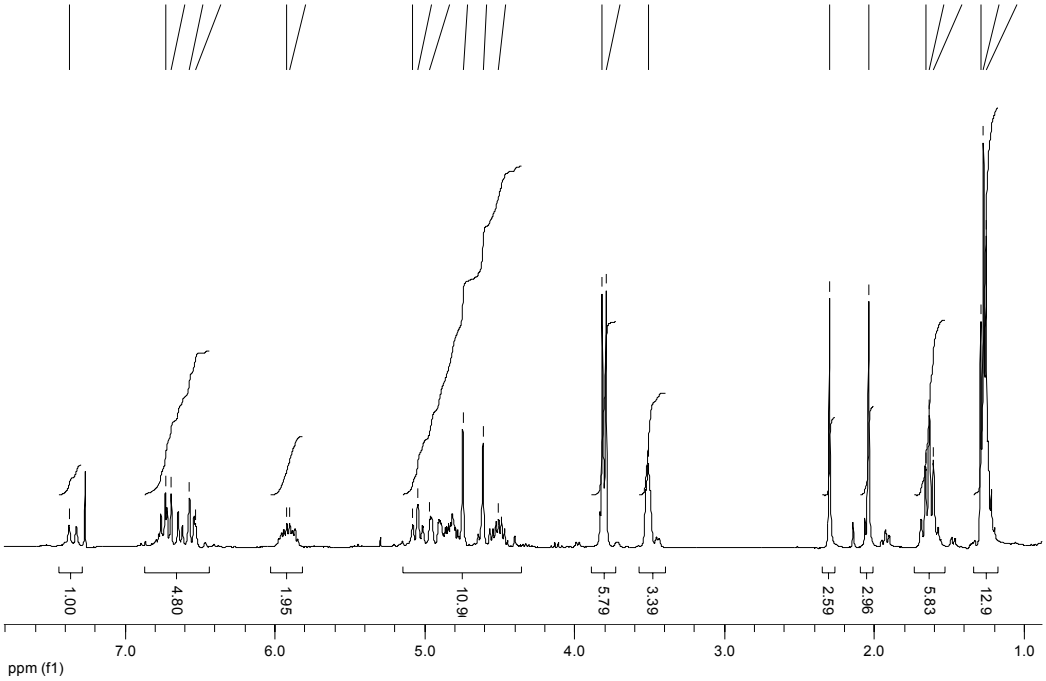


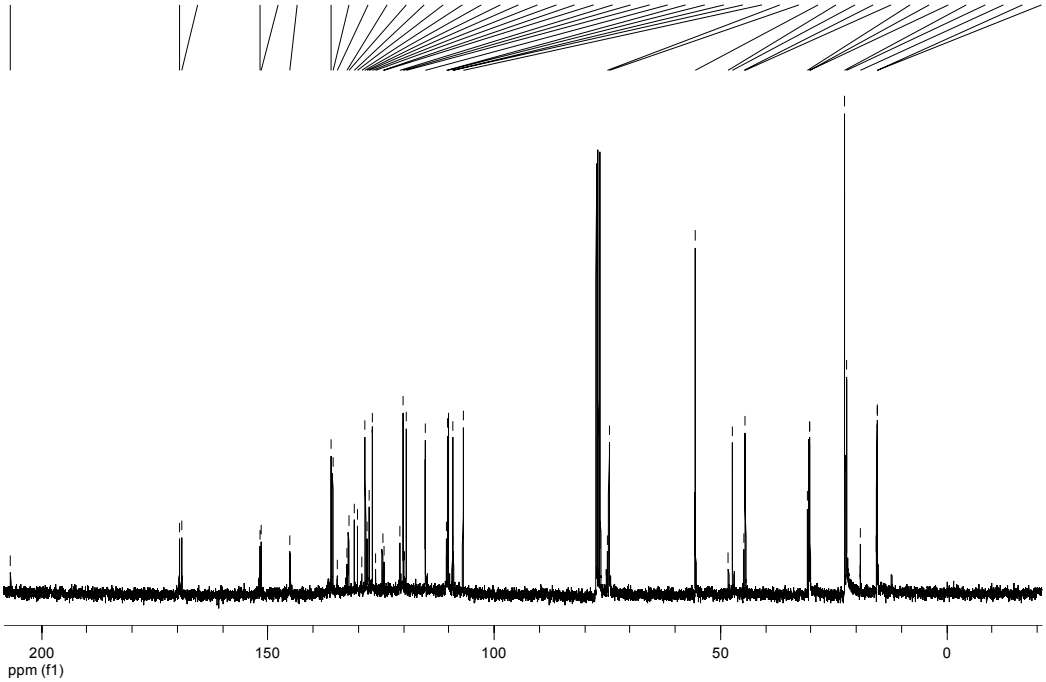




***N*-(2-Allyl-3-isopropoxy-4-methoxybenzyl)-*N*-(1-propenyl)**

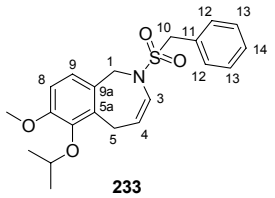


**acetamide 227**

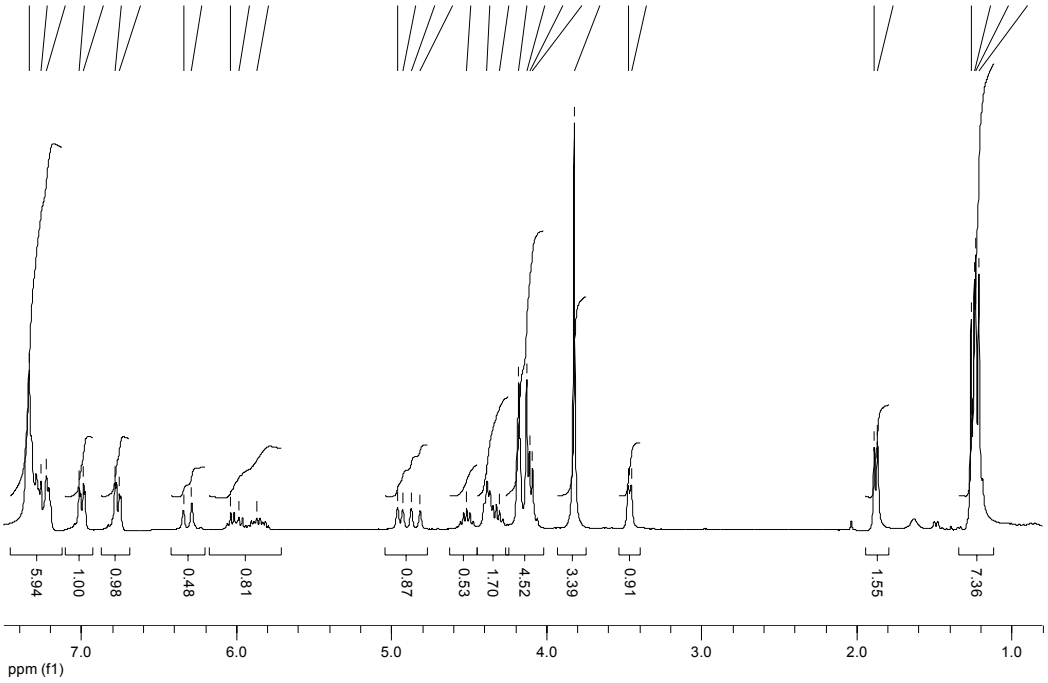


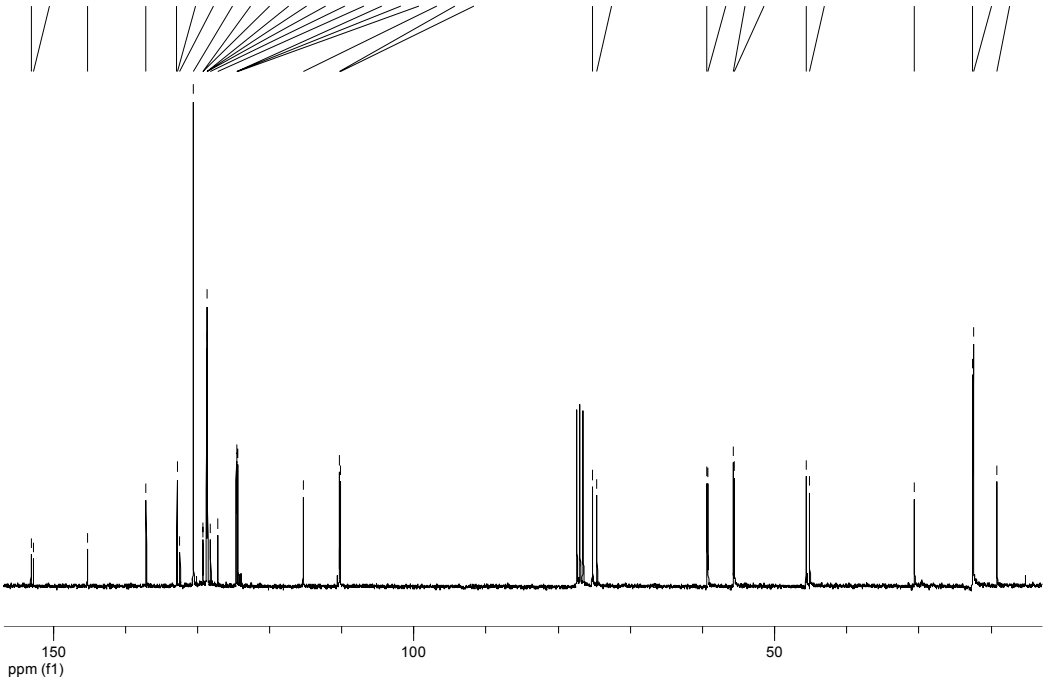




**2-(Benzylsulfonyl)-6-isopropoxy-7-methoxy-2,5-dihydro-1*H*-2-**



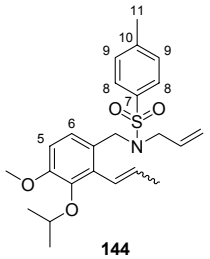
**benzazepine 233**



***N*-Allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-propenyl)benzyl]-4-methylbenzenesulfonamide**

**144**

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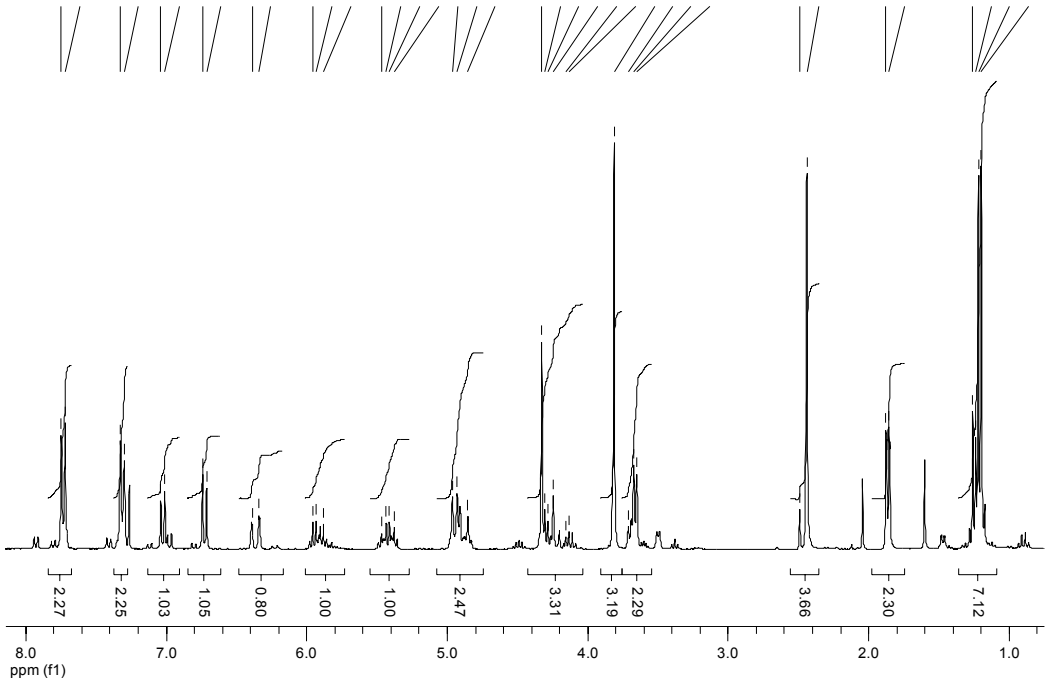
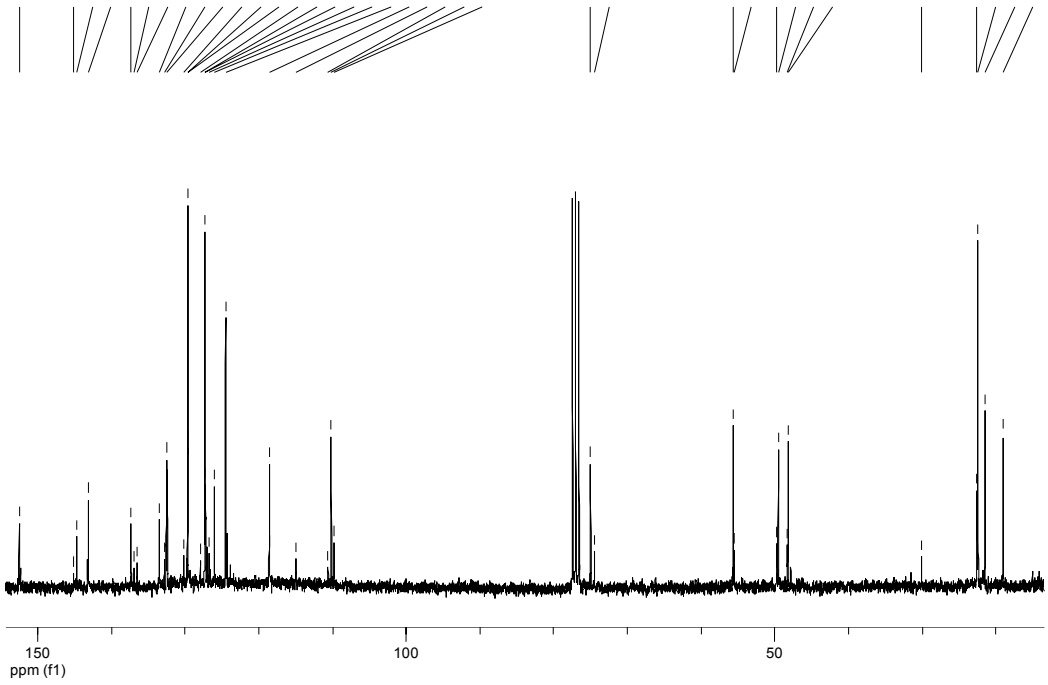
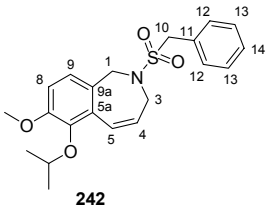


**2-(Benzylsulfonyl)-6-isopropoxy-7-methoxy-2,3-dihydro-1*H*-2-benzazepine 242**

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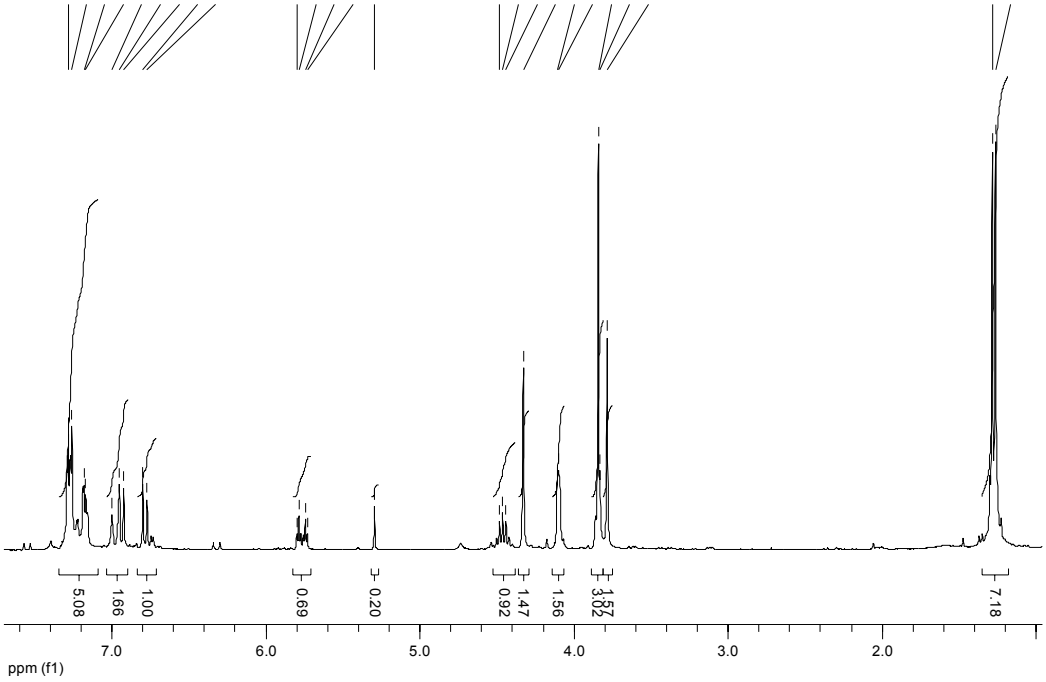
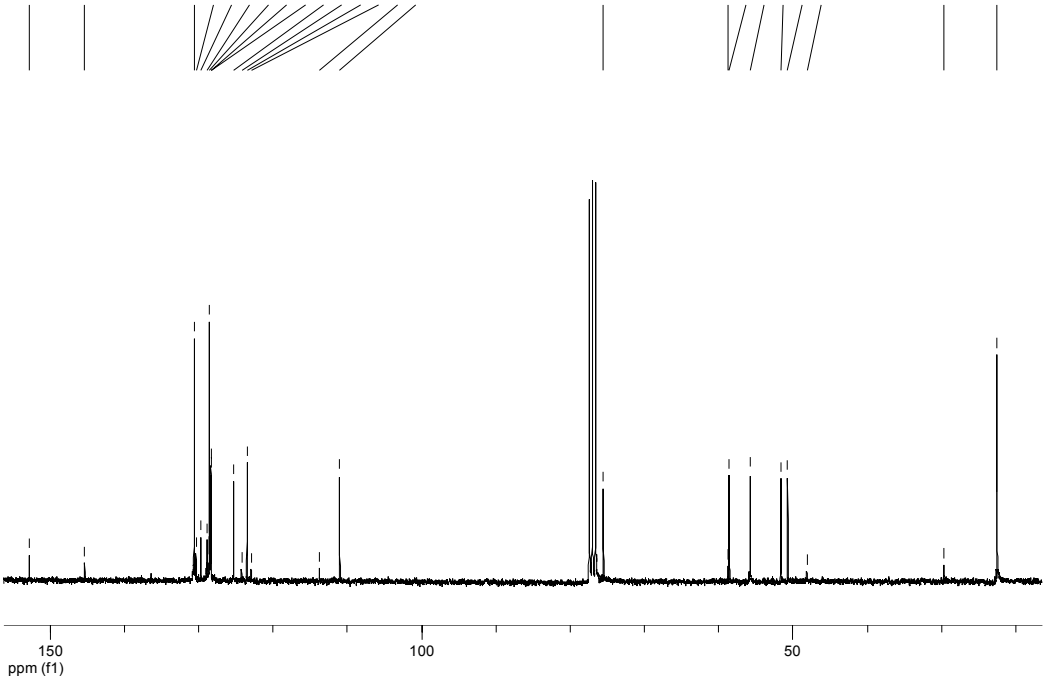
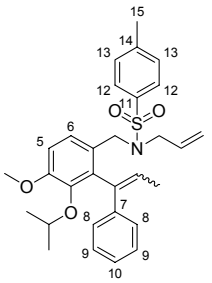


***N*-Allyl-*N*-[3-isopropoxy-4-methoxy-2-(1-phenyl-1-Propenyl)benzyl]-4-methylbenzenesulfonamide 253**

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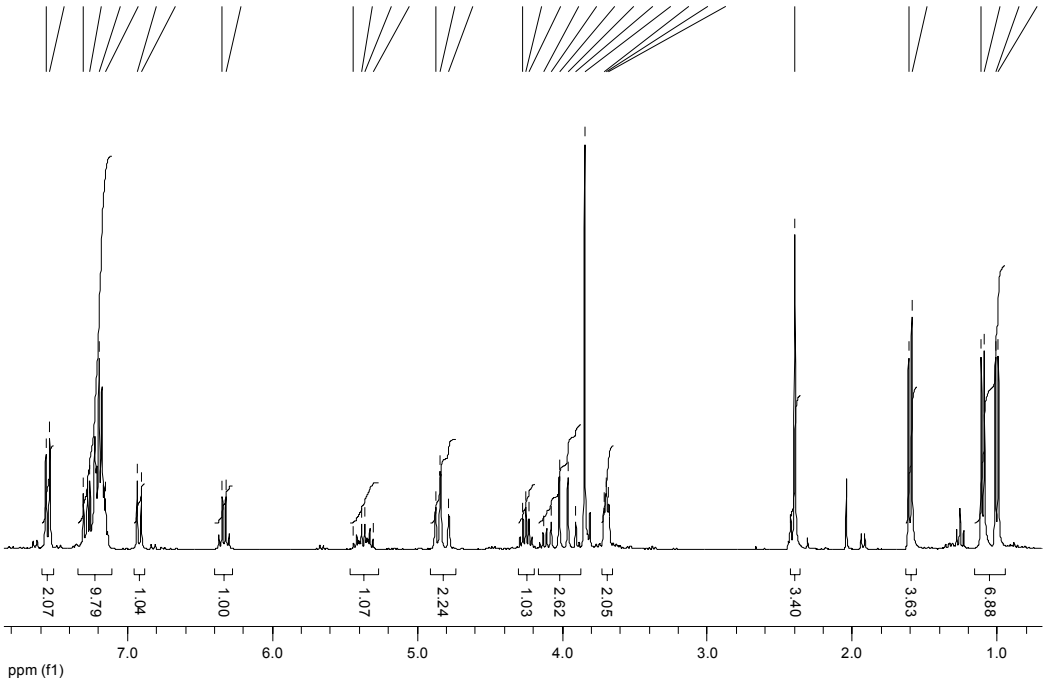
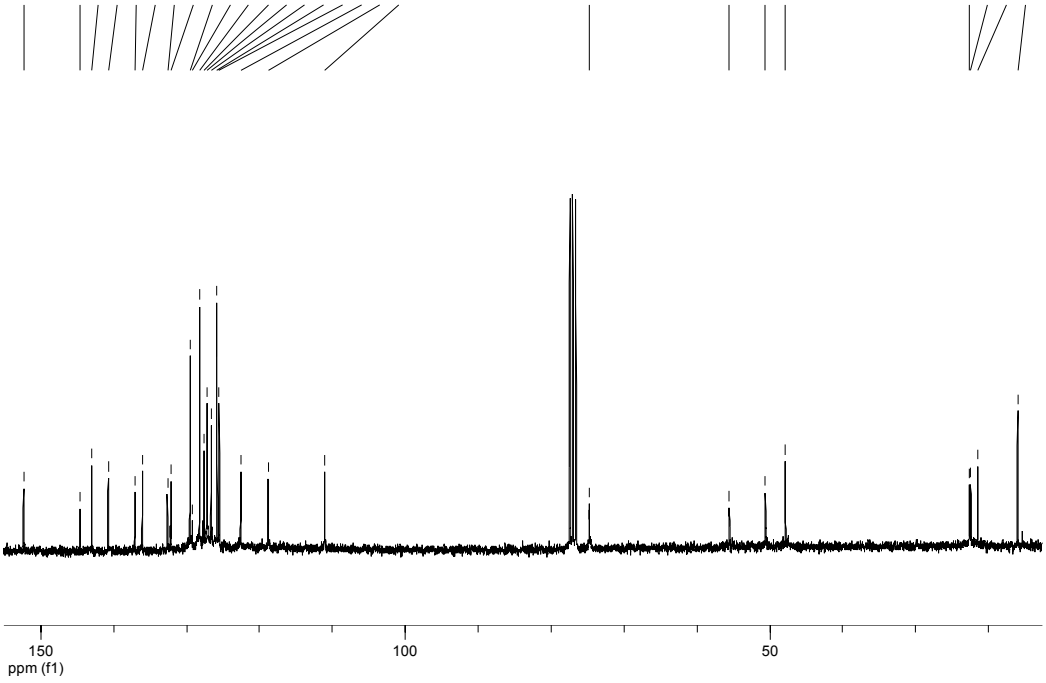
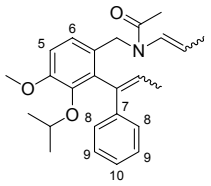


***N*-[3-Isopropoxy-4-methoxy-2-(1-phenyl-1-propenyl)benzyl]-*N*-(1-propenyl)acetamide 258**

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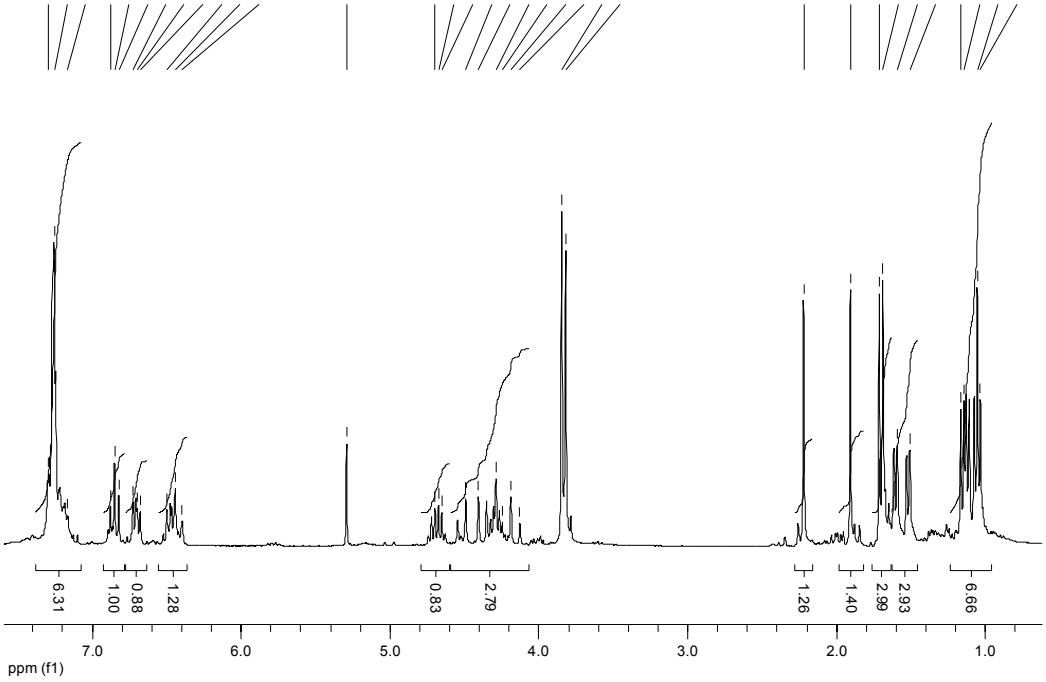
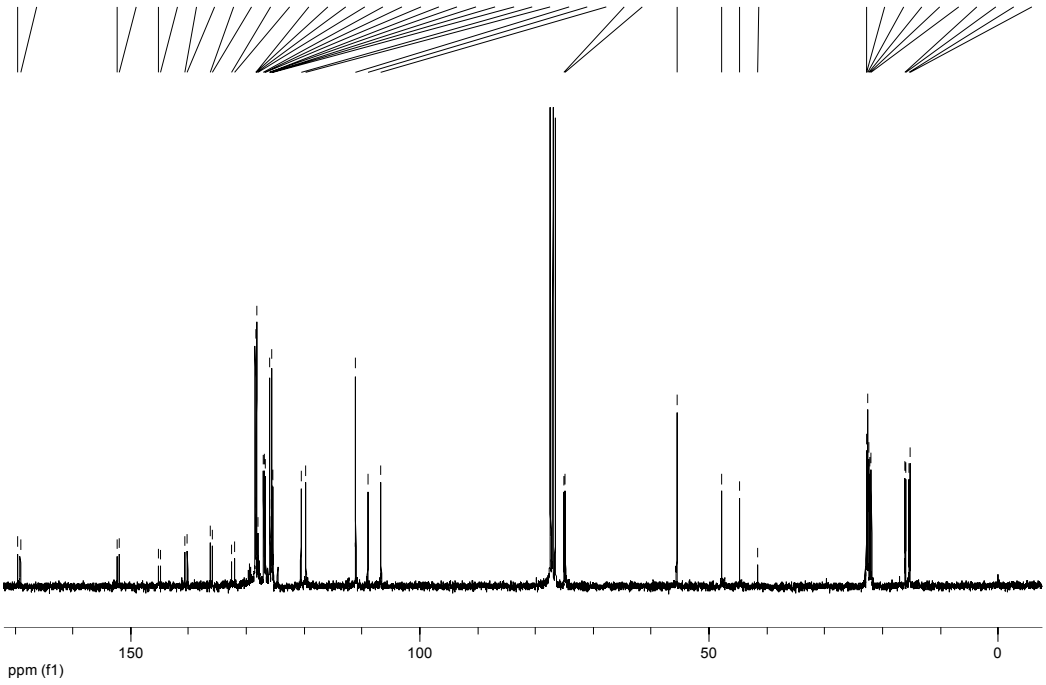
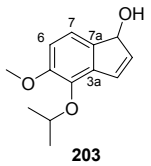
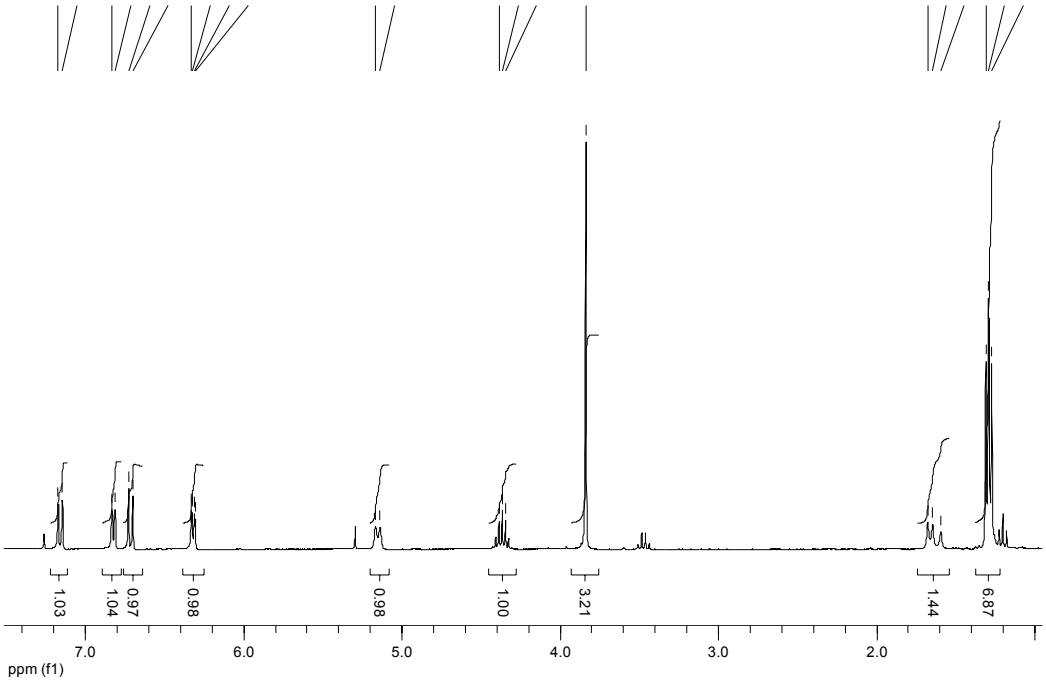


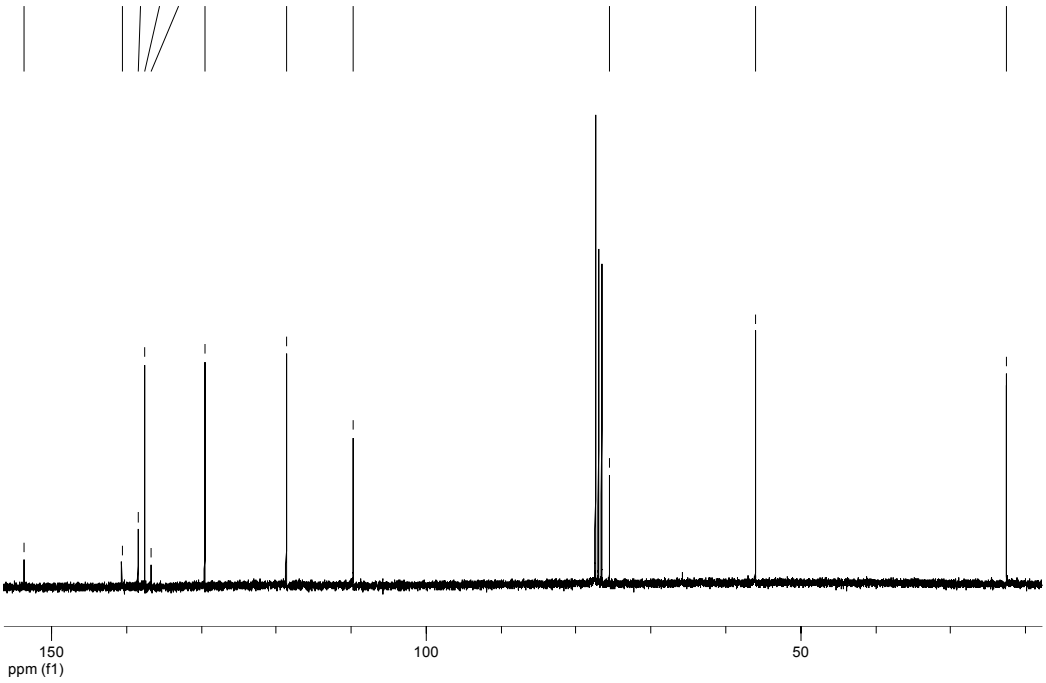



**4-Isopropoxy-5-methoxy-1*H*-inden-1-ol 203**




**203**



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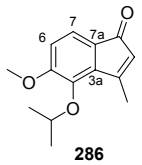
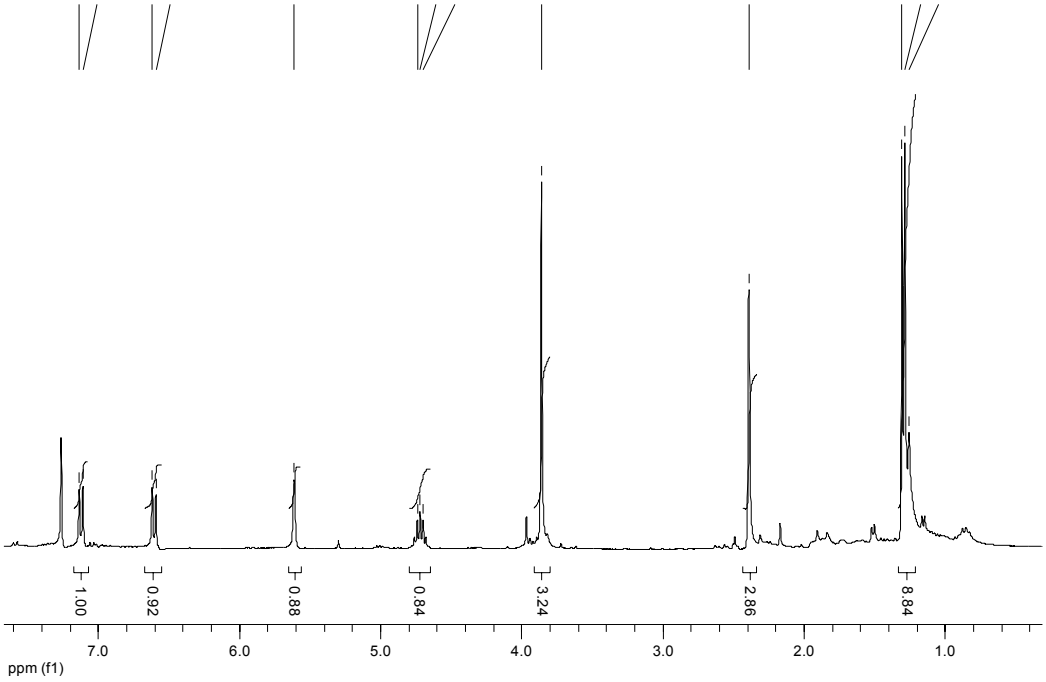
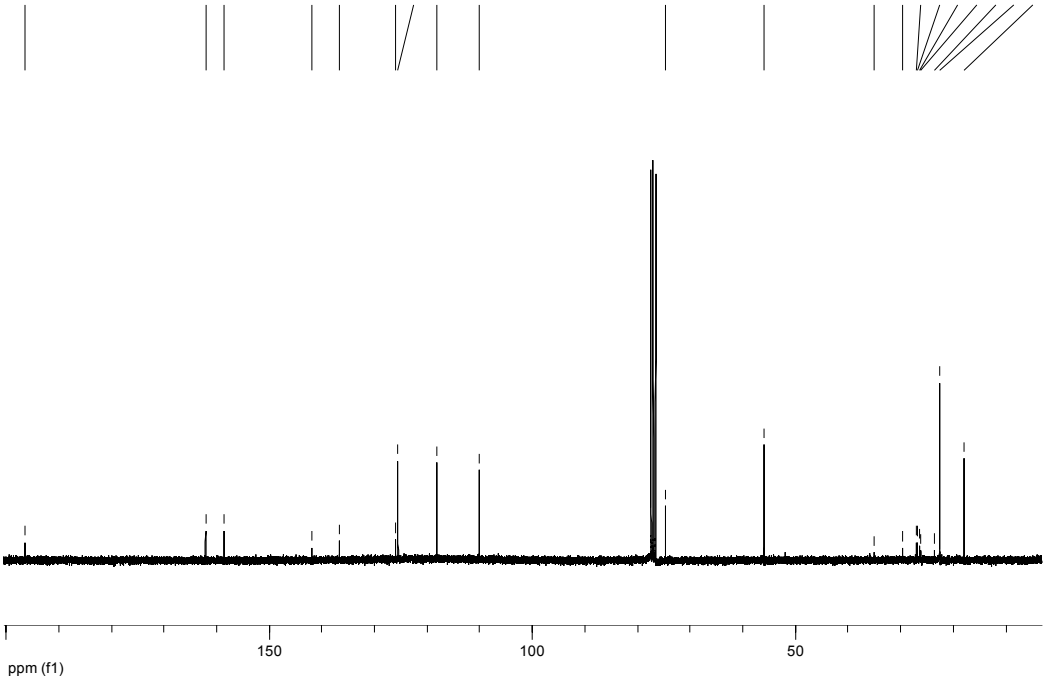
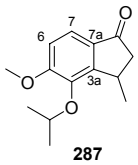



**286**

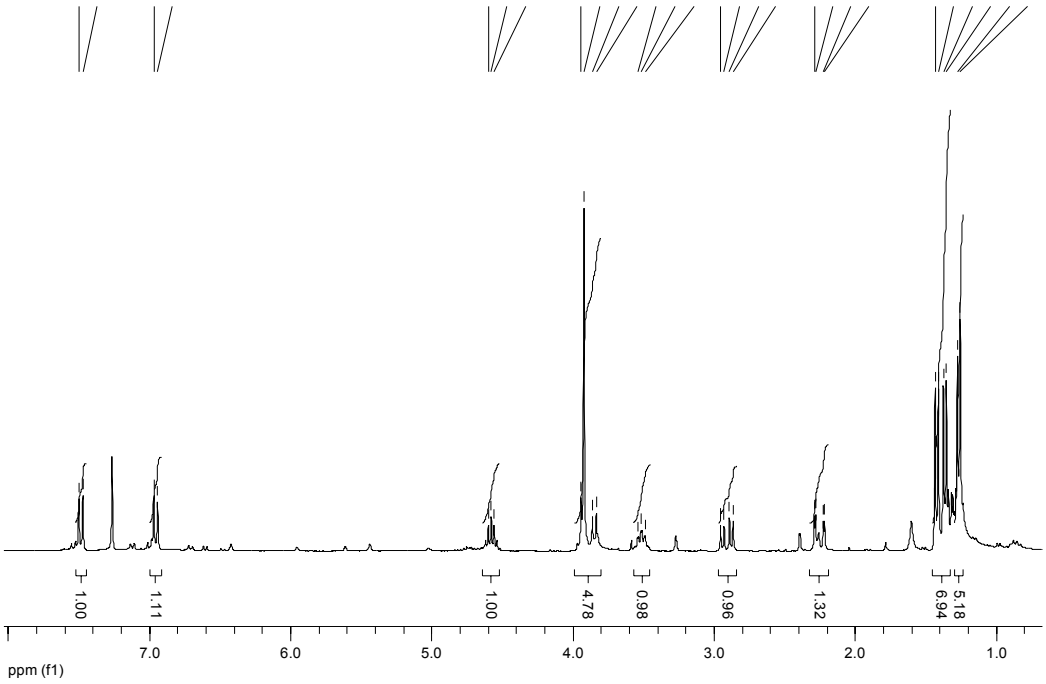


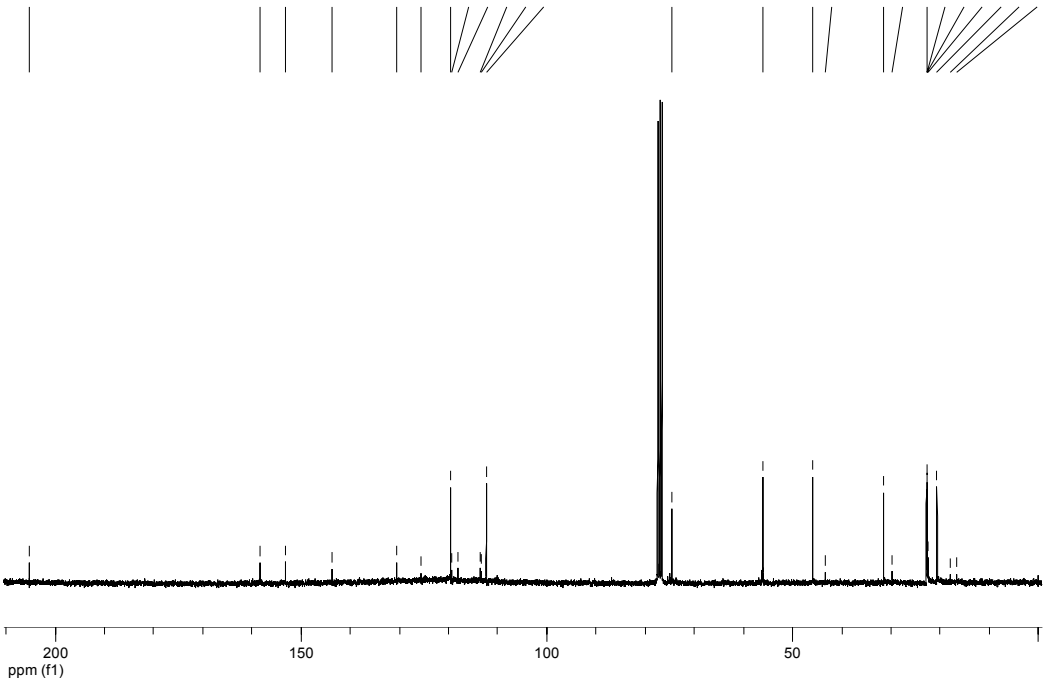



**4-Isopropoxy-5-methoxy-3-methyl-1-indanone 287**




**287**

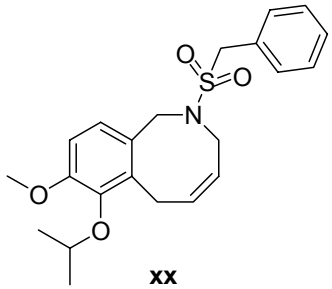


# *Appendix B:*

# *Single-Crystal X-Ray Diffraction Data*

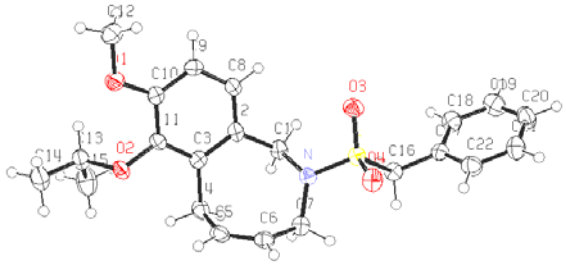
*1.1 Crystal Structure Data for Compound **XX***



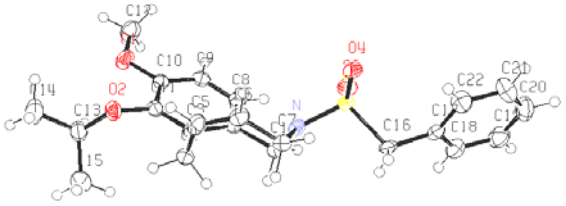

**xx**

**Table 1** Crystal Data and Structure Refinement for Compound **XX**

**ORTEP Diagrams**
**(50% probability thermal ellipsoids fo all non-hydrogen atoms)**




Top View




Side View

**Mercury Diagrams**

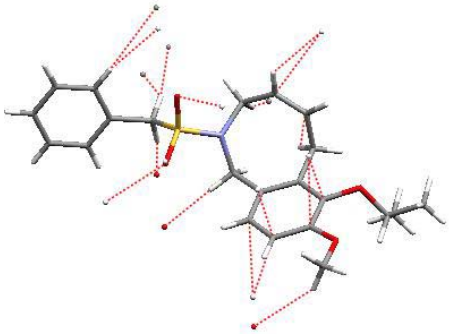
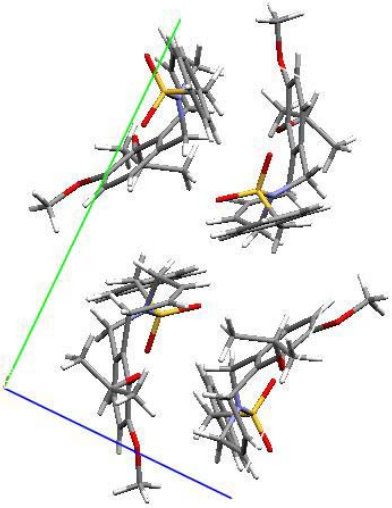
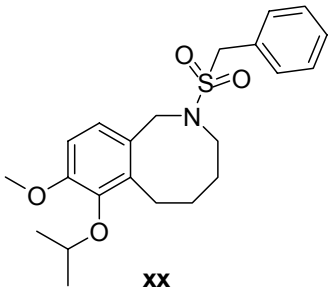


Diagram with Short Contacts



Packing Diagram

*1.2 Crystal Structure Data for Compound **XX***

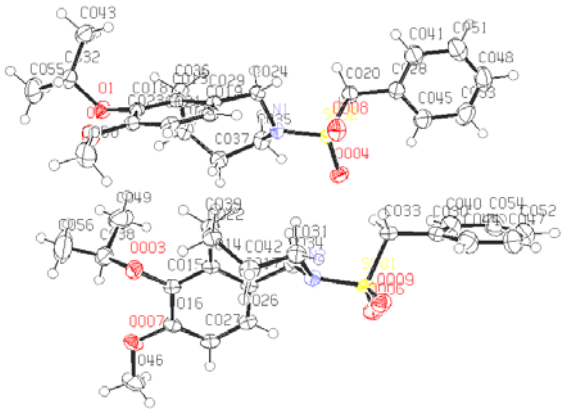



**xx**

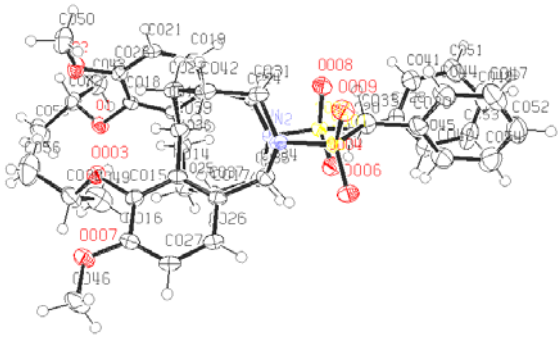
**Table 1** Crystal Data and Structure Refinement for Compound **XX**

**ORTEP Diagrams**

**(50% probability thermal ellipsoids fo all non-hydrogen atoms)**



Top View



Side View

**Mercury Diagrams**

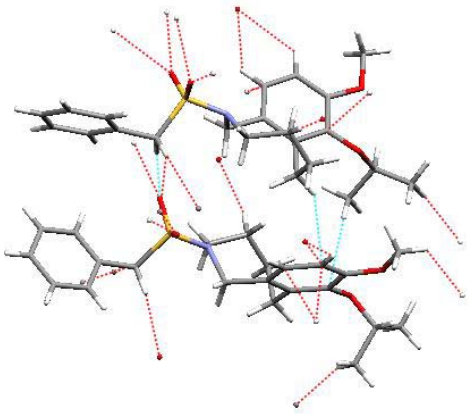
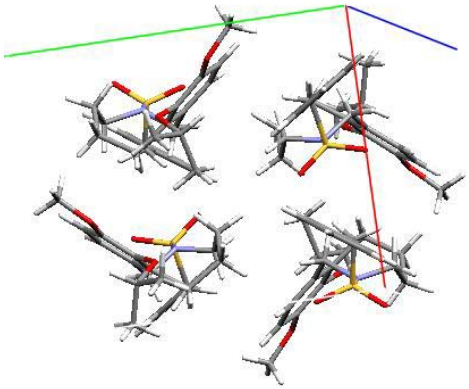
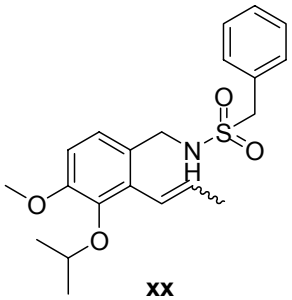


Diagram with Short Contacts



Packing Diagram

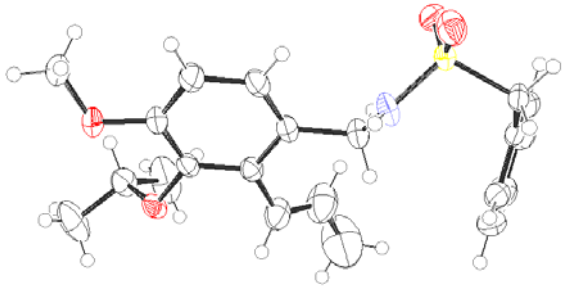
*1.3 Crystal Structure Data for Compound **XX***



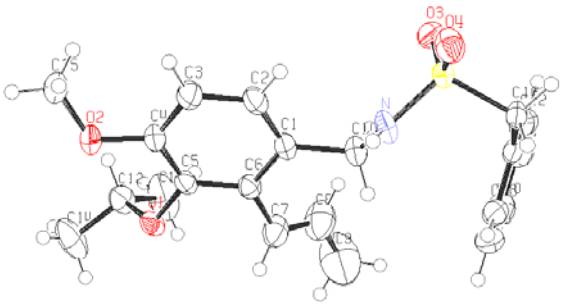

**xx**

**Table 1** Crystal Data and Structure Refinement for Compound **XX**

**ORTEP Diagrams**
**(50% probability thermal ellipsoids fo all non-hydrogen atoms)**



Top View




Side View

**Mercury Diagrams**

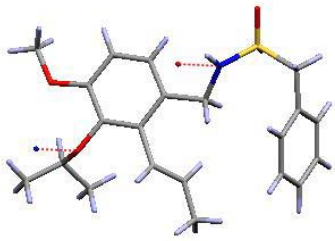


Diagram with Hydrogen-bonding

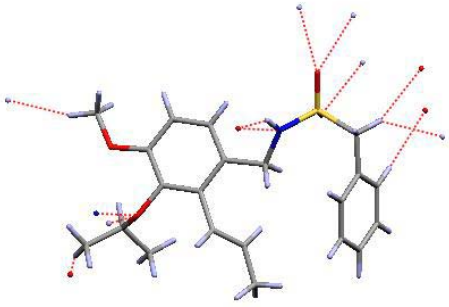
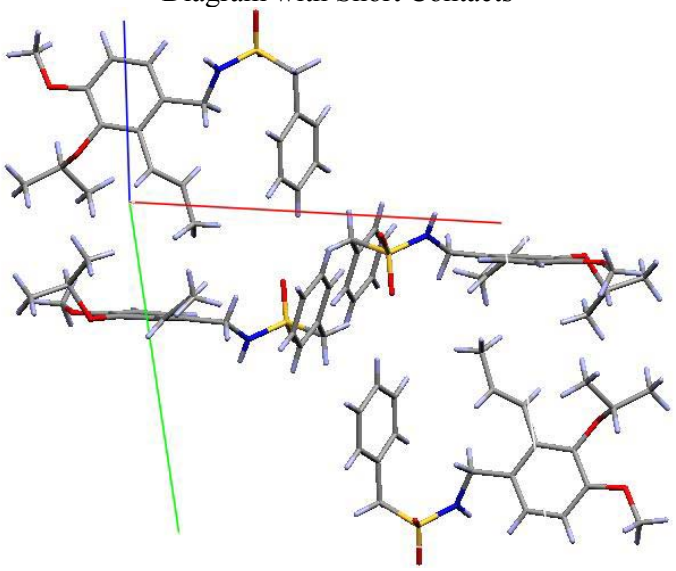
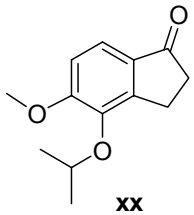


Diagram with Short Contacts



Packing Diagram

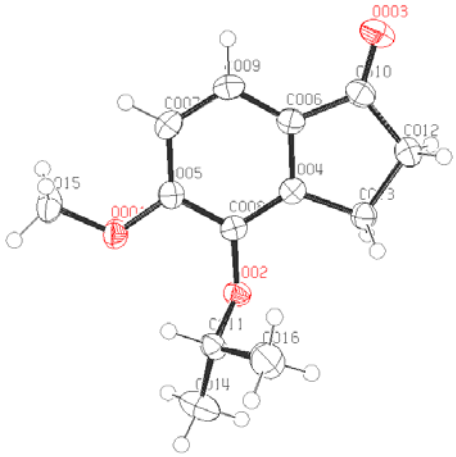
*1.4 Crystal Structure Data for Compound **XX***



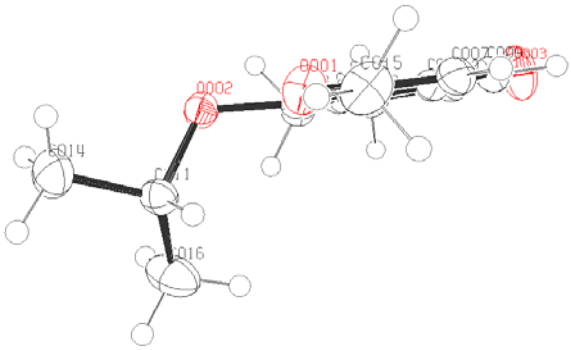

**xx**

**Table 1** Crystal Data and Structure Refinement for Compound **XX**

**ORTEP Diagrams**
**(50% probability thermal ellipsoids fo all non-hydrogen atoms)**




Top View



Side View

**Mercury Diagrams**

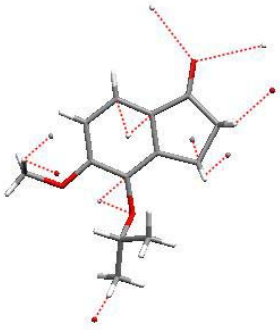
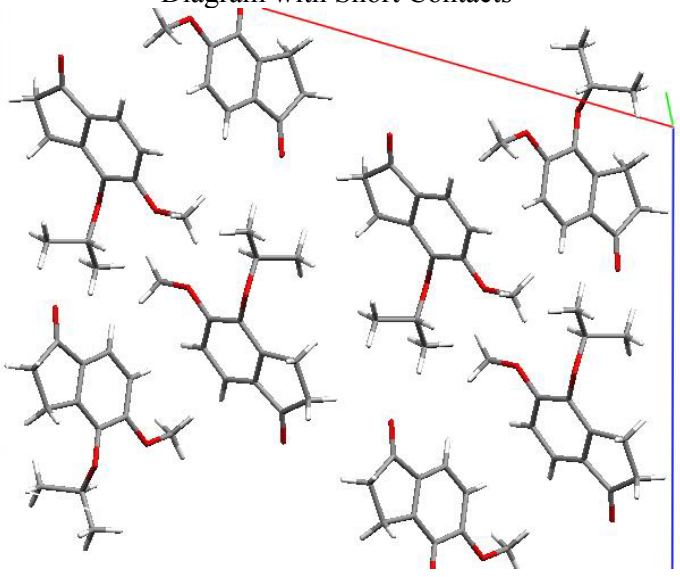
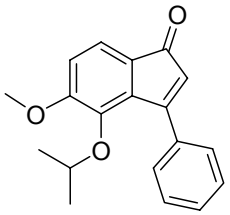


Diagram with Short Contacts



Packing Diagram

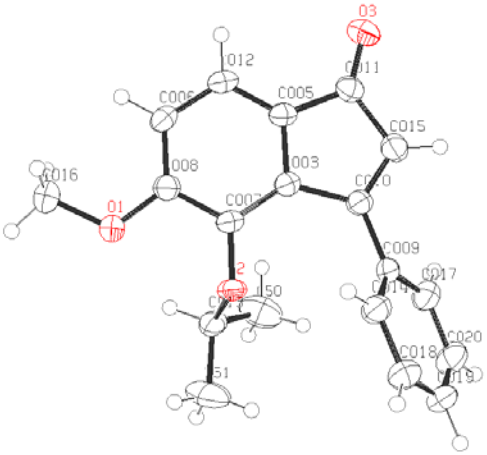
## *1.5 Crystal Structure Data for Compound **XX***



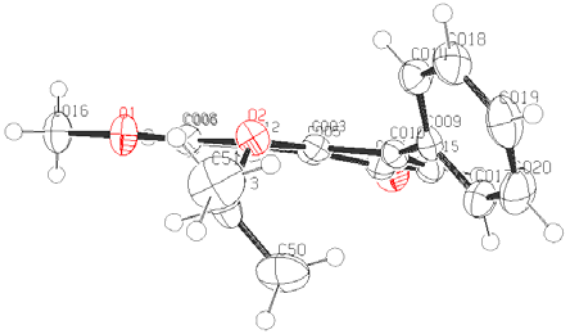

**xx**

**Table 1** Crystal Data and Structure Refinement for Compound **XX**

**ORTEP Diagrams**
**(50% probability thermal ellipsoids fo all non-hydrogen atoms)**




Top View




Side View

**Mercury Diagrams**

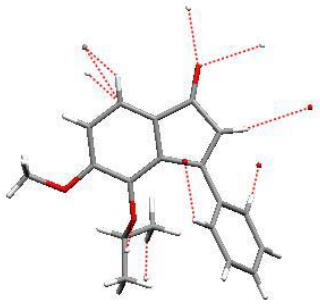
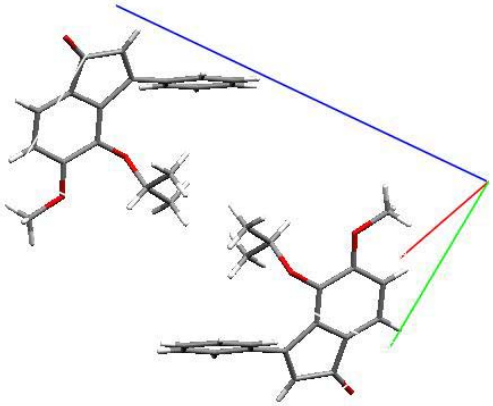


Diagram with Short Contacts

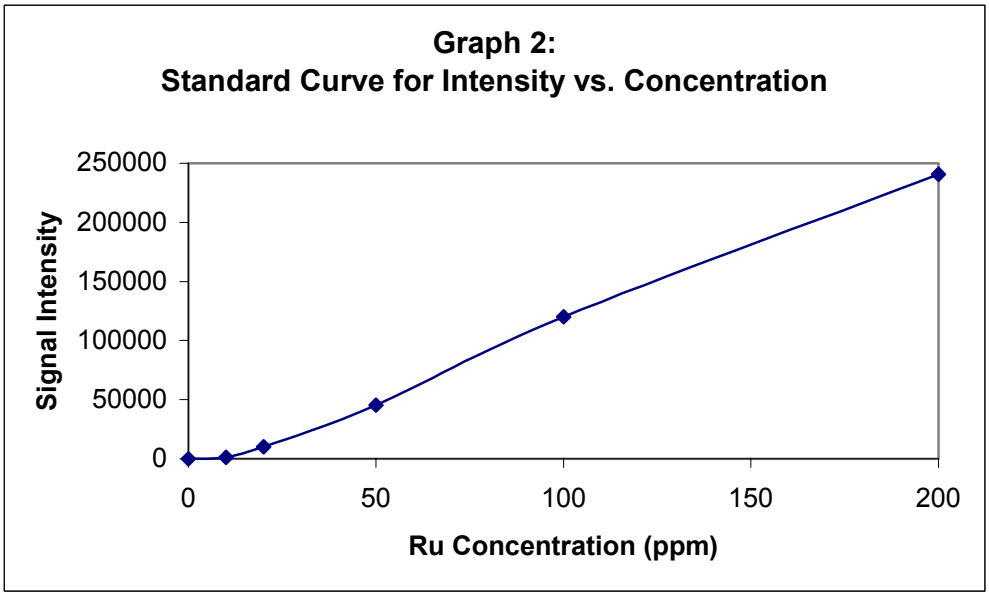


Packing Diagram

# *Appendix C:*

# *ICP-MS Data*

1. *The Standard Curve*




2. *MS Operating Conditions:*

- *Generator Parameters:*
    - Plasma Power: 1350W
    - Pump Step: 2
    - Coolant Step: 3
    - Auxiliary Step: 1
    - Nebulizer Step: 1
    - Nebulizer Flow 925ml/min
- *Detector Parameters:*
    - Sensitivity Range: E01-E05
    - SEM: -2600V
    - Resolution: Normal
    - Pause Calibration: Factor 3.0

# *Appendix D:*

# *Published Papers*