
[http://theses.gla.ac.uk/8006/](http://theses.gla.ac.uk/8006/)

Copyright and moral rights for this work are retained by the author

A copy can be downloaded for personal non-commercial research or study, without prior permission or charge

This work cannot be reproduced or quoted extensively from without first obtaining permission in writing from the author

The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the author

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given

Glasgow Theses Service
[http://theses.gla.ac.uk/](http://theses.gla.ac.uk/)
theses@glam.ac.uk
Novel One-Pot Multi-Bond Forming Reaction Processes for the Preparation of Biologically Active Heterocycles

Salaheddin Ahmad Ibrahim Sharif, M. Sci.

A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

School of Chemistry
College of Science & Engineering
University of Glasgow

January 2017
Abstract

During the course of this PhD, a new one-pot thermal Overman rearrangement and ring-closing metathesis process was developed for the preparation of polycyclic compounds. In this method, commercially available phenols and anilines were converted to alkene derived allylic alcohols and then transformed via a one-pot process into 5-amino 2,5-dihydro-1-benzoepines and 5-amino 2,5-dihydro-1H-benzazepines. The synthetic utility of these compounds was explored with the preparation of highly substituted hydroxylated analogues as well as a highly active hypotensive agent.

A novel one-pot process was also developed for the synthesis of allylic amide derived 2H-chromenes. The key substrates, propargyloxy cinnamyl alcohols were rapidly prepared from readily available salicylaldehydes. One-pot thermal Overman rearrangement of the corresponding allylic trichloroacetimidates, followed by a gold(I)-catalysed hydroarylation gave the 2H-chromenes in high yields. A mild chemoselective method for the oxidation of the 2H-chromenes to give coumarins was also discovered.
Contents

Abstract 2
Acknowledgements 6
Author’s Declaration 7
Abbreviations 8

1.0 Introduction 12
1.1 Claisen rearrangement 12
1.2 Aza-Claisen rearrangement 12
1.3 Overman rearrangement 13
1.3.1 Thermal Overman rearrangement 14
1.3.2 Metal-catalysed Overman rearrangement 17
1.3.3 Asymmetric Overman rearrangement 21
1.3.3.1 Chiral Pd(II)-catalysed stereoselective Overman rearrangement 21
1.3.3.2 Chiral substrate-directed Pd(II)-catalysed Overman rearrangement 23
1.3.4 Applications of the Overman rearrangement 26
1.3.5 Conclusions 33
1.4 Ring-closing metathesis (RCM) 34
1.4.1 Olefin metathesis 34
1.4.2 Ring-closing metathesis 36
1.4.3 Catalysis of the ring-closing metathesis (well-defined catalyst systems) 38
1.4.4 Scope of the ring-closing metathesis reaction 42
1.4.5 Applications of the ring-closing metathesis reaction 48
1.4.6 Conclusions 59
1.5 One-pot multi-reaction processes 60
1.5.1 General concepts 60
1.5.2 Types of one-pot processes 60
1.5.2.1 Domino reactions 61
1.5.2.2 Cascade reactions
1.5.2.3 Tandem reactions
1.5.2.4 One-pot multi-reaction processes
1.5.3 Application of the one-pot multi-reaction process
1.5.4 Conclusions

2.0 Results and discussion
2.1 Synthesis of 5-amino-substituted 2,5-dihydro-1-benzoxepines
2.1.1 Previous work within the Sutherland group
2.1.2 Aims
2.1.3 Synthesis of allylic alcohols
2.1.4 The one-pot multi-reaction synthesis of 1-benzoxepines
2.1.5 Synthesis of 8-chloro-5-guanidino-2,3,4,5-tetrahydro-1-benzoxepine
2.1.6 Dihydroxylation of 5-amino-substituted 2,5-dihydro-1-benzoxepine
2.1.6.1 Synthesis of cis-3,4-diols of 5-amino-1-benzoxepines
2.1.6.2 Synthesis of trans-3,4-diols of 5-amino-1-benzoxepines
2.1.7 Conclusions

2.2 Synthesis of 5-amino-substituted 2,5-dihydro-1H-benzazepines
2.2.1 Aims
2.2.2 Synthesis of allylic alcohols
2.2.3 Optimisation of one-pot multi-reaction process for 1H-benzazepines
2.2.4 Synthesis of 5-amino-substituted 2,5-dihydro-1H-benzazepines
2.2.5 Formal synthesis of mozavaptan
2.2.6 Conclusions

2.3 Synthesis of 2H-chromenes
2.3.1 Introduction
2.3.2 Cycloisomerisation
2.3.3 Aims
2.3.4 Synthesis of allylic alcohols
2.3.5 Investigation of the key steps of the one-pot process
2.3.5.1 Optimisation of the Overman rearrangement 116
2.3.5.2 Optimisation of the hydroarylation reaction 118
2.3.6 Stepwise gold(I)-catalysed synthesis of 2H-chromenes 120
2.3.7 Optimisation of one-pot synthesis of 2H-chromenes 122
2.3.8 One-pot gold(I)-catalysed synthesis of 2H-chromenes 123
2.3.9 Optimisation of the Pd(II)-catalysed Overman rearrangement 125
2.3.10 Optimisation of the one-pot palladium(II)-catalysed Overman rearrangement and gold(I)-catalysed hydroarylation process 126
2.3.11 Chemoselective oxidation of 2H-chromenes to coumarins 127
2.3.12 Conclusions 128
2.3.13 Synthesis of 6-amino-substituted 6,11-dihydrodibenz[b,e]oxepines 129
2.3.13.1 Previous work within the Sutherland group 129
2.3.13.2 Aims 130
2.3.13.3 Investigation of the one-pot multi-reaction process 132
2.3.13.3.1 Optimisation of ring-closing enyne metathesis step 132
2.3.13.3.2 Optimisation of Diels-Alder reaction 133

3.0 Future work 134
3.1 Synthesis of 11-amino-substituted 5,11-dihydro-1-benzoxepino, benzazepino, and benzthiapino[4,3-b]pyridines 134
3.2 Coumarin derived α-amino acids 136

4.0 Experimental 138

5.0 References 223
Acknowledgements

First of all, Praise and Thank be to Allah, Lord of the Worlds.

I would like to express my sincere thanks to my supervisor, Dr. Andrew Sutherland, for giving me the opportunity to undertake this PhD programme within his research group. I greatly appreciate his guidance, encouragement, patience, support and help during my PhD study.

Thanks to my previous second supervisor Dr. Rudi Marquez and my present second supervisor Dr. Goetz Bucher. Thanks also to the academic and technical staff for their appreciated assistance throughout my PhD period: David (NMR), Jim and Harry (MS), Stuart and Arlene (IT), Ted, Bruce and Paul (Stores).

Thanks to all the past and present members of the Sutherland research group: Ahmed, Mark, Adele, Ewen, Filip, Alex, Nikki, Mohamed, Kerry, Tomas, Tim, Réka, and Jonathan for the good times and working together in this team. Thanks to summer students: Marie and Fábio. Thanks to members of the Hartley group.

I would like to express my deepest appreciation and love to my parents: my father, Ahmad, who passed away before seeing this work, and my mother Aisha, who always has been praying for me and for her love. I would like to express my deepest gratitude to my family: my wife, Seham, for her love, patience, prayers, and support for me, and also for my kids: Taqwa, Talia, and Ahmad, who have spent a lot of time away from me and whose smiles and laughs always make life more hopeful. I would like to thank my brothers and sisters for their encouragement, support and help, in particular, my brothers Hamza and Abdulhakim. I would like to thank my wife’s family, in particular, my mother-in-law, Soaad for her help and prayers, and my brothers-in-law and my sisters-in-law for their support and help.

Finally, the Libyan government and University of Benghazi are gratefully acknowledged for financial funding and support. Also, thanks to the School of Chemistry and the University of Glasgow for additional financial support (William Hamilton Award).
Author’s Declaration

I declare that this thesis represents the original work of Salaheddin A. I. Sharif unless otherwise referred to in the text and has not been submitted for any other degree at the University of Glasgow or any other institution. The work upon which it is based was carried out at the University of Glasgow in the Loudon Laboratory under the supervision of Dr. Andrew Sutherland between June 2013 and May 2016. Aspects of the work described herein have previously been published elsewhere as stated below.


Signature

Printed Name
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ</td>
<td>Reflux</td>
</tr>
<tr>
<td>ACAT</td>
<td>Acyl-CoA, Cholesterol O-Acyl Transferase</td>
</tr>
<tr>
<td>aq.</td>
<td>Aqueous</td>
</tr>
<tr>
<td>BHT</td>
<td>3,5-Di-tert-butyl-4-hydroxytoluene</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>'Bu</td>
<td>tert-Butyl</td>
</tr>
<tr>
<td>cat</td>
<td>Catalyst</td>
</tr>
<tr>
<td>Cbz</td>
<td>Carboxybenzyl</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical Ionisation</td>
</tr>
<tr>
<td>CM</td>
<td>Cross Metathesis</td>
</tr>
<tr>
<td>COP</td>
<td>Cobalt Oxazoline Palladacycle</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DCE</td>
<td>Dichloroethane</td>
</tr>
<tr>
<td>DCDMH</td>
<td>1,3-Dichloro-5,5-dimethylhydantoin</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminium Hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N,N-Diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>Dimethoxyethane</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl Sulfoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>dr</td>
<td>Diastereomeric Ratio</td>
</tr>
<tr>
<td>EDDA</td>
<td>Ethylenediammonium Diacetate</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric Excess</td>
</tr>
<tr>
<td>EI</td>
<td>Electron Impact</td>
</tr>
<tr>
<td>endo</td>
<td>Endocyclic</td>
</tr>
<tr>
<td>eq</td>
<td>Equivalents</td>
</tr>
<tr>
<td>exo</td>
<td>Exocyclic</td>
</tr>
<tr>
<td>Hex</td>
<td>Hexyl</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>HWE</td>
<td>Horner-Wadsworth-Emmons</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>J</td>
<td>NMR Spectra Coupling Constant</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>Lithium Hexamethyldisilazide</td>
</tr>
<tr>
<td>m-</td>
<td>meta-</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>MBH</td>
<td>Morita-Baylis-Hillman</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-Chloroperbenzoic Acid</td>
</tr>
<tr>
<td>Mes</td>
<td>Mesityl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>MS</td>
<td>Molecular Sieves</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxymethyl</td>
</tr>
<tr>
<td>mp</td>
<td>Melting Point</td>
</tr>
<tr>
<td>MW</td>
<td>Microwave</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td>N-Chlorosuccinimide</td>
</tr>
<tr>
<td>NIS</td>
<td>N-Iodosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser Effect Spectroscopy</td>
</tr>
<tr>
<td>OM</td>
<td>Olefin Metathesis</td>
</tr>
<tr>
<td>ortho-</td>
<td></td>
</tr>
<tr>
<td>para-</td>
<td></td>
</tr>
<tr>
<td>BQ</td>
<td>p-Benzquinone</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium Dichromate</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts Per Million</td>
</tr>
<tr>
<td>py</td>
<td>Pyridine</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>RCEYM</td>
<td>Ring-Closing Enyne Metathesis</td>
</tr>
<tr>
<td>RCM</td>
<td>Ring-Closing Metathesis</td>
</tr>
<tr>
<td>ROM</td>
<td>Ring-Opening Metathesis</td>
</tr>
<tr>
<td>ROMP</td>
<td>Ring-Opening Metathesis Polymerisation</td>
</tr>
<tr>
<td>quant.</td>
<td>Quantitative</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Chemical Description</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>rt</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium Fluoride</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBTU</td>
<td>O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium Tetrafluoroborate</td>
</tr>
<tr>
<td>TEMPO</td>
<td>(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl</td>
</tr>
<tr>
<td>TEPA</td>
<td>Triethyl Phosphonoacetate</td>
</tr>
<tr>
<td>tert</td>
<td>Tertiary</td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic Acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-Tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>p-Toluenesulfonyl</td>
</tr>
</tbody>
</table>
1.0 Introduction

1.1 Claisen Rearrangement

Sigmatropic rearrangements as a class of pericyclic reactions are powerful and useful tools in organic synthesis in which a new C-C bond is formed due to an intramolecular process. Claisen, Cope and Carroll rearrangements which follow a [3,3]-sigmatropic rearrangement are the most common and widely used types of sigmatropic reactions. The Claisen rearrangement was first discovered by Ludwig Claisen in 1912\(^1\) where he reported “the thermal isomerisation of an allyl vinyl ether 1 - or of its nitrogen or sulfur containing analogue derivatives - to afford a bifunctionalised molecule 2,” and since then it has found widespread applications in organic chemistry (Scheme 1).\(^2\)

![Scheme 1: Claisen rearrangement.](image)

In that report, Claisen described the first formation of α-allyl acetoacetate 4 from the distilled O-allylated ethyl acetoacetate 3 in the presence of NH\(_4\)Cl via a [3,3]-sigmatropic rearrangement which was known later as the Claisen rearrangement (Scheme 2).\(^1,2\)

![Scheme 2: The first aliphatic Claisen rearrangement.](image)

1.2 Aza-Claisen Rearrangement

In 1937, Mumm and Möller reported that an allylic imidate can be rearranged thermally to give an amide in a [3,3]-sigmatropic rearrangement process which is called an aza-Claisen rearrangement and since then it has been utilised as a new
alternative route in the synthesis of amino compounds (Scheme 3). This reaction requires harsher conditions than that required for the Claisen rearrangement for both aliphatic and aromatic molecules.

![Scheme 3: Aza-Claisen rearrangement.](image)

### 1.3 Overman Rearrangement

The first report of a thermal allylic trichloroacetimidate rearrangement was published by Overman in 1974. Overman also showed the first use of a transition metal complex, mercuric trifluoroacetate, to catalyse this transformation. Formally, the Overman rearrangement represents the conversion of a 1,3-allylic alcohol 7 to an allylic amine 10. This can be achieved thermally or using a metal catalyst (Scheme 4).

![Scheme 4: Allylic trichloroacetimidate “Overman” rearrangement.](image)

As a potential tool for synthetic organic chemistry and due to the recent developments in catalysts, the Overman rearrangement has found widespread application and uses in the construction of naturally occurring and unnatural nitrogen-containing products with enhancement in the yield and control of the stereoselectivity.
1.3.1 Thermal Overman Rearrangement

Many factors of the Overman rearrangement have been studied extensively, such as steric effects, substitution effect, thermodynamic parameters, solvents, additives, regioselectivity and stereoselectivity. The thermal Overman rearrangement as a [3,3]-sigmatropic process occurs via a concerted suprafacial mechanism and this hypothesis is in accordance with Woodward-Hoffmann rules. The reaction pathways progress via a highly ordered chair-like transition state that allows complete chirality transfer to the product with transposition of the allylic alcohol to the amide functional group (Scheme 5).

![Scheme 5: Transfer of chirality in the thermal Overman rearrangement.](image)

This reaction proceeds for a wide variety of allylic alcohols and follows first-order kinetics where primary allylic alcohols react slower than secondary and tertiary alcohols. Due to a postulation of a partially charged transition state, the reaction rate enhancement was observed in changing the solvent system from xylene, a non-polar solvent, to nitrobenzene, a polar solvent. Allylic trichloroacetimidates can be rearranged at a range of temperatures from 0–140 °C under reflux. For example, some cinnamyl imidates rearrange in refluxing xylenes to afford moderate to high yields, while using chloroform, toluene or THF is unsuitable due to their low boiling points (Scheme 6).

![Scheme 6: Solvent effects in the thermal Overman rearrangement.](image)

Addition of a small amount of sodium or potassium carbonate has a positive effect on the reaction. This addition prevents the acid-catalysed decomposition of the
imidate during the rearrangement process and consequently increases the products yield (Scheme 7). \(^\text{11}\)

![Scheme 7: Additive effect in the thermal Overman rearrangement.](image)

Steric hindrance has an effect on the outcome of the thermal Overman rearrangement. For example, the yields of the rearrangement of ortho- and para-substitution of the cinnamyl imidates 11 were significantly different. While the ortho-substituted imidate rearranged in 30% yield after 24 hours from the corresponding allylic alcohol, the para-substituted imidate formed in 82% yield in just 12 hours (Scheme 8). \(^\text{10}\)

![Scheme 8: Steric hindrance effect in the thermal Overman rearrangement.](image)

Presence of substituents attached to the double bond at C-2 and C-3 of the allylic trichloroacetimidates such as oxygen atom has a significant effect on the thermal Overman rearrangement. For example, allylic alcohol 13 with 3-position oxygen atom undergoes the Overman rearrangement smoothly at 0 °C to give the produced amide 14 in 78% yield directly without observing the intermediate (Scheme 9). \(^\text{12}\)
Regioselectivity of the thermal Overman rearrangement is generally not high. For example, the rearrangement of \( 15 \) leads to two regioisomers in a 60:40 ratio (Scheme 10).\(^5\)

Although the thermal Overman rearrangement has a high degree of stereoselectivity due to the complete chirality transfer observed, the diastereoselectivity is affected by the temperature required for the reaction (Scheme 11).\(^13\)
1.3.2 Metal-Catalysed Overman Rearrangement

Since the first report introduced by Overman\(^4\) using mercury(II) salt to catalyse the [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates, a variety of transitional metals including palladium, platinum, gold, and nickel have been examined for catalysing the allylic trichloroacetimidate rearrangement. Overman reported the general requirements for metal-catalysed rearrangements,\(^4\) which were applied in the construction of a broad spectrum of organic compounds and contributed to the expansion and development of the [3,3]-sigmatropic rearrangement.\(^5,6,14–17\)

While the thermal Overman rearrangement proceeds at high temperatures, the metal-catalysed Overman rearrangement takes place at room temperature under milder conditions to give the products in enhanced yields. Employment of catalysts not only allows milder conditions, but also better control of stereoselectivity and regioselectivity.\(^4,5,15,18–20\)

Although the first used metal in the Overman rearrangement was a Hg(II) catalyst,\(^4\) the Pd(II) catalysts are considered the most effective and useful.\(^19\) Palladium(II)-catalysts react easily and rapidly with substrates at low temperature and low loading. Palladium(II)-catalysts can also react cleanly with substrates forming the products in high yields and with high stereoselectivity.\(^15,20–23\)

According to previous extensive mechanistic studies of the metal-catalysed [3,3]-sigmatropic rearrangement by the Henry, Overman, Schoop, Ikariya and Bosnich research groups,\(^5,15,19,21–25\) the metal-catalysed Overman rearrangement proceeds via a cyclisation-induced rearrangement mechanism. The cyclisation-induced mechanism of the Pd(II)-catalysed Overman rearrangement, which proceeds via a stepwise pathway, begins with Pd(II)-coordination to the π-system of the allylic substrate forming the intermediate-palladium complex 16. This intermediate undergoes cyclisation via an anti-intramolecular nucleophilic attack by the nitrogen atom to form cyclic carbocation intermediate 17. Finally, reductive elimination leads to the amide product and regeneration of the catalyst PdX\(_2\) through an irreversible step due to the driving force of amide formation (Scheme 12).
More importantly, Ikariya and Bosnich groups, from their study of the Pd(II)- and Pd(0)-catalysed [3,3]-sigmatropic rearrangements, showed that the Pd(II)-catalysts mainly give a [3,3]-product (Claisen product), while Pd(0)-catalysts form a [1,3]-product (anti-Claisen product).\textsuperscript{23,25} Ikariya also reported that Pd(0) can rearrange allylic \textit{N}-phenylformimidates and \textit{N}-phenylbenzimidates to Claisen and anti-Claisen products via the [3,3]- and [1,3]-sigmatropic rearrangements, respectively (Scheme 13).\textsuperscript{25} In 1997, Overman and co-workers reported the formation of both the Claisen and the anti-Claisen products by utilising the Pd(II)-catalyst.

Sutherland and co-workers suggested that the formation of these (Overman and anti-Overman) products was due to the presence of the two species, Pd(II) and Pd(0), during the rearrangement process. They overcame this problem by adding a catalytic amount of re-oxidant such as \textit{p}-benzoquinone (BQ), which is widely used to re-oxidise the Pd(0)-species to the Pd(II)-species. This prevents the
formation of the [1,3]-product and increases the yield of the [3,3]-product (Scheme 14).²⁰

Scheme 14: Oxidant effect on the formation of [1,3]- and [3,3]-Overman rearrangement products.

Based on the previous observations, Sutherland and co-workers stated that “1,3-product is formed via a Pd(0)-catalysed allylic substitution reaction and that the Pd(0) likely arises by a competing β-elimination process during the slow Pd(II)-catalysed rearrangement of allylic imidate” (Scheme 15).²⁰

Scheme 15: Pd(0)-catalysed formation of 1,3-anti-Overman product (anti-Claisen).

Interestingly, in 1998, Spilling and co-workers reported that halogenation reagents such as N-bromosuccinimide (NBS) or N-iodosuccinimide (NIS) can catalyse the Overman rearrangement if there is an electron withdrawing group R¹ attached to the trichloroacetimidate (R¹ is phosphonate or cyano groups) (Scheme 16).²⁷
Recently, Tang and co-workers reported that the Overman rearrangement can be carried out from allylic imidates of primary allylic alcohols within a one-pot reaction process using the halogenation reagents (NCS, NBS or NIS) or in the presence of 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) (Scheme 17).^{28}

Gold-catalysed Overman rearrangements have drawn attention for some research groups and these studies showed that this transformation can be efficiently performed utilising Au(I) and Au(III) salts.^{29–32} More recently, Yang and Xing reported highly efficient gold(I)-catalysed Overman rearrangements in water.^{33} They showed that the gold(I)-catalysed Overman rearrangement proceeds very cleanly in water under very mild conditions leading to the formation of allylic trichloroacetamides in high yields (67–96%) during short reaction times (2–6 h) and this transformation can also be performed on a gram-scale. For example, conversion of allylic trichloroacetimidate 22 to the corresponding amide 23 utilising a catalytic amount of gold(I) chloride finished in 2 hours giving the product in high
yield (Scheme 18). This exact yield is also observed in the case of a gram-scale reaction during the same reaction time.

\[
\begin{align*}
\text{CCl}_3 & \quad \text{O} \quad \text{NH} \\
\text{O} & \quad \text{C} \quad \text{H}_2 & \quad \text{O} \quad \text{C} \quad \text{H}_2
\end{align*}
\]

\[\text{AuCl (5 mol\%)} \quad \text{H}_2\text{O}, 55 ^\circ\text{C}, 2 \text{~h} \quad 92\%
\]

\[
\begin{align*}
\text{CCl}_3 & \quad \text{O} \quad \text{NH} \\
\text{O} & \quad \text{C} \quad \text{H}_2 & \quad \text{O} \quad \text{C} \quad \text{H}_2
\end{align*}
\]

Scheme 18: Gold-catalysed Overman rearrangement in water.

1.3.3 Asymmetric Overman Rearrangement

The Pd(II)-catalysed Overman rearrangement has attracted attention from many research groups for the development of asymmetric catalysis toward the successful synthetic applications of the Overman rearrangement through design of new chiral catalysts. Moreover, chiral-substrate Pd(II)-catalysed Overman rearrangement has also been studied and supports the development of asymmetric catalysis. The palladium-catalysed stereoselective Overman rearrangement can be divided into two approaches, the chiral Pd(II)-catalysed stereoselective Overman rearrangement, which is mainly used in enantioselective synthesis, and the chiral-substrate Pd(II)-catalysed stereoselective Overman rearrangement, which leads to the preparation of diastereomers.

1.3.3.1 Chiral Pd(II)-Catalysed Stereoselective Overman Rearrangement

A new era of asymmetric catalysis of the Overman rearrangement was established by the first report from Overman and co-workers in 1997,\(^{19}\) in which they described the first enantioselective Pd(II)-catalysed aza-Claisen rearrangement of allylic imidates to allylic amides. Based on the available studies and observations of palladium catalysis, further efforts reported by the research groups of Overman, Hayashi, Zhang, Williams, Kang, and List\(^{8,17,26,34-43}\) have contributed in the development of the asymmetric Pd(II)-catalysed [3,3]-sigmatropic rearrangement of allylic imidates including, in particular, the Overman rearrangement.
The development of the palladium-catalysed enantioselective rearrangement of allylic imidates was initially based on a detailed understanding of the enantioselective step. The first class of catalysts was the cationic catalysts which are formed utilising oxazoline ligands or diamine ligands (Figure 1). The second generation of the chiral catalysts is the neutral catalysts which are formed using ferrocenyl amine ligands, ferrocenyl imine ligands, ferrocenyl oxazoline ligands, or chromium tricarbonyl arylimine ligands. The development of the second generation of catalysts led to an improvement in the enantioselectivity of the formed products in addition to an increase in the yield.

**Figure 1: Structure of some catalysts.**
The monomeric cobalt oxazoline palladacycle (COP) catalysts, such as (S)-COP-Cl 24 and (R)-COP-Cl 25 are the most effective catalysts that can achieve the Overman rearrangement to form chiral allylic amines from prochiral allylic alcohols in high yield and excellent enantiomeric excess (Figure 2). These results were supported by a detailed kinetic and computational analysis of the Pd(II)-catalysed asymmetric Overman rearrangement.8

![Figure 2: Cobalt oxazoline palladacycle catalysts.](image)

For example, the asymmetric Overman rearrangement of 26 utilising chiral Pd(II) catalyst (S)-COP-Cl 24 leads to the formation of chiral Overman product 27 in 93% yield and 93% ee (Scheme 19).39

![Scheme 19: Use of the chiral COP-Cl catalyst 24 for the asymmetric Overman rearrangement.](image)

1.3.3.2 Chiral Substrate-Directed Pd(II)-Catalysed Overman Rearrangement

The chiral substrate-directed Pd(II)-catalysed Overman rearrangement represents the second approach for performing asymmetric reactions. Employment of chiral directing-groups on the allylic trichloroacetimidates effectively encourages the
catalysis to occur on one face of the π-system of the allylic imidate leading to high diastereoselectivity. Although the preparation of diastereomers from chiral substrates was reported by the research groups of Schoop and Larchevêque in 1992, this type of asymmetric transformation was further developed in 1993 when Bellûs and co-workers reported the synthesis of diamines from chiral allylic alcohols via the diastereoselective Overman rearrangement utilising the effect of a chiral amino group to orient the catalyst addition (Scheme 20). The highly observed selectivity (dr >99:1) was explained using a chair-like conformer.

Scheme 20: Chiral amine-directed Pd(II)-catalysed asymmetric Overman rearrangement.

In 2005, the Sutherland group reported a chiral ether-directing substrate for the Pd(II)-catalysed asymmetric Overman rearrangement. Among different ether groups, the MOM group was the most effective. The study showed the effectiveness of the MOM ether group in directing the facial coordination of the Pd(II) catalyst to the allylic double bond during the Overman rearrangement process to afford an excellent diastereoselectivity of the product (Scheme 21). Steric factors associated with ether groups had a significant effect on the minor diastereomer yield where more bulky ethers increase the chance of coordination of the palladium catalyst to the less bulky face of the double bond causing an increase of its yield. The authors also described that changing the MOM group with a carbon analogue showed a significant decrease of diastereoselectivity to 2:1.
Scheme 21: Chiral ether-directed Pd(II)-catalysed asymmetric Overman rearrangement.

Sutherland and co-workers reported further improvement of the MOM-ether directing effect on the yield and diastereoselectivity. The authors developed a new method for a highly diastereoselective synthesis of \((2S,3S)\)-β-hydroxy-α-amino acids from enantiopure α-hydroxy acids using the chiral MOM-ether-directed Pd(II)-catalysed asymmetric Overman rearrangement. This efficient process led to a significant diastereoselectivity up to 14:1 along with increase of the yield. Further work in the Sutherland group showed the bulky side-chains during the MOM-ether directed rearrangement caused side-reactions, formation of Pd(0) and subsequent production of the 1,3-product. This problem was overcome by the addition of re-oxidant, in particular \(p\)-benzoquinone, to oxidise the Pd(0)-catalyst back to the Pd(II)-catalyst. This modification led to the sole formation of the desired 3,3-product (Scheme 14).

More recently, Sutherland and co-workers expanded the scope and limitations of the ether-directed Pd(II)-catalysed stereoselective Overman rearrangement via the study of non-coordinating solvents, and understanding the origin of the directing effect. Those improvements have been utilised in stereoselective syntheses of a number of natural products such as β-hydroxy-α-amino acids, alkaloids, anti-vicinal amino alcohols and the first total synthesis of clavaminols.
1.3.4 Applications of the Overman Rearrangement

Overman rearrangements are commonly used as the key step of many synthetic organic routes in widespread applications to simply and efficiently access naturally occurring and unnatural nitrogen-containing products.

In 2002, Chida and co-workers reported a total synthesis of sphingofungin E \( \text{E 39} \) from D-glucose via the thermal Overman rearrangement as a key step.\(^{52}\) Diacetone-D-glucose \( \text{34} \) was converted to 1,2-O-isopropylidene-3-O-methoxymethyl-\( \alpha \)-D-glucofuranose in two steps in 90% yield followed by selective benzylation to give \( \text{35} \) in 95% yield (Scheme 22). The glucofuranose \( \text{35} \) was subjected to Swern oxidation and Wittig reaction and gave the corresponding ester in 95% over two steps. A DIBAL-H reduction was carried out on the resulting ester, followed by subsequent chromatographic separation which led to \((Z)\)-allyl alcohol \( \text{36} \) in 71% yield and 13% yield of its \((E)\)-isomer. The \((Z)\)-isomer was allowed to react with trichloroacetonitrile and a catalytic amount of DBU, followed by Overman rearrangement conditions which led to \( \text{37} \) and its C-5 epimer \( \text{38} \) in 60% and 14% yields from \( \text{36} \), respectively. Further transformations were carried out on Overman product \( \text{37} \) that led to the sphingofungin E \( \text{E 39} \).
Scheme 22: Total synthesis of sphingofungin E 39.

In 2004, Sutherland and co-workers reported the first enantioselective synthesis of the amino acid, (2S,3S,4R)-γ-hydroxyisoleucine 46 using a palladium(II)-catalysed Overman rearrangement. The route started with the conversion of poly (R)-hydroxybutanoate 40 to allylic trichloroacetimidate 41 in seven separate steps (Scheme 23). Using the thermal Overman rearrangement gave a 3:2 ratio of diastereomers 42 and 43, while the Pd(II)-catalysed Overman rearrangement of 41 gave the desired product 43 in higher yield and an improved selectivity (1:7 ratio).
Scheme 23: Overman rearrangement of trichloroacetimidate 41.\textsuperscript{18}

Ozonolysis of the 1:7 diastereomeric mixture in an alcoholic base gave the corresponding esters 44 and 45, which were separated using column chromatography (Scheme 24). Deprotection under acidic conditions and ion exchange chromatography gave the desired product 46 in high yield.

Scheme 24: Synthesis of amino acid 46.
Synthesis of α-alkylidene-β-lactam derivatives in high yields and excellent enantioselectivity was carried out utilising optically active α-alkylidene-β-amino esters via the thermal Overman rearrangement as a key step.\(^5\) (Z)-β-Iodo Morita-Baylis-Hillman (MBH) esters have been formed using highly enantioselective and (Z)-stereocontrolled three-component coupling of acetylenic esters, aldehydes, and trimethylsilyl iodide (TMSI) in the presence of chiral cationic oxazaborolidinium catalyst in good to excellent yield and enantioselectivity (Scheme 25). Then, a metal-catalysed cross-coupling reaction was carried out on these esters to give β-branched MBH esters in highly enantioselectivity, up to 96% ee. In the second stage, the resulting allylic alcohols were subjected to the thermal Overman rearrangement conditions to form the corresponding α-alkylidene-β-amino esters in moderate to quantitative yields and highly (E)-enantioselectivity (E/Z, up to >99/1). These precursors were converted to α-alkylidene-β-lactams. For instance, basic hydrolysis of the Overman products 47 using water/ethanol system gave the corresponding amino acid 48. Treatment of 48 with 2,2'-dipyridyl disulfide and triphenylphosphine (PPh\(_3\)) led to the formation of the α-alkylidene-β-lactam derivative 49 in 85% yield.
Scheme 25: Synthesis of α-alkylidene-β-lactam derivative 49.

The use of a palladium(II)-catalysed MOM-ether directed Overman rearrangement was recently reported as an alternative method for the stereoselective synthesis of the bicyclic guanidine alkaloid (+)-monanchorin 63. The key step of this route is the formation of a second stereogenic centre via the Overman rearrangement. First, preparation of the required allylic alcohol 51 for the Overman rearrangement begins with using the commercially available (R)-glycidol 50 utilising a sequence of reactions (Scheme 26). In the second stage, allylic alcohol 51 was transformed to
the corresponding allylic trichloroacetimidate 52 using trichloroacetonitrile in the presence of a catalytic amount of DBU at room temperature, followed by the MOM-ether directed Pd(II)-catalysed Overman rearrangement to give two diastereomers 54 and 55 in a 12:1 ratio, in addition to a trace amount of the 1,3-product 56. The addition of a catalytic amount of p-benzoquinone (BQ) to the rearrangement step inhibited the formation of the 1,3-product and increased the yield of 54 to 84%.

Scheme 26: Diastereoselective synthesis of 54 via the Overman rearrangement key step.

In the last stage, exchanging the trichloroacetyl protecting group of the desired Overman product 54 with the Cbz-protecting group was necessary. This transformation was carried out via basic hydrolysis, using sodium hydroxide, followed by the addition of benzyl chloroformate in a one-pot reaction to form the
carbamate 57 in 81% yield (Scheme 27). This carbamate was transformed to 59 through cross metathesis utilising a catalytic amount of Grubbs 2nd generation catalyst (10 mol%) and 2-vinyl-1,3-dioxolane 58 to form the product 59 in 87% yield. Hydrogenation of the double bond and removal of the Cbz-group using palladium on carbon under an atmosphere of hydrogen gave the corresponding amine 60. This was reacted with the commercially available N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine 61 in the presence of Hünig’s base leading to the formation of guanidine 62 in 87% yield. Completion of the route was achieved by reaction of 62 with trifluoroacetic acid (TFA) to produce the natural alkaloid 63 in 75% yield.

Scheme 27: Synthesis of the natural product (+)-monanchorin 63.
1.3.5 Conclusions

The Overman rearrangement is considered as an effective and powerful transformation that has been utilised as a key step in synthetic organic chemistry for the construction of a wide spectrum of nitrogen-containing compounds. This transformation can proceed thermally or catalytically via a number of soft metal catalysts such as Hg(II), Pd(II), Pt(II) and Au(I) under milder conditions.

Further developments of Pd(II)-catalysts have led to the synthesis of some useful and efficient highly enantioselective asymmetric catalysts such as the COP family which have become commercially available catalysts. Those catalysts have found widespread synthetic applications and significantly contributed to the synthesis of natural products.

More recently, the highly diastereoselective chiral group-directing substrate Overman rearrangement, in particular using the MOM-directing group, has been developed and provided an alternative approach for the construction of naturally occurring and unnatural products.
1.4 Ring-Closing Metathesis (RCM)

1.4.1 Olefin Metathesis

Olefin metathesis (OM) is a transition metal alkylidene-catalysed transposition process of two olefin groups to form a new carbon-carbon double bond.\textsuperscript{54–64} The first use of this \textit{Greek} term, which means change of the olefin position, was in 1967 by Calderon and co-workers.\textsuperscript{65} Olefin metathesis emerged as a useful and effective approach in synthetic organic chemistry. This methodology has played a remarkable role in construction of highly substituted alkenes and synthesis of natural products and contributed significantly to the development of polymer chemistry. Since the mid-1950s, when this reaction was first reported, till the early 1980s, the olefin metathesis was promoted by ill-defined multi-component catalyst systems. Tungsten, molybdenum and rhenium catalysts compromised the most used catalysts at that stage. For example, tungsten(VI) chloride/tetrabutyltin (WCl\textsubscript{6}/Bu\textsubscript{4}Sn), molybdenum(VI) oxide/silicon dioxide (MoO\textsubscript{3}/SiO\textsubscript{2}) and rhenium(VII) oxide/aluminium oxide (Re\textsubscript{2}O\textsubscript{7}/Al\textsubscript{2}O\textsubscript{3}) were commercially available, but had some limitations. Utilising these catalysts required harsh conditions and strong Lewis acids making them incompatible with most functional groups. Further improvements on the design of catalysts and detailed mechanistic studies led to the first use of single-component catalysts in olefin metathesis processes, such as diphenylcarbene(pentacarbonyl)tungsten(0) ((CO)\textsubscript{5}W=CPh\textsubscript{2}) which was reported by Katz and co-workers.\textsuperscript{66}

Olefin metathesis includes ring-closing metathesis (RCM), ring-opening metathesis polymerisation (ROMP), cross-metathesis (CM), ring-opening metathesis (ROM) and acyclic diene metathesis polymerisation (ADMET) (Figure 3). The most used of these processes is the ROMP, which is exclusively used in polymer chemistry, and the RCM, which is widely used in preparation of different ring sizes of carbo- and heterocyclic compounds in organic syntheses.\textsuperscript{54–64,67}
Olefin metathesis proceeds according to the Chauvin mechanism (Scheme 28).\textsuperscript{55–58,68–70} First, an olefin substrate reacts with a metal alkylidene complex to form a metallacyclobutane intermediate via a [2+2] cycloaddition process. Then, a [2+2] cycloreversion transformation leads to an olefin metathesis product and a new metal alkylidene complex. This mechanism appears to be the same for all catalysts and proceeds under thermodynamic control.

![Scheme 28: Mechanism of olefin metathesis.](image-url)
1.4.2 Ring-Closing Metathesis

The first use of the ring-closing metathesis (RCM) reaction in organic synthesis was reported by Tsuji and Villemin in 1980.\(^7\) For example, the ring-closing metathesis reaction of oleyl oleate 64 using WCl\(_6\) and Cp\(_2\)TiMe\(_2\) as a co-catalyst gave metathesis product 65 in 18% yield (Scheme 29).\(^7\) The ester 64 was readily prepared from oleic acid and oleyl alcohol. Conduction of this reaction, separation of the product and recovery of the starting material were all easy. The authors expected that this transformation would be a promising technique when they wrote “therefore, this method may be a good synthetic method of macrolides by further improvement.” This cyclisation by intramolecular metathesis is well-known as macrocyclisation in the ring-closing metathesis perspective.

![Scheme 29: First reaction of ring-closing metathesis.](image)

In the last three decades, the ring-closing metathesis reaction has attracted great attention as a versatile carbon-carbon double bond forming method. Further comprehensive studies reported mainly by the Schrock, Grubbs, Hoveyda and other research groups on well-defined catalyst systems led to a dramatic development of the ring-closing metathesis approach.\(^5\) This unique strategy was considered as an effective method in synthetic organic chemistry and provided unprecedented route to cyclic compounds that were difficult to form or inaccessible by any other methods. Further advances in catalyst design made the RCM reaction successfully used in widespread applications in different chemistry fields. It was efficiently used on acyclic dienes, enynes, and dienynes precursors with high tolerance to many functional groups for the synthesis of medium rings and macrocyclic molecules. Molybdenum- and ruthenium-based alkylidene
catalysts are the most common, useful and effective catalysts in RCM reactions (Figure 4).

![Schrock catalyst](image1) 1987  
![Schrock-Hoveyda II](image2) generation catalyst 1998 - ARCM  
![1st Ru-catalyst](image3) 1992  
![Grubbs I](image4) generation catalyst 1995  
![Grubbs II](image5) generation catalyst 1999  
![Hoveyda I](image6) generation catalyst 1999  
![Hoveyda II](image7) generation catalyst 2000

**Figure 4: The ring-closing metathesis well-defined catalyst systems.**

According to detailed mechanistic studies and experimental observations, the catalytic ring-closing metathesis mechanism proceeds via two general steps, an initiation step and a propagation step (Scheme 30). In the initiation step, a generated active carbene- or alkylidene-metal catalyst complex reacts via cross metathesis with one side of olefin substrate to give metallacyclobutane presumably a reversible step. While in path A the olefin substrate might be regenerated, in path B two σ-bonds are supposedly cleaved to form a new active metal complex intermediate with liberated ethylene. Thereafter, this intermediate cross-metathesises to give new metallacyclobutane which dissociates into metathesis product and new M=C intermediate. The catalytic cycle is then completed and the last formed active metal complex initiates a new catalytic cycle through the propagation step. The reaction driving force is that metathesis product does not react via ring-opening metathesis with active metal catalyst complex.


1.4.3 Catalysis of the Ring-Closing Metathesis (Well-Defined Catalyst Systems)

The 1990s was the most important decade with regard to contribution to the development of ring-closing metathesis chemistry. Development of molybdenum and ruthenium catalyst systems, in particular the well-defined ruthenium-based catalysts, has made ring-closing metathesis to be a common, efficient and powerful methodology in organic synthesis.

The first synthesis of an effective catalyst (Schrock catalyst 66) for initiation of the ring-closing metathesis reaction was reported in 1987 by Schrock and co-workers (Figure 4).\(^7^7\) This catalyst was utilised later by Grubbs and co-worker for synthesis of oxygen and nitrogen heterocycles via ring-closing metathesis reaction (Table 1).\(^7^8,7^9\) In addition, synthesis of cycloalkenes was easily and efficiently accessible via the ring-closing metathesis of dienes and carbonyl olefination using the Mo-based catalyst 66.\(^8^0\)

Scheme 30: Mechanism of the ring-closing metathesis reaction.
Table 1: Synthesis of cyclic olefins via RCM using Schrock catalyst 66.\textsuperscript{80}

Although the Schrock catalyst exhibited high activity for the RCM reaction, looking for more efficient catalyst systems was required to increase activity, functional group tolerance, higher thermal stability and air and moisture stability. On the basis of detailed mechanistic studies, ligand design provided more effective molybdenum and ruthenium alkylidene complex systems. In 1992, the Grubbs research group reported the synthesis of the first well-defined ruthenium-based olefin metathesis catalyst 68.\textsuperscript{81} This ruthenium carbene complex was used by
Grubbs and co-workers to initiate the ring-closing metathesis reaction of functionalised dienes for preparing functionalised heterocyclic alkenes and dienynes that were used for construction of fused bicyclic rings.\textsuperscript{82,83} For example, cyclisation of dienes via the RCM reaction utilising the ruthenium carbene catalyst 68 (2–4 mol\%) at room temperature gave a range of functionalised heterocycles in high yields (Table 2).\textsuperscript{82} Five-, six-, and seven-membered rings were efficiently synthesised. The cyclisation of the substrate in entry 3 failed using the molybdenum alkylidene catalyst.\textsuperscript{78}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate 1" /></td>
<td>20</td>
<td>1</td>
<td><img src="image2.png" alt="Product 1" /></td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Substrate 2" /></td>
<td>20</td>
<td>1</td>
<td><img src="image4.png" alt="Product 2" /></td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Substrate 3" /></td>
<td>20</td>
<td>6</td>
<td><img src="image6.png" alt="Product 3" /></td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Substrate 4" /></td>
<td>20</td>
<td>2</td>
<td><img src="image8.png" alt="Product 4" /></td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Substrate 5" /></td>
<td>20</td>
<td>8</td>
<td><img src="image10.png" alt="Product 5" /></td>
<td>72</td>
</tr>
</tbody>
</table>

Table 2: Cyclisation of dienes via the RCM reaction using Ru catalyst 68.\textsuperscript{82}

In addition, the construction of fused bicyclic rings was efficiently performed using the ruthenium alkylidene catalyst 68. For example, acyclic dienynes with unsymmetrical diene tethers gave bicyclo[4.4.0] and bicyclo[5.3.0] rings, as sole products, in 83% and 78% yields, respectively (Table 3).\textsuperscript{83}
Table 3: Construction of fused bicyclic rings via the RCM reaction using Ru catalyst 68.$^83$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst loading (mol%)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate Image" /></td>
<td>3</td>
<td>65</td>
<td>6</td>
<td><img src="image2.png" alt="Product Image" /></td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Substrate Image" /></td>
<td>16</td>
<td>100</td>
<td>1.5</td>
<td><img src="image4.png" alt="Product Image" /></td>
<td>78</td>
</tr>
</tbody>
</table>

The catalyst 68 also showed stability to air and moisture, and more functional group tolerance than Schrock catalyst 66. Consequently, the Grubbs research group also reported cyclisation of a variety of conformationally constrained amino acids and peptides utilising the same catalyst 68.$^84$

Later, ruthenium alkylidene catalyst 68 was used as precursor for synthesis of Grubbs first-generation catalyst 69. This development led to discovery of a more active catalyst (Grubbs second-generation catalyst) 70 in 1999 (Figure 4).$^{85,86}$ Although ruthenium benzylidene complex (Grubbs I catalyst) 69 possessed some advantages over the alkoxy-imido molybdenum complex (Schrock catalyst) 66, Grubbs II catalyst 70 exhibited an increased ring-closing metathesis activity at elevated temperature and low catalyst loading could be used. Furthermore, the Schrock and Grubbs research groups have reported the synthesis of a series of Mo- and Ru-based catalyst systems and supported these syntheses with detailed mechanistic investigations and a variety of applications.$^{57,58,67,87–89}$ Meanwhile, Hoveyda and co-workers have contributed to the development of molybdenum and ruthenium catalyst systems for the ring-closing metathesis reaction. As a result, they reported synthesis of Hoveyda first- and second-generation catalysts 71 and 72, respectively, in addition to Schrock-Hoveyda catalyst 67.$^{90–92}$ These active catalysts were easily obtained and exhibited high stability to air and moisture. Furthermore, their studies showed that these catalysts can be recycled in high
yield by silica gel column chromatography, which is considered as a unique property. Hoveyda second-generation catalyst 72 also exhibited the ability to synthesise tetrasubstituted olefins through the ring-closing metathesis reaction (Table 4).91

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst 72 loading (mol%)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate" /></td>
<td>5</td>
<td>22</td>
<td>44</td>
<td><img src="image2" alt="Product" /></td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate" /></td>
<td>5</td>
<td>80</td>
<td>0.5</td>
<td><img src="image4" alt="Product" /></td>
<td>65</td>
</tr>
</tbody>
</table>

Table 4: Synthesis of tetrasubstituted olefins via RCM using Ru catalyst 72.91

1.4.4 Scope of the Ring-Closing Metathesis Reaction

The ring-closing metathesis reaction attracted the attention of many research groups as a useful and powerful reaction in synthetic organic chemistry. In addition, development of the well-defined, stable molybdenum and ruthenium catalyst systems has made them commercially available. These active catalysts contributed to the expansion of the scope of olefin metathesis and its subcategories. In particular, the RCM reaction showed significantly high flexibility and tolerance to functional group, ring size, reaction conditions and stereochemistry of molecules. The catalytic ring-closing metathesis reaction was carried out on dienes, enynes and dienynes and employed efficiently in synthesis of tri- and tetrasubstituted cyclic olefins.54–56,92 Tandem (ROM/RCM) catalysis,68,93–97 macrocyclisation,68,94,98–101 ring expansion,102 and peptide chemistry68 were also initiated by the well-defined catalyst complexes. High enantioselectivity via asymmetric ring-closing metathesis (ARCM) using chiral catalysts,68,103–114 construction of heterocycles,115,116 natural product synthesis117 and synthesis of aromatic compounds59,118,119 were also efficiently performed.
The Grubbs first-generation catalyst 69, for example, was utilised in the tandem ring opening-ring closing metathesis reaction of strained cyclic olefins. Consequently, this method was applied for the construction of four- to eight-membered rings of diene substrates (Table 5). The metathesis products were obtained in good to high yields.\textsuperscript{94}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst loading (mol%)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>3</td>
<td>45</td>
<td>1.5</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>5</td>
<td>60</td>
<td>2</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>6</td>
<td>45</td>
<td>6</td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>6</td>
<td>45</td>
<td>2</td>
<td></td>
<td>68</td>
</tr>
</tbody>
</table>

Table 5: Tandem ring opening-ring closing metathesis reaction using the ruthenium alkylidene catalyst 69.\textsuperscript{94}

Furthermore, a range of macrocycles were generated for cycloalkenes and acyclic dienes by a ring-expansion method using Grubbs second-generation catalyst 70.\textsuperscript{102} This new approach combined three metathesis transformations; ring-opening, cross, and ring-closing metathesis reactions. The authors showed that for the ring expansion to be efficiently performed, several conditions had to be considered. “The cycloalkenes must be able to undergo the ring-opening reaction. Once opened, they must react selectively with the acyclic diene for CM and RCM to minimise side products. In addition, the acyclic diene should not undergo reactions with itself such as cyclisation or cross metathesis.” For example, bis-acrylate substrates were expanded via the ring-expansion metathesis process. These transformations gave the macrocycles in moderate yields using the catalyst
70 (5 mol%) under reflux conditions, in dichloromethane (5 mM) (Table 6). Also, the ring sizes were adjusted by using a range of readily available cyclic alkenes.

Table 6: Ring-expansion via olefin metathesis using the ruthenium alkylidene catalyst 69.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Olefin (equiv.)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>50</td>
</tr>
</tbody>
</table>

Table 6: Ring-expansion via olefin metathesis using the ruthenium alkylidene catalyst 69.102
Prevention of undesirable isomerisation during olefin metathesis\textsuperscript{117} and recyclability\textsuperscript{90,91,121} of some of these catalysts added other unique characterisations of this methodology. In addition, the well-defined catalyst systems were used to efficiently initiate the RCM reaction as a key step in one-pot reaction processes.\textsuperscript{122–123} Some additives, in particular 1,4-benzoquinones, showed significant efficiency for the prevention of undesirable olefin isomerisation of a number of olefins.\textsuperscript{120} For example, the RCM reaction of diallyl ether using the ruthenium catalyst 70 gave the corresponding metathesis product 2,5-dihydrofuran P1 after 1 h (Table 7). After extended reaction time, the isomer 2,3-dihydrofuran P2 was observed. The authors suggested that this was due to prolonged reaction time and also to the decomposition caused by the catalyst. A number of additives were examined such as acetic acid, 1,4-benzoquinone, 3,5-di-tert-butyl-4-hydroxytoluene (BHT), (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), phenol, and 4-methoxyphenol. Only acetic acid and 1,4-benzoquinone were effective.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Additive</th>
<th>Equiv. (relative to diallyl ether)</th>
<th>Product Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>none</td>
<td>&lt;5</td>
</tr>
<tr>
<td>acetic acid</td>
<td>0.1</td>
<td>&gt;95</td>
</tr>
<tr>
<td>1,4-benzoquinone</td>
<td>0.1</td>
<td>&gt;95</td>
</tr>
<tr>
<td>galvinoxyl</td>
<td>0.2</td>
<td>80</td>
</tr>
<tr>
<td>TEMPO</td>
<td>0.5</td>
<td>7</td>
</tr>
<tr>
<td>4-methoxyphenol</td>
<td>0.5</td>
<td>17</td>
</tr>
<tr>
<td>BHT</td>
<td>0.5</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 7: Role of additives in the prevention of undesirable isomerisation during the ring-closing metathesis reaction.\textsuperscript{120}
Although acetic acid prevented the isomerisation of the diallyl ether metathesis products, it did not exhibit any efficiency when self-metathesis reaction of (Z)-1,4-bis(tert-butyldimethylsiloxyl)-2-butene was applied (Table 8). Whereas, the 1,4-benzoquinone additive showed the same efficiency.

\[
\text{TBDMSO-} \underbrace{\text{-}}_{\text{OTBDMS}} \text{P3} + \text{TBDMSO-} \underbrace{\text{-}}_{\text{OTBDMS}} \text{P4}
\]

<table>
<thead>
<tr>
<th>Additive</th>
<th>Product Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>acetic acid</td>
<td>&gt;95</td>
</tr>
<tr>
<td>1,4-benzoquinone</td>
<td>92%</td>
</tr>
</tbody>
</table>

Table 8: 1,4-Benzoquinone as the most effective additive in the prevention of undesirable isomerisation during olefin metathesis.\(^{120}\)

The Hoveyda research group reported a number of Ru-based catalysts that were recyclable as olefin metathesis initiators. These active catalysts such as the Hoveyda first- and second-generation catalysts 71 and 72 were easily obtained from the Grubbs first- and second-generation catalysts 69 and 70, respectively.\(^{90,91}\) For example, the Hoveyda first-generation catalyst 71 which exhibited high activity for the ring-closing metathesis reaction was recovered after silica gel chromatography as a homogeneous solid residue in up to 95% yield (Table 9).\(^{90}\) The catalyst 71 (5 mol%) converted acyclic alkenes in dichloromethane at 22 °C to the corresponding metathesis products in high yields.
Table 9: The RCM reaction of acyclic dienes using the Ru-catalyst 71.\(^{90}\)

The \(^1\)H NMR and \(^{13}\)C NMR spectra and elemental analysis of the recovered catalyst and recrystallised form of 71 were identical. Thereafter, the recovered catalyst 71 was reused directly in the subsequent ring-closing metathesis reactions and exhibited the same efficiency (Table 10). The recycled catalyst 71 was transferred to a new reaction vessel and charged with the substrate and solvent. Then, the RCM reaction of the same substrates (in Table 9) was repeated three times at 22 °C using the recycled catalyst 71 (5 mol\%) in dichloromethane. Yields of the products and the recovered catalyst were consistent with yields of the first use of the same catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Product yield (%)</th>
<th>Recycled 71 yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OTBS</td>
<td>TBSO</td>
<td>0.5</td>
<td>90</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>Ns</td>
<td>Ns</td>
<td>1</td>
<td>99</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>Ns</td>
<td>Ns</td>
<td>1</td>
<td>72</td>
<td>95</td>
</tr>
</tbody>
</table>

Table 10: The RCM reaction using the recycled ruthenium-catalyst 71.\(^{90}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Cycle</th>
<th>Product yield (%)</th>
<th>Recovered 71 yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OTBS</td>
<td>TBSO</td>
<td>1</td>
<td>77</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>71</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>85</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>Ns</td>
<td>Ns</td>
<td>1</td>
<td>&gt;98</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>&gt;98</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>&gt;98</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>Ns</td>
<td>Ns</td>
<td>1</td>
<td>72</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>64</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>67</td>
<td>-</td>
</tr>
</tbody>
</table>
1.4.5 Applications of the Ring-Closing Metathesis Reaction

Over two decades, the ring-closing metathesis reaction has played an important role as an attractive and powerful transformation in olefin cyclisation chemistry. However, development of the well-defined RCM catalysts led to impressive synthetic applications. The Fürstner research group used development of the ring-closing metathesis reaction for synthesis of natural products. For example, they utilised Mo- and Ru-based catalysts in the total syntheses of marine natural products. In 1996, they reported a concise total synthesis of dactylol 87 and its epimer 88 via the ring-closing metathesis reaction and using Schrock catalyst 66. Consequently, this novel and short method efficiently afforded this natural product and its epimer in six steps (Scheme 31). First, cyclopentenone 80 was subjected to two reaction steps to give enone 81. Afterwards, chemo- and diastereoselective hydrogenation of 81 with tri-n-butyltin hydride in the presence of zinc chloride and a catalytic amount of Pd(PPh3)4 gave 82 in 83% yield. Next, treatment of the resulting trans-isomer 82 with mixture of Grignard reagent of 3-bromo-2-methyl-1-propene and suspension of anhydrous cerium(III) chloride in THF gave 83 and 84 in a 1:1.2 ratio. Thereafter, column chromatographic separation of the diastereomers followed by O-silylation using in situ formed N,O-bis(trimethylsilyl)acetamide from (Me3Si)2NH, acetyl chloride, and dimethylaminopyridine (DMAP) gave stable silyl ethers 85 and 86 in 93% and 95% yield, respectively. Finally, cyclisation of 85 and 86 using a relatively low loading of Schrock catalyst 66 afforded the corresponding alkenes which were subjected to desilylation using tetra-n-butylammonium fluoride (TBAF) to give doctylol 87 and 3a-epi-dactylol 88 in 92% and 85% yield, respectively. Therefore, this approach demonstrated a successful application of the RCM process for synthesis of challenging 8-membered rings and for synthesis of the natural product 87 and its epimer 88.
Scheme 31: Total synthesis of dactylol 87 and its epimer 88.
In addition, Fürstner and co-workers reported total syntheses of amphidinolide T1, T3, T4, and T5. These cytotoxic macrocycles of marine origin were synthesised utilising the ring-closing metathesis process as a key step. Amphidinolide T1 and T4, for example, were synthesised from commercially available hydroxyl ester 89 which was converted to compound 90 through a series of steps (Scheme 32). Hereafter, intermediate 90 underwent macrocyclisation using ruthenium catalyst 91 to generate intermediate 92 in 86% yield (E/Z, 6:1). Next, hydrogenation of the macrocycle followed by methylation using Nysted’s reagent 93 gave 19-membered macrocyclic ring 94 in good yield.

Scheme 32: Synthesis of macrocycle 94.
In the last stage, the macrocycle precursor 94 was used to synthesise amphidinolide T1 (96) and T4 (98) (Scheme 33). In one route, selective deprotection of the TBDPS group using [(Me₂N)₃S][Me₃SiF₂] gave 95 in 84% yield. Then, Dess-Martin oxidation of the resulting alcohol 95 followed by MOM group removal under slightly acidic conditions using Dowex AG 50W-X4 resin in MeOH gave amphidinolide T1 (96) in 52% yield. Alternatively, removal of the MOM group using TMSBr generated in situ, followed by Dess-Martin oxidation and selective cleavage of the TBDPS group led to formation of amphidinolide T4 (98) in high yields over three steps.

Scheme 33: Total syntheses of amphidinolide T1 (96) and T4 (98).
(Z/E)-Steroselective macrocyclisation was one of the key features of ruthenium-, molybdenum- and tungsten-catalysed RCM reactions. For example, Grubbs and co-workers utilised the ruthenium-catalysed RCM approach for the formation of diverse of macrocycles in high Z-selectivity from different dienes with a variety of functional groups and ring sizes (Scheme 34).

Scheme 34. Z-Selective macrocyclisation using ruthenium catalyst.

Molybdenum- and ruthenium-based catalytic tandem, domino and multi-olefin metathesis transformations have attracted the attention of many research groups as a unique approach in total synthesis of natural products. Martin and co-workers reported the first total synthesis of novel sesquiterpene lactone (+)-8-epi-xanthatin (104) via a domino ring-closing enyne metathesis (RCEYM)/cross metathesis (CM) reaction. This natural product, which exhibits a range of biological activities, was synthesised from commercially available ester 99 in 14 steps and in 5.5% overall yield (Scheme 35). Firstly, the starting material 99 was tosylated using TsCl in the presence of Et₃N and DMAP to give 100 in 96% yield. Then, a series of sequential transformations were carried out on 100 that led to enol triflate 101. Afterwards, palladium-catalysed carbonylation of 101 gave the corresponding acrylate 102 in 85% yield. Thereafter, treatment of 102 with TBAF to remove the silyl protecting groups followed by spontaneous lactonisation of the intermediate generated the desired enyne 103 in 78% yield. For the last step, the domino RCEYM/CM reaction process of enyne 103 and methyl vinyl ketone in the presence of Hoveyda second-generation catalyst 72 afforded lactone (+)-8-epi-xanthatin (104) in 83% yield.
In 2004, Nolan, Mioskowski and co-workers reported a new method for the synthesis of a highly substituted dihydorufuran ring utilising a ruthenium imidazolylidene catalytic ring-closing metathesis process. The strategy was applied in synthesis of solamin (111) (Scheme 36). The natural product 111 was obtained from commercially available propargylic alcohol in sequential reaction steps. First of all, the substrate precursor for the RCM reaction was synthesised from a coupling reaction between two fragments 105 and 106, which were both obtained from propargylic alcohol. Epoxide ring-opening reaction of 106 by 105 in the presence of Cu(OTf)₂ reagent gave the corresponding ether 107 in 35% isolated yield and recovery of 105 in 46% yield. Then, the resulting ether was converted to the silyl protected diene 108 in 95% yield.
While cyclisation of 108 using Mo-based Schrock catalyst 110 failed to give the metathesis product, initiation of the RCM reaction using Grubbs first-generation catalyst 69 was slow and gave 109 in 35% yield. Alternatively, catalyst 91, 1,3-dimesitylimidazol-2-ylidene ruthenium benzylidene, (5 mol%) afforded 109 in 80% isolated yield. The next six steps transformed the metathesis product 109 to the natural product, solamin (111).
Synthesis of chiral molybdenum and ruthenium catalysts was a point of interest of many research groups. Accordingly, detailed mechanistic studies and comprehensive synthetic investigations led to the development and synthesis of a number of effective chiral molybdenum and ruthenium catalysts. Some of these catalysts exhibit efficient use in total synthesis of natural products and construction of chiral molecules.\textsuperscript{103–114} The Schrock and Hoveyda research groups developed enantioselective synthesis of cyclic secondary amines, cyclic amides and amines, and cyclic enol ethers through the molybdenum-catalysed asymmetric ring-closing metathesis (ARCM) reaction.\textsuperscript{130–132} For example, the authors reported the enantioselective synthesis of cyclic unsaturated secondary amines which was carried out by the Mo-catalysed ARCM reaction of an achiral olefin in up to 93\% ee.\textsuperscript{130} First, achiral polyene substrate \textsuperscript{112} was converted efficiently to secondary bicyclic amine \textsuperscript{114} after 3 h at 55 °C in 75\% isolated yield and 93\% ee (Scheme 37). This enantioselective transformation was initiated by chiral molybdenum alkylidene complex \textsuperscript{113}. The resulting optically enriched benzazepine \textsuperscript{114} (93\% ee) was converted to a polycyclic structure. During this stage, allylation with allyl bromide and benzylpotassium (C\textsubscript{7}H\textsubscript{7}K) followed by addition of achiral Schrock catalyst \textsuperscript{66} gave tricyclic amine \textsuperscript{115} in 69\% yield and 93\% ee.

\begin{center}
\textbf{Scheme 37: Enantioselective synthesis of bicyclic amine \textsuperscript{114} and its conversion to tricyclic amine \textsuperscript{115}.}
\end{center}
The first enantioselective synthesis of cyclic amides and amines via the Mo-catalysed ARCM reaction with up to 98% ee was reported in 2005. Key substrates were prepared from commercially available materials and underwent the ARCM reaction using a number of molybdenum alkylidene catalysts. For example, cyclic amide 116 was subjected to triallylborane 117 according to Bubnov conditions to afford amine 118 in 65% yield (Scheme 38). Thereafter, allylation of 118 in the presence of benzylpotassium gave the desired triene 119 in 92% yield. Then, the catalytic ARCM reaction of 119 led to formation of N-fused 5,6-bicyclic amide 121 in 91% isolated yield and >98% ee after 48 h using 10 mol% loading of binaphthol-based molybdenum complex 120 as the most effective chiral catalyst among the others screened.

Scheme 38: The first enantioselective synthesis of optically enriched N-fused bicyclic amide 121.
Within this context, Martin and co-workers reported the first enantioselective synthesis of (+)-isolysergol (130) via asymmetric ring-closing metathesis.\textsuperscript{134} This new method involved microwave-mediated, diastereomeric Mo-catalysed ARCM reaction as a key step towards total synthesis of natural product (130) from commercially available substrate 122 (Scheme 39). The starting material 122 was converted through a series of steps to 123 which was subjected to bispentadienylzinc and gave a mixture of 124 and 125 in 91\% yield (in 2:1 regioselectivity) which was easily separated. Subsequently, the separated triene 124 was microwave-irradiated (50 W, 0.5 h) in the presence of Schrock-Hoveyda II catalyst 67 to afford 126 and 127 in 55\% and 20\% yields, respectively. During this process, Grubbs I 69, Grubbs II 70, and Schrock catalyst 66 in addition to several other chiral molybdenum-based catalysts were examined but without improved levels of diastereoselectivity of 126 or 127. Selective dihydroxylation of 126 utilising Donohoe conditions gave diol 128 in 74\% yield.\textsuperscript{135} Afterwards, oxidative cleavage of diol 128 with periodic acid in the presence of trifluoroacetic acid, followed by reduction using sodium cyanoborohydride gave 129 in 83\% yield. In the last step, quantitative yield of the desired natural product (130) was obtained from removal of the tosyl protecting group.
Scheme 39: The first enantioselective synthesis of (+)-isolysergol (130).
1.4.6 Conclusions

The ring-closing metathesis (RCM) reaction has emerged as an effective, common and powerful transformation that has been universally used as a key step in synthetic organic chemistry for the total syntheses of natural products. This method can be initiated using transition metals such as tungsten, rhenium, molybdenum, and ruthenium.

Well-defined molybdenum and ruthenium alkylidene catalyst complexes exhibited the most effective catalysis of the RCM reaction. Developments of these catalytic systems led efficiently to construction of a range of cyclic systems, with the catalyst becoming commercially available.

Further developments led to the synthesis of chiral Mo- and Ru-based catalyst systems which were utilised efficiently for the construction of chiral cyclic compounds. The asymmetric ring-closing metathesis (ARCM) catalysts have contributed widely to the total synthesis of natural products. (Z/E)-Stereo Selective macrocyclisation using specially designed catalysts was also utilised for the synthesis of natural products.
1.5 One-Pot Multi-Reaction Processes

1.5.1 General Concepts

“Green chemistry efficiently utilises (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.”\textsuperscript{136} On the basis of these principles, organic chemists turned their attention towards decreasing the environmental footprint of chemistry. Their efforts focused on development, design or discovery of efficient methods for synthesis of environmentally benign or safe organic products. Design of such processes can be guided by the twelve principles reported by Anastas and co-workers.\textsuperscript{137,138}

Awareness of environmental impact during the design of organic processes made discovery of new approaches and methods a challenge. The best synthetic processes involve reactions that proceed simply, selectively (chemo-, regio-, diastereo-, and enantioselectivity) and in environmentally friendly fashion (atom economy) to generate products.\textsuperscript{139} Combination of efficiency (step economy), environmental impact (atom economy), and pot economy concepts in synthetic chemistry leads to considerable enhancement of greener methodologies.\textsuperscript{140} While the step economy term means the reduction in the number of synthetic steps for more efficient methods, the pot economy term refers to conducting many sequential reactions in the same vessel without the need for work-up or purification between synthetic steps.\textsuperscript{140} Ultimately, development and discovery of organic syntheses that meet our needs and environmental requirements led to accepting the concept of one-pot processes as an efficient and promising approach in organic synthesis.\textsuperscript{141}

1.5.2 Types of One-Pot Processes

Conduction of sequential and/or multi-step reactions in one vessel (one-pot synthesis) was described by using several terminologies, such as domino reactions, cascade reactions, tandem reactions, or multi-step multi-reaction processes.\textsuperscript{122,141–146}
1.5.2.1 Domino Reactions

Tietze and Beifuss termed “one-pot reactions” as “sequential transformations” and classified them into two main categories; domino reactions and consecutive reactions. According to the Tietze definition, the domino reaction is “a process in which more than one bond-forming transformation (usually C-C bonds) takes place in one vessel and under the same conditions without an addition of any reagent or catalyst” (Scheme 40). In consecutive reactions, the addition of another reagent, or catalyst was allowed after the first transformation without isolation of the formed product.

![Scheme 40: Domino Knoevenagel hetero-Diels-Alder reaction.](image)

1.5.2.2 Cascade Reactions

In case of cascade reactions, Tietze suggested that “cascade” terminology is close to the meaning of the “domino” term and it is commonly used in literature to describe sequential reactions, but it does not describe the real meaning (Scheme 41). Furthermore, Sutherland and co-workers classified the one-pot processes into two categories: domino or cascade reactions, and multi-step multi-reaction processes. Whereas Fogg and dos Santos described the cascade reactions as a “multiple domino sequence.”
1.5.2.3 Tandem Reactions

Fogg and dos Santos defined the tandem reaction as sequential reactions of substrate that are initiated by one or more catalysts via two or more mechanistically distinct processes which proceed through cooperative mechanisms or one after the other. The authors also classified the tandem sequences to orthogonal, assisted, and auto-tandem catalysis (Figure 5). In the case of the orthogonal tandem catalysis, all catalysts which initiate two or more distinct mechanisms are non-interfering and present from the outset of reaction. The auto-tandem processes involve “two or more mechanistically distinct catalyses promoted by a single catalyst precursor: both cycles occur spontaneously by cooperative interaction of the various species (catalyst, substrate, additional reagents if required) present at the outset of reaction. No reagents beyond those originally present need be added to trigger the change in mechanism.” In the assisted tandem processes, an addition of a further reagent is necessary to trigger a change in mechanism by changing a single catalyst species, found from the outset of reaction, to another species that causes another transformation.
1.5.2.4 One-Pot Multi-Reaction Processes

Definition of one-pot multi-reaction processes is more comprehensive than other terms of the sequential transformations (domino, cascade, and tandem reactions) and simply combines all of those terminologies. They can be defined as multi-step reactions that are carried out in one vessel without the need for workup or isolation procedures between each step until the formation of final products. In addition, changing of reaction conditions and/or addition of any reagent or catalyst at any stage is allowed.\textsuperscript{122,141,142}

From the previous definitions of all types of the one-pot syntheses and according to taxonomy reported by Fogg and dos Santos, these processes can be simplified and illustrated (Figure 6).\textsuperscript{144}
One-pot syntheses were considered effective, efficient and greener approaches for construction of complex molecules such as biologically active molecules, pharmaceutical and medicinal compounds, natural products and other targets. Indeed, they reduced the number of reaction steps which lead to decrease of reaction times, costs, efforts, and environmental impact. From the perspective of the pot economy, these approaches avoided the need of several workup procedures, isolations, and purification of intermediates. Consequently, the need and necessity to develop or discover ideal and typical chemical reactions to increase selectivity and efficiency with minimal waste were always demanded as a high priority and a main goal for organic chemists in both academia and industry. Synthesis of tropinone (131) reported by Robinson, an entire century ago, was considered as an early, elegant example of one-pot synthesis (first domino reaction) (Scheme 42). Later, efforts by organic chemists working on this type of chemistry were centred around two issues; efficiency and environmental sustainability.

Scheme 42: One-pot synthesis of tropinone (131).
One-pot multi-reaction syntheses, whether they are tandem, domino, cascade or sequential catalytic transformations attracted attention of organic chemists as unique, potential strategies for widespread application in organic syntheses, such as total synthesis of natural products and construction of biologically active compounds. Development of this methodology also played a major role in the generation of environmentally benign products taking account of economic and environmental concerns.\textsuperscript{122,141,143,146} As discussed in the ring-closing metathesis section, organic chemists have used tandem and domino strategies utilising RCM catalysts for construction of a wide range of cyclic structures and total synthesis of natural products.\textsuperscript{78,93–97,128} For example, Grubbs and co-workers reported the total synthesis of (\textit{R})-(\textit{\textdegree})-muscone (135) via auto-tandem three-step ruthenium-catalysed reactions (Scheme 43). The RCM reaction of readily available diene 132 using Grubbs II catalyst 70 (7 mol\%) followed by ruthenium-catalysed transfer dehydrogenation of intermediate 133 in the presence of 3-pentanone and sodium hydroxide gave macrocycle 134.\textsuperscript{96} The resulting ketone 134 was hydrogenated, again using Grubbs II catalyst 70 to afford the natural product (\textit{R})-(\textit{\textdegree})-muscone (135) in 56\% yield over three steps.

\textbf{Scheme 43: Auto-tandem three-step Ru-catalysed synthesis of natural product (\textit{R})-(\textit{\textdegree})-muscone (135).}\textsuperscript{96}
The concept of the pot economy strategy was efficiently embodied by the Hayashi research group. Recently, three-pot nine-step, three-pot eight-step, and one-pot six-step reaction processes were used for the total synthesis of biologically active and pharmaceutical compounds.\(^{147-149}\) For example, a high-yielding enantioselective total synthesis of the DPP4-selective inhibitor ABT-341 (147) via a one-pot six-step reaction process was effectively achieved (Scheme 44).\(^{149}\) During this process, the inhibitor ABT-341 (147) was synthesised from four components: nitroalkene 136, acetaldehyde 138, vinyl phosphonate 140, and amine 145. In step one, an enantioselective Michael reaction of nitroalkene 136 and acetaldehyde 138 was initiated by diphenylprolinol silyl ether organocatalyst 137 (10 mol\%) and the excess of 138 was removed under reduced pressure to afford intermediate 139. Next, the intermediate 139 was charged with vinyl phosphonate 140 and cesium carbonate (Cs\(_2\)CO\(_3\)) in dichloromethane at 0 °C which promoted a Michael reaction and was followed by a Horner-Wadsworth-Emmons (HWE) reaction that afforded 141 and 142. Then, addition of ethanol to the reaction mixture in the presence of TMSCI drove conversion of the ester 141 to the cis-substituted cyclohexene 142 at room temperature. In step three, isomerisation of the cis-substituted cyclohexene 142 to trans-substituted isomer 143 was achieved by addition of Hüng’s base (EtN(i-Pr)\(_2\)) at room temperature. Then, treatment of the crude mixture of 143 with trifluoroacetic acid (TFA) in dichloromethane afforded the corresponding acid 144. Afterwards, a coupling reaction of the carboxylic acid 144 with heterocyclic amine 145 in the presence of O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) and Et\(_3\)N in N,N-dimethylformamide (DMF) generated the corresponding amide 146. In the last step, the nitro group was reduced utilising a mixture of zinc and acetic acid in ethyl acetate to provide the inhibitor ABT-341 (147) in 63% yield over six steps.
Scheme 44: One-pot six-step total synthesis of DPP4-selective inhibitor ABT-341 (147).
Interestingly, Overman rearrangement products showed remarkable tolerance towards different reaction conditions when they were charged with further catalysts to promote subsequent transformations in the same vessel. As a result, this property has been efficiently exploited by the Sutherland group. Over the past decade, they have developed a combination of the thermal and metal-catalysed Overman rearrangements with the ring-closing metathesis (RCM) reactions in the one-pot multi-step multi-reaction syntheses for construction of nitrogen-containing compounds and synthesis of natural products and biologically active molecules.\textsuperscript{122,150–160} For example, Sutherland and co-workers, reported the stereoselective synthesis of alkaloid, (+)-physoperuvine (155), using a one-pot strategy of the Overman rearrangement and the ring-closing metathesis reaction as a key step (Scheme 45).\textsuperscript{151} The first step of this synthesis was conversion of commercially available ethyl 6-heptenoate 148 into allylic alcohol 151 in four steps. First, a DIBAL-H reduction of 148 gave primary alcohol 149 in 94\% yield. Next, a one-pot Swern oxidation and Horner-Wadsworth-Emmons (HWE) reaction afforded the corresponding (E)-\(\alpha,\beta\)-unsaturated ester 150 in 85\% yield over two steps. Then, a DIBAL-H reduction of the ester 150 led to a quantitative formation of the key substrate, allylic alcohol 151. In the second stage, (S)-N-(cycloheptenyl)trichloroacetamide 154 was synthesised from allylic alcohol 151 using a one-pot process. The allylic alcohol 151 was converted to allylic trichloroacetimidate 152 using a catalytic amount of DBU followed by the one-pot, two-step reaction process of the asymmetric palladium(II)-catalysed Overman rearrangement, using (S)-COP-Cl 24 (10 mol\%), and the RCM reaction with Grubbs first-generation catalyst 69 (10 mol\%) to give the amino-substituted cycloheptene 154 in 82\% yield over three steps. Finally, subsequent transformations led to the total synthesis of (+)-physoperuvine (155).
1.5.4 Conclusion

One-pot reaction processes have attracted attention of organic chemists as an important strategy to access advanced synthetic intermediates, rapidly and efficiently, and to significantly minimise environmental impact. These methods have been utilised efficiently as key stages in the construction of a wide range of organic compounds and natural products. According to how substrates, catalysts, and reagents are added, one-pot reaction syntheses have been classified into domino, cascade and tandem reactions, in addition to one-pot multi-step multi-reaction processes. The one-pot multi-step multi-reaction processes have wider definition than others and are more flexible in applications for synthesis of organic compounds over the other approaches.
2.0 Results and Discussion

2.1 Synthesis of 5-Amino-Substituted 2,5-Dihydro-1-benzoxepines

2.1.1 Previous Work within the Sutherland Group

Previously, the Sutherland group has developed access to cyclic allylic amide systems via one-pot reaction processes. This strategy was utilised for the total synthesis of natural products and the construction of complex molecules that have biological activity (Scheme 46).\textsuperscript{150–152,155,160}

\[ \text{Scheme 46: One-pot Overman rearrangement and RCM reaction process.} \]

The first synthesis of the cyclic allylic amide systems utilising this methodology began by preparation of allylic alcohols as the key substrates. Commercially available alken-1-ols 156a–d were converted to the corresponding allylic alcohols 158a–d in three steps (Scheme 47).\textsuperscript{150} First, a one-pot Swern oxidation and Horner-Wadsworth-Emmons (HWE) reaction process using Masamune-Roush conditions led to the formation of the corresponding (E)-\(\alpha,\beta\)-unsaturated esters 157a–d in 69–90% yield.\textsuperscript{161,162} Next, DIBAL-H reduction of the resulting esters 157a–d afforded allylic alcohols 158a–d in high to quantitative yield. The precursor allylic alcohols were reacted with trichloroacetonitrile and a catalytic amount of DBU to form allylic trichloroacetimidates 159a–d. These intermediates 159a–d were then subjected to a one-pot palladium(II)-catalysed Overman rearrangement and ruthenium(II)-catalysed ring-closing metathesis reaction process to give the cyclic allylic trichloroacetamides 160a–d in high yields over three steps.
Scheme 47: Development of the one-pot Overman rearrangement and RCM reaction process.

Further work showed that this process could be extended for the synthesis of heterocyclic ring systems. These type of structural variations were utilised efficiently for the synthesis of different heterocyclic systems such as bicyclic \( \gamma \)-lactams (Scheme 48).\(^{153,154,157}\)

Scheme 48: Synthesis of heterocyclic bicyclic \( \gamma \)-lactams via the one-pot process.

For example, synthesis of 3-amidoazepine using a one-pot multi-bond forming three-step process represented a typical target for this new methodology.\(^{157}\) Initially, commercially available 2-aminoethanol 161 was converted quantitatively to 162 via a coupling reaction with 4-bromo-1-butene in the presence of sodium
iodide (Scheme 49). The resulting alcohol 162 was protected with TBDPSCl which then allowed Boc protection of the secondary amine to give 163. Then, silyl deprotection using TBAF at 0 °C afforded alcohol 164. Next, Swern oxidation of alcohol 164 followed by a Witting reaction using (triphenylphosphoranylidene)acetaldehyde afforded 165. Afterwards, sodium borohydride reduction of the resulting aldehyde 165 generated (E)-allylic alcohol 166 in 88% isolated yield.

\[
\begin{align*}
\text{H}_2\text{N} \rightarrow \text{OH} & \quad \text{Br} \quad \text{Nal, MeOH, } \Delta \quad 100\% \\
161 & \quad \text{HN} \rightarrow \text{OH} \quad \text{BocN} \rightarrow \text{OTBDPS} \\
162 & \quad \text{BocN} \rightarrow \text{CHO} \quad \text{BocN} \rightarrow \text{OH} \quad \text{NaBH}_4 \rightarrow \text{MeOH, } 0 \, ^\circ\text{C}, 88\% \\
166 & \quad \text{BocN} \rightarrow \text{CHO} \quad \text{BocN} \rightarrow \text{OH} \quad \text{BocN} \rightarrow \text{CHO} \rightarrow \text{MeOH, } -78 \, ^\circ\text{C}, 94\% \\
165 & \quad \text{TBAF, THF, } 0 \, ^\circ\text{C, 100\%} \\
164 & \quad (\text{COCl})_2, \text{DMSO, Et}_3\text{N, CH}_2\text{Cl}_2, -78 \, ^\circ\text{C}, 100\% \\
167 & \quad \text{BocN} \rightarrow \text{CHO} \rightarrow \text{toluene, 80 \, ^\circ\text{C, 75\%}} \\
168 & \quad \text{BocN} \rightarrow \text{CHO} \rightarrow \text{tetracyclic azepine, 10 \, ^\circ\text{C, 70\%}} \\
169 & \quad \text{BocN} \rightarrow \text{CHO} \rightarrow \text{tetracyclic azepine, 80 \, ^\circ\text{C, 75\%}} \\
165 & \quad \text{BocN} \rightarrow \text{CHO} \rightarrow \text{tetracyclic azepine, 80 \, ^\circ\text{C, 75\%}} \\
164 & \quad \text{BocN} \rightarrow \text{CHO} \rightarrow \text{tetracyclic azepine, 80 \, ^\circ\text{C, 75\%}} \\
166 & \quad \text{BocN} \rightarrow \text{CHO} \rightarrow \text{tetracyclic azepine, 80 \, ^\circ\text{C, 75\%}}
\end{align*}
\]

Scheme 49: Synthesis of allylic alcohol 166 for the one-pot process.

With the key substrate 166 in hand, this was then subjected to the one-pot Overman rearrangement and ring-closing metathesis reaction process (Scheme 50). Allylic alcohol 166 was converted to 167 using trichloroacetonitrile and a catalytic amount of DBU at room temperature. Next, the crude mixture of this reaction was charged with bis(acetonitrile)palladium(II) chloride (10 mol%) to generate the Overman rearrangement intermediate 168 which was then cyclised utilising Grubbs second-generation catalyst 70 (10 mol%) to give 2,3,6,7-tetrahydro-3-amidoazepine 169 in 79% yield over three steps.
Further developments within the Sutherland group demonstrated that cyclic allylic amides as synthetic intermediates could be functionalised by directed oxidation reactions for the diastereoselective synthesis of hydroxylated aminocarbocyclic and aminoheterocyclic scaffolds.\textsuperscript{155,157} The study showed that directed epoxidation followed by epoxide ring opening or directed dihydroxylation could be efficiently achieved under standard conditions to form highly functionalised cyclic allylic amides.\textsuperscript{157} For example, stereoselective oxidation of the 3-amidoazepine ring 169 was performed via two different routes to give 3-aminoazepan-4-ol 172 and 3-aminoazepan-4,5-diol 173 (Scheme 51). Initially, 3-amidoazepine 169 was subjected to directed epoxidation using \textit{m}-CPBA to give epoxide 170 in 58\% yield.\textsuperscript{163,164} Lithium aluminium hydride was then used to conduct a regioselective reductive epoxide opening followed by Boc group deprotection and hydrolysis of the unpurified oxazolidinone intermediate 171 to give the cis-diastereomer, (3\textit{S},4\textit{R})-3-aminoazepin-4-ol (172) in 61\% yield over two steps. In addition, directed selective dihydroxylation of 3-amidoazepine ring 169 under Donohoe conditions using osmium tetroxide (OsO\textsubscript{4}) and \textit{N},\textit{N},\textit{N'},\textit{N''}-
tetramethylethylenediamine (TMEDA) gave syn-diol 173 as a single diastereomer in 81% yield.\textsuperscript{165,166} Then, removal of the trichloroacetamide protecting group under basic conditions followed by removal of the Boc-protecting group under acidic conditions afforded (3$S^*$,4$S^*$,5$R^*$)-3-aminoazepane-4,5-diol (174) in 78% yield.

Scheme 51: Functionalisation of 3-amidoazepine 169 via directed oxidation.

### 2.1.2 Aims

The aim of this project was to expand the scope of the previously developed one-pot reaction processes for the preparation of 5-amino-substituted 2,5-dihydro-1-benzoxepines. 1-Benzoxepines are interesting seven-membered heterocyclic substances. They are found in many natural products and make up a wide spectrum of synthetic scaffolds that have biological activities and medicinal applications (Figure 7).\textsuperscript{167–170} For example, the guanidine derivative of 1-benzoxepine 175 has hypotensive effects,\textsuperscript{167} while 2,3,4,5-tetrahydro-1-benzoxepine 176 is a potent acyl-CoA, cholesterol O-acyl transferase (ACAT) inhibitor.\textsuperscript{168} A number of 1-benzoxepino[3,4-b]pyridines 177 which display antiulcer activity have also been synthesised.\textsuperscript{169} The 2,5-dihydro-1-benzoxepine pterulone (178) was isolated from a \textit{Pterula} fungal species and showed antibacterial properties.\textsuperscript{171}
Figure 7. Structures of some biologically active 1-benzoxepines.

It was proposed that substituted salicylaldehydes could be efficiently converted into the required allylic alcohols (Scheme 52). The one-pot process of a thermal Overman rearrangement followed by a ruthenium-catalysed ring-closing metathesis reaction would give the target compounds. This approach would allow the synthesis of a small library of 5-amino-substituted 2,5-dihydro-1-benzoxepines that could then be used for the preparation of biologically active compounds such as the hypotensive agent 175 (Figure 7).

Scheme 52: Proposed access to 5-amino-2,5-dihydro-1-benzoxepines from salicylaldehydes using the one-pot multi-reaction process.
2.1.3 Synthesis of Allylic Alcohols

As mentioned above, various allylic alcohols which are the key substrates for the one-pot reaction process were prepared in three steps. Initially, starting material 180c was prepared from commercially available 3-chlorophenol (179). Formylation of 3-chlorophenol (179) was carried out using paraformaldehyde in the presence of magnesium chloride and triethylamine (Scheme 53).\(^{172}\) This gave 4-chloro-2-hydroxybenzaldehyde (180c) in 39% isolated yield. By-product 6-chloro-2-hydroxybenzaldehyde (181) was also isolated. The low yield of the desired product was due to moisture sensitivity of magnesium chloride and the formation of 181.

![Scheme 53. Synthesis of salicylaldehyde (180c).](image)

Then, 4-chlorosalicylaldehyde (180c) and other commercially available substituted salicylaldehydes 180a–g were converted to the corresponding O-allylic 2-hydroxybenzaldehydes 182a–g via reaction with allyl bromide in the presence of potassium carbonate (Figure 8).\(^{173,174}\) The allylation of 2-hydroxybenzaldehydes required only a short time to afford almost quantitative yields of the products. A range of analogues were required to demonstrate the scope of the methodology. In addition to the unsubstituted benzene ring of the starting material 180a, an electron donating group such as a methyl group in substrate 180a and an electron withdrawing group such as chloro-substituted analogue 180c were also used. Polysubstituted analogues were also investigated (180d–g) for the preparation of more complex targets.\(^{175}\)
Next, Horner-Wadsworth-Emmons (HWE) reaction under mild Masamune-Roush conditions was carried out to form the corresponding (E)-α,β-unsaturated esters 183a–g (Table 11). In this transformation, 2-allyloxybenzaldehydes 182a–g were reacted with triethyl phosphonoacetate (TEPA) and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in the presence of lithium bromide. Using these conditions the products were obtained exclusively as the E-alkene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>182</th>
<th>183 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = H, 182a</td>
<td>183a (95)</td>
</tr>
<tr>
<td>2</td>
<td>R = 5-Me, 182b</td>
<td>183b (88)</td>
</tr>
<tr>
<td>3</td>
<td>R = 4-Cl, 182c</td>
<td>183c (94)</td>
</tr>
<tr>
<td>4</td>
<td>R = 3,5-Cl₂, 182d</td>
<td>183d (quant.)</td>
</tr>
<tr>
<td>5</td>
<td>R = 4,5-F₂, 182e</td>
<td>183e (93)</td>
</tr>
<tr>
<td>6</td>
<td>R = 3-OMe, 5-NO₂, 182f</td>
<td>183f (quant.)</td>
</tr>
<tr>
<td>7</td>
<td>2-Hydroxy-1-naphthaldehyde, 182g</td>
<td>183g (92)</td>
</tr>
</tbody>
</table>

Table 11. Synthesis of (E)-α,β-unsaturated esters 183a–g.
All the resulting \((E)\)-\(\alpha,\beta\)-unsaturated esters showed a large coupling constant greater than 16.0 Hz in the \(^1\)H NMR spectra. For example, the coupling constant for the 2-\(H\) and 3-\(H\) hydrogen atoms of \(183a\) showed a value of 16.2 Hz, indicative of a disubstituted \(E\)-alkene (Figure 9).

Figure 9: The \textit{trans}-geometry of the \((E)\)-\(\alpha,\beta\)-unsaturated ester 183a.
Treatment of the resulting (E)-α,β-unsaturated esters 183a–g with diisobutylaluminium hydride (DIBAL-H) produced the corresponding (E)-allylic alcohols 184a–g in excellent yields (Figure 10). Overall, the conditions used for the three steps yielded the products in high to quantitative yields for all types of substituents.

![Figure 10: Synthesis of allylic alcohols 184a–g.](image)

2.1.4 The One-Pot Multi-Reaction Synthesis of 1-Benzoxepines

This reaction was developed by a previous group member (Ewen Calder) who showed that the RCM step could be catalysed by Grubbs second-generation catalyst (5 mol%) to give a 65% overall yield of 187a (Scheme 5).\textsuperscript{176,177} Repeat of this one-pot process in this project under the same conditions gave 187a in a similar yield of 68% over the three steps.
1-Benzoxepine analogues 187a–g were synthesised according to the optimal conditions of the ring-closing metathesis step developed by Calder and based on the standard conditions of the one-pot Overman rearrangement-ring closing metathesis reaction process that has been developed within the Sutherland group.122,150,160,177 In the first step, allylic alcohols 184a–g were transformed to allylic trichloracetimidate intermediates 185a–g by treatment with trichloroacetonitrile in the presence of a catalytic amount of DBU (Figure 11). The Overman rearrangement step was then performed under thermal conditions to generate the corresponding allylic trichloroacetamides 186a–g. Next, the one-pot reaction process was completed by addition of Grubbs second-generation catalyst 70 (5 mol%) to produce the substituted 5-amino-2,5-dihydro-1-benzoxepines 187a–g in good yields over three steps. It was found that substrates bearing electron-withdrawing groups required more time during the Overman rearrangement step to proceed to completion. Accordingly, analogues 187c and 187e required 24 hours, while 187f required 48 hours for the Overman rearrangement step. Slightly lower yields were observed for ortho-substituted compounds which may be due to steric hindrance during the RCM step.
Figure 11. Synthesis of 5-amino-substituted 2,5-dihydro-1-benzoxepines 187a–g.
2.1.5 Synthesis of 8-Chloro-5-guanidino-2,3,4,5-tetrahydro-1-benzoxepine

As this approach allowed efficient access to 2,5-dihydro-1-benzoxepines, it was decided to use this strategy for the preparation of a pharmaceutically important compound. Hypotensive agent \textbf{175} was synthesised from the previously prepared chlorine-derived 1-benzoxepine analogue \textbf{187c}. Initially, optimal conditions of each step were investigated. Previous attempts within the Sutherland groups showed that hydrogenation using palladium on charcoal was an efficient method to reduce trichloroacetamide-containing alkenes.\textsuperscript{178} Hydrogenation of \textbf{187c} under these conditions was used to reduce the alkene moiety of \textbf{187c} (Scheme 55). This also led to reduction of the trichloromethyl moiety and gave \textbf{188} in 94%.

\begin{center}
\begin{tikzpicture}
  \node[align=center, above, text width=1.5cm] (A) at (0,0) {H,N, \text{CCl}_3};
  \node[align=center, above, text width=1.5cm] (B) at (2,0) {H,N, \text{CHCl}_2};
  \node[align=center, above, text width=1.5cm] (C) at (0,0.5) {\text{Cl} \text{O} \text{C} \text{Cl}_3};
  \node[align=center, above, text width=1.5cm] (D) at (2,0.5) {\text{Cl} \text{O} \text{C} \text{CHCl}_2};
  \draw[->] (A) edge node[above] {H, Pd/C, EtOAc} (B);
\end{tikzpicture}
\end{center}

\textit{Scheme 55. Hydrogenation of 1-benzoxepine 187c.}

Removal of the dichloroacetyl group required harsher conditions than a typical trichloroacetyl group. According to previous work in the Sutherland group, it was found that removal of a dichloroacetyl group required acidic conditions (6 M aq. HCl, MeOH, 60 °C and 24 h) (Table 12).\textsuperscript{178} Using these conditions gave low conversions (11\%) of the desired intermediate \textbf{189} (entry 1). Further investigation for the reaction temperature and time were performed to access optimal conditions. Removal of the dichloroacetyl protecting group of \textbf{188} required a temperature of 100 °C and a reaction time of 144 hours (entry 4).
Table 12. Removal of the dichloroacetyl protecting group of 186.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>72</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>48</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>144</td>
<td>78</td>
</tr>
</tbody>
</table>

Coupling of 5-amino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepine (189) with \(N,N'-\text{bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (190)}\) was then investigated (Scheme 56). Bernatowicz and co-workers reported the importance of 190 as a guanylation agent of amines under mild conditions.\(^{179,180}\) Sutherland and co-workers reported efficient use of this reagent 190 for the preparation of several guanidine-containing bio-active compounds.\(^{49,181}\) The guanylation of the free amine moiety of 189 with \(N,N'-\text{bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (190)}\) in the presence of Hünig’s base gave protected guanidine derivative 191 in 80% isolated yield after 48 hours at room temperature.

Scheme 56: Guanylation of 189.
To improve the efficiency of deprotection of the dichloroacetyl group and guanylation, the two steps were repeated without purification of the intermediate amine 189. This gave the protected guanidine derivative 191 in 75% yield over the two steps (Scheme 57).

Scheme 57: Synthesis of the protected guanidine derivative 191.

Finally, removal of the Boc-protecting groups of the guanidine derivative 191 to form the hypotensive agent 175 was investigated (Table 13). Initially, deprotection using trifluoroacetic acid was attempted at room temperature to show only the starting material 191 after 6 h (entry 1). Increasing the reaction time to 32 hours gave a low conversion (11%) of the desired product 175 (entry 2). Further investigation of the reaction time and temperature led to 100% conversion at 45 °C after 48 h (entry 5). Using the optimal conditions gave 8-chloro-5-guanidino-2,3,4,5-tetrahydro-1-benzoxepine (175) in quantitative yield. The high efficiency of the one-pot process and the latter steps of this route allowed the synthesis of 8-chloro-5-guanidino-2,3,4,5-tetrahydro-1-benzoxepine (175) in 40% overall yield form 4-chloro-2-hydroxybenzaldehyde (180c).
Table 13. Deprotection of 191 under acidic conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>rt</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>rt</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>27</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>48</td>
<td>100</td>
</tr>
</tbody>
</table>

2.1.6 Dihydroxylation of 5-Amino-Substituted 2,5-Dihydro-1-benzoxepines

The next stage of this project investigated the stereoselective oxidation of the 2,5-dihydro-1-benzoxepines. Hydroxylated 5-amino-1-benzoxepines such as cathepsin S inhibitor 192 have significant pharmaceutical activity (Figure 12). Therefore, dihydroxylation of 5-amino-substituted 2,5-dihydro-1-benzoxepines yielding the corresponding syn- and anti-3,4-diols might produce compounds with interesting biological activity.

Figure 12. Cathepsin S inhibitor 192, a hydroxylated 5-amino-1-benzoxepine.
2.1.6.1 Synthesis of cis-3,4-Diols of 5-Amino-1-benzoxepines

Direct dihydroxylation of selected 1-benzoxepines under Donohoe conditions was investigated.\textsuperscript{165,166} Osmium tetroxide was used to react with 5-amino-substituted 2,5-dihydro-1-benzoxepines 187b, 187f, and 187g in the presence of tetramethylethlenediamine (TMEDA) to afford the corresponding diastereomeric (3\textsuperscript{R*},4\textsuperscript{S*},5\textsuperscript{S*})-diols 193b, 193f and 193g (Figure 13). Overall, the products were formed as single cis-diastereomers in high yields. The cis-selectivity of dihydroxylation is likely controlled by hydrogen bonding between the N–H group of the amide as a hydrogen bond donor and the OsO\textsubscript{4}/TMEDA complex 194 as a hydrogen bond acceptor.\textsuperscript{165,166} Initially, TMEDA base chelates to OsO\textsubscript{4} to form OsO\textsubscript{4}/TMEDA complex 194 which interacts with 1-benzoxepine to form intermediate 195 via hydrogen bonding. In complex 194, the electron density of the osmium atom and attached oxygen atoms increases due to the electronic donation from the nitrogen atoms. This results in the hydrogen bonding associated with the directed intermediate during the dihydroxylation. Cleavage of the intermediate complex 196 and release of the desired diol is achieved during work up.
Figure 13. Synthesis of cis-3,4-diols 193b, 193f and 193g.

The relative stereochemistry of 193b, 193f and 193g was confirmed by NOE experiments that showed the cis-relationship of the vicinal amino diol motifs (Figure 14).

Figure 14. NOE analysis of 193b, 193f and 193g.
2.1.6.2 Synthesis of trans-3,4-Diols of 5-Amino-1-benzoxepines

It was proposed that epoxidation of 1-benzoxepines under O'Brien conditions followed by acid mediated hydrolysis would lead to oxirane ring opening and the formation of the analogous trans-3,4-diols (Figure 15).\textsuperscript{164} Initially, epoxidation of 1-benzoxepines \textit{187b}, \textit{187e} and \textit{187g} was conducted by addition of \textit{m}-chloroperbenzoic acid (\textit{m}-CPBA) to give intermediates \textit{198b}, \textit{198e}, and \textit{198g} as two diastereomers. The diastereomeric ratio ranged from 3:1 to 6:1. These results were consistent with Henbest's rule.\textsuperscript{163} Henbest reported that the \textit{cis}-epoxidation via transition state intermediate \textit{197} was preferable over the \textit{trans}-epoxidation due to the hydrogen bond that formed between N-H group and oxygen atom of the perbenzoic acid (\textit{m}-CPBA). The low diastereoselectivity for \textit{198g} may be due to the \textit{ortho}-substitution of the amide directing effect by the naphthalene moiety. Next, acid-mediated epoxide ring opening of \textit{198b}, \textit{198e}, and \textit{198g} led to the formation of the corresponding diols (dr 3:1 to 6:1). The major diastereomeric (3\textit{S}*,4\textit{S}*,5\textit{S}*)-diols \textit{199b}, \textit{199e}, and \textit{199g} were isolated in good overall yields.
Figure 15. Synthesis of trans-3,4-diols 199b, 199e and 199g.

The relative stereochemistry of the major diastereomers 199b, 199e and 199g was also confirmed using NOE experiments (Figure 16).

Figure 16. NOE analysis of 199b, 199e and 199g.
2.1.7 Conclusions

In summary, a new one-pot thermal Overman rearrangement and ring-closing metathesis process allowed access to a diverse library of 5-amino-2,5-dihydro-1-benzoepines from O-allylic cinnamyl alcohols in high yields. These key substrates for this process were rapidly prepared from salicylaldehydes in high yields. By this outcome, this method minimises the negative impact of chemistry on the environment. In addition, the generality of this approach allowed the construction of important heterocyclic compounds such as a hypotensive agent. The importance of this approach was also demonstrated with functionalisation of the products under mild conditions. Stereoselective oxidation of the alkene moiety of the 5-amino-substituted 2,5-dihydro-1-benzoepines gave access to pharmaceutically interesting scaffolds.
2.2 Synthesis of 5-Amino-Substituted 2,5-Dihydro-1\textit{H}-benzazepines

5-Amino-1\textit{H}-benzazepines have been widely shown to be biologically active, finding application as inhibitors for the treatment of a wide range of diseases and disorders (Figure 17).\textsuperscript{184,185} For example, 5-dimethylamino-1-[4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1\textit{H}-benzazepine (200), mozavaptan (OPC-31260), is an effective vasopressin \textit{V}_2 receptor antagonist. Its enantiomeric metabolites, which showed significant biological activity, have recently been synthesised for more investigations with regard to medicinal applications.\textsuperscript{184} A wide spectrum of substituted 2,3,4,5-tetrahydro-1\textit{H}-benzazepine analogues such as 201 were developed for the treatment of dyslipidemia.\textsuperscript{185}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{structure.png}
\caption{Figure 17. Structure of some medicinally active 1\textit{H}-benzazepines.}
\end{figure}

2.2.1 Aims

Due to the success of the one-pot approach for the synthesis of 5-amino-2,5-dihydro-1-benzocepines, it was decided to extend this process to the corresponding 1\textit{H}-benzazepines. It was proposed that this one-pot reaction strategy would allow easy, efficient synthesis of a small library of 5-amino-substituted 2,5-dihydro-1\textit{H}-benzazepines from commercially available anilines (Scheme 58). The suggested strategy consisted of two main stages. First, commercially available substituted anilines would be transformed into cinnamyl alcohol substrates via five sequential reactions. This would involve iodination of the anilines, followed by a Mizio-Hot reaction to form the cinnamyl esters.
Protection and allylation of the amino groups and finally reduction of the esters would give the cinnamyl alcohols. In the second stage, a one-pot synthesis of 1H-benzazepines would be then performed using the previously prepared cinnamyl alcohols. The product of the one-pot process would then be used for the synthesis of medicinally important substances such as mozavaptan (200), a drug for treatment of hyponatremia (Figure 17).

Scheme 58: Proposed access to 5-amino-2,5-dihydro-1H-benzazepines from substituted anilines using a one-pot multi-reaction process.

2.2.2 Synthesis of Allylic Alcohols

The first aim of this project was the preparation of \((E)\)-(2-allylamino)cinnamyl alcohols for the one-pot reaction process. These key substances were formed from selected commercially available substituted anilines 202b,d–f and commercially available 2-iodoaniline (203a). Selected commercially available substituted anilines 202b,d–f were subjected to standard iodination to afford the corresponding substituted 2-iodoanilines 203b,d–f (Table 14).\(^\text{186,187}\) As shown, the aniline with the electron-donating substituent (Me) afforded the highest isolated yield (93%, entry 1). In contrast, analogues with electron-withdrawing groups required a higher temperature and prolonged reaction times to afford the desired products in lower isolated yields. As expected, analogue 203e was isolated in low
yield of 15% (entry 3) due to the formation of by-products such as 5-fluoro-2,4-diiodoaniline (204).

![Chemical structure and reaction scheme]

**Table 14: Standard aromatic iodination of anilines (203b,d–f).**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>203 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>24</td>
<td>203b (93)</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>60</td>
<td>203d (81)</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>50</td>
<td>203e (15)</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>90</td>
<td>203f (59)</td>
</tr>
</tbody>
</table>

For the other analogues, 2-iodoaniline (203a) was used from commercial sources, while 2-iodo-4-methoxyaniline (203c) was prepared from 3-iodoanisole (205) in an alternative route. A one-pot electrophilic aromatic nitration of 3-iodoanisole (205) and reduction process using iron metal in the presence of ammonium chloride gave 2-iodo-4-methoxyaniline (203c) in 30% yield over the two steps (Scheme 59). This route was chosen due to the fact that the methoxy substituent is a very powerful electron-donating group. Attempted electrophilic aromatic iodination of 4-methoxyaniline led to poly-iodinated by-products.

![Synthesis scheme]

**Scheme 59: Alternative route to synthesis of 2-iodo-4-methoxyaniline (203c).**
On preparation of the 2-iodoanilines, a number of transformations were performed to form the allylic alcohols, key substrates for the one-pot reaction process. For achieving this plan, optimal conditions for the transformation of substituted 2-iodoanilines into the precursor allylic alcohols were investigated. First, Mizoroki-Heck reaction using 2-iodoaniline (203a) was investigated (Table 15). 2-iodoaniline (203a) was subjected to the Mizoroki-Heck reaction using methyl acrylate (2 equiv) and catalysed by palladium(II) acetate (1 mol%) to give (E)-α,β-unsaturated methyl ester 206a in 50% isolated yield (entry 1). This gave only the E-alkene. Further investigation showed that a higher catalyst loading (5 mol%) allowed efficient preparation of 206a in quantitative isolated yield after a significantly shorter reaction time (entry 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(II) (mol%)</th>
<th>PPh₃ (mol%)</th>
<th>K₂CO₃ (equiv)</th>
<th>TBAB (mol%)</th>
<th>Mixture conc. (M)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>0.5</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>0.2</td>
<td>16</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>25</td>
<td>0.1</td>
<td>1</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>10</td>
<td>1</td>
<td>25</td>
<td>0.1</td>
<td>2</td>
<td>99</td>
</tr>
</tbody>
</table>

Table 15. Optimisation of the Mizoroki-Heck reaction of 203a.

The free amine group was then protected with tosyl chloride in the presence of pyridine to give 207a in 93% yield (Scheme 60). Allylation of the corresponding amine 207a using allyl bromide under standard conditions formed the allylated amine 208a in quantitative yield.189

Scheme 60. Tosylation and allylation of 206a.
Finally, conversion of the resulting ester 208a to allylic alcohol 209a was also investigated (Table 16). DIBAL-H reduction under standard conditions allowed access to the desired allylic alcohol in 77% isolated yield after 2 h (entry 1). Increasing the reaction mixture concentration (0.1 M) and extending the reaction time to 18 h afforded cinnamyl alcohol 209a in very high yield (entry 3).

Having established the optimal conditions for the synthesis of allylic alcohol 209a from commercially available 2-iodoaniline (203a), these conditions were used for the other substituted anilines 203b–f. Initially, 2-iodoanilines 203b–f were subjected to the Mizoroki-Heck reaction using methyl acrylate and catalysed by palladium(II) acetate (5 mol%) to give (E)-α,β-unsaturated methyl esters 206b–f in high to quantitative yields (Table 17). The free amine group was then protected with tosyl chloride in the presence of pyridine to give 207b–f in very high yields. Allylation of the corresponding amines 207b–f using allyl bromide under standard conditions formed the allylated amines 208b–f in high to quantitative yields. Finally, DIBAL-H reduction of the resulting esters 209b–f allowed access to the desired allylic alcohols in high isolated yields. As illustrated in Table 17, all the used conditions for each step allowed rapid, easy and efficient access to the desired products in high to quantitative yield.
Table 17. Synthesis of allylic alcohols 209b–f.

<table>
<thead>
<tr>
<th>Entry</th>
<th>203</th>
<th>206 (%)</th>
<th>207 (%)</th>
<th>208 (%)</th>
<th>209 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = 4-Me, 203b</td>
<td>206b (quant.)</td>
<td>207b (99)</td>
<td>208b (91)</td>
<td>209b (98)</td>
</tr>
<tr>
<td>2</td>
<td>R = 4-OMe, 203c</td>
<td>206c (quant.)</td>
<td>207c (93)</td>
<td>208c (92)</td>
<td>209c (80)</td>
</tr>
<tr>
<td>3</td>
<td>R = 4-F, 203d</td>
<td>206d (81)</td>
<td>207d (88)</td>
<td>208d (84)</td>
<td>209d (98)</td>
</tr>
<tr>
<td>4</td>
<td>R = 5-F, 203e</td>
<td>206e (84)</td>
<td>207e (97)</td>
<td>208e (79)</td>
<td>209e (99)</td>
</tr>
<tr>
<td>5</td>
<td>R = 4-Cl, 203f</td>
<td>206f (76)</td>
<td>207f (91)</td>
<td>208f (quant.)</td>
<td>209f (92)</td>
</tr>
</tbody>
</table>

To fully explore the scope of this approach, a substrate with a powerful electron-withdrawing moiety such as nitro group was required. Utilising the same synthetic route as described above for the 4-nitro analogue failed. First, iodination of 4-nitroaniline under standard conditions and elevated temperature and extended reaction times did not afford any evidence for the formation of 2-iodo-4-nitroaniline (203g). Instead, iodination of commercially available 4-nitroaniline (202g) utilising the newly developed methodology reported by the Sutherland research group gave 2-iodo-4-nitroaniline (203g) in quantitative yield (entry 1, Table 18). The reaction involves the use of catalytic amounts of silver(I) triflimide to activate N-iodosuccinimide (NIS) for the electrophilic aromatic iodination of 4-nitroaniline (202g) via 210. Optimisation of this reaction showed that more concentrated reaction mixtures gave high yields and allowed lower catalyst loading (entries 2 and 3). The optimal conditions (0.2 M) with low catalyst loading (2.0 mol%)
afforded the desired product in a similar yield (99%), but the reaction required a longer time to reach 100% completion (entry 4). Scale-up of this transformation was also demonstrated with gram-scale synthesis of 203g (entry 3).

![Chemical reaction diagram]

Table 18: Silver(I) triflimide catalysed iodination of 4-nitroaniline (202g).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc. (M)</th>
<th>AgNTf₂ (mol%)</th>
<th>NIS (equiv.)</th>
<th>Time (h)</th>
<th>203g (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>7.5</td>
<td>1</td>
<td>1.5</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>2</td>
<td>1</td>
<td>1.5</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>2</td>
<td>1.1</td>
<td>4</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>2</td>
<td>1</td>
<td>24</td>
<td>99</td>
</tr>
</tbody>
</table>

Having efficient access to 2-iodo-4-nitroaniline (203g), it was then subjected to the same conditions of the Mizoroki-Heck reaction. This reaction led to the formation of undesired product 211 (Figure 18). Analysis of the ¹H NMR spectrum showed that the product 211 was formed as the sole compound. It was proposed that this occurred by conjugate addition of the amine followed by the Mizoroki-Heck reaction.
Figure 18. Formation of 211 as a result of an attempted Mizoroki-Heck reaction of nitro analogue 203g.

To confirm the order of events, a second attempt under the same conditions was carried out with the reaction being stopped after 1 hour (Figure 19). According to the $^1$H NMR spectrum of the crude reaction mixture, it was found that 44% of starting material was converted to the conjugate addition intermediate 212 after 1 hour. This showed that conjugate addition was definitely taking place before the Mizoroki-Heck reaction.
Figure 19. $^1$H NMR spectrum of an attempted Mizoroki-Heck reaction of the 4-nitro analogue 203g after 1 hour indicating a mixture of the starting material 203g and the undesired coupling product 212.
As a result of this unexpected outcome, another route for access to the 4-nitro-derived allylic alcohol was investigated. It was proposed that interchanging the order of steps between the Mizoroki-Heck reaction and the tosylation of 203g might prevent the amino group being involved in the coupling reaction with methyl acrylate. Tosylation of 2-iodo-4-nitroaniline (203g) using tosyl chloride was carried out at room temperature to give conversion of 1% of 203g (Table 19, entry 1). Raising the reaction temperature and increasing the amount of tosyl chloride (1.5 equivalents) led to conversion to the tosylated amine 213 and by-product 214 in 47% and 16%, respectively (entry 2). By elevating the reaction temperature (100 °C), the conversion to the product 213 decreased (entry 3). Due to these modest results, an alternative method was investigated.

![Chemical structure of 203g, 213, and 214](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>TsCl (equiv)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conversion of 203g (%)</th>
<th>Conversion to 213 (%)</th>
<th>Conversion to 214 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>rt</td>
<td>15</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>50</td>
<td>192</td>
<td>-</td>
<td>47</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>100</td>
<td>54</td>
<td>-</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.0</td>
<td>130</td>
<td>23</td>
<td>33</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 19: Tosylation of the nitro analogue 203g. <sup>a</sup>Pyridine (4.0 equiv.) was added and p-xylene was used as a solvent.
Due to the powerful electron-withdrawing effect of the nitro moiety, using a stronger base to activate the amino group was investigated. Kelly and McNeil reported easy access to protected aryl amines with the Boc-protecting group using lithium hexamethyldisilazide (LiHMDS) under mild conditions.\textsuperscript{192} A previous Sutherland group member used Kelly conditions to protect 4-iodo-2-nitroaniline in 60% isolated yield.\textsuperscript{193} Tosylation of 2-iodo-4-nitroaniline 203\textsubscript{g} using tosyl chloride under Kelly conditions was investigated (Table 20). Treatment of 203\textsubscript{g} with tosyl chloride (1 equiv) in the presence of LiHMDS (2 equiv) at room temperature led to just 2\% conversion of aryl amine 203\textsubscript{g} to the protected aryl amine 213 after 16 h (entry 1). By doubling the amounts of reagents and increasing the reaction time to 42 h led to a slight increase of conversion to the desired product (entry 2). Further increase of the amount of tosyl chloride (4 equiv) along with raising the reaction temperature to 50 °C led to the tosylated aniline 213 in moderate conversion (entry 3). Further addition of tosyl chloride did not show any improvement in the formation of 213 (entry 4). This method led to the formation of 213 without appearance of the by-product 214.

![Tosylation of the nitro analogue 203g using LiHMDS.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>TsCl (equiv)</th>
<th>LiHMDS (equiv)</th>
<th>Conc. (M)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conv. of 203g (%)</th>
<th>Conv. to 213 (%)</th>
<th>Conv. to 214 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0.10</td>
<td>0°C–rt</td>
<td>16</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>4</td>
<td>0.10</td>
<td>rt</td>
<td>42</td>
<td>4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>4</td>
<td>0.10</td>
<td>50</td>
<td>20</td>
<td>-</td>
<td>51</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>4</td>
<td>0.06</td>
<td>50</td>
<td>74</td>
<td>-</td>
<td>45</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 20:** Tosylation of the nitro analogue 203g using LiHMDS.

Having access to the tosylated aniline 213, the Mizoroki-Heck reaction was then investigated (Table 21). Coupling of iodoaniline 213 with methyl acrylate using palladium(II) acetate under the optimised conditions led to formation of \((E)-\alpha,\beta-\)
unsaturated methyl ester 207g in relatively low conversion. A higher catalyst loading (10 mol%) with prolonged reaction time was unsuccessful.

![Mizoroki-Heck reaction of 213](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(II) (mol%)</th>
<th>PPh₃ (mol%)</th>
<th>K₂CO₃ (equiv)</th>
<th>TBAB (mol%)</th>
<th>Time (h)</th>
<th>Conversion to 207g (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>10</td>
<td>2</td>
<td>25</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>20</td>
<td>4</td>
<td>50</td>
<td>48</td>
<td>10</td>
</tr>
</tbody>
</table>

**Table 21. Optimisation of the Mizoroki-Heck reaction of 213.**

Due to the unsatisfactory yields and the formation of by-products that are associated with the nitro analogue transformations, it was decided that using a different strategy should be investigated. Consequently, a different method was developed for the nitro analogue (Table 22). Initially, a nucleophilic aromatic substitution reaction with p-toluenesulfonamide (1 equiv) in the presence of potassium carbonate was carried out with commercially available 2-chloro-5-nitrobenzaldehyde (215) and afforded substituted aminobenzaldehyde 216 in 70% yield after 18 h (entry 1). Increasing the amount of p-toluenesulfonamide (2 equiv) decreased the reaction time to 2 h and gave 216 in 86% isolated yield (entry 2).

![Nucleophilic aromatic substitution reaction of 215](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>TsNH₂ (equiv)</th>
<th>K₂CO₃ (equiv)</th>
<th>Time (h)</th>
<th>216 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>18</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>86</td>
</tr>
</tbody>
</table>

**Table 22. Nucleophilic aromatic substitution reaction of 215.**
In the next stage, a Horner–Wadsworth–Emmons (HWE) reaction with triethyl phosphonoacetate (TEPA) under Masamune–Roush conditions was carried out to transform the resulting aldehyde 216 into the corresponding (E)-α,β-unsaturated ester 217 in 99% yield (Scheme 61). This gave only the E-alkene. Utilising the same conditions for allylation as before afforded 218 in 55% yield. This moderate isolated yield was due to the decreased nucleophilicity of this compound compared to other analogues in this series. Finally, DIBAL-H reduction of 208 under standard conditions led to synthesis of nitro analogue 209g in high isolated yield.

Scheme 61. Synthesis of allylic alcohol 209g.

2.2.3 Optimisation of One-Pot Multi-Reaction Process for 1H-Benzazepines

Having performed the first part of this study, the synthesis of cinnamyl alcohols, it was proposed that the use of the previously optimised conditions for the 1-benzoxepines might allow access to 5-amino-substituted 2,3-dihydro-1H-benzazepines. Initially, the most simple cinnamyl alcohol 203a was investigated for the one-pot reaction process (Table 23). The thermal Overman rearrangement required 140 °C and 48 h for reaction completion. With regard to the RCM step, it required Grubbs second-generation catalyst 70 (10 mol%), 50 °C and 48 h to complete conversion of 220a to 221a. These conditions gave the metathesis
product 221a in 69% isolated yield over three steps (entry 1). Increasing the temperature of the Overman rearrangement step to 160 °C reduced the reaction time to 24 h and afforded the product 221a in 70% from allylic alcohol 209a (entry 2). Consequently, it was proposed that further investigation of the RCM reaction might lead to increased isolated yield. As discussed before, change of the reaction concentration and decreasing the catalyst amount were investigated. Doubling the concentration of the RCM step from 0.008 M to 0.016 M and using Grubbs second-generation catalyst 70 (2.5 mol%) at a higher temperature (60 °C) afforded the product 211a in a lower yield of 58% (entry 3). Attempting the one-pot process by increasing the Grubbs second-generation catalyst loading (5 mol%) reduced the RCM step time to 18 h and afforded 221a in 81% isolated yield from allylic alcohol 209a (entry 4).

![Chemical Structures]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Overman rearrangement</th>
<th>Conc. (M)</th>
<th>RCM reaction</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>140 °C , 48 h</td>
<td>0.008</td>
<td>Grubbs II (10 mol%), 50 °C, 48 h</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>160 °C, 24 h</td>
<td>0.008</td>
<td>Grubbs II (10 mol%), 50 °C, 48 h</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>160 °C, 24 h</td>
<td>0.016</td>
<td>Grubbs II (2.5 mol%), 60 °C, 48 h</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>160 °C, 24 h</td>
<td>0.016</td>
<td>Grubbs II (5 mol%), 60 °C, 18 h</td>
<td>81</td>
</tr>
</tbody>
</table>

Table 23. Optimisation of the one-pot synthesis of 1H-benzazepine 221a.
2.2.4 Synthesis of 5-Amino-Substituted 2,5-Dihydro-1H-benzazepines

Having established the optimal conditions for the one-pot synthesis of 1H-benzazepines, the scope of this process was explored. The optimal conditions were used for the prepared (E)-(2-allylamino)cinnamyl alcohols 209b–g (Figure 20). The one-pot reaction process for all substituents of allylic alcohols afforded the 5-amino-2,5-dihydro-1H-benzazepines 221b–g in high yields over three step. Only analogue 209g with a powerful electron-withdrawing group required prolonged reaction times for the Overman rearrangement (43 h) and the RCM reaction (31 h) steps. Under these conditions the corresponding 1H-benzazepine 221g was obtained in 49% isolated yield.
Figure 20. Synthesis of 5-amino-2,5-dihydro-1H-benzazepines 221b–g.
2.2.5 Formal Synthesis of Mozavaptan

The importance and generality of this developed methodology was demonstrated with easy access to 5-amino-2,3,4,5-tetrahydro-1H-benzoazepine 228 (Scheme 59), an advanced intermediate of the pharmaceutical active substance, mozavaptan (200) (Figure 17). For the synthesis of this intermediate 228, a number of transformations were studied. Initially, hydrogenation of 221a under standard conditions was investigated (Table 24). Hydrogenation of 221a using palladium on charcoal (20%) under an atmosphere of hydrogen at room temperature led to low conversion (10%) to 223 (entry 1). Attempted hydrogenation with higher catalyst loading (40%) and prolonged reaction times showed high conversion to the sole product 223 (entries 2 and 3). Further investigation using 50% of the catalyst loading at 55 °C led to conversion to 223 and 224 in 36% and 28%, respectively, after 72 h.

![Diagram of the reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd/C (%)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conversion 222 (%)</th>
<th>Conversion 223 (%)</th>
<th>Conversion 224 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>rt</td>
<td>21</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>50</td>
<td>43</td>
<td>0</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>50</td>
<td>70</td>
<td>0</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>55</td>
<td>72</td>
<td>0</td>
<td>36</td>
<td>28</td>
</tr>
</tbody>
</table>

Table 24. Hydrogenation of 221a using standard conditions.
On the other hand, reduction of \(221\text{a}\) using \(p\)-toluenesulfonyl hydrazide (TsNHNH\(_2\)) in the presence of potassium acetate was investigated (Table 25).\(^{175}\) As with the previous method, these conditions led to hydrogenation of the alkene in addition to reduction of the trichloroacetyl moiety to form two compounds \(222\) and \(223\) (entry 1). Reduction of \(221\text{a}\) using TsNHNH\(_2\) at 70 °C led to a 49% conversion to \(222\) (entry 2). In contrast to the previous method, formation of the by-product \(224\) was not observed.

![Chemical structure](image)

Table 25. Hydrogenation of \(211\text{a}\) using TsNHNH\(_2\).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(222) (%)</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>49</td>
</tr>
</tbody>
</table>

Due to the formation of dichloro- and monochloroacetamide by-products during attempted hydrogenation of \(221\text{a}\) under standard conditions and using \(p\)-toluenesulfonyl hydrazide, it was proposed that exchanging the protecting group was required. This was necessary to avoid the formation of side products during the hydrogenation step which would affect the isolated yield. Consequently, the trichloroacetamide was replaced with the Boc-protecting group using standard conditions developed by previous Sutherland group members via a one-pot approach.\(^{48,159}\) Initially, removal of the trichloroacetyl protecting groups under basic conditions was investigated (Table 26). Treatment of \(221\text{a}\) with sodium hydroxide (2M) at room temperature for 6 h did not lead to the removal of the trichloroacetyl protecting group (entry 1). Addition of methanol to the reaction mixture and raising the reaction temperature to 60 °C led to removal of the
protecting group. Then, addition of di-tert-butyl dicarbonate (Boc₂O) to the reaction mixture at room temperature gave 226 in 51% isolated yield after 24 h (entry 2). Further attempts at the conversion of 221a to the Boc-protected analogue 226 via the one-pot approach using a mixture of sodium hydroxide and methanol (5:3) at 60 °C for 18 h followed by reprotection by the addition of di-tert-butyl dicarbonate (Boc₂O) at room temperature gave 226 in 73% isolated yield after 24 h (entry 4).

![Chemical structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>NaOH:MeOH</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>225 Conversion (%)</th>
<th>226 Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:0</td>
<td>rt</td>
<td>6</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>5:1</td>
<td>60</td>
<td>24</td>
<td>100</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>1:1</td>
<td>60</td>
<td>18</td>
<td>100</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>5:3</td>
<td>60</td>
<td>18</td>
<td>100</td>
<td>73</td>
</tr>
</tbody>
</table>

Table 26. One-pot approach for the conversion of 221a to 226.

With success of exchanging the protecting group, hydrogenation of 226 using standard conditions under an atmosphere of hydrogen was investigated (Table 27). Based on the observations of the hydrogenation of 1-benzoexepine 185c and 1H-benzazepine 221a, hydrogenation of 1H-benzazepine 226 using palladium on charcoal (20%) for the formation of 227 at room temperature failed (entry 1). Changing the conditions to a higher catalyst loading (50%) and raising the reaction temperature to 50 °C led to completion of the reaction after 24 h (entry 2). Increasing the reaction temperature to 60 °C with a 30% catalyst loading also led to complete conversion of 226 (entry 3). Changing form ethyl acetate to methanol was less efficient (entries 4 and 5).
Table 27. Hydrogenation of the Boc-protected 1H-benzazepine 226.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd/C (%)</th>
<th>Solvent (0.02 M)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>EtOAc</td>
<td>rt</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>EtOAc</td>
<td>50</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>EtOAc</td>
<td>60</td>
<td>17</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>MeOH</td>
<td>50</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>MeOH</td>
<td>50</td>
<td>72</td>
<td>50</td>
</tr>
</tbody>
</table>

Removal of the tosyl protecting group of 227 was also investigated (Scheme 62). Treatment of 227 with magnesium under reflux gave the corresponding 1H-benzazepine 228 in 78% isolated yield after 4 h.


Having access to the optimal conditions for the hydrogenation and the deprotection of the tosyl protecting group, further attempts at both reactions were performed (Scheme 63). Hydrogenation of 226 using standard conditions under an atmosphere of hydrogen followed by removal of the tosylate group with magnesium under reflux without purification of the intermediate led to isolation of 228 in 88% over two steps. This approach allows access to the hyponatremia late-stage intermediate 228 efficiently in 46% overall yield over eleven steps, compared to the conventional methods which require intermediate separation in each step.
The Matsubara research group reported the synthesis of mozavaptan (200) from the intermediate 228 via three steps (Scheme 64). Benzoylation of the Boc-protected 1H-benzazepine 228 with 4-(2-methylbenzoylamino)benzoyl chloride (229) followed by removal of the Boc-protecting group and reductive amination of the resulting free amine with formaldehyde.

2.2.6 Conclusions

In conclusion, a new one-pot thermal Overman rearrangement and ring-closing metathesis process was utilised for the synthesis of a library of 5-amino-2,5-dihydro-1H-benzazepines from allylic trichloroacetimidates. The allylic alcohols were rapidly and efficiently prepared from anilines in five subsequent reactions. A strong electron-withdrawing group analogue was efficiently prepared under mild conditions. The generality of this approach was utilised for the late-stage synthesis of mozavaptan.
2.3 Synthesis of 2H-Chromenes

2.3.1 Introduction

2H-Chromenes which are also known as 2H-benzopyrans are common heterocycles found as natural products and synthetic compounds. They display a variety of pharmaceutical and biological activities.\textsuperscript{195} The natural product, α-monomethyl 2H-chromene 230, was isolated from the leaf essential oil of \textit{Calyptranthes tricona} (Figure 21).\textsuperscript{196} The natural product, cannabichromene (231) which has analgesic, anti-inflammatory, and antiviral properties is another example of a natural product of 2H-chromenes.\textsuperscript{197} Synthetic 2H-chromenes also play an important role in medicinal and pharmaceutical applications such as iclaprim (232), an antibiotic used for skin infections.\textsuperscript{198} Daurichromenic acid (233) which is a highly potent anti-HIV agent represents a synthetic 2H-chromene.\textsuperscript{199}

Due to the biological and medicinal significance of 2H-chromenes, a range of methods were developed for the construction of these heterocycles. The most common methods for the synthesis of 2H-chromenes are thermal or metal-catalysed cyclisation or ring-closing metathesis reactions.\textsuperscript{200,201} Thermal intramolecular electrophilic hydroarylation via a Claisen rearrangement has been used for the synthesis of 2H-chromenes.\textsuperscript{200} This \textit{6-endo-dig} cycloisomerisation approach can also be catalysed using transitional metals such as gold(I), gold(III), platinum(IV), indium(III), mercury(II), and palladium(II).\textsuperscript{202–208} In addition, the
construction of 3,4-disubstituted $2H$-chromenes under metal-free conditions, using reagents such as $I_2$, ICl and PhSeBr, can be performed via electrophilic cyclisation of substituted propargylic aryl ethers.\textsuperscript{209,210}

2.3.2 Cycloisomerisation

Cycloisomerisation or electrophilic hydroarylation, is a rearrangement of aryl-tethered alkynes to afford a $6$-endo-dig compound.\textsuperscript{202,203,211} In particular, the gold-catalysed cycloisomerisation of substituted aryl propargyl ethers will give substituted $2H$-chromenes. The proposed mechanism of the hydroarylation reaction is initiated by addition of a gold(I) catalyst (Scheme 65). As a result of the high aurophilicity of the alkyne moiety of 234, the aryl propargyl ether is activated by gold(I) metal to form the auropropargyl complex 235. The high electrophilicity of Au(I) species to the electronic cloud of the $\pi$-system of the alkyne supports the endo-selective hydroarylation to form the Wheland-type intermediate, arenium ion, 236.\textsuperscript{202,203,211} Release of the gold(I) catalyst affords $2H$-chromene 237.

Scheme 65. Mechanism of gold(I)-catalysed cycloisomerisation reaction.
2.3.3 Aims

Due to the importance of 2H-chromenes, the aim of this project was to develop a novel one-pot Overman rearrangement and gold(I)-catalysed hydroarylation reaction process. This project was based on the previously developed one-pot multi-step multi-reaction processes in the Sutherland group.\textsuperscript{122,150–160} This methodology would allow the synthesis of a number of allylic amine derived 2H-chromenes (Scheme 66). This proposed approach would begin with the preparation of allylic alcohols from commercially available salicylaldehydes. In the next stage, allylic alcohols would be subjected to a one-pot Overman rearrangement and hydroarylation reaction processes to form the 2H-chromenes. Once this chemistry was developed, it was proposed that this strategy would be then used to access the corresponding coumarin analogues via chemoselective allylic oxidation.

Scheme 66: Proposed synthesis of 2H-chromenes and coumarins.
2.3.4 Synthesis of Allylic Alcohols

As discussed before for the synthesis of 1-benzoepines (Section 2.1), the same standard conditions for the synthesis of allylic alcohols were used.\(^{173,174}\) Alkylation of commercially available salicylaldehydes \(180a,h–k\) using propargyl bromide in the presence of potassium carbonate gave \(O\)-propargyl benzaldehydes \(238a–e\) in essentially quantitative yields (Figure 22).\(^{212}\)

![Propargylation reaction](image)

**Figure 22:** Allylation of 2-hydroxybenzaldehydes \(238a–e\).

Next, Horner-Wadsworth-Emmons (HWE) reaction with triethyl phosphonoacetate (TEPA) under mild Masamune-Roush conditions was carried out to form the corresponding \((E)\)-\(\alpha,\beta\)-unsaturated esters \(239a–e\) in quantitative yields (Table 28).\(^{162}\) As observed from the \(^1H\) NMR spectra of the products, this method gave only the \(E\)-alkene. DIBAL-H reduction of the resulting esters under standard conditions gave cinnamyl alcohols \(240a–e\) in high isolated yields. Overall, conversion of commercially available starting materials to the key substrates (allylic alcohols) was easily and rapidly performed under mild conditions. Consequently, all investigated analogues containing either electron-donating and electron-withdrawing groups were efficiently prepared using this synthetic approach.
Table 28: Synthesis of O-propargyl cinnamyl alcohols 240a–e.

<table>
<thead>
<tr>
<th>Entry</th>
<th>238</th>
<th>239 (%)</th>
<th>240 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = H, 238a</td>
<td>239a (quant.)</td>
<td>240a (93)</td>
</tr>
<tr>
<td>2</td>
<td>R = 5-OME, 238b</td>
<td>239b (99)</td>
<td>240b (89)</td>
</tr>
<tr>
<td>3</td>
<td>R = 4-OME, 238c</td>
<td>239c (quant.)</td>
<td>240c (92)</td>
</tr>
<tr>
<td>4</td>
<td>R = 5-Cl, 238d</td>
<td>239d (quant.)</td>
<td>240d (93)</td>
</tr>
<tr>
<td>5</td>
<td>R = 5-NO₂, 238e</td>
<td>239e (98)</td>
<td>240e (96)</td>
</tr>
</tbody>
</table>

2.3.5 Investigation of the Key Steps of the One-Pot Process

Synthesis of 2H-chromenes required optimisation of the Overman rearrangement and hydroarylation steps, separately. First, thermal or metal-catalysed Overman rearrangements would be investigated to establish the optimal conditions. It was proposed that investigation of thermal or metal-mediated hydroarylation would give a clear insight for the best conditions for the one-pot approach. Finally, combination of the developed optimal conditions of both steps would allow the one-pot process to be developed and access to the 2H-chromenes.

2.3.5.1 Optimisation of the Overman Rearrangement

With the key substrates for the one-pot process in hand, optimal conditions of the Overman rearrangement were investigated (Scheme 67). Initially, cinnamyl alcohol 240a was treated with trichloroacetonitrile and a catalytic amount of DBU to form the allylic trichloroacetimidate intermediate. The thermal Overman rearrangement of the resulting intermediate under standard conditions (140 °C, 24 h) afforded the corresponding allylic trichloroacetamide 241a in 68% isolated yield over the two steps. Decreasing the Overman rearrangement step time to 18 h afforded the
Overman product 241a in 97% yield. This shorter reaction time minimises any decomposition leading to a higher yield.

Scheme 67: Overman rearrangement for the synthesis of 241a.

Having successfully accessed the optimal conditions of the Overman rearrangement, the scope of this transformation was explored (Figure 23). Thus, cinnamyl alcohols 240b–e were treated with trichloroacetonitrile and a catalytic amount of DBU to form the allylic trichloroacetimidate. The thermal Overman rearrangement of the resulting intermediates under the optimised conditions afforded the corresponding allylic trichloroacetamides 241b–e in high yields over the two steps. While analogues 240b and 240c required 18 h to proceed to completion for the Overman rearrangement step, the reaction times for electron-deficient analogues 240d and 240e required 48 h and 72 h, respectively.
2.3.5.2 Optimisation of the Hydroarylation Reaction

During the investigation of the thermal Overman rearrangement step, analysis of the $^1$H NMR spectra of the crude reaction mixtures indicated that low amounts (<10%) of the 2H-chromenes were formed. Consequently, optimal conditions using a thermal hydroarylation reaction were first investigated for the synthesis of 2H-chromenes (Table 29). Initially, a thermal 6-endo-dig cycloisomerisation of analogue 241a was investigated at a higher temperature of 160 °C. Analysis of the $^1$H NMR spectra of the crude reaction mixture indicated that 35% of the precursor 241a converted to product 242a after four days (entry 1). Increasing the reaction temperature up to 180 °C with an extended reaction time of five days led to a slight increase in the conversion to 50% (entry 2). Alternatively, microwave heating of the reaction mixture at 180 °C with significantly shorter reaction time (3 h) showed
higher conversion (66%) (entry 3). As a result of this, further microwave heating of analogue 241a at 200 °C for 2 h gave a high conversion of 91%, but only a 34% isolated yield of 242a (entry 4). This low isolated yield is likely due to decomposition caused by the high temperature. It was thought that changing to milder conditions such as metal-catalysed cycloisomerisation would give higher yields. Thus, gold(I)-catalysed hydroarylation reaction of 241a was next investigated. Chloro(triphenylphosphine)gold(I) (Ph₃PAuCl) (243) (2.5 mol%) which was activated by silver(I) hexafluoroantimonate (AgSbF₆) (244) (2.5 mol%) at 80 °C was used for the cyclisation of 241a to 242a. This gave 242a with a conversion of 85% after 4 h (entry 5). The more active catalyst, (triphenylphosphine)gold(I) triflimide (Ph₃PAuNTf₂) catalyst (245) was then investigated. Reaction of 241a with the active gold(I) catalyst 245 (2.5 mol%) pushed the reaction to completion in four hours under the same conditions to afford 100% conversion of the product (entry 6). Additionally, analysis of the ¹H NMR spectrum of the crude reaction mixture showed that the gold(I)-catalysed cycloisomerisation was a clean transformation and gave exclusive formation of the 6-endo-dig product 242a.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>reaction conditions</th>
<th>time (h)</th>
<th>conversion (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>160 °C</td>
<td>96</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>180 °C</td>
<td>120</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>180 °C (MW)</td>
<td>3</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>200 °C (MW)</td>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>Ph₃PAuCl 243 (2.5 mol%), and AgSbF₆ 244 (2.5 mol%), 80 °C</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>Ph₃PAuNTf₂ 245 (2.5 mol%), 80 °C</td>
<td>4</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 29. Optimisation of the hydroarylation reaction of 241a to 242a.

<sup>a</sup>Conversions were measured using ¹H NMR spectroscopy.
2.3.6 Stepwise Gold(I)-Catalysed Synthesis of 2H-Chromenes

Having the optimal conditions of the cycloisomerisation reaction developed, the scope of this method was explored (Figure 24). The allylic trichloroacetamides 241a–e were treated with the active gold(I) catalyst 245 (2.5 mol%) at 80 °C to give after 4 h, the corresponding 2H-chromenes 242a–d in essentially quantitative yields. Attempted hydroarylation using gram-scale quantities (2–3 g) of analogue 241a under the same reaction time and temperature, allowed a lower catalyst loading (1 mol%) and gave 2H-chromene 242a in quantitative yield.

![Chemical structures and reaction scheme](image)

Figure 24. Stepwise gold(I)-catalysed synthesis of 2H-chromenes 242a–e.
Nitro-analogue 241e, afforded the corresponding 2H-chromene 242e in 66% isolated yield under the same conditions. Interestingly, analysis of the $^1$H NMR spectrum of the crude reaction mixture showed the presence of a number of side products including 2-methylbenzofuran 242f (<10%). This minor by-product was likely formed via a 5-exo-trig cycloisomerisation reaction through an ortho-allenyl phenolate intermediate 249 (Scheme 68). According to previous reports, the propargyl moiety of an aryl substance with a strongly electron-withdrawing group can undergo this alternative reaction route through the Au(I)-catalysed hydroarylation reaction to form 2-methylfurans.$^{202,203,211}$

Scheme 68. Cycloisomerisation mechanism of 241e to form 242f.
2.3.7 Optimisation of One-Pot Synthesis of 2H-Chromenes

As a consequence of the positive results, a combination of the thermal Overman rearrangement and gold(I)-catalysed hydroarylation reaction for the preparation of 2H-chromenes 242a–e in a one-pot reaction process was next investigated (Scheme 69). The one-pot process of analogues 240a–e under the optimised conditions gave none of the corresponding 2H-chromenes 242a–e. While the Overman rearrangements were successful, the gold(I)-catalysed hydroarylations gave none of the 2H-chromenes. It was proposed that this was because the Ph₃PAuNTf₂ catalyst 245 was not compatible with the conditions of the Overman rearrangement. To support this view, a combination of Ph₃PAuCl 243 and silver(I) triflimide (AgNTf₂) catalyst 250, which forms Ph₃PAuNTf₂ 245 in situ, was used for the cycloisomerisation step of the one-pot synthesis of 2H-chromene 242a. This also did not show any formation of 2H-chromene 242a. Alternatively, it was decided that a less active gold(I) complex might be more compatible with the Overman step. Therefore, the combination of Ph₃PAuCl 243 with AgSbF₆ 244 for the hydroarylation step within the one-pot process was investigated. Using this catalytic system for the second step of the one-pot process gave 2H-chromene 242a in 80% overall yield.

Scheme 69. One-pot synthesis of 2H-chromene 242a.
2.3.8 One-Pot Gold(I)-Catalysed Synthesis of 2H-Chromenes

The one-pot process was subjected to further optimisation for the other substrates. It was found that the optimal conditions for the hydroarylation step required higher catalyst loading (7.5 mol% for each) and an extended reaction time of 48 h (Figure 25). The one-pot reaction process under the optimal conditions gave high yields of 2H-chromenes 242b–e over three steps. For nitro-analogue 240e, the Overman rearrangement was complete after 72 h and the hydroarylation step required 65 h and a catalyst loading of 10 mol% of both Ph₃PAuCl 243 and AgSbF₅ 244 to generate 2H-chromene 242e in 54% yield over three steps. As with the Ph₃PAuNTf₂ catalysed hydroarylation, a number of minor by-products were also observed from the one-pot process.
Figure 25. One-pot synthesis of 2H-chromenes 242a–e.
2.3.9 Optimisation of the Pd(II)-Catalysed Overman Rearrangement

The next aim of this project was to develop a one-pot palladium(II)-catalysed Overman rearrangement and gold(I)-catalysed cycloisomerisation process for the synthesis of 2H-chromenes. Thus, optimal conditions for the Pd(II)-catalysed Overman rearrangement step were investigated (Table 30). Treatment of allylic trichloroacetimidate intermediate with bis(acetonitrile)palladium(II) chloride catalyst (10 mol%) at room temperature gave a conversion of 50% to allylic trichloroacetamide 241a (entry 1). Raising the reaction temperature to 40 °C led to an increase in the formation of the desired product (entry 2). Use of bis(acetonitrile)palladium(II) chloride catalyst at 60 °C or lower catalyst loading (5 mol%) but higher temperature (80 °C) afforded a quantitative conversion to allylic trichloroacetamide 241a (entries 3 and 4). Analysis of the 1H NMR spectrum of the crude reaction mixture of the Overman rearrangement (at 80 °C) in the absence of palladium(II) catalyst showed no formation of the product 241a (entry 5). Thus, the catalyst is responsible for the transformation at 80 °C.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Pd(II) (mol%)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>22</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>26</td>
<td>10</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>24</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>24</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 30: Optimisation of Pd(II)-catalysed Overman rearrangement of 240a.
2.3.10 Optimisation of the One-Pot Pd(II)-Catalysed Overman Rearrangement and Gold(I)-Catalysed Hydroarylation Process

The next stage of investigation was the development of the one-pot, two catalyst process for the synthesis of 2H-chromenes. Initially, the Pd(MeCN)$_2$Cl$_2$ catalyst was used for the investigation of the Overman rearrangement within the one-pot process (Table 31). It was found that this step required 66 h to go to completion in dichloromethane at 40 °C and gave, after the hydroarylation step, 33% isolated yield (entry 1). Changing the solvent to toluene and using the optimised temperature (80 °C), the Overman rearrangement step was complete in 16 h and the 2H-chromene 242a was isolated after the hydroarylation step in 56% yield (entry 2). As a palladium(II)-catalysed Overman rearrangement as part of a one-pot process for the synthesis of 2H-chromene 242a was not as efficient as the one-pot process using a thermal rearrangement, optimisation using Pd(II)-catalysed was not investigated further.

![Reaction scheme showing the conversion of 240a to 241a](image_url)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>40</td>
<td>66</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>80</td>
<td>16</td>
<td>56</td>
</tr>
</tbody>
</table>

Table 31. Optimisation of one-pot process using Pd(II)-catalysed Overman rearrangement.
2.3.11 Chemoselective Oxidation of 2H-Chromenes to Coumarins

Coumarins are found in a variety of natural products. The importance of these compounds has led to the development of various strategies for their construction.\(^{213-217}\) However, there are not many reported methods for the synthesis of coumarins from 2H-chromenes.\(^{218-221}\) Therefore, the next aim of this project was to develop an effective method to access coumarins from the 2H-chromenes using a chemoselective allylic oxidation (Table 32). First, the chemoselective allylic oxidation of 2H-chromene 242a using tert-butyl hydroperoxide (tBuOOH) afforded the corresponding coumarin 251a in 34% yield (entry 1). Next, the use of pyridinium dichromate (PDC) to promote the chemoselective allylic oxidation of 2H-chromene 242a at room temperature was investigated. These conditions led to the formation of coumarin 251a in 58% isolated yield (entry 2). The optimal conditions were found using a reaction time of 6 days which afforded coumarin 251a in 65% isolated yield (entry 3). Increasing the reaction temperature was also investigated to reduce the reaction time; however, this led to a decrease in yield (entry 4).

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tBuOOH</td>
<td>benzene</td>
<td>40</td>
<td>24</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>PDC</td>
<td>CH(_2)Cl(_2)</td>
<td>rt</td>
<td>13</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>PDC</td>
<td>CH(_2)Cl(_2)</td>
<td>rt</td>
<td>144</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>PDC</td>
<td>CH(_2)Cl(_2)</td>
<td>50</td>
<td>100</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 32. Optimisation for the chemoselective allylic oxidation of 242a.
In work performed by Alex Harkiss in the group, some of the other $2H$-chromenes 242b, 242d, and 242e were also converted to the corresponding coumarins under similar conditions and in good yields (Figure 26).

![Chemical Structures]

**Figure 26.** Formation of $2H$-chromenes 251b–d via PDC oxidation.

### 2.3.12 Conclusions

In summary, a novel one-pot Overman rearrangement and gold(I)-catalysed hydroarylation reaction process was used for the synthesis of a number of allylic amine derived $2H$-chromenes from allylic trichloroacetimidates in very high yields. The precursor allylic alcohols were obtained rapidly and in three highly efficient transformations from salicylaldehydes. Mild chemoselective allylic oxidation of the $2H$-chromenes allowed the preparation of novel coumarins.
2.3.13 Synthesis of 6-Amino-Substituted 6,11-Dihydrodibenz[\(b,e\)]oxepines

2.3.13.1 Previous Work within the Sutherland Group

Having shown that 2-propargyloxy cinnamyl alcohols could be used in one-pot multi-bond forming reactions, it was proposed that these compounds could be used in other one-pot processes. Previous work in the Sutherland group had discovered a one-pot multi-bond forming, four-step process for the construction of drug-like polycyclic scaffolds.\textsuperscript{158} This one-pot process utilised alkyne derived allylic alcohols with an Overman rearrangement, ring-closing enyne metathesis and a hydrogen bonding directed Diels-Alder reaction (Scheme 70).

Further application of this methodology led to the synthesis of heteroaromatic structures such as amino-substituted indanes and tetralines \textit{via} consecutive two-pot multi-bond forming processes (Figure 27).\textsuperscript{222} First, a one-pot process involving a thermal Overman rearrangement and ruthenium(II)-catalysed ring-closing enyne metathesis led to the formation of a number of cyclic dienes from various allylic alcohols. In the second one-pot reaction process, a highly regioselective Diels-Alder reaction with alkynes, quinones or nitriles followed by an oxidation reaction gave a diverse library of the amino-substituted indanes and tetralines.
Figure 27. Consecutive multi-bond forming processes.

2.3.13.2 Aims

The aim of this project was to develop a new one-pot, four-step reaction process for the preparation of 6-amino-substituted 6,11-dihydrodibenzo[b,e]oxepines. Dibenzo[b,e]oxepines are pharmacologically interesting polycyclic compounds. For example, Melloni and co-workers reported the synthesis of a number of tricyclic benzoepines. These compounds displayed anti-depressant activity. The study showed that tricyclic derivatives which were attached to an azetidine moiety were the most effective structure of these synthesised polycyclic systems and in particular, that bearing a basic group in position three of the azetidine ring (Figure 28).
It was proposed that the previously prepared allylic alcohols 240a–e (Section 2.3.4) could be used for the synthesis of tricyclic benzoxepines (Scheme 71). The one-pot multi-reaction process of a thermal Overman rearrangement followed by a ruthenium(II)-catalysed ring-closing enyne metathesis and Diels-Alder reaction would be investigated. This approach would allow the formation of a small library of 6-amino-substituted 6,11-dihydrodibenz[b,e]oxepines that could then be utilised for the preparation of pharmacologically active compounds such as anti-depressant agent 252 (Figure 28).

Scheme 71. Proposed synthesis of tricyclic systems 254a–e.
2.3.13.3 Investigation of the One-Pot Multi-Reaction Process

2.3.13.3.1 Optimisation of Ring-Closing Enyne Metathesis (RCEYM) Step

The allylic alcohols 240a–e that were required for the one-pot reaction process were previously prepared and transformed to the enyne products 241b–e via the formation of the allylic trichloroacetimidate in high yields (Figure 23). The optimal conditions of the ring-closing enyne metathesis reaction were established by a previous group member (Ewen Calder) who showed that the RCEYM reaction could be catalysed by Grubbs first-generation catalyst (10 mol%) at 50 °C. Using these preliminary results, the ring-closing enyne metathesis (RCEYM) for the conversion of enyne 241c to diene 253 was then investigated (Table 33). Initially, enyne product 241c was catalysed by Grubbs first-generation catalyst (10 mol%) at 50 °C and led to 40% conversion to the corresponding diene 253 after 9 h (entry 1). Further investigation showed that a higher catalyst loading (15 mol%) allowed preparation of 253 in 17% isolated yield after a reaction time of 30 h (entry 2). Using the optimal catalyst loading (10 mol%) with a longer reaction time gave a similar isolated yield (entry 3). Due to time limitations, optimisation and the full scope of this process was not investigated.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Grubbs I (mol%)</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>9</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>30</td>
<td>48</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>72</td>
<td>-</td>
<td>18</td>
</tr>
</tbody>
</table>

Table 33. Optimisation of the RCEYM reaction of 253.
2.3.13.3.2 Optimisation of the Diels-Alder Reaction

A preliminary study was conducted to investigate whether diene 253 would undergo an amide directed Diels-Alder reaction with \(N\)-phenylmaleimide to give the adduct as a major diastereomer (Scheme 72). Reaction at 50 °C and for 24 hours gave tricyclic benzoxepine 254 in 63% as a single diastereomer.

Scheme 72: Synthesis of polycyclic compound 254.

Again due to time restrictions, full analysis of the relative stereochemistry was not performed. However, based on previous work,\textsuperscript{156} it is likely the Diels-Alder reaction proceeds via a hydrogen bond directed \textit{endo}-transition state leading to diastereomer 254 which has \textit{syn}-hydrogen atoms at C-6, C-6a, C-6b and C-9a. Future work will fully investigate the enyne metathesis and Diels-Alder reactions and hopefully lead to a one-pot synthesis of the tricyclic benzoxepines.
3.0 Future Work

3.1 Synthesis of 11-Amino-Substituted 5,11-Dihydro-1-benzoxepino, benzazepino, and benzthiapino[4,3-b]pyridines

Wolin and co-workers reported the synthesis of tricyclic systems (Figure 29). These compounds have displayed inhibition of the enzyme farnesyl-protein transferase (FPT). These pharmaceutical structures can be used for inhibiting the abnormal growth of cells and for inhibiting proliferative diseases.

\[
\text{Figure 29. Structure of FPT-inhibitors.}
\]

Due to the pharmaceutical importance of these compounds, future work building on the research developed in this PhD would optimise the one-pot multi-step reactions for their synthesis. The aim of future work would be focused on the synthesis of 11-amino-substituted 5,11-dihydro-1-benzoxepino, benzazepino, and benzthiapino[4,3-b]pyridines. This proposed approach would begin with the preparation of a diverse series of allylic alcohols from commercially available anilines, phenols, and thiophenols (Scheme 73). In the next stage, the corresponding allylic alcohols would be subjected to one-pot Overman rearrangement, ring-closing enyne metathesis and Diels-Alder reaction processes to form the tricyclic systems. Once these approaches were developed, it was proposed that this strategy would be then used to access a number of Ras-FPT inhibitors (Figure 30).
These tricyclic systems can be then used for the synthesis of Ras-FPT inhibitors 258. Decarboxylation of 255 under Larrosa conditions followed by removal of the trichloroacetyl group of 256 under standard conditions would lead to the formation of the free amine derived heterocycles 257 (Scheme 74). Treatment of 257 with bis(2-chloroethyl)amine hydrochloride under standard condition would give the FPT inhibitors 258.
3.2 Coumarin Derived α-Amino Acids

Coumarins (2H-chromen-2-ones) are found in natural product systems and they display biological and pharmaceutical activities.\cite{216,217} One outstanding aspect of coumarins and their derivatives is fluorescence. Recently, this physical property has been widely used for the monitoring of biological systems. Some natural and synthetic coumarins showed useful optical imaging applications.\cite{228,229} Coumarin motifs linked to α-amino acids, for example, constitutes one of the coumarin classes that have showed potent application as fluorescent probes in various bioscience research areas such as medicine, molecular and cellular biology, biotechnology, chemical biology and biophysics. These fluorescent compounds contributed to the development of medical and biomolecular science and their relevant research areas.\cite{230} As a consequence of their promising significance, coumarin-based α-amino acids have attracted the attention of biomolecular science researchers. A number of developed methods for the design and synthesis of coumarins and their derivatives such as coumarin α-amino acids have been reported.\cite{230–232} These have been used in various applications such as coumarin-based α-amino acid 259 which was used to mimic phosphotyrosine and showed fluorescence activity inside cells (Figure 30).\cite{233}

![Figure 30. Fluorescent coumarin-based α-amino acid 259.](image)

Due to the potential fluorescence activity and application of coumarins α-amino acids, future work based from this PhD programme would be to use the allylic amine derived coumarins for the synthesis of the corresponding α-amino acids (Scheme 75). Regioselective olefin oxidation of the coumarins with ruthenium(III) trichloride under Sharpless conditions to form coumarin-based α-amino acids
would be investigated. Then, acid mediated removal of the trichloroacetyl group would give the desired α-amino acids 260a–e.\textsuperscript{20,31,46,234} Fluorescence properties of these coumarin derived α-amino acids would then be analysed.

\textbf{Scheme 75. Proposed synthesis of coumarin-based α-amino acids 260a–e.}
4.0 Experimental

4.1 General Experimental

All reagents and starting materials were obtained from commercial sources and used as received. Dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV254) were used for thin layer chromatography and were visualised by staining with KMnO₄. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker DPX 400 or 500 spectrometer with chemical shift values in ppm relative to TMS (δ_H 0.00 and δ_C 0.0), or residual chloroform (δ_H 7.26 and δ_C 77.2) as standard. Proton and carbon assignments are based on two-dimensional COSY and DEPT experiments, respectively. Mass spectra were obtained using a JEOL JMS-700 spectrometer for EI and CI or Bruker Microtof-q for ESI. Infrared spectra were obtained neat using a Shimadzu IR Prestige-21 spectrometer. Melting points were determined on a Reichert platform melting point apparatus. Microwave reactions were conducted using a CEM Discover™ Synthesis Unit (CEM Corp., Matthews, NC) and performed in glass vessels (capacity 10 mL) sealed with a septum.
4-Chloro-2-hydroxybenzaldehyde (180c)<sup>235</sup>

Triethylamine (0.529 mL, 3.80 mmol) was added to a solution of 3-chlorophenol (0.128 g, 1.00 mmol) and magnesium chloride (0.143 g, 1.50 mmol) in acetonitrile (5 mL). The mixture was stirred for 0.5 h at room temperature. Paraformaldehyde (0.201 g, 6.70 mmol) was added. The reaction mixture was heated under reflux for 24 h. The mixture was cooled to room temperature, acidified with 2M aqueous hydrochloric acid (5 mL), extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuo. Purification by column chromatography (petroleum ether) afforded 4-chloro-2-hydroxybenzaldehyde (180c) (0.185 g, 39%) as white crystals. Spectroscopic data were consistent with the literature.<sup>235</sup> Mp 44–46 °C; R<sub>f</sub> 0.75 (50% diethyl ether/petroleum ether); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 7.01–7.05 (2H, m, 3-H and 5-H), 7.52 (1H, dd, J 8.0, 0.6 Hz, 6-H), 9.90 (1H, d, J 0.3 Hz, OH), 11.20 (1H, s, CHO); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 118.0 (CH), 119.3 (C), 120.7 (CH), 134.6 (CH), 143.3 (C), 162.3 (C), 195.5 (CH); m/z (Cl) 157 (MH<sup>+</sup>, 100%), 146 (5), 113 (24), 97 (13), 81 (22), 73 (76).

2-Allyloxybenzaldehyde (182a)<sup>173</sup>

 Allyl bromide (0.311 mL, 3.60 mmol) was added to a stirred solution of 2-hydroxybenzaldehyde (180a) (0.366 g, 3.00 mmol) and potassium carbonate (0.829 g, 6.00 mmol) in dimethylformamide (15 mL) and warmed to 70 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with 5% aqueous lithium chloride solution (20 mL) and extracted with diethyl ether (20 mL). The organic layer was washed with 5% aqueous lithium chloride solution (3 × 10 mL), brine (10 mL), dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo. Purification by column chromatography (diethyl ether/petroleum ether, 1:4) yielded 2-allyloxybenzaldehyde (182a) (0.481 g, 99%) as a colourless oil. Spectroscopic data were consistent with the literature.<sup>173</sup> R<sub>f</sub> 0.68 (50% diethyl ether/petroleum
ether); \( \delta_H \) (400 MHz, CDCl\(_3\)) 4.66 (2H, dt, \( J \) 5.1, 1.5 Hz, 2'-H\(_2\)), 5.34 (1H, dq, \( J \) 10.5, 1.5 Hz, 4'-H\(_H\)), 5.45 (1H, dq, \( J \) 17.3, 1.5 Hz, 4'-H\(_H\)), 6.08 (1H, ddt, \( J \) 17.3, 10.5, 5.1 Hz, 3'-H), 6.98 (1H, d, \( J \) 8.4 Hz, 3-H), 7.03 (1H, br t, \( J \) 7.5 Hz, 5-H), 7.53 (1H, ddd, \( J \) 8.4, 7.5, 1.9 Hz, 4-H), 7.84 (1H, dd, \( J \) 7.5, 1.9 Hz, 6-H), 10.54 (1H, d, \( J \) 0.7 Hz, CHO); \( \delta_C \) (101 MHz, CDCl\(_3\)) 69.4 (CH\(_2\)), 113.0 (CH), 118.2 (CH\(_2\)), 121.0 (CH), 125.3 (C), 128.6 (CH), 132.6 (CH), 135.9 (CH), 161.1 (C), 189.9 (CH); m/z (CI) 163 (MH\(^+\), 100%), 135 (34), 121 (8), 85 (12), 79 (11).

2-Allyloxy-5-methylbenzaldehyde (182b)

The reaction was carried out as described for the synthesis of 2-allyloxybenzaldehyde (182a) using 2-hydroxy-5-methylbenzaldehyde (180b) (0.136 g, 1.00 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:4) gave 2-allyloxy-5-methylbenzaldehyde (182b) (0.173 g, 98%) as a colourless oil. Spectroscopic data was consistent with literature.\(^{236}\) \( R_f \) 0.7 (50% diethyl ether/petroleum ether); \( \delta_H \) (500 MHz, CDCl\(_3\)) 2.31 (3H, s, 5-CH\(_3\)), 4.63 (2H, dt, \( J \) 5.2, 1.6 Hz, 2'-H\(_2\)), 5.32 (1H, dq, \( J \) 10.6, 1.6 Hz, 4'-H\(_H\)), 5.44 (1H, dq, \( J \) 17.3, 1.6 Hz, 4'-H\(_H\)), 6.07 (1H, ddt, \( J \) 17.3, 10.6, 5.2 Hz, 3'-H), 6.88 (1H, d, \( J \) 8.5 Hz, 3-H), 7.33 (1H, ddd, \( J \) 8.5, 2.3, 0.6 Hz, 4-H), 7.64 (1H, d, \( J \) 2.3 Hz, 6-H), 10.51 (1H, s, CHO); \( \delta_C \) (126 MHz, CDCl\(_3\)) 20.3 (CH\(_3\)), 69.3 (CH\(_2\)), 113.0 (CH), 117.9 (CH\(_2\)), 124.9 (C), 128.5 (CH), 130.3 (C), 132.6 (CH), 136.5 (CH), 159.1 (C), 189.9 (CH); m/z (ESI) 199 (MNa\(^+\), 100%), 190 (3), 185 (4), 171 (5), 158 (16), 136 (2).

2-Allyloxy-4-chlorobenzaldehyde (182c)

The reaction was carried out as described for the synthesis of 2-allyloxybenzaldehyde (182a) using 4-chloro-2-hydroxybenzaldehyde (180c) (0.936
g, 6.00 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:4) gave 2-allyloxy-4-chlorobenzaldehyde (182c) (1.17 g, quantitative) as a white solid. Mp 48–49 °C; R_f 0.75 (50% diethyl ether/petroleum ether); ν_{max}/cm\(^{-1}\) (neat) 2867 (CH), 1685 (CO), 1589, 1413, 1240, 1222, 996, 904; δ\(_H\) (400 MHz, CDCl\(_3\)) 4.67 (2H, dt, J 5.2, 1.5 Hz, 2'\(-\)H\(_2\)), 5.39 (1H, dq, J 10.5, 1.5 Hz, 4'\(-\)H), 5.08 (1H, ddt, J 17.2, 10.5, 5.2 Hz, 3'\(-\)H), 6.95 (1H, d, J 1.7 Hz, 3-H), 7.03 (1H, ddd, J 8.3, 1.7, 0.7 Hz, 5-H), 7.79 (1H, d, J 8.3 Hz, 6-H), 10.46 (1H, d, J 0.7 Hz, CHO); δ\(_C\) (101 MHz, CDCl\(_3\)) 69.5 (CH\(_2\)), 113.5 (CH), 118.6 (CH\(_2\)), 121.4 (CH), 123.6 (C), 129.5 (CH), 131.7 (CH), 141.8 (C), 161.2 (C), 188.4 (CH); m/z (EI) 196.0288 (M\(^+\), C\(_{10}\)H\(_9\)ClO\(_2\) requires 196.0291), 167 (38%), 155 (100), 126 (30), 99 (32), 63 (29), 53 (6).

2- Allyloxy-3,5-dichlorobenzaldehyde (182d)

The reaction was carried out as described for the synthesis of 2-allyloxybenzaldehyde (182a) using 3,5-dichloro-2-hydroxybenzaldehyde (180d) (0.573 g, 3.00 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:4) gave 2-allyloxy-3,5-dichlorobenzaldehyde (182d) (0.693 g, quantitative) as a white solid. Mp 39–41 °C; R_f 0.80 (50% diethyl ether/petroleum ether); ν_{max}/cm\(^{-1}\) (neat) 2871 (CH), 1693 (CO), 1438, 1213, 1167, 754; δ\(_H\) (500 MHz, CDCl\(_3\)) 4.63 (2H, dt, J 6.2, 1.3 Hz, 2'\(-\)H\(_2\)), 5.35 (1H, dq, J 10.6, 1.3 Hz, 4'\(-\)H\(_2\)), 5.40 (1H, dq, J 17.3, 1.3 Hz, 4'-H\(_2\)), 6.08 (1H, ddt, J 17.3, 10.6, 6.2 Hz, 3'\(-\)H), 7.63 (1H, d, J 2.6 Hz, 4-H), 7.71 (1H, d, J 2.6 Hz, 6-H), 10.29 (1H, s, CHO); δ\(_C\) (126 MHz, CDCl\(_3\)) 76.5 (CH\(_2\)), 120.0 (CH\(_2\)), 126.4 (CH), 129.9 (C), 130.3 (C), 131.6 (C), 131.8 (CH), 135.4 (CH), 156.1 (C), 187.5 (CH); m/z (Cl) 230.9982 (MH\(^+\), C\(_{10}\)H\(_9\)Cl\(_2\)O\(_2\) requires 230.9980), 203 (14%), 191 (5), 81 (7), 69 (9).
2-Allyloxy-4,5-difluorobenzaldehyde (182e)

The reaction was carried out as described for the synthesis of 2-alloyloxybenzaldehyde (182a) using 4,5-difluoro-2-hydroxybenzaldehyde (180e) (0.079 g, 0.500 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:4) gave 2-allyloxy-4,5-difluorobenzaldehyde (182e) (0.099 g, quantitative) as white crystals. Mp 35–36 °C; Rf 0.72 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 2872 (CH), 1686 (CO), 1604 (C=C), 1511, 1434, 1323, 1203, 990, 893, 758; δH (500 MHz, CDCl₃) 4.63 (2H, dt, J 5.2, 1.6 Hz, 2'-H₂), 5.38 (1H, dq, J 10.6, 1.6 Hz, 4'H), 5.46 (1H, dq, J 17.3, 1.6 Hz, 4'H), 6.05 (1H, ddt, J 17.3, 10.6, 5.2 Hz, 3'-H), 6.81 (1H, dd, J₁HF 11.5, J₄HF 5.2 Hz, 3'-H), 7.66 (1H, dd, J₂HF 11.5, J₄HF 9.4 Hz, 6-H), 10.39 (1H, d, J₅HF 3.1 Hz, CHO); δC (126 MHz, CDCl₃) 70.2 (CH₂), 103.0 (d, J₁CF 21.1 Hz, CH), 116.4 (dd, J₁CF 18.5, J₃CF 2.9 Hz, CH), 118.9 (CH₂), 121.5 (t, J₃CF 3.2 Hz, C), 131.6 (CH), 145.2 (dd, J₁CF 244.6, J₂CF 13.0 Hz, C), 154.9 (dd, J₁CF 258.5, J₂CF 14.5 Hz, C), 157.8 (dd, J₃CF 8.2, J₄CF 1.8 Hz, C), 187.2 (CH); m/z (EI) 198.0489 (M⁺, C₁₀H₈F₂O₂ requires 198.0492), 156 (11%), 119 (4), 101 (6), 84 (100).

2-Allyloxy-3-methoxy-5-nitrobenzaldehyde (182f)

The reaction was carried out as described for the synthesis of 2-alloyloxybenzaldehyde (182a) using 2-hydroxy-3-methoxy-5-nitrobenzaldehyde (180f) (0.197 g, 1.00 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:4) gave 2-allyloxy-3-methoxy-5-nitrobenzaldehyde (182f) (0.209 g, 88%) as a white solid. Mp 82–84 °C; Rf 0.48 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3101, 2898 (CH), 1695 (CO), 1684, 1583 (C=C), 1527, 1480, 1336, 1278, 1230, 1091, 954, 938, 743; δH (500 MHz, CDCl₃)
4.02 (3H, s, 3-OCH₃), 4.84 (2H, dt, J 6.2, 1.3 Hz, 2'-H₂), 5.32 (1H, dq, J 10.3, 1.3 Hz, 4''-H), 5.38 (1H, dq, J 17.1, 1.3 Hz, 4'''-H), 6.05 (1H, ddt, J 17.1, 10.3, 6.2 Hz, 3'-H), 7.96 (1H, d, J 2.7 Hz, 4-H), 8.33 (1H, d, J 2.7 Hz, 6-H), 10.43 (1H, s, CHO); δC (126 MHz, CDCl₃) 56.6 (CH₃), 75.4 (CH₂), 111.5 (CH), 115.0 (CH), 120.0 (CH₂), 129.3 (C), 132.3 (CH), 143.6 (C), 153.3 (C), 155.8 (C), 188.2 (CH); m/z (EI) 237.0630 (M⁺, C₁₁H₁₁NO₅ requires 237.0637), 220 (4%), 196 (27), 180 (27), 150 (15), 122 (11), 84 (100).

2-Allyloxy-1-naphthaldehyde (182g)¹⁷³

The reaction was carried out as described for the synthesis of 2-allyloxybenzaldehyde (182a) using 2-hydroxy-1-naphthaldehyde (180g) (0.172 g, 1.00 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:4) gave 2-allyloxy-1-naphthaldehyde (182g) (0.208 g, 98%) as a white solid. Mp 72–74 °C (lit.¹⁷⁰ 79–80 °C); Rf 0.62 (50% diethyl ether/petroleum ether); Spectroscopic data was consistent with literature.¹⁷³ δH (400 MHz, CDCl₃) 4.83 (2H, dt, J 5.2, 1.6 Hz, 2'-H₂), 5.39 (1H, dq, J 10.6, 1.6 Hz, 4''-H), 5.50 (1H, dq, J 17.3, 1.6 Hz, 4'''-H), 6.13 (1H, ddt, J 17.3, 10.6, 5.2 Hz, 3'-H), 7.30 (1H, d, J 9.3 Hz, 3-H), 7.45 (1H, ddd, J 8.5, 8.4, 1.3 Hz, 6-H), 7.65 (1H, ddd, J 8.5, 8.4, 1.3 Hz, 7-H), 7.80 (1H, br d, J 8.4 Hz, 5-H), 8.06 (1H, d, J 9.3 Hz, 4-H), 9.31 (1H, br d, J 8.4 Hz, 8-H), 10.98 (1H, s, CHO); δC (101 MHz, CDCl₃) 69.9 (CH₂), 113.7 (CH), 116.8 (C), 118.1 (CH₂), 124.7 (CH), 124.9 (CH), 128.3 (CH), 128.5 (C), 129.7 (CH), 131.5 (C), 132.4 (CH), 137.4 (CH), 163.0 (C), 191.8 (CH); m/z (ESI) 235 (MNa⁺, 100%), 218 (6), 194 (16).
Lithium bromide (1.043 g, 12.0 mmol) was added to a solution of triethyl phosphonoacetate (2.02 mL, 10.2 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.52 mL, 10.2 mmol) in acetonitrile (50 mL) and stirred at room temperature for 0.5 h. 2-Allyloxybenzaldehyde (182a) (0.480 g, 3.00 mmol) was added and the solution was stirred at room temperature for 2 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (10 mL), concentrated to half volume in vacuo and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (diethyl ether/petroleum ether, 1:10) yielded ethyl (2E)-3-(2'-allyloxyphenyl)prop-2-enoate (183a) (0.731 g, 100%) as a pale yellow oil. Spectroscopic data was consistent with literature.²³⁷ Rₕ 0.65 (50% diethyl ether/petroleum ether); δₖ (400 MHz, CDCl₃) 1.34 (3H, t, J 7.1 Hz, OCH₂CH₃), 4.26 (2H, q, J 7.1 Hz, OCH₂CH₃), 4.63 (2H, dt, J 5.2, 1.6 Hz, 2''-H₂), 5.31 (1H, dq, J 10.6, 1.6 Hz, 4''-H₂), 5.43 (1H, dq, J 17.3, 1.6 Hz, 4''-HH), 6.08 (1H, ddt, J 17.3, 10.6, 5.2 Hz, 3''-H), 6.52 (1H, d, J 16.2 Hz, 2-H), 6.90 (1H, d, J 8.4 Hz, 3'-H), 6.96 (1H, br t, J 7.5 Hz, 5'-H), 7.32 (1H, ddd, J 8.4, 7.5, 1.7 Hz, 4'-H), 7.52 (1H, dd, J 7.5, 1.7 Hz, 6'-H), 8.04 (1H, d, J 16.2 Hz, 3-H); δₖ (126 MHz, CDCl₃) 14.4 (CH₃), 60.3 (CH₂), 69.2 (CH₂), 112.6 (CH), 117.8 (CH₂), 118.9 (CH), 120.9 (CH), 123.8 (C), 128.8 (CH), 131.3 (CH), 132.9 (CH), 139.9 (CH), 157.3 (C), 167.5 (C); m/z (EI) 232 (M⁺, 38%), 187 (20), 175 (14), 159 (28), 131 (23), 118 (70), 86 (100).

The reaction was carried out as described for the synthesis of ethyl (2E)-3-(2'-allyloxy-5'-methylphenyl)prop-2-enoate (183a) using 2-allyloxy-5-methylbenzaldehyde...
(182b) (0.167 g, 0.950 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:10) yielded ethyl (2E)-3-(2'-allyloxy-5'-methylphenyl)prop-2-enoate (183b) (0.206 g, 88%) as an oil. Rf 0.7 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3021 (CH), 1701 (CO), 1631 (C=C), 1494, 1217, 1178, 750; δH (400 MHz, CDCl₃) 1.33 (3H, t, J 7.1 Hz, OCH₂C₂H₃), 2.29 (3H, s, 5'-CH₃), 4.25 (2H, q, J 7.1 Hz, OCH₂C₂H₃), 4.59 (2H, dt, J 5.2, 1.6 Hz, 2''-H₂), 5.29 (1H, dq, J 10.6, 1.6 Hz, 4''-H), 5.41 (1H, dq, J 17.3, 1.6 Hz, 4''-H), 6.07 (1H, ddt, J 17.3, 10.6, 5.2 Hz, 3''-H), 6.51 (1H, d, J 16.2 Hz, 2'-H), 6.80 (1H, d, J 8.4 Hz, 3'-H), 7.11 (1H, dd, J 8.4, 2.0 Hz, 4'-H), 7.32 (1H, d, J 2.0 Hz, 6'-H), 8.01 (1H, d, J 16.2 Hz, 3'-H); δC (101 MHz, CDCl₃) 14.4 (CH₃), 20.4 (CH₃), 60.3 (CH₂), 69.4 (CH₂), 112.6 (CH), 117.6 (CH₂), 118.6 (CH), 123.5 (C), 129.2 (CH), 130.1 (C), 131.8 (CH), 133.1 (CH), 140.0 (CH), 155.3 (C), 167.5 (C); m/z (ESI) 269.1139 (MNa⁺, C₁₅H₁₈NaO₃ requires 269.1148), 236 (6%), 228 (4), 218 (2).

Ethyl (2E)-3-(2'-allyloxy-4'-chlorophenyl)prop-2-enoate (183c)

![Structure of ethyl (2E)-3-(2'-allyloxy-4'-chlorophenyl)prop-2-enoate](image)

The reaction was carried out as described for the synthesis of ethyl (2E)-3-(2'-allyloxyphenyl)prop-2-enoate (183a) using 2-allyloxy-4-chlorobenzaldehyde (182c) (0.150 g, 0.760 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:10) yielded ethyl (2E)-3-(2'-allyloxy-4'-chlorophenyl)prop-2-enoate (183c) (0.192 g, 94%) as an oil. Rf 0.73 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 2989 (CH), 1707 (CO), 1632 (C=C), 1592, 1486, 1312, 1178, 908, 732; δH (500 MHz, CDCl₃) 1.35 (3H, t, J 7.1 Hz, OCH₂C₂H₃), 4.27 (2H, q, J 7.1 Hz, OCH₂C₂H₃), 4.63 (2H, dt, J 5.2, 1.3 Hz, 2''-H₂), 5.36 (1H, dq, J 17.2, 1.3 Hz, 4''-H), 5.46 (1H, dq, J 10.6, 1.3 Hz, 4''-H), 6.08 (1H, ddt, J 17.2, 10.6, 5.2 Hz, 3''-H), 6.51 (1H, d, J 16.2 Hz, 2'-H), 6.91 (1H, d, J 1.9 Hz, 3'-H), 6.97 (1H, dd, J 8.3, 1.9 Hz, 5'-H), 7.45 (1H, d, J 8.3 Hz, 6'-H), 7.96 (1H, d, J 16.2 Hz, 3'-H); δC (126 MHz, CDCl₃) 14.3 (CH₃), 60.4 (CH₂), 69.5 (CH₂), 113.2 (CH), 118.3 (CH₂), 119.2 (CH), 121.2 (CH), 122.3 (C), 129.5 (CH), 132.2 (CH), 136.6 (C), 138.8 (CH), 140.0 (CH), 155.3 (C), 167.5 (C); m/z (ESI) 269.1139 (MNa⁺, C₁₅H₁₈NaO₃ requires 269.1148), 236 (6%), 228 (4), 218 (2).
157.5 (C), 167.1 (C); m/z (ESI) 289.0595 (MNa\(^+\), C\(_{14}H_{15}ClO_3\) requires 289.0602), 286 (27%), 279 (5), 275 (1), 270 (1), 262 (5).

**Ethyl (2E)-3-(2'-allyloxy-3',5'-dichlorophenyl)prop-2-enoate (183d)**

![Structure of ethyl (2E)-3-(2'-allyloxy-3',5'-dichlorophenyl)prop-2-enoate (183d)](structure.png)

The reaction was carried out as described for the synthesis of ethyl (2E)-3-(2'-allyloxyphenyl)prop-2-enoate (183a) using 2-allyloxy-3,5-dichlorobenzaldehyde (182d) (0.693 g, 3.00 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:10) gave ethyl (2E)-3-(2'-allyloxy-3',5'-dichlorophenyl)prop-2-enoate (183d) (0.903 g, 100%) as a white solid. Mp 44–46 °C; R\(_f\) 0.80 (50% diethyl ether/petroleum); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 2984 (CH), 1724 (CO), 1639 (C=C), 1448, 1310, 1183, 1166, 974; \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.34 (3H, t, J 7.1 Hz, OCH\(_2\)C\(_6\)H\(_5\)), 4.27 (2H, q, J 7.1 Hz, OCH\(_2\)C\(_6\)H\(_5\)), 4.48 (2H, dt, J 6.0, 1.3 Hz, 2''-H), 5.31 (1H, dq, J 10.6, 1.3 Hz, 4''-H), 5.42 (1H, dq, J 17.3, 1.3 Hz, 4'''-HH), 6.10 (1H, ddt, J 17.3, 10.6, 6.0 Hz, 3''-H), 6.46 (1H, d, J 16.2 Hz, 2'-H), 7.40 (1H, d, J 2.5 Hz, 4'-H), 7.43 (1H, d, J 2.5 Hz, 6'-H), 7.86 (1H, d, J 16.2 Hz, 3'-H); \(\delta_C\) (126 MHz, CDCl\(_3\)) 14.3 (CH\(_3\)), 60.8 (CH\(_2\)), 75.4 (CH\(_2\)), 119.3 (CH\(_2\)), 121.8 (CH\(_2\)), 125.9 (CH\(_2\)), 129.8 (C), 129.9 (C), 131.3 (CH), 131.5 (C), 132.5 (CH), 137.6 (CH), 152.5 (C), 166.3 (C); m/z (ESI) 323.0202 (MNa\(^+\), C\(_{14}H_{14}Cl_2NaO_3\) requires 323.0212).

**Ethyl (2E)-3-(2'-allyloxy-4',5'-difluorophenyl)prop-2-enoate (183e)**

![Structure of ethyl (2E)-3-(2'-allyloxy-4',5'-difluorophenyl)prop-2-enoate (183e)](structure.png)

The reaction was carried out as described for the synthesis of ethyl (2E)-3-(2'-allyloxyphenyl)prop-2-enoate (183a) using 2-allyloxy-4,5-difluorobenzaldehyde (182e) (0.093 g, 0.470 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:10) gave ethyl (2E)-3-(2'-allyloxy-4',5'-difluorophenyl)prop-2-enoate (183e) (0.117 g, 93%) as white crystals. Mp 52–53
°C; Rf 0.72 (50% diethyl ether/petroleum ether); ν<sub>max</sub>/cm<sup>-1</sup> (neat) 2985 (CH), 1690 (CO), 1599 (C=C), 1511, 1273, 1224, 1174, 987, 857; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 1.33 (3H, t, J 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.26 (2H, q, J 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.57 (2H, dt, J 5.2, 1.6 Hz, 2''-H<sub>2</sub>), 5.34 (1H, dq, J 10.6, 1.6 Hz, 4''-H), 5.43 (1H, dq, J 17.3, 1.6 Hz, 4''-H<sub>2</sub>), 6.04 (1H, ddt, J 17.3, 10.6, 5.2 Hz, 3'-H), 6.41 (1H, d, J 16.2 Hz, 2-H), 6.72 (1H, dd, 3''<sub>HF</sub> 11.5, 4''<sub>HF</sub> 5.2 Hz, 3''-H), 7.91 (1H, dd, J<sub>HF</sub> 16.2, 5''<sub>HF</sub> 1.0 Hz, 3-H); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 14.3 (CH<sub>3</sub>), 56.4 (CH<sub>3</sub>), 60.7 (CH<sub>2</sub>), 74.8 (CH<sub>2</sub>), 108.0 (CH), 114.9 (CH), 119.2 (CH<sub>2</sub>), 121.9 (CH), 129.1 (C), 132.9 (CH), 137.5 (CH), 143.7 (C), 151.8 (C), 153.1 (C),

Ethyl (2E)-3-(2'-allyloxy-3'-methoxy-5'-nitrophenyl)prop-2-enoate (183f)

![Chemical Structure](image)

The reaction was carried out as described for the synthesis of ethyl (2E)-3-(2'-allyloxyphenyl)prop-2-enoate (183a) using 2-allyloxy-3-methoxy-5-nitrobenzaldehyde (182f) (0.617 g, 2.60 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:10) gave ethyl (2E)-3-(2'-allyloxy-3'-methoxy-5'-nitrophenyl)prop-2-enoate (183f) (0.798 g, 100%) as a white solid. Mp 82–83 °C; Rf 0.58 (50% diethyl ether/petroleum ether); ν<sub>max</sub>/cm<sup>-1</sup> (neat) 3022 (CH), 1711 (CO), 1641 (C=C), 1582, 1527, 1466, 1340, 1278, 1179, 979; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 1.35 (3H, t, J 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.97 (3H, s, 3'-OCH<sub>3</sub>), 4.28 (2H, q, J 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.69 (2H, dt, J 6.1, 1.3 Hz, 2''-H<sub>2</sub>), 5.28 (1H, dq, J 10.3, 1.3 Hz, 4''-H), 5.37 (1H, dq, J 17.2, 1.3 Hz, 4''-H<sub>2</sub>), 6.05 (1H, ddt, J 17.2, 10.3, 6.1 Hz, 3'-H), 6.56 (1H, d, J 16.2 Hz, 2-H); 7.77 (1H, d, J 2.6 Hz, 4'-H<sub>2</sub>), 7.99 (1H, d, J 16.2 Hz, 3-H), 8.10 (1H, d, J 2.6 Hz, 6'-H); δ<sub>C</sub> (126 MHz, CDCl<sub>3</sub>) 14.3 (CH<sub>3</sub>), 56.4 (CH<sub>3</sub>), 60.7 (CH<sub>2</sub>), 74.8 (CH<sub>2</sub>), 108.0 (CH), 114.9 (CH), 119.2 (CH<sub>2</sub>), 121.9 (CH), 129.1 (C), 132.9 (CH), 137.5 (CH), 143.7 (C), 151.8 (C), 153.1 (C),

m/z (ESI) 291.0797 (M<sub>Na</sub><sup>+</sup>, C<sub>14</sub>H<sub>14</sub>F<sub>2</sub>NaO<sub>3</sub> requires 291.0803), 236 (100%), 218 (5).
166.3 (C); m/z (ESI) 330.0934 (MNa\(^+\), C\(_{15}\)H\(_{17}\)NNaO\(_6\) requires 330.0948), 284 (2%), 236 (10).

**Ethyl (2E)-3-(2'-allyloxynaphthalen-1'-yl)prop-2-enoate (183g)**

The reaction was carried out as described for the synthesis of ethyl (2E)-3-(2'-allyloxyphenyl)prop-2-enoate (183a) using 2-allyloxy-1-naphthaldehyde (182g) (0.620 g, 2.94 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:10) gave ethyl (2E)-3-(2'-allyloxynaphthalen-1'-yl)prop-2-enoate (183g) (0.760 g, 92%) as a white solid. Mp 46–48 °C; R\(_f\) 0.65 (50% diethyl ether/petroleum ether); \(\nu\)\(_{\text{max}}\)/cm\(^{-1}\) (neat) 2981 (CH), 1701 (CO), 1617 (C=C), 1264, 1159, 907, 727; \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 1.37 (3H, t, \(J\) 7.1 Hz, OCH\(_2\)C\(_H\)_3), 4.32 (2H, q, \(J\) 7.1 Hz, OCH\(_2\)CH\(_3\)), 4.75 (2H, dt, \(J\) 5.2, 1.6 Hz, 2''-H\(_2\)), 5.31 (1H, dq, \(J\) 10.6, 1.6 Hz, 4''-H\(_H\)), 5.44 (1H, dq, \(J\) 17.3, 1.6 Hz, 4''-H\(_H\)), 6.10 (1H, ddt, \(J\) 17.3, 10.6, 5.2 Hz, 3''-H), 6.77 (1H, d, \(J\) 16.2 Hz, 2'-H), 7.25 (1H, d, \(J\) 9.3 Hz, 3'-H), 7.38 (1H, ddd, \(J\) 8.5, 8.4, 1.0 Hz, 6'-H), 7.52 (1H, ddd, \(J\) 8.5, 8.4, 1.0 Hz, 7'-H), 7.78 (1H, dd, \(J\) 8.4, 1.0 Hz, 5'-H), 7.81 (1H, d, \(J\) 9.3 Hz, 4'-H), 8.19 (1H, dd, \(J\) 8.4, 1.0 Hz, 8'-H), 8.36 (1H, d, \(J\) 16.2 Hz, 3'-H); \(\delta\)\(_C\) (101 MHz, CDCl\(_3\)) 14.4 (CH\(_3\)), 60.4 (CH\(_2\)), 70.0 (CH\(_2\)), 114.3 (CH), 117.5 (C), 117.8 (CH\(_2\)), 123.5 (CH), 123.7 (CH), 124.0 (CH), 127.3 (CH), 128.5 (CH), 129.1 (C), 131.3 (CH), 132.8 (C), 133.1 (CH), 137.7 (CH), 155.6 (C), 167.8 (C); m/z (ESI) 305.1139 (MNa\(^+\), C\(_{18}\)H\(_{18}\)NaO\(_3\) requires 305.1148), 246 (12%), 227 (3), 191 (2).
Diisobutylaluminium hydride (3.21 mL, 2.82 mmol, 1 M in hexane) was added dropwise with stirring, to a solution of ethyl (2E)-3-(2'-allyloxyphenyl)prop-2-enoate (183a) (0.298 g, 1.28 mmol) in diethyl ether (30 mL) at −78 °C. The solution was stirred at −78 °C for 3 h, then allowed to return to room temperature over 15 h. The reaction was quenched with 10% aqueous potassium sodium tartrate solution (30 mL), extracted with diethyl ether (2 × 20 mL), washed with water (100 mL), brine (100 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (diethyl ether/petroleum ether, 1:3) yielded (2E)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (184a) (0.211 g, 87%) as a white solid. Mp 44–46 °C; Rₜ 0.28 (50% diethyl ether/petroleum ether); Spectroscopic data was in accordance with literature values.²³⁷ δH (500 MHz, CDCl₃) 1.46 (1H, t, J 5.9 Hz, OH), 4.33 (2H, td, J 5.9, 0.8 Hz, 1-H₂), 4.58 (2H, dt, J 5.2, 1.5 Hz, 2''-H₂), 5.29 (1H, dq, J 10.5, 1.5 Hz, 4''-H), 6.08 (1H, ddt, J 17.3, 10.5, 5.2 Hz, 3''-H), 6.40 (1H, dt, J 16.0, 5.9 Hz, 2-H), 6.86 (1H, d, J 8.2 Hz, 3'-H), 6.93 (1H, t, J 7.5 Hz, 5'-H), 6.96 (1H, br d, J 16.0 Hz, 3-H), 7.21 (1H, ddd, J 8.2, 7.5, 1.7 Hz, 4'-H), 7.46 (1H, dd, J 7.5, 1.7 Hz, 6'-H); δC (126 MHz, CDCl₃) 64.3 (CH₂), 69.2 (CH₂), 112.4 (CH), 117.5 (CH₂), 120.9 (CH), 126.0 (C), 126.3 (CH), 127.0 (CH), 128.7 (CH), 129.2 (CH), 133.4 (CH), 155.8 (C); m/z (EI) 190 (57%), 149 (59), 131 (92), 121 (60), 119 (46), 91 (100), 77 (40).

(2E)-3-(2'-Allyloxy-5'-methylphenyl)prop-2-en-1-ol (184b)

The reaction was carried out as described for the synthesis of (2E)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (184a) using ethyl (2E)-3-(2'-allyloxy-5'-methylphenyl)prop-2-enoate (183b) (0.198 g, 0.750 mmol). Purification by flash column chromatography (diethyl ether/petroleum ether, 1:3) yielded (2E)-3-(2'-allyloxy-5'-methylphenyl)prop-2-en-1-ol (184b) (0.164 g, quantitative) as a
colourless oil. Rf 0.32 (50% diethyl ether/petroleum ether); $\nu_{\max}$/cm\(^{-1}\) (neat) 3370 (OH), 2922 (CH), 1494, 1243, 1220, 997, 909; $\delta_h$ (500 MHz, CDCl\(_3\)) 1.39 (1H, br s, OH), 2.29 (3H, s, 5'-CH\(_3\)), 4.32 (2H, d, $J$ 5.2 Hz, 1'-H\(_2\)), 4.54 (2H, dt, $J$ 5.2, 1.6 Hz, 2''-H\(_2\)), 5.27 (1H, dq, $J$ 10.6, 1.6 Hz, 4''-H\(_H\)), 5.40 (1H, dq, $J$ 17.3, 1.6 Hz, 4''-HH), 6.07 (1H, ddt, $J$ 17.3, 10.6, 5.2 Hz, 3''-H), 6.38 (1H, dt, $J$ 16.2, 5.2 Hz, 2-H), 6.76 (1H, d, $J$ 8.3 Hz, 3'-H), 6.94 (1H, d, $J$ 16.2 Hz, 3-H), 7.00 (1H, dd, $J$ 8.3, 2.1 Hz, 4''-H), 7.27 (1H, d, $J$ 2.1 Hz, 6'-H); $\delta_c$ (126 MHz, CDCl\(_3\)) 20.6 (CH\(_3\)), 64.2 (CH\(_2\)), 69.4 (CH\(_2\)), 112.5 (CH), 117.4 (CH\(_2\)), 125.8 (C), 126.2 (CH), 127.6 (CH), 129.1 (2 x CH), 130.1 (C), 133.6 (CH), 153.8 (C); $m/z$ (El) 204.1153 (M\(^+\), C\(_{13}\)H\(_{16}\)O\(_2\) requires 204.1150), 163 (31%), 145 (61), 133 (64), 105 (97), 84 (100), 77 (24), 69 (13).

(2E)-3-(2'-Allyloxy-4'-chlorophenyl)prop-2-en-1-ol (184c)

\[
\text{Cl} \quad \begin{array}{c}
\text{O} \\
\text{3'} & \text{4'} \\
\text{2} & \text{OH}
\end{array}
\]

The reaction was carried out as described for the synthesis of (2E)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (184a) using ethyl (2E)-3-(2'-allyloxy-4'-chlorophenyl)prop-2-enoate (183c) (0.193 g, 0.720 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:3) yielded (2E)-3-(2'-allyloxy-4'-chlorophenyl)prop-2-en-1-ol (184c) (0.138 g, 85%) as a white solid. Mp 45–47 °C; Rf 0.32 (50% diethyl ether/petroleum ether); $\nu_{\max}$/cm\(^{-1}\) (neat) 3350 (OH), 2869 (CH), 1590 (C=C), 1485, 1408, 1245, 1226, 1015, 998, 972, 905, 730; $\delta_h$ (400 MHz, CDCl\(_3\)) 1.59 (1H, t, $J$ 5.1 Hz, OH), 4.34 (2H, br t, $J$ 5.1 Hz, 1-H\(_2\)), 4.57 (2H, dt, $J$ 5.2, 1.4 Hz, 2''-H\(_2\)), 5.33 (1H, dq, $J$ 10.6, 1.4 Hz, 4''-H\(_H\)), 5.44 (1H, dq, $J$ 17.2, 1.4 Hz, 4''-HH), 6.07 (1H, ddt, $J$ 17.2, 10.6, 5.2 Hz, 3''-H), 6.38 (1H, dt, $J$ 16.0, 5.1 Hz, 2-H), 6.86 (1H, d, $J$ 1.8 Hz, 3'-H), 6.88–6.94 (2H, m, 3-H and 5'-H), 7.37 (1H, d, $J$ 8.3 Hz, 6'-H), $\delta_c$ (126 MHz, CDCl\(_3\)) 64.1 (CH\(_2\)), 69.4 (CH\(_2\)), 112.8 (CH), 117.9 (CH\(_2\)), 120.9 (CH), 124.6 (C), 125.1 (CH), 127.7 (CH), 129.6 (CH), 132.6 (CH), 133.8 (C), 156.1 (C); $m/z$ (El) 224.0600 (M\(^+\), C\(_{13}\)H\(_{15}\)ClO\(_2\) requires 224.0604), 183 (99%), 165 (73), 155 (100), 125 (55), 120 (10), 91 (48), 77 (14).
(2E)-3-(2'-Allyloxy-3',5'-dichlorophenyl)prop-2-en-1-ol (184d)

The reaction was carried out as described for the synthesis of (2E)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (184a) using ethyl (2E)-3-(2'-allyloxy-3',5'-dichlorophenyl)prop-2-enoate (183d) (0.903 g, 3.00 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:3) gave (2E)-3-(2'-allyloxy-3',5'-dichlorophenyl)prop-2-en-1-ol (184d) (0.691 g, 89%) as a white solid. Mp 49–51 °C; R_f 0.30 (50% diethyl ether/petroleum ether); ν_max/cm⁻¹ (neat) 3245 (OH), 2857 (CH), 1643, 1555, 1441, 1262, 1014, 970, 858; δ_H (400 MHz, CDCl₃) 1.47 (1H, t, J 5.6 Hz, OH), 4.35 (2H, td, J 5.6, 1.6 Hz, 1'-H₂), 4.43 (2H, dt, J 5.6, 1.3 Hz, 2''-H₂), 5.28 (1H, dq, J 10.6, 1.3 Hz, 4''-H), 5.41 (1H, dq, J 17.3, 1.3 Hz, 4''-H), 6.09 (1H, ddt, J 17.3, 10.6, 5.6 Hz, 3''-H), 6.40 (1H, dt, J 16.2, 5.6 Hz, 2-H), 6.83 (1H, dt, J 16.2, 1.6 Hz, 3-H), 7.28 (1H, d, J 2.5 Hz, 4''-H), 7.36 (1H, d, J 2.5 Hz, 6'-H); δ_C (101 MHz, CDCl₃) 63.5 (CH₂), 74.7 (CH₂), 118.5 (CH₂), 123.8 (CH), 125.1 (CH), 128.9 (CH), 129.4 (C), 129.6 (C), 132.4 (CH), 133.0 (CH), 133.5 (C), 151.1 (C); m/z (EI) 258.0218 (M⁺, C₁₂H₁₂Cl₂O₂ requires 258.0214), 227 (5%), 199 (57), 187 (43), 159 (44), 154 (12), 125 (21), 84 (100).

(2E)-3-(2'-Allyloxy-4',5'-difluorophenyl)prop-2-en-1-ol (184e)

The reaction was carried out as described for the synthesis of (2E)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (184a) using ethyl (2E)-3-(2'-allyloxy-4',5'-difluorophenyl)prop-2-enoate (183e) (0.090 g, 0.340 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:3) gave (2E)-3-(2'-allyloxy-4',5'-difluorophenyl)prop-2-en-1-ol (184e) (0.071 g, 94%) as a yellow oil. R_f 0.32 (50% diethyl ether/petroleum ether); ν_max/cm⁻¹ (neat) 3341 (OH), 2867 (CH), 1610 (C=C), 1507, 1422, 1192, 991, 969; δ_H (400 MHz, CDCl₃) 1.57 (1H, br s, OH), 4.32
(2H, br d, \(J\ 5.2\ \text{Hz},\ 1'-\text{H}\)), 4.51 (2H, dt, \(J\ 5.2,\ 1.6\ \text{Hz},\ 2'''-\text{H}\)), 5.31 (1H, dq, \(J\ 10.6,\ 1.6\ \text{Hz},\ 4''''-\text{H}\)), 5.41 (1H, dq, \(J\ 17.3,\ 1.6\ \text{Hz},\ 4''''-\text{H}\)), 6.03 (1H, ddt, \(J\ 17.3,\ 10.6,\ 5.2\ \text{Hz},\ 3'''-\text{H}\)), 6.28 (1H, dt, \(J\ 16.0,\ 5.2\ \text{Hz},\ 2'-\text{H}\)), 6.67 (1H, dd, \(J_{HF}\ 11.5,\ 4''''-\text{H}\)), 6.85 (1H, dd, \(J_{HF}\ 11.5,\ 4''''-\text{H}\)), 6.94 (1H, ddt, \(J_{HF}\ 11.5,\ 9.0\ \text{Hz},\ 6'''-\text{H}\)); \(\delta\ C\ (101\ \text{MHz, CDCl}_3)\ 63.9\ (\text{CH}_2),\ 70.1\ (\text{CH}_2),\ 114.7\ (\text{dd},\ 2J_CF\ 18.3,\ 3J_CF\ 1.4\ \text{Hz},\ \text{CH}),\ 118.1\ (\text{CH}_2),\ 122.5\ (\text{dd},\ 3J_CF\ 5.1,\ 4J_CF\ 3.8\ \text{Hz},\ \text{C}),\ 124.2\ (\text{CH}),\ 129.9\ (\text{d},\ 4J_CF\ 2.2\ \text{Hz},\ \text{CH}),\ 132.6\ (\text{CH}),\ 144.8\ (\text{dd},\ 1J_CF\ 240.5,\ 2J_CF\ 13.0\ \text{Hz},\ \text{C}),\ 149.7\ (\text{dd},\ 1J_CF\ 248.7,\ 2J_CF\ 13.9\ \text{Hz},\ \text{C}),\ 151.8\ (\text{dd},\ 3J_CF\ 7.1,\ 4J_CF\ 1.8\ \text{Hz},\ \text{C}); m/z (EI) 226.0806 (M+\ ^{\text{Na}}\ ^{12}\ \text{C}_{12}\ ^{12}\ \text{F}_2\ ^2\ \text{O}_2\ \text{Na} requires 226.0802), 185 (74%), 167 (100), 157 (60), 127 (94), 119 (22), 84 (97).

(2\text{E})-3-(2'-'\text{Allyloxy}-3'-'\text{methoxy}-5'-'\text{nitrophenoxy})-\text{prop-2-en-1-ol (184f)}

![Chemical Structure](image)

The reaction was carried out as described for the synthesis of (2\text{E})-3-(2'-'\text{allyloxyphenyl})-\text{prop-2-en-1-ol (184a)} using ethyl (2\text{E})-3-(2'-'\text{allyloxy}-3'-'\text{methoxy}-5'-'\text{nitrophenoxy})-\text{prop-2-enoate (183f)} (0.798 g, 2.59 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:2) gave (2\text{E})-3-(2'-'\text{allyloxy}-3'-'\text{methoxy}-5'-'\text{nitrophenoxy})-\text{prop-2-en-1-ol (184f)} (0.604 g, 88%) as a white solid. Mp 58–60 °C; Rf 0.2 (50% diethyl ether/petroleum ether); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3267 (OH), 2933 (CH), 1657, 1579, 1511, 1471, 1336, 1265, 1210, 1104, 1071, 977; \(\delta\ H\ (500\ \text{MHz, CDCl}_3)\ 1.59\ (1H, t, \text{J} 5.6\ \text{Hz},\ \text{OH}),\ 3.95\ (3H, s, 3'-'\text{OCH}_3),\ 4.38\ (2H, td, \text{J} 5.6,\ 1.6\ \text{Hz},\ 1'-\text{H}),\ 4.60\ (2H, dt, \text{J} 6.0,\ 1.3\ \text{Hz},\ 2'''-\text{H}),\ 5.26\ (1H, dd, \text{J} 10.5,\ 1.3\ \text{Hz},\ 4''''-\text{H}),\ 5.37\ (1H, dq, \text{J} 17.1,\ 1.3\ \text{Hz},\ 4''''-\text{H}),\ 6.06\ (1H, ddt, \text{J} 17.1,\ 10.5,\ 6.0\ \text{Hz},\ 3'''-\text{H}),\ 6.50\ (1H, dt, \text{J} 16.2,\ 5.6\ \text{Hz},\ 2'-\text{H}),\ 6.95\ (1H, dt, \text{J} 16.2,\ 1.6\ \text{Hz},\ 3'-\text{H}),\ 7.66\ (1H, d, \text{J} 2.6\ \text{Hz},\ 4'-\text{H}),\ 8.04\ (1H, d, \text{J} 2.6\ \text{Hz},\ 6'-\text{H}); \(\delta\ C\ (126\ \text{MHz, CDCl}_3)\ 56.2\ (\text{CH}_3),\ 63.3\ (\text{CH}_2),\ 74.4\ (\text{CH}_2),\ 105.9\ (\text{CH}),\ 114.1\ (\text{CH}),\ 118.7\ (\text{CH}_2),\ 123.4\ (\text{CH}),\ 131.5\ (\text{C}),\ 132.7\ (\text{CH}),\ 133.3\ (\text{CH}),\ 143.8\ (\text{C}),\ 150.3\ (\text{C}),\ 153.0\ (\text{C}); m/z (ESI) 288.0837 (MNa\ ^{+},\ ^{13}\text{C}_{12}\text{H}_{15}\text{NNaO}_5 requires 288.0842).
(2E)-3-(2’-Allyloxynaphthalen-1’-yl)prop-2-en-1-ol (184g)

The reaction was carried out according to the procedure described for the synthesis of (2E)-3-(2’-allyloxyphenyl)prop-2-en-1-ol (184a) using ethyl (2E)-3-(2’-allyloxynaphthalen-1’y)prop-2-enolate (183g) (0.760 g, 2.69 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:3) gave (2E)-3-(2’-allyloxynaphthalen-1’y)prop-2-en-1-ol (184g) (0.592 g, 92%) as a yellow solid. Mp 56–58 °C; Rf 0.28 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3391 (OH), 2865 (CH), 1591 (C=C), 1510, 1217, 1011, 805; δH (500 MHz, CDCl₃) 1.52 (1H, t, J 6.0 Hz, OH), 4.47 (2H, td, J 6.0, 1.6 Hz, 1-H₂), 4.70 (2H, dt, J 5.2, 1.6 Hz, 2’-H₂), 5.29 (1H, dq, J 10.5, 1.6 Hz, 4’’-HH), 5.44 (1H, dq, J 17.3, 1.6 Hz, 4’-HH), 6.10 (1H, ddt, J 17.3, 10.5, 5.2 Hz, 3’-H), 6.46 (1H, dt, J 16.2, 6.0 Hz, 2-H), 7.04 (1H, dt, J 16.2, 1.6 Hz, 3-H), 7.25 (1H, d, J 9.0 Hz, 3’-H), 7.35 (1H, d, d, J 8.5, 8.4, 1.0 Hz, 6’-H), 7.46 (1H, d, d, J 8.5, 8.4, 1.0 Hz, 7’-H), 7.74 (1H, d, J 9.0 Hz, 4’-H), 7.78 (1H, dd, J 8.4, 1.0 Hz, 5’-H), 8.16 (1H, dd, J 8.4, 1.0 Hz, 8’-H); δC (126 MHz, CDCl₃) 64.4 (CH₂), 70.2 (CH₂), 114.9 (CH), 117.5 (CH₂), 120.7 (C), 123.7 (CH), 123.9 (CH), 124.3 (CH), 126.5 (CH), 128.3 (CH), 128.8 (CH), 129.4 (C), 132.6 (C), 133.6 (CH), 135.3 (CH), 153.5 (C); m/z (EI) 240.1153 (M⁺, C₁₆H₁₆O₂ requires 240.1150), 199 (25%), 181 (56), 169 (93), 141 (100), 115 (38), 83 (95), 69 (10).

5-(2’,2’,2’-Trichloromethylcarbonylamino)-2,5-dihydro-1-benzoexepine (187a)

(2E)-3-(2’-Allyloxyphenyl)prop-2-en-1-ol (184a) (0.050 g, 0.260 mmol) was dissolved in dichloromethane (15 mL) and cooled to 0 °C under argon with stirring. Trichloroacetonitrile (0.040 mL, 0.400 mmol) was added to the solution, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.020 mL, 0.130 mmol) and the reaction
was allowed to return to room temperature over 1 h. The reaction mixture was filtered through a short pad of alumina (neutral, Brockman V) with diethyl ether (150 mL) and concentrated in vacuo to yield the crude allylic trichloroacetimidate (185) as a yellow oil which was used without further purification. The allylic trichloroacetimidate was transferred to a dry Schlenk tube containing a stirrer bar and potassium carbonate (15 mg, 3 mg/mL) to which p-xylene (5 mL) was then added. The tube was purged with argon, sealed and heated to 140 °C for 18 h. The reaction was allowed to cool to room temperature and Grubbs 2nd generation catalyst (0.110 g, 0.013 mmol, 5 mol%) was added. The reaction mixture was heated to 50 °C for 24 h. The reaction mixture was concentrated in vacuo and purified by column chromatography (diethyl ether/petroleum ether, 1:10) gave 5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187a) (0.055 g, 68%) as a white solid. Mp 96–98 °C; Rf 0.62 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3260 (NH), 3055 (CH), 1686 (CO), 1539, 1269, 1227, 1072, 822, 725; δH (400 MHz, CDCl₃) 4.44 (1H, dddd, J 17.6, 2.6, 2.0, 1.0 Hz, 2-HH), 4.82 (1H, dddd, J 17.6, 3.5, 2.0, 1.0 Hz, 2-HH), 5.41 (1H, br t, J 7.7 Hz, 5-H), 5.67–5.73 (1H, m, 3-H), 6.11 (1H, ddt, J 11.5, 7.7, 2.0 Hz, 4-H), 7.10–7.16 (2H, m, 8-H and 9-H), 7.27–7.34 (2H, m, 6-H and 7-H), 7.63 (1H, br d, J 7.7 Hz, NH); δC (101 MHz, CDCl₃) 51.5 (CH), 71.1 (CH₂), 92.7 (C), 122.1 (CH), 125.1 (CH), 126.0 (CH), 128.3 (CH), 130.1 (CH), 131.6 (CH), 134.9 (C), 157.3 (C), 160.6 (C); m/z (CI) 307.9830 (MH⁺). C₁₂H₁₁Cl₂CNO₂ requires 307.9827, 272 (37%), 257 (62), 197 (13), 157 (28), 145 (64), 113 (35), 71 (53).

7-Methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187b)

![Diagram of 7-Methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine](attachment)

The reaction was carried out as described for the synthesis of 5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187a) using (2E)-3-(2'-allyloxyphenyl-5'-methyl)prop-2-en-1-ol (184b) (0.150 g, 0.730 mmol). Purification
by column chromatography using (diethyl ether/petroleum ether, 1:10) gave 7-methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187b) (0.173 g, 73%) as a white solid. Mp 146–148 °C; Rf 0.62 (50% diethyl ether/petroleum ether); \( \nu_{\text{max}} \text{cm}^{-1} \) (neat) 3306 (NH), 1713 (CO), 1530, 1494, 1234, 1064, 825; \( \delta_H \) (500 MHz, CDCl$_3$) 2.31 (3H, s, 7-CH$_3$), 4.40 (1H, br dt, \( J = 17.6, 2.1 \) Hz, 2-HH), 4.79 (1H, ddd, \( J = 17.6, 3.5, 2.1 \) Hz, 2-HH), 5.33 (1H, t, \( J = 8.1 \) Hz, 5-H), 5.66–5.72 (1H, m, 3-H), 6.11 (1H, ddt, \( J = 11.5, 8.1, 2.1 \) Hz, 4-H), 7.01 (1H, d, \( J = 8.3 \) Hz, 9-H), 7.08–7.12 (2H, m, 6-H and 8-H), 7.65 (1H, d, \( J = 8.1 \) Hz, NH); \( \delta_C \) (126 MHz, CDCl$_3$) 20.8 (CH$_3$), 51.5 (CH), 71.2 (CH$_2$), 92.7 (C), 121.7 (CH), 126.0 (CH), 128.9 (CH), 130.4 (CH), 131.7 (CH), 134.5 (C), 134.7 (C), 155.0 (C), 160.6 (C); \( m/z \) (ESI) 341.9811 (MNa$^+$, C$_{13}$H$_{12}$Cl$_3$NaNO$_2$ requires 341.9826), 236 (5%), 218 (1), 159 (2).

8-Chloro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187c)

The reaction was carried out as described for the synthesis of 5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187a) using (2E)-3-(2'-allyloxy-4'-chlorophenyl)prop-2-en-1-ol (184c) (0.130 g, 0.580 mmol). The Overman rearrangement step was heated to 140 °C for 24 h. Flash column chromatography using (diethyl ether/petroleum ether, 1:10) gave 8-chloro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187c) (0.141 g, 71%) as a yellow oil. Rf 0.57 (50% diethyl ether/petroleum ether); \( \nu_{\text{max}} \text{cm}^{-1} \) (neat) 3416 (NH), 2960 (CH), 1700 (CO), 1598 (C=C), 1490, 1480, 1271, 1225, 1077, 906, 836, 821, 731; \( \delta_H \) (400 MHz, CDCl$_3$) 4.45 (1H, br dt, \( J = 17.6, 2.1 \) Hz, 2-HH), 4.82 (1H, ddd, \( J = 17.6, 3.4, 2.1 \) Hz, 2-HH), 5.38 (1H, t, \( J = 7.8 \) Hz, 5-H), 5.69–5.75 (1H, m, 3-H), 6.07 (1H, ddt, \( J = 11.5, 7.8, 2.1 \) Hz, 4-H), 7.11 (1H, dd, \( J = 8.1, 2.0 \) Hz, 7-H), 7.14 (1H, d, \( J = 2.0 \) Hz, 9-H), 7.23 (1H, d, \( J = 8.1 \) Hz, 6-H), 7.50 (1H, d, \( J = 7.8 \) Hz, NH); \( \delta_C \) (101 MHz, CDCl$_3$) 51.0 (CH), 71.2 (CH$_2$), 92.5 (C), 122.8 (CH), 125.2
7,9-Dichloro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187d)

The reaction was carried out as described for the synthesis of 5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187a) using (2E)-3-(2'-allyloxy-3',5'-dichlorophenyl)prop-2-en-1-ol (184d) (0.230 g, 0.890 mmol). Purification by column chromatography using (diethyl ether/petroleum ether, 1:30) gave 7,9-dichloro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187d) (0.113 g, 34%) as a white solid. Mp 58–60 °C; Rf 0.58 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3320 (NH), 2920 (CH), 1701 (CO), 1513, 1463, 1173, 908, 839; δH (500 MHz, CDCl₃) 4.47 (1H, dd, J 17.8, 3.5, 2.1 Hz, 2-HH), 4.85 (1H, ddd, J 17.8, 3.5, 2.1 Hz, 2-HH), 5.39 (1H, t, J 8.0 Hz, 5-H), 5.70–5.77 (1H, m, 3-H), 6.06 (1H, ddt, J 11.6, 8.0, 2.1 Hz, 4-H), 7.20 (1H, d, J 2.4 Hz, 8-H), 7.38 (1H, d, J 2.4 Hz, 6-H), 7.54 (1H, br d, J 8.0 Hz, NH); δC (126 MHz, CDCl₃) 50.7 (CH), 70.1 (CH₂), 92.3 (C), 125.3 (CH), 126.8 (CH), 128.5 (C), 130.0 (CH), 130.4 (C), 131.4 (CH), 137.8 (C), 151.4 (C), 160.9 (C); m/z (ESI) 395.8878 (MNa⁺, C₁₂H₉Cl₅NaO₂ requires 395.8890).
7,8-Difluoro-5-(2’,2’,2’-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187e)

![Chemical Structure Image]

The reaction was carried out as described for the synthesis of 5-(2’,2’,2’-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187a) using (2E)-3-(2’-allyloxy-4’,5’-difluorophenyl)prop-2-en-1-ol (184e) (0.040 g, 0.180 mmol). The Overman rearrangement step was heated to 140 °C for 24 h. Purification by column chromatography using (diethyl ether/petroleum ether, 1:30) gave 7,8-difluoro-5-(2’,2’,2’-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187e) (0.042 g, 68%) as a white solid. Mp 106–108 °C; Rf 0.45 (50% diethyl ether/petroleum ether); \( \nu_{\text{max}} / \text{cm}^{-1} \) (neat) 3264 (NH), 2925 (CH), 1711 (CO), 1691 (C=C), 1620, 1542, 1500, 1267, 1161, 888; \( \delta_H \) (500 MHz, CDCl\(_3\)) 4.44 (1H, ddd, \( \text{J} 17.6, 3.5, 2.1 \text{ Hz} \), 2-HH), 4.79 (1H, ddd, \( \text{J} 17.6, 2.8, 2.1 \text{ Hz} \), 2-HH), 5.34 (1H, t, \( \text{J} 7.8 \text{ Hz} \), 5-H), 5.70–5.76 (1H, m, 3-H), 6.05 (1H, ddt, \( \text{J} 11.5, 7.8, 2.1 \text{ Hz} \), 4-H), 6.97 (1H, dd, \( \text{J} 3_{\text{HF}} 10.2, \text{J} 4_{\text{HF}} 6.8 \text{ Hz} \), 9-H), 7.14 (1H, dd, \( \text{J} 3_{\text{HF}} 10.2, \text{J} 4_{\text{HF}} 8.7 \text{ Hz} \), 6-H), 7.47 (1H, d, \( \text{J} 7.8 \text{ Hz} \), NH); \( \delta_C \) (101 MHz, CDCl\(_3\)) 50.7 (CH), 71.3 (CH\(_2\)), 92.4 (C), 111.8 (d, \( \text{J} 3_{\text{CF}} 18.3 \text{ Hz} \), CH), 116.8 (dd, \( \text{J} 2_{\text{CF}} 19.0, \text{J} 4_{\text{CF}} 1.4 \text{ Hz} \), CH), 125.4 (CH), 131.3 (dd, \( \text{J} 3_{\text{CF}} 5.1, \text{J} 4_{\text{CF}} 3.6 \text{ Hz} \), C), 131.6 (CH), 147.0 (dd, \( \text{J} 1_{\text{CF}} 247.0, \text{J} 2_{\text{CF}} 12.5 \text{ Hz} \), C), 150.1 (dd, \( \text{J} 1_{\text{CF}} 251.6, \text{J} 2_{\text{CF}} 13.7 \text{ Hz} \), C), 153.1 (dd, \( \text{J} 3_{\text{CF}} 8.3, \text{J} 4_{\text{CF}} 3.1 \text{ Hz} \), C), 160.8 (C); \( m/z \) (Cl) 341.9665 (MH\(^+\), C\(_{12}\)H\(_9\)Cl\(_3\)F\(_2\)NO\(_2\) requires 341.9667), 308 (49%), 274 (8), 238 (18), 181 (96), 81 (20), 69 (28).
9-Methoxy-7-nitro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187f)

The reaction was carried out as described for the synthesis of 5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187a) using (2E)-3-(2'-allyloxy-3'-methoxy-5'-nitrophenyl)prop-2-en-1-ol (184f) (0.215 g, 0.810 mmol). The Overman rearrangement step was heated to 140 °C for 48 h. Purification by column chromatography using (diethyl ether/petroleum ether, 1:2) gave 9-methoxy-7-nitro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187f) (0.162 g, 52%) as a white solid. Mp 180–182 °C; Rf 0.2 (50% diethyl ether/petroleum ether); ν_max/cm⁻¹ (neat) 3327 (NH), 2943 (CH), 1702 (CO), 1526, 1342, 1056, 909, 822; δ_H (500 MHz, CDCl₃) 3.99 (3H, s, 9-OMe), 4.52 (1H, ddd, J 17.8, 3.5, 2.1 Hz, 2-H), 4.89 (1H, ddd, J 17.8, 2.8, 2.1 Hz, 2-H), 5.54 (1H, t, J 8.1 Hz, 5-H), 5.75–5.9 (1H, m, 3-H), 6.09 (1H, ddt, J 11.6, 8.1, 2.1 Hz, 4-H), 7.54 (1H, br d, J 8.1 Hz, NH), 7.85 (1H, d, J 2.5 Hz, 8-H), 7.86 (1H, d, J 2.5 Hz, 6-H); δ_C (126 MHz, CDCl₃) 50.8 (CH), 56.6 (CH₃), 70.4 (CH₂), 92.3 (C), 108.1 (CH), 115.3 (CH), 125.4 (CH), 131.4 (C), 137.3 (C), 144.6 (C), 150.7 (C), 152.9 (C), 160.9 (C); m/z (ESI) 402.9609 (MNa⁺, C₁₃H₁₁Cl₃NaN₂O₅ requires 402.9626), 363 (2%), 301 (1), 236 (11), 227 (9), 218 (2), 159 (2).

5-(2',2',2'-Trichloromethylcarbonylamino)-2,5-dihydro-1-naphtho[2,1-b]oxepine (187g)
The reaction was carried out as described for the synthesis of 5-(2',2',2'-
trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187a) using (2E)-3-(2'-
allyloxynaphthyl)prop-2-en-1-ol (184g) (0.205 g, 0.850 mmol). Purification by
column chromatography (diethyl ether/petroleum ether, 1:30) gave 5-
(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-naphth[2,1-b]oxepine (187g)
(0.140 g, 46%) as a white solid. Mp 136–138 °C; Rf 0.65 (50% diethyl ether/petroleum ether); ν\text{max}/cm\text{−1} (neat) 3406 (NH), 2940 (CH), 1701 (CO), 1492,
1220, 1045, 818; δ\text{H} (400 MHz, CDCl₃) 4.48 (1H, br dt, J 17.6, 2.1 Hz, 2-HH), 4.93
(1H, br t, J 8.4 Hz, 5-H), 5.74–5.79 (1H, m, 3-H), 6.25–6.30 (1H, m, 4-
H), 6.32 (1H, br t, J 8.4 Hz, 5-H), 7.60 (1H, dd, J 8.5, 8.4, 1.3 Hz, 7-H), 7.83–7.87 (2H, m, 9-H
and 10-H), 7.99 (1H, d, J 8.4 Hz, NH), 8.29 (1H, br d, J 8.4 Hz, 6-H); δ\text{C} (126 MHz,
CDCl₃) 44.9 (CH), 70.5 (CH₂), 92.7 (C), 121.5 (CH), 122.9 (CH), 125.4 (CH), 126.0
(CH), 127.4 (CH), 128.6 (CH), 129.7 (C), 130.6 (C), 130.8 (CH), 131.4 (C), 131.8
(CH), 155.4 (C), 160.8 (C); m/z (ESI) 377.9808 (MNa\text{+}, C₁₆H₁₂Cl₃NaNO₂ requires
377.9826).

8-Chloro-5-(2',2'-dichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-
benzoxepine (188)

<table>
<thead>
<tr>
<th>Cl</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>HN</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>CH₂</td>
<td></td>
</tr>
<tr>
<td>2'</td>
<td></td>
</tr>
</tbody>
</table>

20% Palladium on charcoal (0.03 g) was added to a solution of 8-chloro-5-(2',2',2'-
trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187c) (0.120 g, 0.350
mmol) in ethyl acetate (7 mL). The mixture was stirred under an atmosphere of
hydrogen at room temperature for 1.5 h. The reaction mixture was filtered through
a short pad of Celite® with diethyl ether (100 mL), concentrated in vacuo and
purified by column chromatography (diethyl ether/petroleum ether, 1:10). This
gave 8-chloro-5-(2',2'-dichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-
benzoxepine (188) (0.102 g, 94%) as a white solid. Mp 106–108 °C; ν\text{max}/cm\text{−1}
(neat) 3263 (NH), 2936 (CH), 1670 (CO), 1561, 1479, 1284, 1223, 1213, 1080,
1602, 983, 952, 808; δH (500 MHz, CDCl₃) 1.73–1.93 (2H, m, 3- HH and 4-HH), 2.18–2.30 (2H, m, 3- HH and 4-HH), 3.76 (1H, td, J 12.0, 2.0 Hz, 2-HH), 4.38 (1H, dt, J 12.0, 1.1 Hz, 2-HH), 5.16 (1H, ddd, J 7.8, 6.2, 1.6 Hz, 5-H), 5.94 (1H, s, CHCl₂), 7.05 (1H, dd, J 8.0, 2.1 Hz, 7-H), 7.07 (1H, d, J 2.1 Hz, 9-H), 7.17 (1H, d, J 8.0 Hz, 6-H), 7.20 (1H, d, J 7.8 Hz, NH); δC (126 MHz, CDCl₃) 26.4 (CH₂), 29.8 (CH₂), 53.2 (CH), 66.5 (CH), 74.1 (CH₂), 122.9 (CH), 124.6 (CH), 130.3 (CH), 132.3 (C), 134.5 (C), 160.1 (C), 163.0 (C); m/z (ESI) 329.9812 (MNa⁺, C₁₂H₁₂Cl³NaNO₂ requires 329.9826).

5-Amino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepine (189)

A solution of 8-chloro-5-(2',2'-dichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (188) (0.163 g, 0.530 mmol) and 6M aqueous hydrochloric acid (10 mL) in methanol (1 mL) was stirred at 100 °C for 144 h. The methanol was removed in vacuo and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The remaining aqueous layer was basified by adding aqueous sodium carbonate solution and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were concentrated to afford 5-amino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepine (189) (0.081 g, 78%) as a white solid. Mp 90–92 °C; νmax/cm⁻¹ (neat) 3412 (NH), 2938 (CH), 1594 (C=C), 1478, 1228, 1082, 946, 906, 729; δH (400 MHz, CDCl₃) 1.72 (2H, br s, NH₂), 1.80–1.96 (3H, m, 3-HH and 4-H₂), 2.13–2.22 (1H, m, 3-HH), 3.92 (1H, ddd, J 10.8, 8.0, 2.4 Hz, 5-H), 4.04–4.09 (2H, m, 2-H₂), 7.00 (1H, d, J 2.1 Hz, 9-H), 7.02 (1H, dd, J 8.0, 2.1 Hz, 7-H), 7.20 (1H, d, J 8.0 Hz, 6-H); δC (126 MHz, CDCl₃) 27.2 (CH₂), 33.8 (CH₂), 54.1 (CH), 73.8 (CH₂), 122.4 (CH), 123.9 (CH), 128.4 (CH), 132.7 (C), 135.8 (C), 159.5 (C); m/z (CI) 198.0695 (MH⁺, C₁₀H₁₃Cl³NO requires 198.0686), 181 (100%), 165 (7), 153 (7), 125 (2), 91 (4), 85 (49), 69 (22).
5-N,N'-Bis(tert-butoxycarbonyl)guanidino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepine (191)

Diisopropylethylamine (0.168 mL, 0.960 mmol), and N,N'-bis(tert-butoxycarbonyl)-1H-pyrazole-1-carboxamidine (190) (0.056 g, 0.180 mmol) were added to a solution of 5-amino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepine (189) (0.024 g, 0.120 mmol) in methanol (10 mL) and stirred for 48 h at room temperature. The methanol was removed in vacuo. The resulting residue was dissolved in diethyl ether (10 mL) and acidified by 0.2M aqueous hydrochloric acid (1 mL). The organic layer was washed with brine (10 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography (diethyl ether/petroleum ether, 1:15) gave 5-N,N'-bis(tert-butoxycarbonyl)guanidino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepine (191) (0.043 g, 80%) as a white solid. Mp 169–171 °C (decomposition); Rf 0.73 (50% diethyl ether/petroleum ether); v max/cm⁻¹ (neat) 3321 (NH), 2981 (CH), 1722 (CO), 1637, 1612 (C=C), 1560, 1479, 1412, 1324, 1227, 1154, 1124, 1057, 909, 732; δ H (400 MHz, CDCl₃) 1.48 (9H, s, O₄Bu), 1.50 (9H, s, O₄Bu), 1.72–1.80 (1H, m, 4-HH), 1.85–1.93 (1H, m, 4-HH), 2.15–2.27 (2H, m, 3-H₂), 3.80 (1H, ddd, J 12.0, 10.1, 2.1 Hz, 2-HH), 4.31 (1H, dt, J 12.0, 4.2 Hz, 2-HH), 5.50 (1H, ddd, J 9.0, 6.6, 2.0 Hz, 5-H), 7.02 (1H, dd, J 8.1, 2.1 Hz, 7-H), 7.05 (1H, d, J 2.1 Hz, 9-H), 7.24 (1H, d, J 8.1 Hz, 6-H), 9.01 (1H, d, J 9.0 Hz, NH), 11.46 (1H, s, NH); δ C (101 MHz, CDCl₃) 26.9 (CH₂), 28.1 (3 × CH₃), 28.3 (3 × CH₃), 30.4 (CH₂), 52.5 (CH), 73.9 (CH₂), 79.1 (C), 83.0 (C), 122.7 (CH), 124.1 (CH), 130.5 (CH), 133.1 (C), 133.8 (C), 153.0 (C), 155.1 (C), 160.3 (C), 163.7 (C); m/z (EI) 439.1873 (M⁺, C₂₁H₃₀⁵Cl₃N₃O₅ requires 439.1874), 383 (8%), 327 (63), 266 (35), 196 (11), 181 (24), 82 (44), 59 (100).
8-Chloro-5-guanidino-2,3,4,5-tetrahydro-1-benzoxepine trifluoroacetic acid (175)

A solution of 5-N,N'-bis(tert-butoxycarbonyl)guanidino-8-chloro-2,3,4,5-tetrahydro-1-benzoxepine (191) (0.012 g, 0.027 mmol) in dichloromethane (0.450 mL) and trifluoroacetic acid (0.011 mL, 0.140 mmol) was stirred at 45 °C for 48 h. The reaction mixture was concentrated in vacuo to afford 8-chloro-5-guanidino-2,3,4,5-tetrahydro-1-benzoxepine trifluoroacetic acid (175) (0.096 g, quantitative) as a white solid. Mp 229–231 °C (decomposition); νmax/cm⁻¹ (neat) 3364 (NH), 3160 (NH), 2925 (CH), 1679, 1613, 1481, 1201, 1187, 1144, 972, 843, 801, 724; δH (400 MHz, CDCl₃) 1.96–2.16 (2H, m, 3-H₂ and 4-H₂), 4.00 (1H, ddd, J 9.6, 5.2, 2.4 Hz, 2-HH), 4.07 (1H, ddd, J 9.6, 5.6, 2.8 Hz, 2-HH), 4.84 (1H, t, J 4.0 Hz, 5-H), 7.08 (1H, d, J 2.1 Hz, 9-H), 7.12 (1H, dd, J 8.2, 2.1 Hz, 7-H), 7.21 (1H, d, J 8.2 Hz, 6-H); δC (101 MHz, CDCl₃) 27.2 (CH₂), 31.2 (CH₂), 53.7 (CH), 73.2 (CH₂), 122.4 (CH), 123.9 (CH), 128.1 (CH), 132.5 (C), 133.9 (C), 156.5 (C), 159.7 (C); m/z (ESI) 240.0902 (MH⁺, C₁₁H₁₅Cl₃N₃O requires 240.0898).

(3R*,4S*,5S*)-3,4-Dihydroxy-7-methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (193b)

Tetramethylethylenediamine (0.013 mL, 0.080 mmol) was added to a solution of 7-methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187b) (0.024 g, 0.076 mmol) in dichloromethane (2 mL) and cooled to −78 °C. After 0.2 h, a solution of osmium tetroxide (0.021 g, 0.080 mmol) in dichloromethane (1 mL)
was added dropwise. The solution was stirred at −78 °C for 1 h, allowed to return to room temperature over 2 h and then concentrated in vacuo. The residue was taken up in a solution of methanol (4 mL) and 12M aqueous hydrochloric acid (0.5 mL) and stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo. The resulting residue was purified by column chromatography (ethyl acetate/petroleum ether, 1:1) to yield (3R*,4S*,5S*)-3,4-dihydroxy-7-methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (193b) (0.016 g, 61%) as a white solid. Mp 146–148 °C; Rf 0.15 (75% diethyl ether/petroleum ether); ν_{max}/cm⁻¹ (neat) 3413 (NH and OH), 2927 (CH), 1707 (CO), 1510, 1500, 828, 756; δ_H (400 MHz, CDCl₃) 2.31 (3H, s, 7-CH₃), 2.98 (1H, d, J 2.2 Hz, OH), 3.13 (1H, d, J 5.4 Hz, OH), 3.89 (1H, d, J 13.2 Hz, 2-HH), 4.07–4.12 (1H, m, 4-H), 4.20–4.26 (1H, m, 3-H), 4.33 (1H, dd, J 13.2, 3.6 Hz, 2-HH), 5.15 (1H, dd, J 8.1, 2.1 Hz, 5-H), 5.96 (1H, d, J 8.2, 9-H), 7.08 (1H, dd, J 8.2, 2.0 Hz, 6-H), 7.14 (1H, d, 2.0 Hz, 7-H), 8.75 (1H, br d, J 8.1 Hz, NH); δ_C (126 MHz, CDCl₃) 20.8 (CH₃), 60.1 (CH), 71.1 (CH), 73.8 (CH₂), 77.2 (CH), 92.6 (C), 121.8 (CH), 128.3 (C), 130.8 (CH), 131.3 (CH), 134.6 (C), 157.5 (C), 162.3 (C); m/z (ESI) 375.9866 (MNa⁺, C₁₃H₁₄Cl₃NNaO₄ requires 375.9881).

(3R*,4S*,5S*)-3,4-Dihydroxy-9-methoxy-7-nitro-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (193f)

The reaction was carried out as described for the synthesis of (3R*,4S*,5S*)-3,4-dihydroxy-7-methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (193b) using 9-methoxy-7-nitro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187f) (0.043 g, 0.11 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:1) gave (3R*,4S*,5S*)-3,4-dihydroxy-9-methoxy-7-nitro-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (193f) (0.034 g, 74%) as a white foam. Rf 0.10 (50% diethyl ether/petroleum ether); ν_{max}/cm⁻¹...
(neat) 3344 (NH and OH), 2926 (CH), 1704 (CO), 1528, 1215, 756; δH (400 MHz, CDCl3) 2.47 (1H, br s, OH), 2.71 (1H, br s, OH), 3.98 (3H, s, OCH3), 4.03 (1H, dd, J 12.0, 8.9 Hz, 2-HH), 4.20 (1H, dd, J 12.0, 2.8 Hz, 2-HH), 4.24–4.31 (2H, m, 3-H and 4-H), 5.38 (1H, t, J 7.6 Hz, 5-H), 7.34 (1H, d, J 7.6 Hz, NH), 7.82 (1H, d, J 2.3 Hz, 8-H), 7.88 (1H, d, J 2.3 Hz, 6-H); δC (101 MHz, CDCl3) 54.5 (CH), 56.6 (CH3), 69.3 (CH), 69.5 (CH), 72.3 (CH2), 92.1 (C), 108.0 (CH), 116.9 (CH), 131.4 (C), 144.6 (C), 152.4 (C), 152.6 (C), 161.9 (C); m/z (ESI) 436.9671 (MNa+, C13H1335Cl3N2NaO7 requires 436.9681).

(3R*,4S*,5S*)-3,4-Dihydroxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-naphtho[2,1-b]oxepine (193g)

The reaction was carried out as described for the synthesis of (3R*,4S*,5S*)-3,4-dihydroxy-7-methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (193b) using 5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-naphtho[2,1-b]oxepine (187g) (0.027 g, 0.080 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:1) gave (3R*,4S*,5S*)-3,4-dihydroxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-naphtho[2,1-b]oxepine (193g) (0.030 g, quantitative) as a white foam. Rf 0.42 (50% ethyl acetate/petroleum ether); νmax/cm−1 (neat) 3354 (NH and OH), 2922 (CH), 1690 (CO), 1508, 1218, 1066, 835, 815, 755, 728; δH (400 MHz, CDCl3) 2.39 (1H, d, J 8.5 Hz, OH), 2.50 (1H, d, J 5.2 Hz, OH), 3.76 (1H, t, J 12.0 Hz, 2-HH), 4.28–4.48 (2H, m, 2-HH and 3-H), 4.68 (1H, br s, 4-H), 6.40 (1H, t, J 7.6 Hz, 5-H), 7.29 (1H, d, J 8.5 Hz, 11-H), 7.45–7.72 (3H, m, 7-H, 8-H and NH), 7.88 (2H, d, J 8.5 Hz, 9-H and 10-H), 8.23 (1H, d, J 8.5 Hz, 6-H); δC (101 MHz, CDCl3) 49.3 (CH), 68.7 (CH), 68.8 (CH), 71.0 (CH2), 92.2 (C), 121.6 (CH), 122.4 (C), 122.7 (CH), 125.4 (CH), 127.8 (CH), 128.9 (CH), 131.5 (C), 131.6 (CH), 133.1 (C), 157.3 (C), 161.7 (C); m/z (ESI) 411.9861 (MNa+, C16H1435Cl3N2NaO7 requires 411.9881).
(3S*,4S*,5S*)-3,4-Dihydroxy-7-methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoepine (199b)

3-Chloroperbenzoic acid (0.112 g, 0.70 mmol) was added to a stirred solution of 7-methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoepine (187b) (0.042 g, 0.13 mmol) in dichloromethane (3 mL) at 0 °C. The reaction mixture was stirred from 0 °C to room temperature over 18 h then cooled to 0 °C before 3-chloroperbenzoic acid (0.112 g, 0.70 mmol) was added. The reaction mixture was stirred for a further 24 h, quenched by the addition of an aqueous saturated solution of sodium sulfite (5 mL) and extracted with dichloromethane (2 × 5 mL). The combined organic layers were washed with an aqueous saturated solution of sodium hydrogen carbonate (3 × 10 mL), water (10 mL) and brine (10 mL), then dried (MgSO₄), filtered and concentrated in vacuo. 1M Aqueous sulfuric acid (2 mL) was added to the resulting white solid in 1,4-dioxane (2 mL) and stirred at room temperature for 24 h. The reaction was quenched by addition of an aqueous saturated solution of sodium hydrogen carbonate (3 mL) and extracted with diethyl ether (2 × 10 mL). The organic layer was washed with water (10 mL), brine (10 mL), then dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (ethyl acetate/petroleum ether, 1:1) gave (3S*,4S*,5S*)-3,4-dihydroxy-7-methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoepine (199b) (0.027 g, 58%) as a white foam. Rᵣ 0.10 (75% diethyl ether/petroleum ether); vₘₐₓ/cm⁻¹ (neat) 3413 (NH and OH), 2927 (CH), 1707 (CO), 1510, 1500, 1215, 828, 756; δₜ (400 MHz, CDCl₃) 2.33 (3H, s, CH₃), 2.70 (1H, d, J 3.1 Hz, OH), 3.47 (1H, d, J 6.0 Hz, OH), 3.65 (1H, dd, J 12.2, 4.2 Hz, 2'-H₂), 3.78–3.85 (1H, m, 4-H), 4.06–4.15 (1H, m, 3-H), 4.40 (1H, dd, J 12.2, 4.2 Hz, 2'-H₂), 5.28 (1H, dd, J 7.8, 1.6 Hz, 5-H), 6.99 (1H, d, J 8.2, 9-H), 7.08–7.15 (2H, m, 6-H and 8-H), 7.33 (1H, d, J 7.8 Hz, NH); δₛ (126 MHz, CDCl₃) 20.7 (CH₃), 58.3 (CH), 71.0 (CH), 74.1 (CH₂), 76.5 (CH), 92.2, (C), 122.1 (CH), 128.1 (C), 130.5 (CH), 131.2 (CH), 135.1 (C), 156.5 (C), 163.2 (C); m/z (ESI) 375.9874 (MNa⁺, C₁₃H₁₄³⁵Cl₃NNaO₄ requires 375.9881).
(3S*,4S*,5S*)-3,4-Dihydroxy-7,8-difluoro-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (199e)

The reaction was carried out as described for the synthesis of (3S*,4S*,5S*)-3,4-dihydroxy-7-methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (199b) using 7,8-difluoro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (187e) (0.026 g, 0.080 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:1) gave (3S*,4S*,5S*)-3,4-dihydroxy-7,8-difluoro-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (199e) (0.017 g, 62%) as a white foam. $\nu_{\text{max}}$ cm$^{-1}$ (neat) 3426 (NH and OH), 2937 (CH), 1669 (CO), 1504, 1162, 905, 727; $\delta$H (400 MHz, CDCl$_3$) 2.75 (1H, d, $J$ 4.0 Hz, OH), 3.32 (1H, d, $J$ 4.9 Hz, OH), 3.82 (1H, dd, $J$ 12.4, 7.9 Hz, 2-HH), 3.88–3.95 (1H, m, 4-H), 4.01–4.09 (1H, m, 3-H), 4.32 (1H, dd, $J$ 12.4, 3.4 Hz, 2-HH), 5.33 (1H, dd, $J$ 8.2, 1.6 Hz, 5-H), 6.97 (1H, dd, $^3J_{HF}$ 10.3, $^4J_{HF}$ 6.9 Hz, 9-H), 7.11 (1H, dd, $^3J_{HF}$ 10.3, $^4J_{HF}$ 8.5 Hz, 6-H), 7.36 (1H, d, $J$ 8.2 Hz, NH); $\delta$C (126 MHz, CDCl$_3$) 55.9 (CH), 70.9 (CH), 73.6 (CH$_2$), 75.1 (CH), 92.1 (C), 112.0 (d, $^2J_{CF}$ 18.3 Hz, CH), 117.7 (d, $^2J_{CF}$ 21.3 Hz, CH), 125.3 (d, $^3J_{CF}$ 5.0 Hz, C), 147.4 (dd, $^1J_{CF}$ 247.3, $^2J_{CF}$ 12.5 Hz, C), 150.2 (dd, $^1J_{CF}$ 253.5, $^2J_{CF}$ 14.4 Hz, C), 154.3 (dd, $^3J_{CF}$ 8.1, $^4J_{CF}$ 2.9 Hz, C), 162.9 (C); m/z (ESI) 397.9522 (MNa$^+$, C$_{12}$H$_{10}$Cl$_3$F$_2$NNaO$_4$ requires 397.9536).

(3S*,4S*,5S*)-3,4-Dihydroxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-naphtho[2,1-b]oxepine (199g)

The reaction was carried out as described for the synthesis of (3S*,4S*,5S*)-3,4-dihydroxy-7-methyl-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-
benzoxepine (199b) using 5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-naphtho[2,1-b]oxepine (187g) (0.060 g, 0.17 mmol), except that the second step was heated at 50 °C. Purification by column chromatography (ethyl acetate/petroleum ether, 1:1) gave (3S*,4S*,5S*)-3,4-dihydroxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-naphtho[2,1-b]oxepine (199g) (0.029 g, 44%) as a white solid. Mp 170 °C (decomposition); Rf 0.12 (75% diethyl ether/petroleum ether); v max/cm−1 (neat) 3427 (NH and OH), 2930 (CH), 1696 (CO), 1514, 1067, 1049, 907, 822, 732, 649; δ H (400 MHz, CDCl3) 2.12 (1H, d, J 6.4 Hz, OH), 2.37 (1H, d, J 3.6 Hz, OH), 4.09–4.14 (1H, m, 3-H), 4.22 (2H, dd, J 13.0, 2.1 Hz, 2-HH), 4.41 (1H, ddd, J 13.0, 3.5, 0.8 Hz, 2-HH), 4.47–4.53 (1H, m, 4-H), 6.21 (1H, dd, J 8.4, 5.6 Hz, 5-H), 7.29 (1H, d, J 8.8 Hz, 11-H), 7.47 (1H, ddd, J 8.3, 6.9, 0.8 Hz, 8-H), 7.61 (1H, ddd, J 8.6, 6.9, 1.4 Hz, 7-H), 7.84–7.86 (2H, m, 9-H and 10-H), 8.30 (1H, dd, J 8.6, 0.8 Hz, 6-H), 8.64 (1H, d, J 8.4 Hz, NH); δ C (101 MHz, CDCl3) 52.6 (CH), 69.9 (CH), 72.2 (CH2), 74.0 (CH), 92.0 (C), 121.7 (CH), 122.8 (C), 123.1 (CH), 125.3 (CH), 127.6 (CH), 128.8 (CH), 131.4 (C), 131.5 (CH), 133.4 (C), 157.6 (C), 161.7 (C); m/z (ESI) 411.9867 (MNa+, C16H1435Cl3NaNO4 requires 411.9881).

2-Iodo-4-methylaniline (203b)187

Iodine (7.12 g, 28.0 mmol) was added to a stirred solution of 4-methylaniline (202b) (2.00 g, 18.7 mmol) and sodium hydrogen carbonate (2.35 g, 28.1 mmol) in toluene and water (52 mL, 9:1) and warmed to 50 °C for 24 h. The mixture was diluted with 5% aqueous sodium thiosulfate solution (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (50 mL), dried (MgSO4), filtered and concentrated in vacuo. Purification by column chromatography (diethyl ether/petroleum ether, 1:40) yielded 2-iodo-4-methylaniline (203b) (4.03 g, 93%) as a brown oil. Spectroscopic data were consistent with the literature.187 Rf 0.63 (50% diethyl ether/petroleum ether); δ H (400 MHz, CDCl3) 2.20 (3H, s, CH3), 3.93 (2H, br s, NH2), 6.66 (1H, d, J 8.0 Hz, 6-H), 6.94 (1H, dd, J 8.0, 1.5 Hz, 5-H), 7.47 (1H, d, J 1.5 Hz, 3-H); δ C (101 MHz,
CDCl₃) 19.8 (CH₃), 84.3 (C), 114.7 (CH), 129.5 (C), 130.1 (CH), 139.0 (CH), 144.3 (C); m/z (EI) 233 (M⁺, 100%), 232 (16), 157 (5), 127 (5), 106 (20), 77 (8), 51 (5).

2-Iodo-4-methoxyaniline (203c)¹⁸⁸

Fuming nitric acid (0.0630 g, 1.00 mmol) and concentrated sulfuric acid (2 drops) were added to 3-iodoanisole (205) (0.234 g, 1.00 mmol) at 0 °C and the reaction mixture was stirred for 6 h. The mixture was allowed to warm to room temperature and stirred for 18 h. The mixture was diluted with water (5 mL) and extracted with ethyl acetate (50 mL), washed with brine (5 mL), dried (MgSO₄), filtered and concentrated in vacuo to yield 2-iodo-4-methoxy-1-nitrobenzene as a brown oil which was used without further purification. Iron (0.558 g, 10.0 mmol) and ammonium chloride (0.214 g, 4.00 mmol) were added to 2-iodo-4-methoxy-1-nitrobenzene in methanol (9 mL) and water (3 mL) and warmed to 50 °C for 24 h. The reaction mixture was cooled to room temperature and filtered. The liquid phase was diluted with water (10 mL), extracted with ethyl acetate (50 mL), washed with brine (5 mL), dried (MgSO₄), filtered, concentrated in vacuo. Purification by column chromatography (diethyl ether/petroleum ether, 1:20) gave 2-iodo-4-methoxyaniline (203c) (0.076 g, 30%) as a brown oil. Spectroscopic data were consistent with the literature.¹⁸⁸ Rf 0.45 (50% diethyl ether/petroleum ether); δH (400 MHz, CDCl₃) 3.72 (3H, s, OCH₃), 3.75 (2H, br s, NH₂), 6.69 (1H, d, J 8.7 Hz, 6-H), 6.77 (1H, dd, J 8.7, 2.8 Hz, 5-H), 7.20 (1H, d, J 2.8 Hz, 3-H); δC (101 MHz, CDCl₃) 56.0 (CH₃), 84.3 (C), 115.4 (CH), 116.2 (CH), 123.6 (CH), 140.9 (C), 152.7 (C); m/z (ESI) 250 (MH⁺, 100%), 227 (5), 122 (20), 108 (15).

4-Fluoro-2-idoaniline (203d)¹⁸⁷

The reaction was carried out as described for the synthesis of 2-iodo-4-methylaniline (203b) using 4-fluoroaniline (202d) (3.00 g, 27.0 mmol), iodine (13.7 g, 54.0 mmol) and sodium hydrogencarbonate (4.50 g, 54.0 mmol). The reaction
was heated to 70 °C for 60 h. Purification by column chromatography (diethyl ether/petroleum ether, 1:30) gave 4-fluoro-2-iodoaniline (203d) (5.18 g, 81%) as a brown oil. Spectroscopic data were consistent with the literature.\textsuperscript{187} R<sub>f</sub> 0.55 (50% diethyl ether/petroleum ether); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 3.94 (2H, br s, NH<sub>2</sub>), 6.68 (1H, dd, J 8.8, \textit{J}_{HF} 4.9 Hz, 6-H), 6.89 (1H, ddd, J 8.8, \textit{J}_{HF} 8.0, 2.8 Hz, 5-H), 7.37 (1H, dd, \textit{J}_{HF} 7.9, J 2.8 Hz, 3-H); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 82.7 (d, \textit{J}_{CF} 8.8 Hz, C), 114.7 (d, \textit{J}_{CF} 7.5 Hz, CH), 116.2 (d, \textit{J}_{CF} 22.3 Hz, CH), 125.1 (d, \textit{J}_{CF} 24.7 Hz, CH), 143.3 (d, \textit{J}_{CF} 2.2 Hz, C), 155.3 (d, \textit{J}_{CF} 240.7 Hz, C); m/z (ESI) 238 (MH<sup>+</sup>, 100%).

5-Fluoro-2-iodoaniline (203e)\textsuperscript{238}

![5-Fluoro-2-iodoaniline](image)

The reaction was carried out as described for the synthesis of 2-iodo-4-methylaniline (203b) using 3-fluoroaniline (202e) (3.00 g, 27.0 mmol), iodine (13.7 g, 54.0 mmol) and sodium hydrogencarbonate (4.50 g, 54.0 mmol). The reaction was heated to 70 °C for 50 h. Purification by column chromatography (diethyl ether/petroleum ether, 1:30) gave 5-fluoro-2-iodoaniline (203e) (0.93 g, 15%) as a brown oil. Spectroscopic data were consistent with the literature.\textsuperscript{238} R<sub>f</sub> 0.60 (50% diethyl ether/petroleum ether); δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 4.18 (2H, br s, NH<sub>2</sub>), 6.25 (1H, ddd, J 8.7, \textit{J}_{HF} 8.3, 2.8 Hz, 4-H), 6.46 (1H, dd, \textit{J}_{HF} 10.5, J 2.8, Hz, 6-H), 7.54 (1H, dd, J 8.7, \textit{J}_{HF} 6.2 Hz, 3-H); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 76.9 (d, \textit{J}_{CF} 3.0 Hz, C), 101.5 (d, \textit{J}_{CF} 25.6 Hz, CH), 107.2 (d, \textit{J}_{CF} 22.3 Hz, CH), 139.7 (d, \textit{J}_{CF} 9.6 Hz, CH), 148.1 (d, \textit{J}_{CF} 11.0 Hz, C), 164.0 (d, \textit{J}_{CF} 244.7 Hz, C); m/z (EI) 237 (M<sup>+</sup>, 100%), 184 (3), 156 (11), 127 (4), 110 (20), 83 (12), 65 (5).
4-Chloro-2-iodoaniline (203f)\textsuperscript{187}

![Chemical Structure]

The reaction was carried out as described for the synthesis of 2-iodo-4-methylaniline (203b) using 4-chloroaniline (202f) (3.00 g, 23.5 mmol), iodine (12.0 g, 47.0 mmol) and sodium hydrogencarbonate (4.00 g, 47.0 mmol). The reaction was heated to 70 °C for 90 h. Purification by column chromatography (diethyl ether/petroleum ether, 1:30) gave 4-chloro-2-iodoaniline (203f) (3.51 g, 59%) as a brown oil. Spectroscopic data were consistent with the literature.\textsuperscript{187} R\textsubscript{f} 0.50 (50% diethyl ether/petroleum ether); \( \delta \textsubscript{H} \) (400 MHz, CDCl\textsubscript{3}) 4.08 (2H, br s, NH\textsubscript{2}), 6.66 (1H, d, \( J \textsubscript{8.6} \text{ Hz, 6-H} \)), 7.10 (1H, dd, \( J \textsubscript{8.6, 2.3} \text{ Hz, 5-H} \)), 7.60 (1H, d, \( J \textsubscript{2.3} \text{ Hz, 3-H} \)), \( \delta \textsubscript{C} \) (101 MHz, CDCl\textsubscript{3}) 83.5 (C), 115.0 (CH), 123.2 (C), 129.3 (CH), 137.8 (CH), 145.6 (C); \textit{m/z} (Cl) 254 (MH\textsuperscript{+}, 10%), 184 (5), 133 (23), 128 (49), 113 (100), 109 (12), 97 (56), 85 (41), 71 (80).

Methyl (2\textit{E})-3-(2\textquoteleft-aminophenyl)prop-2-enoate (206a)\textsuperscript{187}

![Chemical Structure]

Methyl acrylate (1.53 mL, 18.3 mmol) was added to a solution of 2-iodoaniline (203a) (2.00 g, 9.13 mmol), palladium acetate (0.110 g, 0.460 mmol), triphenylphosphine (0.239 g, 0.913 mmol), potassium carbonate (1.26 g, 9.13 mmol) and tetrabutylammonium bromide (0.741 g, 2.30 mmol) in \( N,N\textquoteleft \)-dimethylformamide (90 mL). The reaction mixture was stirred at 80 °C for 2 h. The mixture was cooled to room temperature, diluted with water (50 mL) and extracted with diethyl ether (3 x 50 mL). The organic layer was washed with 5% aqueous lithium chloride solution (10 mL) and brine (10 mL), dried (MgSO\textsubscript{4}), filtered and concentrated in vacuo. The residue was purified by column chromatography (diethyl ether/petroleum ether, 1:4) to give methyl (2\textit{E})-3-(2\textquoteleft-aminophenyl)prop-2-enoate (206a) (1.59 g, 99%) as a yellow solid. Mp 64–66 °C; Spectroscopic data were consistent with the literature.\textsuperscript{187} R\textsubscript{f} 0.33 (50% diethyl ether/petroleum ether; \( \delta \textsubscript{H} \) (400 MHz, CDCl\textsubscript{3}) 3.80 (3H, s, OCH\textsubscript{3}), 3.98 (2H, br s, NH\textsubscript{2}), 6.36 (1H, d, \( J \textsubscript{15.8} \text{ Hz} \)).
Hz, 2-H), 6.70 (1H, dd, J 8.0, 1.3 Hz, 3'-H), 6.77 (1H, ddd, J 7.9, 1.3 Hz, 4'-H), 7.17 (1H, ddd, J 7.9, 1.3 Hz, 5'-H), 7.38 (1H, dd, J 7.9, 1.3 Hz, 6'-H), 7.83 (1H, d, J 15.8 Hz, 3-H); δC (101 MHz, CDCl₃) 51.7 (CH₃), 116.7 (CH), 117.7 (CH), 119.0 (CH), 119.9 (C), 128.1 (CH), 131.3 (CH), 140.3 (CH), 145.6 (C), 167.7 (C); m/z (ESI) 200 (MNa⁺, 4%), 168 (26), 159 (3), 146 (100), 128 (31).

Methyl (2E)-3-(2'-amino-5'-methoxyphenyl)prop-2-enoate (206b)

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2'-aminophenyl)prop-2-enoate (206a) using 4-methoxy-2-iodoaniline (203b) (2.00 g, 8.58 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:3) gave methyl (2E)-3-(2'-amino-5'-methoxyphenyl)prop-2-enoate (206b) (1.64 g, quantitative) as a yellow solid. Mp 84–86 °C; Spectroscopic data were consistent with the literature. Rf 0.28 (50% diethyl ether/petroleum ether); δH (400 MHz, CDCl₃) 2.24 (3H, s, 5'-CH₃), 3.79 (3H, s, OCH₃), 3.86 (2H, br s, NH₂), 6.34 (1H, d, J 15.8 Hz, 2-H), 6.62 (1H, d, J 8.1 Hz, 3'-H), 6.99 (1H, dd, J 8.1, 1.5 Hz, 4'-H), 7.19 (1H, d, J 1.5 Hz, 6'-H), 7.82 (1H, d, J 15.8 Hz, 3-H); δC (101 MHz, CDCl₃) 20.4 (CH₃), 51.6 (CH₃), 117.0 (CH), 117.4 (CH), 119.9 (C), 128.2 (C), 128.2 (CH), 132.3 (CH), 140.4 (CH), 143.3 (C), 167.8 (C); m/z (ESI) 214 (MNa⁺, 100%), 192 (11), 182 (23).

Methyl (2E)-3-(2'-amino-5'-methoxyphenyl)prop-2-enoate (206c)

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2'-aminophenyl)prop-2-enoate (206a) using 4-methoxy-2-iodoaniline (203c) (0.170 g, 0.680 mmol) and potassium carbonate (0.188 g, 1.36 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:3) gave methyl (2E)-3-
(2’-amino-5’-methoxyphenyl)prop-2-enoate (206c) (0.141 g, quantitative) as a yellow solid. Mp 93–95 °C; Spectroscopic data were consistent with the literature.\(^\text{240}\) R\(_f\) 0.20 (50% diethyl ether/petroleum ether); \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 3.71 (2H, br s, NH\(_2\)), 3.76 (3H, s, OCH\(_3\)), 3.81 (3H, s, OCH\(_3\)), 6.35 (1H, d, J 15.8 Hz, 2-H), 6.67 (1H, d, J 8.7 Hz, 3’-H), 6.82 (1H, dd, J 8.7, 2.9 Hz, 4’-H), 6.92 (1H, d, J 2.9 Hz, 6’-H), 7.82 (1H, d, J 15.8 Hz, 3-H); \(\delta\)\(_C\) (101 MHz, CDCl\(_3\)) 51.7 (CH\(_3\)), 55.8 (CH\(_3\)), 111.6 (CH), 117.9 (CH), 118.4 (CH), 118.7 (CH), 120.8 (C), 139.6 (C), 140.2 (CH), 152.9 (C), 167.6 (C); \(m/z\) (ESI) 208 (MH\(^+\), 100%).

**Methyl (2E)-3-(2’-amino-5’-fluorophenyl)prop-2-enoate (206d)\(^\text{187}\)**

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2’-aminophenyl)prop-2-enoate (206a) using 4-fluoro-2-iodoaniline (203d) (3.77 g, 16.0 mmol) and potassium carbonate (4.40 g, 32.0 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:3) gave methyl (2E)-3-(2’-amino-5’-fluorophenyl)prop-2-enoate (206d) (2.50 g, 81%) as a yellow solid. Mp 96–98 °C (lit.\(^\text{187}\) 93–95 °C); R\(_f\) 0.28 (50% diethyl ether/petroleum ether); \(\delta\)\(_H\) (400 MHz, CDCl\(_3\)) 3.80 (3H, s, OCH\(_3\)), 3.86 (2H, br s, NH\(_2\)), 6.33 (1H, d, J 15.8 Hz, 2-H), 6.65 (1H, dd, J 8.7, 4\(_J\)\(_HF\) 4.8 Hz, 3’-H), 6.90 (1H, td, J 8.7, 2.9 Hz, 4’-H), 7.08 (1H, dd, 3\(_J\)\(_HF\) 9.5, J 2.9 Hz, 6’-H), 7.76 (1H, dd, J 15.8, 5\(_J\)\(_HF\) 1.1 Hz, 3-H); \(\delta\)\(_C\) (101 MHz, CDCl\(_3\)) 51.8 (CH\(_3\)), 113.4 (d, 2\(_J_{CF}\) 22.7 Hz, CH), 118.0 (d, 3\(_J_{CF}\) 7.7 Hz, CH), 118.3 (d, 2\(_J_{CF}\) 23.0 Hz, CH), 118.9 (CH), 120.8 (d, 3\(_J_{CF}\) 7.2 Hz, C), 139.1 (d, 4\(_J_{CF}\) 2.2 Hz, CH), 141.8 (C), 156.2 (d, 1\(_J_{CF}\) 237.0 Hz, C), 167.3 (C); \(m/z\) (ESI) 218 (MNa\(^+\), 100%), 169 (25), 186 (13), 164 (20).

**Methyl (2E)-3-(2’-amino-4’-fluorophenyl)prop-2-enoate (206e)\(^\text{240}\)**
The reaction was carried out as described for the synthesis of methyl (2E)-3-(2'-aminophenyl)prop-2-enoate (206a) using 5-fluoro-2-iodoaniline (203e) (0.926 g, 3.90 mmol) and potassium carbonate (1.08 g, 7.80 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:3) gave methyl (2E)-3-(2'-amino-4'-fluorophenyl)prop-2-enoate (206e) (0.639 g, 84%) as a yellow solid. Mp 107–109 °C; Spectroscopic data were consistent with the literature.240 Rf 0.25 (50% diethyl ether/petroleum ether); δH (400 MHz, CDCl3) 3.80 (3H, s, OCH3), 4.11 (2H, br s, NH2), 6.29 (1H, d, J 15.8 Hz, 2-H), 6.39 (1H, dd, JHF 10.5, J 2.5 Hz, 3'-H), 6.47 (1H, td, J 8.7, 2.5 Hz, 5'-H), 7.34 (1H, dd, J 8.7, JHF 6.4 Hz, 6'-H), 7.74 (1H, d, J 15.8 Hz, 3-H); δC (101 MHz, CDCl3) 51.7 (CH3), 117.9 (CH), 121.1 (C), 123.7 (C), 126.5 (C), 131.0 (CH), 138.9 (CH), 144.0 (C), 167.3 (C); m/z (ESI) 218 (MNa+, 100%), 186 (59), 164 (6).

Methyl (2E)-3-(2'-amino-5'-chlorophenyl)prop-2-enoate (206f)187

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2'-aminophenyl)prop-2-enoate (206a) using 4-chloro-2-iodoaniline (203f) (0.975 g, 3.90 mmol) and potassium carbonate (1.08 g, 7.80 mmol). The reaction mixture was stirred at 80 °C for 8 h. Purification by column chromatography (ethyl acetate/petroleum ether, 1:3) gave methyl (2E)-3-(2'-amino-5'-chlorophenyl)prop-2-enoate (206f) (0.622 g, 76%) as a yellow solid. Mp 92–94 °C; Spectroscopic data were consistent with the literature.187 Rf 0.18 (50% diethyl ether/petroleum ether); δH (400 MHz, CDCl3) 3.81 (3H, s, OCH3), 3.97 (2H, br s, NH2), 6.34 (1H, d, J 15.8 Hz, 2-H), 6.64 (1H, d, J 8.6 Hz, 3'-H), 7.12 (1H, dd, J 8.6, 2.4 Hz, 4'-H), 7.34 (1H, d, J 2.4 Hz, 6'-H), 7.73 (1H, d, J 15.8 Hz, 3-H); δC (101 MHz, CDCl3) 51.8 (CH3), 117.9 (CH), 119.0 (CH), 121.1 (C), 123.7 (C), 127.3 (CH), 131.0 (CH), 138.9 (CH), 144.0 (C), 167.3 (C); m/z (ESI) 234 (MNa+, 64%), 202 (46), 186 (100).
Methyl (2E)-3-(2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207a)\textsuperscript{241}

\[
\begin{align*}
\text{4'} & \quad \text{3'} & \quad \text{NHTs} & \quad \text{5'} & \quad \text{2'} & \quad \text{1} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

\(p\)-Toluenesulfonfonyl chloride (2.50 g, 13 mmol) was added to a solution of methyl (2E)-3-(2'-aminophenyl)prop-2-enoate (206a) (1.53 g, 8.70 mmol) in pyridine (43 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (3 × 50 mL), washed with aqueous lithium chloride solution (10 mL) and brine (10 mL), dried (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo}. Flash column chromatography (diethyl ether/petroleum ether, 1:1) afforded methyl (2E)-3-(2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207b) (2.66 g, 93%) as a white solid. Mp 156–158 °C (lit.\textsuperscript{241} 160–162 °C); R\textsubscript{f} 0.13 (50% diethyl ether/petroleum ether); \(\delta\)\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 2.35 (3H, s, CH\textsubscript{3}), 3.77 (3H, s, OCH\textsubscript{3}), 6.11 (1H, d, J 15.8 Hz, 2-H), 7.17 (2H, d, J 8.2 Hz, 2 × ArH), 7.20–7.27 (2H, m, NH and 5'-H), 7.34 (1H, td, J 8.0, 1.5 Hz, 4'-H), 7.40 (1H, dd, J 8.0, 1.2 Hz, 3'-H), 7.45 (1H, dd, J 8.0, 1.5 Hz, 6'-H), 7.54 (2H, d, J 8.2 Hz, 2 × ArH), 7.62 (1H, d, J 15.8 Hz, 3-H); \(\delta\)\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 21.5 (CH\textsubscript{3}), 51.9 (CH\textsubscript{3}), 120.2 (CH), 127.1 (CH), 127.2 (CH), 127.3 (2 × CH), 127.6 (CH), 129.6 (2 × CH), 130.6 (C), 130.9 (CH), 134.8 (C), 135.9 (C), 139.3 (CH), 144.0 (C), 167.0 (C); m/z (ESI) 354 (MNa\textsuperscript{+}, 100%), 233 (8).

Methyl (2E)-3-(5'-methyl-2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207b)\textsuperscript{242}

\[
\begin{align*}
\text{4'} & \quad \text{3'} & \quad \text{NHTs} & \quad \text{5'} & \quad \text{2'} & \quad \text{1} & \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207a) using methyl (2E)-3-(2'-amino-5'-methylphenyl)prop-2-enoate (206b) (1.50 g, 7.84 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:4) gave methyl (2E)-3-
(5'-methyl-2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207a) (2.68 g, 99%) as a white solid. Mp 164–166 °C (lit.242 160–162 °C); Rf 0.20 (50% diethyl ether/petroleum ether); δH (400 MHz, CDCl3) 2.32 (3H, s, CH3), 2.35 (3H, s, CH3), 3.77 (3H, s, OCH3), 6.10 (1H, d, J 15.9 Hz, 2-H), 6.99 (1H, br s, NH), 7.12–7.19 (3H, m, 3'-H and 2 × ArH), 7.23–7.26 (2H, m, 4'-H and 6'-H), 7.50–7.57 (3H, m, 3-H and 2 × ArH); δC (101 MHz, CDCl3) 21.0 (CH3), 21.5 (CH3), 51.8 (CH3), 119.7 (CH), 127.3 (2 × CH), 127.4 (CH), 128.0 (CH), 129.6 (2 × CH), 130.7 (C), 131.8 (CH), 132.1 (C), 135.9 (C), 137.4 (C), 139.4 (CH), 143.8 (C), 167.0 (C); m/z (ESI) 368 (MNa+, 100%).

Methyl (2E)-3-(5'-methoxy-2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207c)

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207a) using methyl (2E)-3-(2'-amino-5'-methoxyphenyl)prop-2-enoate (206c) (0.014 g, 0.070 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:4) gave methyl (2E)-3-(5'-methoxy-2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207c) (0.023 g, 93%) as a white solid. Mp 162–164 °C; Rf 0.23 (33% ethyl acetate/petroleum ether); νmax/cm⁻¹ (neat) 3256 (NH), 3023 (CH), 1701 (CO), 1637 (C=C), 1495, 1214, 1325, 1161, 750; δH (500 MHz, CDCl3) 2.37 (3H, s, CH3), 3.78 (3H, s, OCH3), 3.81 (3H, s, OCH3), 6.09 (1H, d, J 15.9 Hz, 2-H), 6.53 (1H, br s, NH), 6.89 (1H, dd, J 8.8, 2.9 Hz, 4'-H), 6.95 (1H, d, J 2.9 Hz, 6'-H), 7.19 (2H, d, J 8.2 Hz, 2 × ArH), 7.23 (1H, d, J 8.8 Hz, 3'-H), 7.46 (1H, d, J 15.9 Hz, 3-H), 7.52 (2H, d, J 8.2 Hz, 2 × ArH); δC (101 MHz, CDCl3) 21.5 (CH3), 51.8 (CH3), 55.5 (CH3), 111.4 (CH), 116.7 (CH), 120.1 (CH), 127.3 (C), 127.4 (2 × CH), 129.6 (2 × CH), 130.6 (CH), 133.1 (C), 135.8 (C), 139.2 (CH), 143.9 (C), 158.9 (C), 166.7 (C); m/z (ESI) 384.0864 (MNa+, C18H15NNaO5S requires 384.0876).
Methyl (2E)-3-(5′-fluoro-2′-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207d)\textsuperscript{242}

\[
\begin{align*}
\text{F} & \quad 3' \quad \text{NHTs} \\
2' & \quad 5' \quad 1 \\
\text{CO}_2\text{Me} & \quad 4'
\end{align*}
\]

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2′-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207a) using methyl (2E)-3-(2′-amino-5′-fluorophenyl)prop-2-enoate (206d) (2.50 g, 13.0 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:5) gave methyl (2E)-3-(5′-fluoro-2′-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207d) (3.94 g, 88%) as a white solid. Mp 156–158 °C (lit. \textsuperscript{242} 156–158 °C); R\textsubscript{f} 0.13 (50% diethyl ether/petroleum ether); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 2.36 (3H, s, CH\textsubscript{3}), 3.78 (3H, s, OCH\textsubscript{3}), 6.07 (1H, d, J \textsubscript{15.8 Hz}, 2-H), 6.96 (1H, br s, NH), 7.06 (1H, ddd, J \textsubscript{8.8, 3J\textsubscript{HF} 7.7, J \textsubscript{2.9 Hz}, 4′-H), 7.14 (1H, dd, 3J\textsubscript{HF} 9.2, J \textsubscript{2.9 Hz}, 6′-H), 7.19 (2H, d, J \textsubscript{8.1 Hz}, 2 × ArH), 7.35 (1H, dd, J \textsubscript{8.8, 4J\textsubscript{HF} 5.2 Hz}, 3′-H), 7.50 (1H, dd, J \textsubscript{15.8, 5J\textsubscript{HF} 1.5 Hz}, 3-H), 7.52 (2H, d, J \textsubscript{8.1 Hz}, 2 × ArH); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 21.5 (CH\textsubscript{3}), 52.0 (CH\textsubscript{3}), 113.3 (d, 2J\textsubscript{CF} 23.5 Hz, CH), 117.9 (d, 2J\textsubscript{CF} 22.7 Hz, CH), 121.2 (CH), 127.3 (2 × CH), 129.7 (2 × CH), 130.6 (d, 4J\textsubscript{CF} 2.9 Hz, C), 130.7 (d, 3J\textsubscript{CF} 8.8 Hz, CH), 133.4 (d, 3J\textsubscript{CF} 8.4 Hz, C), 135.6 (C), 138.2 (d, 4J\textsubscript{CF} 2.2 Hz, CH), 144.2 (C), 161.5 (d, 1J\textsubscript{CF} 248.4 Hz, C), 166.5 (C); m/z (ESI) 372 (MNa\textsuperscript{+}, 100%).

Methyl (2E)-3-(4′-fluoro-2′-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207e)\textsuperscript{240}

\[
\begin{align*}
\text{F} & \quad 3' \quad \text{NHTs} \\
2' & \quad 5' \quad 1 \\
\text{CO}_2\text{Me} & \quad 4'
\end{align*}
\]

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2′-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207a) using methyl (2E)-3-(2′-amino-4′-fluorophenyl)prop-2-enoate (206e) (0.620 g, 3.20 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:5) gave methyl (2E)-3-(4′-fluoro-2′-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207e) (1.08 g, 97%) as a yellow solid. Mp 157–159 °C; Spectroscopic data were consistent with the literature.\textsuperscript{240} R\textsubscript{f} 0.13 (50% diethyl ether/petroleum ether); δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3})
2.38 (3H, s, CH₃), 3.79 (3H, s, OCH₃), 6.11 (1H, d, J 15.8 Hz, 2-H), 6.92 (1H, td, J 8.7, 2.6 Hz, 5'-H), 7.00 (1H, br s, NH), 7.20–7.26 (3H, m, 3'-H and 2 × ArH), 7.41 (1H, dd, J 8.7, 6'H), 6.48 (1H, d, J 15.8 Hz, 3-H), 7.63 (2H, d, J 8.3 Hz, 2 × ArH); δC (101 MHz, CDCl₃) 21.5 (CH₃), 51.9 (CH₃), 112.8 (d, ²JCF 24.9 Hz, CH), 114.1 (d, ²JCF 21.8 Hz, CH), 120.5 (CH), 125.1 (d, ⁴JCF 3.4 Hz, C), 127.3 (2 × CH), 128.9 (d, ³JCF 9.5 Hz, CH), 129.9 (2 × CH), 135.7 (C), 136.5 (d, ³JCF 10.8 Hz, C), 137.8 (CH), 144.4 (C), 163.8 (d, ¹JCF 251.8 Hz, C), 166.7 (C); m/z (ESI) 372 (MNa⁺, 100%), 363 (37).

**Methyl (2E)-3-(5'-chloro-2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207f)**

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207a) using methyl (2E)-3-(2'-amino-5'-chlorophenyl)prop-2-enoate (206f) (0.406 g, 1.90 mmol). The reaction mixture was stirred at room temperature for 18 h. Purification by column chromatography (ethyl acetate/petroleum ether, 1:5) gave methyl (2E)-3-(5'-chloro-2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207f) (0.638 g, 91%) as a yellow solid. Mp 152–154 °C (lit.²⁴² 149–151 °C); Rf 0.43 (33% ethyl acetate/petroleum ether); δH (400 MHz, CDCl₃) 2.36 (3H, s, CH₃), 3.78 (3H, s, OCH₃), 6.09 (1H, d, J 15.8 Hz, 2-H), 7.19 (2H, d, J 8.0 Hz, 2 × ArH), 7.28 (1H, br s, NH), 7.31 (1H, dd, J 8.6, 2.4 Hz, 4'-H), 7.36 (1H, d, J 8.6 Hz, 3'-H), 7.40 (1H, d, J 2.4 Hz, 6'-H), 7.50–7.56 (3H, m, 3-H and 2 × ArH); δC (101 MHz, CDCl₃) 21.5 (CH₃), 52.1 (CH₃), 121.3 (CH), 126.9 (CH), 127.3 (2 × CH), 129.1 (CH), 129.8 (2 × CH), 130.8 (CH), 132.2 (C), 133.1 (C), 133.3 (C), 135.6 (C), 138.1 (CH), 144.2 (C), 166.7 (C); m/z (ESI) 388 (MNa⁺, 100%).
Methyl (2E)-3-(2’-[N-allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (208a)

Allallyl bromide (0.830 mL, 9.60 mmol) was added to a stirred solution of methyl (2E)-3-(2’-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207a) (2.66 g, 8.00 mmol) and potassium carbonate (2.21 g, 16.0 mmol) in N,N'-dimethylformamide (50 mL). The reaction mixture was heated to 70 °C for 1 h. The reaction mixture was cooled to room temperature, diluted with 5% aqueous lithium chloride solution (20 mL) and extracted with diethyl ether (50 mL). The organic layer was washed with 5% aqueous lithium chloride solution (3 × 10 mL), brine (10 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (diethyl ether/petroleum ether, 1:1) gave methyl (2E)-3-(2’-[N-allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (208a) (2.98 g, quantitative) as a white solid. Mp 104–106 °C; Rᵣ 0.38 (50% diethyl ether/petroleum ether); νₘᵋₓ/ cm⁻¹ (neat) 2951 (CH), 1716 (CO), 1636 (C=C), 1436, 1319, 1164, 763; δ ᵃₛ (400 MHz, CDCl₃) 2.42 (3H, s, CH₃), 3.79 (3H, s, OCH₃), 4.02 (1H, br s, 2''-H), 4.27 (1H, br s, 2''-HH), 4.93–5.02 (2H, m, 4''-H₂), 5.74 (1H, ddt, J 17.0, 10.0, 6.8 Hz, 3''-H), 6.33 (1H, d, J 16.1 Hz, 2-H), 6.84 (1H, dd, J 7.8, 1.1 Hz, 3'-H), 7.24–7.35 (4H, m, 4'-H, 5'-H and 2 × ArH), 7.56 (2H, d, J 8.2 Hz, 2 × ArH), 7.64 (1H, dd, J 7.8, 1.5 Hz, 6'-H), 7.86 (1H, d, J 16.1 Hz, 3'-H); δ ᵃ_C (101 MHz, CDCl₃) 21.6 (CH₃), 51.7 (CH₃), 54.9 (CH₂), 119.7 (CH), 119.8 (CH₂), 127.1 (CH), 128.0 (2 × CH), 128.8 (CH), 129.6 (2 × CH), 129.9 (CH), 130.4 (CH), 132.2 (CH), 135.6 (C), 135.7 (C), 138.3 (C), 140.3 (CH), 143.8 (C), 166.9 (C); m/z (ESI) 394.1067 (MNa⁺, C₂₀H₂₁NNaO₄S requires 394.1083).
Methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-methylphenyl)prop-2-enoate (208b)

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (208a) using methyl (2E)-3-(5'-methyl-2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207b) (2.00 g, 5.79 mmol) and a reaction time of 3 h. Purification by column chromatography (ethyl acetate/petroleum ether, 1:5) gave methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-methylphenyl)prop-2-enoate (208b) (2.03 g, 91%) as a white solid. Mp 118–120 °C; Rf 0.25 (50% diethyl ether/petroleum ether); νmax/cm−1 (neat) 2950 (CH), 1717 (CO), 1639 (C=C), 1435, 1347, 1160, 759; δH (400 MHz, CDCl3) 2.34 (3H, s, CH3), 2.42 (3H, s, CH3), 3.78 (3H, s, OCH3), 3.99 (1H, br s, 2''-H), 4.26 (1H, br s, 2''-H), 4.93–5.02 (2H, m, 4''-H), 5.74 (1H, ddt, J 17.0, 10.1, 6.8 Hz, 3''-H), 6.31 (1H, d, J 16.1 Hz, 2'-H), 6.71 (1H, d, J 8.1 Hz, 3'-H), 7.08 (1H, dd, J 8.1, 1.6 Hz, 4'-H), 7.26 (2H, d, J 8.2 Hz, 2 × ArH), 7.43 (1H, d, J 1.6 Hz, 6'-H), 7.56 (2H, d, J 8.2 Hz, 2 × ArH), 7.82 (1H, d, J 16.1 Hz, 3'-H); δC (101 MHz, CDCl3) 21.2 (CH3), 21.5 (CH3), 51.7 (CH3), 54.9 (CH2), 119.4 (CH), 119.6 (CH2), 127.6 (CH), 128.0 (2 × CH), 129.6 (2 × CH), 131.1 (CH), 132.3 (CH), 135.2 (C), 135.7 (C), 135.7 (C), 138.7 (C), 140.5 (CH), 143.7 (C), 167.0 (C); m/z (ESI) 408.1220 (MNa+), C21H23NNaO4S requires 408.1240).

Methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-methoxyphenyl)prop-2-enoate (208c)

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (208a) using methyl (2E)-3-(5'-methoxy-2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207c) (0.145 g, 0.400 mmol) and a reaction time of 2 h. Purification by column
chromatography (ethyl acetate/petroleum ether, 1:5) gave methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-methoxyphenyl)prop-2-enoate (208c) (0.149 g, 92%) as a white solid. Mp 153–155 °C; Rf 0.40 (33% ethyl acetate/petroleum ether); νmax/cm⁻¹ (neat) 3022 (CH), 1709 (CO), 1642 (C=C), 1495, 1289, 1215, 1163, 751; δH (400 MHz, CDCl₃) 2.42 (3H, s, CH₃), 3.79 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.96–4.01 (1H, m, 2''-H-H), 4.24–4.29 (1H, m, 2''-H-H), 4.93–5.03 (2H, m, 4''-H₂), 5.74 (1H, ddt, J 16.9, 10.1, 6.8 Hz, 3''-H), 6.29 (1H, d, J 16.1 Hz, 2-H), 6.74 (1H, d, J 8.8 Hz, 3'-H), 6.81 (1H, dd, J 8.8, 2.8 Hz, 4'-H), 7.09 (1H, d, J 2.8 Hz, 6'-H), 7.26 (2H, d, J 8.2 Hz, 2 × ArH), 7.56 (2H, d, J 8.2 Hz, 2 × ArH), 7.79 (1H, d, J 2.8 Hz, 6'-H); δC (101 MHz, CDCl₃) 21.6 (CH₃), 51.7 (CH₃), 55.0 (CH₂), 55.5 (CH₃), 111.2 (CH), 116.5 (CH), 119.7 (CH₂), 119.8 (CH), 128.0 (2 × CH), 129.6 (2 × CH), 131.0 (CH), 132.3 (CH), 135.7 (C), 136.6 (C), 140.4 (CH), 143.7 (2 × C), 159.3 (C), 166.8 (C); m/z (ESI) 424.117 (MNa⁺, C₂₁H₂₃NNaO₅S requires 424.1189).

Methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-fluorophenyl)prop-2-enoate (208d)

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (208a) using methyl (2E)-3-(5'-fluoro-2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (207d) (3.74 g, 11.0 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:7) gave methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-fluorophenyl)prop-2-enoate (208d) (3.50 g, 84%) as a white solid. Mp 108–110 °C; Rf 0.43 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 2951 (CH), 1718 (CO), 1650 (C=C), 1488, 1323, 1275, 1160, 862, 728; δH (400 MHz, CDCl₃) 2.40 (3H, s, CH₃), 3.77 (3H, s, OCH₃), 3.95 (1H, br s, 2''-H-H), 4.25 (1H, br s, 2''-H-H), 4.95 (1H, dd, J 17.0, 1.2 Hz, 4''-H-H), 5.00 (1H, dd, J 10.1, 1.2 Hz, 4''-H-H), 5.71 (1H, ddt, J 17.0, 10.1, 6.8 Hz, 3''-H), 6.28 (1H, d, J 16.1 Hz, 2-H), 6.80 (1H, dd, J 8.8, 4''HSF 5.3 Hz, 3'-H), 6.95 (1H, ddd, J 8.8, 3''JH 7.6, J 2.9 Hz, 4'-H), 7.26 (2H, d, J
8.2 Hz, 2 × ArH), 7.28 (1H, dd, $^3J_{HF}$ 9.4, J 2.9 Hz, 6'-H), 7.54 (2H, d, J 8.2 Hz, 2 × ArH), 7.76 (1H, dd, J 16.1, $^5J_{HF}$ 1.6 Hz, 3-H); $\delta_C$ (101 MHz, CDCl$_3$) 21.5 (CH$_3$), 51.8 (CH$_3$), 55.0 (CH$_2$), 113.5 (d, $^2J_{CF}$ 23.4 Hz, CH), 117.4 (d, $^2J_{CF}$ 23.0 Hz, CH), 120.1 (CH$_2$), 120.9 (CH), 127.9 (2 × CH), 129.7 (2 × CH), 131.8 (d, $^3J_{CF}$ 8.9 Hz, CH), 131.9 (CH), 134.2 (d, $^4J_{CF}$ 3.1 Hz, C), 135.3 (C), 137.8 (d, $^3J_{CF}$ 8.5 Hz, C), 139.2 (d, $^4J_{CF}$ 2.0 Hz, CH), 144.0 (C), 162.0 (d, $^1J_{CF}$ 249.4 Hz, C), 166.5 (C); m/z (ESI) 412.0969 (MNa$^+$, C$_{20}$H$_{20}$FNNaO$_4$S requires 412.0989). Methyl (2E)-3-([N-allyl-N-(p-toluenesulfonyl)amino]-4'-fluorophenyl)prop-2-enoate (208e)

The reaction was carried out as described for the synthesis of methyl (2E)-3-([N-allyl-N-(p-toluenesulfonyl)amino][phenyl]prop-2-enoate (208a) using methyl (2E)-3-([4'-fluoro-2'-[N-(p-toluenesulfonyl)amino][phenyl]prop-2-enoate (207e) (1.07 g, 3.00 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:7) gave methyl (2E)-3-([N-allyl-N-(p-toluenesulfonyl)amino]-4'-fluorophenyl)prop-2-enoate (208e) (0.946 g, 79%) as a white solid. Mp 111–113 °C; R$_f$ 0.38 (50% diethyl ether/petroleum ether); $\nu_{max}$/cm$^{-1}$ (neat) 2951 (CH), 1712 (CO), 1602 (C=C), 1497, 1353, 1256, 1164, 908, 730; $\delta_H$ (400 MHz, CDCl$_3$) 2.43 (3H, s, CH$_3$), 3.78 (3H, s, OCH$_3$), 4.02 (1H, br s, 2''-H), 4.21 (1H, br s, 2''-H), 4.95–5.05 (2H, m, 4''-H), 5.72 (1H, ddt, J 16.9, 10.1, 6.8 Hz, 3''-H), 6.27 (1H, d, J 16.1 Hz, 2-H), 6.57 (1H, dd, $^3J_{HF}$ 9.2, J 2.8 Hz, 3'-H), 7.06 (1H, td, J 8.8, 2.8 Hz, 5'-H), 7.29 (2H, d, J 8.2 Hz, 2 × ArH), 7.58 (2H, d, J 8.2 Hz, 2 × ArH), 7.62 (1H, dd, J 8.8, $^4J_{HF}$ 6.2 Hz, 6'-H), 7.78 (1H, d, J 16.1 Hz, 3-H); $\delta_C$ (101 MHz, CDCl$_3$) 21.6 (CH$_3$), 51.7 (CH$_3$), 54.9 (CH$_2$), 116.4 (d, $^2J_{CF}$ 21.6 Hz, CH), 117.0 (d, $^2J_{CF}$ 21.9 Hz, CH), 119.5 (CH), 120.2 (CH$_2$), 128.0 (2 × CH), 128.6 (d, $^3J_{CF}$ 9.4 Hz, CH), 129.7 (2 × CH), 131.7 (CH), 132.1 (d, $^4J_{CF}$ 3.7 Hz, C), 135.2 (C), 139.3 (CH), 139.8 (d, $^3J_{CF}$ 9.2 Hz, C), 144.2 (C), 163.1 (d, $^1J_{CF}$ 253.1 Hz, C), 166.8 (C); m/z (ESI) 412.0970 (MNa$^+$, C$_{20}$H$_{20}$FNNaO$_4$S requires 412.0989).
Methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-chlorophenyl)prop-2-enoate (208f)

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (208g) using methyl (2E)-3-(5'-chloro-2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (208g) (0.600 g, 1.60 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:5) gave methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-chlorophenyl)prop-2-enoate (208f) (0.664 g, quantitative) as a yellow solid. Mp 104–106 °C; Rf 0.58 (33% ethyl acetate/petroleum ether); νmax/cm⁻¹ (neat) 2951 (CH), 1720 (CO), 1610 (C=C), 1353, 1164, 908, 730; δH (400 MHz, CDCl₃) 2.44 (3H, s, CH₃), 3.80 (3H, s, OCH₃), 3.99 (1H, br s, 2''-H), 4.26 (1H, br s, 2''-H), 4.97 (1H, dd, J 17.0, 1.1 Hz, 4''-H), 5.03 (1H, dd, J 10.1, 1.1 Hz, 4''-H), 5.73 (1H, ddt, J 17.0, 10.1, 6.8 Hz, 3''-H), 6.31 (1H, d, J 16.1 Hz, 2-H), 6.78 (1H, d, J 8.6 Hz, 3'-H), 7.24 (1H, dd, J 8.6, 2.4 Hz, 4'-H), 7.29 (2H, d, J 8.2 Hz, 2 × ArH), 7.57 (2H, d, J 8.2 Hz, 2 × ArH), 7.60 (1H, d, J 2.4 Hz, 6'-H), 7.75 (1H, d, J 16.1 Hz, 3-H); δC (101 MHz, CDCl₃) 21.6 (CH₃), 51.8 (CH₃), 54.9 (CH₂), 120.2 (CH₂), 121.0 (CH), 127.1 (CH), 128.0 (2 × CH), 129.7 (2 × CH), 130.3 (CH), 131.2 (CH), 131.8 (CH), 134.7 (C), 135.3 (C), 136.7 (C), 137.4 (C), 139.0 (CH), 144.1 (C), 166.5 (C); m/z (ESI) 428.0673 (MNa⁺, C₂₀H₂₀₃ClINaO₄S requires 428.0694).

(2E)-3-(2'-[N-Allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-en-1-ol (209a)

Diisobutylaluminium hydride (4.1 mL, 4.1 mmol, 1 M in hexane) was added dropwise with stirring to a solution of methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (208a) (0.690 g, 1.86 mmol) in dichloromethane (19 mL) at −78 °C. The solution was stirred at −78 °C for 2 h,
then allowed to warm to room temperature over 16 h. The reaction was quenched with 10% aqueous potassium sodium tartrate solution (5 mL), extracted with diethyl ether (2 x 10 mL), washed with water (20 mL), brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (ethyl acetate/petroleum ether, 1:2) gave (2E)-3-(2'-%N-allyl-%N-%(p-toluenesulfonyl)amino)prop-2-en-1-ol (209a) (0.611 g, 96%) as a colourless oil. Rf 0.13 (50% diethyl ether/petroleum ether); v_{max}/cm⁻¹ (neat) 3491 (OH), 2924 (CH), 1597 (C=C), 1534, 1161, 726; δH (400 MHz, CDCl₃) 1.97 (1H, br s, OH), 2.43 (3H, s, CH₃), 4.00 (1H, br s, 2''-H), 4.18–4.29 (3H, m, 1'-H₂ and 2''-H), 4.93–5.01 (2H, m, 3''-H), 6.33 (1H, dt, J 16.0, 5.4 Hz, 2-H), 6.68 (1H, dd, J 1.3 Hz, 3'-H), 6.83 (1H, d, J 16.0 Hz, 3-H), 7.12 (1H, td, J 7.8, 1.3 Hz, 5'-H), 7.23–7.30 (3H, m, 4'-H and 2 × ArH), 7.55–7.61 (3H, m, 6'-H and 2 × ArH); δC (101 MHz, CDCl₃) 21.6 (CH₃), 54.8 (CH₂), 63.8 (CH₂), 119.4 (CH₂), 126.5 (CH), 126.7 (CH), 127.8 (CH), 127.9 (2 × CH), 128.6 (CH), 129.4 (CH), 129.5 (2 × CH), 130.8 (CH), 132.4 (CH), 136.1 (C), 136.6 (C), 137.8 (C), 143.6 (C); m/z (ESI) 366.1119 (MNa⁺, C₁₉H₂₁NNaO₃S requires 366.1134).

(2E)-3-(2'-%N-allyl-%N-%(p-toluenesulfonyl)amino)-5'-methylphenyl)prop-2-en-1-ol (209b)

The reaction was carried out as described for the synthesis of (2E)-3-(2'-%N-allyl-%N-%(p-toluenesulfonyl)amino)prop-2-en-1-ol (209a) using methyl (2E)-3-(2'-%N-allyl-%N-%(p-toluenesulfonyl)amino)-5'-methylphenyl)prop-2-enoate (208b) (1.50 g, 3.89 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:2) gave (2E)-3-(2'-%N-allyl-%N-%(p-toluenesulfonyl)amino)-5'-methylphenyl)prop-2-en-1-ol (209b) (1.37 g, 98%) as a colourless oil. Rf 0.10 (50% diethyl ether/petroleum ether); v_{max}/cm⁻¹ (neat) 3510 (OH), 2921 (CH), 1598 (C=C), 1491, 1340, 1159, 859, 734; δH (400 MHz, CDCl₃) 2.15 (1H, br s, OH), 2.31 (3H, s, CH₃), 2.42 (3H, s, CH₃), 3.96 (1H, br s, 2''-H), 4.19–4.28 (3H, m, 1-H₂ and
The reaction was carried out as described for the synthesis of (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-methoxyphenyl)prop-2-en-1-ol (209a) using methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-methoxyphenyl)prop-2-enoate (208c) (0.140 g, 0.350 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:2) gave (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-methoxyphenyl)prop-2-enoate (209c) (0.104 g, 80%) as a colourless oil. Rf 0.18 (33% ethyl acetate/petroleum ether); νmax/cm⁻¹ (neat) 3523 (OH), 2944 (CH), 1601 (C=C), 1495, 1345, 1161, 752; δH (400 MHz, CDCl₃) 2.07 (1H, t, J 5.4 Hz, OH), 2.42 (3H, s, CH₃), 3.79 (3H, s, OCH₃), 3.91–3.98 (1H, m, 2''-H H), 4.18–4.28 (3H, m, 1-H₂ and 2''-HH), 4.93–5.01 (2H, m, 4''-H₂), 5.72 (1H, ddt, J 16.9, 10.2, 6.7 Hz, 3''-H), 6.30 (1H, dt, J 16.0, 5.4 Hz, 2-H), 6.58 (1H, d, J 8.8 Hz, 3'-H), 6.65 (1H, dd, J 8.8, 2.9 Hz, 4'-H), 6.77 (1H, dt, J 16.0, 1.5 Hz, 3-H), 7.07 (1H, d, J 2.9 Hz, 6'-H), 7.27 (2H, d, J 8.2 Hz, 2 × ArH), 7.57 (2H, d, J 8.2 Hz, 2 × ArH); δC (101 MHz, CDCl₃) 21.5 (CH₃), 54.9 (CH₂), 55.4 (CH₃), 63.7 (CH₂), 110.7 (CH), 113.9 (CH), 119.3 (CH₂), 126.6 (CH), 127.9 (2 × CH), 129.4 (C), 129.7 (2 × CH), 130.5 (CH), 130.9 (CH), 132.5 (CH), 136.2 (C), 138.9 (C), 143.5 (C), 159.2 (C); m/z (ESI) 396.1223 (MNa⁺, C₂₀H₂₃NNaO₅S requires 396.1240).
(2E)-3-(2'-[N-Allyl-N-(p-toluenesulfonyl)amino]-5'-fluorophenyl)prop-2-en-1-ol (209d)

The reaction was carried out as described for the synthesis of (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-en-1-ol (209a) using methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-fluorophenyl)prop-2-enoate (208d) (3.30 g, 8.50 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:3) gave (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-fluorophenyl)prop-2-en-1-ol (209d) (2.99 g, 98%) as a colourless oil. Rf 0.10 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3507 (OH), 2920 (CH), 1600 (C=C), 1488, 1345, 1161, 752; δH (400 MHz, CDCl₃) 2.35 (1H, t, J5.6 Hz, OH), 2.42 (3H, s, CH₃), 3.95 (1H, dd, J13.4, 6.8, 2''-H), 4.17–4.28 (3H, m, 1''-H and 2''-H), 4.91–5.01 (2H, m, 4''-H), 5.70 (1H, ddt, J16.9, 10.1, 6.8 Hz, 3''-H), 6.30 (1H, dt, J16.0, 5.5 Hz, 2-H), 6.65 (1H, dd, J8.8, 4JHF 5.4 Hz, 3'-H), 6.73–6.83 (2H, m, 3-H and 4'-H), 7.24 (1H, dd, 3JHF 10.0, J2.9 Hz, 6'-H), 7.27 (2H, d, J8.3 Hz, 2 × ArH), 7.56 (2H, d, J8.3 Hz, 2 × ArH); δC (101 MHz, CDCl₃) 21.5 (CH₃), 54.9 (CH₂), 63.4 (CH₂), 112.8 (d, 2JCF 23.3 Hz, CH), 114.7 (d, 2JCF 23.1 Hz, CH), 119.7 (CH₂), 125.4 (d, 4JCF 1.7 Hz, CH), 127.9 (2 × CH), 129.6 (2 × CH), 131.2 (d, 3JCF 9.1 Hz, CH), 132.1 (CH), 132.3 (CH), 132.4 (d, 4JCF 2.8 Hz, C), 135.9 (C), 140.2 (d, 3JCF 8.6 Hz, C), 143.8 (C), 162.2 (d, 1JCF 247.9 Hz, C); m/z (ESI) 384.1023 (MNa⁺, C₁₉H₂₀FNNaO₃S requires 384.1040).

(2E)-3-(2'-[N-Allyl-N-(p-toluenesulfonyl)amino]-4'-fluorophenyl)prop-2-en-1-ol (209e)

The reaction was carried out as described for the synthesis of (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-en-1-ol (209a) using methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-4'-fluorophenyl)prop-2-enoate (208e) (0.790 g,
Purification by column chromatography (ethyl acetate/petroleum ether, 1:3) gave (2E)-3-(2′-[N-allyl-N-(p-toluenesulfonyl)amino]-4′-fluorophenyl)prop-2-en-1-ol (209e) (0.728 g, 99%) as a colourless oil. Rf 0.08 (50% diethyl ether/petroleum ether); v_{max}/cm⁻¹ (neat) 3507 (OH), 2923 (CH), 1600 (C=C), 1495, 1347, 1161, 908, 727; δ_H (400 MHz, CDCl₃) 2.18 (1H, t, J 5.6 Hz, OH), 2.43 (3H, s, CH₃), 3.96 (1H, br s, 2''-H), 4.09–4.27 (3H, m, 1-H₂ and 2''-H), 4.94–5.03 (2H, m, 4''-H), 5.69 (1H, ddt, J 16.9, 10.1, 6.7 Hz, 3''-H), 6.25 (1H, dt, J 16.0, 5.3 Hz, 2-H), 6.41 (1H, dd, δ_H 3''HF 9.3, J 2.6 Hz, 3''-H), 6.75 (1H, d, J 16.0 Hz, 3-H), 6.99 (2H, td, J 8.6, 2.6 Hz, 5''-H), 7.29 (2H, d, J 8.2 Hz, 2 × ArH), 7.55 (1H, dd, J 6.8, 4''HF 6.3 Hz, 6''-H), 7.58 (2H, d, J 8.2 Hz, 2 × ArH); δ_C (101 MHz, CDCl₃) 21.6 (CH₃), 54.7 (CH₂), 63.6 (CH₂), 116.0 (d, δ_C 21.2 Hz, CH), 116.2 (d, δ_C 21.2 Hz, CH), 119.8 (CH₂), 125.7 (CH), 127.7 (d, δ_C 8.9 Hz, CH), 127.9 (2 × CH), 129.7 (2 × CH), 130.7 (d, δ_C 1.8 Hz, CH), 132.0 (CH), 134.3 (d, δ_C 3.7 Hz, C), 135.7 (C), 137.7 (d, δ_C 8.8 Hz, C), 144.0 (C), 161.5 (d, δ_C 248.9 Hz, C); m/z (ESI) 384.1023 (MNa⁺, C₁₉H₂₀FNNaO₃S requires 384.1040).

The reaction was carried out as described for the synthesis of (2E)-3-(2′-[N-allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-en-1-ol (209a) using methyl (2E)-3-(2′-[N-allyl-N-(p-toluenesulfonyl)amino]-5′-chlorophenyl)prop-2-enoate (208f) (0.660 g, 1.60 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:3) gave (2E)-3-(2′-[N-allyl-N-(p-toluenesulfonyl)amino]-5′-chlorophenyl)prop-2-en-1-ol (209f) (0.566 g, 92%) as a colourless oil. Rf 0.28 (33% ethyl acetate/petroleum ether); v_{max}/cm⁻¹ (neat) 3505 (OH), 2923 (CH), 1597 (C=C), 1478, 1343, 1161, 907, 727; δ_H (400 MHz, CDCl₃) 2.23 (1H, br s, OH), 2.43 (3H, s, CH₃), 3.94 (1H, br s, 2''-H), 4.17–4.29 (3H, m, 1-H₂ and 2''-H), 4.92–5.02 (2H, m, 4''-H), 5.69 (1H, ddt, J 17.0, 10.1, 6.8 Hz, 3''-H), 6.32 (1H, dt, J 16.0, 5.1 Hz, 2-H), 6.60 (1H, d, J 8.6 Hz, 3''-H), 6.75 (1H, dt, J 16.0, 1.5 Hz, 3-H), 7.07
(1H, dd, J 8.6, 2.4 Hz, 4'-H), 7.28 (2H, d, J 8.2 Hz, 2 × ArH), 7.54–7.59 (3H, m, 6'-H and 2 × ArH); δ_C (101 MHz, CDCl₃) 21.6 (CH₃), 54.8 (CH₂), 63.4 (CH₂), 119.8 (CH₂), 125.2 (CH), 126.5 (CH), 127.8 (CH), 127.9 (2 × CH), 129.7 (2 × CH), 130.7 (CH), 132.0 (CH), 132.4 (CH), 134.5 (C), 135.0 (C), 135.8 (C), 139.6 (C), 143.9 (C); m/z (ESI) 400.0729 (MNa⁺, C₁₉H₂₀ClNNaO₃S requires 400.0745).

2-Iodo-4-nitroaniline (203g)²⁴³

Silver triflimide (0.023 g, 0.058 mmol) was added to a stirred solution of 4-nitroaniline (202g) (0.40 g, 2.9 mmol) and N-iodosuccinimide (0.65 g, 2.9 mmol) in dichloromethane (15 mL) and warmed to 40 °C for 24 h in the dark. The mixture was diluted with dichloromethane (15 mL) and washed with dilute aqueous solutions of sodium hydrogen carbonate (50 mL) and 5% aqueous sodium thiosulfate solution (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (ethyl acetate/petroleum ether, 1:7) yielded 2-iodo-4-nitroaniline (203g) (0.76 g, 99%) as a bright yellow solid. Mp 99–101 °C (lit.²⁴³ 103–104 °C); R_f 0.38 (30% ethyl acetate/petroleum ether); δ_H (400 MHz, CDCl₃) 4.83 (2H, br s, NH₂), 6.70 (1H, d, J 9.0 Hz, 6-H), 8.06 (1H, dd, J 9.0, 2.5 Hz, 5-H), 8.57 (1H, d, J 2.5 Hz, 3-H); δ_C (126 MHz, CDCl₃) 80.5 (C), 112.3 (CH), 125.7 (CH), 135.5 (CH), 139.3 (C), 152.3 (C); m/z (EI) 264 (M⁺, 100%), 234 (38), 218 (11), 127 (5), 91 (31).
5-Nitro-2-[N-(p-toluenesulfonyl)amino]benzaldehyde (216)

\[
\begin{align*}
\text{O}_2\text{N} & \quad 4 \\
\text{NHTs} & \quad 3 \\
\text{CHO} & \quad 2
\end{align*}
\]

\(p\)-Toluenesulfonamide (0.148 g, 0.86 mmol) was added to a solution of 2-chloro-5-nitrobenzaldehyde (215) (0.080 g, 0.43 mmol), and potassium carbonate (0.107 g, 0.780 mmol) in \(N,N'\)-dimethylformamide (2 mL) and heated to 90 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with water (2 mL) and extracted with ethyl acetate (10 mL). The organic layer was washed with 1 M aqueous hydrochloric acid solution (3 × 2 mL) and brine (2 mL), dried (MgSO\(_4\)), filtered and concentrated in vacuo. Purification by column chromatography (ethyl acetate/petroleum ether, 1:5) gave 5-nitro-2-[N-(p-toluenesulfonyl)amino]benzaldehyde (216) (0.122 g, 86%) as a white solid. Mp 172–174 °C; \(R_f\) 0.38 (33% ethyl acetate/petroleum ether); \(v_{\text{max}}/\text{cm}^{-1}\) (neat) 3164 (NH), 1673 (CO), 1586 (C=C), 1450, 1414, 1215, 1164, 749; \(\delta\) (400 MHz, CDCl\(_3\)) 2.40 (3H, s, CH\(_3\)), 7.31 (2H, d, \(J\) 8.2 Hz, 2 × ArH), 7.81 (1H, d, \(J\) 9.3 Hz, 3-H), 7.83 (2H, d, \(J\) 8.2 Hz, 2 × ArH), 8.31 (1H, d, \(J\) 2.6 Hz, 6-H), 8.54 (1H, d, \(J\) 2.6 Hz, 6-H), 9.94 (1H, \(\text{d}\), \(J\) 0.6 Hz, N-H), 11.19 (1H, \(\text{br s}\), CHO); \(\delta\) (101 MHz, CDCl\(_3\)) 21.6 (CH\(_3\)), 117.3 (CH), 120.5 (C), 127.4 (2 × CH), 130.2 (2 × CH), 130.5 (CH), 131.5 (CH), 135.6 (C), 142.1 (C), 145.0 (C), 145.3 (C), 193.5 (CH); \(m/z\) (ESI) 343.0350 (MNa\(^+\), C\(_{14}\)H\(_{12}\)N\(_2\)NaO\(_5\)S requires 343.0359).

Ethyl (2E)-3-(5′-nitro-2′-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (217)

\[
\begin{align*}
\text{O}_2\text{N} & \quad 4' \\
\text{NHTs} & \quad 3' \\
\text{CO}_2\text{Et} & \quad 2
\end{align*}
\]

Lithium bromide (0.043 g, 0.50 mmol) was added to a solution of triethyl phosphonoacetate (0.085 mL, 0.43 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.064 mL, 0.430 mmol) in acetonitrile (2 mL) and stirred at room temperature for 0.5 h. 5-nitro-2-[N-(p-toluenesulfonyl)amino]benzaldehyde (216) (0.040 g, 0.130 mmol) was added and the solution was stirred at room temperature for 3 h. The reaction was quenched with 10% aqueous potassium sodium tartrate solution (2
mL), concentrated to half volume in vacuo and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with water (2 mL), brine (2 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (ethyl acetate/petroleum ether, 1:3) gave ethyl (2E)-3-(5'-nitro-2'-[N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (217) (0.048 g, 99%) as a white solid. Mp 158–160 °C; Rf 0.28 (33% ethyl acetate/petroleum ether); v_max/cm⁻¹ (neat) 3255 (NH), 2980 (CH), 1700 (CO), 1640 (C=C), 1527, 1344, 1166, 908, 757; δ_H (400 MHz, CDCl₃) 1.34 (3H, t, J 7.1 Hz, OCH₂C₃H₃), 2.38 (3H, s, CH₃), 4.27 (2H, q, J 7.1 Hz, OC₂H₂CH₃), 6.35 (1H, d, J 15.7 Hz, 2'-H), 7.26 (2H, d, J 8.2 Hz, 2 × ArH), 7.65–7.72 (4H, m, 3'-H, NH and 2 × ArH), 8.16 (1H, dd, J 9.0, 2.6 Hz, 4'-H), 8.28 (1H, d, J 2.6 Hz, 6'-H); δ_C (101 MHz, CDCl₃) 14.2 (CH₃), 21.6 (CH₃), 61.3 (CH₂), 123.0 (CH), 123.1 (CH), 124.4 (CH), 125.5 (CH), 127.3 (2 × CH), 127.9 (C), 130.1 (2 × CH), 135.6 (C), 136.5 (CH), 140.6 (C), 144.7 (C), 144.9 (C), 165.9 (C); m/z (ESI) 413.0760 (MNa⁺, C₁₈H₁₉N₂NaO₆S requires 413.0778).

Ethyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-nitrophenyl)prop-2-enoate (218)

The reaction was carried out as described for the synthesis of methyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-enoate (208a) using ethyl (2E)-3-(2'-[N-(p-toluenesulfonyl)amino]-5'-nitrophenyl)prop-2-enoate (217) (0.020 g, 0.05 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:10) gave ethyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-nitrophenyl)prop-2-enoate (218) (0.012 g, 55%) as a white solid. Mp 128–130 °C; Rf 0.50 (33% ethyl acetate/petroleum ether); v_max/cm⁻¹ (neat) 2956 (CH), 1716 (CO), 1529 (C=C), 1349, 1215, 908, 730; δ_H (400 MHz, CDCl₃) 1.35 (3H, t, J 7.1 Hz, OCH₂C₂H₃), 2.44 (3H, s, CH₃), 4.16 (2H, br s, 2''-H₂), 4.28 (2H, q, J 7.1 Hz, OCH₂C₂H₃), 4.98 (1H, dd, J 17.0, 1.1 Hz, 4''-HH), 5.04 (1H, dd, J 10.0, 1.1 Hz, 4''-HH), 5.72 (1H, ddt, J 17.0, 10.0, 6.8 Hz, 3''-H), 6.47 (1H, d, J 16.1 Hz, 2-H), 7.05
(1H, d, J 8.8 Hz, 3'-H), 7.31 (2H, d, J 8.2 Hz, 2 × ArH), 7.57 (2H, d, J 8.2 Hz, 2 × ArH), 7.80 (1H, d, J 16.1 Hz, 3-H), 8.11 (1H, dd, J 8.8, 2.6 Hz, 4'-H), 8.49 (1H, d, J 2.6 Hz, 6'-H); δ_C (101 MHz, CDCl_3) 14.3 (CH_3), 21.6 (CH_3), 54.8 (CH_2), 60.9 (CH_2), 120.7 (CH_2), 122.3 (CH), 122.9 (CH), 124.4 (CH), 127.9 (2 × CH), 129.9 (2 × CH), 131.1 (CH), 131.4 (CH), 134.9 (C), 137.6 (C), 138.0 (CH), 143.7 (C), 144.6 (C), 147.4 (C), 165.7 (C); m/z (ESI) 453.1073 (MNa^+), C_{21}H_{22}N_2NaO_6S requires 453.1091).

(2E)-3-(2'-[N-Allyl-N-(p-toluenesulfonyl)amino]-5'-nitrophenyl)prop-2-en-1-ol (209g)

The reaction was carried out as described for the synthesis of (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]phenyl)prop-2-en-1-ol (209a) using ethyl (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-nitrophenyl)prop-2-enolate (218) (0.143 g, 0.330 mmol). Purification by column chromatography (ethyl acetate/petroleum ether, 1:2) gave (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-nitrophenyl)prop-2-en-1-ol (209g) (0.110 g, 85%) as a colourless oil. R_f 0.18 (33% ethyl acetate/petroleum ether); v_{max}/cm^{-1} (neat) 3537 (OH), 2924 (CH), 1524 (C=C), 1347, 1162, 748; δ_H (400 MHz, CDCl_3) 2.05 (1H, br s, OH), 2.45 (3H, s, CH_3), 4.12 (2H, br s, 2''-H_2), 4.33 (2H, br d, J 4.9 Hz, 1''-H_2), 4.92–5.04 (2H, m, 4''-H_2), 5.69 (1H, ddt, J 17.0, 10.1, 6.8 Hz, 3''-H), 6.49 (1H, dt, J 16.0, 4.9 Hz, 2-H), 6.85 (1H, dt, J 16.0, 1.6 Hz, 3-H), 6.86 (1H, d, J 8.8 Hz, 3'-H), 7.32 (2H, d, J 8.2 Hz, 2 × ArH), 7.57 (2H, d, J 8.2 Hz, 2 × ArH), 7.95 (1H, dd, J 8.8, 2.7 Hz, 4'-H), 8.43 (1H, d, J 2.7 Hz, 6'-H); δ_C (101 MHz, CDCl_3) 21.6 (CH_3), 54.7 (CH_2), 63.2 (CH_2), 120.4 (CH_2), 121.7 (CH), 122.1 (CH), 124.4 (CH), 127.9 (2 × CH), 129.9 (2 × CH), 130.5 (CH), 131.5 (CH), 134.1 (CH), 135.4 (C), 139.9 (C), 142.0 (C), 144.4 (C), 147.5 (C); m/z (ESI) 411.0970 (MNa^+, C_{19}H_{20}N_2NaO_6S requires 411.0985).
N-(p-Toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1H-benzazepine (221a)

(2E)-3-(2'-[N-Allyl-N-(p-toluenesulfonyl)amino]prop-2-en-1-ol (209a) (0.313 g, 0.911 mmol) was dissolved in dichloromethane (45 mL) and cooled to 0 °C under argon with stirring. Trichloroacetonitrile (0.137 mL, 1.37 mmol) was added to the solution, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.068 mL, 0.460 mmol) and the reaction was allowed to warm to room temperature over 2 h. The reaction mixture was filtered through a short pad of alumina (neutral, Brockman V) with diethyl ether (150 mL) and concentrated in vacuo to yield the crude allylic trichloroacetimidate as a yellow oil which was used without further purification. The allylic trichloroacetimidate was transferred to a dry Schlenk tube containing a stirrer bar and potassium carbonate (0.030 g, 5 mg/mL) to which p-xylene (6 mL) was then added. The tube was purged with argon, sealed and heated to 160 °C for 24 h. The reaction mixture was allowed to cool to room temperature and Grubbs 2nd generation catalyst (0.039 g, 0.046 mmol, 5 mol%) and p-xylene (51 mL, 0.016 M) were added. The reaction mixture was heated to 60 °C for 18 h. The reaction mixture was concentrated in vacuo and purified by column chromatography (diethyl ether/petroleum ether, 1:3) which gave N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1H-benzazepine (221a) (0.339 g, 81%) as a white solid. Mp 160–163 °C (decomposition); Rf 0.28 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3337 (NH), 2925 (CH), 1701 (CO), 1496, 1341, 1159, 906, 727; δH (400 MHz, CDCl₃) 2.47 (3H, s, CH₃), 3.86 (1H, br s, 2-H), 4.66 (1H, br s, 2-HH), 5.58 (1H, br t, J 7.7 Hz, 5-H), 5.84 (1H, br d, J 9.0 Hz, 3-H), 6.04 (1H, br s, 4-H), 6.82 (1H, br s, 9-H), 7.23 (1H, td, J 8.4, 1.6 Hz, 8-H), 7.31 (1H, td, J 8.4, 1.3 Hz, 7-H), 7.36 (2H, d, J 8.2 Hz, 2 × ArH), 7.42 (1H, br d, J 8.4 Hz, 6-H), 7.77 (2H, d, J 8.2 Hz, 2 × ArH), 8.37 (1H, br s, NH); δC (101 MHz, CDCl₃) 21.6 (CH₃), 49.1 (CH₂), 52.7 (CH), 92.5 (C), 125.8 (CH), 127.4 (2 × CH), 128.2 (CH), 129.3 (CH), 129.7 (CH), 130.0 (2 × CH), 130.8 (2 × CH), 137.7 (C),
138.1 (C), 139.2 (C), 144.2 (C), 161.4 (C); m/z (ESI) 480.9904 (MNa⁺, C₁₉H₁₇³⁵Cl₃N₂NaO₃S requires 480.9918).

7-Methyl-N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1H-benzazepine (221b)

The reaction was carried out as described for the synthesis of N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1H-benzazepine (221a) using (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-methylylphenyl)-prop-2-en-1-ol (209b) (0.170 g, 0.480 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:3) gave 7-methyl-N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1H-benzazepine (221b) (0.179 g, 80%) as a white solid. Mp 174–176 °C; Rᵣ 0.30 (50% diethyl ether/petroleum ether); ν_max/cm⁻¹ (neat) 3333 (NH), 2923 (CH), 1701 (CO), 1505, 1340, 1155, 1112, 909, 727; δ_H (400 MHz, CDCl₃) 2.33 (3H, s, 7-CH₃), 2.47 (3H, s, CH₃), 3.82 (1H, br s, 2-HH), 4.67 (1H, br s, 2-HH), 5.53 (1H, br t, 7.8 Hz, 5-H), 5.84 (1H, br d, 8.6 Hz, 3-H), 6.04 (1H, br s, 4-H), 6.67 (1H, br s, 9-H), 7.02 (1H, dd, 8.1, 1.4 Hz, 8-H), 7.23 (1H, br s, 6-H), 7.36 (2H, d, 8.2 Hz, 2 × ArH), 8.76 (2H, d, 8.2 Hz, 2 × ArH), 8.43 (1H, br s, NH); δ_C (101 MHz, CDCl₃) 21.1 (CH₃), 21.6 (CH₃), 49.1 (CH₂), 52.7 (CH), 92.6 (C), 125.8 (CH), 127.4 (2 × CH), 127.9 (CH), 130.0 (2 × CH), 130.2 (2 × CH), 130.9 (CH), 135.4 (C), 137.8 (C), 138.8 (C), 139.4 (C), 144.1 (C), 161.4 (C); m/z (ESI) 495.0053 (MNa⁺, C₂₀H₁₉³⁵Cl₃N₂NaO₃S requires 495.0074).
7-Methoxy-\(N\)-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1\(H\)-benzazepine (221c)

The reaction was carried out as described for the synthesis of \(N\)-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1\(H\)-benzazepine (221a) using (2\(E\))-3-(2'-[N-allyl-\(N\)-(p-toluenesulfonyl)amino]-5'-methoxyphen-yl)prop-2-en-1-ol (209c) (0.076 g, 0.20 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:3) gave 7-methoxy-\(N\)-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1\(H\)-benzazepine (221c) (0.079 g, 79%) as a white solid. Mp 190–195 °C (decomposition); R\(_f\) 0.20 (50% diethyl ether/petroleum ether); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3337 (NH), 2935 (CH), 1701 (CO), 1502, 1215, 1156, 749; \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 2.46 (3H, s, CH\(_3\)), 3.61–3.84 (4H, m, 2-\(H\)H and 7-OCH\(_3\)), 4.72 (1H, br s, 2-\(H\)H), 5.51 (1H, br t, \( J = 7.6\) Hz, 5-\(H\)), 5.85 (1H, br s, 3-\(H\)), 6.05 (1H, br s, 4-\(H\)), 6.64 (1H, br s, 9-\(H\)), 6.71 (1H, dd, \( J = 8.6, 2.8\) Hz, 8-\(H\)), 6.93 (1H, br s, 6-\(H\)), 7.35 (2H, d, \( J = 8.2\) Hz, 2 × Ar\(H\)), 7.74 (2H, d, \( J = 8.2\) Hz, 2 × Ar\(H\)), 8.58 (1H, br s, NH); \(\delta_{\text{C}}\) (101 MHz, CDCl\(_3\)) 21.6 (CH\(_3\)), 49.2 (CH\(_2\)), 52.9 (CH\(_2\)), 55.6 (CH\(_3\)), 92.5 (C), 114.9 (CH), 125.5 (CH), 127.4 (2 × CH), 129.3 (CH), 130.0 (2 × CH), 130.4 (CH), 131.2 (CH), 137.7 (C), 140.5 (C), 144.1 (C), 159.7 (2 × C), 161.5 (C); \(m/z\) (ESI) 512.9973 (M\(Na^+\), C\(_{20}\)H\(_{19}\)Cl\(_2\)Cl\(_2\)O\(_4\)N\(_2\)Na requires 512.9994).

7-Fluoro-\(N\)-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1\(H\)-benzazepine (221d)
The reaction was carried out as described for the synthesis of N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1H-benzazepine (221a) using (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-fluorophenyl)-prop-2-en-1-ol (209d) (0.189 g, 0.520 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:3) gave 7-fluoro-N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1H-benzazepine (221d) (0.204 g, 82%) as a white solid. Mp 181–183 °C; Rf 0.25 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3333 (NH), 3034, 1705 (CO), 1503, 1344, 1159, 907, 729; δH (400 MHz, CDCl₃) 2.47 (3H, s, CH₃), 3.81 (1H, br s, 2-H-H), 4.62 (1H, br s, 2-H-H), 5.52 (1H, br t, J 7.4 Hz, 5-H), 5.85 (1H, br s, 3-H), 5.98 (1H, br s, 4-H), 6.81 (1H, br s, 9-H), 6.91 (1H, td, J 8.2, 2.9 Hz, 8-H), 7.12 (1H, br s, 6-H), 7.36 (2H, d, J 8.2 Hz, 2 × ArH), 7.75 (2H, d, J 8.2 Hz, 2 × ArH), 8.40 (1H, br s, NH); δC (101 MHz, CDCl₃) 21.6 (CH₃), 48.9 (CH₂), 52.2 (CH), 92.4 (C), 116.1 (CH), 116.4 (CH), 125.4 (CH), 127.4 (2 × CH), 130.1 (3 × CH), 131.1 (CH), 133.9 (C), 137.3 (C), 141.7 (C), 144.4 (C), 161.4 (C), 162.1 (d, JJC 250.6 Hz, C); m/z (ESI) 498.9809 (MNa⁺, C₁₉H₁₆⁵Cl₃FN₂NaO₃S requires 498.9823).

8-Fluoro-N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1H-benzazepine (221e)

The reaction was carried out as described for the synthesis of N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1H-benzazepine (221a) using (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-fluorophenyl)-prop-2-en-1-ol (209e) (0.222 g, 0.610 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:3) gave 8-fluoro-N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1H-benzazepine (221e) (0.269 g, 92%) as a white solid. Mp 147–149 °C; Rf 0.28 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3340 (NH), 2925 (CH), 1704 (CO), 1599 (C=C), 1501, 1343, 1160, 909, 731; δH (400 MHz, CDCl₃) 2.48 (3H, s, CH₃),
195

3.86 (1H, br d, J 17.8 Hz, 2-HH), 4.62 (1H, br d, J 17.8 Hz, 2-HH), 5.56 (1H, br t, J 7.8 Hz, 5-H), 5.85 (1H, ddd, J 11.4, 4.5, 1.8 Hz, 3-H), 6.02 (1H, dd, J 11.4, 7.8 Hz, 4-H), 6.55 (1H, br d, J_H 8.0 Hz, 9-H), 7.02 (1H, td, J 8.2, 2.6 Hz, 7-H), 7.38 (2H, d, J 8.2 Hz, 2 × ArH), 7.41 (1H, dd, J 8.2, 4.5 Hz, 6-H), 7.77 (2H, d, J 8.2 Hz, 2 × ArH), 8.24 (1H, br s, NH); δ_C (101 MHz, CDCl_3) 21.7 (CH_3), 48.8 (CH_2), 52.1 (CH), 92.4 (C), 115.6 (d, J_CF 22.9 Hz, CH), 116.2 (d, J_CF 21.0 Hz, CH), 125.6 (CH), 127.4 (2 × CH), 130.2 (2 × CH), 130.7 (CH), 132.0 (CH), 135.3 (d, J_CF 3.5 Hz, C), 137.2 (C), 139.4 (d, J_CF 9.9 Hz, C), 144.6 (C), 161.3 (C), 162.5 (d, J_CF 230.0 Hz, C); m/z (ESI) 498.9804 (MNa^+), C_{19}H_{16}Cl_3FN_2NaO_3S requires 498.9823).

7-Chloro-N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarboxylamino)-2,5-dihydro-1H-benzazepine (221f)

![Chemical structure of 7-Chloro-N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarboxylamino)-2,5-dihydro-1H-benzazepine (221f)]

The reaction was carried out as described for the synthesis of N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarboxylamino)-2,5-dihydro-1H-benzazepine (221a) using (2E)-3-(2'-[N-allyl-N-(p-toluenesulfonyl)amino]-5'-chlorophenyl)-prop-2-en-1-ol (209f) (0.290 g, 0.770 mmol). The RCM step was heated to 60 °C for 24 h. Purification by column chromatography (diethyl ether/petroleum ether, 1:3) gave 7-chloro-N-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarboxylamino)-2,5-dihydro-1H-benzazepine (221f) (0.300 g, 79%) as a white solid. Mp 158–160 °C; R_f 0.25 (50% diethyl ether/petroleum ether); v_max/cm^{-1} (neat) 3341 (NH), 2925 (CH), 1705 (CO), 1495, 1343, 1159, 908, 730; δ_H (400 MHz, CDCl_3) 2.47 (3H, s, CH_3), 3.88 (1H, br s, 2-HH), 4.60 (1H, br s, 2-HH), 5.51 (1H, br t, J 7.6 Hz, 5-H), 5.84 (1H, br d, J 9.0 Hz, 3-H), 5.97 (1H, br s, 4-H), 6.79 (1H, br s, 9-H), 7.20 (1H, dd, J 8.4, 2.4 Hz, 8-H), 7.36 (2H, d, J 8.2 Hz, 2 × ArH), 7.40 (1H, br s, 6-H), 7.75 (2H, d, J 8.2 Hz, 2 × ArH), 8.26 (1H, br s, NH); δ_C (101 MHz, CDCl_3) 21.7 (CH_3), 48.9 (CH_2), 52.1 (CH), 92.3 (C), 125.4 (CH), 127.4 (2 × CH), 129.6 (2 × CH), 130.2
(2 × CH), 131.0 (2 × CH), 134.9 (C), 136.5 (C), 137.2 (C), 141.0 (C), 144.5 (C), 161.4 (C); m/z (ESI) 514.9515 (MNa$^+$, C$_{19}$H$_{16}^{35}$Cl$_4$N$_2$NaO$_3$S requires 514.9528).

7-Nitro-N($\rho$-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1$H$-benzazepine (221g)

The reaction was carried out as described for the synthesis of N($\rho$-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1$H$-benzazepine (221a) using (2E)-3-(2'-[N-allyl-N($\rho$-toluenesulfonyl)amino]-5'-nitrophenyl)-prop-2-en-1-ol (209g) (0.084 g, 0.216 mmol). The Overman rearrangement was heated to 160 °C for 43 h and the RCM step was heated to 60 °C for 31 h. Purification by column chromatography (diethyl ether/petroleum ether, 1:3) gave 7-nitro-N($\rho$-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1$H$-benzazepine (221g) (0.053 g, 49%) as a white solid. Mp 180–185 °C (decomposition); R$_f$ 0.28 (50% diethyl ether/petroleum ether); $\nu_{\text{max}}$/cm$^{-1}$ (neat) 3335 (NH), 3020, 1709 (CO), 1592 (C=C), 1530, 1350, 1215, 1161, 749; $\delta$$_H$ (400 MHz, CDCl$_3$) 2.49 (3H, s, CH$_3$), 4.03 (1H, br d, $J$ 18.5 Hz, 2-H), 4.54 (1H, br d, $J$ 18.5 Hz, 2-HH), 5.64 (1H, br t, $J$ 7.2 Hz, 5-H), 5.86 (1H, br d, $J$ 11.4 Hz, 3-H), 5.95–6.02 (1H, m, 4-H), 7.18 (1H, d, $J$ 8.6 Hz, 9-H), 7.41 (2H, d, $J$ 8.2 Hz, 2 × ArH), 7.79 (2H, d, $J$ 8.2 Hz, 2 × ArH), 7.98 (1H, br s, NH), 8.13 (1H, dd, $J$ 8.6, 2.6 Hz, 8-H), 8.29 (1H, d, $J$ 2.6 Hz, 6-H); $\delta$$_C$ (101 MHz, CDCl$_3$) 21.7 (CH$_3$), 48.7 (CH$_2$), 51.8 (CH), 92.1 (C), 124.6 (2 × CH), 125.1 (CH), 127.4 (2 × CH), 129.6 (CH), 130.4 (2 × CH), 130.7 (CH), 136.8 (C), 141.2 (C), 143.8 (C), 145.0 (C), 147.4 (C), 161.5 (C); m/z (ESI) 525.9761 (MNa$^+$, C$_{19}$H$_{16}^{35}$Cl$_3$F$_3$NaO$_5$S requires 525.9768).
5-tert-Butoxycarbonylamino-N-(p-toluenesulfonyl)-2,5-dihydro-1\textit{H}-benzazepine (226)

2M Aqueous sodium hydroxide (5 mL) was added to a solution of \textit{N}-(p-toluenesulfonyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1\textit{H}-benzazepine (221a) (0.165 g, 0.359 mmol) in methanol (3 mL) at 60 °C and stirred for 18 h. The mixture was allowed to cool to room temperature and then di-\textit{tert}-butyl dicarbonate (0.393 g, 1.80 mmol) was added. The reaction mixture was stirred for a further 24 h. The reaction mixture was extracted with ethyl acetate (3 × 5 mL), dried (MgSO\textsubscript{4}), filtered, and concentrated \textit{in vacuo}. Purification by column chromatography (ethyl acetate/petroleum ether, 1:20) gave 5-tert-butoxycarbonylamino-\textit{N}-(p-toluenesulfonyl)-2,5-dihydro-1\textit{H}-benzazepine (226) (0.108 g, 73%) as a white solid. Mp 149–151 °C (decomposition); R\textsubscript{f} 0.28 (33% ethyl acetate/petroleum ether); \( v_{\text{max}} / \text{cm}^{-1} \) (neat) 3393 (NH), 2978 (CH), 1698 (CO), 1494, 1343, 1159, 908, 728; \( \delta_{\text{H}} \) (400 MHz, CDCl\textsubscript{3}) 1.44 (9H, s, O\textit{t}Bu), 2.45 (3H, s, CH\textsubscript{3}), 4.14 (1H, br s, 2-HH), 4.35 (1H, br s, 2-HH), 5.33 (1H, br t, \( J \) 7.2 Hz, 5-H), 5.50 (1H, br s, NH), 5.61 (1H, br d, \( J \) 10.7 Hz, 3-H), 5.81 (1H, br s, 4-H), 7.05 (1H, d, \( J \) 7.6 Hz, 9-H), 7.21 (1H, td, \( J \) 7.6, 1.6 Hz, 8-H), 7.27–7.36 (4H, m, 6-H, 7-H and 2 × ArH), 7.77 (2H, br d, \( J \) 8.2 Hz, 2 × ArH); \( \delta_{\text{C}} \) (126 MHz, CDCl\textsubscript{3}) 21.6 (CH\textsubscript{3}), 28.4 (3 × CH\textsubscript{3}), 48.9 (CH\textsubscript{2}), 51.3 (CH), 79.5 (C), 127.3 (2 × CH), 127.9 (CH), 128.5 (3 × CH), 128.7 (2 × CH), 129.9 (2 × CH), 137.6 (C), 138.0 (C), 141.4 (C), 143.8 (C), 154.9 (C); \( m/z \) (ESI) 437.1486 (MNa\textsuperscript{+}, C\textsubscript{22}H\textsubscript{26}N\textsubscript{2}O\textsubscript{4}S requires 437.1505).
Palladium on charcoal (20%, 0.017 g) was added to a solution of 5-tert-butoxycarbonylamino-N-(p-toluenesulfonyl)-2,5-dihydro-1H-benzazepine (226) (0.057 g, 0.14 mmol) in ethyl acetate (4 mL). The mixture was stirred under an atmosphere of hydrogen at 60 °C for 17 h. The reaction mixture was filtered through a short pad of Celite® with diethyl ether (50 mL), concentrated in vacuo to give 5-tert-butoxycarbonylamino-N-(p-toluenesulfonyl)-2,3,4,5-tetrahydro-1H-benzazepine (227) (0.050 g) as a white solid. 5-tert-Butoxycarbonylamino-N-(p-toluene-sulfonyl)-2,3,4,5-tetrahydro-1H-benzazepine (0.050 g, 0.12 mmol) was dissolved in methanol (5 mL) and magnesium turnings (0.082 g, 3.36 mmol) were added. The mixture was heated under reflux for 4 h. The reaction mixture was cooled to 0 °C and 1M aqueous hydrochloric acid solution (10 mL) was added dropwise. The solution was extracted with ethyl acetate (3 × 10 mL), dried (MgSO₄) and concentrated in vacuo. Purification by column chromatography using (ethyl acetate/petroleum ether, 1:20) gave 5-tert-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-benzazepine (228) (0.032 g, 88%) as a white solid. Mp 151–153 °C (lit.¹⁸³ 153–154 °C); Rf 0.45 (30% ethyl acetate/petroleum ether); δH (400 MHz, CDCl₃) 1.42 (9H, s, OtBu), 1.55–1.80 (2H, m, 3-HH and 4-HH), 2.83 (1H, td, J 12.8, 2.0 Hz, 2-HH), 3.21–3.35 (1H, m, 2-H)N, 3.61 (1H, dd, J 7.3, 1.1 Hz, 9-H), 6.89 (1H, td, J 7.3, 1.1 Hz, 7-H), 7.08 (1H, td, J 7.3, 1.6 Hz, 8-H), 7.23 (1H, br d, J 7.3 Hz, 6-H); δC (101 MHz, CDCl₃) 25.5 (CH₃), 28.5 (3 × CH₃), 30.9 (CH₂), 49.1 (CH₂), 55.1 (CH), 79.0 (C), 120.5 (CH), 121.9 (CH), 128.0 (CH), 130.0 (CH), 133.7 (C), 149.1 (C), 155.2 (C); m/z (ESI) 285 (MNa⁺, 100%), 185 (25), 146 (4).
Propargyl bromide (3.34 mL, 30.0 mmol) was added to a stirred solution of 2-hydroxybenzaldehyde (180a) (3.00 g, 25.0 mmol) and potassium carbonate (7.00 g, 50.0 mmol) in N,N'-dimethylformamide (120 mL) and heated to 70 °C for 3 h. The reaction mixture was cooled to room temperature, diluted with 5% aqueous lithium chloride solution (20 mL) and extracted with diethyl ether (3 × 50 mL). The organic layer was washed with 5% aqueous lithium chloride solution (3 × 50 mL), brine (50 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (diethyl ether/petroleum ether, 1:4) gave 2-propargyloxybenzaldehyde (238a) (3.94 g, quantitative) as a white solid. Mp 69–70 °C (lit. 242 69–70 °C); Rf 0.65 (50% diethyl ether/petroleum ether); δ_H (500 MHz, CDCl₃) 2.57 (1H, t, J 2.5 Hz, 4'-H), 4.81 (2H, d, J 2.5 Hz, 2'-H₂), 7.06 (1H, br t, J 7.5 Hz, 5-H), 7.10 (1H, d, J 8.5 Hz, 3-H), 7.54 (1H, ddd, J 8.5, 7.5, 1.9 Hz, 4-H), 7.83 (1H, dd, J 7.5, 1.9 Hz, 6-H), 10.46 (1H, br d, J 0.6 Hz, CHO); δ_C (126 MHz, CDCl₃) 56.4 (CH₂), 76.5 (CH), 77.7 (C), 113.2 (CH), 121.7 (CH), 125.4 (C), 128.5 (CH), 135.7 (CH), 159.7 (C), 189.5 (CH); m/z (EI) 160 (M⁺, 30%), 131 (100), 121 (49), 109 (40), 83 (47), 65 (30), 39 (34).

5-Methoxy-2-propargyloxybenzaldehyde (238b)

The reaction was carried out as described for the synthesis of 2-propargyloxybenzaldehyde (238a) using 2-hydroxy-5-methoxybenzaldehyde (180h) (0.152 g, 1.00 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:4) gave 5-methoxy-2-propargyloxybenzaldehyde (238b) (0.190 g, quantitative) as a white solid. Mp 60–62 °C; Rf 0.91 (50% diethyl ether/petroleum ether); Spectroscopic data was consistent with literature. δ_H (500 MHz, CDCl₃) 2.55 (1H, t, J 2.4 Hz, 4'-H), 3.81 (3H, s, 5-OCH₃), 4.78 (2H, d, J
2.4 Hz, 2'-H), 7.08 (1H, d, J 9.1 Hz, 3-H), 7.14 (1H, dd, J 9.1, 3.3 Hz, 4-H), 7.34 (1H, d, J 3.3 Hz, 6-H), 10.44 (1H, s, CHO); δ C (126 MHz, CDCl₃) 55.8 (CH₃), 57.4 (CH₂), 76.4 (CH), 77.9 (C), 110.4 (CH), 115.7 (CH), 123.2 (CH), 126.2 (C), 126.2 (C), 154.5 (C), 189.4 (CH); m/z (ESI) 213 (MNa⁺, 75%), 206 (40), 174 (100).

4-Methoxy-2-propargyloxybenzaldehyde (238c)

The reaction was carried out as described for the synthesis of 2-propargyloxybenzaldehyde (238a) using 2-hydroxy-4-methoxybenzaldehyde (180i) (0.152 g, 1.00 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:4) gave 4-methoxy-2-propargyloxybenzaldehyde (238c) (0.188 g, 99%) as a white solid. Mp 82–84 °C (lit. 245 76–78 °C); Rf 0.41 (50% diethyl ether/petroleum ether); δ H (500 MHz, CDCl₃) 2.58 (1H, t, J 2.4 Hz, 4'-H), 3.87 (3H, s, 4-OCH₃), 4.80 (2H, d, J 2.4 Hz, 2'-H₂), 6.58–6.61 (2H, m, 3-H and 5-H), 7.81–7.84 (1H, m, 6-H), 10.29 (1H, br d, J 0.6 Hz, CHO); δ C (126 MHz, CDCl₃) 55.7 (CH₃), 56.4 (CH₂), 76.6 (CH), 77.6 (C), 99.5 (CH), 106.9 (CH), 119.6 (C), 130.6 (CH), 161.5 (C), 165.9 (C), 188.1 (CH); m/z (ESI) 213 (MNa⁺, 100%).

5-Chloro-2-propargyloxybenzaldehyde (238d)

The reaction was carried out as described for the synthesis of 2-propargyloxybenzaldehyde (238a) using 2-hydroxy-5-chlorobenzaldehyde (180j) (1.57 g, 10.0 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:4) gave 5-chloro-2-propargyloxybenzaldehyde (238d) (1.93 g, 99%) as a white solid. Mp 74–75 °C (lit. 245 74–76 °C); Rf 0.58 (50% diethyl ether/petroleum ether); δ H (500 MHz, CDCl₃) 2.59 (1H, t, J 2.4 Hz, 4'-H), 4.82 (2H, d, J 2.4 Hz, 2'-H₂), 7.08 (1H, d, J 8.9 Hz, 3-H), 7.50 (1H, dd, J 8.9, 2.8 Hz, 4-H), 7.80 (1H, d, J 2.8 Hz, 6-H), 10.40 (1H, s, CHO); δ C (126 MHz, CDCl₃) 56.8 (CH₂),
76.9 (C), 77.2 (CH), 115.0 (CH), 126.5 (C), 127.5 (C), 128.1 (CH), 135.2 (CH), 158.1 (C), 188.2 (CH); m/z (ESI) 217 (MNa+, 100%), 210 (4), 194 (4), 178 (8), 159 (8), 131 (4).

5-Nitro-2-propargyloxybenzaldehyde (238e)

The reaction was carried out as described for the synthesis of 2-propargyloxybenzaldehyde (238a) using 2-hydroxy-5-nitrobenzaldehyde (180k) (2.75 g, 16.5 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:4) gave 5-nitro-2-propargyloxybenzaldehyde (238e) (3.31 g, 98%) as a white crystalline solid. Mp 90–91 °C (lit. 246 91.5–93 °C); Rf 0.32 (50% diethyl ether/petroleum ether); δH (400 MHz, CDCl3) 2.71 (1H, t, J 2.4 Hz, 4'-H), 5.01 (2H, d, J 2.4 Hz, 2'-H2), 7.32 (1H, d, J 9.2 Hz, 3-H), 8.45 (1H, dd, J 9.2, 2.9 Hz, 4-H), 8.69 (1H, d, J 2.9 Hz, 6-H), 10.45 (1H, s, CHO); δC (101 MHz, CDCl3) 57.2 (CH2), 76.3 (C), 77.9 (CH), 113.8 (CH), 124.5 (CH), 125.2 (C), 130.4 (CH), 142.2 (C), 163.4 (C), 187.3 (CH); m/z (EI) 205 (M+, 16%), 176 (53), 167 (100), 137 (34), 120 (36), 92 (27), 65 (46).

Ethyl (2E)-3-(2'-propargyloxyphenyl)prop-2-enoate (239a)

Lithium chloride (4.20 g, 98.4 mmol) was added to a solution of triethyl phosphonoacetate (16.6 mL, 83.6 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (12.5 mL, 83.6 mmol) in acetonitrile (100 mL) and stirred at room temperature for 0.5 h. 2-Propargyloxybenzaldehyde (238a) (3.94 g, 24.6 mmol) was added and the solution was stirred at room temperature for 3.5 h. The reaction was quenched by the addition of an aqueous saturated solution of ammonium chloride (10 mL), concentrated to half volume in vacuo and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried (MgSO4), filtered and concentrated in vacuo. Purification by column
chromatography (diethyl ether/petroleum ether, 1:10) yielded ethyl (2E)-3-(2'-propargyloxyphenyl)prop-2-enolate (239a) (5.67 g, quantitative) as a colourless oil. Rf 0.70 (50% diethyl ether/petroleum ether); v_max/cm⁻¹ (neat) 2983 (CH), 1701 (CO), 1632 (C=C), 1486, 1316, 1220, 1175, 1022, 750, 731; δ_H (400 MHz, CDCl₃) 1.34 (3H, t, J 7.1 Hz, OCH₂CH₃), 2.53 (1H, t, J 2.4 Hz, 4''-H), 4.26 (2H, q, J 7.1 Hz, OCH₂CH₃), 4.78 (2H, d, J 2.4 Hz, 2''-H₂), 6.51 (1H, d, J 16.2 Hz, 2-H), 7.01 (1H, br t, J 7.6 Hz, 5'-H), 7.05 (1H, br d, J 8.3 Hz, 3'-H), 7.35 (1H, ddd, J 8.3, 7.6, 1.6 Hz, 4'-H), 7.53 (1H, dd, J 7.6, 1.6 Hz, 6'-H), 8.00 (1H, d, J 16.2 Hz, 3-H); δ_C (101 MHz, CDCl₃) 14.4 (CH₃), 56.1 (CH₂), 76.1 (CH), 78.2 (C), 112.7 (CH), 119.1 (CH), 121.6 (CH), 124.1 (C), 128.8 (CH), 131.2 (CH), 139.6 (CH), 156.1 (C), 167.3 (C); m/z (EI) 230.0944 (M⁺, C₁₄H₁₄O₃ requires 230.0943), 201 (44%), 185 (39), 157 (40), 147 (46), 118 (100), 103 (14), 91 (66).

Ethyl (2E)-3-(5'-methoxy-2'-propargyloxyphenyl)prop-2-enolate (239b)

The reaction was carried out as described for the synthesis of ethyl (2E)-3-(2'-propargyloxyphenyl)prop-2-enolate (239a) using 5-methoxy-2-propargyloxybenzaldehyde (238b) (0.167 g, 0.880 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:10) gave ethyl (2E)-3-(5'-methoxy-2'-propargyloxyphenyl)prop-2-enolate (239b) (0.225 g, 99%) as a colourless oil. Rf 0.60 (50% diethyl ether/petroleum ether); v_max/cm⁻¹ (neat) 3020 (CH), 1701 (CO), 1633 (C=C), 1494, 1288, 1214, 1179, 1043, 752; δ_H (400 MHz, CDCl₃) 1.34 (3H, t, J 7.1 Hz, OCH₂CH₃), 2.51 (1H, t, J 2.4 Hz, 4''-H), 3.80 (3H, s, 5'-OCH₃), 4.27 (2H, q, J 7.1 Hz, OCH₂CH₃), 4.72 (2H, d, J 2.4 Hz, 2''-H₂), 6.48 (1H, d, J 16.2 Hz, 2-H), 6.91 (1H, dd, J 9.0, 3.1 Hz, 4'-H), 7.01 (1H, d, J 9.0 Hz, 3'-H), 7.06 (1H, d, J 3.1 Hz, 6'-H), 7.98 (1H, d, J 16.2 Hz, 3-H); δ_C (126 MHz, CDCl₃) 14.4 (CH₃), 55.7 (CH₃), 57.0 (CH₂), 60.4 (CH₂), 75.8 (CH), 78.5 (C), 112.9 (CH), 114.7 (CH), 116.9 (CH), 119.3 (CH), 125.0 (C), 139.4 (CH), 150.5 (C), 154.3 (C), 167.2 (C); m/z (ESI) 283.0932 (MNa⁺, C₁₅H₁₆NaO₄ requires 283.0941), 271 (5%), 244 (35).
Ethyl (2E)-3-(4'-methoxy-2'-propargyloxyphenyl)prop-2-enoate (239c)

\[
\text{MeO-}4\text{'}^3 5\text{'}^4 3\text{'}^5 2\text{'}^6 1\text{'}^7
\]

The reaction was carried out as described for the synthesis of ethyl (2E)-3-(2'-propargyloxyphenyl)prop-2-enoate (239a) using 4-methoxy-2-propargyloxybenzaldehyde (238c) (1.73 g, 9.07 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:10) gave ethyl (2E)-3-(4'-methoxy-2'-propargyloxyphenyl)prop-2-enoate (239c) (2.35 g, quantitative) as a colourless oil. Rf 0.46 (50% diethyl ether/petroleum ether); ν_{max}/cm⁻¹ (neat) 2984 (CH), 1704 (CO), 1605 (C=C), 1258, 1161, 1021, 970; δ_H (400 MHz, CDCl₃) 1.32 (3H, t, J₇.₁ Hz, OCH₂CH₃), 2.54 (1H, t, J₂.₅ Hz, 4''-H), 3.83 (3H, s, 4'-OCH₃), 4.24 (2H, q, J₇.₁ Hz, OCH₂CH₃), 4.75 (2H, d, J₂.₅ Hz, 2''-H₂), 6.40 (1H, d, J₁₆.₁ Hz, 2-H), 6.54 (1H, dd, J₈.₆ Hz, 5'-H), 6.60 (1H, d, J₂.₄ Hz, 3'-H), 7.46 (1H, d, J₈.₆ Hz, 6'-H), 7.90 (1H, d, J₁₆.₁ Hz, 3'-H); δ_C (101 MHz, CDCl₃) 14.4 (CH₃), 55.5 (CH₂), 56.4 (CH₂), 60.2 (CH₂), 76.2 (CH), 78.0 (C), 99.9 (CH), 106.4 (CH), 116.5 (CH), 117.1 (C), 130.2 (CH), 139.5 (CH), 157.6 (C), 162.4 (C), 167.7 (C); m/z (ESI) 283.0935 (M⁺Na⁺, C₁₅H₁₆NaO₄ requires 283.0941), 247 (100%).

Ethyl (2E)-3-(5'-chloro-2'-propargyloxyphenyl)prop-2-enoate (239d)

\[
\text{Cl-}4\text{'}^3 5\text{'}^4 3\text{'}^5 2\text{'}^6 1\text{'}^7
\]

The reaction was carried out as described for the synthesis of ethyl (2E)-3-(2'-propargyloxyphenyl)prop-2-enoate (239a) using 5-chloro-2-propargyloxybenzaldehyde (238d) (0.120 g, 0.620 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:10) gave ethyl (2E)-3-(5'-chloro-2'-propargyloxyphenyl)prop-2-enoate (239d) (0.163 g, quantitative) as a colourless oil. Rf 0.60 (50% diethyl ether/petroleum ether); ν_{max}/cm⁻¹ (neat) 3020 (CH), 1705 (CO), 1635 (C=C), 1480, 1216, 1181, 1024, 747; δ_H (400 MHz, CDCl₃) 1.33 (3H, t, J₇.₁ Hz, OCH₂CH₃), 2.54 (1H, t, J₂.₄ Hz, 4''-H), 4.26 (2H, q, J₇.₁ Hz, OCH₂CH₃), 4.76 (2H, d, J₂.₄ Hz, 2''-H₂), 6.47 (1H, d, J₁₆.₄ Hz, 2-H), 6.99 (1H, d,
J 8.9 Hz, 3'-H), 7.29 (1H, dd, J 8.9, 2.6 Hz, 4''-H), 7.49 (1H, d, J 2.6 Hz, 6'-H), 7.90 (1H, d, J 16.4 Hz, 3-H); δC (101 MHz, CDCl3) 14.3 (CH₃), 56.4 (CH₂), 60.6 (CH₂), 76.4 (CH), 77.8 (C), 114.2 (CH), 120.4 (CH), 125.7 (C), 126.8 (C), 128.2 (CH), 130.6 (CH), 138.1 (CH), 154.6 (C), 166.9 (C); m/z (ESI) 287.0434 (MNa⁺, C₁₄H₁₃ClNaO₃ requires 287.0445), 247 (17%), 227 (10), 159 (3).

**Ethyl (2E)-3-(5'-nitro-2'-propargyloxyphenyl)prop-2-enoate (239e)**

![Chemical Structure](image)

The reaction was carried out as described for the synthesis of ethyl (2E)-3-(2'-propargyloxyphenyl)prop-2-enoate (239a) using 5-nitro-2-propargyloxynbenzaldehyde (238e) (0.140 g, 0.680 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:10) gave ethyl (2E)-3-(5'-nitro-2'-propargyloxyphen-yl)prop-2-enoate (239e) (0.183 g, 98%) as a white solid. Mp 95–96 °C; Rᵣ 0.45 (50% diethyl ether/petroleum ether); νₑₑₑₑ cm⁻¹ (neat) 2986 (CH), 1701 (CO), 1581 (C=C), 1514, 1343, 1270, 1233, 1016, 750; δH (400 MHz, CDCl₃) 1.34 (3H, t, J 7.1 Hz, OCH₂CH₃), 2.61 (1H, t, J 2.4 Hz, 4''-H), 4.28 (2H, q, J 7.1 Hz, OCH₂CH₃), 4.90 (2H, d, J 2.4 Hz, 2''-H₂), 6.60 (1H, d, J 16.4 Hz, 2'-H), 7.15 (1H, d, J 9.2 Hz, 3'-H), 7.93 (1H, d, J 16.4 Hz, 3-H), 8.25 (1H, dd, J 9.2, 2.8 Hz, 4'-H), 8.43 (1H, d, J 2.8 Hz, 6'-H); δC (101 MHz, CDCl₃) 14.3 (CH₃), 56.7 (CH₂), 60.8 (CH₂), 76.7 (CH), 77.4 (C), 112.5 (CH), 121.9 (CH), 124.0 (CH), 124.9 (C), 126.4 (CH), 137.1 (CH), 142.0 (C), 160.2 (C), 166.5 (C); m/z (ESI) 298.0672 (MNa⁺, C₁₄H₁₃NNaO₅ requires 298.0686), 247 (17%), 227 (22).
Diisobutylaluminium hydride (54.0 mL, 54.0 mmol, 1 M in hexane) was added dropwise with stirring to a solution of ethyl (2E)-3-(2''-propargyloxyphenyl)prop-2-enoate (239a) (5.66 g, 24.6 mmol) in dichloromethane (100 mL) at −78 °C. The solution was stirred at −78 °C for 2 h, and then allowed to return to room temperature over 2 h. The reaction was quenched with 10% aqueous potassium sodium tartrate solution (10 mL), extracted with diethyl ether (2 × 50 mL), washed with water (100 mL), brine (100 mL), dried (MgSO₄), filtered and concentrated in vacuo. Purification by column chromatography (diethyl ether/petroleum ether, 1:2) gave (2E)-3-(2''-propargyloxyphenyl)prop-2-en-1-ol (240a) (4.30 g, 93%) as a colourless oil. Rᵋ 0.25 (50% diethyl ether/petroleum ether); νₑₒₓₑₑ/(cₑₑ) (neat) 3304 (OH), 2870 (CH), 1598 (C=C), 1487, 1217, 1024, 974, 748; δ_H (400 MHz, CDCl₃) 2.02 (1H, br s, OH), 2.51 (1H, t, J 2.4 Hz, 4''-H), 4.30 (2H, br d, J 5.7 Hz, 1-H₂), 4.70 (2H, d, J 2.4 Hz, 2''-H₂), 6.36 (1H, dt, J 16.2, 5.7 Hz, 2-H), 6.92 (1H, d, J 16.2 Hz, 3-H), 6.95–6.99 (2H, m, 3'-H and 5'-H), 7.19–7.24 (1H, m, 4'-H), 7.44 (1H, dd, J 8.0, 1.3 Hz, 6'-H); δ_C (101 MHz, CDCl₃) 56.2 (CH₂), 64.1 (CH₂), 75.7 (CH), 78.7 (C), 112.7 (CH), 121.7 (CH), 125.8 (CH), 126.5 (C), 127.1 (CH), 128.6 (CH), 129.7 (CH), 154.7 (C); m/z (EI) 188.0838 (M⁺, C₁₂H₁₂O₂ requires 188.0837), 149 (46%), 131 (100), 121 (55), 91 (84), 77 (43), 65 (13).

The reaction was carried out as described for the synthesis of (2E)-3-(2''-propargyloxyphenyl)prop-2-en-1-ol (240a) using ethyl (2E)-3-(5'-methoxy-2''-propargyloxyphenyl)prop-2-enoate (239b) (1.87 g, 7.17 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:2) gave (2E)-3-(5'-'
methoxy-2’-propargyloxyphenyl)prop-2-en-1-ol (240b) (1.39 g, 89%) as a colourless oil. Rf 0.13 (50% diethyl ether/petroleum ether); νmax/cm−1 (neat) 3288 (OH), 2920 (CH), 1583 (C=C), 1492, 1286, 1202, 1041, 970, 803, 751; δH (400 MHz, CDCl3) 1.59 (1H, br s, OH), 2.50 (1H, t, J 2.4 Hz, 4”-H), 4.67 (2H, d, J 2.4 Hz, 2”-H), 6.37 (1H, dt, J 16.0, 5.8 Hz, 2-H), 6.78 (1H, dd, J 8.9, 3.1 Hz, 4’-H), 6.92 (1H, dt, J 16.0, 1.6 Hz, 3-H), 6.95 (1H, d, J 8.9 Hz, 3’-H), 7.02 (1H, d, J 3.1 Hz, 6’-H); δC (101 MHz, CDCl3) 55.7 (CH3), 57.3 (CH2), 64.1 (CH2), 75.4 (CH), 78.9 (C), 112.1 (CH), 113.7 (CH), 114.9 (CH), 125.7 (CH), 127.7 (C), 129.9 (CH), 149.2 (C), 154.5 (C); m/z (ESI) 241.0829 (MNa+). C13H14NaO3 requires 241.0835, 236 (7%), 227 (5), 218 (4), 202 (100), 199 (6), 161 (3).

(2E)-3-(4’-Methoxy-2’-propargyloxyphenyl)prop-2-en-1-ol (240c)

The reaction was carried out as described for the synthesis of (2E)-3-(2’-propargyloxyphenyl)prop-2-en-1-ol (240a) using ethyl (2E)-3-(4’-methoxy-2’-propargyloxyphenyl)prop-2-enolate (239c) (2.48 g, 9.40 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:2) gave (2E)-3-(4’-methoxy-2’-propargyloxyphenyl)prop-2-en-1-ol (240c) (1.99 g, 92%) as a white solid. Mp 66–68 °C; Rf 0.16 (50% diethyl ether/petroleum ether); νmax/cm−1 (neat) 3302 (OH), 2929 (CH), 1608 (C=C), 1503, 1258, 1194, 1161, 750; δH (500 MHz, CDCl3) 1.86 (1H, br s, OH), 2.53 (1H, t, J 2.4 Hz, 4”-H), 3.80 (3H, s, 4’-OCH3), 4.28 (2H, dd, J 6.1, 1.1 Hz, 1-H2), 4.69 (2H, d, J 2.4 Hz, 2’-H2), 6.26 (1H, dt, J 16.0, 6.1 Hz, 2-H), 6.51 (1H, dd, J 8.5, 2.4 Hz, 5’-H), 6.56 (1H, d, J 2.4 Hz, 3’-H), 6.82 (1H, br d, J 16.0 Hz, 3-H), 7.36 (1H, d, J 8.5 Hz, 6’-H); δC (126 MHz, CDCl3) 55.4 (CH3), 56.3 (CH2), 64.3 (CH2), 75.8 (CH), 78.5 (C), 100.0 (CH), 106.2 (CH), 119.3 (C), 125.8 (CH), 127.4 (CH), 127.9 (CH), 155.8 (C), 160.3 (C); m/z (ESI) 241.0830 (MNa+, C13H14NaO3 requires 241.0835), 224 (3%), 213 (16), 202 (13), 185 (3), 175 (4), 162 (4).
The reaction was carried out as described for the synthesis of \((2E)-3-(2'\text{-propargyloxyphenyl})\text{prop-2-en-1-ol (240a)}\) using ethyl \((2E)-3-(5'\text{-chloro-2'\text{-propargyloxyphenyl})prop-2-enoate (239d)}\) (2.48 g, 9.40 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:2) gave \((2E)-3-(5'\text{-chloro-2'\text{-propargyloxyphenyl})prop-2-en-1-ol (240d)}\) (1.95 g, 93%) as a white solid. Mp 67–68 °C; \(R_f\) 0.25 (50% diethyl ether/petroleum ether); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3285 (OH), 2929 (CH), 1480, 1222, 1025, 963; \(\delta_H\) (500 MHz, CDCl\(_3\)) 2.20 (1H, br s, OH), 2.53 (1H, t, \(J\) 2.5 Hz, 4''-H), 4.30 (2H, br d, \(J\) 5.4 Hz, 1'H\(_2\)), 4.68 (2H, d, \(J\) 2.5 Hz, 2''-H\(_2\)), 6.34 (1H, dt, \(J\) 16.1, 5.4 Hz, 2-H), 6.84 (1H, dt, J 16.1, 1.5 Hz, 3-H), 1H, d, \(J\) 8.9 Hz, 3'-H), 7.15 (1H, dd, \(J\) 8.9, 2.7 Hz, 4'-H), 7.39 (1H, d, \(J\) 2.7 Hz, 6'-H); \(\delta_C\) (126 MHz, CDCl\(_3\)) 56.5 (CH\(_2\)), 63.7 (CH\(_2\)), 76.1 (CH\(_2\)), 78.2 (C), 114.0 (CH), 124.3 (CH), 126.8 (CH), 128.0 (C), 131.0 (CH), 153.2 (C); \(m/z\) (ESI) 245.0333 (MNa\(^+\), C\(_{12}\)H\(_{11}\)ClNaO\(_2\) requires 245.0340), 236 (35%), 227 (13), 218 (11), 205 (13), 170 (11), 141 (7).

\((2E)-3-(5'\text{-Nitro-2'\text{-propargyloxyphenyl})prop-2-en-1-ol (240e)}\)

The reaction was carried out as described for the synthesis of \((2E)-3-(2'\text{-propargyloxyphenyl})\text{prop-2-en-1-ol (240a)}\) using ethyl \((2E)-3-(5'\text{-nitro-2'\text{-propargyloxyphenyl})prop-2-enoate (239e)}\) (1.25 g, 4.54 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:2) gave \((2E)-3-(5'\text{-nitro-2'\text{-propargyloxyphenyl})prop-2-en-1-ol (240e)}\) (1.02 g, 96%) as a white solid. Mp 92–93 °C; \(R_f\) 0.16 (50% diethyl ether/petroleum ether); \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3299 (OH), 2917 (CH), 1584 (C=C), 1514, 1343, 1230, 1011, 747; \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.56 (1H, t, \(J\) 5.6 Hz, OH), 2.59 (1H, t, \(J\) 2.4 Hz, 4''-H), 4.39 (2H, td, \(J\) 5.6, 1.7 Hz, 1-H\(_2\)), 4.85 (2H, d, \(J\) 2.4 Hz, 2''-H\(_2\)), 6.51 (1H, dt, J 16.1, 5.6 Hz, 2-H), 6.92 (1H, dt, 5.6 Hz, 2-H).
$J$ 16.1, 1.7 Hz, 3-H), 7.08 (1H, d, $J$ 9.1 Hz, 3'-H), 8.15 (1H, dd, $J$ 9.1, 2.8 Hz, 4'-H), 8.36 (1H, d, $J$ 2.8 Hz, 6'-H); $\delta$ C (101 MHz, CDCl$_3$) 56.5 (CH$_2$), 63.6 (CH$_2$), 76.9 (C), 77.1 (CH), 112.0 (CH), 122.6 (CH), 123.3 (CH), 124.2 (CH), 127.4 (C), 132.6 (CH), 142.1 (C), 159.0 (C); $m/z$ (ESI) 256.0570 (MNa$^+$, C$_{12}$H$_{11}$NNaO$_4$ requires 256.0580), 227 (27%), 185 (4), 159 (7).

3-(2'-Propargyloxyphenyl)-3-(2",2",2"'-trichloromethylcarbonylamino)prop-1-ene (241a)

(2E)-3-(2'-Propargyloxyphenyl)prop-2-en-1-ol (240a) (0.200 g, 1.06 mmol) was dissolved in dichloromethane (16 mL) and cooled to 0 °C under argon with stirring. Trichloroacetonitrile (0.160 mL, 1.60 mmol) was added to the solution, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.080 mL, 0.540 mmol) and the reaction mixture was allowed to warm to room temperature over 2 h. The reaction mixture was filtered through a short pad of alumina (neutral, Brockman V) with diethyl ether (150 mL) and concentrated in vacuo to yield the crude allylic trichloroacetimidate as a yellow oil which was used without further purification. The allylic trichloroacetimidate was transferred to a dry Schlenk tube containing a stirrer bar and potassium carbonate (15 mg, 3 mg/mL) to which p-xylene (5 mL) was then added. The tube was purged with argon, sealed and heated to 140 °C for 18 h. The reaction mixture was concentrated in vacuo and purified by column chromatography (diethyl ether/petroleum ether, 1:20) to give 3-(2'-propargyloxyphenyl)-3-(2",2",2"'-trichloromethylcarbonylamino)prop-1-ene (241a) (0.331 g, 97%) as a white solid. Mp 46–48 °C; $R_l$ 0.72 (50% diethyl ether/petroleum ether); $\nu_{max}$/cm$^{-1}$ (neat) 3410 (NH), 3297 (CH), 1707 (CO), 1502, 1489, 1223, 1020, 818, 751; $\delta$ H (500 MHz, CDCl$_3$) 2.53 (1H, t, $J$ 2.4 Hz, 4''-H), 4.77 (2H, d, $J$ 2.4 Hz, 2'''-H$_2$), 5.16–5.26 (2H, m, 1-H$_2$), 5.56–5.65 (1H, m, 3-H), 6.06 (1H, ddd, $J$ 17.1, 10.3, 5.4 Hz, 2-H), 6.98–7.07 (2H, m, 3'-H and 4'-H), 7.27 (1H, dd, $J$ 7.7, 1.6 Hz, 6'-H), 7.30–7.37 (1H, m, 5'-H), 7.93 (1H, br d, $J$ 7.9 Hz, NH); $\delta$ C (101 MHz, CDCl$_3$) 56.0 (CH), 56.0 (CH$_2$), 76.2 (CH), 77.8 (C), 92.9 (C),...
112.6 (CH), 116.1 (CH<sub>2</sub>), 122.1 (CH), 127.1 (C), 129.5 (CH), 129.7 (CH), 135.8 (CH), 155.1 (C), 160.8 (C); m/z (ESI) 330.9937 (M<sup>+</sup>, C<sub>14</sub>H<sub>12</sub>Cl<sub>3</sub>NO<sub>2</sub> requires 330.9934), 296 (90%), 260 (22), 186 (29), 171 (41), 131 (100), 114 (61), 103 (68), 77 (75).

3-(5'-Methoxy-2'-propargyloxyphenyl)-3-(2'″,2'″,2'″-trichloromethylcarbonylamino)prop-1-ene (241b)

The reaction was carried out as described for the synthesis of 3-(2'-propargyloxyphenyl)-3-(2'″,2'″,2'″-trichloromethylcarbonylamino)prop-1-ene (241a) using (2E)-3-(5'-methoxy-2'-propargyloxyphenyl)prop-2-en-1-ol (240b) (0.302 g, 1.38 mmol). Flash column chromatography (diethyl ether/petroleum ether, 1:10) gave 3-(5'-methoxy-2'-propargyloxyphenyl)-3-(2'″,2'″,2'″-trichloromethylcarbonylamino)prop-1-ene (241b) (0.441 g, 88%) as a yellow oil. R<sub>f</sub> 0.43 (50% diethyl ether/petroleum ether); v<sub>max</sub>/cm<sup>−1</sup> (neat) 3404 (NH), 3298, 2917 (CH), 1707 (CO), 1493, 1205, 1041, 817, 709; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 2.52 (1H, t, J 2.4 Hz, 4''-H), 3.78 (3H, s, OCH<sub>3</sub>), 4.71 (2H, d, J 2.4 Hz, 2''-H<sub>2</sub>), 5.15–5.30 (2H, m, 1-H<sub>2</sub>), 5.52–5.61 (1H, m, 3-H), 6.04 (1H, ddd, J 17.1, 10.3, 5.4 Hz, 2-H), 6.78–6.87 (2H, m, 4'-H and 3'-H), 6.92–6.99 (1H, m, 6'-H), 7.95 (1H, br d, J 8.4 Hz, NH); δ<sub>C</sub> (101 MHz, CDCl<sub>3</sub>) 55.7 (CH<sub>3</sub>), 56.0 (CH), 56.7 (CH<sub>2</sub>), 76.0 (CH), 78.1 (C), 92.9 (C), 113.7 (CH), 114.1 (CH), 115.5 (CH), 116.2 (CH<sub>2</sub>), 128.2 (C), 135.7 (CH), 149.1 (C), 154.6 (C), 160.9 (C); m/z (Cl) 362.0116 (MH<sup>+</sup>, C<sub>15</sub>H<sub>15</sub>Cl<sub>3</sub>NO<sub>3</sub> requires 362.0118), 328 (42%), 292 (10), 236 (11), 201 (100), 163 (5).
3-(4'-Methoxy-2'-propargyloxyphenyl)-3-(2'',2'',2''-trichloromethylcarbonylamino)prop-1-ene (241c)

The reaction was carried out as described for the synthesis of 3-(2'-propargyloxyphenyl)-3-(2'',2'',2''-trichloromethylcarbonylamino)prop-1-ene (241a) using (2E)-3-(4'-methoxy-2'-propargyloxyphenyl)prop-2-en-1-ol (240c) (0.100 g, 0.459 mmol). Flash column chromatography (diethyl ether/petroleum ether, 1:10) gave 3-(4'-methoxy-2'-propargyloxyphenyl)-3-(2'',2'',2''-trichloromethylcarbonylamino)prop-1-ene (241c) (0.142 g, 84%) as a yellow oil. Rf 0.46 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3416 (NH), 3305, 3018 (CH), 1709 (CO), 1614, 1500, 1197, 1162, 1025, 820, 751; δH (400 MHz, CDCl₃) 2.54 (1H, t, J 2.4 Hz, 4'''-H), 3.81 (3H, s, OCH₃), 4.73 (2H, d, J 2.4 Hz, 2'''-H₂), 5.17–5.22 (2H, m, 1- H₂), 5.52–5.59 (1H, m, 3- H), 6.04 (1H, ddd, J 17.0, 10.4, 5.3 Hz, 2- H), 6.53 (1H, dd, J 8.4, 2.4 Hz, 5'-H), 6.60 (1H, d, J 2.4 Hz, 3'-H), 7.17 (1H, d, J 8.4 Hz, 6'-H), 7.80 (1H, br d, J 8.3 Hz, NH); δC (101 MHz, CDCl₃) 55.4 (CH₃), 55.5 (CH), 56.1 (CH₂), 76.3 (CH), 77.7 (C), 93.0 (C), 100.6 (CH), 105.6 (CH), 115.8 (CH₂), 119.5 (C), 130.3 (CH), 136.1 (CH), 156.1 (C), 160.8 (C), 160.8 (C); m/z (ESI) 383.9914 (MNa⁺, C₁₅H₁₄Cl₃NNaO₃ requires 383.9931), 201 (18%).

3-(5'-Chloro-2'-propargyloxyphenyl)-3-(2'',2'',2''-trichloromethylcarbonylamino)prop-1-ene (241d)

The reaction was carried out as described for the synthesis of 3-(2'-propargyloxyphenyl)-3-(2'',2'',2''-trichloromethylcarbonylamino)prop-1-ene (241a) using (2E)-3-(5'-chboro-2'-propargyloxyphenyl)prop-2-en-1-ol (240d) (0.10 g, 0.45...
The Overman rearrangement was heated to 140 °C for 48 h. Flash column chromatography (diethyl ether/petroleum ether, 1:10) gave 3-(5'-chloro-2'-propargyloxyphenyl)-3-(2'',2'',2'''-trichloromethylcarbonylamino)prop-1-ene (241d) (0.161 g, 98%) as a white solid. Mp 64–66 °C; Rf 0.56 (50% diethyl ether/petroleum ether); v_{max}/cm^{-1} (neat) 3422 (NH), 3306, 2931 (CH), 1713 (CO), 1504, 1486, 1215, 1022, 749; δ_{H} (400 MHz, CDCl_{3}) 2.54 (1H, t, J 2.2 Hz, 4'''-H), 4.75 (2H, d, J 2.2 Hz, 2'''-H), 5.15–5.35 (2H, m, 1-H_{2}), 5.55–5.65 (1H, m, 3-H), 6.03 (1H, ddd, J 17.0, 10.4, 5.3 Hz, 2'-H), 6.96 (1H, d, J 8.6 Hz, 3''-H), 7.20–7.40 (2H, m, 4'-H and 6'-H), 7.70 (1H, br d, J 8.3 Hz, NH); δ_{C} (101 MHz, CDCl_{3}) 55.1 (CH), 56.4 (CH_{2}), 76.6 (CH), 77.3 (C), 92.8 (C), 113.9 (CH), 116.8 (CH_{2}), 127.1 (C), 128.9 (C), 129.1 (CH), 129.5 (CH), 135.0 (CH), 153.6 (C), 160.9 (C); m/z (ESI) 387.9424 (MNa^+), C_{14}H_{11}^{35}Cl_{4}NNaO_{2} requires 387.9436, 381 (14%), 353 (11), 236 (4), 227 (6), 205 (4).

The reaction was carried out as described for the synthesis of 3-(2'-propargyloxyphenyl)-3-(2'',2'',2'''-trichloromethylcarbonylamino)prop-1-ene (241a) using (2E)-3-(5'-nitro-2'-propargyloxyphenyl)prop-2-en-1-ol (240e) (0.100 g, 0.429 mmol). The Overman rearrangement was heated to 140 °C for 72 h. Flash column chromatography (diethyl ether/petroleum ether, 1:10) gave 3-(5'-nitro-2'-propargyloxyphenyl)-3-(2'',2'',2'''-trichloromethylcarbonylamino)prop-1-ene (241e) (0.155 g, 96%) as a white crystalline solid. Mp 140–142 °C; Rf 0.3 (50% diethyl ether/petroleum ether); v_{max}/cm^{-1} (neat) 3422 (NH), 3305, 2926 (CH), 1708 (CO), 1516, 1343, 1263, 1010, 821, 751; δ_{H} (400 MHz, CDCl_{3}) 2.62 (1H, t, J 2.3 Hz, 4'''-H), 4.89 (2H, d, J 2.3 Hz, 2'''-H), 5.29 (1H, d, J 17.1 Hz, 1-H_{H}), 5.33 (1H, d, J 10.3 Hz, 1-H_{H}), 5.70–5.85 (1H, m, 3-H), 6.06 (1H, ddd, J 17.1, 10.3, 5.4 Hz, 2-H), 7.15 (1H, d, J 9.0 Hz, 3''-H), 7.51 (1H, br d, J 8.3 Hz, NH), 8.21 (1H, d, J 2.7 Hz, 6''-H),
8.25 (1H, dd, J 9.0, 2.7 Hz, 4'-H); δC (101 MHz, CDCl3) 54.1 (CH), 56.8 (CH2), 76.5 (CH), 77.4 (C), 92.5 (C), 112.5 (CH), 117.9 (CH2), 124.7 (CH), 125.6 (CH), 128.6 (C), 134.2 (CH), 142.1 (C), 159.7 (C), 161.0 (C); m/z (ESI) 398.9662 (MNa+, C14H11Cl3N2NaO4 requires 398.9677).

8-[1’-(2”,2”,2”-Trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242a)

3-(2’-Propargyloxyphenyl)-3-(2”,2”,2”-trichloromethylcarbonylamino)prop-1-ene (241a) (0.820 g, 2.48 mmol) was dissolved in p-xylene (10 mL) under argon followed by [bis(trifluoromethanesulfonyl)imidate](triphenylphosphine)gold(I) (2:1) toluene adduct (245) (0.097 g, 0.062 mmol) and the reaction was heated to 80 °C for 4 h. The reaction mixture was concentrated in vacuo and purified by column chromatography (diethyl ether/petroleum ether, 1:15) to give 8-[1’-(2”,2”,2”-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242a) (0.820 g, quantitative) as a colourless oil. Rf 0.67 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3418 (NH), 2930 (CH), 1707 (CO), 1700, 1507, 1215, 821, 747; δH (500 MHz, CDCl3) 4.86 (2H, dd, J 3.6, 1.9 Hz, 2-H2), 5.18–5.24 (2H, m, 3’-H2), 5.55 (1H, ddt, J 8.2, 5.4, 1.7 Hz, 1’-H), 5.82 (1H, dt, J 9.9, 3.6 Hz, 3-H), 6.03 (1H, ddd, J 17.1, 10.4, 5.4 Hz, 2’-H), 6.45 (1H, dt, J 9.9, 1.9 Hz, 4-H), 6.88 (1H, t, J 7.6 Hz, 6-H), 6.96 (1H, dd, J 7.6, 1.7 Hz, ArH), 7.06 (1H, dd, J 7.6, 1.7 Hz, ArH), 7.94 (1H, br d, J 8.2 Hz, NH); δC (126 MHz, CDCl3) 55.4 (CH), 65.7 (CH2), 93.0 (C), 116.0 (CH2), 121.8 (CH), 122.0 (CH), 123.1 (C), 124.5 (CH), 125.3 (C), 126.8 (CH), 128.9 (CH), 135.9 (CH), 151.4 (C), 160.8 (C); m/z (EI) 330.9939 (M+, C14H12Cl3NO2 requires 330.9934), 296 (47%), 260 (22), 224 (10), 196 (7), 170 (100), 128 (35), 115 (30), 77 (10).
6-Methoxy-8-[1’-(2″,2″,2″-trichloromethylcarbonylamino)-2'-propenyl]-2H-chromene (242b)

The reaction was carried out as described for the synthesis of 8-[1’-(2″,2″,2″-trichloromethylcarbonylamino)-2'-propenyl]-2H-chromene (242a) using 3-(5’-methoxy-2’-propargyloxyphenyl)-3-(2″,2″,2″-trichloromethylcarbonylamino)prop-1-ene (241b) (0.060 g, 0.165 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:15) gave 6-methoxy-8-[1’-(2″,2″,2″-trichloromethylcarbonylamino)-2'-propenyl]-2H-chromene (242b) (0.060 g, quantitative) as a colourless oil. Rf 0.6 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3404 (NH), 2955 (CH), 1708 (CO), 1503, 1472, 1203, 818; δH (400 MHz, CDCl₃) 3.75 (3H, s, 6-OCH₃), 4.78 (2H, dd, J 3.6, 1.9 Hz, 2-H₂), 5.18–5.24 (2H, m, 3’-H₂), 5.49 (1H, ddt, J 8.6, 5.4, 1.6 Hz, 1’-H), 5.86 (1H, dt, J 9.9, 3.6 Hz, 3-H), 6.01 (1H, ddd, J 17.1, 10.3, 5.4 Hz, 2’-H), 6.41 (1H, dt, J 9.9, 1.9 Hz, 4-H), 6.53 (1H, d, J 2.9 Hz, 5-H), 6.62 (1H, d, J 2.9 Hz, 7-H), 8.01 (1H, br d, J 8.6 Hz, NH); δC (101 MHz, CDCl₃) 55.7 (CH₃), 55.7 (CH), 65.5 (CH₂), 92.9 (C), 111.9 (CH), 113.9 (CH), 116.1 (CH₂), 123.1 (CH), 124.1 (C), 124.6 (CH), 126.0 (C), 135.7 (CH), 145.1 (C), 154.2 (C), 160.8 (C); m/z (Cl) 362.0113 (MH⁺, C₁₅H₁₅Cl₃NO₃ requires 362.0118), 328 (5%), 290 (4), 243 (4), 201 (100), 85 (4).

5-Methoxy-8-[1’-(2″,2″,2″-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242c)
The reaction was carried out as described for the synthesis of 8-[1’-(2",2",2"-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242a) using 3-(4’-methoxy-2’-propargyloxyphenyl)-3-(2",2",2"-trichloromethylcarbonylamino)prop-1-ene (241c) (0.025 g, 0.070 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:15) gave 5-methoxy-8-[1’-(2",2",2"-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242c) (0.025 g, 99%) as a colourless oil. Rf 0.53 (50% diethyl ether/petroleum ether); ν\textsubscript{max}/cm\textsuperscript{-1} (neat) 3421 (NH), 2928 (CH), 1707 (CO), 1492, 1215, 1109, 821, 747; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 3.82 (3H, s, 5-OCH\textsubscript{3}), 4.78 (2H, dd, J 3.6, 1.6 Hz, 2-H\textsubscript{2}), 5.16–5.22 (2H, m, 3’-H\textsubscript{2}), 5.49 (1H, ddt, J 8.4, 5.3, 1.6 Hz, 1’-H), 5.77 (1H, dt, J 10.0, 3.6 Hz, 3-H), 6.02 (1H, ddd, J 17.0, 10.4, 5.3 Hz, 2’-H), 6.44 (1H, d, J 8.6 Hz, 6-H), 6.77 (1H, dt, J 10.0, 1.6 Hz, 4-H), 7.02 (1H, d, J 8.6 Hz, 7-H), 7.86 (1H, br d, J 8.4 Hz, NH); δ\textsubscript{C} (101 MHz, CDCl\textsubscript{3}) 55.3 (CH\textsubscript{3}), 55.7 (CH), 65.2 (CH\textsubscript{2}), 93.0 (C), 103.8 (CH), 112.5 (C), 115.7 (CH\textsubscript{2}), 118.2 (C), 119.4 (CH), 119.9 (CH), 129.0 (CH), 136.2 (CH), 152.1 (C), 155.3 (C), 160.7 (C); m/z (ESI) 383.9916 (MNa\textsuperscript{+}, C\textsubscript{15}H\textsubscript{14}Cl\textsubscript{3}NNaO\textsubscript{3} requires 383.9931).

6-Chloro-8-[1’-(2",2",2"-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242d)

The reaction was carried out as described for the synthesis of 8-[1’-(2",2",2"-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242a) using 3-(5’-chloro-2’-propargyloxyphenyl)-3-(2",2",2"-trichloromethylcarbonylamino)prop-1-ene (241d) (0.062 g, 0.169 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:10) gave 6-chloro-8-[1’-(2",2",2"-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242d) (0.061 mg, 98%) as a white solid. Mp 62–64 °C; Rf 0.68 (50% diethyl ether/petroleum ether); ν\textsubscript{max}/cm\textsuperscript{-1} (neat) 3418 (NH), 2927 (CH), 1713 (CO), 1504, 1466, 1214, 821, 748; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 4.86 (2H, dd, J 3.6, 1.9 Hz, 2-H\textsubscript{2}), 5.20–5.26 (2H, m, 3’-H\textsubscript{2}),
5.52 (1H, ddt, J 8.6, 5.3, 1.6 Hz, 1'-H), 5.86 (1H, dt, J 9.9, 3.6 Hz, 3-H), 6.00 (1H, ddd, J 17.0, 10.4, 5.3 Hz, 2'-H), 6.38 (1H, dt, J 9.9, 1.9 Hz, 4-H), 6.94 (1H, d, J 2.5 Hz, 5-H), 7.04 (1H, d, J 2.5 Hz, 7-H), 7.72 (1H, br d, J 8.6 Hz, NH); δC (101 MHz, CDCl₃) 54.6 (CH), 65.9 (CH₂), 92.8 (C), 116.7 (CH₂), 123.4 (CH), 123.6 (CH), 124.4 (C), 126.3 (CH), 126.5 (C), 127.0 (C), 128.2 (CH), 135.1 (CH), 149.9 (C), 160.8 (C); m/z (ESI) 387.9419 (MNa⁺, C₁₄H₁₁₃₅Cl₄NNaO₂ requires 387.9436), 381 (33%), 353 (33), 236 (9).

6-Nitro-8-[1'-(2'',2'',2''-trichloromethylcarbonylamino)-2'-propenyl]-2H-chromene (242e)

The reaction was carried out as described for the synthesis of 8-[1'-(2'',2'',2''-trichloromethylcarbonylamino)-2'-propenyl]-2H-chromene (242a) using 3-(5'-nitro-2'-propargyloxyphenyl)-3-(2'',2'',2''-trichloromethylcarbonyl-amino)prop-1-ene (241e) (0.150 g, 0.400 mmol). Purification by column chromatography (diethyl ether/petroleum ether, 1:10) gave 6-nitro-8-[1'-(2'',2'',2''-trichloromethylcarbonylamino)-2'-propenyl]-2H-chromene (242e) (0.098 mg, 66%) as a yellow solid. Mp 138–140 °C; Rf 0.48 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3418 (NH), 2924 (CH), 1710 (CO), 1518, 1338, 1216, 837, 754; δH (500 MHz, CDCl₃) 5.05 (2H, dd, J 3.4, 2.0 Hz, 2'-H₂), 5.28 (1H, dd, J 17.2, 1.7 Hz, 3''-H), 5.33 (1H, dd, J 10.4, 1.7 Hz, 3''-H'), 5.68 (1H, ddt, J 8.3, 5.4, 1.7 Hz, 1''-H), 5.93 (1H, dt, J 10.1, 3.4 Hz, 3-H), 6.03 (1H, ddd, J 17.2, 10.4, 5.4 Hz, 2'-H), 6.47 (1H, dt, J 10.1, 2.0 Hz, 4-H), 7.41 (1H, br d, J 8.3 Hz, NH), 7.83 (1H, d, J 2.7 Hz, ArH), 8.00 (1H, d, J 2.7 Hz, ArH); δC (126 MHz, CDCl₃) 53.5 (CH), 67.1 (CH₂), 92.5 (C), 117.7 (CH₂), 122.0 (CH), 122.6 (C), 123.0 (CH), 123.8 (CH), 124.1 (CH), 126.5 (C), 134.3 (CH), 141.7 (C), 156.6 (C), 160.9 (C); m/z (ESI) 398.9665 (MNa⁺, C₁₄H₁₁₃₅Cl₄N₂NaO₄ requires 398.9677).
(2E)-3-(2’-Propargyloxyphenyl)prop-2-en-1-ol (240a) (0.050 g, 0.27 mmol) was dissolved in dichloromethane (4.0 mL) and cooled to 0 °C under argon with stirring. Trichloroacetonitrile (0.040 mL, 0.040 mmol) was added to the solution, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.020 mL, 0.130 mmol) and the reaction was allowed to warm to room temperature over 2 h. The reaction mixture was filtered through a short pad of alumina (neutral, Brockman V) with diethyl ether (100 mL) and concentrated in vacuo to yield the crude allylic trichloroacetimidate as a yellow oil which was used without further purification. The allylic trichloroacetimidate was transferred to a dry Schlenk tube containing a stirrer bar and potassium carbonate (12 mg, 3 mg/mL) to which p-xylene (4 mL) was then added. The tube was purged with argon, sealed and heated to 140 °C for 18 h. The reaction mixture was allowed to cool to room temperature and chloro(triphenylphosphine)gold(I) (243) (0.0040 g, 0.0070 mmol) and silver(I) hexafluoroantimonate (244) (0.0020 g, 0.0070 mmol) were added. The reaction mixture was heated to 80 °C for 4 h. The reaction mixture was concentrated in vacuo and purified by column chromatography (diethyl ether/petroleum ether, 1:15) to give 8-[1’-(2”,2”,2”-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242a) (0.069 g, 80%) as a colourless oil. Spectroscopic data was as described above.
6-Methoxy-8-[1’-(2”,2”,2”-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242b)

The reaction was carried out as described for the synthesis of 8-[1’-(2”,2”,2”-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242a) using (2E)-3-(5’-methoxy-2’-propargyloxyphenyl)prop-2-en-1-ol (240b) (0.100 g, 0.460 mmol), chloro(triphenylphosphine)gold(I) (243) (0.017 g, 0.035 mmol) and silver(I) hexafluoroantimonate (244) (0.008 g, 0.035 mmol). The hydroarylation step was heated to 80 °C for 48 h. Purification by column chromatography (diethyl ether/petroleum ether, 1:15) gave 6-methoxy-8-[1’-(2”,2”,2”-trichloromethylcarbonylamino)-2’-pro-penyl]-2H-chromene (242b) (0.152 g, 91%) as a colourless oil. Spectroscopic data was as described above.

5-Methoxy-8-[1’-(2”,2”,2”-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242c)

The reaction was carried out as described for the synthesis of 8-[1’-(2”,2”,2”-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242a) using (2E)-3-(4’-methoxy-2’-propargyloxyphenyl)prop-2-en-1-ol (240c) (0.100 g, 0.460 mmol), chloro(triphenylphosphine)gold(I) (243) (0.017 g, 0.035 mmol) and silver(I) hexafluoroantimonate (244) (0.008 g, 0.035 mmol). The hydroarylation step was heated to 80 °C for 48 h. Purification by column chromatography (diethyl ether/petroleum ether, 1:15) gave 5-methoxy-8-[1’-(2”,2”,2”-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242c) (0.152 g, 91%) as a colourless oil. Spectroscopic data was as described above.
ylamino)-2'-propenyl]-2H-chromene (242c) (0.129 g, 78%) as a colourless oil. Spectroscopic data was as described above.

6-Chloro-8-[1'-(2''',2''',2'''-trichloromethylcarbonylamino)-2'-propenyl]-2H-chromene (242d)

The reaction was carried out as described for the synthesis of 8-[1'-(2'',2'',2''-trichloromethylcarbonylamino)-2'-propenyl]-2H-chromene (242a) using (2E)-3-(5'-chloro-2'-propargyloxyphenyl)prop-2-en-1-ol (240d) (0.105 g, 0.472 mmol), chloro(triphenylphosphine)gold(I) (243) (0.018 g, 0.035 mmol) and silver(I) hexafluoroantimonate (244) (0.009 g, 0.035 mmol). The Overman rearrangement was heated to 140 °C for 48 h. The hydroarylation step was heated to 80 °C for 48 h. Purification by column chromatography (diethyl ether/petroleum ether, 1:15) gave 6-chloro-8-[1'-(2''',2''',2'''-trichloromethylcarbonylamino)-2'-propenyl]-2H-chromene (242d) (0.131 g, 76%) as a white solid. Spectroscopic data was as described above.

6-Nitro-8-[1'-(2''',2''',2'''-trichloromethylcarbonylamino)-2'-propenyl]-2H-chromene (242e)

The reaction was carried out as described for the synthesis of 8-[1'-(2'',2'',2''-trichloromethylcarbonylamino)-2'-propenyl]-2H-chromene (242a) using (2E)-3-(5'-nitro-2'-propargyloxyphenyl)prop-2-en-1-ol (240e) (0.085 g, 0.364 mmol), chloro(triphenylphosphine)gold(I) (243) (0.018 g, 0.036 mmol) and silver(I) hexafluoroantimonate (244) (0.009 g, 0.036 mmol). The Overman rearrangement
was heated to 140 °C for 72 h. The isomerisation step was heated to 80 °C for 65 h. Purification by column chromatography (diethyl ether/petroleum ether, 1:10) gave 6-nitro-8-[1’-(2”,2”,-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242e) (0.074 g, 54%) as a white solid. Spectroscopic data was as described above.

8-[1’-(2”,2”,-Trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242a)

(2E)-3-(2’-Propargyloxynyl)prop-2-en-1-ol (240a) (0.050 g, 0.27 mmol) was dissolved in dichloromethane (4 mL) and cooled to 0 °C under argon with stirring. Trichloroacetonitrile (0.040 mL, 0.040 mmol) was added to the solution, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.020 mL, 0.13 mmol) and the reaction was allowed to warm to room temperature over 2 h. The reaction mixture was filtered through a short pad of alumina (neutral, Brockman V) with diethyl ether (100 mL) and concentrated in vacuo to yield the crude allylic trichloroacetimidate as a yellow oil, which was used without further purification. The allylic trichloroacetimidate was transferred to a dry Schlenk tube containing a stirrer bar and bis(acetonitrile)palladium(II) chloride (0.0070 g, 0.027 mmol) to which toluene (4 mL) was then added. The tube was purged with argon, sealed and heated to 80 °C for 16 h. The reaction mixture was allowed to cool to room temperature and chloro(triphenylphosphine)gold(I) (243) (0.0040 g, 0.0070 mmol) and silver(I) hexafluoroantimonate (244) (0.0020 g, 0.0070 mmol) were added. The reaction mixture was heated to 80 °C for 4 h. The reaction mixture was cooled to room temperature, concentrated in vacuo and purified by column chromatography (diethyl ether/petroleum ether, 1:15) to give 8-[1’-(2”,2”,-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242a) (0.048 g, 56%) as a colourless oil. Spectroscopic data was as described above.
8-[1’-(2”',2”',2”'-trichloromethylcarbonylamino)-2’-propenyl]-2H-chrom-2-one (251a)

Pyridinium dichromate (0.070 g, 0.186 mmol) was added to a stirred solution of 8-[1’-(2”',2”',2”'-trichloromethylcarbonylamino)-2’-propenyl]-2H-chromene (242a) (0.030 g, 0.090 mmol) in dichloromethane (1 mL) and stirred at room temperature for 6 days. The reaction mixture was concentrated in vacuo and purified by column chromatography (diethyl ether/petroleum ether, 1:1) to give 8-[1’-(2”',2”',2”'-trichloromethylcarbonylamino)-2’-propenyl]-2H-chrom-2-one (251a) (0.020 g, 65%) as a white solid. Mp 136–138 °C; Rf 0.13 (50% diethyl ether/petroleum ether); νmax/cm⁻¹ (neat) 3424 (NH), 2926 (CH), 1711 (CO), 1604, 1505, 1117, 907, 833, 726; δH (400 MHz, CDCl₃) 5.23–5.34 (2H, m, 3’-H₂), 5.83 (1H, ddt, J 8.4, 5.7, 1.6 Hz, 1’-H), 6.16 (1H, ddd, J 17.1, 10.3, 5.7 Hz, 2’-H), 6.44 (1H, d, J 9.6 Hz, 3-H), 7.29 (1H, t, J 7.7 Hz, 6-H), 7.46 (1H, dd, J 7.7, 1.6 Hz, ArH), 7.52 (1H, dd, J 7.7, 1.6 Hz, ArH), 7.73 (1H, d, J 9.6 Hz, 4-H), 7.80 (1H, br d, J 8.4 Hz, NH); δC (101 MHz, CDCl₃) 54.9 (CH), 92.5 (C), 116.8 (CH), 117.9 (CH₂), 119.4 (C), 124.6 (CH), 126.6 (C), 128.2 (CH), 131.4 (CH), 134.6 (CH), 143.7 (CH), 151.8 (C), 159.2 (C), 161.1 (C); m/z (ESI) 367.9606 (MNa⁺, C₁₄H₁₀Cl₃NNaO₃ requires 367.9618).
(Z)-8-Methoxy-5-(2',2',2'-trichloromethylcarbonylamino)-3-vinyl-2,5-dihydro-1-benzoxepine (253)

3-(4'-Methoxy-2'-propargyloxyphenyl)-3-(2',2',2'-trichloromethylcarbonylamino)prop-1-ene (241c) (0.030 g, 0.090 mmol) was dissolved in p-xylene (1.5 mL) and Grubbs first-generation catalyst (0.006 g, 0.007 mmol) was added and the reaction mixture was heated for 24 h at 50 °C. A further portion of Grubbs 1st generation catalyst (0.0020 g, 0.0020 mmol) was added and the reaction mixture was stirred at 50 °C for 48 h. The reaction mixture was concentrated in vacuo and purified by column chromatography (diethyl ether/petroleum ether, 1:10) gave (Z)-8-methoxy-5-(2',2',2'-trichloromethylcarbonylamino)-3-vinyl-2,5-dihydro-1-benzoxepine (253) (0.0060 g, 18%) as a colourless oil. Rf 0.57 (50% diethyl ether/petroleum ether); δH (400 MHz, CDCl3) 3.80 (3H, s, OCH3), 4.57 (1H, dd, J 16.4, 1.8 Hz, 2-HH), 5.04 (1H, d, J 16.4 Hz, 2-HH), 5.07 (2H, m, 2''-H2), 5.42 (1H, t, J 8.3 Hz, 5-H), 6.10 (1H, br d, J 8.3 Hz, 4-H), 6.24 (1H, dd, J 18.0, 11.3 Hz, 1''-H), 6.65 (1H, dd, J 8.3, 2.5 Hz, 7-H), 6.72 (1H, d, J 2.5 Hz, 9-H), 7.20 (1H, d, J 8.3 Hz, 6-H), 7.55 (1H, d, J 8.3 Hz, NH); δC (101 MHz, CDCl3) 50.6 (CH3), 55.5 (CH), 71.2 (CH2), 92.6 (C), 108.0 (CH), 110.1 (CH), 113.8 (CH2), 126.5 (C), 127.0 (CH), 128.9 (CH), 136.7 (CH), 139.1 (C), 158.4 (C), 160.6 (C), 161.0 (C).

(Z)-8-Methoxy-5-(2’,2’,2’-trichloromethylcarbonylamino)-3-vinyl-2,5-dihydro-1-benzoxepine (253) (0.0060 g, 0.016 mmol) was dissolved in p-xylene (0.27 mL) and N-phenylmaleimide (0.0040 g, 0.025 mmol) was added and the reaction mixture was heated at 50 °C for 24 h. The reaction mixture was concentrated in vacuo and purified by column chromatography (100% diethyl ether) gave (6S*,6aR*,6bR*,9aS*)-3-methoxy-8-phenyl-6-(2’,2’,2’-trichloromethylcarbonylamino)-1-benzoepin[e]isoindol-7,9(2H)-dione (254) (0.0060 g, 63%) as a white solid. Rf 0.03 (50% diethyl ether/petroleum ether); δH (400 MHz, CDCl3) 2.35–2.47 (1H, m, 10-HH), 2.66–2.80 (1H, m, 10-HH), 2.83 (1H, ddd, J 15.9, 6.3, 3.0 Hz, 9a-H), 3.37–3.46 (1H, m, 6a-H), 3.52–3.61 (1H, m, 6b-H), 3.78 (3H, s, OCH3), 4.62 (1H, d, J 12.9 Hz, 12-HH), 4.77 (1H, d, J 12.9 Hz, 12-HH), 5.80 (1H, t, J 8.8 Hz, 6-H), 6.10 (1H, t, J 4.1 Hz, 11-H), 6.47 (1H, d, J 2.6 Hz, 2-H), 6.58 (1H, dd, J 8.8, 2.6 Hz, 4-H), 7.18 (2H, br d, J 7.5 Hz, 2 × ArH), 7.22 (1H, d, J 8.8 Hz, 5-H), 7.35–7.41 (1H, m, ArH), 7.43 (2H, br d, J 7.5 Hz, 2 × ArH), 7.61 (1H, d, J 8.8 Hz, NH); δC (101 MHz, CDCl3) 24.1 (CH2), 40.0 (CH), 41.6 (CH), 42.4 (CH), 53.3 (CH), 55.3 (CH3), 72.2 (CH2), 92.6 (C), 105.6 (CH), 109.0 (CH), 126.4 (2 × CH), 126.8 (CH), 128.1 (CH), 128.7 (CH), 129.0 (2 × CH), 131.2 (C), 131.6 (C), 137.3 (C), 156.4 (C), 160.6 (C), 161.0 (C), 175.9 (C), 177.9 (C).
5.0 References


