The Development of One-Pot Multi-Reaction Processes for the Synthesis of Natural Products and Biologically Active Compounds

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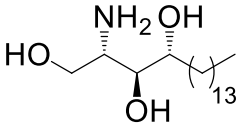
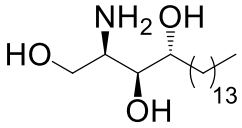
Abstract

This thesis is divided into four chapters in which one-pot processes have been developed and utilised for the synthesis of biologically active compounds. The work in the first chapter outlines the 13-step total synthesis of D-*ribo*- and L-*arabino*-phytosphingosine from D-ribose. This process employed a microwave promoted Overman rearrangement of an allylic trichloroacetimidate to install the amine functionality.

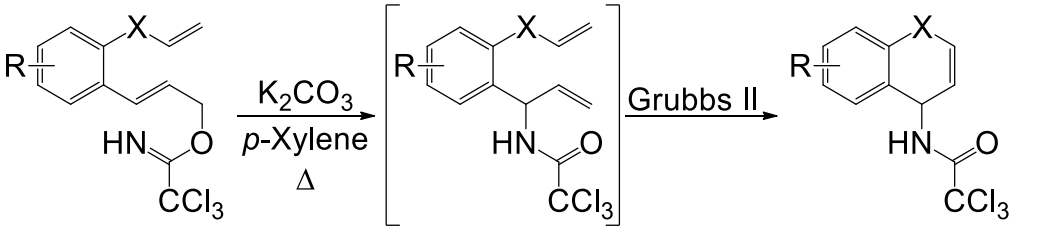


D-*ribo*-phytosphingosine



L-*arabino*-phytosphingosine

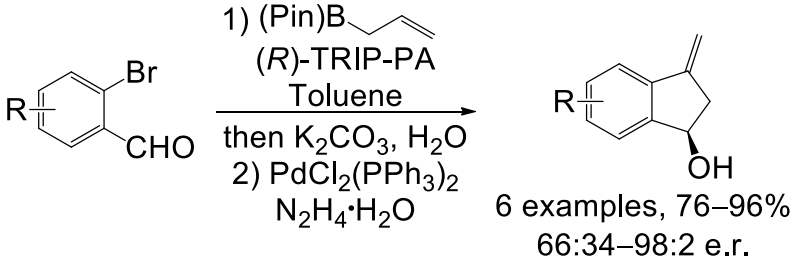
In the second and third chapters, the development of a one-pot, two-step Overman/ring closing metathesis process is detailed. The synthesis of three different classes of starting material is also shown. This one-pot process was used as the key step in the synthesis of four oxybenzo[c]phenanthridine natural products and the partial synthesis of an ACAT inhibitor. The potential for further functionalisation of the products by oxidation and reduction was also explored.



X = –, -CH_2-, -OCH_2-

22 examples, 56–98%

In the final chapter, a one-pot allylboration/Heck process for the synthesis of indan-1-ols is described. Optimisation and an investigation of the scope of the process are also presented. The process was then altered to allow the use of a chiral phosphoric acid catalyst for the asymmetric synthesis of these compounds.



6 examples, 76–96%
66:34–98:2 e.r.

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Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, this thesis represents the original work of Ewen D. D. Calder 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 October 2011 and April 2015. Aspects of the work described herein have previously been published elsewhere as stated below.

E. D. D. Calder, A. M. Zaed and A. Sutherland, Preparation of *anti*-Vicinal Amino Alcohols: Asymmetric Synthesis of D-*erythro*-Sphinganine, (+)-Spisulosine, and D-*ribo*-Phytosphingosine, *J. Org. Chem.*, 2013, **78**, 7223.

E. D. D. Calder, F. I. McGonagle, A. H. Harkiss, G. A. McGonagle and A. Sutherland, Preparation of Amino-Substituted Indenes and 1,4-Dihydronaphthalenes Using a One-Pot Multireaction Approach: Total Synthesis of Oxybenzo[c]phenanthridine Alkaloids, *J. Org. Chem.*, 2014, **79**, 7633.

E. D. D. Calder, S. A. I. Sharif, F. I. McGonagle and A. Sutherland, One-Pot Synthesis of 5-Amino-2,5-Dihydro-1-Benzoxepines: Access to Pharmacologically Active Heterocyclic Scaffolds, *J. Org. Chem.*, 2015, **80**, 4683.

E. D. D. Calder and A. Sutherland, Enantioselective Synthesis of 3-Methylene-indan-1-ols via a One-pot Allylboration-Heck Reaction of 2-Bromobenzaldehydes, *Org. Lett.*, 2015, **17**, 2514.

Signature _____

Printed name _____

Abbreviations

°C	Degrees Centigrade
µW	Microwave
Δ	Reflux
ACAT	Acyl-CoA, Cholesterol *O*-Acyl Transferase
Ac	Acetyl
Ar	Aromatic
Boc	*tert*-Butyloxycarbonyl
BINAP	(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)
BINOL	1,1'-Bi-2-naphthol
br	Broad
Bu	Butyl
Cat	Catalyst
CDI	Carbonyl Diimidazole
CBS	Corey-Bakshi-Shibata
COP	Cobat Oxazoline Palladacycle
Cy	Cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminium Hydride
DIPEA	*N,N*-Diisopropylethylamine

DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
dppf	Diphenylphosphinoferrocene
d.r.	Diastereomeric Ratio
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
e.e.	Enantiomeric Excess
endo	Endocyclic
eq	Equivalents
e.r.	Enantiomeric Ratio
Et	Ethyl
exo	Exocyclic
FOP	Ferrocenyl Oxazoline Palladacycle
GSL	Glycosphingolipid
h	Hour
HBTU	*N,N,N′,N′*-Tetramethyl-*O*-(1*H*-benzotriazol-1-yl)uronium hexafluorophosphate
HCMV	Human Cytomegalovirus
Hex	Hexyl
HIV	Human Immunodeficiency Virus
HPLC	High-Performance Liquid Chromatography
HWE	Horner-Wadsworth-Emmons
Hz	Hertz

IPA	Isopropyl Alcohol
IR	Infrared
kcal	Kilocalorie
m-	*Meta*-
M	Molar
m-CPBA	*meta*-Chloroperbenzoic Acid
Me	Methyl
MEM	Methoxyethoxymethyl
mL	Millilitres
mmol	Millimoles
mol	Mole
mol. sieves	Molecular Sieves
MOM	Methoxymethyl
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect Spectroscopy
o-	*Ortho*-
p-	*Para*-
p-BQ	*para*-Benzoquinone
Ph	Phenyl
Pin	Pinacol
ppm	Parts Per Million
Pr	Propyl
q	Quartet

RCEYM	Ring closing Ene-Yne Metathesis
RCM	Ring closing Metathesis
rt	Room Temperature
s	Singlet
SPINOL	1,1′-Spirobiindane-7,7′-diol
t	Triplet
TBAF	Tetrabutylammonium Fluoride
TBDPS	*tert*-Butyldiphenyl Silyl
TEPA	Triethyl Phosphonoacetate
tert	Tertiary
Tf	Triflate
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	*N,N,N′,N′*-Tetramethylethylenediamine
TRIP	3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
Ts	4-Toluenesulfonyl

Chapter 1 The Synthesis of D-*ribo*- and L-*arabino*-Phytosphingosine

1.1 Introduction

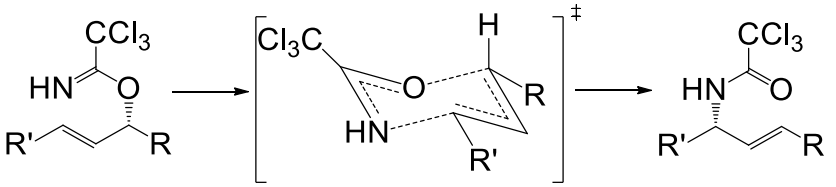
1.1.1 The Overman rearrangement

Sigmatropic rearrangements are a valuable class of reactions in the synthetic chemists' toolbox. Carbon-carbon and carbon-nitrogen bond forming rearrangements are especially important and reactions such as the Claisen and Cope rearrangements are commonly used in many areas of synthetic chemistry.[1,2] The [3,3]-sigmatropic rearrangement of an allylic imidate to an allylic amide is known as an aza-Claisen reaction and is a very efficient method for the installation of a protected amine functionality. The conversion of an imidate to an amide is essentially irreversible as the reaction is exothermic by approximately 15 kcal mol^{-1}.[3,4] A number of types of imidate have been used for the aza-Claisen with varying degrees of success. It was the discovery by Overman in 1974 of the [3,3]-rearrangement of allylic trihaloacetimidates to their corresponding amides that allowed the field to grow dramatically. This was due to the wide scope and comparatively milder conditions of this sub-set of the aza-Claisen.[5–7] This reaction has subsequently become known as the Overman rearrangement.

The trichloroacetimidates that can be used in the Overman rearrangement are easily synthesised by the base-promoted reaction between an allylic alcohol and trichloroacetonitrile. This base can either be stoichiometric and strong enough to irreversibly deprotonate the allylic alcohol and imidate until work-up (e.g. sodium hydride)[7] or can be used catalytically as a proton transfer agent, as in the case of DBU.[8]

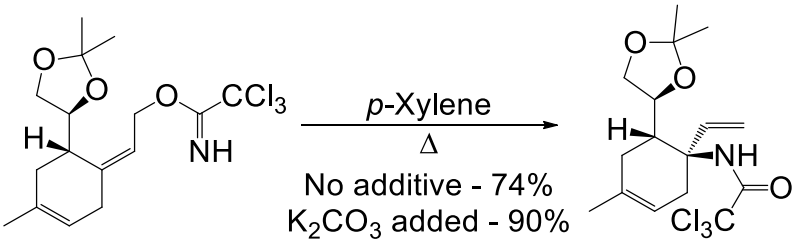
The Overman rearrangement can be carried out under either thermal or metal-catalysed conditions. The reaction rate is highly dependent on the electronics and sterics of the allylic system. In general, the more substituted the allylic position of the chain, the more rapid the reaction. This can be rationalised by the formation of a partial positive charge in the transition state of the rearrangement. The reaction is slowed by a second or bulky substituents on the β-position of the allylic system due to steric hindrance. In addition, electron-donating groups which stabilise the

partial positive charge on the allylic position, enhance the reaction rate further. As with all sigmatropic rearrangements, the Overman rearrangement is highly concerted and consequently there is complete transfer of chirality, if present, from the allylic imidate (Scheme 1, R ≠ H). The highly ordered, chair transition state of the reaction was proposed by Shimoda and co-workers in 1976.[9]



Scheme 1: The chair transition state of the Overman rearrangement.

The most common conditions for the thermal Overman rearrangement employ heating the imidate in toluene or xylenes in the presence of small quantities of potassium carbonate. Isobe and co-workers first reported the addition of small quantities of base to thermal Overman rearrangements in 1998.[10] It was found that, at the elevated temperatures necessary for the rearrangement to proceed, small amounts of acidic by-products or impurities could cause decomposition of the starting imidate. By the addition of a small quantity of base, this problem was alleviated and yields were greatly improved (Scheme 2).

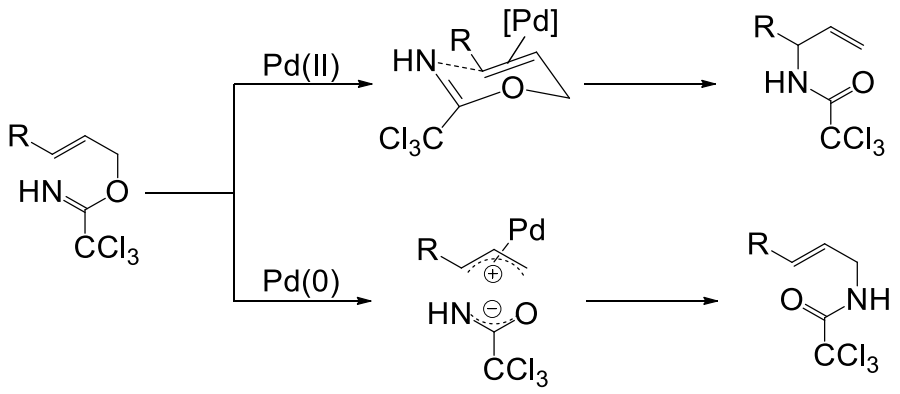


Scheme 2: Work by Isobe and co-workers showing beneficial addition of K_2CO_3.

The Overman rearrangement can also be performed using transition metal catalysis. This has the benefits, in some cases, of increasing the yield, stereoselectivity or cleanliness of the reaction. The original metal-catalysed Overman rearrangements were performed using mercury(II)-catalysts, for which a dramatic acceleration in rate is observed.[5] These vast increases in rate allow for the reactions to be carried out at room temperature or even at −78 °C. The conditions are much milder than those used for the thermal rearrangement and so also broaden the scope of the reaction. Palladium(II)-catalysts are now preferred

over mercury(II) based systems as they have been shown to equilibrate with the substrate at a greater rate than other transition metal catalysts and so, generally, will provide a faster reaction in higher yield. This, in turn, allows lower catalyst loadings to be used without detriment to the results.

A common impurity in metal-catalysed Overman rearrangements is the [1,3]-rearranged product. This is postulated to form *via* a palladium(0)-catalysed, non-concerted [1,3]-rearrangement of the acetimidate. The metal-catalysed rearrangements of allylic imidates have been studied by the groups of Ikariya and Bosnich.[11,12] They found that the oxidation state of the palladium complex used in the rearrangement process had a direct impact on the product formed. Palladium(II) predominantly formed the [3,3]-product while palladium(0) formed the [1,3]- through a non-concerted ionisation pathway (Scheme 3). It has been shown that the addition of *p*-benzoquinone (*p*-BQ) can counteract this reaction pathway by oxidising any palladium(0)[13,14] formed back to the catalytically active palladium(II) species.[15]



Scheme 3: Difference in mechanism between [1,3]- and [3,3]-rearrangements.

Studies into the mechanism of the palladium(II)-catalysed rearrangement have shown that it is likely to proceed through a similar mechanism to that proposed by Henry for palladium-catalysed allylic acetate rearrangements.[16] As with the thermal rearrangement, a chair transition state is proposed, in which the palladium adopts an equatorial position. This chair transition state again explains the complete suprafacial transfer of chirality that is observed in these reactions. It is postulated that the mechanism proceeds through coordination of palladium to the olefin, which is then activated to intramolecular nucleophilic attack by the nitrogen of the acetimidate. The alkene is then reinstalled with the decyclisation and regeneration of the palladium(II)-catalyst (Figure 1).

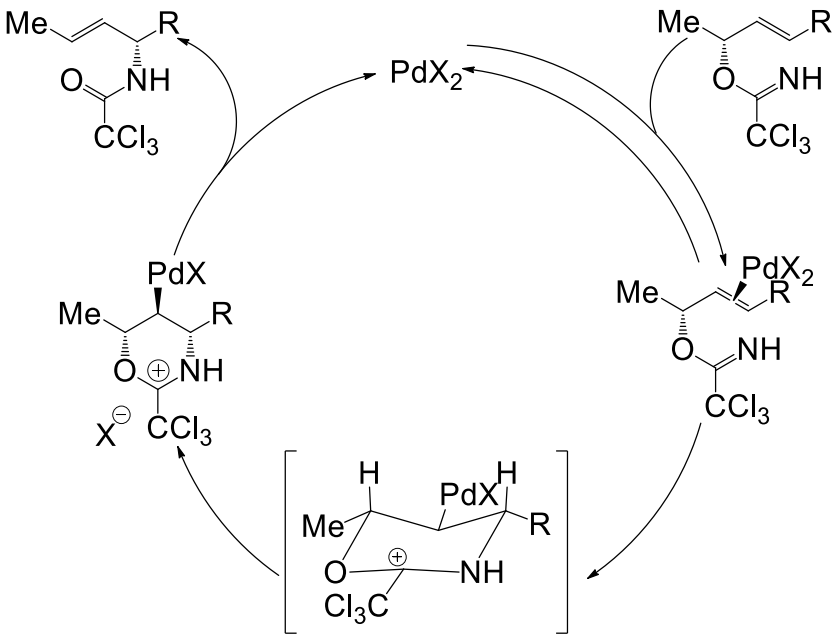
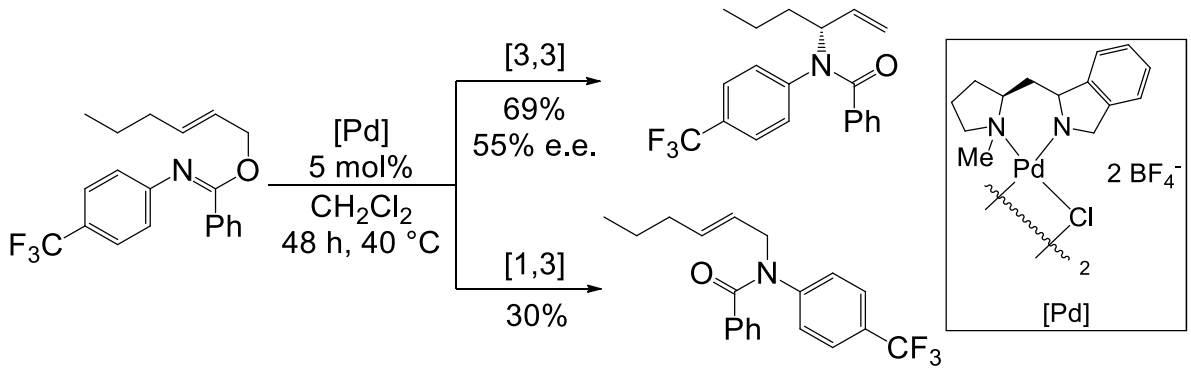


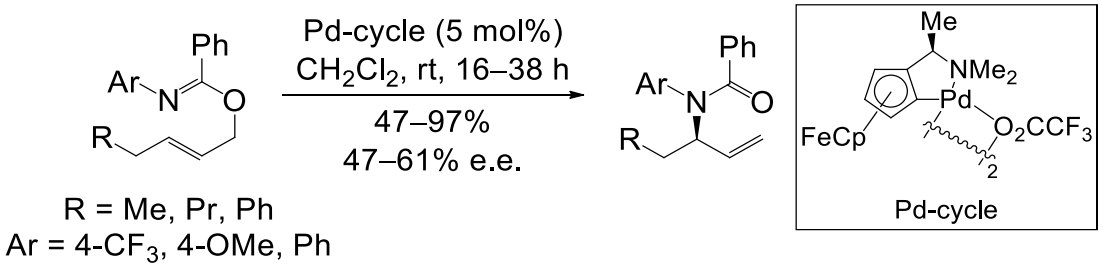
Figure 1: Proposed mechanism for palladium(II)-catalysed Overman rearrangement.

Since the first reports of transition metal-catalysed Overman rearrangements, a number of chiral ligand-bearing palladium catalysts have been developed in an effort to perform an asymmetric Overman rearrangement on an achiral starting material. The first chiral diamine ligands were successful only on *N*-arylbenzimidates, gave only modest enantioselectivity and formed a significant amount of the unwanted [1,3]-rearrangement side-product (Scheme 4).[17]



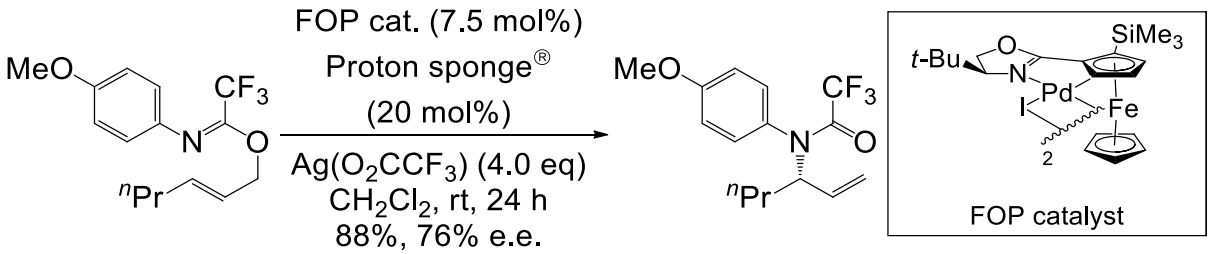
Scheme 4: [1,3]- vs [3,3]-rearrangement in the first asymmetric aza-Claisen rearrangement.

The next generation of asymmetric catalysts were designed to reduce the quantity of [1,3]-rearrangement side-product. The ferrocenyl palladacycles reported by Overman and co-workers were compatible with only *N*-arylbenzimidates and still yielded only modest enantioselectivity but the [1,3]-product was no longer observed and the yield of [3,3]-rearranged product was much improved (Scheme 5).[18]



Scheme 5: The ferrocenyl palladacycle first reported by Overman in 1997.

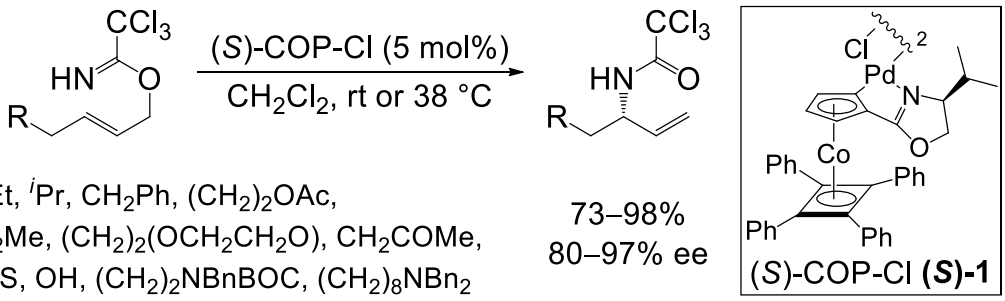
The ferrocenyl oxazoline palladacycle (FOP) catalysts further improved upon the closely related, original palladacycle catalysts (Scheme 6).[19] The FOP catalysts provided higher enantioselectivity and, as was shown by Overman, would tolerate *N*-aryltrifluoroacetimidate substrates as well as *N*-arylbenzimidates.[20] This was an important result as it was the first time a prochiral trihaloacetimidate had been rearranged to give an enantioenriched allylic amide in good yield. Although the reaction proceeds at room temperature with a good catalyst loading, the addition of four equivalents of silver trifluoroacetate — necessary to preactivate the catalyst as its TFA salt — and the use of strong oxidants to remove the *p*-methoxyphenyl group after the rearrangement, limited the utility of this process and catalyst.



Scheme 6: First report of an asymmetric trihaloacetimidate aza-Claisen rearrangement.

The more recently developed cobalt oxazoline palladacycle (COP) catalysts **1** are, as yet, the most synthetically useful. They encompass the widest range of substrates and provide high enantioselectivities with *E*-allylic trichloroacetimidates (Scheme 7).[21] The scope of the COP-catalysed process includes various Lewis basic groups, moderately bulky substituents and even free alcohols and does not require an aryl group on the imidate nitrogen. However, the system will still not tolerate unprotected primary or secondary amines, directly conjugated aromatic systems or very bulky olefin substituents such as *tert*-butyl groups. In the case of a conjugated system derived from a cinnamyl alcohol or a bulky *tert*-butyl group, the

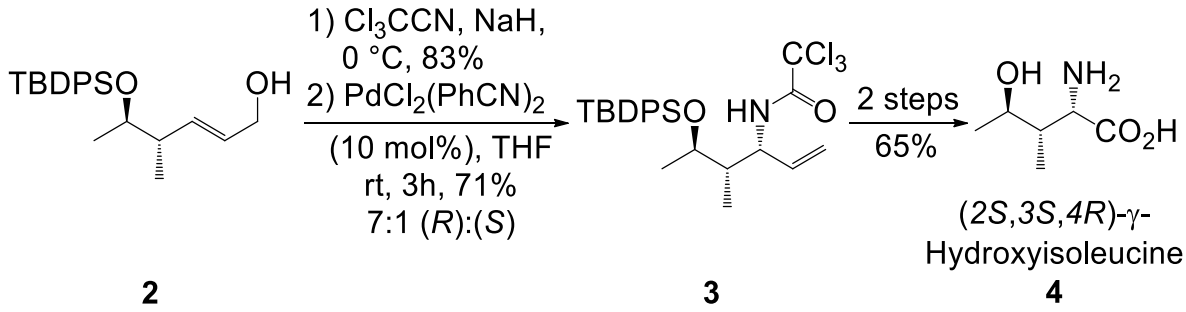
reaction slowed so drastically that the [1,3]-process was observed and yields decreased to around 10%.



Scheme 7: Highly enantioselective (*S*)-COP-Cl catalysed Overman rearrangement.

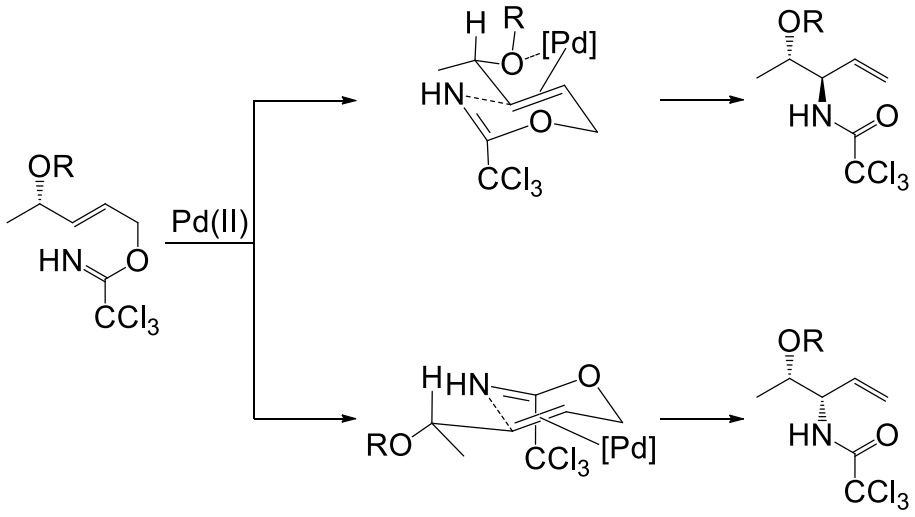
1.1.2 Previous work within the Sutherland group

Within the Sutherland group, the Overman rearrangement has been used for the synthesis of a large number of small molecule and natural product targets. The first target studied by the group was (*2S*,*3S*,*4R*)-*γ*-hydroxyisoleucine (**4**).[22] In 5 steps and 61% total yield, the necessary allylic alcohol **2** was synthesised from poly-(*R*)-hydroxybutanoate. The corresponding trichloroacetimidate was then formed by the reaction with sodium hydride and trichloroacetonitrile. Exposing the imidate to 10 mol% of palladium(II) dichloride bisbenzonitrile in THF at room temperature caused rearrangement to the desired (*3R*)-trichloroacetamide **3** in just 3 hours. The steric bulk of the TBDPS protecting group is thought to encourage binding of the palladium catalyst to the less hindered face through the reduction of 1,3-allylic strain in the chair transition state. This is supported by the reversal of selectivity observed upon use of thermal rearrangement conditions. Under these conditions, a 3:2 ratio in favour of the (*S*)-isomer is observed. Ozonolysis followed by acidic deprotection of both the amine and alcohol functionalities delivered (*2S*,*3S*,*4R*)-*γ*-hydroxyisoleucine (**4**) in a 19% overall yield over 10 steps (Scheme 8).



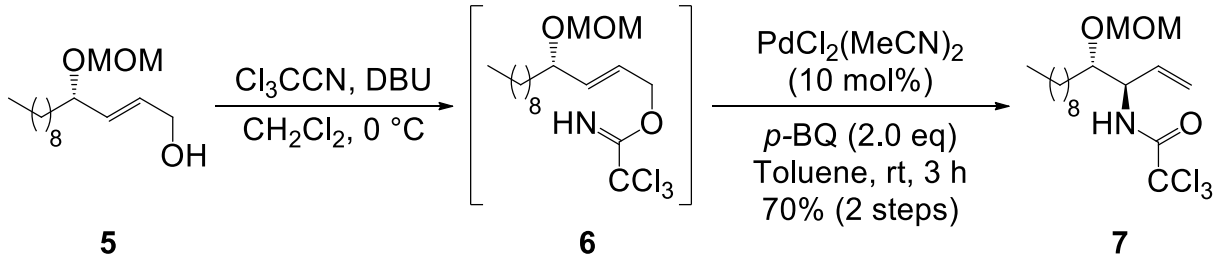
Scheme 8: The first enantioselective synthesis of (*2S,3S,4R*)-*γ*-hydroxyisoleucine.

Following this successful synthesis, the group went on to develop a highly selective ether-directed Overman rearrangement.[23] In the synthesis of (*2S*,*3S*,*4R*)-*γ*-hydroxyisoleucine (**4**), the TBDPS protecting group had caused direction by inducing 1,3-allylic strain on the system. The ether-directed system used a *γ*-hydroxy allylic alcohol with a protecting group such as MOM or MEM to coordinate the palladium catalyst to the same face as the protected alcohol. This directed the Overman rearrangement to the least hindered face of the molecule: *anti*- to the alcohol and gave the major product (Scheme 9, top pathway). In the case of larger protecting groups such as trityl or TBDPS, the coordination still occurred but, due to the steric hindrance of the protecting group causing 1,3-allylic strain, the effect was less pronounced (Scheme 9, bottom pathway). This in turn yielded a lower diastereoselectivity (3:1 vs 10:1). This methodology allowed the synthesis of protected, *anti*-1,2-amino alcohols in high yields and selectivities (78% yield and 28:1 d.r. in one example).[24]



Scheme 9: Proposed transition states for the ether-directed rearrangement.

Using this methodology as the key step, a number of amino alcohol-derived natural products have been synthesised. A recent example of this is the synthesis of three members of the clavaminol family of natural products.[25] In seven steps and an overall yield of 85% the allylic alcohol **5** was synthesised from (*R*)-glycidol. Using standard conditions with catalytic DBU, the imidate **6** was formed.[8] It was then used crude in the palladium-catalysed Overman rearrangement to give the key intermediate **7** in a high yield (Scheme 10). As mentioned earlier, it is necessary in some cases to add *p*-BQ to metal-catalysed Overman rearrangements to stop the formation of the [1,3]-rearrangement product. This intermediate allowed access to clavaminols A and C in 14 steps and 29% yield each and clavaminol H in 12 steps and 48% overall yield.

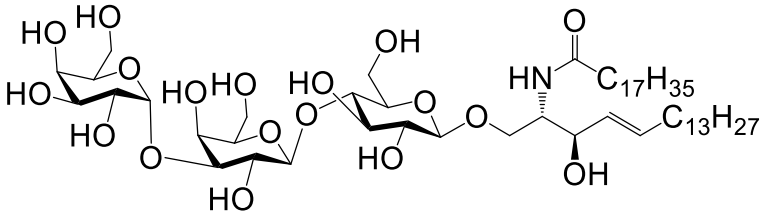


5 **6** **7**

Scheme 10: Overman rearrangement step in the synthesis of clavaminols A, C and H.

1.1.3 Introduction to sphingoid bases

Sphingolipids are found in almost all plants, animals, fungi and some prokaryotic organisms and viruses.[26] Sphingolipids are comprised of two sections: a fatty acid or lipid chain, attached through an amide bond, and a sphingoid base such as sphingosine. The sphingoid bases are a family of long chain amino alcohols ranging from 12 to 22 carbons in length. The long chain can contain unsaturation and various hydroxyl and/or methyl substituents at other sites along the chain.[27,28] Sphingolipids are important as structural components of skin, membranes, lipoproteins, and as cell signalling mediators and modulators.[26] Glycosylated sphingolipids, also called glycosphingolipids (GSLs), containing a number of saccharide units, such as iGB_3 **8** (Figure 2), are characteristic components of the cell membrane of eukaryotic cells.[29,30]

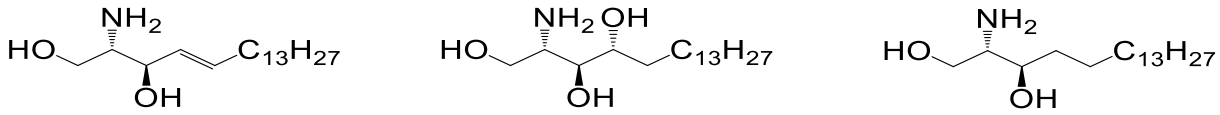


iGB$_3$ **8**

Figure 2: iGB$_3$, a linear tri-saccharide containing GSL.

Sphingolipids and GSLs are involved in a number of higher-order physiological processes[31] such as inflammation[32] and vasculogenesis[33] and, over the last two decades, have also been investigated in relation to a wide range of diseases. Most recently GSLs have been implicated in a number of important human diseases such as HIV,[34] microbial infections,[35] cancer,[36] diabetes[37] and neurological diseases.[38] In addition to the sphingolipids, the more structurally simple sphingoid bases also have potent biological activities. For example, D-*erythro*-sphingosine (**9**) strongly inhibits protein kinase C,[39] while D-*ribo*-phytosphingosine (**10a**) is a potential heat-stress signal in yeast cells.[40,41]

The principal sphingoid bases in the majority of sphingolipids present in mammalian cells are sphingosine (**9**) or dihydrosphingosine (**11**), otherwise known as sphinganine, with the minority being comprised mainly of 4-hydroxysphinganine (**10a**), also named phytosphingosine (Figure 3).[26]



D-*erythro*-Sphingosine (**9**) D-*ribo*-Phytosphingosine (**10a**) D-*erythro*-Sphinganine (**11**)

Figure 3: The three most common mammalian sphingoid bases.

1.1.4 Aims

The aim of this project was to complete the total synthesis of D-*ribo*- and L-*arabino*-phytosphingosine from the chiral pool starting material D-ribose. The proposed synthesis utilised cross metathesis to attach the long alkyl chain of the products and a diastereoselective Overman rearrangement from a primary allylic alcohol to install the amine functionality at C-2 (Figure 4).

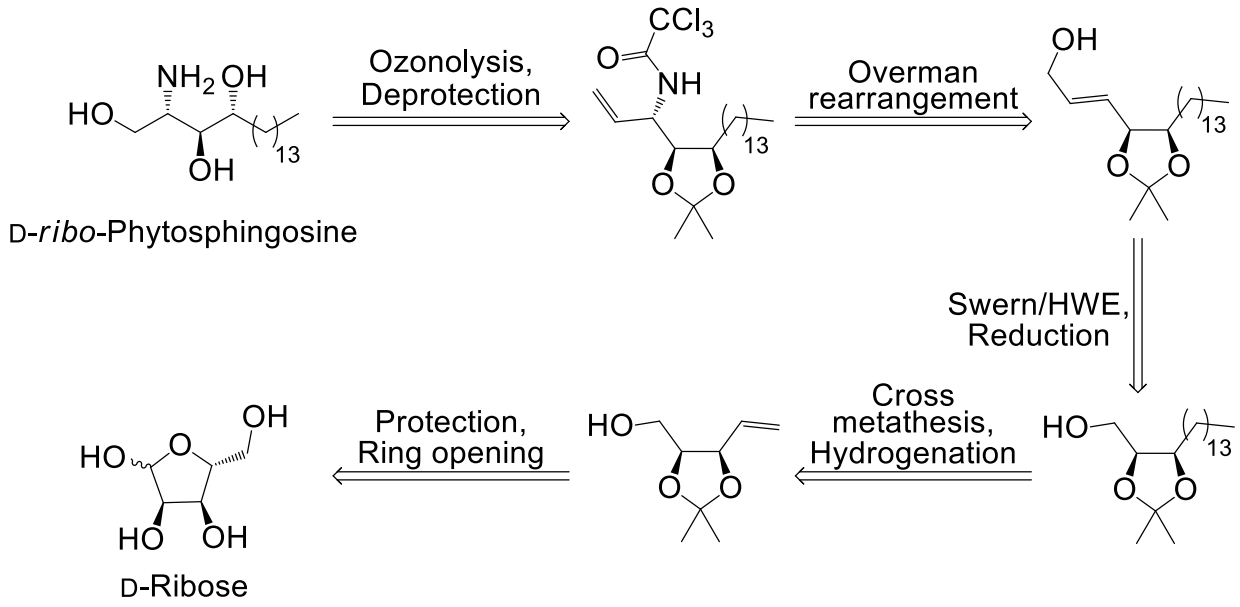
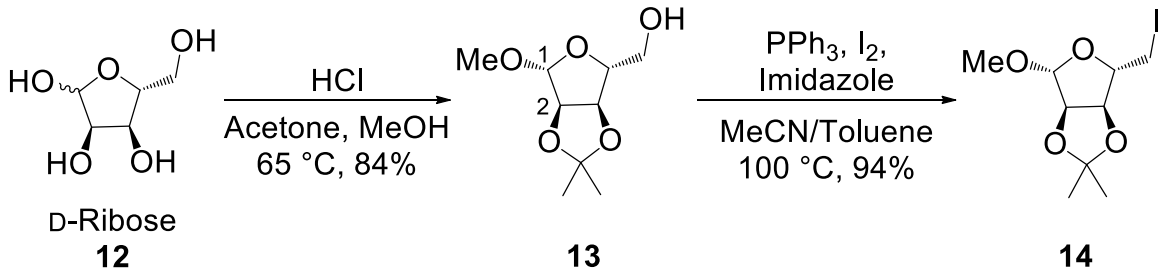


Figure 4: Retrosynthesis of D-*ribo*-phytosphingosine.

1.2 Results and discussion

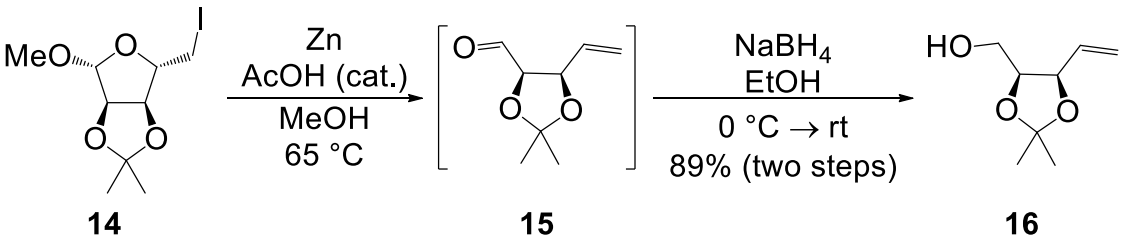
1.2.1 Synthesis of long chain triol

Protection of D-ribose (**12**) as the di-acetal **13**, following a modified version of the procedure used by Bailey and co-workers proceeded in high yield, with no purification necessary (Scheme 11).[42] The protection of the hemiacetal of D-ribose leads to the isolation of only the 1,2-*anti*-furan. This was confirmed by the ^{1}H NMR spectrum of the compound, in which a ^{3}J-coupling is not observed between the two hydrogens at these positions. This can only be accounted for by there being around a 90° dihedral torsional angle between these hydrogens, which would not occur in the 1,2-*syn*-furan. This was followed by iodination of the primary alcohol under Appel-like conditions.



Scheme 11: Protection and iodination of D-ribose.

Ring opening of the iodide **14** under Vasella fragmentation conditions yielded the aldehyde **15**, however purification of this compound was complicated by its lack of stability during silica column chromatography (Scheme 12).[43] Previous syntheses utilising this aldehyde had purified it by vacuum distillation.[42] To circumvent this problem and allow for simpler purification, the aldehyde **15** was reduced with sodium borohydride in ethanol to yield the primary alcohol **16**. Although this initially caused racemisation of the α-position stereocenter when attempted at room temperature, the problem was solved by dropwise addition of the borohydride solution at 0 °C. This improved, two-step procedure allowed isolation of the triol-olefin in a high yield with no further purification necessary after filtration and an extractive work-up



14 **15** **16**

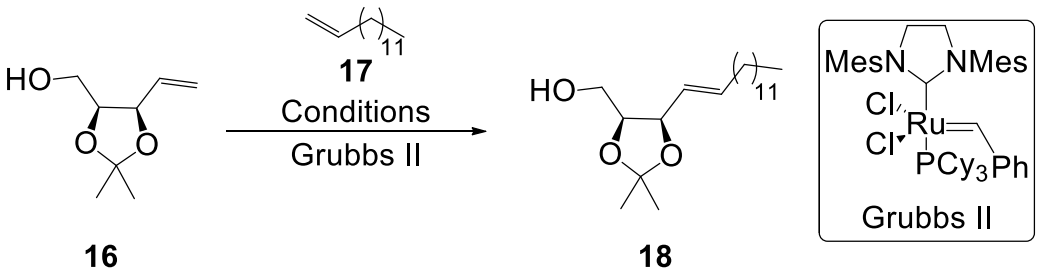
Scheme 12: Vasella fragmentation and subsequent reduction.

Cross metathesis of the protected triol-olefin **16** was proposed as a key feature of the synthesis. The use of cross metathesis with this easily obtained intermediate would allow the length and substitution pattern of the long alkyl chain to be altered. This could make the methodology of use to chemists interested in preparing related analogues for medicinal chemistry or drug design.

Cross metathesis between **16** and tetradec-1-ene (**17**) should proceed rapidly and selectively, as **16** is categorised as a type II olefin, while tetradec-1-ene (**17**) is a type I.[44] While it was broadly true that this was a selective process, separation of remaining starting material **16** from product **18**, especially on a small scale was very challenging. For this reason, conversion to product, as measured by ^{1}H NMR spectroscopy, was used in place of isolated yield as a measure of reaction efficiency during optimisation (Table 1).

Two solvents and three temperatures were identified to start optimisation of this process. Initial attempts at metathesis showed that dichloromethane was a better solvent for the reaction; however the extended reaction times caused

decomposition of the starting material and product and this lead to some of the problems in purification of the products. It was found that at raised temperatures, a shorter reaction time and single addition of catalyst were sufficient to isolate the product in a 63% yield.

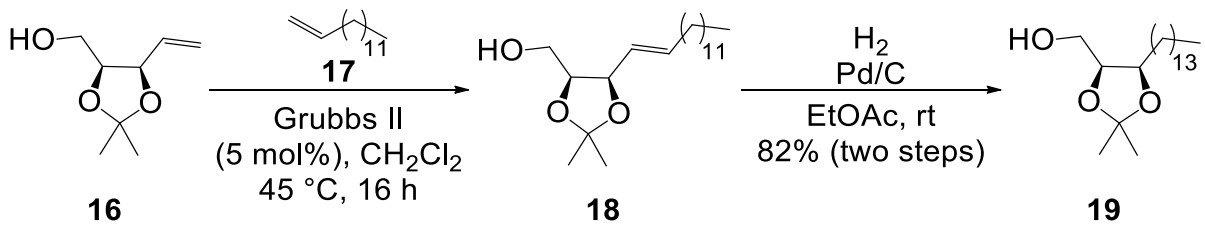


16 **18**

Entry	Solvent	Catalyst loading /mol%	Temperature /°C	Time /h	Conversion to **18** /%[a]
1	CH_2Cl_2	2 × 5	rt	120	61
2	CH_2Cl_2	2 × 5	35	48	24
3	Toluene	2 × 5	35	48	16
4	Toluene	2 × 5	45	48	37
5	CH_2Cl_2	2 × 5	45	48	76 (43)[b]
6	CH_2Cl_2	5	45	10	66 (63)[b]

Table 1: Reactions performed with 1.5 eq of tetradec-1-ene (17) and the stated amount of Grubbs II catalyst. [a]Measured by ^{1}H NMR spectroscopy of crude material. [b]Isolated yield of 18 in brackets.

Due to the problems with purification it was decided to proceed with the crude product through the next step before purification, as this would possibly allow a higher yield over the two steps. Initially hydrogenation in methanol was attempted, however, this caused deprotection of the diol. Changing to ethyl acetate, a less acidic solvent, alleviated this problem. By using the optimised metathesis conditions, then washing the homocoupled side-product, hexacos-13-ene, out of the mixture before hydrogenating the crude product, it was possible to increase the yield of **19** to 82% across the two steps (Scheme 13).



16 **18** **19**

Scheme 13: Optimised cross metathesis and hydrogenation.

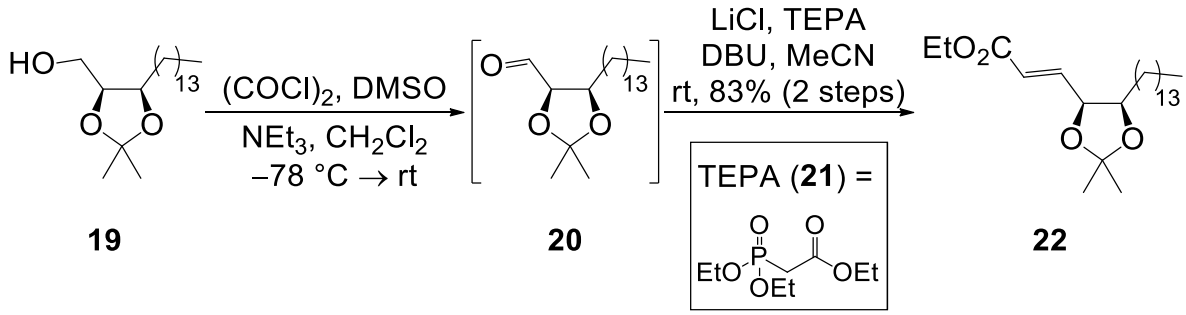
An investigation of the minimum catalyst loading that could be used for metathesis was also undertaken when the process was scaled up. It was found that, on one gram scale, the catalyst loading could be reduced to 1 mol%. However, the slightly extended reaction times, and high concentrations necessary for the reaction to proceed to complete conversion, caused a lower isolated yield over the two steps (Table 2).

Entry	Scale /g	Catalyst loading /mol%	Concentration of **16** /M	Time /h	Isolated yield (2 steps) /%
1	0.10	5.0	0.08	16	82
2	0.25	0.5	0.16	24	27
3	0.25	0.5	0.32	24	27
4	0.25	0.5	0.80	24	39
5	0.25	0.5	1.6	24	33
6	1.0	0.5	3.2	24	43
7	1.0	1.0	3.2	24	52

Table 2: Attempts to lower catalyst loading in scaled up metathesis and hydrogenation. Reactions carried out in CH_2Cl_2 at 45 °C with 1.5 eq of tetradec-1-ene (17).

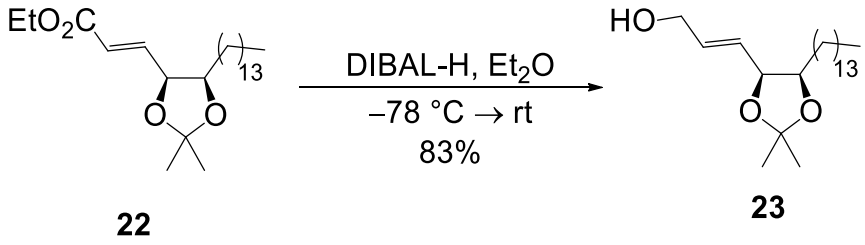
1.2.2 Primary Overman rearrangement route

Having accessed the important intermediate **19**, a one-pot Swern/Horner-Wadsworth-Emmons reaction, developed within the Sutherland group, was applied to access the α,β-unsaturated ester **22** (Scheme 14).[23] In this process, the aldehyde **20** formed in the Swern oxidation was concentrated *in vacuo* and used directly in the subsequent Horner-Wadsworth-Emmons (HWE) reaction with triethyl phosphonoacetate (TEPA, **21**). This process was developed to alleviate problems with purification of volatile or sensitive aldehydes. Epimerisation of the α-stereocenter of the shorter chain, olefin-containing analogue of **20** had been observed during attempts at reduction during the Vasella fragmentation (Scheme 12). By using this one-pot process and employing the mild Masamune-Roush conditions in the HWE step, the α,β-unsaturated ester **22** was synthesised in a high yield over two steps with no epimerisation and entirely as the *E*-isomer.[45]



Scheme 14: One-pot Swern/Horner-Wadsworth-Emmons reaction.

Access to the primary allylic alcohol required for the key Overman rearrangement was gained by DIBAL-H reduction of the α,β-unsaturated ester **22** at −78 °C (Scheme 15). This reduction method has been utilised many times within the Sutherland group for the synthesis of allylic alcohols for Overman rearrangements.[23] Reduction of the α,β-unsaturated ester **22** to alcohol **23** proceeded in a high yield.

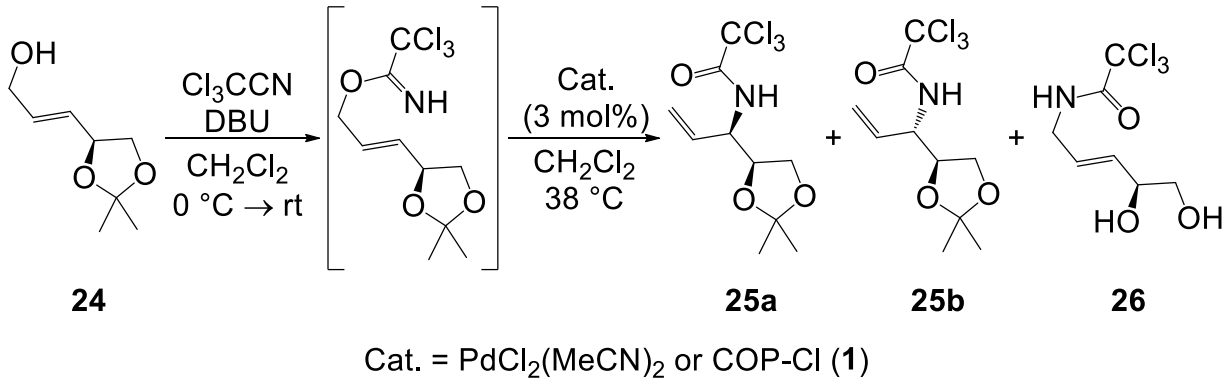


Scheme 15: DIBAL-H reduction of α,β-unsaturated ethyl ester 22.

With the allylic alcohol **23** in hand, the next step was to perform a palladium catalysed diastereoselective Overman rearrangement to install the C-2 amine functionality of phytosphingosine. Previous work within the group had shown that this was possible on a simplified analogue of allylic alcohol **23** that was lacking the long alkyl chain (**24,** Scheme 16).[46] This work did, however, highlight some potential issues that could arise in the use of these catalytic systems when rearranging from acetonide-protected triols.

In the previous work on allylic alcohol **24** the use of a simple palladium(II) catalyst such as bisacetonitrile dichloropalladium(II) yielded a mixture of *syn*- and *anti*-diastereomers (**25a** and **25b** respectively) as well as the undesirable [1,3]-rearrangement-hydrolysis product, **26**. The use of the more complex (*S*)- and (*R*)-COP-Cl catalysts **1** had shown that greater levels of diastereoselectivity could be induced, and that the increased stability of these catalysts could also lower the

quantity of [1,3]-rearrangement-hydrolysis product **26**. In the case of (*R*)-COP-Cl **(*R*)-1**, the observed diastereoselectivity was considerably lower and a small amount of undesired [1,3]-product was still formed. This result is postulated to come from a mismatch between the catalyst and the chiral substrate which slows the reaction and allows time for the catalyst to be reduced.

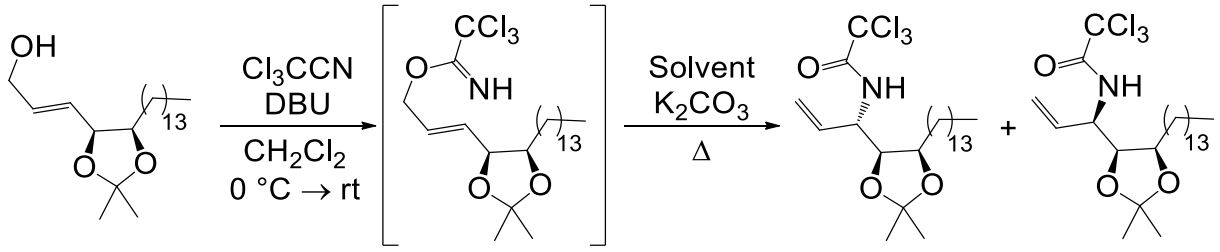


24 **25a** **25b** **26**

Cat. = $PdCl_2(MeCN)_2$ or COP-Cl (**1**)

Scheme 16: Previous work toward a similar diastereoselective Overman rearrangement.

For allylic alcohol **23**, a thermal rearrangement was first investigated. The results from the thermal rearrangement showed that the allylic trichloroacetimidate **27** was more stable than might be expected (Table 3). It was observed that at temperatures of 140 °C or lower, extended reaction periods were necessary to effect full conversion. The use of longer reaction times resulted in increased degradation, which could be minimised by increasing the temperature and reducing the duration of heating. The thermal rearrangement was also performed under microwave irradiation conditions. These conditions allowed for shorter reaction times but also appeared to cause greater degradation of the products. The best results were obtained at 160 °C in *p*-xylene over three days and yielded a mixture of diastereomers that were separated by column chromatography. The crude ratio of diasteromers after work-up did not, however, translate to isolated products. It was observed that upon separation of the two diastereomers, a lower quantity of the desired, *anti*-isomer **28a** was obtained.



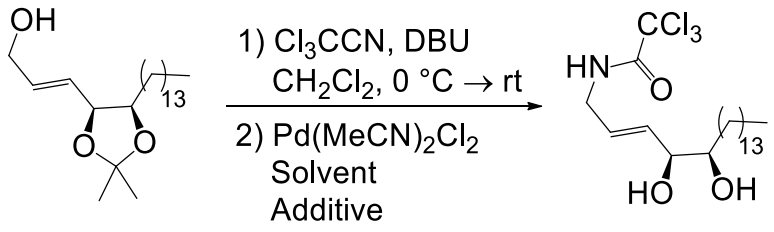
23 **27** **28a** **28b**

Entry	Solvent	Heating method	Temperature /°C	Time	**28a**:**28b**[a]	Yield[b] /%	
						28a	**28b**
1	Toluene	Oil bath	120	7 days	2:1	Incomplete	
2	Toluene	Oil bath	140	5 days	1:1	Incomplete	
3	Toluene	Oil bath	140	14 days	1:1	17	33
4	*p*-Xylene	Oil bath	160	3 days	1:1	26	44
5	Toluene	µW	180	1 h	1:1	12	33
6	Toluene	µW	180	1.5 h	-	Decomposed	

Table 3: Results of thermal Overman rearrangement. Reactions performed in a sealed tube. [a]d.r. measured from ^{1}H NMR spectrum of crude material. [b]Isolated yield of individual diastereomers.

The use of achiral palladium catalysts such as $PdCl_2(MeCN)_2$ was also explored. Previous work within the group on similar reactions had shown that the use of this catalyst could cause the formation of the undesired and deprotected [1,3]-product.[46] This is postulated to form *via* the palladium(II)-catalysed hydrolysis of the acetonide and the palladium(0)-catalysed, non-concerted [1,3]-rearrangement of the acetimidate. The deprotection of acetonides by this catalyst complex had previously been reported in wet THF and acetone, but was unexpected in dry toluene or dichloromethane.[47]

It has been shown that the addition of *p*-BQ can counteract this reaction pathway by oxidising any palladium(0) formed back to the catalytically active palladium(II) species.[15] Upon investigation of the reaction, it was observed that, after 16 hours, **29** was the only product in all cases (Table 4).



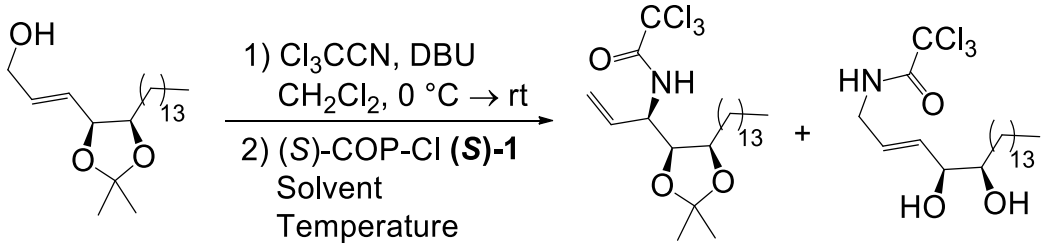
23 **29**

Entry	Solvent	Catalyst loading /mol%	Additive	Isolated yield /% (**29**)
1	Toluene	7	-	16
2	CH_2Cl_2	7	-	18
3	CH_2Cl_2	10	*p*-BQ[a]	13

Table 4: Results of the $Pd(MeCN)_2Cl_2$ catalysed Overman rearrangement. All reactions carried out at room temperature over 16 h. [a]3 mol% *p*-benzoquinone added.

The use of the chiral COP-Cl catalysts was then investigated (Table 5). The (*R*)-COP-Cl catalyst **(*R*)-1**, due to its mismatch with the substrate, was expected to require longer reaction periods and give lower yields. However, it was observed that after prolonged reaction times or under increased temperatures the (*R*)-COP-Cl catalyst **(*R*)-1** failed to produce either of the products, **28a** or **28b** (Table 5, entries 1–3).

The use of (*S*)-COP-Cl **(*S*)-1** allowed the isolation of diastereomerically pure **28b** in low yields (entries 4–7). From the optimisation results, it was observed that high initial catalyst loadings yielded a greater ratio of **29** to **28b** and that increasing the temperature had no beneficial effect on the ratio. Various conditions were screened in an attempt to inhibit the formation of [1,3]-product. These poor results can be attributed to the steric bulk of both the catalyst and the substrate, at the position adjacent to the alkene. Poor yields and loss of selectivity have both been observed when using palladium(II) catalysts with sterically demanding substrates in work on ether-directed Overman rearrangements.[15,23]



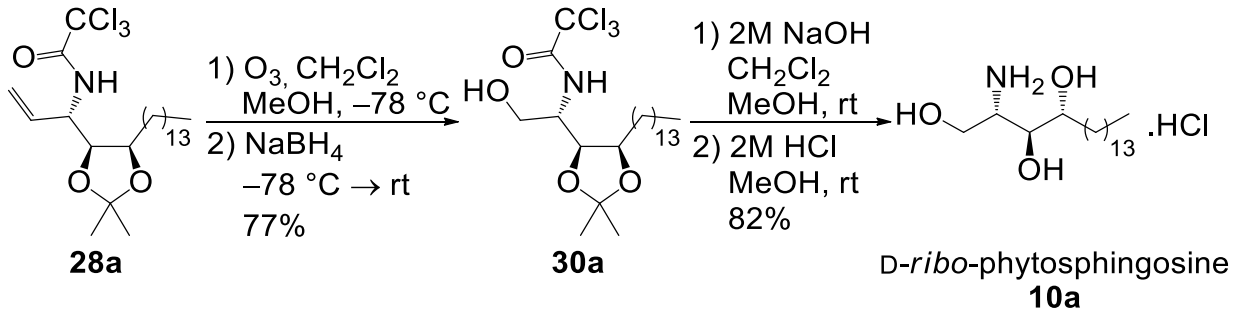
23 **28b** **29**

Entry	Solvent	Catalyst	Loading /mol%	Temperature /°C	Time	**28b**:**29**[a]
1	CH_2Cl_2	(*R*)-COP-Cl	6	38	19 days	NR
2	MeCN	(*R*)-COP-Cl	6	70	6 days	NR
3	Toluene	(*R*)-COP-Cl	6	70	4 days	NR
4	CH_2Cl_2	(*S*)-COP-Cl	9[b]	38	14 days	2:1 (17%)[c]
5	CH_2Cl_2	(*S*)-COP-Cl	9[d]	38	16 days	1:1 (22%)[c]
6	CH_2Cl_2	(*S*)-COP-Cl	10[e]	38	4 days	1:4 (7%)[c]
7	Toluene	(*S*)-COP-Cl	9[c]	60	10 days	1:2 (27%)[c]
8	MeCN	(*S*)-COP-Cl	6	70	6 days	NR

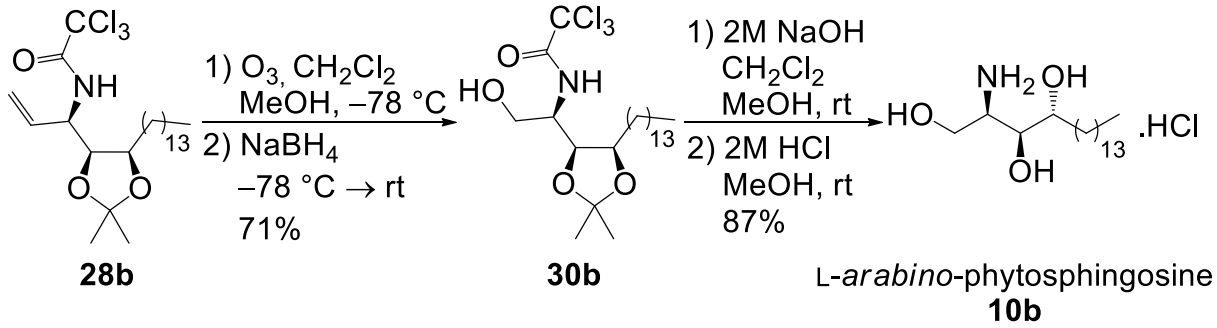
Table 5: Optimisation of COP-Cl-catalysed Overman. [a]Calculated from ^{1}H NMR spectrum of crude material. [b]Added as 3 mol% initially and 3 mol% at 3 and 6 days. [c]Isolated yield of 28b in brackets. [d]Added as 3 mol% initially and 3 mol% at 2 and 4 days. [e]Added as 10 mol% initially.

Having observed the sub-optimal results yielded by both thermal rearrangement and palladium catalysis in this system, it was decided that to improve the route, a secondary Overman rearrangement could be utilised to install the desired stereocenter. Before embarking on this modification to the route, the synthesis was completed with the separated products of the thermal Overman rearrangement. This was to ensure that the final two steps of the proposed route would work.

Ozonolysis with a reductive work-up of compounds **28a** and **28b** afforded the desired, protected phytosphingosines **30a** and **30b** in high yields. These could then be deprotected in a simple two-step procedure to afford, D-*ribo*-phytosphingosine (**10a**) and L-*arabino*-phytosphingosine (**10b**) (Scheme 17 and Scheme 18).



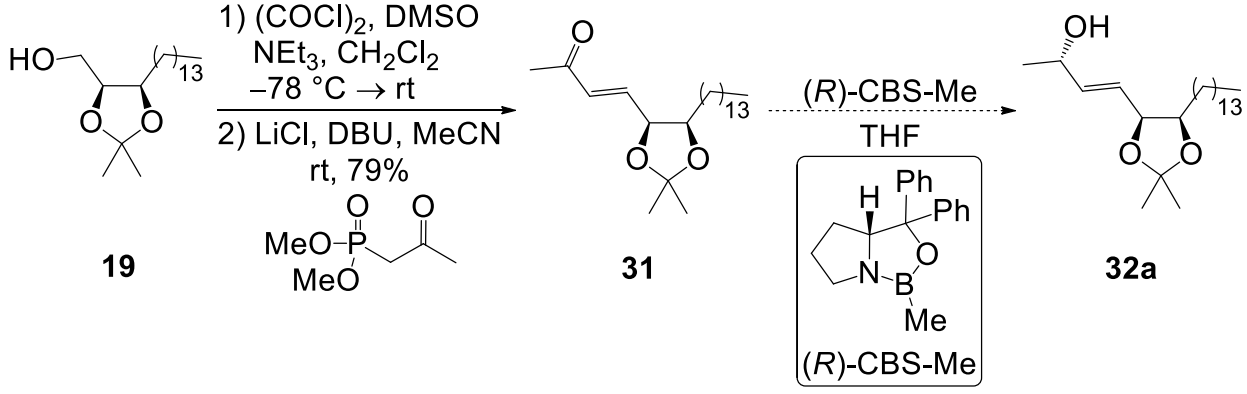
Scheme 17: Ozonolysis and deprotection to D-*ribo*-phytosphingosine, 10a.



Scheme 18: Ozonolysis and deprotection to L-*arabino*-phytosphingosine, 10b.

1.2.3 Secondary Overman rearrangement route

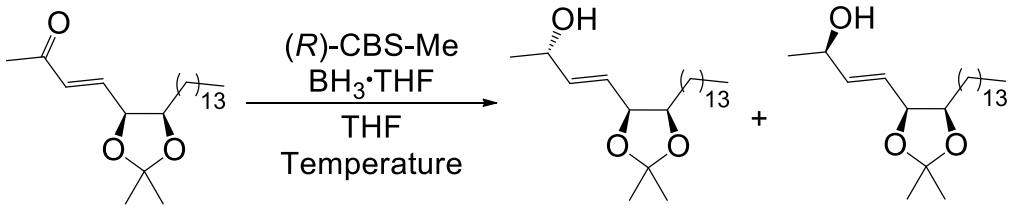
An alternative, diastereoselective route to D-*ribo*- and L-*arabino*-phytosphingosine from the intermediate alcohol **19** was proposed. This used an HWE reaction with dimethyl 2-oxopropylphosphonate followed by a reagent-controlled diastereoselective reduction of the α,β-unsaturated ketone **31** (Scheme 19).



Scheme 19: Diastereoselective route to secondary allylic alcohols.

Upon synthesis of the α,β-unsaturated ketone **31**, a number of trial reactions with the (*R*)-(+)-2-methyl-CBS-oxazaborolidine, (*R*)-CBS reagent were attempted

(Table 6). It had been shown by prior work within the group that for α,β-unsaturated ketones, stoichiometric quantities of the CBS reagent were necessary to produce high yields as well as e.e. and/or d.r.[48] For this reason, a stoichiometric amount of CBS reagent was used in this study. At between −45 °C and −20 °C, the reaction proceeded extremely slowly with a low d.r. The reaction produced only one diastereomer when the temperature was increased to 0 °C. It has been reported in the literature that, at temperatures below −30 °C, there is a sufficient alteration in the equilibria, between borane, the stabilising ligand (eg. THF), the CBS catalyst and the coordinated ketone, to allow intervention by competing, non-selective reduction pathways.[49]



31 **32a** **32b**

Entry	(*R*)-CBS/Eq	BH_3·THF/Eq	Temperature /°C	Time /h	Conversion[a]	**32a**:**32b**[a]
1	1.0	1.1	−45	3	28	3:1
2	1.1	3.0	−40	6	93	2:1
3	1.1	3.0+3.0	−20	24	81	2:1
4	1.1	3.0	0	6	99[b]	**32a** only

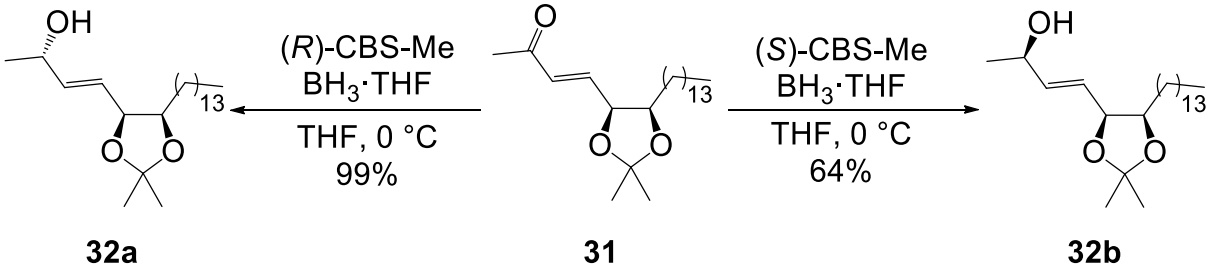
Table 6: Diastereoselective reduction condition screen results. [a]Calculated from ^{1}H NMR spectra of crude material. [b]Isolated yield of 32a after purification.

There are a number of examples in the literature where the enantio- and/or diastereoselectivity of CBS reductions reach a maximum between the temperatures of 30 and 50 °C.[50–52] The exact point at which this occurs is substrate and CBS-analogue dependent. Having achieved near quantitative yields of a single diastereomer at 0 °C, warming the reaction was not attempted.

An additional problem was also identified during the screening of reaction conditions. The most common method for removal of the CBS catalyst by-product is washing with a weak solution of an acid, such as hydrochloric acid. In the case of products **32a** and **32b**, this would cause serious problems due to the lability of the acetonide protecting group. This protecting group had also caused problems in the purification of previous intermediates due to its decomposition during silica chromatography. In response to this problem, a dilute solution of citric acid was

used instead. The use of this work-up allowed the removal of the majority of the amino alcohol while minimising the loss of product.

With the optimised conditions for CBS reduction in hand, these were then applied to the synthesis of the unnatural diastereomer **32b** (Scheme 20). It was observed that in the case of the (*S*)-CBS reduction to **32b,** a considerably lower yield was obtained. This may be due to a mismatch between the catalyst and substrate causing the diastereoselective reaction to slow down, which would allow a slower side process to become more prevalent. This hypothesis is supported by the lack of any **32a**, which would be the product formed by a non-selective reduction pathway, or any **31** remaining after the reaction.

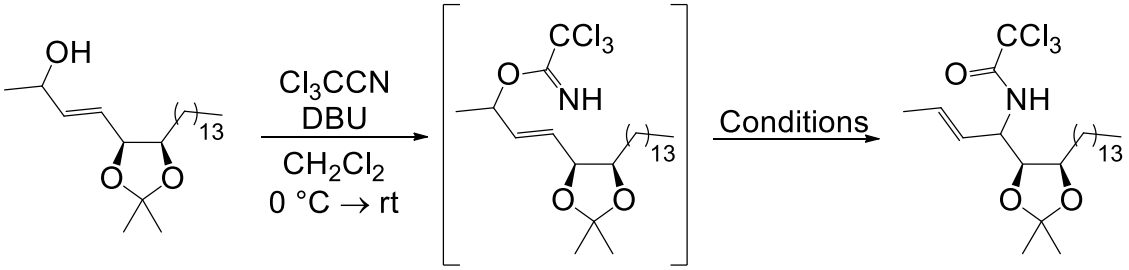


Scheme 20: Diastereoselective reduction to each diastereomer of 32.

The Overman rearrangement of secondary, allylic trichloroacetimidates is known to proceed under thermal conditions at around 110 °C or, at higher temperatures, over much shorter time scales than for a primary rearrangement.[53] As this is less forcing than the rearrangement of similar, primary compounds, a short screen of conditions under which the Overman rearrangement of **33a** and **33b** might proceed was undertaken (Table 7).

Initially, a trial of three different temperatures was conducted (Table 7, entries 1–3). Performing the reaction at 160 °C for 18 hours, a very low yield of **34a** was obtained as the only product. An improved yield was observed when conducting the reaction at 140 °C. However, when the temperature was further lowered to 110 °C, a portion of the intermediate trichloroacetimidate was recovered. As it had been observed in the primary rearrangement, that longer reaction times tended to cause decomposition of the product, the reaction was attempted at 140 °C for 8 hours (entry 4). This gave a much improved yield of the desired product but the ^{1}H NMR spectrum of the crude mixture still showed incomplete conversion of the imidate. An intermediate duration of 10 hours provided an optimised yield of 71%

(entry 6). Using this result as a starting point, it was shown that the reaction at 160 °C was completed in 3 hours with an almost identical yield (entry 7). Applying the group's knowledge of microwave chemistry, it was shown that the reaction could be accelerated using microwave irradiation to finish in only 15 minutes at 140 °C (entry 8). The microwave conditions required the addition of a silicon carbide passive heating element to the reaction vessel to allow heating, as *p*-xylene does not absorb microwave radiation. Attempting the reaction under each of the three conditions produced high yields of diastereomerically pure **34a**. Applying the optimised conditions to the rearrangement of **33b** produced similarly high yields of diastereomerically pure **34b** (entries 9 and 10).

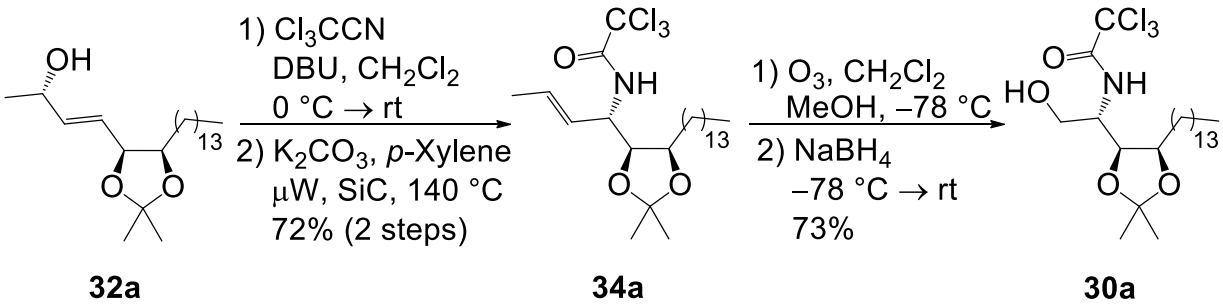


32a - (2*S*,5*S*,6*R*) **33a** **34a**
32b - (2*R*,5*S*,6*R*) **33b** **34b**

Entry	Substrate	Temperature /°C	Time /h	Solvent	Heat source	Yield /%
1	**33a**	160	18	*p*-Xylene	Oil bath	7
2	**33a**	140	18	Toluene	Oil bath	36
3	**33a**	110	18	Toluene	Oil bath	22 (+15% **33a**)
4	**33a**	140	8	*p*-Xylene	Oil bath	53 (+13% **33a**)
5	**33a**	140	8	DMF	Oil bath	Decomposed
6	**33a**	140	10	*p*-Xylene	Oil bath	71
7	**33a**	160	3	*p*-Xylene	Oil bath	72
8	**33a**	140	0.25	*p*-Xylene	µW	72
9	**33b**	160	3	*p*-Xylene	Oil bath	77
10	**33b**	140	0.25	*p*-Xylene	µW	71

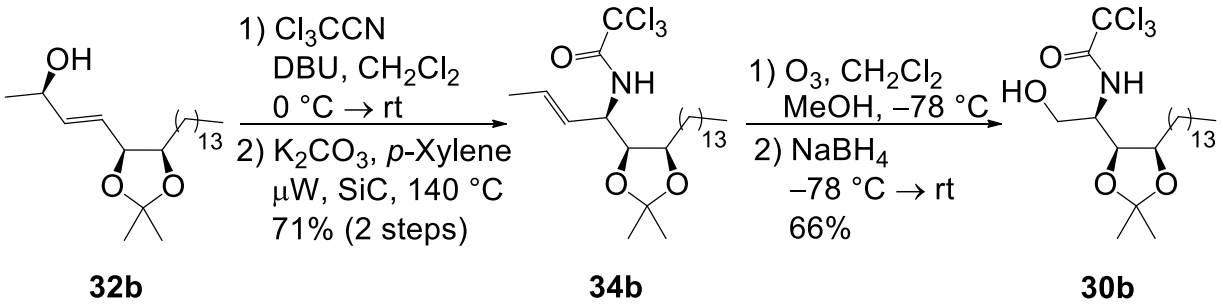
Table 7: Conditions for Overman rearrangement of allylic imidates 33a and 33b.

With the allylic trichloroacetamides **34a** and **34b** in hand, repetition of the ozonolysis conditions utilised previously allowed access to the same, protected phytosphingosines, **30a** and **30b**. The ozonolysis and reductive work-up again proceeded in a good yield for each analogue (Scheme 21 and Scheme 22).



32a **34a** **30a**

Scheme 21: Overman rearrangement and ozonolysis to protected D-*ribo*-phytosphingosine 30a.



32b **34b** **30b**

Scheme 22: Overman rearrangement and ozonolysis to protected L-*arabino*-phytosphingosine 30b.

1.3 Conclusions

A 13-step, diastereoselective synthesis of both D-*ribo*- and L-*arabino*-phytosphingosine from the chiral pool starting material D-ribose has been developed. This synthesis included the use of cross metathesis to install the long chain alkane of the natural products and an Overman rearrangement to install the C-2 amine functionality in a diastereoselective manner. Having experienced problems with the initial route, *via* a primary Overman rearrangement, an alternative strategy using CBS-reduction of an α,β-unsaturated methyl ketone to access each of the chiral secondary allylic alcohols was developed. This method allowed the total synthesis of D-*ribo*- and L-*arabino*-phytosphingosine in 19% and 12% yields, respectively.

Chapter 2 Development of a One-Pot Multi-Reaction Process: The Total Synthesis of Oxybenzo[c]phenanthridine Natural Products

2.1 Introduction

2.1.1 One-pot multi-reaction processes

In recent years the study of one-pot, multi-reaction, tandem, domino and cascade processes has grown rapidly.[54–58] The utilisation of multiple transformations within a single reaction vessel has a number of advantages over traditional step-wise chemistry. These include the minimisation of solvent and other chemical waste by the elimination of purification steps for intermediates and potential gains in yield, where intermediates are sensitive or volatile. Tandem catalysis processes, in particular, where one or more catalysts may perform multiple isolated transformations during a single reaction, can reduce the time needed to synthesise compounds, as well as the quantity of waste created.[56] This can lead to more efficient and more environmentally-friendly synthetic routes to compounds.

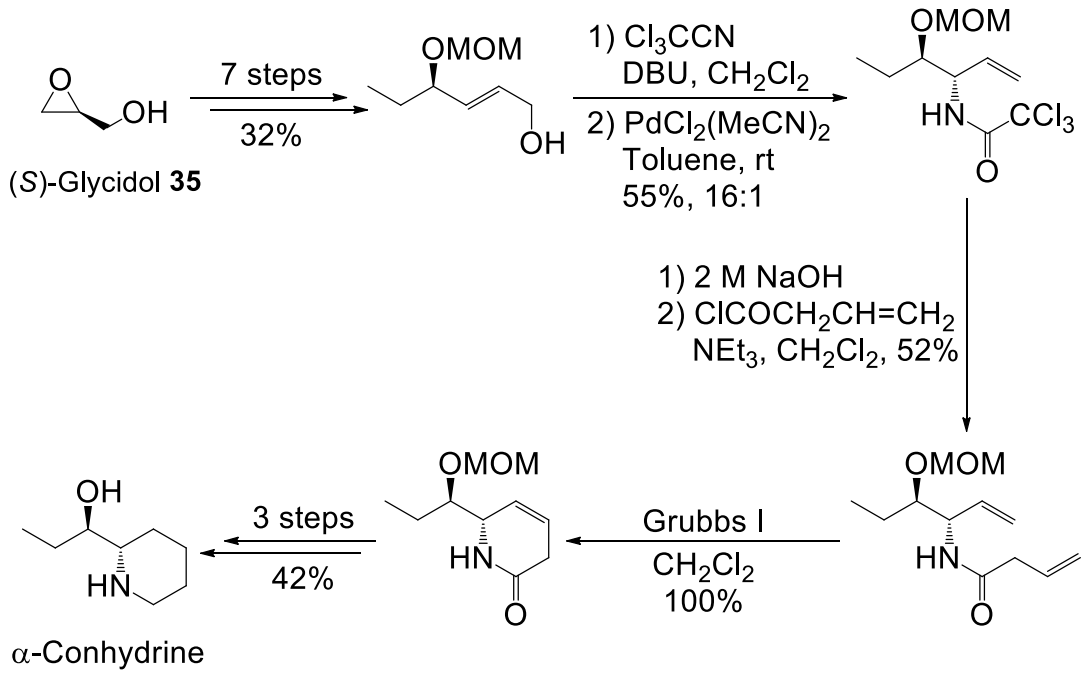
There has been a large amount of discussion in the literature over the proper use of the terms cascade, domino and tandem. As defined by Nicolaou, in all variations of cascade, domino or tandem processes, all reagents or catalysts must be present at the initiation of the first reaction.[54] A further expansion on this by Fogg and dos Santos details that a one-pot process in which:[56]

> *"Modification of an organic moiety via two catalytic elaborations, with addition of the second catalyst only after the first catalytic transformation is complete, is not a* [*sic*] *tandem catalysis, but a one-pot (bicatalytic) reaction."*

In addition, Fogg and dos Santos specify that, for reactions in which there is only a single catalytic step in addition to a stoichiometric one, these cannot fall under the category of tandem but, may be classed as domino only if all reagents are present at the start. As such, in this thesis, where multiple additions and changes in reaction conditions are used in the key processes of the projects that will be detailed below, the processes will be defined as one-pot multi-reaction, and not as cascade, tandem or domino processes.

2.1.2 Previous work within the group

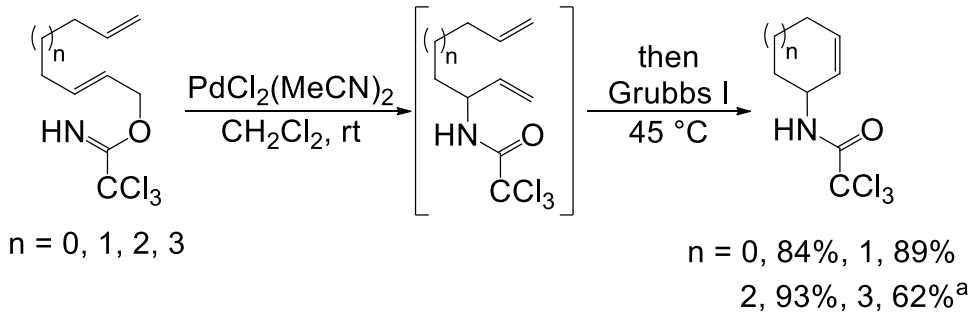
Within the Sutherland group a number of recent projects have focused on the use of an Overman-RCM/RCEYM one-pot process. The initial ideas for this process came about in 2007 as an extension of the group's previous work on ether-directed Overman rearrangements (see section 1.1.2 for information on the ether-directed process).[59] Having demonstrated that the Overman rearrangement could be efficiently controlled by an allylic, ether-protected alcohol, the group set about synthesising a number of natural products using this methodology. Included in these was the piperidine alkaloid, α-conhydrine (Scheme 23).[60] In the synthesis of α-conhydrine, a deprotection-acylation strategy was utilised to install a second alkene in the molecule before using RCM to form the six-membered ring of the natural product.



Scheme 23: Key steps of the Sutherland group's synthesis of α-conhydrine in 2007.

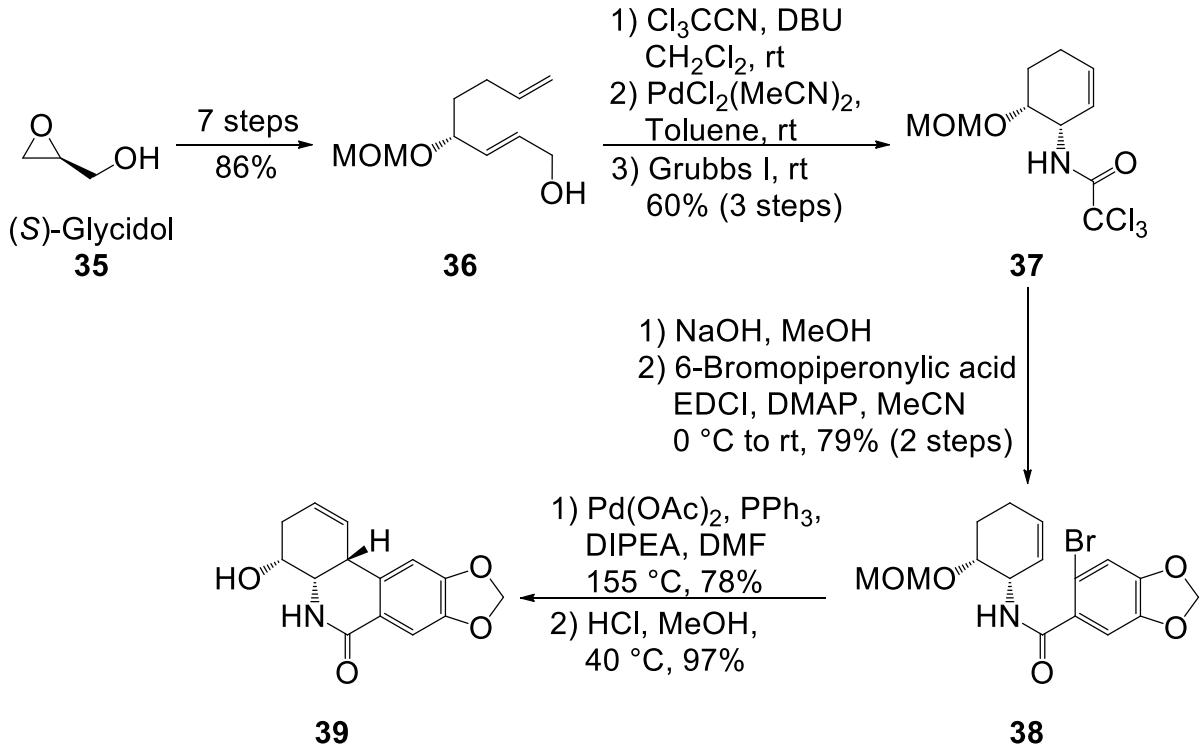
This methodology was complicated by the necessity of changing the protecting group and the difficulties in attaching the olefin-containing chain. Later in the same year, the group published initial attempts at a one-pot Overman-RCM process to overcome the limitations observed in the conhydrine synthesis.[59] Having reported in an intermediate paper that ruthenium-based catalysts had no detrimental effect on allylic trichloroacetimidates, the initial idea had been to perform an orthogonal tandem-catalysis reaction. In such a reaction both the palladium and ruthenium catalysts would be present at the initiation of the reaction. The palladium catalyst

would first perform the Overman rearrangement before the ruthenium catalyst performed RCM. However, a set-back was encountered in this plan — it appeared that the ruthenium metathesis catalysts were decomposing through a side-reaction with the palladium(II) catalyst before the completion of the Overman step — and in all cases only the intermediate trichloroacetamide-diene was isolated. To circumvent this problem, a step-wise addition procedure was utilised that involved performing the palladium-catalysed Overman rearrangement at room temperature before addition of the ruthenium catalyst and warming to 45 °C to effect the RCM (Scheme 24). This allowed access to the desired cyclic allylic amides in high yields. The use of chiral (*S*)-COP-Cl catalyst **(*S*)-1** in this methodology showed that it was also possible to obtain high enantioselectivities (94:6 e.r. prior to crystallisation) in the one-pot two-step process.



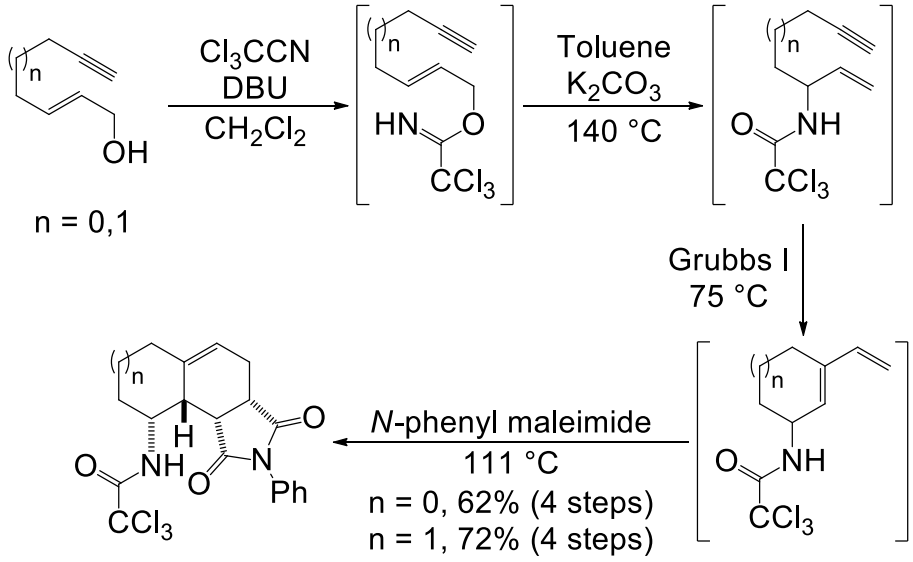
Scheme 24: One-pot Overman rearrangement ring closing metathesis reaction. [a]Performed using Grubbs II.

Having developed a one-pot multi-reaction process for the synthesis of cyclic allylic trichloroacetamides, the group utilised this methodology for the total synthesis of a number of natural products and drug-like compounds such as analogues of (+)-7-deoxypancratistatin.[61] This project combined the ether-directed Overman rearrangement strategy with the one-pot multi-reaction process. Starting from (*S*)-glycidol (**35**), in seven steps and an impressive 86% overall yield, the allylic alcohol **36** was synthesised (Scheme 25). Using this in the one-pot multi-reaction process allowed access to the cyclic allylic amide **37** as a single stereoisomer. Deprotection of the amide and coupling with 6-bromopiperonylic acid gave aryl bromide **38** which was then used in a Heck reaction to close the final ring. This compound was then deprotected under acidic conditions to give the precursor to the (+)-7-deoxypancratistatin analogues **39**. With this compound in hand, the synthesis of three analogues of (+)-7-deoxypancratistatin by oxidation or reduction of the 1,2-alkene was completed.



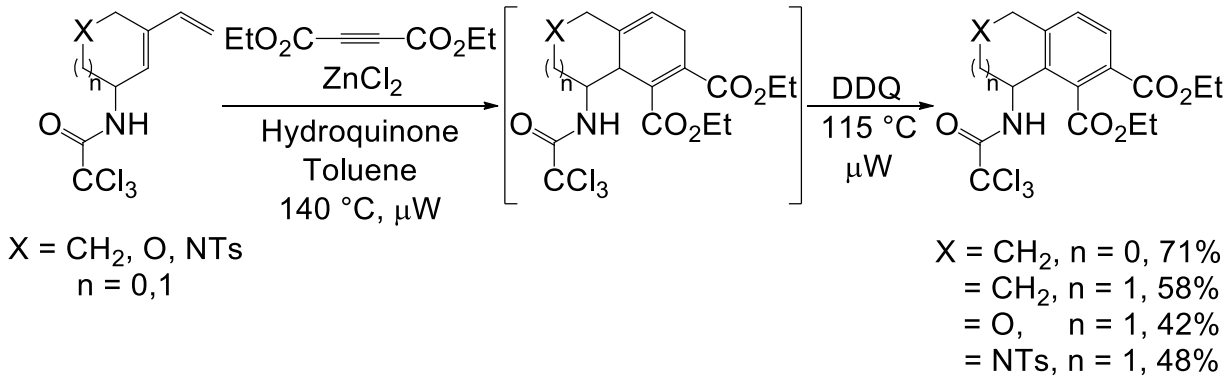
Scheme 25: The key steps in the synthesis of analogues of (+)-7-deoxypancratistatin using a one-pot multi-reaction process.

An obvious extension of this project was the incorporation of an alkyne in place of the terminal alkene. This allowed the process to be expanded and the use of RCEYM furnished a 1,3-diene which was then used in a Diels-Alder reaction.[62] Again, a short synthetic route to the necessary allylic alcohol was developed. After optimising the step-wise process, it was applied as a one-pot three-step procedure (Scheme 26). Performing the Overman rearrangement under thermal conditions and the RCEYM at 75 °C with Grubbs 1st generation catalyst yielded the required 1,3-enyne. At this point a number of different dienophiles were used in a Diels-Alder reaction to form bi- and tri-cyclic compounds.



Scheme 26: One-pot three-step reaction sequence allowing access to substituted octahydroamidonaphthalenes and hexahydroamidoindenes.

The scope of this methodology was then expanded to include Diels-Alder reactions with alkynes and dienes containing heteroatoms in their backbone.[63] This process formed 1,4-dienes, which could then be aromatised using either DDQ or manganese dioxide to yield amidoindanes and amidotetralins (Scheme 27). This project ignited interest within the Sutherland group in developing new one-pot processes that could access these amidoindanes and amidotetralins in a different and complimentary manner.



Scheme 27: One-pot two-step process for the synthesis of amidoindanes and amidotetralins.

2.1.3 The oxybenzo[c]phenanthridine natural products

The first reported isolation of a member of the benzophenanthridine alkaloids dates back to the early 1800s.[64] Since then a large number of related benzophenanthridine natural products have been isolated and characterised.[65] These natural products have gained significant attention due to their potent biological activities. Of particular interest are the fully aromatised oxybenzo[c]phenanthridine natural products. A major source of these alkaloids are plants of the genus *Zanthoxylum*. This genus includes around 250 evergreen and deciduous shrubs, which grow in temperate and subtropical areas of the globe. The bark of a number of these shrubs was historically used for treatment of pain and inflammation, amongst other ailments.[66] For example *Zanthoxylum nitidum*, which has been used as an anti-inflammatory and analgesic in Chinese medicine for over 1000 years, contains a number of benzophenanthridine natural products including nitidine (**40**), dihydrochelerythrine (**41**), 8-methoxychelerythrine (**42**) and oxyavicine (**43**) (Figure 5).[67] These compounds have been shown to have analgesic and anti-inflammatory effects comparable with those of hydrocortisone.[67]

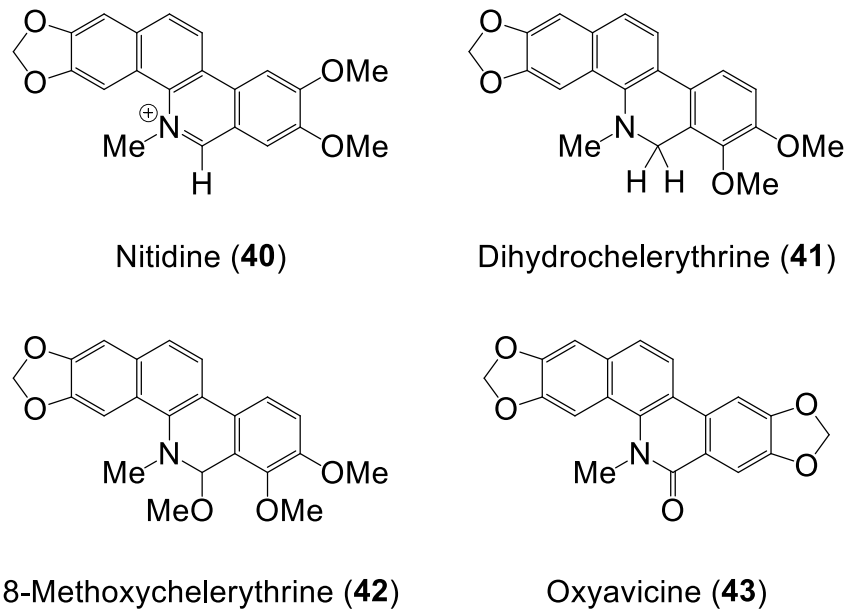


Figure 5: Four of the alkaloid natural products obtained from *Zanthoxylum nitidum*.

Other members of this family of alkaloids show efficacy against a diverse range of biological targets. Examples include oxychelerythrine (**44**), which displays cytotoxic effects against P-388 and HT-29 tumour cell lines,[68] oxysanguinarine (**45**) which inhibits platelet aggregation[69] and oxynitidine (**46**) which inhibits DNA replication in hepatitis B virus.[70] Due to the potent biological activity of a large

number of these alkaloids, and the relatively low quantities that can be extracted from plant sources, they have been the focus of a large number of syntheses.[65]

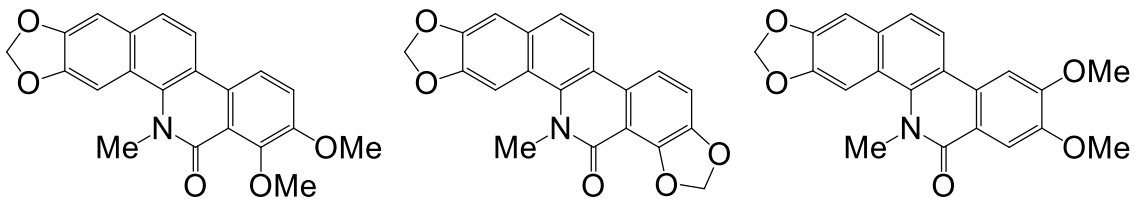
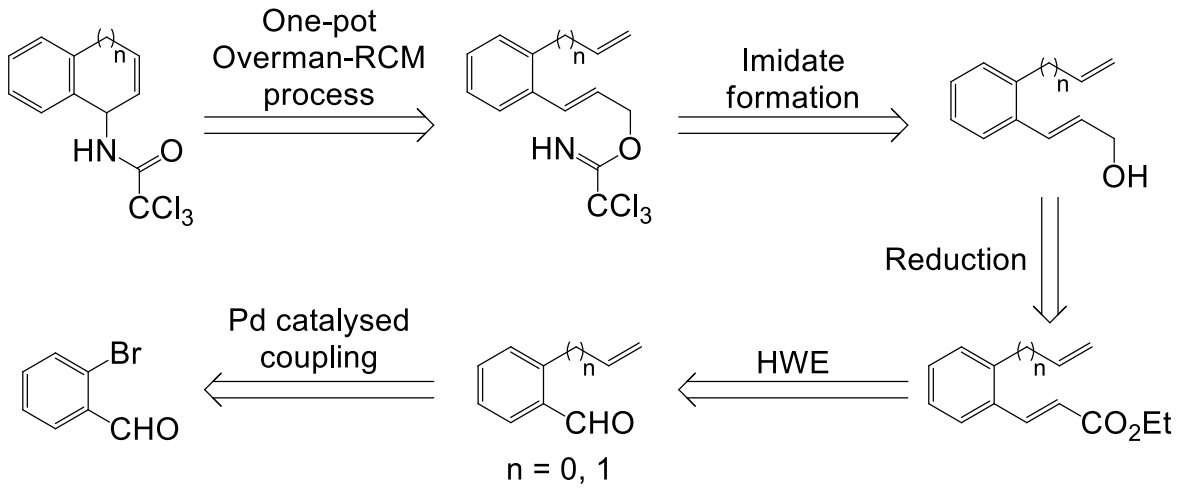


Figure 6: Other members of the family of oxybenzo[c]phenanthridine natural products.

2.1.4 Aims

The aim of this project was to optimise a previously developed one-pot multi-reaction process for the synthesis of a series of C-1 amido substituted indenes and dihydronaphthalenes. This one-pot process would then be applied as the key step in the total synthesis of a number of natural products from the oxybenzo[c]phenanthridine family. To this end, a rapid and versatile synthesis of the 2'-substituted cinnamyl alcohols would also have to be developed (Scheme 28).



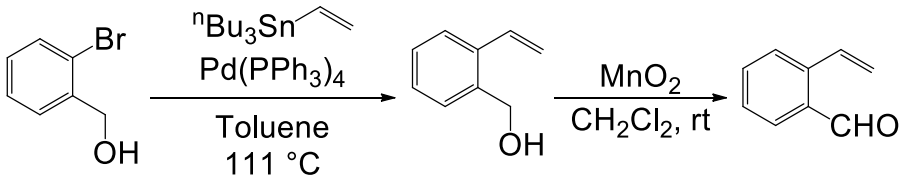
Scheme 28: Proposed access to allylic alcohols and use in one-pot process to form bicyclic systems.

2.2 Results and discussion

2.2.1 A rapid synthesis of 2'-vinylcinnamyl alcohols

2.2.1.1 Stille route to allylic alcohols

The initial route proposed to gain access to the required 2'-vinylcinnamyl alcohols involved the use of a palladium-catalysed Stille coupling between 2-bromobenzyl alcohol (**47**) and vinyl tributyltin (Scheme 29).[71–73] It was then necessary to oxidise the alcohol **48** to the corresponding benzaldehyde **49a**. This oxidation was carried out using manganese dioxide.



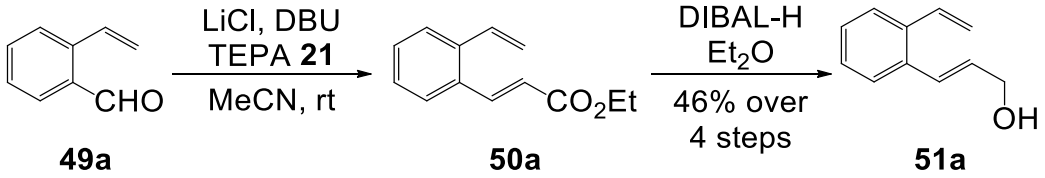
47 **48** **49a**

Scheme 29: Initial reactions to access 2'-vinylbenzaldehyde (49a).

Although the Stille coupling was an extremely efficient reaction, giving full conversion to the product, by ^{1}H NMR analysis, with no protodehalogenation products or starting material returned after the reaction, it was very difficult to remove all the by-products derived from the vinyl tributyltin. A number of different work-ups and column conditions were investigated. The initial conditions were based upon reacting the tributyltin bromide by-product of the reaction with potassium fluoride to form the polymeric tributyltin fluoride and potassium bromide, then removal of the polymeric compound by filtration or column chromatography.[74,75] Although a large quantity of the by-products could be removed in this way, a significant amount always remained inseparable from the desired compound. Differences in the concentration or solvent that the potassium fluoride was introduced in made no difference to the outcome of purification. Heating with the potassium fluoride or prolonged stirring also had no effect. After consultation of the literature, a number of other possibilities were apparent; these included filtration through a Celite® or silica and potassium fluoride mixture,[76] repeated washing of the organic liquors with 1 M aqueous potassium fluoride solution and column chromatography in a ~2–5% triethylamine elution solvent mixture.

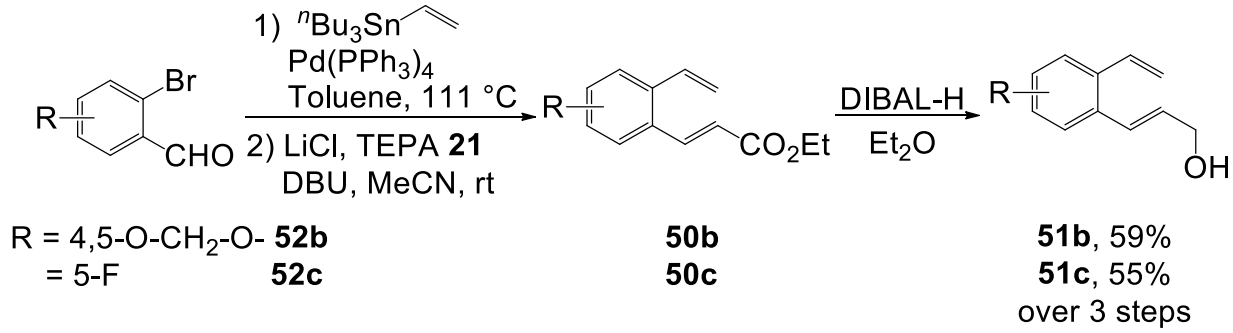
Upon attempting a procedure by Renaud *et al*,[77] in which 1 M aqueous sodium hydroxide was used to form tributyltin hydroxide and bis(tributyltin) ether, which are too polar to elute from silica gel under low polarity solvent mixtures, an unexpected reaction occurred. Having used the Stille coupling to access benzyl alcohol **48**, it was observed that the 2-vinylbenzaldehyde **49a** had formed. This reaction probably goes through the widely accepted mechanism for palladium-catalysed aerobic oxidation of alcohols.[78,79]

By progressing the crude 2'-vinylbenzaldehyde (**49a**) through an HWE reaction with triethyl phosphonoacetate (**21**), under the Masamune-Roush conditions,[45] then reducing the resulting ester **50a** with DIBAL-H, the required cinnamyl alcohol **51a** was formed (Scheme 30). Having carried large quantities of the tributyltin side-product through these two steps, it was impossible to gain good characterisation data or yields for these reactions. It was, however, possible to purify the cinnamyl alcohol at this stage.



Scheme 30: Initial route to 2'-vinylcinnamyl alcohols.

An amended process using benzaldehydes as substrates for the Stille coupling was also investigated (Scheme 31). 4,5-Piperonyl-derived analogue **51b** and the 5-fluoro analogue **51c** were chosen for their differing electronic properties. In both cases it was impossible to separate the products from the tributyltin-related impurity until the final step.

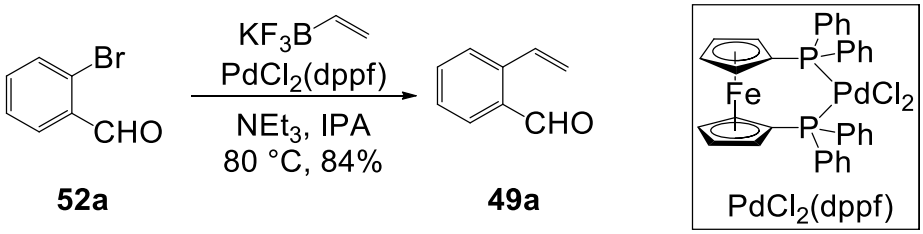


Scheme 31: First synthesis of 4,5-piperonyl- and 5-fluoro-derived cinnamyl alcohols.

Although the Stille coupling route provided enough material to start optimising the one-pot multi-reaction process, it was decided to attempt a different approach to synthesising the key 2'-vinylcinnamyl alcohols. There had also been a number of other complications in the synthesis of the 2'-allylcinnamyl alcohols through this route. These problems will be detailed in section 2.2.3.1.

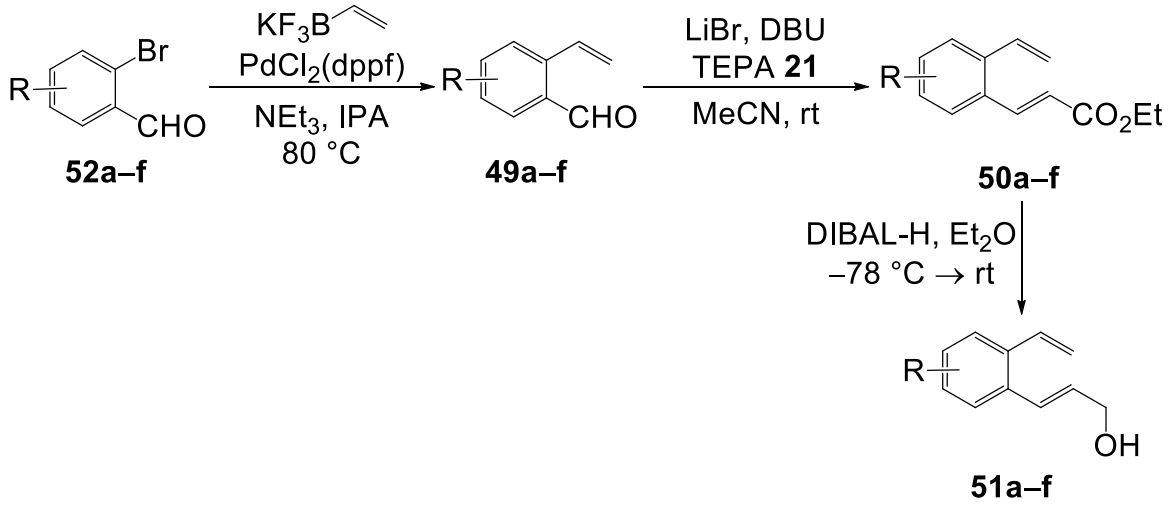
2.2.1.2 Suzuki-Miyaura route to allylic alcohols

Following the problems encountered with the Stille coupling route, it was clear that the first step of the sequence had to be efficient, general, simple and high yielding. Following a literature search, it was decided to attempt a Suzuki-Miyaura coupling of 2-bromobenzaldehyde (**52a**) and potassium vinyltrifluoroborate with palladium(II) dichloride diphenylphosphinoferrocene as the catalyst (Scheme 32).[80] Gratifyingly, this reaction worked in high yield and with no issues with purification and little optimisation required.



Scheme 32: Suzuki-Miyaura coupling of potassium vinyltrifluoroborate and 2-bromobenzaldehyde (52a).

Having synthesised the required 2'-vinylbenzaldehydes **49a–f** cleanly and in high yields using the Suzuki-Miyaura coupling, they were used in an HWE reaction using Masamune-Roush conditions (Table 8). This reaction yielded only the *E*-ethyl cinnamates **50a–f** in very high yields and could be purified by filtration through a silica plug. DIBAL-H reduction of the esters gave the desired 2'-vinylcinnamyl alcohols **51a–f**. This methodology allowed the generation of a reasonable range of substrates in overall yields of between 71% and 89% over the three-step synthesis.



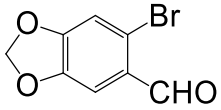
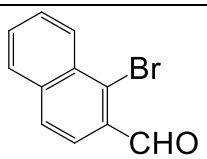
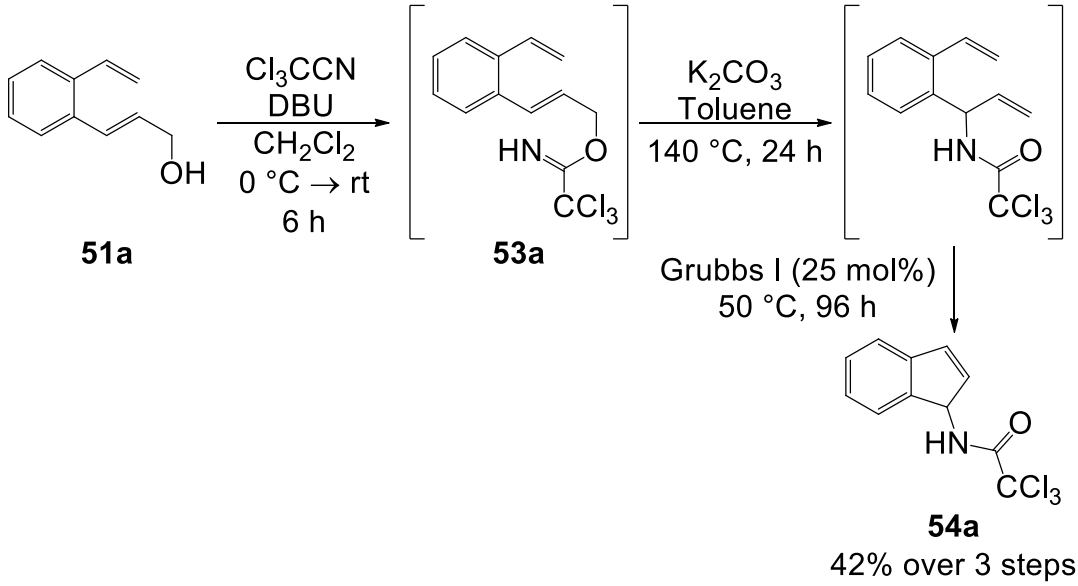
Entry	**52**	**49** (%)	**50** (%)	**51** (%)
1	R = H **52a**	**49a** (84)	**50a** (98)	**51a** (97)
2	 **52b**	**49b** (96)	**50b** (94)	**51b** (99)
3	R = 5-F **52c**	**49c** (91)	**50c** (89)	**51c** (97)
4	R = 4-Me **52d**	**49d** (90)	**50d** (100)	**51d** (92)
5	R = 5-OMe **52e**	**49e** (89)	**50e** (99)	**51e** (89)
6	 **52f**	**49f** (89)	**50f** (87)	**51f** (92)

Table 8: Yields for the three-step synthesis of the (*E*)-2'-vinylcinnamyl alcohols 51a–f.

2.2.2 A one-pot multi-reaction process to form amidoindenes

Initially, replication of the results previously obtained within the group was the main aim (Scheme 33). If these could be replicated then this would form the basis for optimisation of the one-pot multi-reaction process.



Scheme 33: Previous attempt at one-pot process by Fiona McGonagle in the group.[81]

Acid-catalysed elimination of the trichloroacetimidate group during purification of intermediate **53a** on silica had previously been observed to occur on a related series of compounds.[81] To prevent this, the purification method in this project was changed to use Brockman V neutral alumina.

After a single attempt at the Overman rearrangement, it was noticed that the reaction duration needed to be increased to 36 hours as there was still a small quantity of the imidate present. Over the course of five reactions, it was found that the optimised conditions required to form the desired RCM product, in the fastest time with the least catalyst loading, were marginally different from the previous conditions. At the end of the RCM reaction (36 h), the reaction mixture was passed through a pad of Celite®. The crude material obtained appeared to contain only product **54a** and the phosphine ligand from the Grubbs I catalyst.

However, when any of the reaction mixtures were further purified by silica column chromatography, a new set of peaks appeared within the ^{1}H NMR spectra (Figure 7). The quantity of this side-product varied with the length of silica column that was used in the purification and so, in some cases, appeared in less than 2% of the purified product, while in other cases it was the only recovered compound. Full characterisation of this compound could not be obtained but ^{1}H and ^{13}C NMR spectroscopy showed that it appeared to be closely related to the desired product.

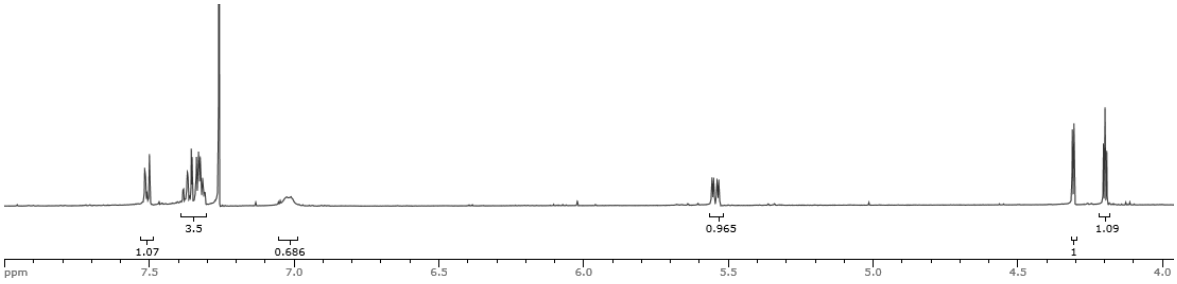
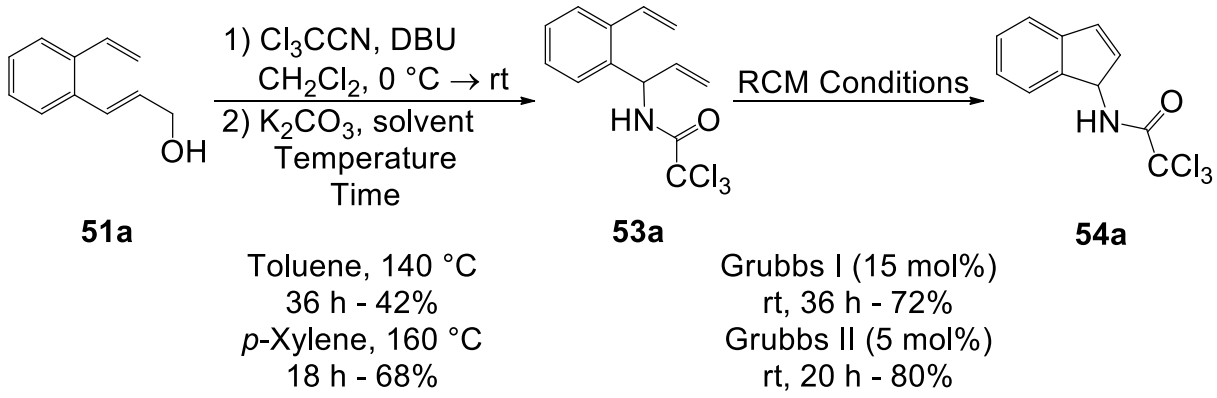


Figure 7: **^{1}H NMR spectrum of isolated, unknown impurity.**

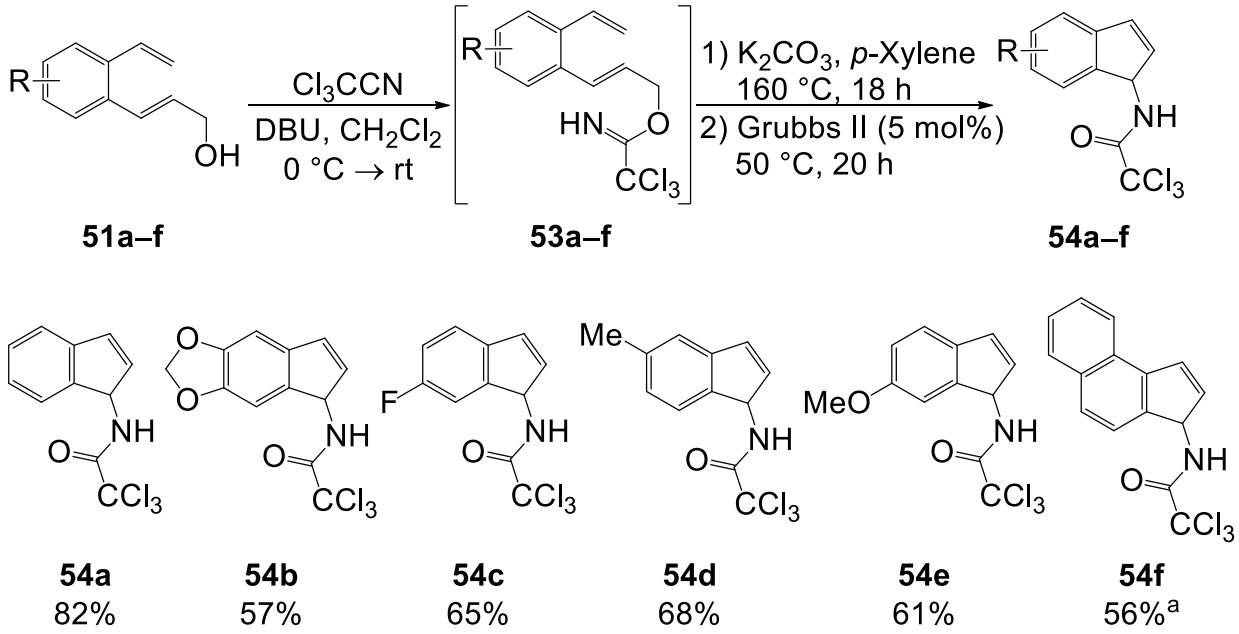
Purification of the reaction mixture through neutral alumina gave a small quantity of a different compound and a complex mixture of unknown decomposition products. At this time, it was decided to investigate if the use of higher temperature or a different catalyst might lead to a reaction mixture that could be purified by filtration through a very short pad of silica. To this end, the one-pot process was repeated in a stepwise fashion (Scheme 34). The optimised conditions for the step-wise process showed that, similar to the results for the synthesis of phytosphingosine, a higher temperature and shorter reaction duration gave higher yields in the Overman rearrangement. In addition, Grubbs 2nd generation catalyst gave a marginal improvement in yield for the RCM process and could be used at just one third of the loading required for Grubbs 1st generation. It was also found that increasing the temperature during the RCM reaction from room temperature to 50 °C improved the conversion.



Scheme 34: **Optimisation of step-wise Overman rearrangement and RCM process.**

These optimised conditions were then applied as a one-pot process to the small family of 2'-vinylcinnamyl alcohols previously synthesised (Scheme 35). Despite achieving a very high yield of 82%, over the three steps for the unsubstituted analogue **54a**, the yields were lower for the other analogues. Although the reaction is tolerant of electron-donating and withdrawing substituents, even a slightly

electron-donating group such as the 4-methyl substituent, **54d**, began to affect the yield adversely. The lowering of yield became more pronounced on the addition of more electron-donating substituents such as a 5,6-methylenedioxy **54b** or 5-methoxy **54e**. Electron-poor compounds, such as 5-fluoro-substituted analogue **54c**, were also tolerated, but again in slightly lower yield than the unsubstituted substrate. In the case of the naphthyl-derived analogue, **54f**, the reduced yield was due to isomerisation of the product to the enamide under the reaction conditions of the RCM step. It was observed that by reducing the reaction time to 12 hours, a better ratio of products could be obtained in the crude mixture (6:1 vs 2:1), as observed by ^{1}H NMR spectroscopy, and this led to the desired product being obtained in a higher yield (56% vs 14% yields).



51a–f **53a–f** **54a–f**

54a	**54b**	**54c**	**54d**	**54e**	**54f**
82%	57%	65%	68%	61%	56%[a]

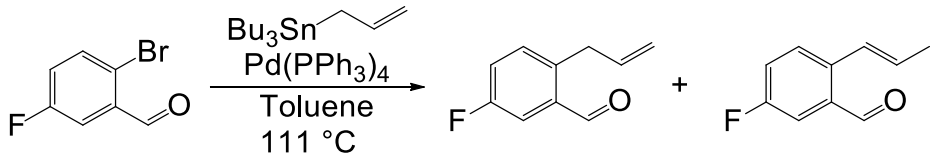
Scheme 35: Optimised yields for the one-pot multi-reaction process. [a]RCM reaction carried out for 12 hours.

2.2.3 A rapid synthesis of 2'-allylcinnamyl alcohols

2.2.3.1 Stille route to allylic alcohols

As for the synthesis of the vinylcinnamyl alcohols, initial attempts at synthesising the 2'-allylcinnamyl alcohols focused on using Stille methodology. However, upon attempting the Stille coupling, it was observed that a mixture of isomers was forming (Scheme 36). This had been previously observed in the original work on

these systems within the group where an inseparable mixture that ranged from 2:1 to 30:1 had been reported.[81]

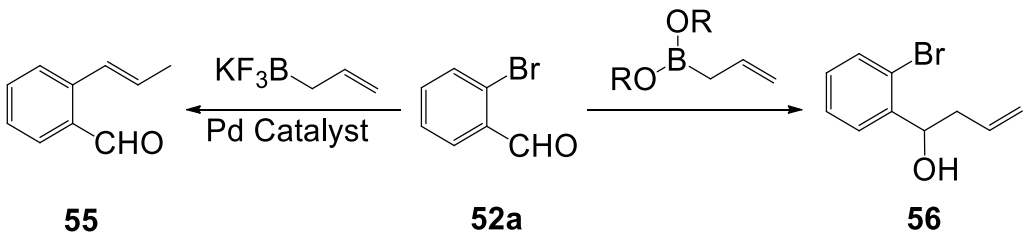


Scheme 36: Initial attempts at Stille coupling with allyl tributyltin.

It was observed that under reflux conditions, the palladium(0)-catalysed isomerisation of the double bond occurred at a comparable rate to that of the Stille coupling itself. Reduction of the reaction time resulted in the isolation of only a mixture of starting material and both isomers. Lowering the temperature to 80 °C allowed the reaction to progress to a single, non-isomerised product. Unfortunately, the same problems encountered in the vinyl Stille coupling, with regards to removal of the tin by-products were experienced here. It was at this point that the change to using a Suzuki-Miyaura coupling for the synthesis of the vinyl systems was made. Having observed that using Suzuki-Miyaura chemistry greatly simplified the process of preparing vinylcinnamyl alcohols, similar methodology was investigated for the synthesis of 2'-allylcinnamyl alcohols.

2.2.3.2 Suzuki-Miyaura route to allylic alcohols

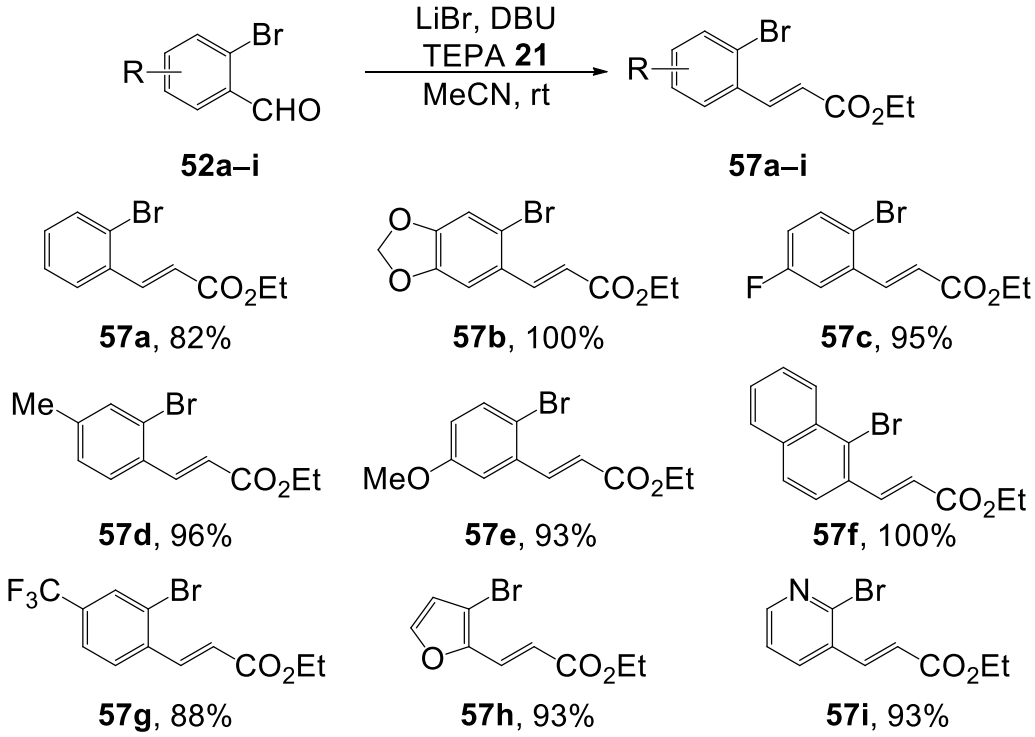
Examining the literature around the planned allyl-Suzuki-Miyaura coupling highlighted two points. Firstly, using the potassium allyltrifluoroborate would most likely yield the internal isomer of the olefin **55**[82] and secondly, that performing the Suzuki-Miyaura coupling before the HWE reaction would give a competing side reaction between the allyl borate and the aldehyde and lead to homoallylic alcohols such as **56** (Scheme 37).[83–85]



Scheme 37: Expected problems with performing the Suzuki-Miyaura reaction as the 1st step of synthesis.

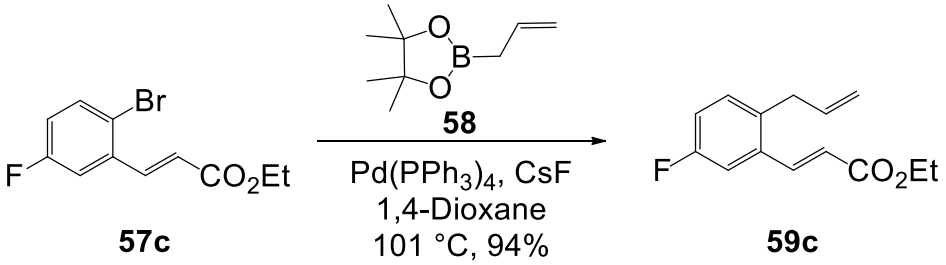
To circumvent these issues it was decided that the HWE reaction would be performed first, followed by the Suzuki-Miyaura reaction using allylboronic acid pinacol ester (**58**). This boronate ester is both commercially available and easily synthesised.[86,87]

The HWE reaction proceeded in high yields under the same conditions used for the 2'-vinylcinnamyl alcohol synthesis, with no optimisation necessary, and again yielded the *E*-isomers as the sole product (Scheme 38). The starting material, **52h**, for the furan-derived analogue **57h** was synthesised in a single step by the formylation, under Rieche conditions, of 3-bromofuran with dichloromethyl methyl ether and titanium tetrachloride, in a 96% yield.[88]

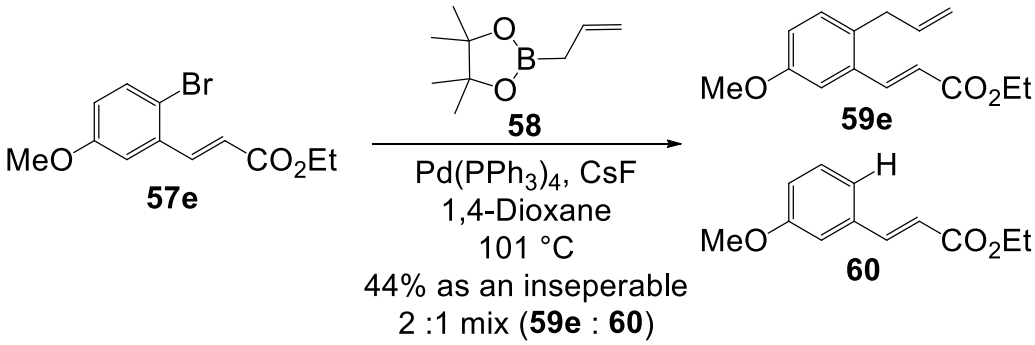


Scheme 38: Results of the HWE reaction of various 2-bromobenzaldehydes.

Under the initial conditions, the Suzuki-Miyaura coupling proceeded in a high yield for electron-poor bromides such as the fluorine containing analogue **57c** (Scheme 39).[89,90] However, optimisation was needed before it could be applied to electron-rich substrates. It was observed that, under the conditions utilised for the electron-poor analogues, an inseparable mixture of product **59e** and proto-dehalogenated side-product **60** was obtained (Scheme 40 and Table 9, entry 1).



Scheme 39: Suzuki-Miyaura coupling of electron-poor aryl bromide.



Scheme 40: Initial problems with Suzuki-Miyaura coupling on electron-rich aryl bromide 57e.

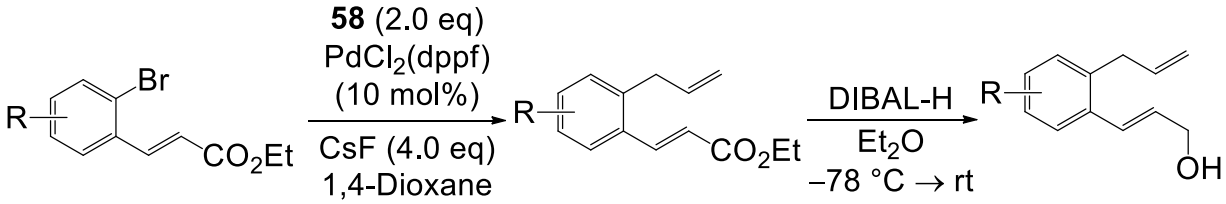
Initially, changing the catalyst to dichloropalladium(II) diphenylphosphinoferrocene was attempted; this gave both an increase in yield and a decrease in debromination (entry 2). It was then observed that at lower temperatures, debromination was completely halted with either catalyst, but that the reaction now no longer proceeded to completion (entries 3 and 4). The number of equivalents of allylboronic acid pinacol ester (**58**) was then increased, raising the conversion to **59e** and the yield to near quantitative levels (entries 5 and 6).

Entry	Catalyst	Equivalents of **58**	Temperature /°C	Time /h	Yield /%[a]	Ratio of **57e**:**59e**:**60**[b]
1	$Pd(PPh_3)_4$	1.5	101	18	44	0:2:1
2	$PdCl_2(dppf)$	1.5	101	18	85	0:10:1
3	$Pd(PPh_3)_4$	1.5	85	24	84	2:3:0
4	$PdCl_2(dppf)$	1.5	85	24	86	3:7:0
5	$PdCl_2(dppf)$	4.0	85	24	98	0:1:0
6	$PdCl_2(dppf)$	2.0	85	24	99	0:1:0

Table 9: Optimisation of Suzuki-Miyaura chemistry for 59e. [a]Yield of mixture of products 59e and 60. [b]Calculated from ^{1}H NMR spectra of purified mixture.

These optimised conditions were then applied to the synthesis of the other analogues (Table 10). Performing the Suzuki-Miyaura coupling and then reducing the ester with DIBAL-H allowed access to a group of nine 2'-allylcinnamyl alcohols in very high yields over the three steps. A small amount of modification of the

optimised conditions was required for the synthesis of the naphthyl-derived analogue **59f** (Table 10, entry 6). Performing the Suzuki-Miyaura coupling at 101 °C and increasing the number of equivalents of **58** to 2.5 gave a quantitative yield of **59f**. This was necessary due to the extra steric hinderance of the second ring. The pyridine-derived analogue **57i** did not perform as well in the Suzuki-Miyaura coupling and suffered from increased proto-dehalogenation (entry 9). However, unlike the other analogues, the desired product **59i** could be separated from the side-products by column chromatography.



57a–i **59a–i** **61a–i**

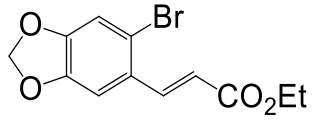
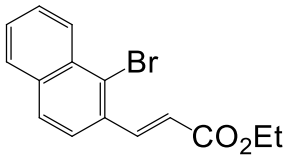
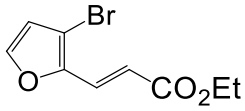
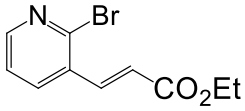
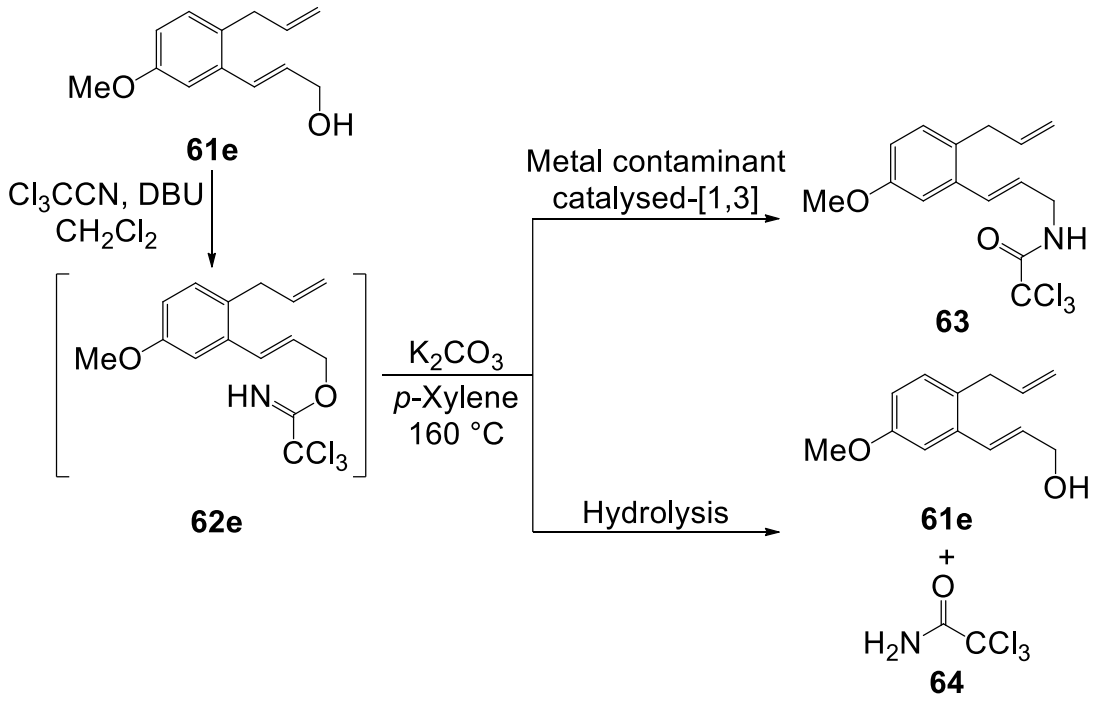
Entry	**57**	**59** (%)	**61** (%)
1	R = H **57a**	**59a** (100)	**61a** (81)
2	 **57b**	**59b** (100)	**61b** (97)
3	R = 5-F **57c**	**59c** (98)	**61c** (92)
4	R = 4-Me **57d**	**59d** (99)	**61d** (88)
5	R = 5-OMe **57e**	**59e** (99)	**61e** (82)
6	 **57f**	**59f** (98)[a]	**61f** (93)
7	R = 4-CF_3 **57g**	**59g** (100)	**61g** (93)
8	 **57h**	**59h** (100)	**61h** (96)
9	 **57i**	**59i** (77)	**61i** (88)

Table 10: Optimised yields for the synthesis of 2'-allylcinnamyl alcohols. [a]Reaction performed at 100 °C with 2.5 eq of 58.

2.2.4 A one-pot multi-reaction process to form amidodihydronaphthalenes

The initial attempts at performing the one-pot multi-reaction process on the 2'-allylcinnamyl alcohols were based around the optimised conditions for the synthesis of amidoindenes. However, while optimising these conditions, a side-*product was formed in as much as a 2:1 ratio versus the desired product. The ^{1}H NMR spectra of this side-product showed that it was closely related to both the allylic alcohol **61e** and the allylic imidate **62e** and was always accompanied by a broad doublet corresponding to the NH_2 group of trichloroacetamide (**64**). It was thought that this impurity could be one of two compounds: the product of [1,3]-rearrangement, the allylic trichloroacetamide **63** (Scheme 41, top path); or the product of hydrolysis of the imidate back to the allylic alcohol **61e** and trichloroacetamide (**64**) (Scheme 41, bottom path).



Scheme 41: Possible decomposition routes in Overman rearrangement.

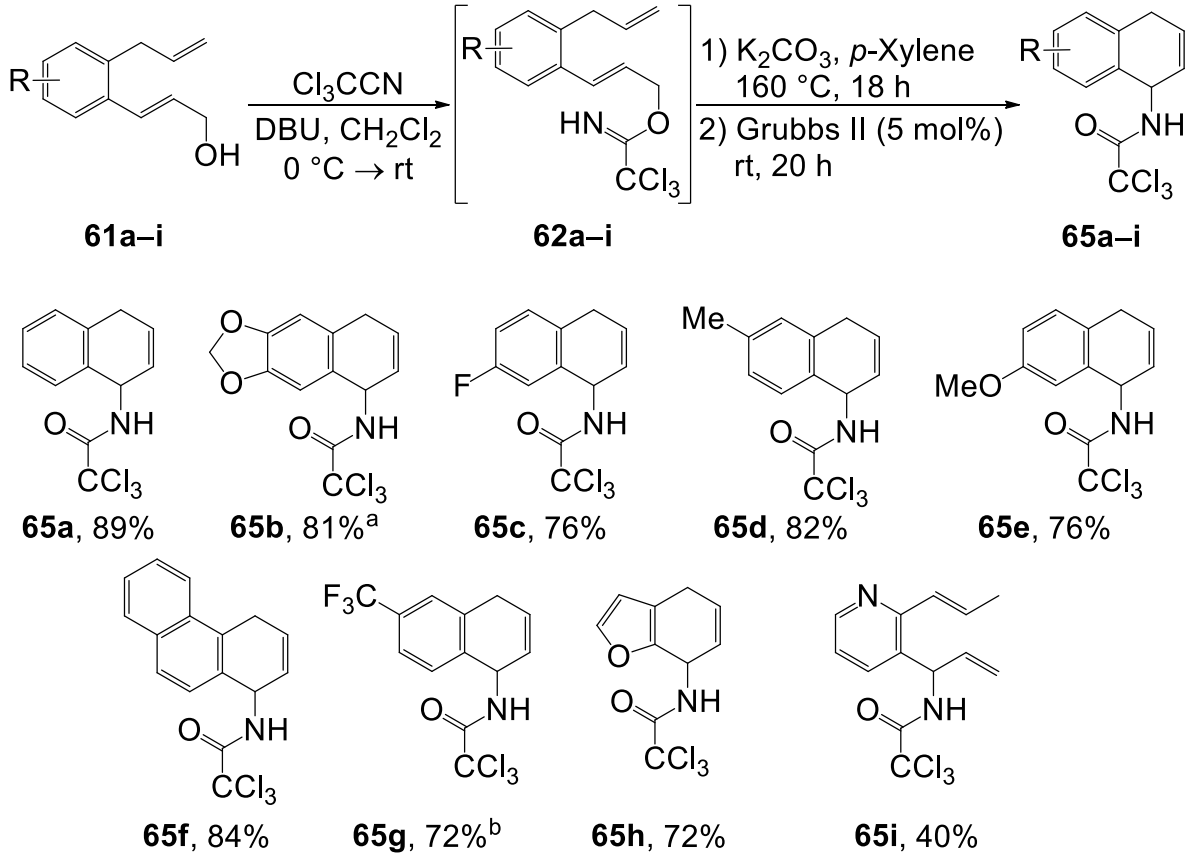
The [1,3]-rearrangement is a known reaction under palladium(0)-catalysed Overman conditions or in the presence of catalytic quantities of acid.[10] However, isolation of a [1,3]-product under thermal Overman conditions in the presence of potassium carbonate is unprecedented; this meant a metal contaminant would have had to be present for the [1,3]-reaction to have occurred. To minimise the chances of the side-product coming from small quantities of metal contaminants

on the Schlenk tubes, the reaction was carried out in a previously unused microwave vial. This had no effect on the ratio of product to side-product.

To investigate the possibility of the side-product coming from hydrolysis of the imidate, 5 Å molecular sieves were added to the Overman rearrangement step. This improved the ratio of product to side-product from 1:2 to 2:1. Following this observation, a fresh bottle of anhydrous *p*-xylene was purchased. It was also observed, during this investigation, that the imidate formation was complete in only one hour and that, especially in the case of the electron-rich analogues, prolonging this step or not using the imidate quickly after its synthesis, gave a lower ratio between [3,3]-product and the side-product. In the optimised process, the allylic alcohol was dried under high vacuum before use, the imidate formation was carried out in one hour and the imidates were kept dry and used rapidly. These changes prevented hydrolysis of the imidate and hence greatly improved the yield of the reaction.

Using the optimised conditions for the imidate formation and one-pot process, it was possible to synthesise eight of the target molecules (Scheme 42). The process tolerates both electron-rich and -poor systems with little change in yield. In the case of the piperonyl-derived analogue **65b** it was shown that, upon scaling up the reaction to 9 mmol, the catalyst loading for this reaction could be lowered to 2.5 mol%. The trifluoromethyl substituted analogue **65g** required two additions of 5 mol% of catalyst over a 48 hour period and heating to 50 °C before the reaction reached completion.

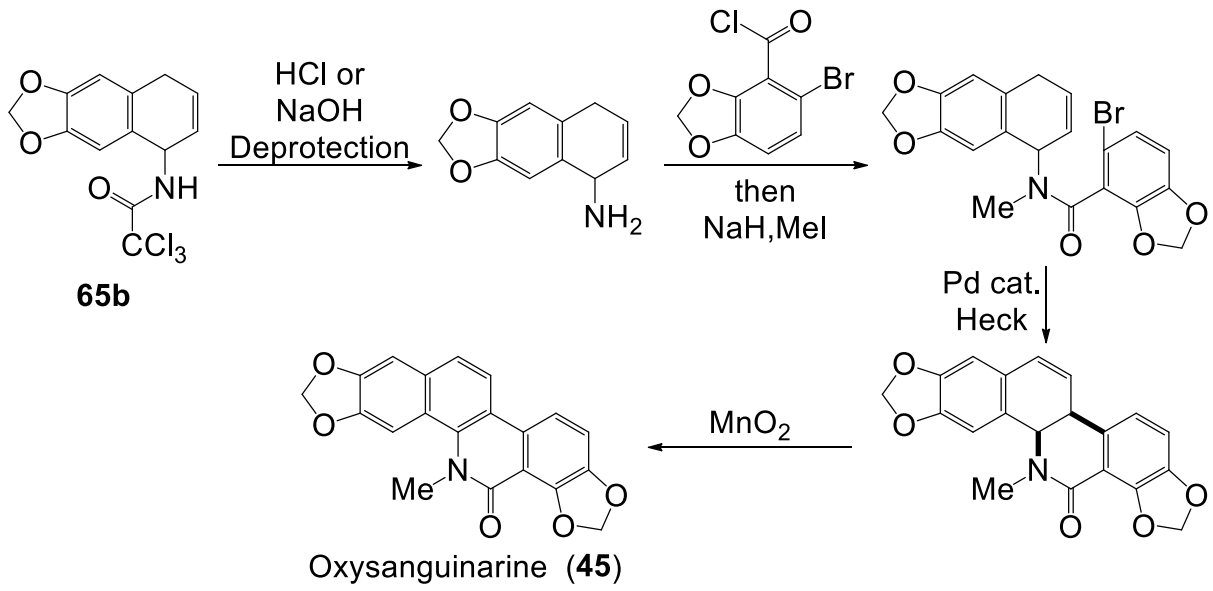
In the case of the pyridine-derived analogue, two problems were encountered. After the Overman rearrangement step it was observed that the alkene of the allyl chain had isomerised to give **65i**. This problem was not investigated further, however, as when RCM was attempted on this compound, the reaction failed. This is due to the nitrogen of the pyridine ligating the Grubbs 2nd generation catalyst. This is well precedented and can be avoided by using the *N*-alkyl salt, or by making the hydrochloride salt of the pyridine.[91,92] These methods would have required protection of the pyridine at the start of the synthesis as the *N*-alkyl species or the addition of hydrochloric acid between the Overman rearrangement and RCM steps.



Scheme 42: Optimised yields for the one-pot multi-reaction process. [a]The RCM step was performed using 2.5 mol% of Grubbs 2nd generation catalyst. [b]The RCM step required 10 mol% of Grubbs second generation catalyst and was performed at 50 °C over 48 h.

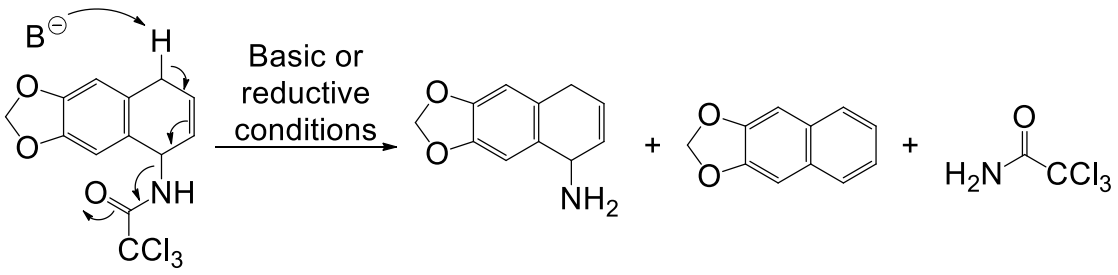
2.2.5 The total synthesis of four oxybenzo[c]phenanthridines

Having demonstrated that a scalable, robust one-pot process had been developed, the next goal was the total synthesis of a number of oxybenzo[c]phenanthridine natural products. Initially, deprotection of the piperonyl-derived product **65b** under the standard acidic or basic conditions was envisioned (Scheme 43). This would then be followed by an amide coupling with a substituted 2-bromobenzoyl chloride and *N*-methylation of this amide. This would give an aryl bromide for use in an intramolecular Heck coupling to give a precursor that could be aromatised to yield oxysanguinarine (**45**).



Scheme 43: Initial approach to oxybenzo[c]phenanthridine natural products.

The proposed first step was to deprotect the amido-dihydronaphthalene **65b**. Under the mildest basic conditions attempted, elimination of the trichloroacetamide moiety was the major product (Table 11). Changing to a more nucleophilic base, such as barium hydroxide, caused a larger quantity of elimination to be observed. However, using acidic deprotection conditions, elimination was the only process observed. Under reductive conditions, that have rarely been used, the elimination process was also the only observed process.[93]



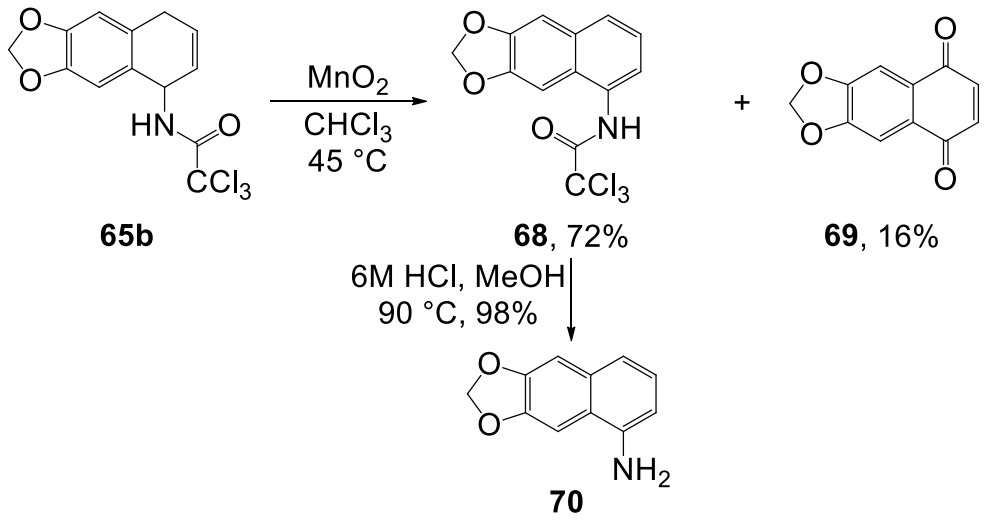
Entry	Reagent	Conditions	**66**:(**67**+**64**)
1	6 M NaOH	65 °C, 48 h	1:1
2	$Ba(OH)_2.8H_2O$	65 °C, 72 h	1:14
3	6 M HCl	65 °C, 48 h	0:1
4	DIBAL-H	−78 °C, 2 h	0:1

Table 11: Results for basic, acidic and reductive deprotections.

As it was clear that there was a significant driving force for **65b** to become aromatic, the synthetic route was altered. By first aromatising **65b** to **68**, it was assumed that the deprotection step would become trivial. Deprotection would now

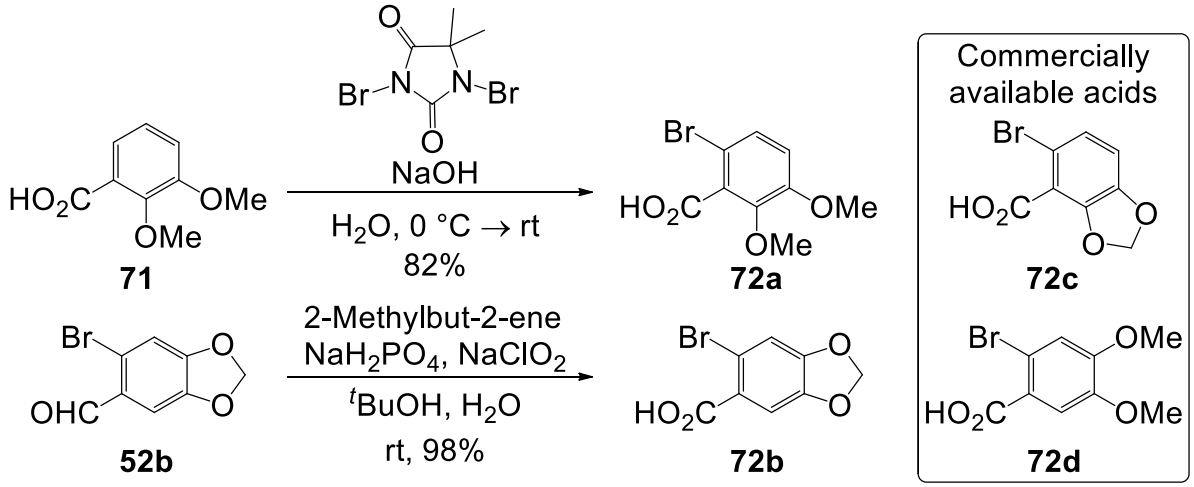
yield a substituted naphthylamine **70** which could then be coupled with a variety of 2-bromobenzoyl chlorides before using a Heck coupling to close the final ring and yield four oxybenzo[c]phenanthridine natural products, through a similar route to that reported by Harayama and co-workers.[94–100]

Indeed, aromatisation of the one-pot process product **65b** proceeded in a high yield with the remainder of the mass made up of the product of benzylic oxidation **69** (Scheme 44). This side-product could not be eliminated, even under strictly degassed conditions or by changing the temperature of the reaction, but was easily separated by column chromatography. Deprotection to the naphthylamine **70** occurred under acidic conditions. The milder basic conditions were not attempted as the acidic conditions gave an almost quantitative yield from the first attempt.



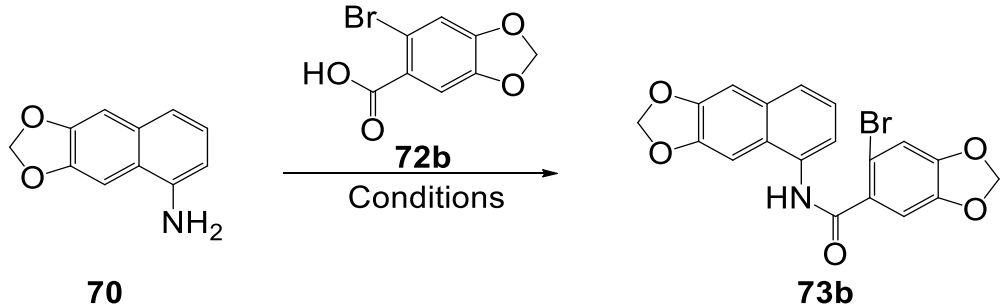
Scheme 44: Aromatisation and deprotection of the one-pot process product.

Four benzoic acids were needed to acess the four oxybenzo[c]phenanthridine targets. Two of these were commercially available, while two had to be synthesised (Scheme 45). The first of these was prepared by *ortho*-bromination[101] of benzoic acid **71** and the other through Pinnick oxidation,[102] from its corresponding 2-bromobenzaldehyde **52b.**



Scheme 45: Syntheses of the two commercially unavailable 2-bromobenzoic acids.

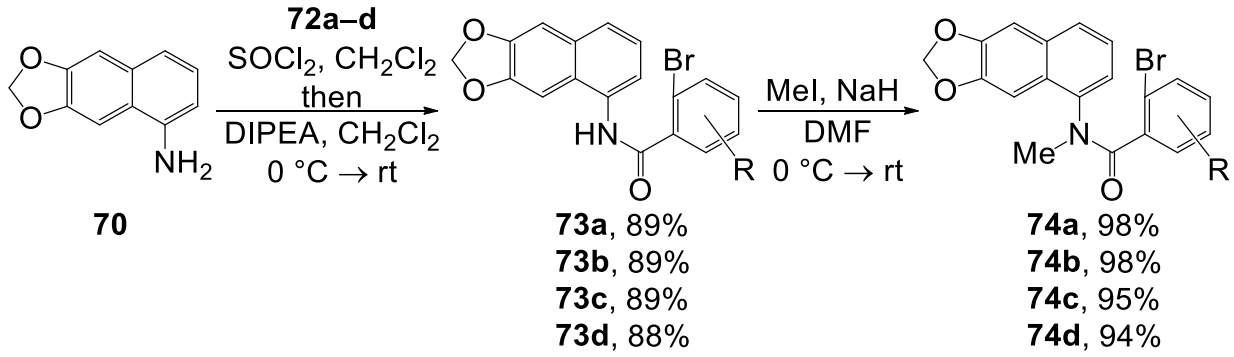
With the amine **70** and acids **72a–d** in hand, the use of a number of coupling agents for the formation of the amides was investigated (Table 12). Optimisation was initially performed with acid **72b**. Using either HBTU or CDI coupling agents returned only starting materials (Table 12, entries 1 and 2) while both EDCI and the triphenylphosphine/DDQ conditions[103] gave low yields (entries 3 and 4). All of these results were attributed to the amine not being sufficiently nucleophilic. Acid chloride formation, followed by reaction with the amine **70** was then investigated. Initially, oxalyl chloride and DMF were tried, but also gave a poor yield (entry 5). It is believed that the DMF may not have been sufficiently dry for these conditions as, when acid chloride formation with thionyl chloride was attempted as the activation step, a yield of 89% was obtained (entry 6).



Entry	Conditions	Yield /%
1	HBTU, DIPEA, 50 °C, 8 days	NR
2	CDI, NEt_3, 70 °C, 19 h	NR
3	EDCI, DMAP, 60 °C, 18 h	18
4	PPh_3, DDQ, rt, 10 mins	20
5	$(COCl)_2$, DMF, NEt_3, 0 °C to rt then 50 °C, 2 h	5
6	$SOCl_2$, DIPEA, 0 °C to rt, 2 h	89

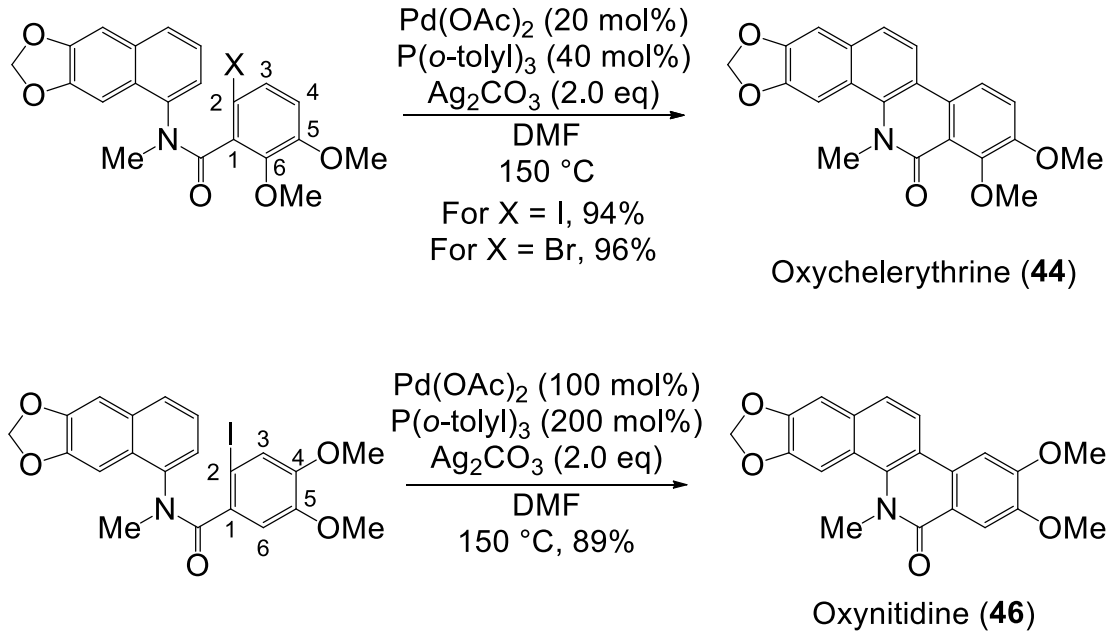
Table 12: Screened conditions for amide coupling.

Having optimised the conditions for amide coupling, they were then applied to the set of four benzoic acids, **72a–d** that would ultimately allow the preparation of four oxybenzo[c]phenanthridine natural products. The amide couplings were then performed under the optimised conditions before methylation with sodium hydride and methyl iodide (Scheme 46).



Scheme 46: Amide formation and *N*-methylation steps.

The group of Harayama has published a number of papers on the intramolecular Heck coupling of similar aryl halides (Scheme 47).[94–100] In their system bromides and iodides, as well as a triflate on one occasion, were used.[95–97] They showed that aryl halides containing a 6-position substituent on the halogenated phenyl ring can undergo the Heck reaction with 20 mol% of palladium(II) acetate and 40 mol% of tri-*ortho*-tolyl phosphine in very high yields.[96] However, in the case of systems that are lacking this 6-position substituent, they were forced to use stoichiometric quantities of palladium and two equivalents of ligand, even when using the more reactive iodide.[97] This marked change in reactivity can be explained by envisioning the conformation that these compounds must adopt for the reaction to occur. In the case of the 6-substituted compounds, such as those leading to oxychelerythrine (**44**), there will be steric repulsion between the 2-position- or the 6-position-substituent and the hydrogen at the reaction centre of the other ring. This must be overcome for the reaction to occur, hence the high temperatures. However, in the case of the substrates lacking in a 6-position substituent, the 6-position is now, relative to the 2-position, unhindered. This leads to an unfavourable pre-organisation within the molecule, where the halide is preferentially kept away from the naphthyl ring system, resulting in the lower reactivity of these substrates.



Scheme 47: Work by Harayama and co-workers on the Heck reaction for the synthesis of oxybenzo[c]phenanthridine natural products.[96-98]

Early attempts in this project followed the precedent of Harayama and co-workers closely.[96–98] For the synthesis of oxychelerythrine (**44**), from **74a**, it was possible to use the palladium(II) acetate and tri-*ortho*-tolyl phosphine conditions and achieve a yield of 97%. However, upon attempting Harayama's conditions for the synthesis of oxynitidine (**46**), using the less reactive bromide **72d**, no product was obtained. It was clear that the bromides, lacking a 6-position substituent, could not be used with Harayama's conditions while obtaining a good yield of product.

Instead, it was decided to change the catalyst. One of the problems that had been noted, upon attempts at using Harayama's conditions for the synthesis of oxynitidine, was that palladium black was precipitating from the solution within 30 minutes of the mixture reaching reaction temperature. With this in mind, a catalyst with similar properties to the tri-*o*-tolyl phosphine/palladium(II) acetate mixture, that would have better longevity at high temperatures, was desirable. The Herrmann-Beller palladacycle fits these traits (Figure 8).[104,105] This palladacycle catalyst has been used for sterically congested Heck and Suzuki-Miyaura couplings at high temperature, has a slower release of the active palladium(0) species and has been shown to have a greater stability at these increased temperatures than the palladium(II) acetate/tri-*o*-tolyl phosphine combination system that it derives from.

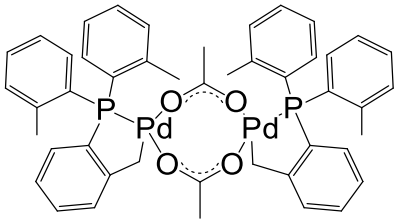
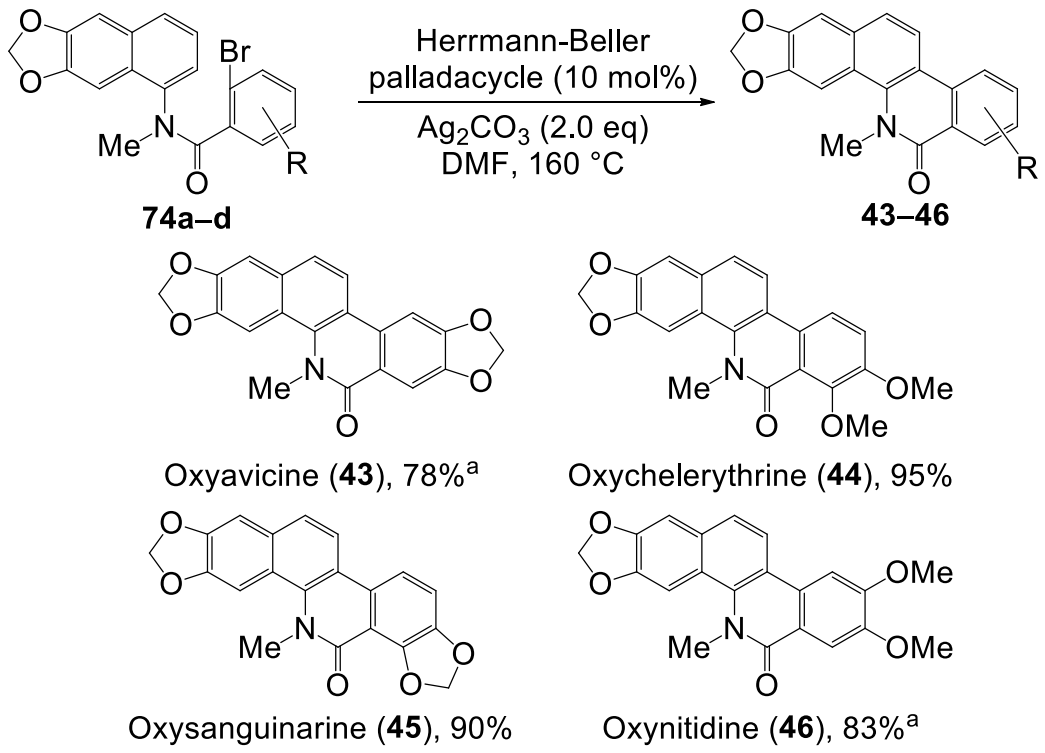


Figure 8: The structure of the Herrmann-Beller palladacycle.

Using this catalyst, the desired biaryl Heck coupling with all four of the aryl bromides was performed (Scheme 48). These reactions took a varying amount of time and, in the case of the two analogues lacking a 6-position substituent, required a slightly higher catalyst loading. This allowed access to oxyavicine (**43**), oxychelerythrine (**44**), oxysanguinarine (**45**) and oxynitidine (**46**) in 11 steps and 38%, 46%, 42% and 38% overall yields, respectively.



Scheme 48: Final step in the synthesis of oxyavicine, oxychelerythrine, oxysanguinarine and oxynitidine. [a]20 mol% of the Herrmann-Beller palladacycle used.

2.2.6 Conclusions

A highly efficient and easily scalable three step synthesis of 2'-vinyl and 2'-allylcinnamyl alcohols has been developed. These cinnamyl alcohols have been used to prepare the corresponding allylic trichloroacetimidates which are the

starting materials for a one-pot multi-reaction process involving an Overman rearrangement and ring closing metathesis. This one-pot process has been optimised to allow the high yielding synthesis of six amidoindenes and eight amido-1,4-dihydronaphthalenes. One of these amido-1,4-dihydronaphthalenes has then been progressed through a divergent five-step route to allow the synthesis of four oxybenzo[c]phenanthridine natural products in a total of 11-steps and between a 38% and 46% overall yield.

Chapter 3 Development of a One-Pot Multi-Reaction Process: The Synthesis of Amido Benzoxepine scaffolds

3.1 Introduction

3.1.1 Benzoxepines in drug molecules

The benzoxepine framework is found in a number of natural products and biologically active molecules.[106–109] One example of this is pterulone (**75**), which was shown to have antibiotic qualities (Figure 9).[106–108] The 5-amino-1-benzoxepines are a pharmaceutically relevant sub-class of the benzoxepines containing compounds such as pyrrolidin-2-one substituted benzoxepine **76**, which is a weak potassium channel activator and smooth muscle relaxant.[110] Other examples include an inhibitor of human cytomegalovirus (HCMV) **77**,[111] which is active at micromolar levels, a class of acyl-CoA, cholesterol *O*-acyl transferase (ACAT) inhibitors based around the core **78** and a sub-micromolar Src homology 2 domain binder **79**.[112]

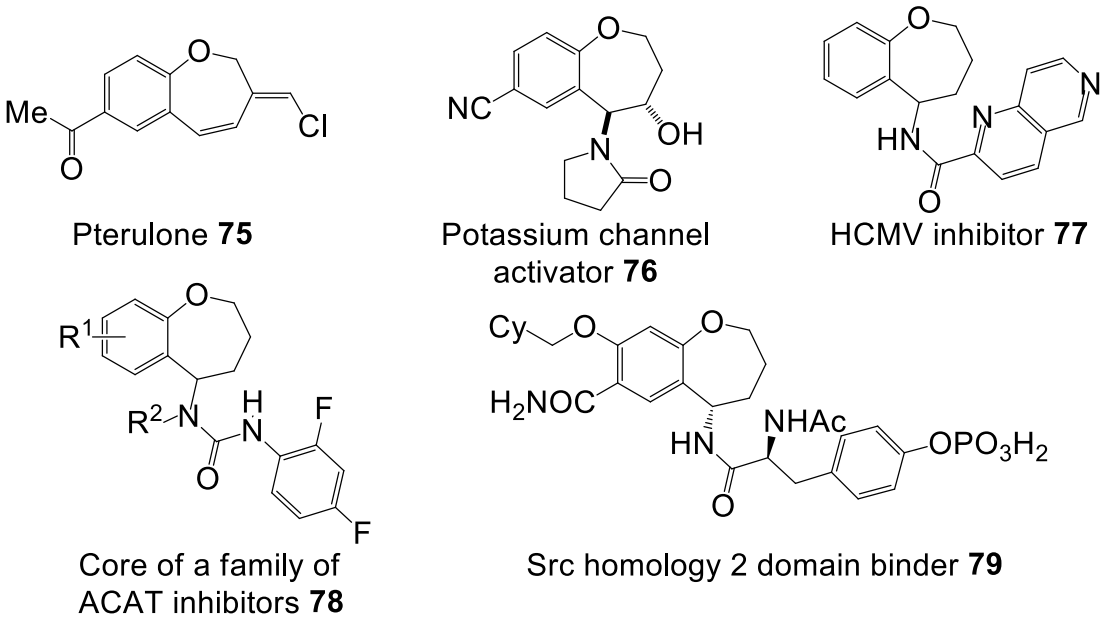
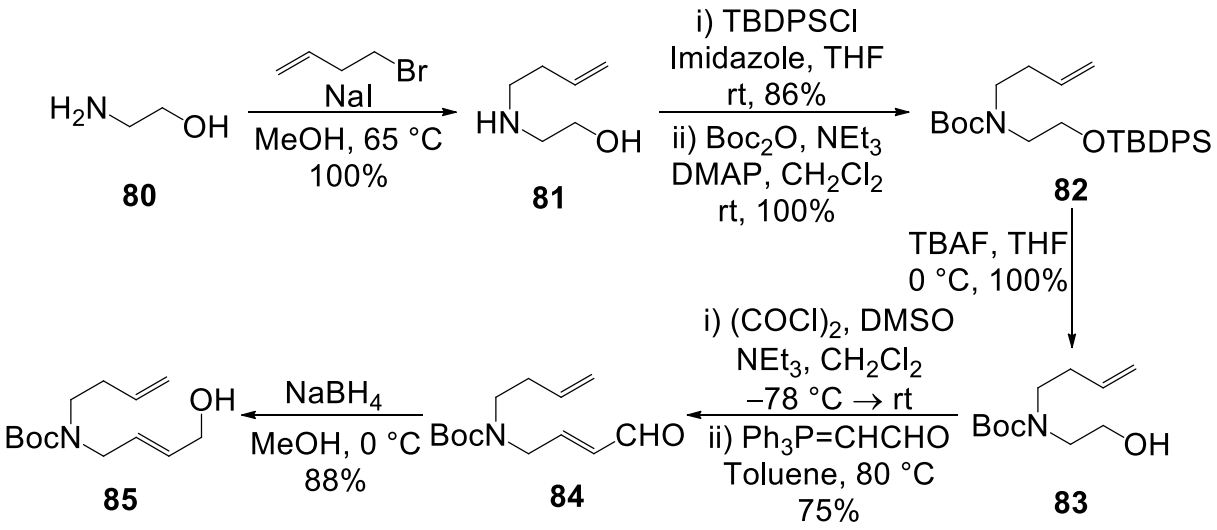


Figure 9: Examples of the benzoxepine scaffold in natural products and biologically active compounds.

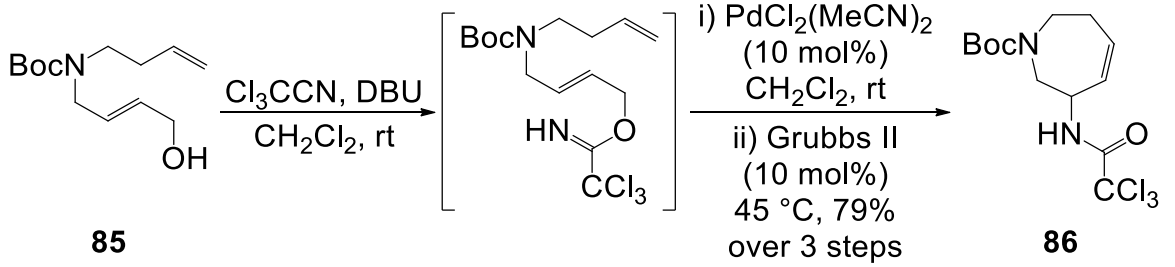
3.1.2 Previous work within the group on heterocyclic scaffolds

As previous work within the Sutherland group had developed a rapid route to cyclic allylic amides with an all-carbon ring system, an obvious extension was to include a heteroatom in the backbone of the compounds. To synthesise the required allylic alcohols for this one-pot process, a different route had to be utilised (Scheme 49).[113] Starting from 2-aminoethanol (**80**) and selectively alkylating the amine gave alcohol **81**. This alcohol was then protected as the TBDPS ether to allow Boc protection of the secondary amine, granting access to compound **82**. Deprotection of the alcohol with TBAF returned primary alcohol **83,** which was then used in a one-pot Swern/Wittig reaction to yield the α,β-unsaturated aldehyde **84**. This was reduced with sodium borohydride in methanol to give the desired allylic alcohol **85**. The standard approach within the group of using a one-pot Swern/HWE with triethyl phosphonoacetate (**21**) followed by DIBAL-H reduction of the resulting ester was attempted, but gave a complex mixture of compounds. This was attributed to a 1,4-addition competing with the 1,2-reduction of the α,β-unsaturated ester, which could occur through complexation of the metal hydride with the heteroatom.[114]



Scheme 49: Synthesis of the allylic alcohol 85 for a heterocyclic variant of the one-pot process.

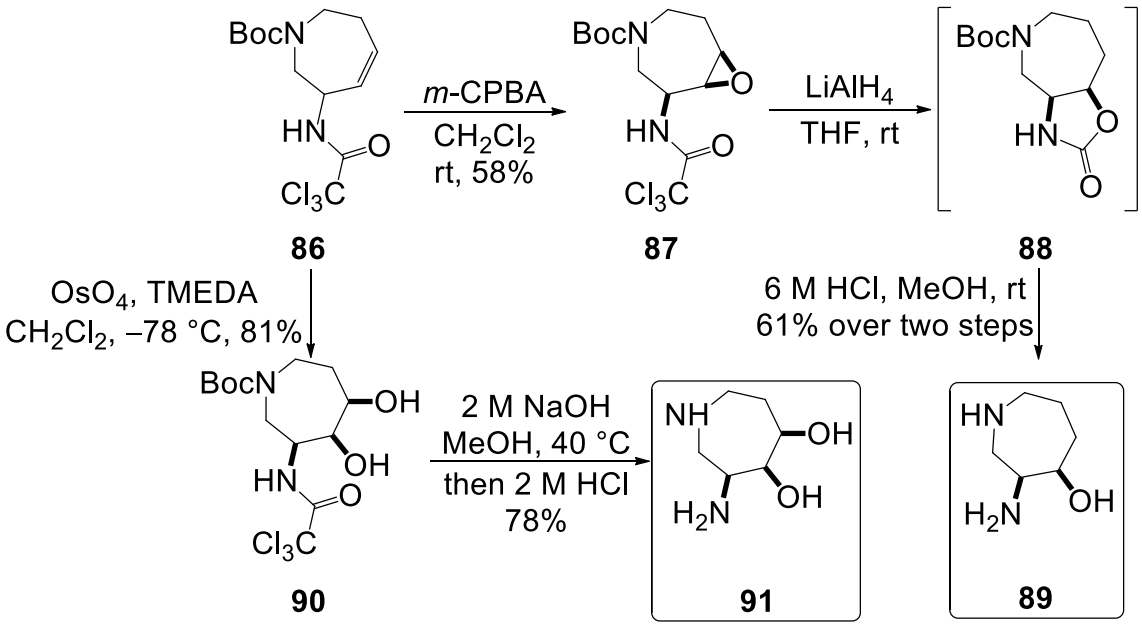
Having successfully synthesised the heteroatom containing allylic alcohol **85** it was then transformed to the corresponding allylic trichloroacetimidate using trichloroacetonitrile and DBU in dichloromethane (Scheme 50). The imidate was then used in a one-pot palladium(II)-catalysed Overman rearrangement and RCM sequence to form the 7-membered nitrogen containing cyclic allylic amide **86**.



85 **86**

Scheme 50: Heteroatom containing variant of one-pot Overman/RCM process.

As cyclic allylic amides are known to be good substrates for directed epoxidation and dihydroxylation reactions, the further functionalisation of the one-pot Overman/RCM products was investigated. Starting from the Boc-protected one-pot process product **86**, epoxidation using *m*-CPBA yielded the *cis*-epoxide **87**.[115] This was then treated with lithium aluminium hydride to open the epoxide and form the *cis*-oxazolidinone **88.** Without further purification the oxazolidinone was hydrolysed and the Boc protecting group removed with hydrochloric acid in methanol to give the *cis*-3-aminoazepin-4-ol **89**. To form the *cis*-diol, directed dihydroxylation of the one-pot process product **86** under the Donohoe conditions with OsO_4 and TMEDA was used.[116] This gave the all *cis*-diol amide **90**. This was deprotected by hydrolysis under basic conditions to cleave the trichloroacetamide and then acidic conditions to remove the Boc group, to give the *cis*-3-aminoazepin-4,5-diol **91**.

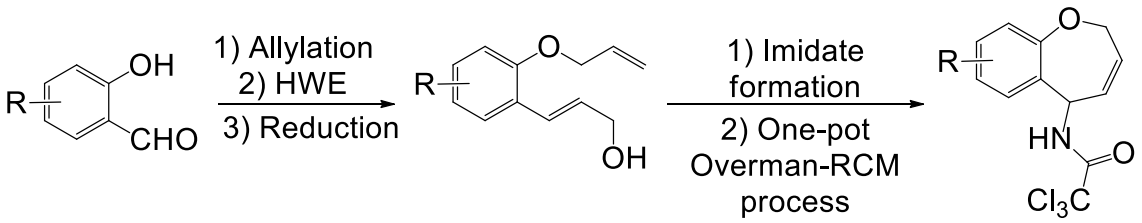


86 **87** **88** **90** **91** **89**

Scheme 51: Previous work on oxidation of one-pot Overman/RCM process products.

3.1.3 Aims

The aim of this project was to optimise the previously developed one-pot multi-reaction process to allow the synthesis of a series of amido-substituted dihydrobenzoxepines (Scheme 52). This methodology would then be applied to the synthesis of a benzoxepine-containing ACAT inhibitor and a number of biologically active hydroxylated amidotetrahydrobenzoxepine scaffolds.

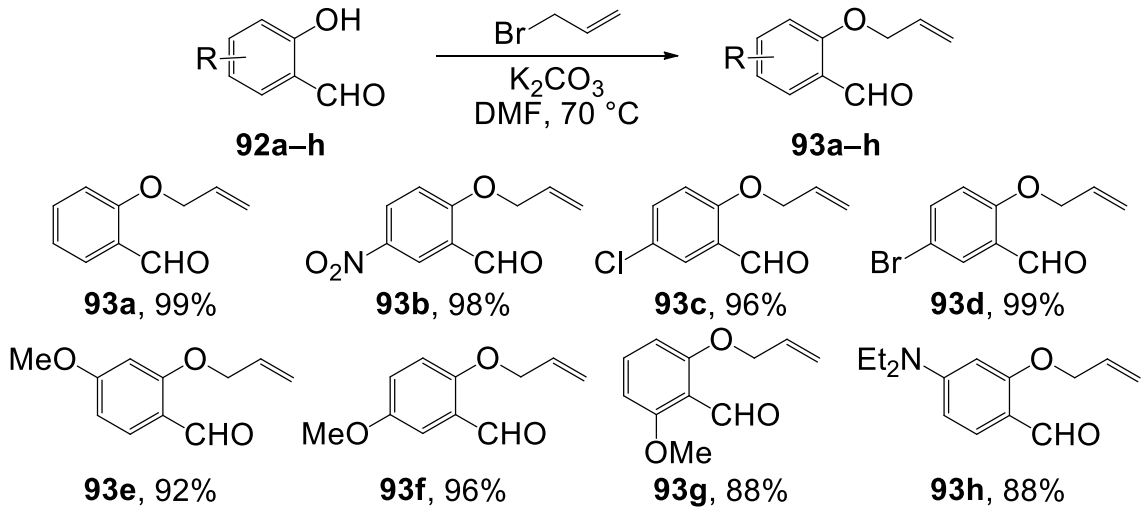


Scheme 52: Proposed access to 2'-allyloxy cinnamyl alcohols and use in one-pot multi-reaction process to form 5-amido-2,5-dihydrobenzoxepines.

3.2 Results and discussion

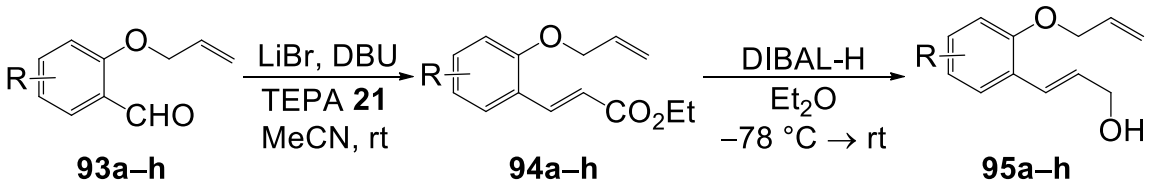
3.2.1 A rapid synthesis of 2'-allyloxycinnamyl alcohols

As for the 5- and 6-membered ring forming processes (Section 2.2), a rapid route to the 2'-substituted cinnamyl alcohols was necessary. For the formation of the oxygen-containing 7-membered ring, a 2'-allyloxy substituent was required. To attach this, allylation of a range of 2-hydroxybenzaldehydes **92a–h** with allyl bromide was carried out (Scheme 53).[117] This method of allylation is fast, high yielding and requires only an aqueous work-up to isolate the product. The chosen analogues allowed testing of the scope of the synthesis and the one-pot process. They included a very electron-poor, nitro-substituted analogue **93b** and a very electron-rich diethylamine-substituted analogue **93h**. Analogues **93c** and **93d** were included as they would allow for further functionalization of the ring system after the one-pot process. The three methoxy-substituted analogues **93e–g** were used to probe if there would be a difference in the synthesis, or the one-pot process, if the substituents were moved between the *ortho*-, *meta*- or *para*-positions.



Scheme 53: Allylation of 2-hydroxybenzaldehydes.

Having synthesised a number of 2-allyloxybenzaldehydes **93a–h** in very high yields, an HWE reaction under the Masamune-Roush conditions was used to form the *E*-cinnamates **94a–h** (Table 13). With these in hand, DIBAL-H reduction yielded the desired 2'-allyloxy cinnamyl alcohols **95a–h**. This methodology allowed extremely rapid access to the eight desired compounds in very high yields.

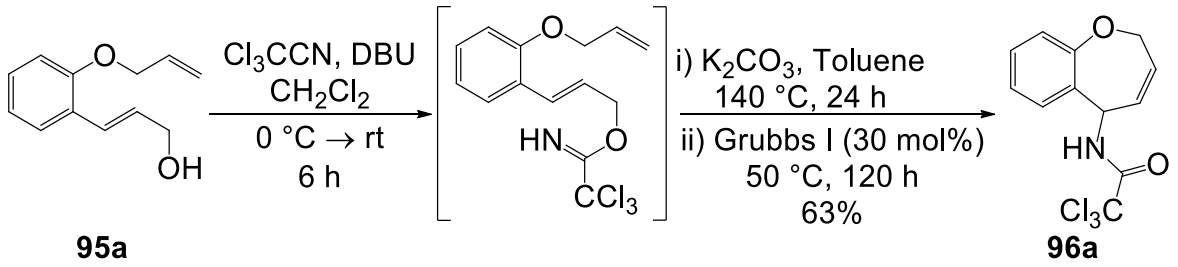


Entry	**93**	**94** (%)	**95** (%)
1	R = H, **93a**	**94a** (95)	**95a** (87)
2	R = 5-NO_2, **93b**	**94b** (91)	**95b** (88)
3	R = 5-Cl, **93c**	**94c** (92)	**95c** (95)
4	R = 5-Br, **93d**	**94d** (97)	**95d** (90)
5	R = 4-OMe, **93e**	**94e** (100)	**95e** (100)
6	R = 5-OMe, **93f**	**94f** (100)	**95f** (83)
7	R = 6-OMe, **93g**	**94g** (85)	**95g** (90)
8	R = 4-NEt_2, **93h**	**94h** (95)	**95h** (92)

Table 13: Optimised yields for the synthesis of 2'-allyloxy cinnamyl alcohols.

3.2.2 A one-pot multi-reaction process to form 5-amido-2,5-dihydrobenzoxepines

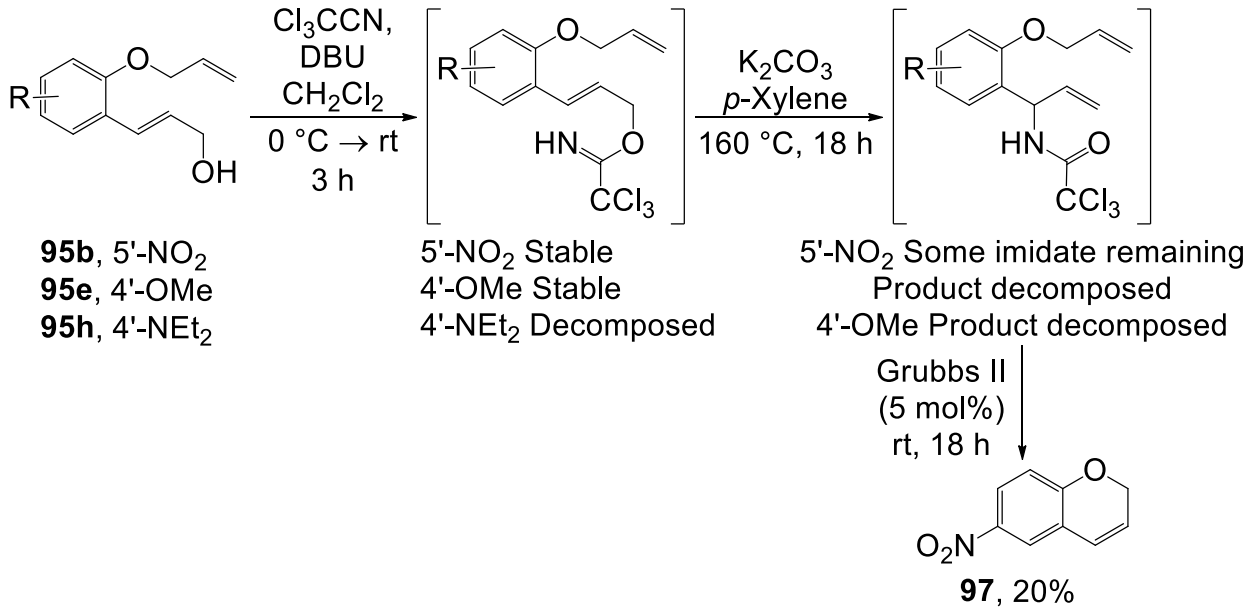
Although results previously obtained within the group provided a good basis for the optimisation of the one-pot process, there was still the opportunity for further improvement (Scheme 54).[81] In particular, the 30 mol% loading of Grubbs 1st generation catalyst and the five day reaction time for the RCM step were seen as points for optimisation.



95a **96a**

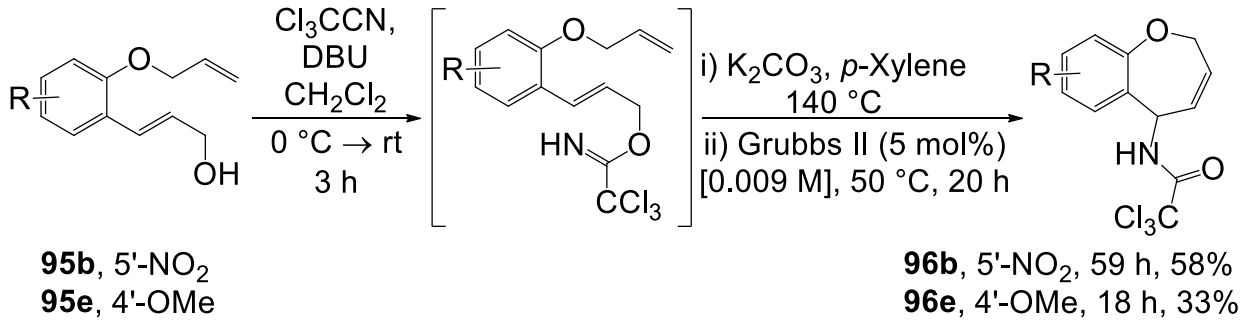
Scheme 54: Previous attempt at one-pot process (McGonagle, unpublished data).[81]

In the development of the one-pot process for the synthesis of amidoindenes, it had been observed that raising the temperature of the Overman rearrangement reaction to 160 °C contributed to a much higher yield than had been previously reported (Scheme 34, Section 2.2.2). Attempting to increase the temperature to 160 °C with the first three analogues synthesised (**95b**, **95e** and **95h**) resulted in the decomposition of all three (Scheme 55). In the case of **95h**, the imidate decomposed as soon as it was synthesised. The imidates of **95b** and **95e** were both found to be more stable. However, after heating to 160 °C for 18 hours then performing RCM with Grubbs 2nd generation catalyst at room temperature overnight, nothing could be isolated from the reaction of **95e**, while **95b** had ring-closed to form a six-membered ring containing compound **97**. In both cases this was presumably the result of the imidate starting materials and amide products of the Overman rearrangement being unstable at the reaction temperature, while the imidate of **95b** rearranges and decomposes at a slower rate and so is still present after 18 hours and is ring closed to form **97**.



Scheme 55: First attempts at optimising the one-pot process for the synthesis of benzoxepines.

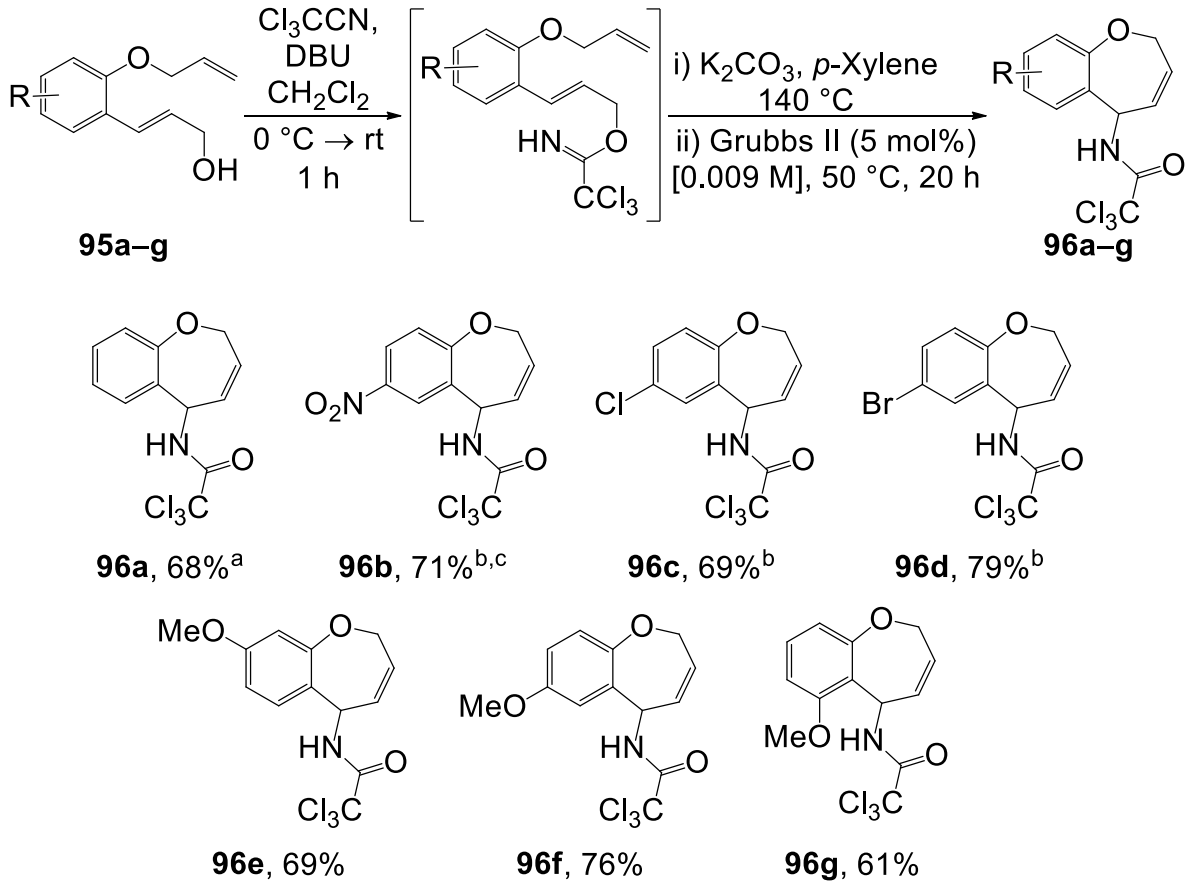
At this point, **95h** was abandoned as the imidate was too unstable to use. For the two other analogues the Overman rearrangement was performed at 140 °C (Scheme 56). It was observed that there was a very strong relationship between the electronics of the aryl ring and the rate of the Overman rearrangement. In the case of the nitro-containing analogue **96b,** the reaction required 59 hours at 140 °C to proceed to completion, while the methoxy-substituted compound **96e** needed only 18 hours at the same temperature. It was also found that increasing the temperature of the RCM step from room temperature to 50 °C improved the cleanliness of the reaction.



Scheme 56: Optimisation of one-pot process for amidobenzoxepine synthesis.

During the optimisation of this process, it was noticed that when the imidate formation was left for any longer than three hours, there was a large decrease in overall yield. Following this observation, the duration of the imidate formation was reduced to one hour and the yields for all analogues increased (Scheme 57). In

particular, the yields for the electron-rich analogues showed the greatest increases. It was found that all of the electron-poor analogues, **96b–d**, required longer reaction times and, to drive the nitro-substituted analogue to completion, a second addition of Grubbs 2nd generation catalyst was necessary.

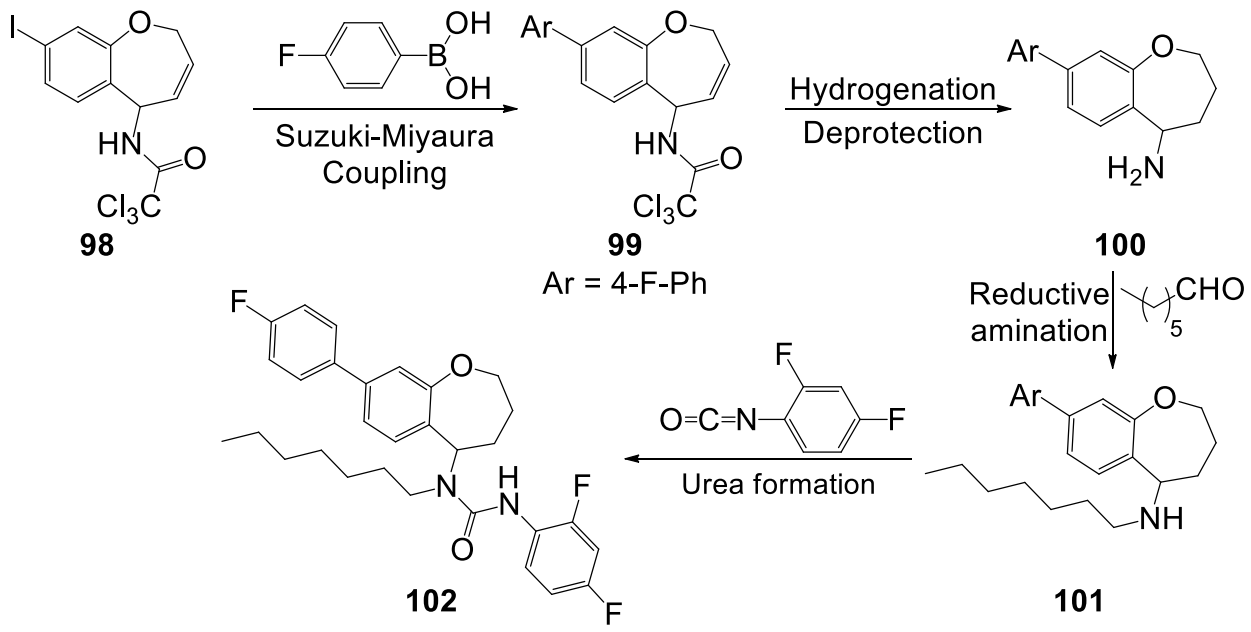


Scheme 57: Optimised yields for the one-pot multi-reaction process. [a]Performed by Salaheddin Sharif in the group, included for completeness. [b]The Overman rearrangement required an extended reaction time (59 h, 96b and 96c, 48 h, 96d). [c]7.5 mol % of Grubbs 2nd generation catalyst was used for the RCM step.

3.2.3 An altered route for the partial synthesis of a drug target

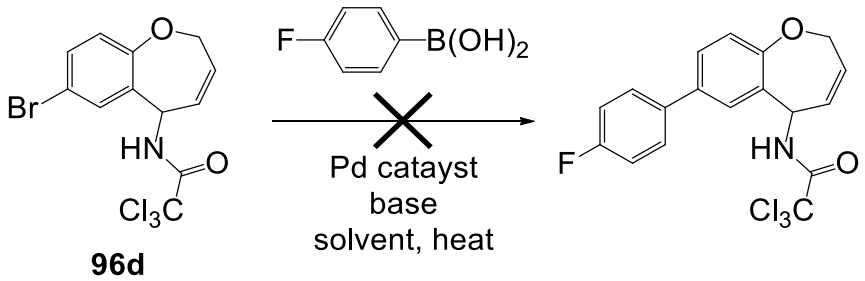
Having shown the generality of this process, the next aim was to apply it to the synthesis of a biologically relevant molecule. The target chosen was the ACAT inhibitor **102** (Scheme 58). It was initially proposed that Suzuki-Miyaura coupling of a halogen-containing product of the one-pot process **98** would allow direct, late-stage formation of the biaryl system, **99**. This could then be followed by selective hydrogenation to remove the alkene without dechlorinating the trichloroacetamide. The amine would be deprotected to give **100** before being reductively aminated with heptaldehyde to give **101** and coupled with an isocyanate to give the target

compound **102**. This method would allow a great deal of flexibility in the groups attached to the core and would therefore be of interest for the synthesis of a family of compounds related to the ACAT inhibitor **102**.



Scheme 58: Proposed synthesis of ACAT inhibitor 102.

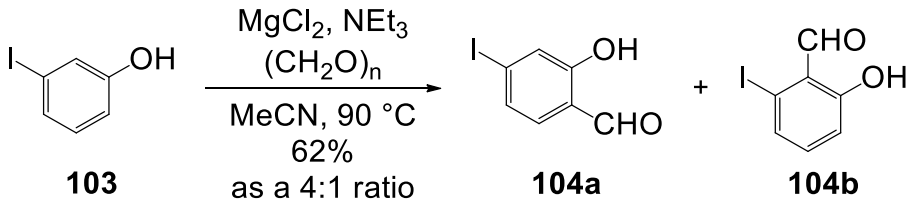
As the 7-bromo-substituted compound **96d** had already been made, a few attempts at this reaction sequence were carried out using it as a model substrate (Scheme 59). However, it was found that under all conditions attempted, the Suzuki-Miyaura coupling would not proceed and only returned starting materials, protodehalogenated starting material or complex mixtures.



Scheme 59: Attempted Suzuki-Miyaura coupling of 96d and 4-fluorophenylboronic acid.

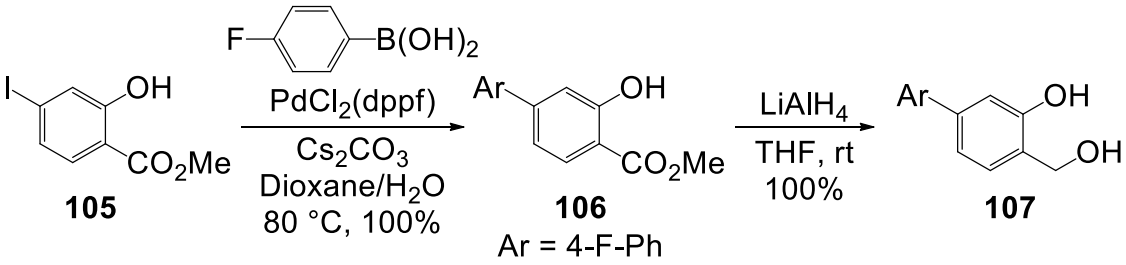
Instead the synthetic route was redesigned to place the formation of the biaryl system near the start of the route, hopefully leading to fewer complications in the later parts of the project. The new route required the synthesis of 2-hydroxy-4-iodobenzaldehyde (**104a**) by formylation of 3-iodophenol (**103**, Scheme 60).[118–120] Although this method of synthesising **104a** showed some promising initial results,

the formation of the 1,2,3-substituted isomer **104b** in significant quantities, which could not be separated from the desired product **104a** without significant loss (isolated yields of **104a** were less than 25%), led to this route being abandoned.



Scheme 60: Formylation of 3-iodophenol 103.

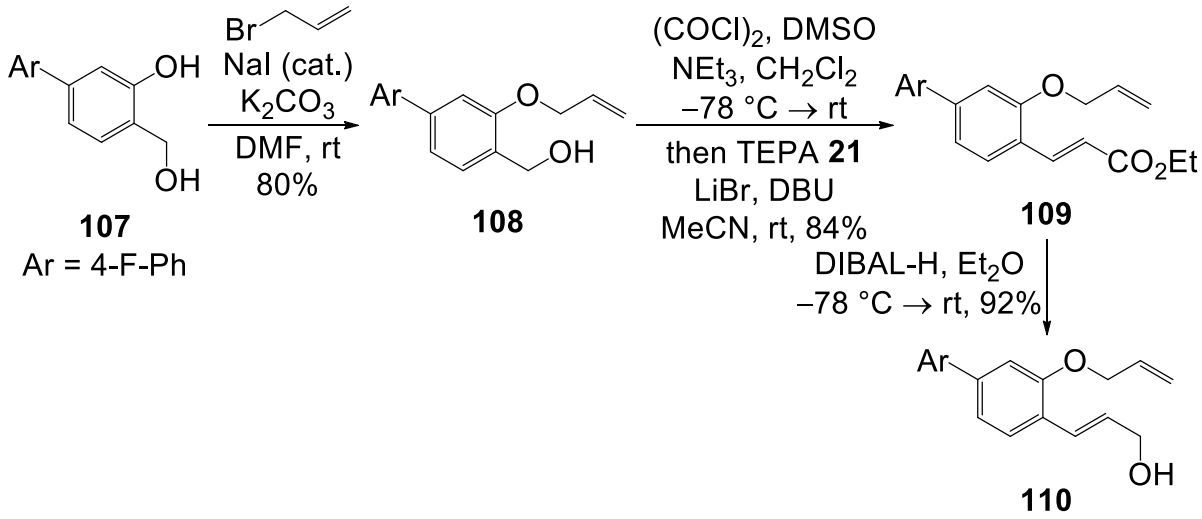
Instead, starting from the commercially available methyl 2-hydroxy-4-iodobenzoate (**105**) and performing a Suzuki-Miyaura coupling with 4-fluorophenylboronic acid gave quantitative access to biaryl compound **106** (Scheme 61).[121] This was then reduced with lithium aluminium hydride to the corresponding benzyl alcohol **107** in quantitative yield.



Scheme 61: Suzuki-Miyaura coupling and $LiAlH_4$ reduction to synthesise benzyl alcohol 107.

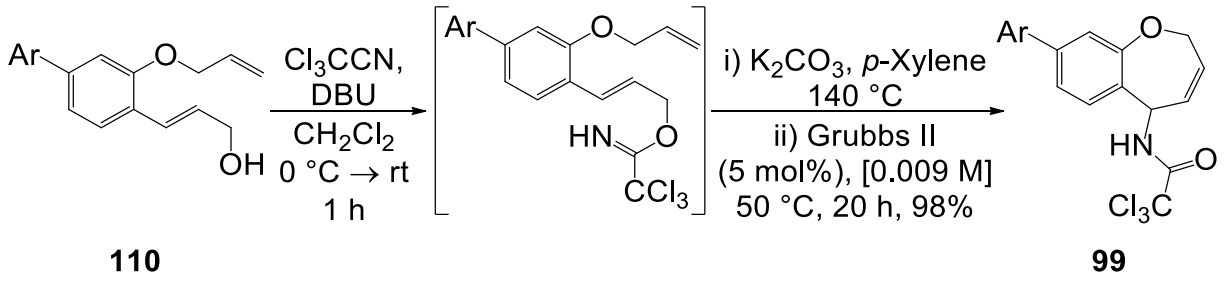
Mono-allylation under a modified version of the allylation conditions used for the synthesis of the 2-allyloxybenzaldehydes **93a–h**, then allowed access to the 2-allyloxy-substituted benzyl alcohol **108** (Scheme 62). Selectivity for the phenolic alcohol over the benzyl alcohol was achieved here due to the relative pK_as of the two alcohols (~10 *vs* ~16). Under these conditions only the phenol was deprotonated. The catalytic quantity of sodium iodide was used to enhance the rate of reaction. This rate enhancement occurs through the Finkelstein reaction[122] of sodium iodide and allyl bromide to form allyl iodide, which is more susceptible to S_N2 attack by the deprotonated phenol. The S_N2 reaction releases the iodide anion back into solution where it can perform another Finkelstein reaction. This method leads to high yield of the mono-allylated benzyl alcohol **108**. The benzyl alcohol was then used in a one-pot Swern/HWE reaction to form the *E*-ethyl cinnamate

109 in a high yield. Reduction of the ester with DIBAL-H then gave the 2'-allyloxy cinnamyl alcohol **110** required for the one-pot Overman/RCM process.



Scheme 62: Synthesis of 2'-allyloxy cinnamyl alcohol 110.

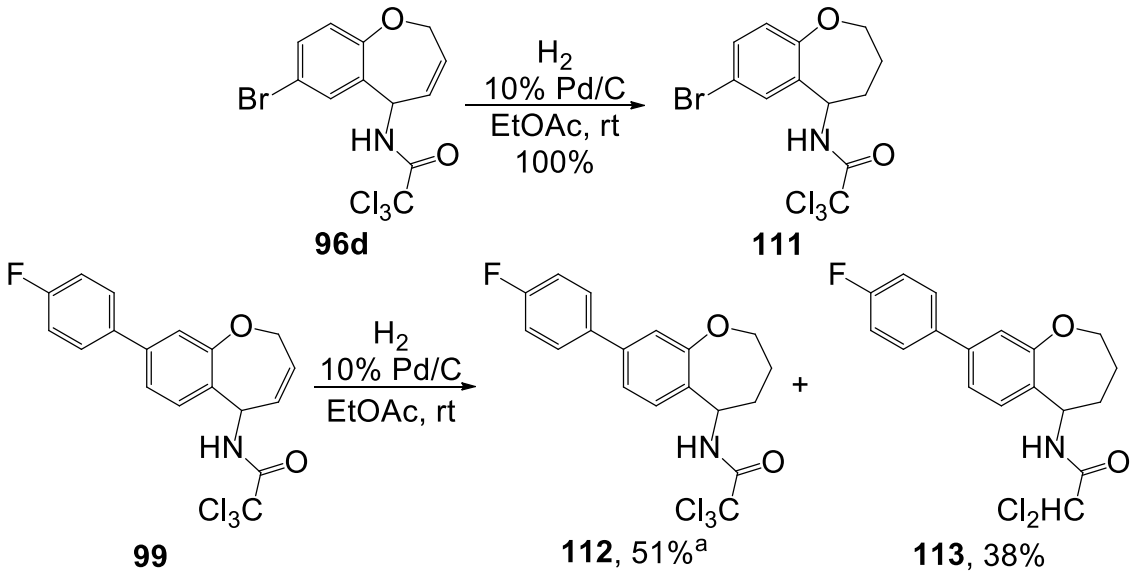
The one-pot process was performed using allylic alcohol **110** at 140 °C for 18 hours and gave the desired 8-aryl-benzoxepine **99** in an almost quantitative yield over three steps (Scheme 63). The greatly increased yield with respect to the other analogues could be due to the stabilisation of the intermediate imidate by the electron-withdrawing fluorine substituent. However, as this stabilisation and increase in yield by an 8-position electron-withdrawing group was not observed in the case of the 8-chloro-substituted analogue synthesised by Salaheddin in the group, and as no other biaryl analogues were synthesised, this explanation remains speculative.[123]



Scheme 63: One-pot process for the synthesis of the 8-aryl-benzoxepine 99.

With the core of the compound now synthesised, the next goal was to hydrogenate the alkene and deprotect the amine to allow reductive amination and urea formation (Scheme 58). First of all, hydrogenation was performed on a model system. Using the 7-bromo analogue **96d** it was possible to selectively reduce the

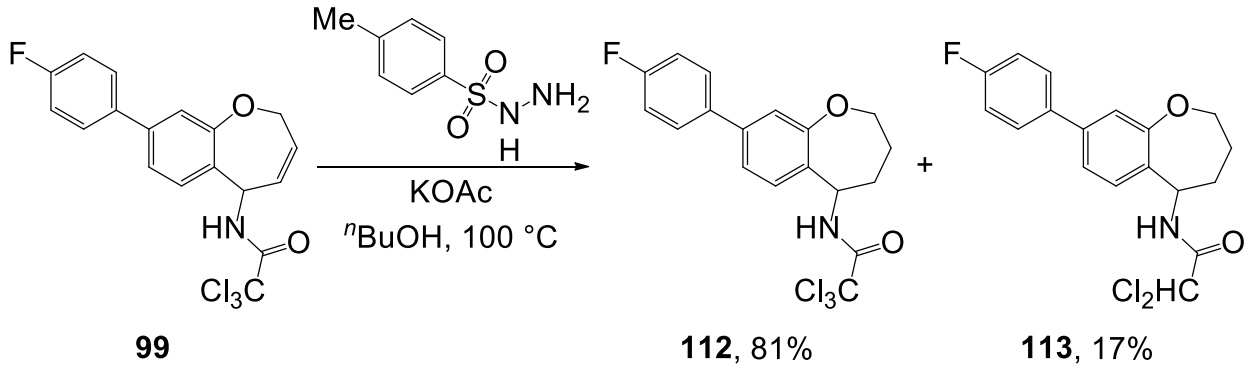
alkene to **111**, without removing any of the chlorines from the trichloroacetamide nor the aromatic bromide under the standard palladium on carbon conditions. These were then applied to the biaryl system **99** (Scheme 64). Unfortunately, under these conditions a 38% yield of mono-dehalogenated product **113** was isolated in addition to an inseparable 1:7 mixture of starting material **99** and product **112**.



Scheme 64: Hydrogenations of 96d and 99. [a]Calculated from ^{1}H NMR spectrum of isolated mixture of starting material 99 and product 112.

Instead of trying to optimise this reaction or use a different catalyst, an alternative method of hydrogenation was pursued. Metal-free hydrogenation conditions provided an attractive route and can be achieved using diimide.[124,125] There are three main methods for the *in situ* generation of diimide. These are: oxidation of hydrazine with oxygen in the presence of a copper(II) catalyst and/or a carboxylic acid;[126] decarboxylation of dipotassium azodicarboxylate in the presence of an acid;[127–130] and thermal decomposition of sulfonylhydrazides.[131] As a metal-free process was desired, the first of these options was not explored. Although it was possible to generate dipotassium azodicarboxylate relatively easily, through the basic deamination of azodicarboxamide, its handling and use proved to be too problematic due to the sensitivity of the compound. Basic, thermal decomposition of tosyl hydrazine to form diimide was therefore investigated (Scheme 65). Although this process gave a high yield of the desired product **112**, ten equivalents of tosyl hydrazine and potassium acetate were necessary to affect the reduction. In addition, a small but significant quantity of the mono-dehalogenated product **113** was also isolated. It is not fully understood how this dehalogenation occurs, as

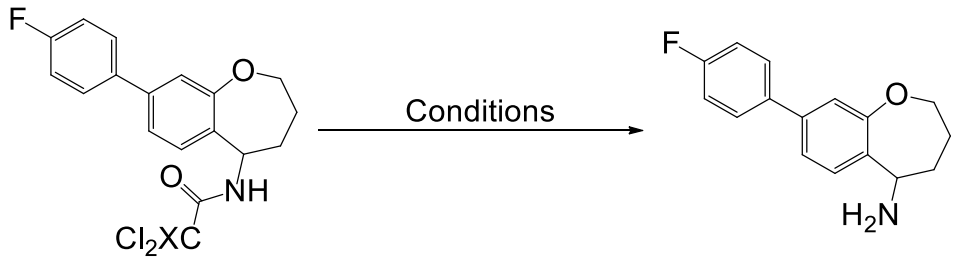
there is no precedent for the reduction of carbon-halogen bonds under diimide conditions. One possible explanation could be dehalogenation by potassium *p*-tolylsulfinate, derived from tosyl hydrazine. Dehalogenation of α-bromo and -iodo sulfones with sodium arenesulfinates has been reported.[132] It is suggested that this reaction proceeds through nucleophilic displacement on the halogen atom and formation of a stabilised carbanion.



99 **112**, 81% **113**, 17%

Scheme 65: Diimide reduction of 99.

Having gained access to the selectively reduced product **112,** the next step was to deprotect the amine. There are a number of methods for cleaving trichloroacetamides, the most common of which are basic hydrolysis[24,133] and the more forcing, acidic hydrolysis.[123,134] Less common methods include reductive conditions with DIBAL-H[93,135,136] or sodium borohydride.[137,138] Initially, deprotection under basic conditions was attempted on the pre-hydrogenation compound **99**. However, this resulted in isolation of only decomposition products (Table 14, entry 1). Attempts at removing the trichloroacetamide of **112** under basic conditions (entries 2 and 3) were unsuccessful and returned only starting material, even when the reaction was heated. One attempt was made at deprotecting with DIBAL-H (entry 4), but this led to the formation of a complex mixture of side-products, which could not be adequately separated or characterised. As a small amount of the dichloroacetamide compound **113** had also been isolated, deprotection of this compound was also attempted (entries 5–8). Under refluxing, highly acidic conditions, no reaction was observed, the only exception being when the reaction was carried out in 1,4-dioxane (entry 8). However, although the desired product could be observed by ^{1}H NMR spectroscopy of the reaction mixture, there was no way to separate it from a contaminant formed when using these conditions. This contaminant appeared to be formed by polymerisation of the dioxane solvent and is a known reaction when performed in tetrahydrofuran.[139]



X = Cl, **112**
X = H, **113**

100

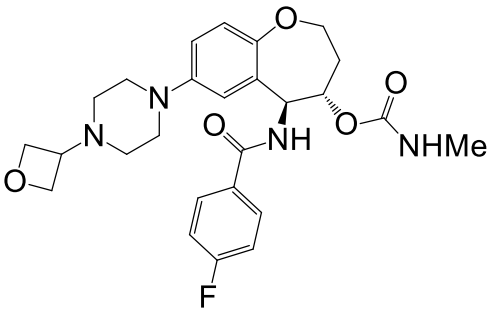
Entry	X	Conditions	Result
1	**99**, X = Cl	6 M NaOH, MeOH, 60 °C, 24 h	Decomposed
2	**113**, X = Cl	6 M NaOH, MeOH, rt, 72 h	No reaction
3	**113**, X = Cl	6 M NaOH, MeOH, 50 °C, 120 h	No reaction
4	**113**, X = Cl	DIBAL-H, CH_2Cl_2, −78 °C, 4 h	Decomposed
5	**112**, X = H	46% HBr, MeOH, 80 °C, 72 h	No reaction
6	**112**, X = H	10% H_2SO_4, AcOH, 110 °C, 24 h	No reaction
7	**112**, X = H	12 M HCl, $(CH_2Cl)_2$, IPA, 85 °C, 18 h	No reaction
8	**112**, X = H	12 M HCl, 1,4-Dioxane, 90 °C, 18 h	Not purified[a]

Table 14: Conditions used for attempted cleavage of tri- and di-chloroacetamide. [a]Product inseparable from polymerised dioxane.

Unfortunately, due to time constraints and the difficulties encountered in deprotecting the amine for further functionalisation, no further work was carried out on the synthesis of this target.

3.2.4 Oxidations of 5-amido-2,5-dihydrobenzoxepines

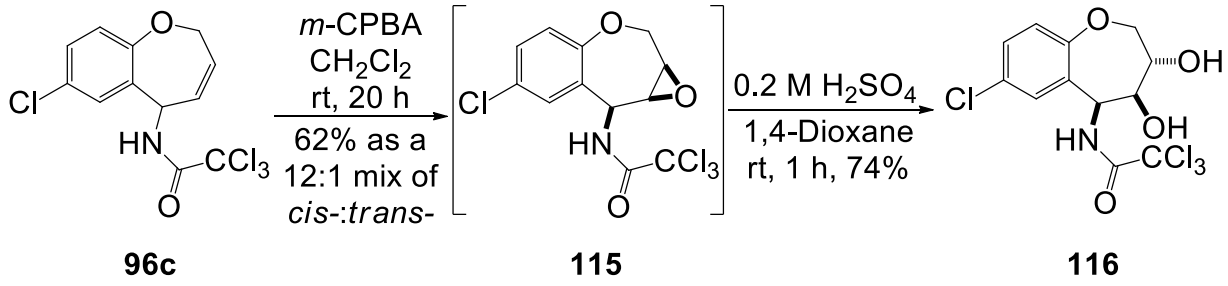
Some of the biologically active benzoxepine-based drugs contain additional functionalisation around the 7-membered ring in the form of hydroxyl groups (**76**, Figure 9 and **114**,[140] Figure 10). As these compounds have a diverse range of biological properties, they were desirable targets for synthesis.



114

Figure 10: An Eli-Lily patented hydroxy-amido-benzoxepine-derived compound for use as a Cathepsin S inhibitor.

As epoxides are a versatile functional group for the installation of single hydroxyl groups and 1,2-*anti*-diols, as well as various other 1,2-*anti*-functionalities, such as 1,2-*anti*-amino-alcohols (*via* opening of the epoxide with an azide), their synthesis was investigated first. Directed epoxidation of the 7-chloro-substituted benzoxepine **96c** under the conditions published by the O'Brien group, gave an inseperable 12:1 ratio of *cis*:*trans*-epoxide products **115** (Scheme 66).[115] The ratio of diastereomers was determined by ^{1}H NMR spectroscopy while the relative geometry of the major diastereomer was proven by NOE experiments (See Chapter 5: Experimental for NOE effect values).



Scheme 66: Epoxidation and subsequent ring opening of one-pot process product 96c.

The good diastereoselectivity in this reaction is due to a hydrogen bonding interaction between *m*-CPBA and the N–H bond of the trichloroacetamide (Figure 11). Due to the curved shape of the molecule however, the *cis*-face is sterically hindered. This causes the reaction to be slower than would otherwise be expected and, because of this, the *m*-CPBA also reacts on the *trans*-face. This competition between the sterics of the molecule and the reduction in energy granted by the hydrogen bond leads to lower diastereoselectivity than has been reported for similar molecules (19:1 on a cyclohexene-derived allylic trichloroacetamide).[115]

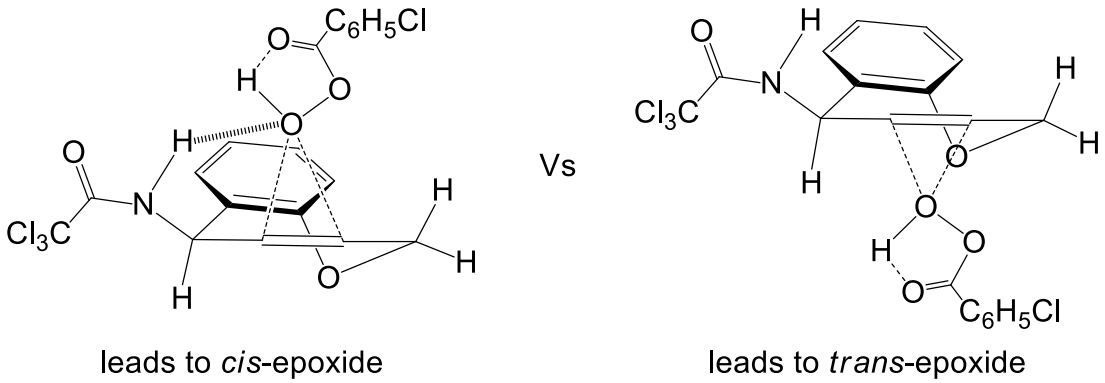
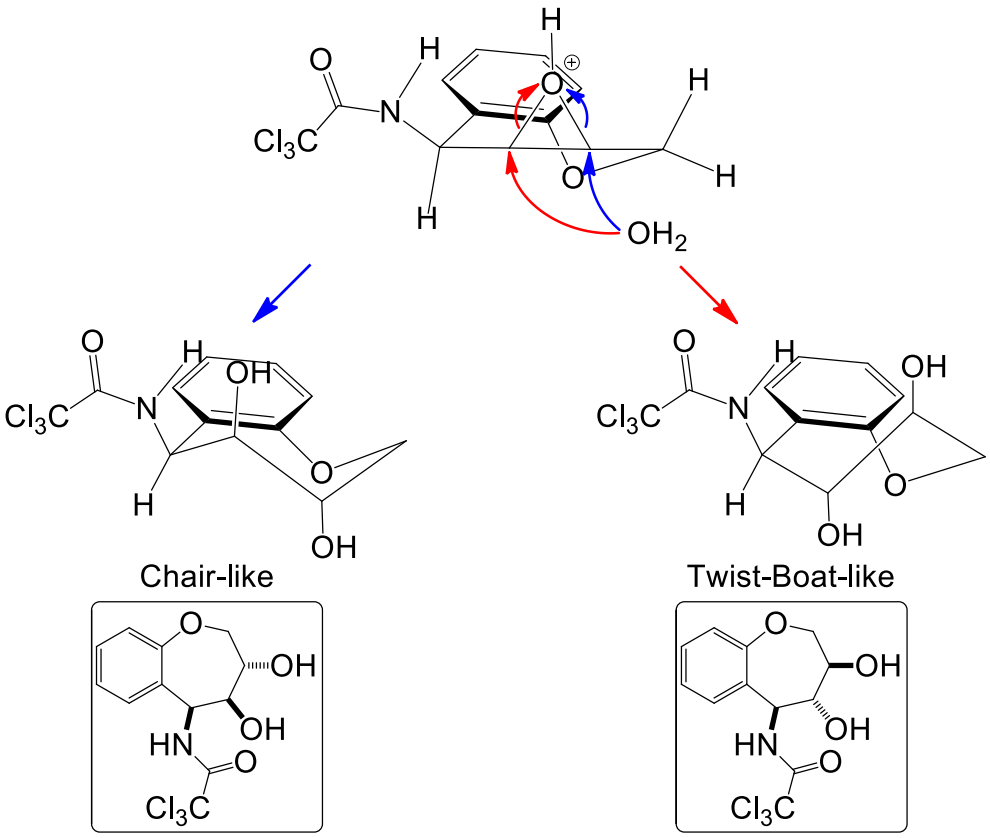


Figure 11: The two transition states showing the formation of the two diastereomeric epoxides.

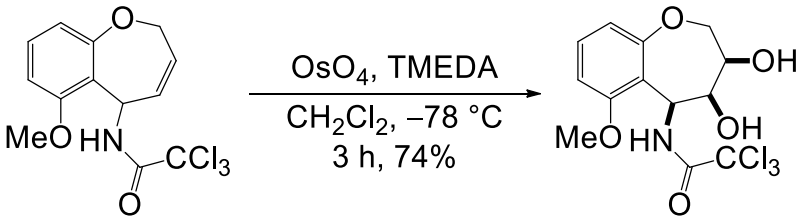
Without major purification, the mixture of epoxides was ring-opened under acidic conditions, resulting in the isolation of 3,4-*trans*-diol **116** in a good yield over two steps (Scheme 66). The minor diastereomer could not be isolated after column chromatography. The product is formed through attack of a molecule of water on the 3-position of the benzoxepine, opening the protonated epoxide (Blue route, Scheme 67). This route is favoured as attack on the 4-position of the benzoxepine would force the reaction to proceed to a twist-boat-like conformation (Red route). This conformation is generally energetically disfavoured due to 1,3-diaxial strain. This epoxide could also have been opened to yield the 4-hydroxy derivative using lithium aluminium hydride, as has been reported previously on a similar system.[113]



Scheme 67: Two different routes for epoxide opening.

Dihydroxylation of the 6-methoxy-substituted benzoxepine **96g** with osmium tetraoxide under the conditions of Donohoe and co-workers also gave a good yield of the *cis*-diol **117** (Scheme 68).[116] The dihydroxylation reaction gives a single diastereomer, as opposed to the 12:1 ratio observed with epoxidation conditions. Again NOE was utilised to determine the relative geometry of the product **117**. The dihydroxylation is also directed by hydrogen bonding between the N–H of the amide and the osmium tetraoxide/TMEDA complex. However, as the reaction is

performed at −78 °C, the rate enhancement gained through hydrogen bonding is able to compensate fully for the increased steric hindrance of the curved molecule.



96g **117**

Scheme 68: Directed dihydroxylation of one-pot process product 96g.

3.2.5 Conclusions

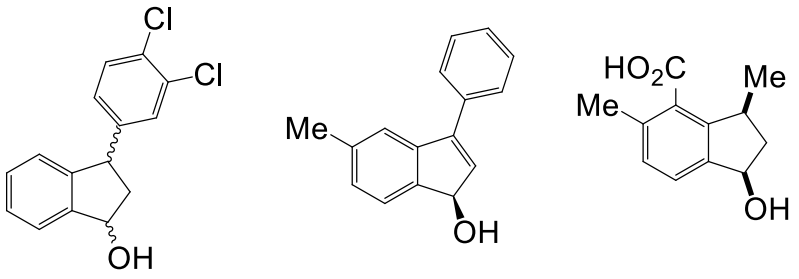
A rapid and highly efficient three-step synthesis of 2'-allyloxy cinnamyl alcohols has been developed. The cinnamyl alcohols were then transformed to the corresponding allylic trichloroacetimidates, which were subsequently used in a one-pot two-step, Overman/RCM process that allowed access to 5-amido-2,5-dihydrobenzoxepines. Having optimised this process, a total of eight amidobenzoxepines were synthesised. One of these benzoxepines was then used for the synthesis of the core structure of an ACAT inhibitor *via* selective hydrogenation. Further functionalisation of two of the 5-amido-2,5-dihydrobenzoxepines was explored, leading to *syn*- and *anti*-diol derivatives with high selectivity and in good yields.

Chapter 4 A One-Pot Allylboration/Heck Process for the Asymmetric Synthesis of 3-Methylene-indan-1-ols

4.1 Introduction

4.1.1 3-Methylene-indan-1-ols

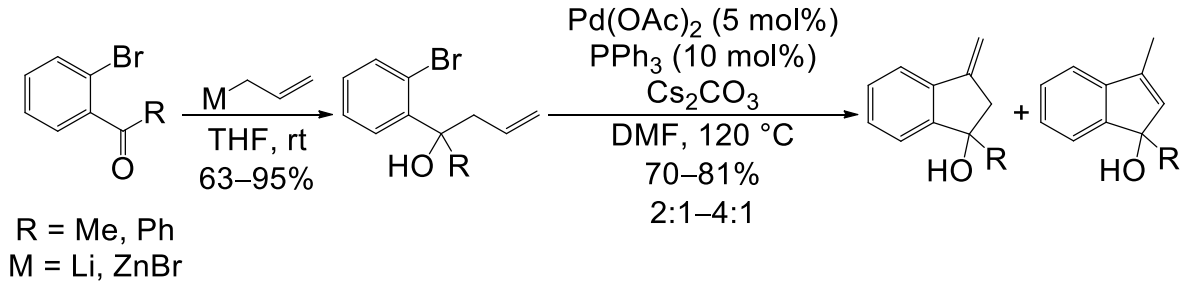
Functionalised indanes and indanols are important scaffolds for drug design and have been used as key intermediates in the synthesis of a variety of biologically active compounds.[141] In particular, an indanol forms the core of a monoamine re-uptake blocker for the treatment of cocaine abuse (Figure 12, **118**).[142] The indanol scaffold has also been a key intermediate (**119**) in the synthesis of the muscarinic receptor antagonist (*R*)-tolterodine[143] and in the formal total synthesis of the sesquiterpene toxin, anisatin (intermediate **120**).[144]



118 **119** **120**

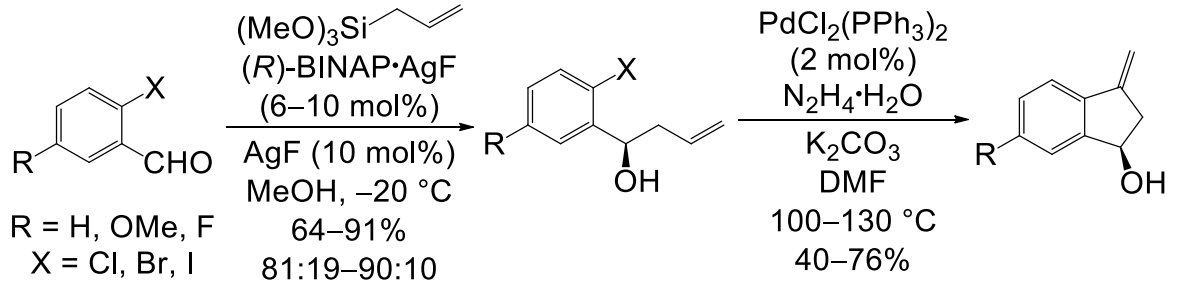
Figure 12: Key indanol intermediates in the synthesis of biologically active compounds.

Due to their importance as synthetic intermediates, a considerable number of papers have been published on their synthesis. The most common strategy for the racemic synthesis of these compounds involves addition of allylmagnesium,[145] allylzinc,[146] allyllithium[146] or allylindium[147] species to a benzaldehyde or acetophenone followed by an intramolecular Heck reaction to close the five-membered ring (Scheme 69). These processes are often limited in scope due to functional group incompatibility and isomerisation of the *exo*-methylene compound to the more stable endocyclic alkene-containing compound**.**



Scheme 69: Sequential allylation/Heck process for the synthesis of indanols.[146]

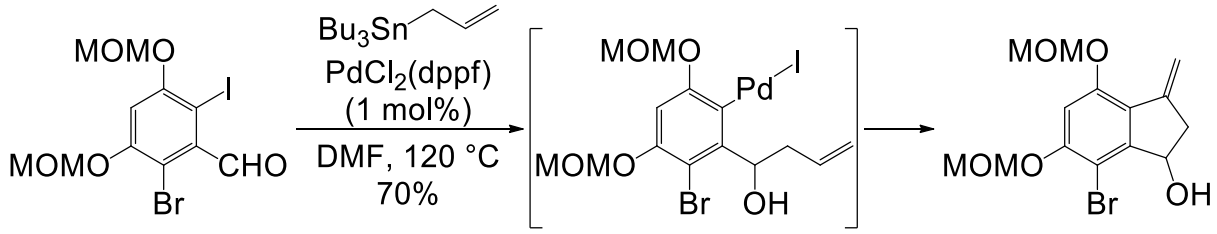
An alternative method, more tolerant of various functional groups, was demonstrated by Mirabdolbaghi and Dudding in their use of a Sakurai−Hosomi−Yamamoto allylation of 2-halobenzaldehydes to form the homoallylic alcohol intermediates (Scheme 70).[148] In this synthesis they used a chiral (*R*)-BINAP-derived silver fluoride salt to form the (*R*)-homoallylic alcohol intermediate in a 64–81% yield and 81:19–90:10 e.r. Attempting to perform the Heck reaction in one-pot with the Sakurai−Hosomi−Yamamoto allylation was reported to afford an "intractable mixture of products". Instead, they were forced to perform the reaction as two separate steps. In the case of both the methoxy- and fluoro-substituted analogues, a reduction in yield was seen for both steps compared to the unsubstituted example. In particular, for the fluoro-substituted analogue they observed a drop in yield from 73% to 40% and 87:13 e.r. to 81:19 e.r., while having to raise the temperature of the Heck step to 130 °C. It can be inferred from our own work[149] that the remainder of the product in their Heck reactions could have been isomerised to the corresponding indanone product, although no mention of this is made in their paper.[148]



Scheme 70: Mirabdolbaghi and Dudding's work on the asymmetric synthesis of indanols.

A recent advance in the synthesis of indanols was achieved by Schmalz and co-workers; while attempting a Stille coupling on a 2-bromo-6-iodobenzaldehyde, they serendipitously discovered a one-pot, domino allylstannylation/Heck reaction (Scheme 71).[150] They proposed that the oxidative addition of palladium activated

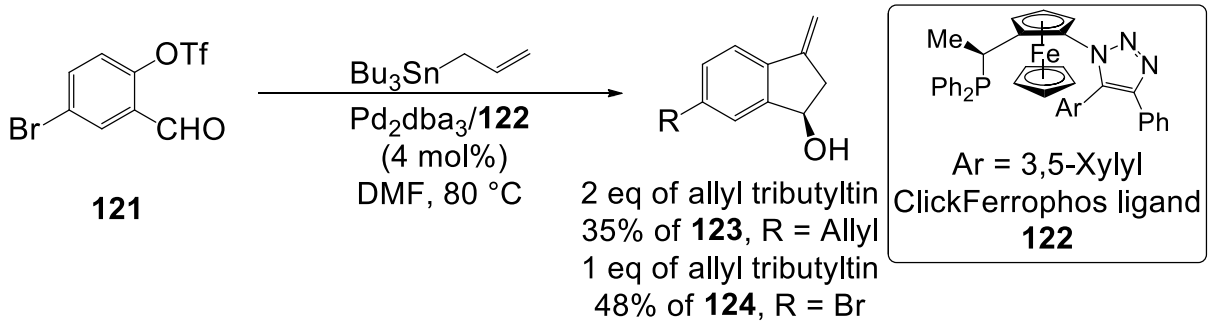
the benzaldehyde to allylstannylation by allyl tributyltin. This process was then demonstrated on another electron-rich bromobenzaldehyde and an electron-poor bromopyridine-derived aldehyde, while the electron-rich substrate still gave good yields the pyridine-derived aldehyde gave a much lower yield. In a subsequent study, an asymmetric variant of the reaction was demonstrated, although only on unsubstituted 2-iodobenzaldehydes and *ortho*-formylphenyl triflates.[151] Although they were able to achieve either high yields (80%, 75:25 er) or high enantioselectivity (52%, 98:2 er) they were unable to achieve both high yield and selectivity for the same substrate.



Scheme 71: Work by Schmalz on the electrophilic activation of benzaldehydes through *ortho*-palladation.

This trade off in yield and selectivity was investigated by Fukuzawa and co-workers (Scheme 72).[152] They developed a palladium/clickferrophos catalyst system **122** to improve on the procedure of Schmalz and co-workers. Their methodology allowed access to chiral indanols in both high yield and enantioselectivity for unsubstituted or electron-rich analogues (64–81%, 86:14–98:2 e.r.). However, their system still has disadvantages: two equivalents of the highly toxic allyl tin reagent are necessary for their reaction and their preferred substrates, the *ortho*-formylphenyl triflates, have “pronounced air sensitivity”.[150] Electron-poor systems are not well tolerated and while high enantioselectivities were still possible, very large reductions in yield were observed. In the case of a very electron-poor nitro-substituted analogue, the reaction gave no product.

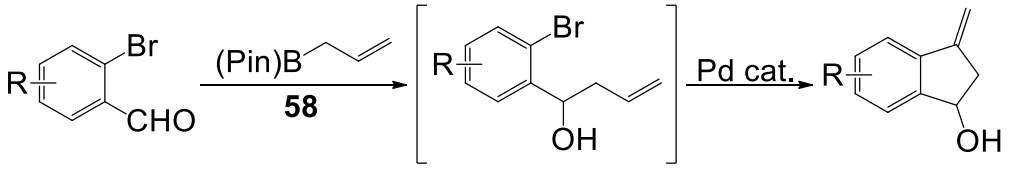
When attempting to utilise 4-bromo-2-formylphenyl triflate **121** with their optimised conditions of two equivalents of allyl tributyltin, they observed a 35% yield of the double addition product **123** (Scheme 72). Upon halving the equivalence of allyl tributyltin, a maximum yield of only 48% of their desired product **124** was observed. Electron-donating 5-position substituents also begin to direct the reaction pathway towards Stille coupling with the triflate rather than electrophilic activation and allylstannylation.



Scheme 72: Different products in allylstannylation/Heck process.

4.1.2 Aims

The aim of this project was to develop a one-pot allylboration/Heck method for the synthesis of 3-methylene-indan-1-ols from readily available 2-bromobenzaldehydes and allylboronic acid pinacol ester (**58**, Scheme 73). It was hoped that by drawing upon the large literature surrounding allylboration reactions, a more general process, that would also replace the highly toxic tin reagents with the non-toxic boronic pinacol ester **58**, could be developed. As there is precedent for asymmetric allylboration reactions, the scope of this method would first be examined before the development of an asymmetric variant.



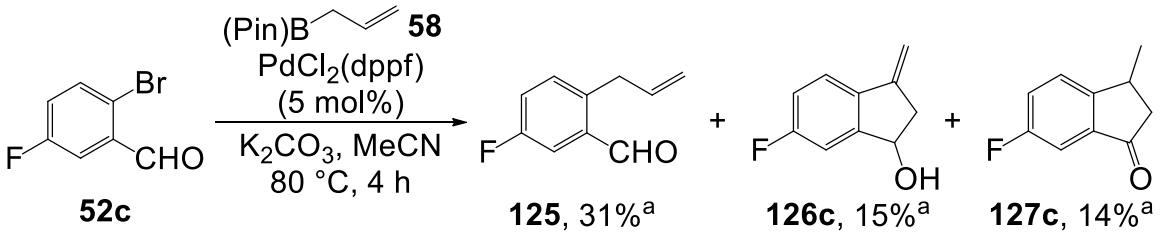
Scheme 73: Proposed allylboration/Heck process for the synthesis of 3-methylene-indan-1-ols.

4.2 Results and discussion

4.2.1 Racemic one-pot allylboration/Heck reaction

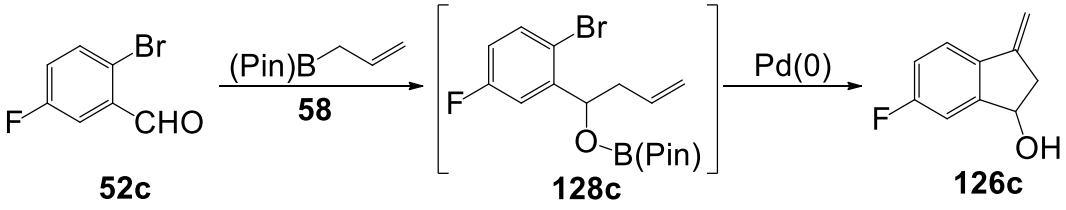
While working on the development of a route to 2'-allylcinnamyl alcohols for the one-pot process towards amido-dihydronaphthalenes, a problem was observed in coupling of the allyl chain to 2-bromobenzaldehydes. When coupling allylboronic acid pinacol ester (**58**) with 2-bromo-5-fluorobenzaldehyde (**52c**) was attempted, it was observed that, while the major product of this reaction was 2-

allylbenzaldehyde **125**, a considerable amount of 6-fluoro-3-methylene-indan-1-ol (**126c**) and ketone product **127c** were present in the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 74).



Scheme 74: Initial observation of one-pot allylboration/Heck process occurring. [a]Yields calculated from ^{1}H NMR spectrum of crude products.

Following this observation, it was proposed that this could occur through a two-step process in which addition of the boronate **58** across the aldehyde would form homoallylic alcohol **128c**, which would then undergo a Heck coupling to form the five-membered ring and the exocyclic alkene **126c** (Scheme 75). The formation of the cyclopentanone product **127c** is unprecedented from intramolecular Heck cyclizations of homoallylic-derived aryl halides. It is believed, however, that under the reaction conditions, heating in a polar solvent with a relatively strong base, palladium chain-walking *via* successive β-hydride eliminations and migratory insertions could occur. This is known as a redox-relay process and is well precedented in the literature.[153–157] The allylboration/Heck process was obviously in competition with the Suzuki-Miyaura coupling. As a method of making 2-allylbenzaldehydes this was abandoned, but it seemed attractive as a new one-pot process which could be developed for the synthesis of useful chemical building blocks.



Scheme 75: Proposed mechanism for allylboration/Heck process.

It was clear that attempting this as a tandem process, in which all reagents are added at the outset of the reaction, would not prevent the Suzuki-Miyaura coupling from occurring in competition with the desired allylboration reaction. To overcome this obstacle, the process was performed as a one-pot, two-step reaction with

addition of the palladium catalyst after the allylboration had already occurred. Early on in the optimisation process, it was observed that if the reaction was carried out in anhydrous acetonitrile, the intermediate species containing a boron-oxygen bond was clearly visible by ^{1}H NMR spectroscopy recorded before addition of the palladium catalyst (Figure 13). It was also noted that these reactions gave incomplete conversion and lower yields. For this reason, acetonitrile was used as supplied and an additional four equivalents of water were added to the reaction to promote hydrolysis of this B–O bond. On addition of the potassium carbonate after the allylboration reaction, the solution effervesces and a large quantity of an extremely fine powdered solid precipitates from the solution. This is thought to be the potassium salt of pinacol boronic acid or, if the pinacol-boron bonds are hydrolysed too, potassium borate. It was decided to add the potassium carbonate at the start of the reaction and this was shown to have no impact on the allylboration.

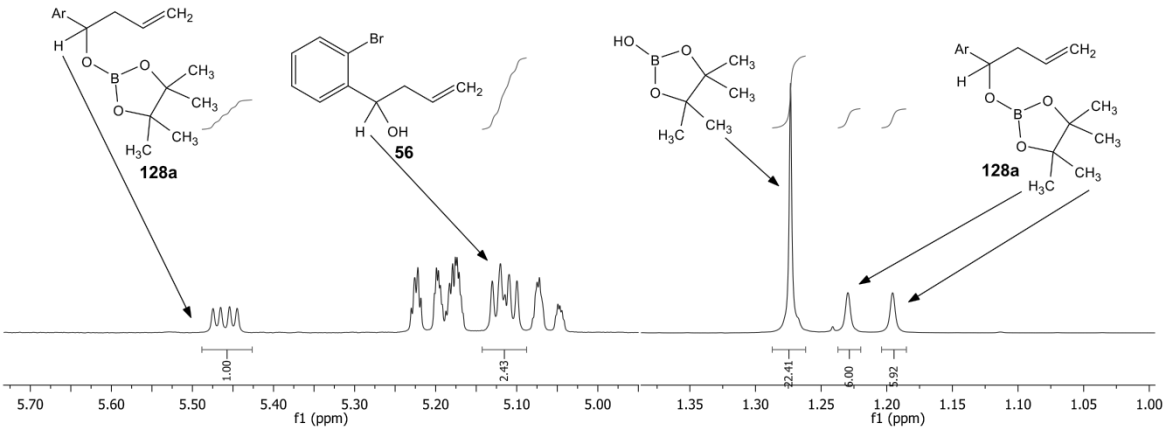
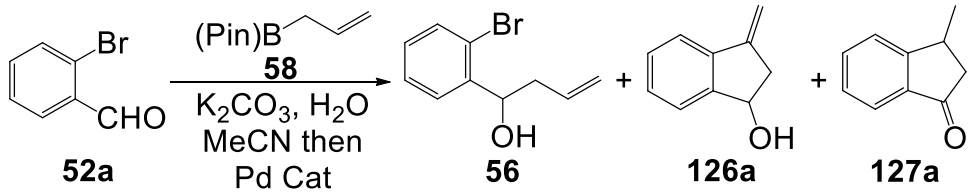


Figure 13: Excerpt from a ^{1}H NMR spectrum of a 2:1 mixture of the intermediates 56 and 128a

Optimisation of the one-pot, two-step reaction continued with an investigation of the most suitable catalyst for the Heck stage of the process (Table 15, entries 1–3). As the product was not easily separated from some of the impurities, the initial optimisation used conversion, as measured by ^{1}H NMR spectroscopy, of the crude product mixture after passing through a short pad of silica. Attempting the one-pot process with palladium(II)dichloride diphenylphosphinoferrocene resulted in a 1:1 ratio of the desired product **126a** and the isomerised product 3-methyl-indan-1-one (**127a**, entry 1). Changing to a palladium(0) species increased the ratio of product **126a** to indanone **127a**, however a considerable quantity of the homoallylic alcohol intermediate **56** was also observed in the ^{1}H NMR spectrum (entry 2). Changing to

a combination of palladium(II) dichloride bistriphenylphosphine with hydrazine monohydrate as an *in situ* reductant, as reported by Dudding, gave a better conversion to product, but an increase in isomerisation (entry 3).[148] Increasing the temperature to 100 °C, which required the reactions to be performed in a sealed tube, pushed the reaction to completion, but again increased the quantity of indanone product that was observed (entry 4). This change gave a reaction that could easily be purified and a 75% yield of the desired product **126a** was isolated. To examine if the hydrazine monohydrate was necessary for the reaction to proceed in good yields and selectivity, a reaction was performed in which it was not added (entry 5). However, a 3:1 ratio of product **126a** and indanone **127a** was observed at the end of this reaction and yielded only 18% of the isolated product.



Entry	Catalyst	Cat loading/ mol%	Temp/ °C	Crude ratio of **56**:**126a**:**127a**[a]	Conversion to **126a**[a]
1	$PdCl_2(dppf)$	5	80	0:1:1	54%
2	$Pd(PPh_3)_4$	5	80	9:23:1	53%
3[b]	$PdCl_2(PPh_3)_2$	7.5	80	2:16:1	83%
4[b]	$PdCl_2(PPh_3)_2$	7.5	100	0:8:1	89% (75%)[c]
5	$PdCl_2(PPh_3)_2$	7.5	100	0:3:1	(18%)[c]

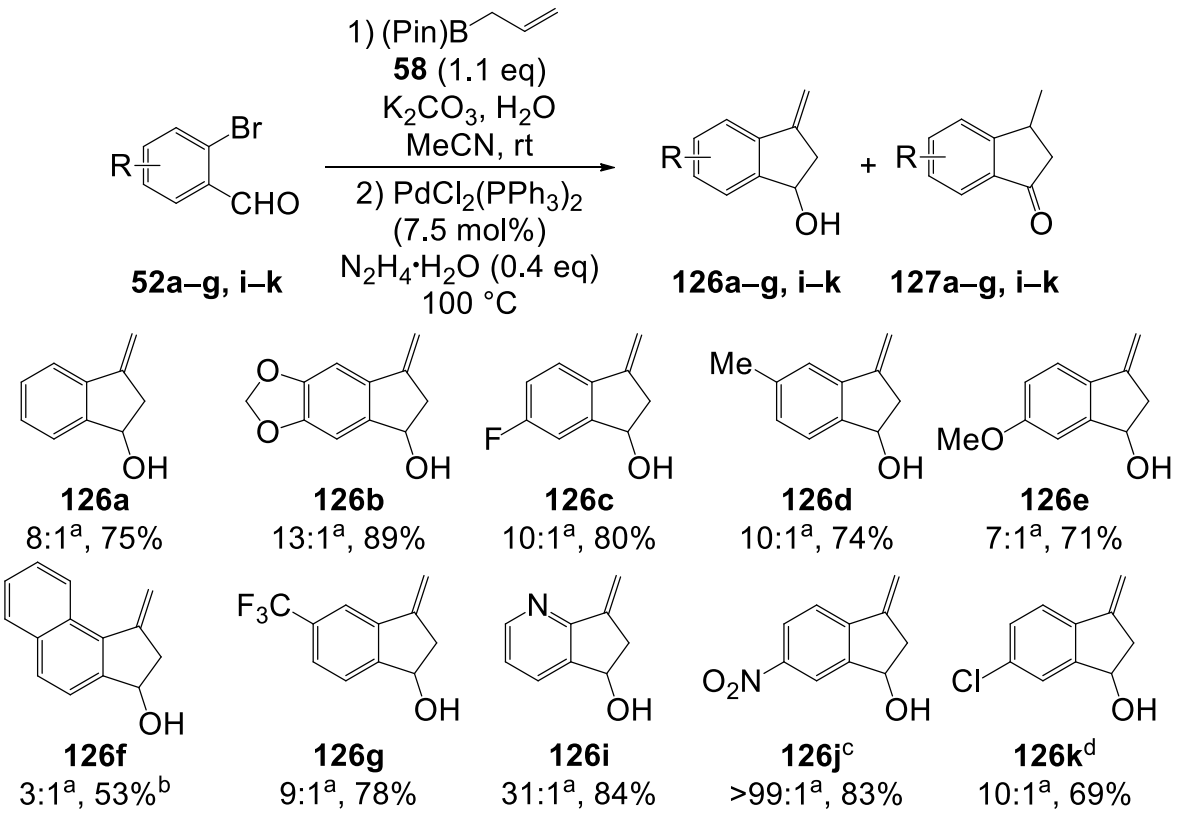
Table 15: Optimisation of one-pot two-step allylboration/Heck process. Unless otherwise noted, all reactions were performed with 58 (1.1 equiv), K_2CO_3 (5.0 equiv), and H_2O (4.0 equiv). [a]Ratio and yield determined through analysis of ^1H NMR spectra of crude reaction mixtures and recovered mass. [b]$N_2H_4.H_2O$ (0.4 equiv) was added with the Pd cat. [c]Isolated yield of 126a in brackets.

Having successfully developed a one-pot allylboration/Heck process it was then applied to a number of 2-bromobenzaldehydes (Scheme 76). A large range of substrates was chosen to fully explore the scope of the reaction. The ratios and yields for compounds **126a**–**e**, **126g** and **126k**, which contain both electron-donating groups and electron-withdrawing groups, are all reasonably constant. The chlorine containing **126k** requires a slightly higher catalyst loading for the reaction to proceed to completion.

The naphthyl-derived compound **126f** appeared to rapidly isomerise to the ketone, 1-methyl-cyclopenta[a]naphthalen-3-one, **127f**. More interestingly however, an inseparable impurity was observed by ^1H NMR spectroscopy (Figure 14). This

impurity appeared to be 1,2-dihydrophenanthren-1-ol, the product of an *endo*-cyclic Heck reaction which should not occur. It is postulated that this product may occur due to steric effects forcing the palladium catalyst to rearrange to the usually less favoured internal position of the alkene before elimination.

The pyridine-containing analogue **126i** was a good substrate for the one-pot reaction, despite concerns that it could chelate the palladium catalyst and slow or halt the reaction. The most electron-poor analogue, nitro-containing **126j**, gave a single product with none of the indanone observed by ^{1}H NMR spectroscopy. In a slight change of conditions, it required less hydrazine monohydrate to be added. This is due to competing reduction of the nitro group under the palladium/hydrazine conditions; when the usual quantity of hydrazine was used a 31% yield was obtained.[158,159] The high yield of **126j** is in direct contrast to the domino allylstannylation/Heck process developed by Fukuzawa and co-workers, where no indanol is observed, making this a more general process.[152]



Scheme 76: Optimised conditions, yields and ratios of product 126 to indanone 127 for the synthesis of methylene-indanols 126a-g, i-k. [a]Ratios calculated from ^{1}H NMR spectrum of crude reaction mixture. [b]126f was isolated as an inseparable mixture of 126f and the 6-*endo*-product 1,2-dihydrophenanthren-1-ol. [c]Reaction performed with $N_2H_4.H_2O$ (0.15 equiv). [d]Reaction performed with $PdCl_2(PPh_3)_2$ (10 mol%).

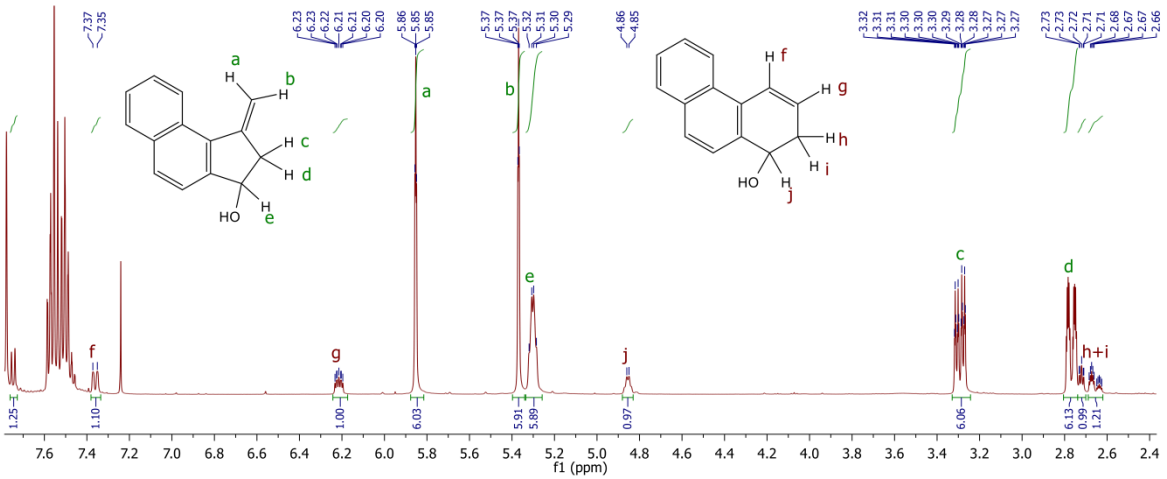
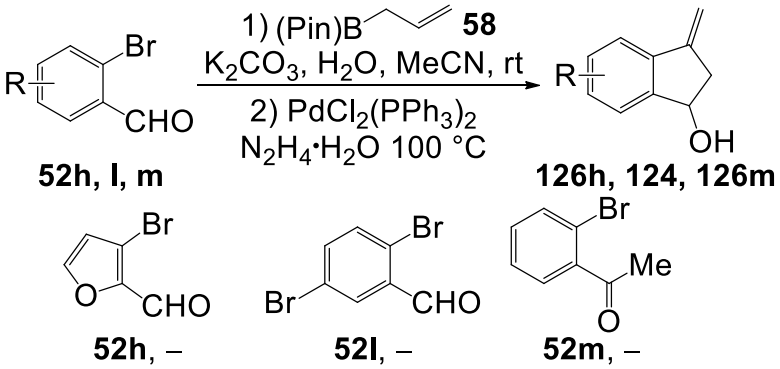


Figure 14: Expansion of ^{1}H NMR spectrum showing key peaks attributed to 126f and 1,2-dihydrophenanthren-1-ol.

The other heterocyclic compound attempted, furan based **52h**, underwent the allylboration reaction perfectly, but the Heck reaction would not go to completion, with the best conversion observed being 25% (Scheme 77). This is probably due to the difficulties of forming a 5,5-bicyclic system through sp^2-sp^2 bond formation. Many reactions which precedent this type of Heck coupling are performed at over 120 °C and/or give low yields.[160–162] Increasing the catalyst loading and temperature only led to decomposition of the homoallylic alcohol intermediate.

Changing to the dibromobenzaldehyde **52l** completely inhibited the Heck reaction with only the homoallylic alcohol recovered even at higher catalyst loadings. The reaction may be able to tolerate bromide functionality if 5-bromo-2-iodobenzaldehyde was used. This would rely on the difference in reactivity between the two halides, in much the same manner as the chloride-containing compound, **52k**. 2'-Bromoacetophenone (**52m**), did not undergo the allylboration step: a Lewis basic indium catalyst is nessecary for this reaction.[163]

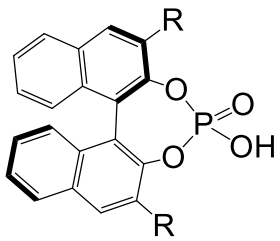


Scheme 77: Substrates that failed to react during optimisation.

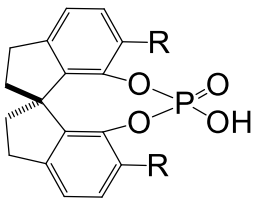
4.2.2 Asymmetric one-pot allylboration/Heck reaction

With a robust one-pot, two-step method for the synthesis of racemic 3-methylene-indan-1-ols developed, the next step was to extend this method to allow the synthesis of chiral 3-methylene-indan-1-ols. Building on the substantial quantity of literature detailing chiral Brønsted acid-catalysed asymmetric allylboration procedures,[164–170] and wishing to avoid using tin-based chiral acids, the work by the groups of Antilla[168] and Hu[169] seemed most attractive. Specifically, the work of Jain and Antilla on asymmetric allylboration of benzaldehydes with the commercially available (*R*)-TRIP phosphoric acid catalyst (**129a**, Figure 15) was of most interest. Although high yields and excellent enantioselectivities were observed by Antilla for *meta*- and *para*-substituted benzaldehydes, lower levels were obtained with the single *ortho*-substituted analogue investigated in this study.

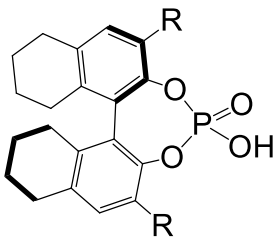
More recent papers by Hu[169] and Kotora[170] have attempted to address this lower selectivity in *ortho*-substituted analogues with some success. The work by Hu and co-workers, however uses the (*R*)-SPINOL phosphoric acid (**130**), which is not commercially available.



R = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$, **(*R*)-129a**
R = 3,5-(CF$_3$)$_2$C$_6$H$_3$, **(*R*)-129b**
R = H, **(*R*)-129c**



R = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$
(*R*)-130

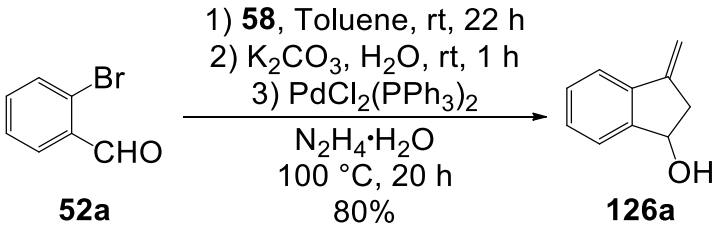


R = 4-(Cl)C$_6$H$_4$
(*R*)-131

Figure 15: Chiral phosphoric acids used in this project and by the Antilla and Hu groups.

As these catalysts had been shown to be most effective in non-coordinating solvents such as dichloromethane and toluene,[168] the first step towards developing an enantioselective variant of the one-pot process was to ensure that the racemic process worked just as well in toluene (Scheme 78). In addition, as the catalyst is a phosphoric acid, the addition of potassium carbonate and water would need to be performed after the allylboration. These conditions worked as well as before, giving **126a** in 80% yield. However, in place of the indanone **127a**, a different side-product was observed in a similar ratio. Due to the small scale that the reactions

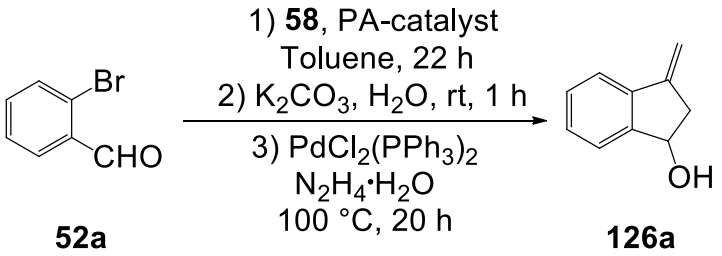
were performed on and the small amount of this impurity that was formed, it could only be observed in the ^{1}H NMR spectrum before purification by column chromatography.



Scheme 78: One-pot allylboration/Heck process performed in toluene.

The next goal was to optimise the asymmetric allylboration reaction for the 2-bromobenzaldehydes. Using the work by Jain and Antilla as a starting point for the allylboration conditions,[168] the reaction mixture was cooled to −30 °C before addition of the allylboronic acid pinacol ester (**58**). The screening of a series of catalysts was carried out, starting with the unsubstituted (*S*)-BINOL-PA **(*S*)-129c** (Table 16). As expected, the unsubstituted catalyst **(*S*)-129c** provided no enantioinduction but did give an improved yield over the uncatalysed process (Table 16, entry 1). Attempting the reaction with the (*R*)-ditrifluoromethylphenyl-substituted catalyst **(*R*)-129b** showed similarly high yields and began to provide some enantioselectivity (entry 2). The (*R*)-TRIP catalyst **(*R*)-129a**, showed considerably better enantioselectivity with only a marginal reduction in yield (entry 3). The octahydro-catalyst with *para*-chlorophenyl substituents **(*R*)-131** appeared to be the least effective of the catalysts used, giving a lower yield than the unsubstituted catalyst **(*S*)-129c** and a lower level of enantioinduction than (*R*)-TRIP **(*R*)-129a** (entry 4). As the enantioselectivity for the reaction of 2-bromobenzaldehyde (**52a**) was lower than expected, it was decided that racemisation in the Heck reaction should be eliminated as a possibility. To this end, a reaction was performed and stopped at the homoallylic alcohol stage (entry 5). This showed that the enantiomeric ratios were not degraded by the later steps and that the 2-bromobenzaldehydes were just poor substrates for this reaction. A reaction without the catalyst was also performed (entry 6), to prove that the lower enantiomeric ratio was due to the slower, uncatalysed racemic process proceeding in the background. As this was clearly the case, and as Brown and co-workers have shown that no reaction occurs between benzaldehydes and allyl borates at −78 °C in dichloromethane, two lower temperatures were attempted.[171] At −50 °C

(entry 7), both the yield and enantioselectivity of the reaction improved; however, when the temperature was reduced to −80 °C (entry 8), in an attempt to eliminate the racemic reaction entirely, both the yield and e.r. began to drop. This was due to poor solubility of both the catalyst and the benzaldehydes below −60 °C. While this could possibly be circumvented by using dichloromethane instead of toluene, this was not explored, as it would have involved switching solvent after the first step of the reaction sequence. The solubility of the SPINOL catalysts **130** (Figure 15) used by Hu and co-workers is much improved at −78 °C, however this would not solve the benzaldehyde solubility problems.



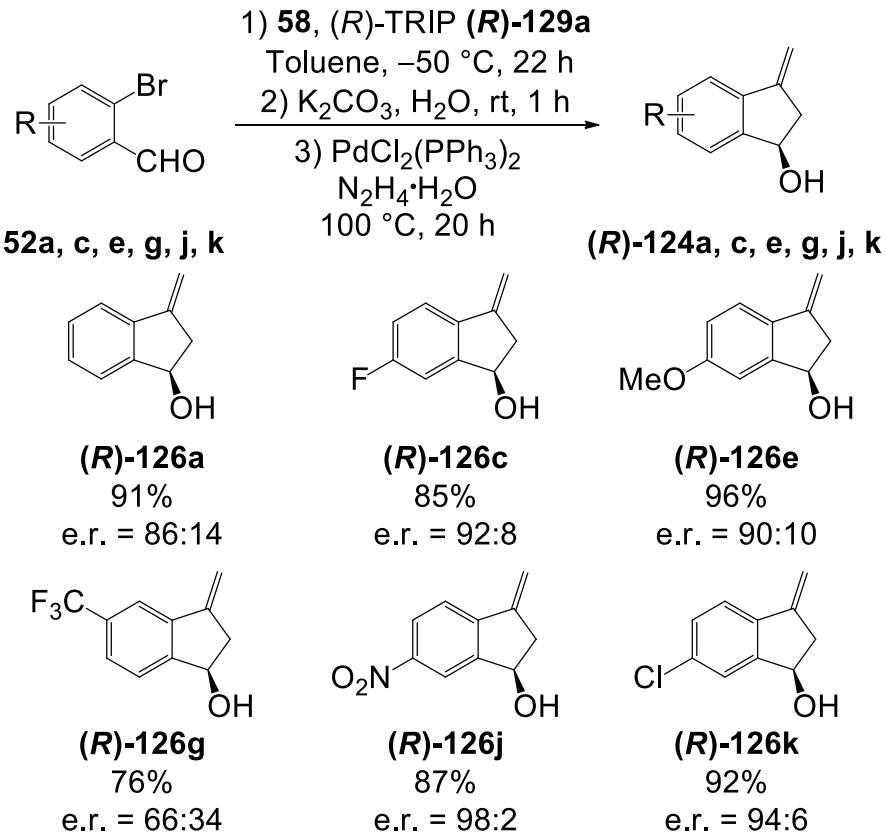
52a **126a**

Entry	Catalyst	Temp/°C	Yield/%[a]	er[b]
1	**(*S*)-129c**	−30	90	50:50
2	**(*R*)-129b**	−30	88	55:45
3	**(*R*)-129a**	−30	83	77:23
4	**(*R*)-131**	−30	82	52:48
5[c]	**(*R*)-129a**	−30	97[d]	75:25[d]
6[e]	**–**	−30	51	–
7	**(*R*)-129a**	−50	91	86:14
8[f]	**(*R*)-129a**	−80	59[f]	80:20

Table 16: Unless otherwise noted, all reactions were performed with 58 (1.2 eq), PA-catalyst (5 mol%), K_2CO_3 (6.0 eq), and H_2O (10.0 eq). [a]Isolated yield of 126a. [b]er was determined using chiral HPLC analysis (see Appendix 1). [c]Reaction was stopped after the allylboration step, and the homoallylic alcohol 56 was isolated. [d]Yield and e.r. for homoallylic alcohol 56. [e]No PA-catalyst present. [f]Reaction performed with 52e and yielded 126e.

Having optimised the asymmetric conditions as far as possible, they were next applied to a range of substrates (Scheme 79). As the naphthyl-derived aldehyde **52f** had not performed well in the racemic process, it was not included in the asymmetric screen. Similarly, compounds which had not undergone the Heck step in the racemic screen were discarded (**52h**, **52l**, **52m**). As the catalyst was a phosphoric acid, the pyridine-aldehyde **52i** could not be used as it would deprotonate the catalyst and, as has been shown by List and co-workers, salts of the phosphoric acid catalysts are not as effective in many reactions.[172] It was found that benzaldehydes **52b** and **52d** were not soluble below −30 °C, so these were also excluded. It is thought that the poor result obtained for the

trifluoromethyl substituted analogue **(*R*)-126g** is also due to reduced solubility. As 2-bromo-4-trifluoromethylbenzaldehyde (**52g**) is a colourless oil, it was not possible to be certain that it was fully dissolved at −50 °C. The asymmetric process gave higher yields than the racemic process. This was in part due to a reduction in quantity of side-products formed, with all analogues showing selectivity towards the desired indanol product over the unknown side-product in the region of 40:1. The asymmetric process showed greater yields and selectivities for electron-poor analogues **(*R*)-126c**, **(*R*)-126j** and **(*R*)-126k**. This is probably due to the fact that the background, racemic allylboration reaction proceeds more slowly on these substrates. This selectivity on electron-poor analogues makes the process highly complementary to the asymmetric allylstannylation reactions of Fukuzawa and co-workers.[152]



Scheme 79: Optimised yields and enantiomeric ratios for the asymmetric one-pot allylboration/Heck process.

4.2.3 Conclusions

A high yielding one-pot allylboration/Heck process has been developed for the racemic and asymmetric synthesis of 3-methylene-indan-1-ols. The racemic

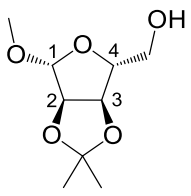
process was shown to be broad in scope and a more general process than those previously reported for the synthesis of 3-methylene-indan-1-ols. This process was then altered to allow the asymmetric synthesis of the same compounds. The asymmetric process has been shown to be higher yielding and shows promising selectivity. However, this process could possibly be improved through altering the catalyst or by performing the first step in dichloromethane, before changing to toluene for the second step of the process.

Chapter 5 Experimental

General Experimental

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV 254) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 or 500 MHz 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 77.16), dimethylsulfoxide (δ_H 2.50 and δ_C 39.52), or methanol (δ_H 3.31 and δ_C 49.00) as standar as standard. Proton and carbon assignments are based on two-dimensional COSY and DEPT experiments, respectively. NOe were recorded on a 500 MHz spectrometer with a D8 delay of 0.30000001 seconds. 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 TM Synthesis Unit (CEM Corp., Matthews, NC) and performed in glass vessels (capacity 10 mL) sealed with a septum. Optical rotations were determined as solutions irradiating with the sodium D line (λ= 589 nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. The chiral HPLC methods were calibrated with their corresponding racemic mixtures.

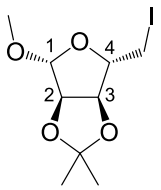
2,3-Isopropylidine-1-methoxy-D-ribofuranoside (13)[173]



Concentrated hydrochloric acid (34–36%, 0.02 mL) was added to a stirred solution of D-ribose (**12**) (0.200 g, 1.34 mmol) in acetone (3 mL) and methanol (3 mL). The solution was heated under reflux for 2 h, before cooling to room temperature. The

reaction was neutralised by addition of a saturated solution of sodium hydrogen carbonate (10 mL), then extracted with ethyl acetate (2 × 50 mL). The organic layers were combined and washed with water (40 mL), brine (40 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 2,3-isopropylidine-1-methoxy-D-ribofuranoside (**13**) (0.228 g, 84%) as a colourless oil. Spectroscopic data as reported in literature.[173] $[\alpha]_D^{25}$ −52.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, C(C*H*$_3$)(CH_3)), 1.48 (3H, s, C(CH_3)(C*H*$_3$)), 3.24 (1H, dd, *J* 10.5, 2.7 Hz, OH), 3.43 (3H, s, OCH_3), 3.61 (1H, ddd, *J* 12.8, 10.5, 2.7 Hz, 5-*H*H), 3.70 (1H, dt, *J* 12.8, 2.7 Hz, 5-H*H*), 4.43 (1H, t, *J* 2.7 Hz, 4-H), 4.59 (1H, d, *J* 5.9 Hz, 2-H), 4.84 (1H, d, *J* 5.9 Hz, 3-H), 4.97 (1H, s, 1-H); δ_C (101 MHz, $CDCl_3$) 24.7 (CH_3), 26.3 (CH_3), 55.5 (CH_3), 64.0 (CH_2), 81.5 (CH), 85.8 (CH), 88.4 (CH), 110.0 (CH), 112.1 (C); *m/z* (CI) 205 (MH^+, 14%), 173 (100), 113 (5), 85 (10), 69 (14).

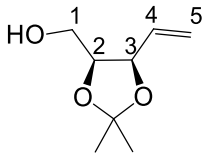
5-Deoxy-5-iodo-2,3-isopropylidine-1-methoxy-D-ribofuranoside (14)[174]



Iodine (0.341 g, 1.34 mmol) was added to a stirred solution of 2,3-isopropylidine-1-methoxy-D-ribofuranoside (**13**) (0.228 g, 1.12 mmol), imidazole (0.114 g, 1.68 mmol) and triphenylphosphine (0.352 g, 1.34 mmol) in toluene (15 mL) and acetonitrile (5 mL). The solution was heated under reflux for 0.1 h before cooling to room temperature. Iodine was then added in 10 mg portions until the solution remained dark-brown in colour. The solution was diluted with diethyl ether (40 mL) and washed with a saturated solution of sodium thiosulfate (80 mL), water (100 mL) and brine (70 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo* and filtered through a short plug of silica (ethyl acetate/petroleum ether, 1:20) to yield 5-deoxy-5-iodo-2,3-isopropylidine-1-methoxy-D-ribofuranoside (**14**) (0.330 g, 94%) as a clear oil. $[\alpha]_D^{25}$ −65.7 (*c* 1.0, $CHCl_3$), lit.[174] $[\alpha]_D^{25}$ −68.3 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 0.4 Hz, C(C*H*$_3$)(CH_3)), 1.48 (3H, d, *J* 0.4 Hz, C(CH_3)(C*H*$_3$)), 3.16 (1H, t, *J* 10.0 Hz, 5-*H*H), 3.29 (1H, dd, *J* 10.0, 6.0 Hz, 5-H*H*), 3.37 (3H, s, OCH_3), 4.44 (1H, ddd, *J* 10.0, 6.0, 0.7 Hz, 4-H), 4.63 (1H, d, *J* 5.9 Hz, 2-H), 4.76 (1H, dd, *J* 5.9, 0.7 Hz, 3-H), 5.05 (1H, s, 1-H); δ_C (101 MHz, $CDCl_3$) 6.8 (CH_2), 25.2 (CH_3), 26.6 (CH_3), 55.4

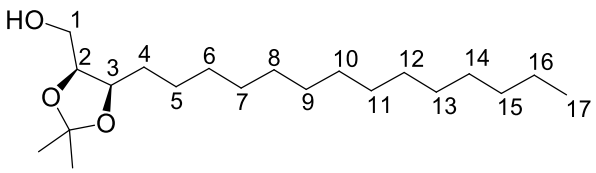
(CH_3), 83.2 (CH), 85.5 (CH), 87.6 (CH), 109.9 (CH), 112.8 (C); *m/z* (CI) 315 (MH^+, 8%), 279 (7), 127 (8), 113 (38), 85 (52), 73 (100).

(2*S*,3*R*)-2,3-(*O*-Isopropylidene)pent-4-en-1,2,3-triol (16)[175]



Zinc (2.44 g, 35.7 mmol) was added to a solution of 5-deoxy-5-iodo-2,3-isopropylidine-1-methoxy-D-ribofuranoside (**14**) (2.24 g, 7.14 mmol) and a catalytic amount of glacial acetic acid (0.06 mL) in methanol (40 mL). The suspension was heated under reflux for 1 h before cooling to 0 °C. A saturated solution of sodium borohydride in ethanol (140 mL) was added dropwise with stirring to the reaction mixture and stirred at 0 °C for 0.5 h before warming to room temperature over 3 h. The mixture was concentrated *in vacuo*. The resulting residue was dissolved in diethyl ether (50 mL) and filtered through Celite®. The filtrate was washed with water (2 × 50 mL), brine (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield (2*S*,3*R*)-2,3-(*O*-isopropylidene)pent-4-en-1,2,3-triol (**16**) (1.01 g, 89%) as a colourless oil. $[\alpha]_D^{25}$ −40.0 (*c* 1.5, $CHCl_3$); lit.[175] $[\alpha]_D^{25}$ −45.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 0.4 Hz, C(C*H*$_3$)(CH_3)), 1.51 (3H, d, *J* 0.4 Hz, C(CH_3)(C*H*$_3$)), 1.81 (1H, t, *J* 6.2 Hz, OH), 3.59 (2H, dd, *J* 6.2, 5.9 Hz, 1-H_2), 4.26 (1H, dt, *J* 6.6, 5.9 Hz, 2-H), 4.65 (1H, tt, *J* 6.6, 1.1 Hz, 3-H), 5.28 (1H, ddd, *J* 10.3, 1.5, 1.1 Hz, 5-*H*H), 5.40 (1H, ddd, *J* 17.5, 1.5, 1.1 Hz, 5-H*H*), 5.87 (1H, ddd, *J* 17.5, 10.3, 6.6 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 25.3 (CH_3), 27.8 (CH_3), 62.1 (CH_2), 78.3 (CH), 78.4 (CH), 108.9 (C), 119.0 (CH_2), 133.1 (CH); *m/z* (CI) 159 (MH^+, 71%), 141 (11), 101 (100), 83 (12).

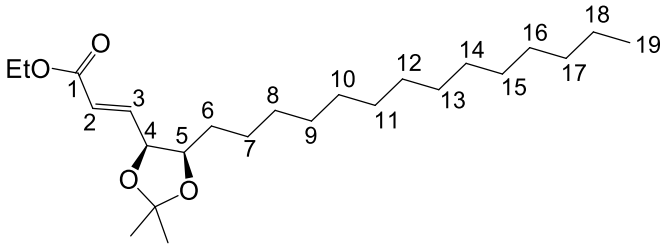
(2*S*,3*R*)-2,3-(*O*-Isopropylidene)heptadecan-1,2,3-triol (19)



A solution of Grubbs second generation catalyst (0.145 g, 0.172 mmol) in dichloromethane (20 mL) was added to a solution of (2*S*,3*R*)-2,3-(*O*-

isopropylidene)pent-4-en-1,2,3-triol (**16**) (0.540 g, 3.41 mmol) and 1-tetradecene (**17**) (1.30 mL, 5.14 mmol) in dichloromethane (20 mL) and heated under reflux for 16 h. The reaction mixture was then concentrated *in vacuo* and filtered through a plug of silica with first petroleum ether (500 mL) and then 25% ethyl acetate in petroleum ether (1000 mL). The second wash was concentrated *in vacuo* to yield the cross metathesis product **18** as a clear oil, which was used without further purification. The alkene was dissolved in ethyl acetate (40 mL) and a suspension of 10% palladium on carbon (0.150 g, 15% w/w) in ethyl acetate (10 mL) was added. The mixture was degassed, purged with hydrogen gas and left to stir at room temperature under a hydrogen atmosphere for 2 h. The suspension was filtered through Celite® with ethyl acetate (100 mL) and purified by column chromatography (ethyl acetate/petroleum ether, 1:5) to yield (2*S*,3*R*)-2,3-(*O*-isopropylidene)heptadecan-1,2,3-triol (**19**) (0.921 g, 82% over two steps) as a colourless oil. ν_{max} (neat)/cm^{-1} 3437 (OH), 2923 (CH), 2854 (CH), 1466, 1379, 1217, 1042; $[\alpha]_D^{24}$ −10.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.8 Hz, 17-H_3), 1.21–1.53 (32H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2 and $C(CH_3)_2$), 1.95 (1H, br s, OH), 3.55–3.63 (2H, m, 1-H_2), 4.10–4.19 (2H, m, 2-H and 3-H); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 22.8 (CH_2), 25.7 (CH_3), 26.8 (CH_3), 28.4 (CH_2), 29.0 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (3 × CH_2), 29.8 (2 × CH_2), 29.8 (CH_2), 32.1 (CH_2), 62.0 (CH_2), 77.2 (CH), 78.1 (CH), 108.2 (C); *m/z* (CI) 329.3051 (MH^+. $C_{20}H_{41}O_3$ requires 329.3056), 313 (13%), 271 (60), 253 (10), 235 (5), 159 (3), 69 (7).

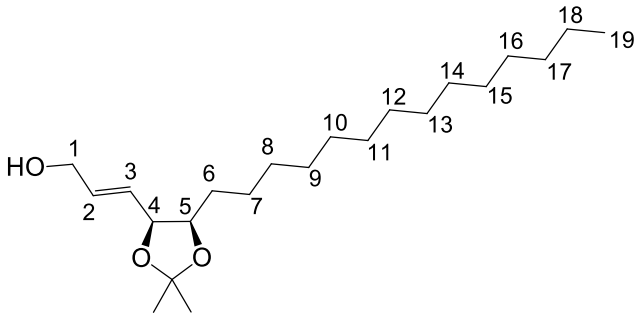
Ethyl (2*E*,4*S*,5*R*)-4,5-(*O*-isopropylidene)-4,5-dihydroxynonadec-2-enoate (22)



Dimethyl sulfoxide (0.61 mL, 8.6 mmol) was slowly added to a stirred solution of oxalyl chloride (0.38 mL, 4.5 mmol) in dichloromethane (15 mL) at −78 °C. The reaction was stirred for 0.3 h before (2*S*,3*R*)-2,3-(*O*-isopropylidene)heptadecan-1,2,3-triol (**19**) (0.95 g, 2.9 mmol) in dichloromethane (15 mL) was added dropwise. The reaction mixture was then stirred for a further 0.3 h before

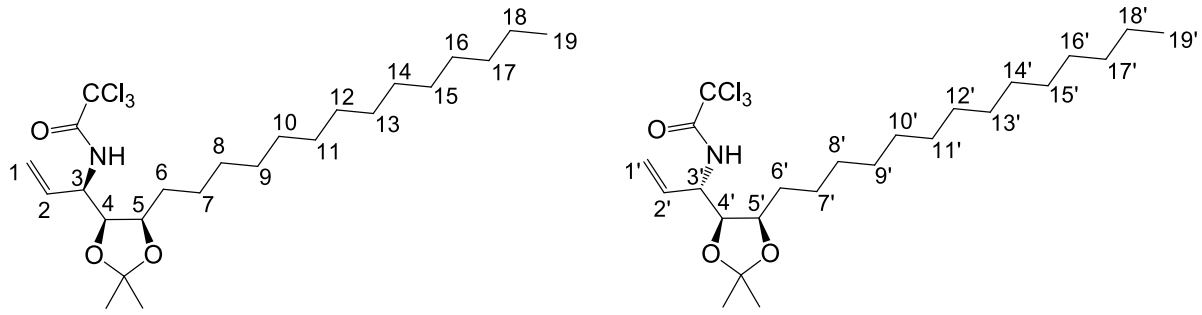
triethylamine (2.0 mL, 15 mmol) was added. The temperature was maintained at −78 °C for 0.5 h then allowed to warm to room temperature over 2 h. Meanwhile, a solution of lithium chloride (0.24 g, 5.8 mmol), triethyl phosphonoacetate (**21**) (0.73 mL, 3.7 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.97 mL, 6.5 mmol) in acetonitrile (30 mL) was prepared and stirred for 1 h. The Swern solution was concentrated *in vacuo* to give a yellow residue **20** to which the Horner–Wadsworth–Emmons solution was added. The reaction mixture was stirred at room temperature for 20 h then quenched by the addition of a saturated solution of ammonium chloride (20 mL), concentrated to give an orange residue and extracted with diethyl ether (2 × 30 mL). The organic layers were combined, washed with water (50 mL), brine (50 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Purified by filtration through a pad of silica (elution with 20% ethyl acetate:petroleum ether) to yield ethyl (2*E*,4*S*,5*R*)-4,5-(*O*-isopropylidene)-4,5-dihydroxynonadec-2-enoate (**22**) (0.95 g, 83%) as a clear yellow oil. (Found: C, 72.5; H, 11.3. $C_{29}H_{44}O_4$ requires C, 72.7; H, 11.2%); ν_{max} (neat)/cm^{-1} 2853 (CH), 1722 (CO), 1661 (C=C), 1466, 1370, 1252, 1161, 1038; $[\alpha]_D^{26}$ −5.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9 Hz, 19-H_3), 1.25–1.53 (35H, m, OCH_2CH_3, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2, 17-H_2, 18-H_2 and $C(CH_3)_2$), 4.17–4.24 (3H, m, 5-H and OCH_2CH_3), 4.63 (1H, td, *J* 6.3, 1.4 Hz, 4-H), 6.06 (1H, dd, *J* 15.6, 1.4 Hz, 2-H), 6.84 (1H, dd, *J* 15.6, 6.3 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 14.4 (CH_3), 22.9 (CH_2), 25.7 (CH_3), 26.5 (CH_2), 28.3 (CH_3), 29.5 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.8 (2 × CH_2), 29.8 (2 × CH_2), 30.6 (CH_2), 32.1 (CH_2), 60.6 (CH_2), 77.6 (CH), 78.7 (CH), 108.9 (C), 123.2 (CH), 144.0 (CH), 166.2 (CH); *m/z* (CI) 397.3312 (MH^+. $C_{29}H_{45}O_4$ requires 397.3318), 379 (12%), 339 (100), 143 (13), 81 (12).

(*2E*,*4S*,5*R*)-4,5-(*O*-Isopropylidene)nonadec-2-en-1,4,5-triol (23)



Diisobutylaluminium hydride (0.55 mL, 1 M in hexanes) was added dropwise to a stirred solution of ethyl (2*E*,4*S*,5*R*)-4,5-(*O*-isopropylidene)-4,5-dihydroxynonadec-2-enoate (**22**) (0.95 g, 2.4 mmol) in diethyl ether (50 mL) at −78 °C. The solution was stirred at −78 °C for 3 h then allowed to return to room temperature over 18 h. The reaction was quenched with saturated ammonium chloride solution (30 mL), filtered through a pad of Celite® then extracted with diethyl ether (30 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purified by column chromatography (elution with 20% ethyl acetate:petroleum ether) to yield (*2E*,4*S*,5*R*)-4,5-(*O*-isopropylidene)nonadec-2-en-1,4,5-triol (**23**) (0.71 g, 83%) as a clear oil. ν_{max} (neat)/cm^{-1} 3417 (OH), 2922 (CH), 1456, 1369, 1216, 1095, 1027; $[\alpha]_D^{24}$ −42.0 (*c* 1.1, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.0 Hz, 19-H_3), 1.22–1.48 (32H, m, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2, 17-H_2, 18-H_2 and $C(CH_3)_2$), 1.62 (1H, br s, OH), 4.12 (1H, ddd, *J* 8.7, 6.3, 4.7 Hz, 5-H), 4.16 (2H, dd, *J* 5.2, 1.5 Hz, 1-H_2), 4.50 (1H, dd, *J* 7.9, 6.3 Hz, 4-H), 5.68 (1H, ddt, *J* 15.5, 7.9, 1.5 Hz, 3-H), 5.88 (1H, dtd, *J* 15.5, 5.2, 0.6 Hz, 2-H); δ_C (126 MHz, $CDCl_3$) 14.3 (CH_3), 22.8 (CH_2), 25.8 (CH_3), 26.4 (CH_2), 28.4 (CH_3), 29.5 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.8 (2 × CH_2), 29.8 (3 × CH_2), 30.5 (CH_2), 32.1 (CH_2), 63.0 (CH_2), 78.5 (CH), 79.1 (CH), 108.2 (C), 127.5 (CH), 133.5 (CH); *m/z* (CI) 355.3211 (MH^+. $C_{22}H_{43}O_3$ requires 355.3212), 337 (20%), 297 (41), 279 (100), 225 (90).

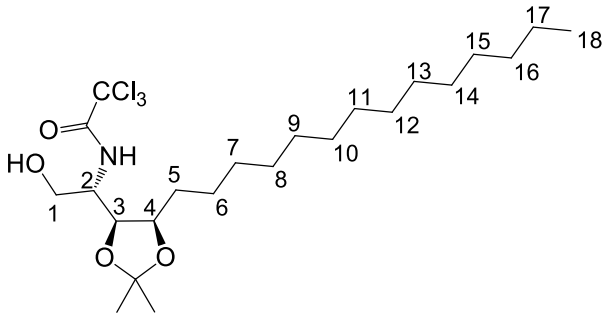
(3*R*,4*S*,5*R*)-3-(Trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)nonadec-1-en-4,5-diol (28b) and (3*S*,4*S*,5*R*)-3-(trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)nonadec-1-en-4,5-diol (28a)



1,8-Diazabicyclo[5.4.0]undec-7-ene (0.070 mL, 0.47 mmol) was added to a stirred solution of (*2E*,4*S*,5*R*)-4,5-(*O*-isopropylidene)nonadec-2-en-1,4,5-triol **(23)** (0.19 g, 0.54 mmol) and trichloroacetonitrile (0.080 mL, 0.80 mmol), at 0 °C, in dichloromethane (28 mL). The solution was stirred at 0 °C for 0.5 h, warmed to room temperature over 3 h then filtered through a pad of silica with dichloromethane (200 mL) and concentrated *in vacuo* to yield the crude trichloroacetimidate as a yellow oil which was used without further purification. The crude trichloroacetimidate **27** was dissolved in *p*-xylene (4 mL) and added to a pressure tube loaded with a stirrer bar and potassium carbonate (0.012 g, 0.087 mmol). The tube was sealed under argon and heated, with stirring, to 160 °C for 60 h. The reaction mixture was filtered through Celite® to yield a crude mixture of diastereomers (d.r. 1:1). Purification by column chromatography (elution with 5% ethyl acetate:petroleum ether) yielded (3*R*,4*S*,5*R*)-3-(trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)nonadec-1-en-4,5-diol (**28b**) (0.12 g, 44%) as a clear, colourless oil and (3*S*,4*S*,5*R*)-3-(trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)nonadec-1-en-4,5-diol (**28a**) (0.071 g, 26%) as a clear, colourless oil. Data for **28b**: ν_{max} (neat)/cm^{-1} 3427 (NH), 2922 (CH), 2853 (CH), 1721 (CO), 1496, 1211, 819; $[\alpha]_D^{27}$ −10.5 (*c* 1.4, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0 Hz, 19-H_3), 1.25–1.55 (32H, m, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2, 17-H_2 , 18-H_2 and $C(CH_3)_2$), 4.22–4.26 (2H, m, 4-H, 5-H), 4.38–4.41 (1H, m, 3-H), 5.27 (1H, d, *J* 10.4 Hz, 1-*H*H), 5.30 (1H, d, *J* 17.1 Hz, 1-H*H*), 5.83 (1H, ddd, *J* 17.1, 10.4, 5.8 Hz, 2-H), 7.19 (1H, d, *J* 7.7 Hz, NH); δ_C (126 MHz, $CDCl_3$) 14.3 (CH_3), 22.9 (CH_2), 24.3

(CH_3), 27.2 (CH_3), 27.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (2 × CH_2), 29.8 (2 × CH_2), 29.8 (CH_2), 29.9 (CH_2), 32.1 (CH_2), 53.2 (CH), 77.6 (CH), 78.4 (CH), 92.9 (C), 108.1 (C), 117.2 (CH_2), 134.8 (CH), 160.8 (C); *m/z* (CI) 498.2307 (MH^+. $C_{24}H_{43}NO_3Cl_3$ requires 498.2309), 440 (31%), 406 (28), 161 (35), 113 (52), 73 (100); Data for **28a**: ν_{max} (neat)/cm^{-1} 3324 (NH), 2922 (CH), 2853 (CH), 1694 (CO), 822; $[\alpha]_D^{27}$ −48.0 (*c* 0.8, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0 Hz, 19-H_3), 1.26–1.50 (32H, m, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2, 17-H_2, 18-H_2 and $C(CH_3)_2$), 4.13 (1H, dd, *J* 6.3, 3.8 Hz, 4'-H), 4.23 (1H, ddd, *J* 9.7, 6.3, 3.7 Hz, 5'-H), 4.55 (1H, dddt, *J* 8.7, 5.2, 3.8, 1.7 Hz, 3'-H), 5.28–5.32 (2H, m, 1'-H_2), 6.01 (1H, ddd, *J* 17.4, 10.5, 5.2 Hz, 2'-H), 6.91 (1H, d, *J* 8.7 Hz, NH); δ_C (126 MHz, $CDCl_3$) 14.3 (CH_3), 22.8 (CH_2), 25.3 (CH_3), 27.0 (CH_3), 27.1 (CH_2), 29.0 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.8 (2 × CH_2), 29.8 (CH_2), 29.9 (CH_2), 32.1 (CH_2), 54.2 (CH), 77.6 (CH), 79.0 (CH), 92.8 (C), 108.7 (C), 118.0 (CH_2), 134.0 (CH), 161.2 (C); *m/z* (CI) 498.2304 (MH^+. $C_{24}H_{43}NO_3Cl_3$ requires 498.2309), 464 (13%), 440 (100), 406 (81), 394 (22), 329 (21).

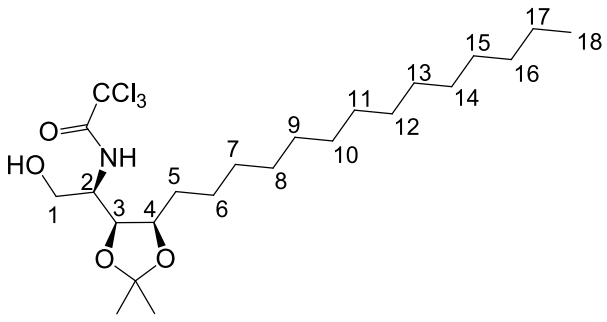
(2*S*,3*S*,4*R*)-2-(Trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (30a)



(3*S*,4*S*,5*R*)-3-(Trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)nonadec-1-en-4,5-diol (**28a**) (0.053 g, 0.11 mmol) was dissolved in a mixture of dichloromethane (10 mL) and methanol (10 mL) and cooled to −78 °C. Ozone was bubbled through the reaction mixture until the solution turned deep blue. After excess ozone was purged with oxygen gas, a solution of sodium borohydride (0.013 g, 0.32 mmol) in ethanol (10 mL) was added dropwise with vigorous stirring. The reaction mixture was then allowed to slowly return to room temperature over 5 h. The reaction mixture was quenched with a saturated solution of ammonium chloride (10 mL) then concentrated *in vacuo* to an aqueous

solution and extracted with diethyl ether (3 × 15 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude product. Purification by column chromatography (diethyl ether/petroleum ether, 1:1) gave (2*S*,3*S*,4*R*)-2-(trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (**30a**) (0.038 g, 71%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3307 (NH), 2918 (CH), 2849 (CH), 1687 (CO), 1533, 1221, 1047, 822; $[\alpha]_D^{20}$ +4.8 (*c* 1.1, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0 Hz, 18-H_3), 1.17–1.33 (24H, m, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2 and 17-H_2), 1.36 (3H, s, C(CH_3)(CH_3)), 1.49 (3H, s, C(CH_3)(CH_3)), 1.52–1.58 (2H, m, 5-H_2), 3.75 (1H, dd, *J* 11.4, 3.2 Hz, 1-*H*H), 4.01 (1H, dd, *J* 11.4, 3.2 Hz, 1-H*H*), 4.05 (1H, ddt, *J* 8.4, 5.6, 3.2 Hz, 2-H), 4.19–4.26 (2H, m, 3-H and 4-H), 7.18 (1H, d, *J* 8.4 Hz, NH); δ_C (126 MHz, $CDCl_3$) 14.2 (CH_3), 22.8 (CH_2), 25.1 (CH_3), 26.9 (CH_2), 27.6 (CH_3), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (2 × CH_2), 32.1 (CH_2), 52.1 (CH), 62.5 (CH_2), 77.8 (CH), 77.8 (CH), 92.7 (C), 108.6 (C), 161.7 (C); *m/z* (CI) 502.2264 (MH^+. $C_{23}H_{43}{}^{35}Cl_3NO_4$ requires 502.2258), 444 (100%), 410 (41), 329 (80), 313 (60), 271 (46), 257 (38), 219 (31), 172 (27), 148 (26), 73 (59).

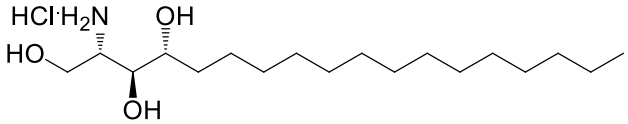
(2*R*,3*S*,4*R*)-2-(Trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (30b)



The reaction was carried out according to the procedure described for (2*S*,3*S*,4*R*)-2-(trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (**30a**) using (2*R*, 3*S*, 4*R*)-2-(trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (**28b**) (0.046 g, 0.18 mmol). This yielded (2*R*,3*S*,4*R*)-2-(trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (**30b**) (0.036 g, 77%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3419 (NH), 2922 (CH), 2853 (CH), 1717 (CO), 1502, 1211, 1050, 820; $[\alpha]_D^{26}$ −20.5 (*c* 1.0,

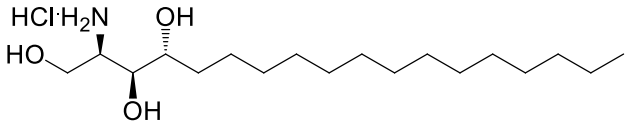
$CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9 Hz, 18-H_3), 1.21–1.33 (26H, m, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2 and 17-H_2), 1.38 (3H, s, C(C*H*$_3$)(CH_3)), 1.53 (3H, s, C(CH_3)(C*H*$_3$)), 3.74 (1H, dd, *J* 11.1, 6.4 Hz, 1-*H*H), 3.80 (1H, dd, *J* 11.1, 5.1 Hz, 1-H*H*), 3.90–3.98 (1H, m, 2-H), 4.21–4.29 (1H, m, 4-H), 4.41 (1H, dd, *J* 7.1, 1.4 Hz, 3-H), 7.25 (1H, d, *J* 7.4 Hz, NH); δ_C (126 MHz, $CDCl_3$) 14.2 (CH_3), 22.8 (CH_2), 24.5 (CH_3), 27.2 (CH_2), 27.2 (CH_3), 29.4 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 32.1 (CH_2), 52.7 (CH), 63.9 (CH_2), 76.0 (CH), 77.7 (CH), 92.9 (C), 108.3 (C), 161.9 (C); *m/z* (CI) 502.2252 (MH^+. $C_{23}H_{43}{}^{35}Cl_3NO_4$ requires 502.2258), 486 (14), 444 (100), 419 (34), 391 (42), 342 (37), 297 (68), 149 (11).

D-*ribo*-Phytosphingosine hydrochloride (10a)[176]



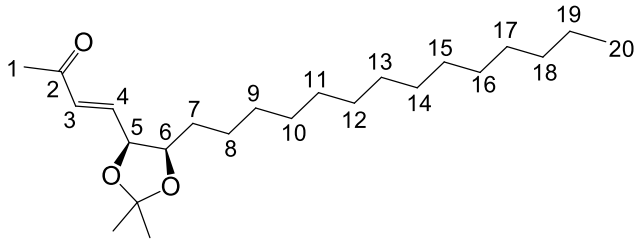
(2*S*,3*S*,4*R*)-2-(Trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (**30a**) (0.026 g, 0.052 mmol) was dissolved in a mixture of dichloromethane (2 mL) and methanol (2 mL). 4 M Sodium hydroxide (4 mL) was added and the reaction mixture stirred for 60 h. The solution was extracted with dichloromethane (3 × 20 mL), washed with water (3 × 20 mL) and concentrated *in vacuo*. The crude oil was then dissolved in a mixture of dichloromethane (2 mL) and methanol (2 mL). To this solution, 6 M hydrochloric acid (2 mL) was added and stirred for 3 h. The reaction was concentrated *in vacuo* and washed with petroleum ether (3 × 10 mL) to yield D-*ribo*-phytosphingosine hydrochloride (**10a**) as a white solid (0.015 g, 82%). Spectroscopic data as reported in literature.[176] $[\alpha]_D{}^{21}$ +4.8 (*c* 0.8, MeOH); δ_H (500 MHz, CD_3OD) 0.90 (3H, t, *J* 7.0 Hz, 18-H_3), 1.28–1.42 (24H, m, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2 and 17-H_2), 1.50–1.57 (1H, m, 5-*H*H), 1.63–1.73 (1H, m, 5-H*H*), 3.38–3.45 (2H, m, 3-H and 4-H), 4.11 (1H, ddd, *J* 8.8, 5.9, 3.2 Hz, 2-H), 4.39 (1H, t, *J* 8.8 Hz, 1-*H*H), 4.46 (1H, dd, *J* 8.8, 5.9 Hz, 1-H*H*); δ_C (126 MHz, CD_3OD) 14.3 (CH_3), 23.6 (CH_2), 26.6 (CH_2), 30.4 (CH_2), 30.7 (2 × CH_2), 30.7 (5 × CH_2), 30.8 (CH_2), 33.0 (CH_2), 34.8 (CH_2), 55.6 (CH), 67.4 (CH_2), 74.0 (CH), 75.8 (CH); *m/z* (ESI) 318.2990 (MH^+. $C_{18}H_{40}NO_3$ requires 318.3003).

L-*arabino*-Phytosphingosine hydrochloride (10b)[176]



The reaction was carried out as described for D-*ribo*-phytosphingosine hydrochloride (**10a**) using (2*R*,3*S*,4*R*)-2-(trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (**30b**) (0.033 g, 0.066 mmol). This gave L-*arabino*-phytosphingosine hydrochloride (**10b**) as a white solid (0.020 g, 87%). Spectroscopic data as reported in literature.[176] $[\alpha]_D^{20}$ −12.2 (*c* 0.9, MeOH); δ_H (500 MHz, CD_3OD) 0.90 (3H, t, *J* 7.0 Hz, 18-H_3), 1.27–1.40 (24H, m, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2 and 17-H_2), 1.49–1.58 (1H, m, 5-*H*H), 1.76 (1H, td, *J* 9.4, 3.4 Hz, 5-H*H*), 3.20 (1H, dd, *J* 8.1, 4.2 Hz, 3-H), 3.42 (1H, td, *J* 8.1, 3.4 Hz, 4-H), 4.13 (1H, ddd, *J* 8.9, 6.3, 4.2 Hz, 2-H), 4.29 (1H, dd, *J* 8.9, 6.3 Hz, 1-*H*H), 4.48 (1H, t, *J* 8.9 Hz, 1-H*H*); δ_C (126 MHz, CD_3OD) 14.3 (CH_3), 23.6 (CH_2), 26.5 (CH_2), 30.4 (CH_2), 30.7 (CH_2), 30.7 (CH_2), 30.7 (5 × CH_2), 30.8 (CH_2), 33.0 (CH_2), 35.1 (CH_2), 55.9 (CH), 69.2 (CH_2), 73.9 (CH), 76.3 (CH); *m/z* (ESI) 318.2990 (MH^+. $C_{18}H_{40}NO_3$ requires 318.3003).

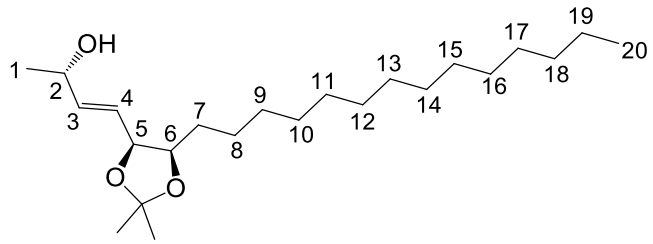
(3*E*,5*S*,6*R*)-5,6-(*O*-Isopropylidene)-5,6-dihydroxyicos-3-en-2-one (31)



The reaction was carried out according to the previously described procedure for ethyl (2*E*,4*S*,5*R*)-4,5-(*O*-isopropylidene)-4,5-dihydroxynonadec-2-enoate (**22**) using (2*S*,3*R*)-2,3-(*O*-isopropylidene)heptadecan-1,2,3-triol (**19**) (0.050 g, 0.15 mmol) and dimethyl 2-oxopropylphosphonate (0.040 mL, 0.29 mmol). This yielded (3*E*,5*S*,6*R*)-5,6-(*O*-isopropylidene)-5,6-dihydroxyicos-3-en-2-one (**31**) (0.043 g, 79%) as a colourless oil. ν_{max} (neat)/cm^{-1} 2916 (CH), 2848 (CH), 1697 (CO), 1676 (C=C), 1632, 1373, 1246, 1217, 1102, 1036; $[\alpha]_D^{21}$ –2.3 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.9 Hz, 20-H_3), 1.21–1.34 (24H, m, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2, 17-H_2, 18-H_2 and 19-H_2), 1.38 (3H, s, C(CH_3)(CH_3)), 1.41–1.49 (2H, m, 7-H_2), 1.51 (3H, s, C(CH_3)(CH_3)), 2.28 (3H, s, 1-

H_3), 4.24 (1H, ddd, *J* 8.7, 6.4, 4.6 Hz, 6-H), 4.64 (1H, td, *J* 6.4, 1.3 Hz, 5-H), 6.28 (1H, dd, *J* 15.9, 1.3 Hz, 3-H), 6.65 (1H, dd, 15.9, 6.4 Hz, 4-H); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 22.8 (CH_2), 25.6 (CH_3), 26.4 (CH_2), 27.7 (CH_3), 28.2 (CH_3), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.8 (2 × CH_2), 29.8 (2 × CH_2), 30.7 (CH_2), 32.1 (CH_2), 77.8 (CH), 78.6 (CH), 109.0 (C), 131.8 (CH), 142.6 (CH), 198.0 (C); *m/z* (CI) 367.3216 (MH^+. $C_{23}H_{43}O_3$ requires 367.3212), 349 (17%), 309 (45), 239 (4), 141 (100), 113 (16), 81 (16).

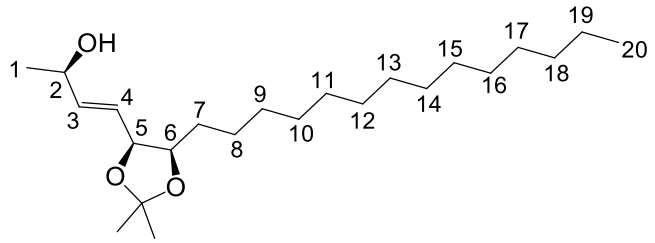
(3*E*,2*S*,5*S*,6*R*)-5,6-(*O*-Isopropylidene)-icos-3-en-2,5,6-triol (32a)



(*R*)-(+)-2-Methyl-CBS-oxazaborolidine (0.60 mL, 0.60 mmol, 1 M solution in toluene) was added dropwise with stirring to a solution of (3*E*,5*S*,6*R*)-5,6-(*O*-isopropylidene)-5,6-dihydroxyicos-3-en-2-one (**31**) (0.20 g, 0.55 mmol) in dry tetrahydrofuran (20 mL) at 0 °C. The solution was stirred for 0.5 h at 0 °C before borane (1.6 mL, 1.6 mmol, 1 M in tetrahydrofuran) was added dropwise and stirring was continued at 0 °C for 7.5 h. The reaction was quenched with methanol (10 mL), then warmed to room temperature and concentrated *in vacuo*. The resulting residue was dissolved in diethyl ether (30 mL) and washed with 1 M citric acid (3 × 50 mL), water (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and purified by column chromatography (ethyl acetate/petroleum ether, 1:6, 1% triethylamine) to yield (3*E*,2*S*,5*S*,6*R*)-5,6-(*O*-isopropylidene)-icos-3-en-2,5,6-triol (**32a**) (0.20 g, 99%) as a clear, colourless oil. ν_{max} (neat)/cm^{-1} 3397 (OH), 2982 (CH), 2922 (CH), 1456, 1368, 1215, 1032; $[\alpha]_D^{22}$ +4.5 (*c* 1.1, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0 Hz, 20-H_3), 1.23–1.32 (27H, m, 1-H_3, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2, 17-H_2, 18-H_2 and 19-H_2), 1.36 (3H, s, C(CH_3)(CH_3)), 1.38–1.46 (2H, m, 7-H_2), 1.48 (3H, s, C(CH_3)(CH_3)), 4.12 (1H, ddd, *J* 8.6, 6.3, 4.7 Hz, 6-H), 4.35 (1H, quin, *J* 5.9 Hz, 2-H), 4.49 (1H, dd, *J* 7.9, 6.3 Hz, 5-H), 5.65 (1H, ddd, *J* 15.5, 7.9, 1.2 Hz, 4-H), 5.81 (1H, ddd, *J* 15.5, 5.9, 0.7 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.3 (CH_3), 22.8 (CH_2), 23.4 (CH_3), 25.8 (CH_3), 26.3 (CH_2), 28.4 (CH_3), 29.5 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.8

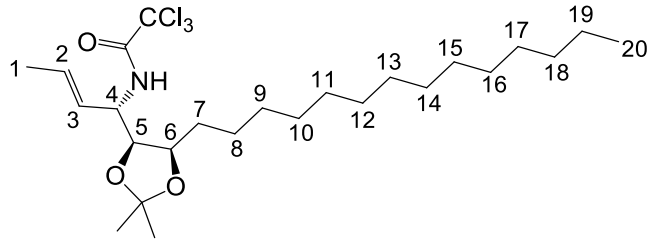
(2 × CH_2), 29.8 (CH_2), 29.8 (2 × CH_2), 30.6 (CH_2), 32.1 (CH_2), 68.2 (CH), 78.5 (CH), 79.0 (CH), 108.2 (C), 125.9 (CH), 138.4 (CH); *m/z* (ESI) 391.3169 (MNa^+. $C_{23}H_{44}NaO_3$ requires 391.3183).

(3*E*,2*R*,5*S*,6*R*)-5,6-(*O*-Isopropylidene)-icos-3-en-2,5,6-triol (32b)



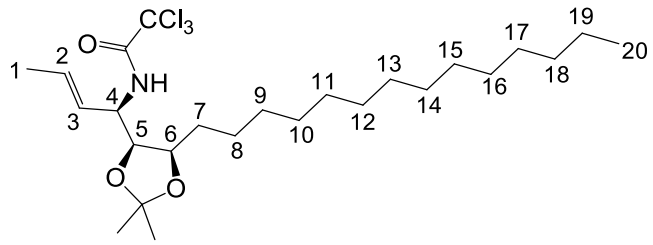
The reaction was carried out according to the procedure described above for (3*E*,2*S*,5*S*,6*R*)-5,6-(*O*-isopropylidene)-icos-3-en-2,5,6-triol (**32a**) using (3*E*,5*S*,6*R*)-5,6-(*O*-isopropylidene)-5,6-dihydroxyicos-3-en-2-one (**31**) (0.10 g, 0.28 mmol) and (*S*)-(−)-2-methyl-CBS-oxazaborolidine (0.30 mL, 0.30 mmol, 1 M solution in tetrahydrofuran). This yielded (3*E*,2*R*,5*S*,6*R*)-5,6-(*O*-isopropylidene)-icos-3-en-2,5,6-triol (**32b**) (0.065 g, 64%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3414 (OH), 2922 (CH), 2853 (CH), 1458, 1370, 1217, 1044, 756; $[\alpha]_D^{24}$ −3.7 (*c* 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9 Hz, 20-H_3), 1.20–1.31 (29H, m, 1-H_3, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2, 17-H_2, 18-H_2 and 19-H_2), 1.35 (3H, s, C(*C*H_3)(CH_3)), 1.47 (3H, s, C(CH_3)(C*H*$_3$)), 4.08–4.15 (1H, m, 6-H), 4.33 (1H, quintet of doublets, *J* 6.5, 0.9 Hz, 2-H), 4.47 (1H, dd, *J* 8.0, 6.2 Hz, 5-H), 5.62 (1H, ddd, *J* 15.5, 8.0, 0.9 Hz, 4-H), 5.78 (1H, ddd, *J* 15.5, 6.5, 0.6 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.3 (CH_3), 22.8 (CH_2), 23.3 (CH_3), 25.8 (CH_3), 26.2 (CH_2), 28.4 (CH_3), 29.5 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (3 × CH_2), 29.8 (CH_2), 29.8 (CH_2), 30.4 (CH_2), 30.5 (CH_2), 32.1 (CH_2), 68.3 (CH), 78.5 (CH), 79.0 (CH), 108.2 (C), 126.1 (CH), 138.5 (CH); *m/z* (CI) 369.3366 (MH^+. $C_{23}H_{45}O_3$ requires 369.3369), 351 (37%), 309 (14), 293 (100), 225 (28), 183 (39), 125 (88).

(2*E*,4*S*,5*S*,6*R*)-4-(Trichloromethylcarbonylamino)-5,6-(*O*-isopropylidene)-icos-2-en-5,6-diol (34a)



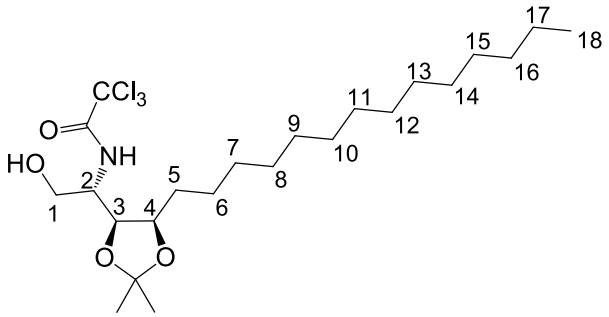
1,8-Diazabicycloundec-7-ene (0.011 g, 0.07 mmol) was added to a stirred solution of (3*E*,2*S*,5*S*,6*R*)-5,6-(*O*-isopropylidene)-icos-3-en-2,5,6-triol (**32a**) (0.053 g, 0.14 mmol) and trichloroacetonitrile (0.031 g, 0.21 mmol) at 0 °C in dichloromethane (3 mL). The solution was stirred at 0 °C for 0.5 h then warmed to room temperature over 3 h. The solution was filtered through a pad of silica with dichloromethane (200 mL) and concentrated *in vacuo* to yield the allylic trichloroacetimidate **33a** as a yellow oil, which was used without further purification. The allylic trichloroacetimidate was dissolved in *p*-xylene (2 mL) and added to a microwave vial loaded with a silicon carbide bar and potassium carbonate (0.012 g, 6 mg/mL). The vial was sealed under argon and heated to 140 °C for 0.25 h in a microwave reactor. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (diethyl ether/petroleum ether, 1:10) gave (2*E*,4*S*,5*S*,6*R*)-4-(trichloromethylcarbonylamino)-5,6-(*O*-isopropylidene)-icos-2-en-5,6-diol (**34a**) (0.053 g, 72%) as a white solid. Mp 53–58 °C; ν_{max} (neat)/cm^{-1} 3356 (NH), 2918 (CH), 2851 (CH), 1688 (CO), 1516, 1219, 959, 818; $[\alpha]_D^{22}$ −28.5 (*c* 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.81 (3H, t, *J* 6.9 Hz, 20-H_3), 1.17–1.31 (27H, m, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2, 17-H_2, 18-H_2, 19-H_2 and C(CH_3)(CH_3)), 1.41 (3H, s, C(CH_3)(CH_3)), 1.50–1.64 (2H, m, 7-H_2), 1.67 (3H, dd, *J* 6.4, 1.4 Hz, 1-H_3), 4.04 (1H, dd, *J* 6.3, 3.8 Hz, 5-H), 4.14 (1H, ddd, *J* 9.6, 6.3, 3.7 Hz, 6-H), 4.40–4.44 (1H, m, 4-H), 5.53 (1H, ddd, *J* 15.5, 5.7, 1.4 Hz, 3-H), 5.64 (1H, dqd, *J* 15.5, 6.4, 1.1 Hz, 2-H), 6.83 (1H, d, *J* 8.7 Hz, NH); δ_C (126 MHz, $CDCl_3$) 14.3 (CH_3), 18.2 (CH_3), 22.9 (CH_2), 25.3 (CH_3), 27.0 (CH_3), 27.1 (CH_2), 29.0 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.8 (2 × CH_2), 29.9 (2 × CH_2), 32.1 (CH_2), 53.8 (CH), 77.6 (CH), 79.1 (CH), 92.9 (C), 108.5 (C), 126.7 (CH), 129.4 (CH), 161.0 (C); *m/z* (ESI) 534.2265 (MH^+. $C_{25}H_{44}{}^{35}Cl_3NNaO_3$ requires 534.2279).

(2*E*,4*R*,5*S*,6*R*)-4-(Trichloromethylcarbonylamino)-5,6-(*O*-isopropylidene)-icos-2-en-5,6-diol (34b)



The reaction was carried out according to the procedure described for (2*E*,4*S*,5*S*,6*R*)-4-(trichloromethylcarbonylamino)-5,6-(*O*-isopropylidene)-icos-2-en-5,6-diol (**34a**) using (3*E*,2*R*,5*S*,6*R*)-5,6-(*O*-isopropylidene)-icos-3-en-2,5,6-triol (**32b**) (0.029 g, 0.079 mmol). This yielded (2*E*,4*R*,5*S*,6*R*)-4-(trichloromethylcarbonylamino)-5,6-(*O*-isopropylidene)-icos-2-en-5,6-diol (**34b**) (0.029 g, 71%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3426 (NH), 2922 (CH), 2853 (CH), 1719 (CO), 1495, 1213, 964, 820; $[\alpha]_D^{22}$ −12.6 (*c* 0.9, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0 Hz, 20-H_3), 1.20–1.33 (24H, m, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2, 17-H_2, 18-H_2 and 19-H_2), 1.38 (3H, s, C(C*H*$_3$)(CH_3)), 1.45–1.51 (2H, m, 7-H_2), 1.54 (3H, s, $C(CH_3)$(C*H*$_3$)), 1.72 (3H, ddd, *J* 6.5, 1.6, 0.9 Hz, 1-H_3), 4.16–4.24 (2H, m, 5-H and 6-H), 4.30–4.37 (1H, m, 4-H), 5.45 (1H, ddq, *J* 15.3, 7.3, 1.6 Hz, 3-H), 5.75 (1H, dqd, *J* 15.3, 6.5, 0.9 Hz, 2-H), 7.18 (1H, d, *J* 7.0 Hz, NH); δ_C (126 MHz, $CDCl_3$) 14.3 (CH_3), 18.0 (CH_3), 22.9 (CH_2), 24.4 (CH_3), 27.2 (CH_3), 27.3 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (2 × CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 32.1 (CH_2), 52.8 (CH), 77.6 (CH), 78.9 (CH), 93.0 (C), 108.0 (C), 127.8 (CH), 129.0 (CH), 160.6 (C); *m/z* (CI) 512.2458 (MH^+. $C_{25}H_{45}{}^{35}Cl_3NO_3$ requires 512.2465), 478 (84%), 442 (100), 408 (55), 297 (20), 189 (34), 113 (14).

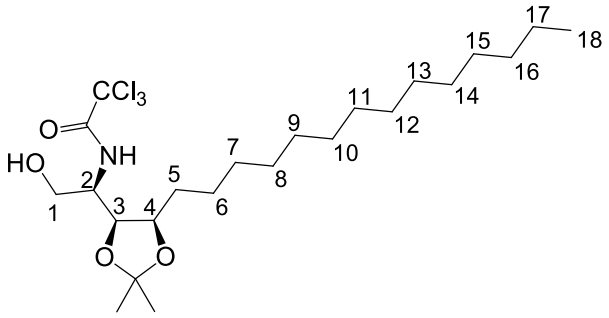
(2*S*,3*S*,4*R*)-2-(Trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (30a)



(2*E*,4*S*,5*S*,6*R*)-4-(Trichloromethylcarbonylamino)-5,6-(*O*-isopropylidene)-icos-2-en-5,6-diol (**32a**) (0.057 g, 0.11 mmol) was dissolved in a mixture of dichloromethane (10 mL) and methanol (10 mL) and cooled to −78 °C. Ozone was bubbled through the reaction mixture until the solution turned deep blue. After excess ozone was purged with oxygen gas, a solution of sodium borohydride (0.013 g, 0.32 mmol) in ethanol (10 mL) was added dropwise with vigorous stirring. The reaction mixture was then allowed to slowly return to room temperature over 5 h. The reaction mixture was quenched with a saturated solution of ammonium chloride (10 mL) then concentrated *in vacuo* to an aqueous solution and extracted with diethyl ether (3 × 15 mL). The combined organic layers were then washed with water (20 mL) and brine (20 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the crude product. Purification by column chromatography (diethyl ether/petroleum ether, 1:1) gave (2*S*,3*S*,4*R*)-2-(trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (**30a**) (0.041 g, 73%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3307 (NH), 2918 (CH), 2849 (CH), 1687 (CO), 1533, 1221, 1047, 822; $[\alpha]_D^{20}$ +4.8 (*c* 1.1, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0 Hz, 18-H_3), 1.17–1.33 (24H, m, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2 and 17-H_2), 1.36 (3H, s, C(C*H*$_3$)(CH_3)), 1.49 (3H, s, C(CH_3)(C*H*$_3$)), 1.52–1.58 (2H, m, 5-H_2), 3.75 (1H, dd, *J* 11.4, 3.2 Hz, 1-*H*H), 4.01 (1H, dd, *J* 11.4, 3.2 Hz, 1-H*H*), 4.05 (1H, ddt, *J* 8.4, 5.6, 3.2 Hz, 2-H), 4.19–4.26 (2H, m, 3-H and 4-H), 7.18 (1H, d, *J* 8.4 Hz, NH); δ_C (126 MHz, $CDCl_3$) 14.2 (CH_3), 22.8 (CH_2), 25.1 (CH_3), 26.9 (CH_2), 27.6 (CH_3), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (2 × CH_2), 32.1 (CH_2), 52.1 (CH), 62.5 (CH_2), 77.8 (CH), 77.8 (CH), 92.7 (C), 108.6 (C), 161.7 (C); *m/z* (CI) 502.2264 (MH^+. $C_{23}H_{43}{}^{35}Cl_3NO_4$ requires

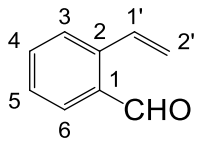
502.2258), 444 (100%), 410 (41), 329 (80), 313 (60), 271 (46), 257 (38), 219 (31), 172 (27), 148 (26), 73 (59).

(2*R*,3*S*,4*R*)-2-(Trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (30b)



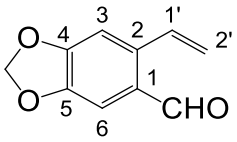
The reaction was carried out according to the procedure described for (2*S*,3*S*,4*R*)-2-(trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (**30a**) using (2*E*,4*R*,5*S*,6*R*)-4-(trichloromethylcarbonylamino)-5,6-(*O*-isopropylidene)-icos-2-en-5,6-diol (**32b**) (0.090 g, 0.18 mmol). This yielded (2*R*,3*S*,4*R*)-2-(trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)octadecan-1,3,4-triol (**30b**) (0.058 g, 66%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3419 (NH), 2922 (CH), 2853 (CH), 1717 (CO), 1502, 1211, 1050, 820; $[\alpha]_D^{26}$ −20.5 (*c* 1.0, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9 Hz, 18-H_3), 1.21–1.33 (26H, m, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2 and 17-H_2), 1.38 (3H, s, C(CH_3)(CH_3)), 1.53 (3H, s, C(CH_3)(CH_3)), 3.74 (1H, dd, *J* 11.1, 6.4 Hz, 1-*H*H), 3.80 (1H, dd, *J* 11.1, 5.1 Hz, 1-H*H*), 3.90–3.98 (1H, m, 2-H), 4.21–4.29 (1H, m, 4-H), 4.41 (1H, dd, *J* 7.1, 1.4 Hz, 3-H), 7.25 (1H, d, *J* 7.4 Hz, NH); δ_C (126 MHz, $CDCl_3$) 14.2 (CH_3), 22.8 (CH_2), 24.5 (CH_3), 27.2 (CH_2), 27.2 (CH_3), 29.4 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 32.1 (CH_2), 52.7 (CH), 63.9 (CH_2), 76.0 (CH), 77.7 (CH), 92.9 (C), 108.3 (C), 161.9 (C); *m/z* (CI) 502.2252 (MH^+. $C_{23}H_{43}{}^{35}Cl_3NO_4$ requires 502.2258), 486 (14), 444 (100), 419 (34), 391 (42), 342 (37), 297 (68), 149 (11).

2-Vinylbenzaldehyde (49a)[177]



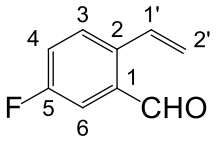
Potassium vinyltrifluoroborate (0.904 g, 6.75 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.276 g, 0.337 mmol) were added to a degassed solution of 2-bromobenzaldehyde (**52a**) (0.624 g, 3.37 mmol) and triethylamine (1.40 mL, 10.1 mmol) in propan-2-ol (34 mL). The solution was then heated to 80 °C for 18 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and purified by filtration through a pad of silica (elution with 20% diethyl ether:petroleum ether) to yield 2-vinylbenzaldehyde (**49a**) (0.374 g, 84%) as a yellow oil. Spectroscopic data was in accordance with literature values.[177] δ_H (400 MHz, $CDCl_3$) 5.52 (1H, dd, *J* 11.0, 1.2 Hz, 2'-*H*H), 5.71 (1H, dd, *J* 17.4, 1.2 Hz, 2'-H*H*), 7.40–7.48 (1H, m, ArH), 7.49–7.60 (3H, m, 1'-H and 2 × ArH), 7.81–7.86 (1H, m, ArH), 10.30 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 119.6 (CH_2), 127.6 (CH), 128.1 (CH), 131.4 (CH), 133.1 (C), 133.5 (CH), 133.9 (CH), 140.7 (C), 192.6 (CH); *m/z* (EI) 132 (M^+, 60%), 131 (20), 104 (53), 103 (52), 86 (92), 84 (100), 78 (42).

4,5-Methylenedioxy-2-vinylbenzaldehyde (49b)[178]



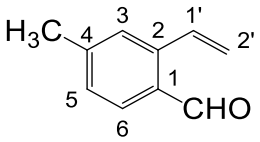
The reaction was carried out according to the previously described procedure for 2-vinylbenzaldehyde (**49a**) using 2-bromo-4,5-methylenedioxybenzaldehyde (**52b**) (0.400 g, 1.75 mmol). This gave 4,5-methylenedioxy-2-vinylbenzaldehyde (**49b**) (0.296 g, 96%) as a yellow solid. Mp 50–53 °C (lit.,[178] 52–54 °C); δ_H (500 MHz, $CDCl_3$) 5.48 (1H, dd, *J* 10.9, 0.8 Hz, 2'-*H*H), 5.62 (1H, dd, *J* 17.3, 0.8 Hz, 2'-H*H*), 6.05 (2H, s, OCH_2O), 6.98 (1H, s, 3-H), 7.31 (1H, s, 6-H), 7.41 (1H, dd, *J* 17.3, 10.9 Hz, 1'-H), 10.21 (1H, s, CHO); δ_C (126 MHz, $CDCl_3$) 102.2 (CH_2), 106.8 (CH), 108.1 (CH), 119.2 (CH_2), 128.2 (C), 132.4 (CH), 138.5 (C), 148.1 (C), 152.7 (C), 189.6 (CH); *m/z* (EI) 176 (M^+, 100%), 147 (91), 84 (90), 49 (68).

5-Fluoro-2-vinylbenzaldehyde (49c)[177]



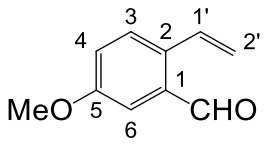
The reaction was carried out according to the previously described procedure for 2-vinylbenzaldehyde (**49a**) using 2-bromo-5-fluorobenzaldehyde (**52c**) (0.500 mg, 2.46 mmol) and potassium vinyltrifluoroborate (0.396 g, 2.96 mmol). This gave 5-fluoro-2-vinylbenzaldehyde (**49c**) (0.336 g, 91%) as a yellow oil. Spectroscopic data was in accordance with literature values.[177] δ_H (400 MHz, $CDCl_3$) 5.50 (1H, d, *J* 11.0 Hz, 2'-*H*H), 5.62 (1H, d, *J* 17.4 Hz, 2'-H*H*), 7.18–7.26 (1H, m, ArH), 7.38 (1H, dd, *J* 17.4, 11.0 Hz, 1'-H), 7.44–7.54 (2H, m, 2 × ArH), 10.24 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 116.1 (CH, d, $^2J_{CF}$ 22.1 Hz), 119.9 (CH_2), 121.1 (CH, d, $^2J_{CF}$ 21.9 Hz), 129.7 (CH, d, $^3J_{CF}$ 7.3 Hz), 132.0 (CH), 134.4 (C, d, $^3J_{CF}$ 5.9 Hz), 137.0 (C, d, $^4J_{CF}$ 3.4 Hz), 162.3 (C, d, $^1J_{CF}$ 249.5 Hz), 190.6 (CHO); *m/z* (EI) 150 (M^+, 79%), 122 (100), 121 (63), 101 (61), 96 (52), 75 (32).

4-Methyl-2-vinylbenzaldehyde (49d)[177]



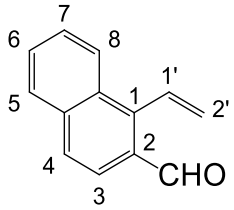
The reaction was carried out according to the previously described procedure for 2-vinylbenzaldehyde (**49a**) using 2-bromo-4-methylbenzaldehyde (**52d**) (0.400 g, 2.01 mmol). This gave 4-methyl-2-vinylbenzaldehyde (**49d**) (0.264 g, 90%) as a yellow oil. Spectroscopic data was in accordance with literature values.[177] δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, 4-CH_3), 5.49 (1H, dd, *J* 11.0, 1.2 Hz, 2'-*H*H), 5.69 (1H, dd, *J* 17.4, 1.2 Hz, 2'-H*H*), 7.24 (1H, d, *J* 7.9 Hz, 5-H), 7.37 (1H, s, 3-H), 7.53 (1H, dd, *J* 17.4, 11.0 Hz, 1'-H), 7.73 (1H, d, *J* 7.9 Hz, 6-H), 10.23 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 22.0 (CH_3), 119.2 (CH_2), 128.2 (CH), 128.9 (CH), 130.9 (C), 131.7 (CH), 133.7 (CH), 140.7 (C), 144.9 (C), 192.2 (CH); *m/z* (EI) 146 (M^+, 100%), 117 (71), 115 (37), 91 (25), 84 (11).

5-Methoxy-2-vinylbenzaldehyde (49e)



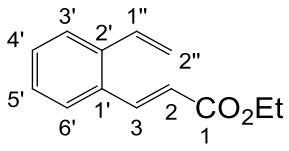
The reaction was carried out according to the previously described procedure for 2-vinylbenzaldehyde (**49a**) using 2-bromo-5-methoxybenzaldehyde (**52e**) (0.400 g, 1.86 mmol). This gave 5-methoxy-2-vinylbenzaldehyde (**49e**) (0.269 g, 89%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2943 (CH), 2838 (CH), 1686 (CO), 1605 (C=C), 1494, 1317, 1246, 1164, 1024; δ_H (400 MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 5.45 (1H, dd, *J* 10.9, 1.1 Hz, 2'-*H*H), 5.61 (1H, dd, *J* 17.3, 1.1 Hz, 2'-H*H*), 7.13 (1H, dd, *J* 8.6, 2.8 Hz, 4-H), 7.34 (1H, d, *J* 2.8 Hz, 6-H), 7.42 (1H, dd, *J* 17.3, 10.9 Hz, 1'-H), 7.51 (1H, d, *J* 8.6 Hz, 3-H), 10.32 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 55.7 (CH_3), 113.0 (CH), 118.3 (CH_2), 121.3 (CH), 129.0 (CH), 132.4 (CH), 133.9 (C), 134.0 (C), 159.5 (C), 191.8 (CH); *m/z* (EI) 162.0680 (M^+, $C_{10}H_{10}O_2$ requires 162.0681), 134 (100%), 119 (42), 91 (41), 84 (39), 49 (28).

1-Vinyl-2-naphthaldehyde (49f)[177]



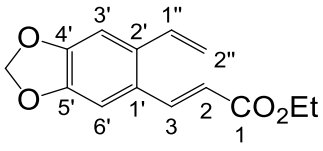
The reaction was carried out according to the previously described procedure for 2-vinylbenzaldehyde (**49a**) using 1-bromo-2-naphthaldehyde (**52f**) (0.400 g, 1.70 mmol). This gave 1-vinyl-2-naphthaldehyde (**49f**) (0.275 g, 89%) as a yellow solid. Spectroscopic data was in accordance with literature values.[177] Mp 68–70 °C; δ_H (400 MHz, $CDCl_3$) 5.49 (1H, dd, *J* 17.5, 1.6 Hz, 2'-*H*H), 6.01 (1H, dd, *J* 11.3, 1.6 Hz, 2'-H*H*), 7.38 (1H, dd, *J* 17.5, 11.3 Hz, 1'-H), 7.58 (1H, ddd, *J* 8.4, 6.9, 1.4 Hz, ArH), 7.63 (1H, ddd, *J* 8.4, 6.9, 1.3 Hz, ArH), 7.83 (1H, d, *J* 8.4 Hz, ArH), 7.87 (1H, dd, *J* 8.4, 1.3 Hz, ArH), 8.00 (1H, d, *J* 8.4 Hz, ArH), 8.18 (1H, dd, *J* 8.4, 0.7 Hz, 3-H), 10.46 (1H, d, *J* 0.7 Hz, CHO); δ_C (101 MHz, $CDCl_3$) 123.1 (CH_2), 126.0 (CH), 126.2 (CH), 127.1 (CH), 128.2 (CH), 128.6 (CH), 129.0 (CH), 130.8 (CH), 131.5 (C), 131.7 (C), 135.9 (C), 143.4 (C), 192.8 (CH); *m/z* (EI) 182 (M^+, 57%), 153 (100), 152 (52), 127 (14), 84 (11), 76 (13).

Ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (50a)[179]



Lithium bromide (0.583 g, 6.70 mmol) was added to a solution of triethyl phosphonoacetate (**21**) (1.13 mL, 5.69 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.848 mL, 5.69 mmol) in acetonitrile (25 mL) and stirred at room temperature for 0.5 h. 2-Vinylbenzaldehyde (**49a**) (0.221 g, 1.67 mmol) was added and the solution was stirred at room temperature for 18 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (30 mL), concentrated to half volume *in vacuo* and extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by filtration through a pad of silica (elution with 20% diethyl ether:petroleum ether) gave ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) (0.331 g, 98%) as a yellow oil. Spectroscopic data was in accordance with literature values.[179] δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 4.27 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 5.43 (1H, dd, *J* 11.0, 1.2 Hz, 2"-*H*H), 5.64 (1H, dd, *J* 17.4, 1.2 Hz, 2"-H*H*), 6.35 (1H, d, *J* 15.9 Hz, 2-H), 7.07 (1H, dd, *J* 17.4, 11.0 Hz, 1"-H), 7.29 (1H, td, *J* 7.5, 1.2 Hz, ArH), 7.36 (1H, td, *J* 7.5, 1.2 Hz, ArH), 7.46–7.55 (2H, m, ArH), 8.04 (1H, d, *J* 15.9 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.5 (CH_3), 60.7 (CH_2), 118.2 (CH_2), 120.5 (CH), 127.1 (CH), 127.2 (CH), 128.1 (CH), 130.1 (CH), 132.7 (C), 134.4 (CH), 138.1 (C), 142.5 (CH), 167.0 (C); *m/z* (EI) 202 (M^+, 10%), 173 (4), 157 (10), 129 (100), 128 (58), 102 (5), 83 (12).

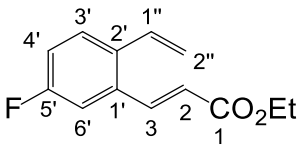
Ethyl (2*E*)-3-(4',5'-methylenedioxy-2'-vinylphenyl)prop-2-enoate (50b)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 4,5-methylenedioxy-2-vinylbenzaldehyde (**49b**) (0.279 g, 1.59 mmol). This gave ethyl (2*E*)-3-(4',5'-methylenedioxy-2-vinylphenyl)prop-2-enoate (**50b**) (0.367 g, 94%) as an off-white solid. Mp 82–84 °C; ν_{max} (neat)/cm^{-1} 2904 (CH), 1714 (CO), 1614 (C=C), 1500,

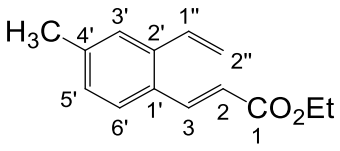
1489, 1284, 1177; δ_H (500 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.26 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.35 (1H, dd, *J* 10.9, 1.0 Hz, 2”-*H*H), 5.53 (1H, dd, *J* 17.2, 1.0 Hz, 2”-H*H*), 5.98 (2H, s, OCH_2O), 6.21 (1H, d, *J* 15.7 Hz, 2-H), 6.95 (1H, s, 3’-H), 7.00 (1H, s, 6’-H), 7.03 (1H, dd, *J* 17.2, 10.9 Hz, 1”-H), 7.98 (1H, d, *J* 15.7 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 13.5 (CH_3), 59.6 (CH_2), 100.7 (CH_2), 105.1 (CH), 105.6 (CH), 115.9 (CH_2), 117.6 (CH), 125.9 (C), 132.8 (C), 132.9 (CH), 140.7 (CH), 147.1 (C), 148.8 (C), 166.1 (C); *m/z* (EI) 246.0889 (M^+, $C_{14}H_{14}O_4$ requires 246.0892), 217 (30%), 201 (30), 173 (100), 143 (38), 115 (96).

Ethyl (2*E*)-3-(5’-fluoro-2’-vinylphenyl)prop-2-enoate (50c)



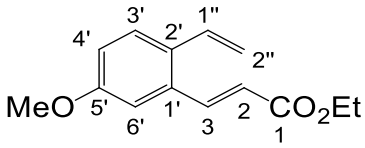
The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2’-vinylphenyl)prop-2-enoate (**50a**) using 5-fluoro-2-vinylbenzaldehyde (**49c**) (0.190 g, 1.27 mmol). This gave ethyl (2*E*)-3-(5’-fluoro-2’-vinylphenyl)prop-2-enoate (**50c**) (0.247 g, 89%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2982 (CH), 2932 (CH), 1712 (CO), 1636 (C=C), 1486, 1316, 1237, 1176, 1034; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.26 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.38 (1H, dd, *J* 10.9, 0.7 Hz, 2”-*H*H), 5.56 (1H, dd, *J* 17.2, 0.7 Hz, 2”-H*H*), 6.31 (1H, d, *J* 15.9 Hz, 2-H), 6.92–7.06 (2H, m, 1”-H and 6’-H), 7.18 (1H, dd, *J* 9.2, $^4J_{HF}$ 2.7 Hz, 3’-H), 7.43 (1H, dd, *J* 9.2, $^3J_{HF}$ 5.7 Hz, 4’-H), 7.94 (1H, dd, *J* 15.9, $^5J_{HF}$ 1.3 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.4 (CH_3), 60.8 (CH_2), 113.2 (CH, d, $^2J_{CF}$ 22.3 Hz), 117.1 (CH, d, $^2J_{CF}$ 21.6 Hz), 118.0 (CH_2), 121.4 (CH), 128.9 (CH, d, $^3J_{CF}$ 8.1 Hz), 133.3 (CH), 134.3 (C, d, $^4J_{CF}$ 3.2 Hz), 134.4 (C, d, $^3J_{CF}$ 7.6 Hz), 141.1 (CH, d, $^4J_{CF}$ 2.3 Hz), 162.3 (C, d, $^1J_{CF}$ 247.3 Hz), 166.5 (C); *m/z* (ESI) 243.0789 (MNa^+, $C_{13}H_{13}FNaO_2$ requires 243.0792), 236 (35%), 218 (5), 147 (8), 135 (4).

Ethyl (2*E*)-3-(4'-methyl-2'-vinylphenyl)prop-2-enate (50d)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 4-methyl-2-vinylbenzaldehyde (**49d**) (0.258 g, 1.77 mmol). This gave ethyl (2*E*)-3-(4'-methyl-2'-vinylphenyl)prop-2-enoate (**50d**) (0.385 g, 100%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2980 (CH), 1710 (CO), 1631 (C=C), 1313, 1266, 1176, 1158, 1037; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.37 (3H, s, 4'-CH_3), 4.26 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.40 (1H, dd, *J* 11.0, 1.3 Hz, 2"-*H*H), 5.62 (1H, dd, *J* 17.3, 1.3 Hz, 2"-H*H*), 6.32 (1H, d, *J* 15.9 Hz, 2-H), 7.06 (1H, dd, *J* 17.3, 11.0 Hz, 1"-H), 7.09–7.12 (1H, m, 5'-H), 7.30 (1H, s, 3'-H), 7.45 (1H, d, *J* 8.0 Hz, 6'-H), 8.01 (1H, d, *J* 15.9 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 21.5 (CH_3), 60.6 (CH_2), 117.9 (CH_2), 119.4 (CH), 127.1 (CH), 127.7 (CH), 129.0 (CH), 129.9 (C), 134.5 (CH), 138.1 (C), 140.3 (C), 142.3 (CH), 167.2 (C); *m/z* (ESI) 239.1035 (MNa^+, $C_{14}H_{16}NaO_2$ requires 239.1043).

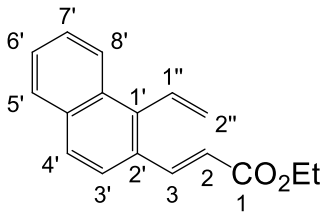
Ethyl (2*E*)-3-(5'-methoxy-2'-vinylphenyl)prop-2-enoate (50e)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 5-methoxy-2-vinylbenzaldehyde (**49e**) (0.266 g, 1.64 mmol). This gave ethyl (2*E*)-3-(5'-methoxy-2'-vinylphenyl)acrylate (**50e**) (0.376 g, 99%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2980 (CH), 1709 (CO), 1634 (C=C), 1603, 1493, 1314, 1236, 1167, 1035, 980; δ_H (500 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.83 (3H, s, OCH_3), 4.27 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.32 (1H, dd, *J* 11.0, 1.1 Hz, 2"-*H*H), 5.54 (1H, dd, *J* 17.3, 1.1 Hz, 2"-H*H*), 6.33 (1H, d, *J* 15.8 Hz, 2-H), 6.92 (1H, dd, *J* 8.6, 2.7 Hz, 4'-H), 7.00 (1H, dd, *J* 17.3, 11.0 Hz, 1"-H), 7.02 (1H, d, *J* 2.7 Hz, 6'-H), 7.43 (1H, d, *J* 8.6 Hz, 3'-H), 8.01 (1H, d, *J* 15.8 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 55.5 (CH_3), 60.7 (CH_2), 111.3 (CH), 116.3 (CH_2), 116.6 (CH), 120.6 (CH), 128.3 (CH), 131.1

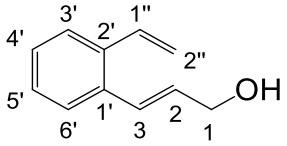
(C), 133.7 (CH), 133.7 (C), 142.4 (CH), 159.3 (C), 166.9 (C); *m/z* (EI) 232.1099 (M^+, $C_{14}H_{16}O_3$ requires 232.1099), 203 (47%), 187 (24), 159 (100), 144 (83), 115 (53).

Ethyl (2*E*)-3-(1'-vinylnaphthalen-2'-yl)prop-2-enoate (50f)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 1-vinyl-2-naphthaldehyde (**49f**) (0.271 g, 1.49 mmol). This gave ethyl (2*E*)-3-(1'-vinylnaphthalen-2'-yl)prop-2-enoate (**50f**) (0.327 g, 87%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2978 (CH), 1711 (CO), 1627 (C=C), 1293, 1256, 1175, 1038; δ_H (500 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.28 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.43 (1H, dd, *J* 17.7, 1.8 Hz, 2"-*H*H), 5.93 (1H, dd, *J* 11.4, 1.8 Hz, 2"-H*H*), 6.48 (1H, d, *J* 16.0 Hz, 2-H), 7.21 (1H, dd, *J* 17.7, 11.4 Hz, 1"-H), 7.49–7.55 (2H, m, 2 × ArH), 7.71 (1H, d, *J* 8.7 Hz, 4'-H), 7.77 (1H, d, *J* 8.7 Hz, 3'-H), 7.80–7.85 (1H, m, ArH), 8.10–8.14 (1H, m, ArH), 8.24 (1H, d, *J* 16.0 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 60.6 (CH_2), 119.1 (CH_2), 123.6 (CH), 124.4 (CH), 126.2 (CH), 126.8 (CH), 127.1 (CH), 128.0 (CH), 128.4 (CH), 129.6 (C), 131.9 (C), 132.7 (CH), 134.1 (C), 138.2 (C), 144.0 (CH), 167.3 (C); *m/z* (ESI) 275.1037 (MNa^+, $C_{17}H_{16}NaO_2$ requires 275.1043).

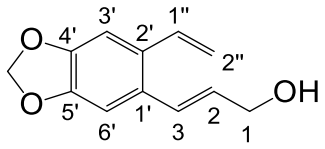
(2*E*)-3-(2'-Vinylphenyl)prop-2-en-1-ol (51a)



Diisobutylaluminium hydride (3.33 mL, 1 M solution in hexanes) was added dropwise with stirring, to a solution of ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) (0.269 g, 1.33 mmol), in diethyl ether (27 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

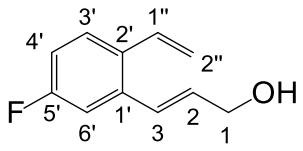
(100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (elution with 50% diethyl ether/petroleum ether) yielded (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) (0.207 g, 97%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3329 (OH), 2922 (CH), 1624 (C=C), 1476, 1414, 1099, 966; δ_H (500 MHz, $CDCl_3$) 1.54 (1H, br s, OH), 4.35 (2H, d, *J* 5.4 Hz, 1-H_2), 5.34 (1H, dd, *J* 11.0, 1.2 Hz, 2"-*H*H), 5.63 (1H, dd, *J* 17.4, 1.2 Hz, 2"-H*H*), 6.24 (1H, dt, *J* 15.7, 5.4 Hz, 2-H), 6.92 (1H, d, *J* 15.7 Hz, 3-H), 7.02 (1H, dd, *J* 17.4, 11.0 Hz, 1"-H), 7.23–7.27 (2H, m, ArH), 7.41–7.47 (2H, m, ArH); δ_C (126 MHz, $CDCl_3$) 64.0 (CH_2), 116.5 (CH_2), 126.5 (CH), 126.7 (CH), 127.9 (CH), 128.0 (CH), 128.9 (CH), 131.2 (CH), 135.0 (CH), 135.1 (C), 136.3 (C); *m/z* (EI) 160.0882 (M^+, $C_{11}H_{12}O$ requires 160.0888), 141 (13%), 129 (100), 115 (21), 91 (9).

(2*E*)-3-(4',5'-Methylenedioxy-2'-vinylphenyl)prop-2-en-1-ol (51b)



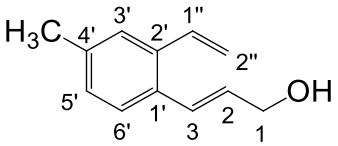
The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(4',5'-methylenedioxy-2-vinylphenyl)prop-2-enoate (**50b**) (0.357 g, 1.45 mmol). This gave (2*E*)-3-(4',5'-methylenedioxy-2'-vinylphenyl)prop-2-en-1-ol (**51b**) (0.292 g, 99%) as a white solid. Mp 73–76 °C; ν_{max} (neat)/cm^{-1} 3332 (OH), 2896 (CH), 1622 (C=C), 1501, 1478, 1245, 1039; δ_H (500 MHz, $CDCl_3$) 1.65 (1H, s, OH), 4.30 (2H, dd, *J* 5.7, 1.5 Hz, 1-H_2), 5.23 (1H, dd, *J* 10.9, 1.0 Hz, 2"-*H*H), 5.49 (1H, dd, *J* 17.3, 1.0 Hz, 2"-H*H*), 5.93 (2H, s, OCH_2O), 6.10 (1H, dt, *J* 15.6, 5.7 Hz, 2-H), 6.84 (1H, dt, *J* 15.6, 1.5 Hz, 3-H), 6.89 (1H, s, ArH), 6.93 (1H, s, ArH), 6.94 (1H, dd, *J* 17.3, 10.9 Hz, 1"-H); δ_C (126 MHz, $CDCl_3$) 62.9 (CH_2), 100.2 (CH_2), 105.0 (CH), 105.2 (CH), 113.9 (CH_2), 127.6 (CH), 128.5 (C), 128.8 (CH), 129.7 (C), 133.4 (CH), 146.8 (C), 146.8 (C); *m/z* (EI) 204.0790 (M^+, $C_{12}H_{12}O_3$ requires 204.0786), 173 (78%), 115 (41), 82 (100).

(2*E*)-3-(5'-Fluoro-2'-vinylphenyl)prop-2-en-1-ol (51c)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(5'-fluoro-2'-vinylphenyl)prop-2-enoate (**50c**) (0.223 g, 1.01 mmol). This gave (2*E*)-3-(5'-fluoro-2'-vinylphenyl)prop-2-en-1-ol (**51c**) (0.174 g, 97%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3329 (OH), 2868 (CH), 1605 (C=C), 1574, 1483, 1096, 964, 912; δ_H (500 MHz, $CDCl_3$) 1.48 (1H, br s, OH), 4.35 (2H, dd, *J* 5.4, 1.5 Hz, 1-H_2), 5.31 (1H, dd, *J* 11.0, 0.9 Hz, 2"-*H*H), 5.55 (1H, dd, *J* 17.4, 0.9 Hz, 2"-H*H*), 6.24 (1H, dt, *J* 15.8, 5.4 Hz, 2-H), 6.87 (1H, dd, *J* 15.8, 1.5 Hz, 3-H), 6.91–6.98 (2H, m, 1"-H and 6'-H), 7.11 (1H, dd, *J* 9.3, $^4J_{HF}$ 2.7 Hz, 3'-H), 7.41 (1H, dd, *J* 9.3, $^3J_{HF}$ 5.9 Hz, 4'-H); δ_C (126 MHz, $CDCl_3$) 63.7 (CH_2), 112.9 (d, $^2J_{CF}$ 22.0 Hz, CH), 114.9 (d, $^2J_{CF}$ 21.6 Hz, CH), 116.4 (CH_2), 127.6 (d, $^4J_{CF}$ 2.2 Hz, CH), 128.3 (d, $^3J_{CF}$ 8.3 Hz, CH), 132.2 (CH), 132.5 (d, $^4J_{CF}$ 3.1 Hz, C), 133.9 (CH), 137.0 (d, $^3J_{CF}$ 7.7 Hz, C), 162.6 (d, $^1J_{CF}$ 246.2 Hz, C); *m/z* (EI) 178.0791 (M^+, $C_{11}H_{11}FO$ requires 178.0794), 160 (11), 147 (100), 133 (13), 127 (10), 84 (5).

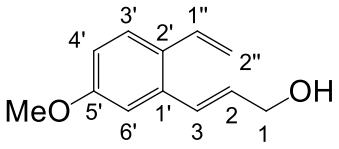
(2*E*)-3-(4'-Methyl-2'-vinylphenyl)prop-2-en-1-ol (51d)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(4'-methyl-2'-vinylphenyl)prop-2-enoate (**50d**) (0.286 g, 1.32 mmol). This gave (2*E*)-3-(4'-methyl-2'-vinylphenyl)prop-2-en-1-ol (**51d**) (0.213 g, 92%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3333 (OH), 2921 (CH), 1488, 1238, 1201, 1005, 910; δ_H (500 MHz, $CDCl_3$) 1.41 (1H, t, *J* 5.7 Hz, OH), 2.34 (3H, s, 4'-CH_3), 4.33 (2H, td, *J* 5.7, 1.0 Hz, 1-H_2), 5.31 (1H, dd, *J* 11.0, 1.4 Hz, 2"-*H*H), 5.61 (1H, dd, *J* 17.4, 1.4 Hz, 2"-H*H*), 6.20 (1H, dt, *J* 15.7, 5.7 Hz, 2-H), 6.88 (1H, d, *J* 15.7 Hz, 3-H), 7.00 (1H, dd, *J* 17.4, 11.0 Hz, 1"-H), 7.06 (1H, d, *J* 7.9 Hz, ArH), 7.26 (1H, s, 3'-H), 7.33 (1H, d, *J* 7.9 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 21.3 (CH_3), 64.2 (CH_2), 116.3 (CH_2), 126.7

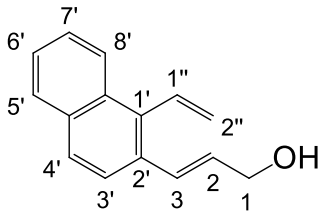
(CH), 127.1 (CH), 128.9 (CH), 128.9 (CH), 130.3 (CH), 132.3 (C), 135.0 (CH), 136.2 (C), 137.6 (C); *m/z* (CI) 157.1021 (MH^+-H_2O, $C_{12}H_{13}$ requires 157.1017), 113 (31%), 97 (38), 85 (85), 71 (100), 69 (90).

(2*E*)-3-(5'-Methoxy-2'-vinylphenyl)prop-2-en-1-ol (51e)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(5'-methoxy-2'-vinylphenyl)prop-2-enoate (**50e**) (0.321 g, 1.38 mmol). This gave (2*E*)-3-(5'-methoxy-2'-vinylphenyl)prop-2-en-1-ol (**51e**) (0.233 g, 89%) as a clear oil. ν_{max} (neat)/cm^{-1} 3345 (OH), 2936 (CH), 1603 (C=C), 1491, 1288, 1246, 1167, 1105, 1024; δ_H (500 MHz, $CDCl_3$) 1.96 (1H, br s, OH), 3.81 (3H, s, OCH_3), 4.33 (2H, d, *J* 5.4 Hz, 1-H_2), 5.22 (1H, dd, *J* 11.0, 1.3 Hz, 2"-*H*H), 5.52 (1H, dd, *J* 17.4, 1.3 Hz, 2"-H*H*), 6.22 (1H, dt, *J* 15.7, 5.4 Hz, 2-H), 6.81 (1H, dd, *J* 8.6, 2.7 Hz, 4'-H), 6.89 (1H, d, *J* 15.7 Hz, 3-H), 6.91–6.98 (2H, m, 1"-H and 6'-H), 7.40 (1H, d, *J* 8.6 Hz, 3'-H); δ_C (126 MHz, $CDCl_3$) 55.5 (CH_3), 63.9 (CH_2), 111.4 (CH), 114.1 (CH), 114.7 (CH_2), 127.7 (CH), 128.9 (CH), 129.3 (C), 131.4 (CH), 134.3 (CH), 136.3 (C), 159.4 (C); *m/z* (EI) 190.0991 (M^+, $C_{12}H_{14}O_2$ requires 190.0994), 172 (8%), 159 (100), 144 (48), 115 (28), 83 (21).

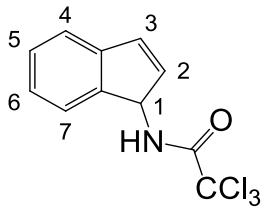
(2*E*)-3-(1'-Vinylnaphthalen-2'-yl)prop-2-en-1-ol (51f)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(1'-vinylnaphthalen-2'-yl)prop-2-enoate (**50f**) (0.325 g, 1.29 mmol). This gave (2*E*)-3-(1'-vinylnaphthalen-2'-yl)prop-2-en-1-ol (**51f**) (0.248 g, 92%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3327 (OH), 3056 (CH), 2859 (CH), 1508, 1418, 1094, 994, 970; δ_H (500 MHz, $CDCl_3$) 1.49 (1H, t, *J* 5.7 Hz, OH), 4.38 (2H, t, *J* 5.7 Hz, 1-H_2), 5.43 (1H,

dd, *J* 17.8, 2.0 Hz, 2”-*H*H), 5.84 (1H, dd, *J* 11.4, 2.0 Hz, 2”-H*H*), 6.41 (1H, dt, *J* 15.9, 5.7 Hz, 2-H), 7.07–7.15 (2H, m, 3-H and 1”-H), 7.43–7.50 (2H, m, 2 × ArH), 7.69 (1H, d, *J* 8.7 Hz, 4’-H), 7.74 (1H, d, *J* 8.7 Hz, 3’-H), 7.79–7.82 (1H, m, ArH), 8.08–8.11 (1H, m, ArH); δ_C (126 MHz, $CDCl_3$) 64.3 (CH_2), 122.9 (CH_2), 123.8 (CH), 125.9 (CH), 125.9 (CH), 126.4 (CH), 127.6 (CH), 128.2 (CH), 129.6 (CH), 130.4 (CH), 131.5 (C), 132.0 (C), 133.1 (C), 133.5 (CH), 134.8 (C); *m/z* (EI) 210.1049 (M^+, $C_{15}H_{14}O$ requires 210.1045), 179 (100%), 165 (29), 152 (19), 139 (6), 115 (5), 67 (21).

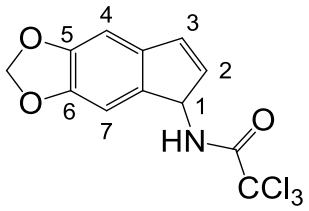
1-(2’,2’,2’-Trichloromethylcarbonylamino)-1*H*-indene (54a)



(2*E*)-3-(2’-Vinylphenyl)prop-2-en-1-ol (**51a**) (0.051 g, 0.32 mmol) was dissolved in dry dichloromethane (8 mL) and cooled to 0 °C under argon with stirring. Trichloroacetonitrile (0.048 mL, 0.48 mmol) was added to the solution, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.024 mL, 0.16 mmol) and the reaction was allowed to return to room temperature over 1.5 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 **53a** 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 160 °C for 18 h. The reaction was allowed to cool to room temperature, Grubbs 2nd generation catalyst (0.011 g, 0.013 mmol) was added and the reaction was heated to 50 °C for 20 h. The reaction mixture was concentrated *in vacuo* and purified by filtration through a short pad of silica (elution with 20% diethyl ether/petroleum ether) to yield 1-(2’,2’,2’-trichloromethylcarbonylamino)-1*H*-indene (**54a**) (0.072 g, 82%) as a white solid. Mp 73–75 °C; ν_{max} (neat)/cm^{-1} 3325 (NH), 2927 (CH), 1697 (CO), 1506, 1235, 819; δ_H (400 MHz, $CDCl_3$) 5.62–5.68 (1H, m, 1-H), 6.42 (1H, dd, *J* 5.6, 1.9 Hz, 2-H), 6.66 (1H, br d, *J* 5.2 Hz, NH), 6.91 (1H, ddd, *J* 5.6, 1.9, 0.8 Hz, 3-H), 7.23–7.28 (1H, m, ArH), 7.33–7.36 (2H, m, ArH), 7.47–7.51 (1H, m, ArH); δ_C (126

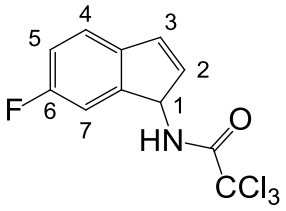
MHz, $CDCl_3$) 58.5 (CH), 92.5 (C), 122.0 (CH), 123.7 (CH), 126.7 (CH), 129.0 (CH), 134.0 (CH), 134.8 (CH), 142.9 (C), 143.2 (C), 162.8 (C); *m/z* (CI) 275.9753 (MH^+, $C_{11}H_9{}^{35}Cl_3NO$ requires 275.9750), 242 (62%), 208 (32), 172 (10), 85 (17), 69 (27).

5,6-Methylenedioxy-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (54b)



The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(4',5'-methylenedioxy-2'-vinylphenyl)prop-2-en-1-ol (**51b**) (0.057 mg, 0.28 mmol). This gave 5,6-methylenedioxy-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54b**) (0.050 g, 57%) as an off-white solid. Mp 106–108 °C; ν_{max} (neat)/cm^{-1} 3325 (NH), 2901 (CH), 1696 (CO), 1502, 1472, 1337, 1276, 1039, 939, 838, 820; δ_H (500 MHz, $CDCl_3$) 5.47–5.52 (1H, m, 1-H), 5.95 (1H, d, *J* 1.4 Hz, OC*H*HO), 5.96 (1H, d, *J* 1.4 Hz, OCH*H*O), 6.30 (1H, dd, *J* 5.6, 2.0 Hz, 2-H), 6.71 (1H, br d, *J* 8.4 Hz, NH), 6.76 (1H, dd, *J* 5.6, 1.3 Hz, 3-H), 6.78 (1H, s, 4-H), 6.96 (1H, s, 7-H); δ_C (126 MHz, $CDCl_3$) 58.1 (CH), 92.5 (C), 101.5 (CH_2), 103.0 (CH), 105.4 (CH), 132.8 (CH), 134.4 (CH), 136.8 (C), 137.0 (C), 147.0 (C), 148.3 (C), 162.7 (C); *m/z* (EI) 320.9539 (M^+, $C_{12}H_8{}^{35}Cl_2{}^{37}ClNO_3$ requires 320.9542), 284 (68%), 248 (100), 218 (21), 202 (32), 174 (80), 159 (61), 116 (52), 103 (58), 89 (58).

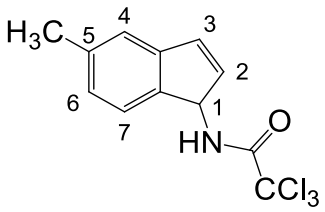
6-Fluoro-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (54c)



The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(5'-fluoro-2'-vinylphenyl)prop-2-en-1-ol (**51c**) (0.048 g, 0.27 mmol). This gave 6-fluoro-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54c**) (0.052 g, 65%) as an off-

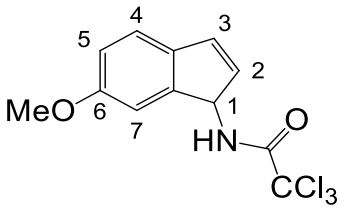
white solid. Mp 92–94 °C; ν_{max} (neat)/cm^{-1} 3321 (NH), 2916 (CH), 1695 (CO), 1506, 1477, 1270, 1234, 839, 821; δ_H (500 MHz, $CDCl_3$) 5.58–5.64 (1H, m, 1-H), 6.38 (1H, dd, *J* 5.6, 2.0 Hz, 2-H), 6.69 (1H, br s, NH), 6.87 (1H, dd, *J* 5.6, 1.6 Hz, 3-H), 7.03 (1H, ddd, $^3J_{HF}$ 8.4, *J* 8.4, 2.4 Hz, 5-H), 7.21 (1H, dd, $^3J_{HF}$ 8.4, *J* 2.4 Hz, 7-H), 7.26 (1H, dd, *J* 8.4, $^4J_{HF}$ 4.9 Hz, 4-H); δ_C (126 MHz, $CDCl_3$) 58.4 (CH, d, $^4J_{CF}$ 2.1 Hz), 92.4 (C), 112.0 (CH, d, $^2J_{CF}$ 24.1 Hz), 115.7 (CH, d, $^2J_{CF}$ 22.8 Hz), 122.7 (CH, d, $^3J_{CF}$ 8.6 Hz), 133.7 (CH, d, $^5J_{CF}$ 4.1 Hz), 134.2 (CH), 138.9 (C, d, $^4J_{CF}$ 2.6 Hz), 145.2 (C, d, $^3J_{CF}$ 8.3 Hz), 162.3 (C, d, $^1J_{CF}$ 246.5 Hz), 162.8 (C); *m/z* (ESI) 315.9461 (MNa^+, $C_{11}H_7{}^{35}Cl_3FNNaO$ requires 315.9469).

5-Methyl-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (54d)



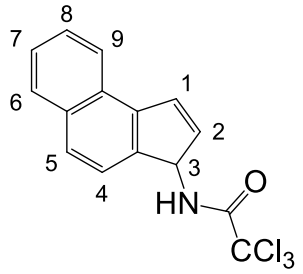
The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(4'-methyl-2'-vinylphenyl)prop-2-en-1-ol (**51d**) (0.063 g, 0.36 mmol). This gave 5-methyl-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54d**) (0.072 g, 68%) as a white solid. Mp 88–92 °C; ν_{max} (neat)/cm^{-1} 3321 (NH), 2923 (CH), 1695 (CO), 1505, 1239, 837, 809; δ_H (500 MHz, $CDCl_3$) 2.39 (3H, s, 5-CH_3), 5.58–5.63 (1H, m, 1-H), 6.40 (1H, dd, *J* 5.6, 2.0 Hz, 2-H), 6.65 (1H, br d, *J* 6.1 Hz, NH), 6.86 (1H, ddd, *J* 5.6, 1.8, 0.6 Hz, 3-H), 7.07 (1H, d, *J* 7.5 Hz, 6-H), 7.16 (1H, s, 4-H), 7.37 (1H, d, *J* 7.5 Hz, 7-H); δ_C (126 MHz, $CDCl_3$) 21.6 (CH_3), 58.2 (CH), 92.5 (C), 122.8 (CH), 123.5 (CH), 127.3 (CH), 134.2 (CH), 134.8 (CH), 139.0 (C), 140.0 (C), 143.5 (C), 162.8 (C); *m/z* (ESI) 311.9707 (MNa^+, $C_{12}H_{10}{}^{35}Cl_3NNaO$ requires 311.9720).

6-Methoxy-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (54e)



The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(5'-methoxy-2'-vinylphenyl)prop-2-en-1-ol (**51e**) (0.049 g, 0.26 mmol). This gave 6-methoxy-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54e**) (0.048 g, 61%) as an off-white solid. Mp 69–71 °C; ν_{max} (neat)/cm^{-1} 3314 (NH), 2940 (CH), 1697 (CO), 1505, 1234, 1026, 818, 737; δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 5.58–5.63 (1H, m, 1-H), 6.27 (1H, dd, *J* 5.6, 2.1 Hz, 2-H), 6.67 (1H, br d, *J* 7.8 Hz, NH), 6.80–6.88 (2H, m, 3-H and 5-H), 7.07 (1H, d, *J* 2.1 Hz, 7-H), 7.23 (1H, d, *J* 8.2 Hz, 4-H); δ_C (126 MHz, $CDCl_3$) 55.8 (CH_3), 58.5 (CH), 92.5 (C), 110.7 (CH), 113.9 (CH), 122.4 (CH), 131.7 (CH), 134.5 (CH), 135.9 (C), 145.0 (C), 159.3 (C), 162.8 (C); *m/z* (EI) 306.9751 (M^+, $C_{12}H_{10}{}^{35}Cl_2{}^{37}ClNO_2$ requires 306.9749), 270 (82%), 234 (48), 192 (15), 160 (60), 145 (64), 130 (40), 115 (42), 83 (100), 77 (21).

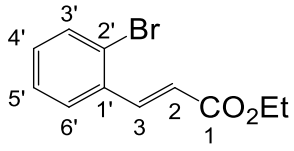
3-(2',2',2'-Trichloromethylcarbonylamino)-3*H*-benz[e]indene (54f)



The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(1'-vinylnaphth-2'-yl)prop-2-en-1-ol (**51f**) (0.055 g, 0.26 mmol). This gave 3-(2',2',2'-trichloromethylcarbonylamino)-3*H*-benz[e]indene (**54f**) (0.048 g, 56%) as an off-white solid. Mp 130–134 °C (decomposition); ν_{max} (neat)/cm^{-1} 3270 (NH), 3050 (CH), 1698 (CO), 1685, 1533, 1514, 1260, 841, 822; δ_H (500 MHz, $CDCl_3$) 5.79–5.84 (1H, m, 3-H), 6.61 (1H, dd, *J* 5.6, 1.8 Hz, 2-H), 6.72 (1H, br d, *J* 6.7 Hz, NH), 7.47–7.59 (3H, m, 1-H and 2 × ArH), 7.63 (1H, d, *J* 8.2 Hz, ArH), 7.79 (1H, d, *J* 8.2

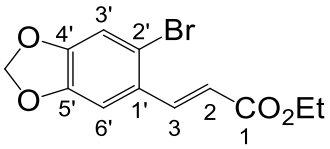
Hz, ArH), 7.91 (1H, d, *J* 7.9 Hz, ArH), 8.06 (1H, d, *J* 7.9 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 59.4 (CH), 92.5 (C), 121.3 (CH), 123.9 (CH), 126.3 (CH), 126.7 (CH), 127.2 (CH), 127.8 (C), 128.8 (CH), 132.1 (CH), 134.1 (C), 134.3 (CH), 139.7 (C), 140.4 (C), 163.0 (C); *m/z* (EI) 324.9829 (M^+, $C_{15}H_{10}{}^{35}Cl_3NO$ requires 324.9828), 290 (54%), 254 (91), 208 (46), 180 (91), 165 (100), 152 (83), 88 (40), 70 (70), 61 (57).

Ethyl (2*E*)-3-(2'-bromophenyl)prop-2-enoate (57a)[180]



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 2-bromobenzaldehyde (**52a**) (0.492 g, 2.66 mmol). This gave ethyl (2*E*)-3-(2'-bromophenyl)prop-2-enoate (**57a**) (0.558 g, 82%) as a colourless oil. Spectroscopic data was in accordance with literature values.[180] δ_H (500 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.28 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 6.39 (1H, d, *J* 15.9 Hz, 2-H), 7.22 (1H, td, *J* 7.6, 1.6 Hz, ArH), 7.32 (1H, t, *J* 7.6 Hz, ArH), 7.60 (1H, dd, *J* 7.6, 1.6 Hz, ArH), 7.61 (1H, dd, *J* 7.6, 1.6 Hz, ArH), 8.05 (1H, d, *J* 15.9 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 60.8 (CH_2), 121.3 (CH), 125.4 (C), 127.8 (CH), 127.9 (CH), 131.3 (CH), 133.6 (CH), 134.7 (C), 143.1 (CH), 166.5 (C); *m/z* (EI) 254 (M^+, 25%), 209 (45), 175 (86), 147 (100), 102 (62), 83 (31), 75 (21).

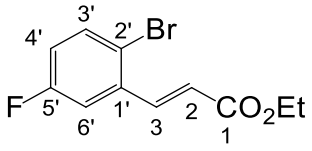
Ethyl (2*E*)-3-(2'-bromo-4',5'-methylenedioxyphenyl)prop-2-enoate (57b)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 2-bromo-4,5-methylenedioxybenzaldehyde (**52b**) (0.600 g, 2.62 mmol). This gave ethyl (2*E*)-3-(2'-bromo-4',5'-methylenedioxyphenyl)prop-2-enoate (**57b**) (0.781 g, 100%) as a white solid. Mp 101–105 °C; ν_{max} (neat)/cm^{-1} 3072 (CH), 1695 (CO), 1501 (C=C), 1476, 1289, 1256, 1228, 1113, 1027, 972; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1

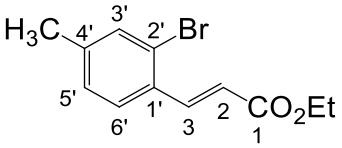
Hz, OCH_2CH_3), 4.25 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 6.01 (2H, s, OCH_2O), 6.22 (1H, d, *J* 15.9 Hz, 2-H), 7.03 (1H, s, ArH), 7.04 (1H, s, ArH), 7.96 (1H, d, *J* 15.9 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.4 (CH_3), 60.7 (CH_2), 102.3 (CH_2), 106.5 (CH), 113.2 (CH), 117.9 (C), 119.1 (CH), 127.8 (C), 142.8 (CH), 148.0 (C), 150.1 (C), 166.7 (C); *m/z* (EI) 297.9837 (M^+, $C_{12}H_{11}{}^{79}BrO_4$ requires 297.9841), 219 (83%), 191 (100), 174 (41), 133 (27), 84 (10).

Ethyl (2*E*)-3-(2'-bromo-5'-fluorophenyl)prop-2-enoate (57c)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 2-bromo-5-fluorobenzaldehyde (**52c**) (0.300 g, 1.48 mmol). This gave ethyl (2*E*)-3-(2'-bromo-5'-fluorophenyl)prop-2-enoate (**57c**) (0.384 g, 95%) as a colourless oil. ν_{max} (neat)/cm^{-1} 2984 (CH), 1709 (CO), 1638 (C=C), 1464, 1316, 1271, 1161, 1030; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.29 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 6.37 (1H, d, *J* 15.9 Hz, 2-H), 6.97 (1H, ddd, *J* 8.8, 7.7, 3.0 Hz, 4'-H), 7.30 (1H, dd, *J* 9.3, 3.0 Hz, 6'-H), 7.57 (1H, dd, *J* 8.8, 5.3 Hz, 3'-H), 7.97 (1H, dd, *J* 15.9, 1.5 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.4 (CH_3), 61.0 (CH_2), 114.6 (d, $^2J_{CF}$ 23.7 Hz, CH), 118.6 (d, $^2J_{CF}$ 22.7 Hz, CH), 119.6 (C), 122.4 (CH), 134.8 (d, $^3J_{CF}$ 7.9 Hz, CH), 136.4 (d, $^3J_{CF}$ 7.7 Hz, C), 142.1 (d, $^4J_{CF}$ 1.9 Hz, CH), 162.1 (d, $^1J_{CF}$ 247.4 Hz, C), 166.2 (C); *m/z* (EI) 271.9854 (M^+, $C_{11}H_{10}{}^{79}BrFO_2$ requires 271.9848), 229 (23%), 193 (36), 165 (100), 120 (47), 84 (20).

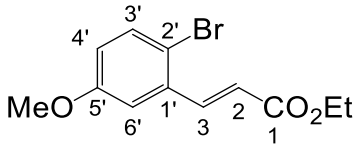
Ethyl (2*E*)-3-(2'-bromo-4'-methylphenyl)prop-2-enoate (57d)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 2-bromo-4-methylbenzaldehyde (**52d**) (0.500 g, 2.51 mmol). This gave ethyl (2*E*)-3-(2'-bromo-4'-methylphenyl)prop-2-enoate (**57d**) (0.648 g, 96%) as an off-white solid.

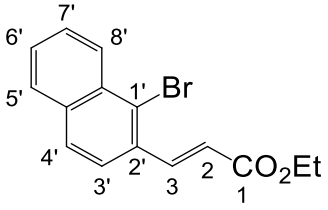
Mp 37–41 °C; ν_{max} (neat)/cm^{-1} 2980 (CH), 1709 (CO), 1634 (C=C), 1603, 1312, 1263, 1165, 1040, 978, 814; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.34 (3H, s, 4'-CH_3), 4.27 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 6.35 (1H, d, *J* 15.9 Hz, 2-H), 7.12 (1H, d, *J* 7.9 Hz, 5'-H), 7.44 (1H, s, 3'-H), 7.50 (1H, d, *J* 7.9 Hz, 6'-H), 8.02 (1H, d, *J* 15.9 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.5 (CH_3), 21.1 (CH_3), 60.8 (CH_2), 120.2 (CH), 125.4 (C), 127.5 (CH), 128.8 (CH), 131.7 (C), 134.0 (CH), 142.1 (C), 143.0 (CH), 166.7 (C); *m/z* (ESI) 290.9981 (MNa^+, $C_{12}H_{13}{}^{79}BrNaO_2$ requires 290.9991), 271 (6%), 236 (22), 223 (64), 144 (19).

Ethyl (2*E*)-3-(2'-bromo-5'-methoxyphenyl)prop-2-enoate (57e)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 2-bromo-5-methoxybenzaldehyde (**52e**) (0.500 g, 2.33 mmol). This gave ethyl (2*E*)-3-(2'-bromo-5'-methoxyphenyl)prop-2-enoate (**57e**) (0.619 g, 93%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2987 (CH), 1710 (CO), 1637 (C=C), 1465, 1288, 1177, 1017; δ_H (500 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.81 (3H, s, OCH_3), 4.28 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 6.37 (1H, d, *J* 15.9 Hz, 2-H), 6.81 (1H, dd, *J* 8.8, 3.0 Hz, 4'-H), 7.11 (1H, d, *J* 3.0 Hz, 6'-H), 7.49 (1H, d, *J* 8.8 Hz, 3'-H), 8.00 (1H, d, *J* 15.9 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 55.7 (CH_3), 60.9 (CH_2), 112.7 (CH), 116.1 (C), 117.8 (CH), 121.4 (CH), 134.1 (CH), 135.4 (C), 143.2 (CH), 159.2 (C), 166.5 (C); *m/z* (ESI) 306.9936 (MNa^+, $C_{12}H_{13}{}^{79}BrNaO_3$ requires 306.9940), 285 (6%), 264 (32), 239 (43), 160 (100).

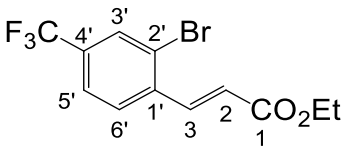
Ethyl (2*E*)-3-(1'-bromonaphthalen-2'-yl)prop-2-enoate (57f)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 1-bromo-2-naphthaldehyde

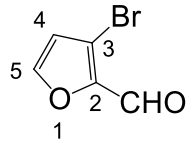
(**52f**) (0.500 g, 2.13 mmol). This gave ethyl (2*E*)-3-(1'-bromonaphthalen-2'-yl)prop-2-enoate (**57f**) (0.647 g, 100%) as a white solid. Mp 117–119 °C; ν_{max} (neat)/cm^{-1} 2976 (CH), 1707 (CO), 1632 (C=C), 1308, 1283, 1180, 1157, 980; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.32 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 6.50 (1H, d, *J* 15.9 Hz, 2-H), 7.53–7.69 (3H, m, 3 × ArH), 7.77–7.88 (2H, m, 2 × ArH), 8.35–8.43 (2H, m, 3-H and ArH); δ_C (101 MHz, $CDCl_3$) 14.5 (CH_3), 60.9 (CH_2), 121.8 (CH), 124.1 (CH), 126.9 (C), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 132.4 (C), 132.8 (C), 135.1 (C), 144.1 (CH), 166.7 (C); *m/z* (EI) 304.0101 (M^+, $C_{15}H_{13}{}^{79}BrO_2$ requires 304.0099), 225 (100%), 197 (43), 152 (15), 76 (4).

Ethyl (2*E*)-3-(2'-bromo-4'-trifluoromethylphenyl)prop-2-enoate (57g)



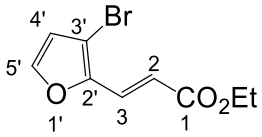
The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 2-bromo-4-trifluoromethylbenzaldehyde (**52g**) (0.500 g, 1.98 mmol). This gave ethyl (2*E*)-3-(2'-bromo-4'-trifluoromethylphenyl)prop-2-enoate (**57g**) (0.562 g, 88%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2984 (CH), 1717 (CO), 1640 (C=C), 1393, 1316, 1265, 1171, 1125, 1078; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.30 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 6.45 (1H, d, *J* 16.0 Hz, 2-H), 7.58 (1H, br d, *J* 8.2 Hz, 5'-H), 7.69 (1H, d, *J* 8.2 Hz, 6'-H), 7.87 (1H, br s, 3'-H), 8.01 (1H, d, *J* 16.0 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.4 (CH_3), 61.1 (CH_2), 123.0 (C, q, $^1J_{CF}$ 272.7 Hz), 123.6 (CH), 124.7 (CH, q, $^3J_{CF}$ 3.6 Hz), 125.2 (C), 128.2 (CH), 130.5 (CH, q, $^3J_{CF}$ 3.9 Hz), 132.9 (C, q, $^2J_{CF}$ 33.4 Hz), 138.3 (C), 141.6 (CH), 166.0 (C); *m/z* (ESI) 344.9693 (MNa^+, $C_{12}H_{10}{}^{79}BrF_3NaO_2$ requires 334.9708), 301 (65%), 275 (40), 258 (26), 243 (19), 236 (49), 201 (28).

3-Bromofuran-2-carboxaldehyde (52h)[181]



Titanium tetrachloride (17.0 mL, 1.0 M in dichloromethane, 17.0 mmol) was added to dichloromethane (70 mL) and cooled to −78 °C. Dichloromethyl methyl ether (1.53 mL, 17.0 mmol) was added dropwise and stirred for 0.1 h before 3-bromofuran (0.300 mL, 3.39 mmol) was added dropwise with vigorous stirring. The reaction mixture was stirred at −78 °C for 2 h then warmed to 0 °C, quenched with water (20 mL) and stirred as a slurry for a further 1 h. A saturated solution of sodium hydrogen carbonate was added until gas evolution ceased. The biphasic reaction mixture was filtered through a pad of celite then extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with water (50 mL) then brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 3-bromofuran-2-carboxaldehyde (**52h**) (0.567 g, 96%) as a light brown oil. Spectroscopic data was in accordance with literature values.[181] δ_H (400 MHz, $CDCl_3$) 6.66 (1H, dd, *J* 1.8, 0.7 Hz, 4-H), 7.63 (1H, dd, *J* 1.8, 0.7 Hz, 5-H), 9.71–9.73 (1H, m, CHO); δ_C (126 MHz, $CDCl_3$) 112.8 (C), 116.8 (CH), 148.1 (CH), 148.3 (C), 176.5 (CH); *m/z* (EI) 175 (M^+, 95%), 173 (74), 149 (39), 111 (53), 97 (72), 85 (78), 71 (98), 57 (100).

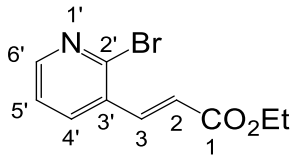
Ethyl (2*E*)-3-(3'-bromofuran-2'-yl)prop-2-enoate (57h)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 3-bromofuran-2-carboxaldehyde (**52h**) (0.550 g, 3.14 mmol). This gave ethyl (2*E*)-3-(3'-bromofuran-2'-yl)prop-2-enoate (**57h**) (0.718 g, 93%) as an orange solid. Mp 44–46 °C; ν_{max} (neat)/cm^{-1} 2986 (CH), 1713 (CO), 1636 (C=C), 1304, 1258, 1173, 1026, 964; δ_H (500 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.25 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 6.39 (1H, d, *J* 15.8 Hz, 2-H), 6.53 (1H, d, *J* 2.0 Hz, 4'-H), 7.42 (1H, d, *J* 2.0 Hz, 5'-H), 7.48 (1H, d, *J* 15.8 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.4

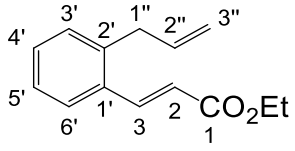
(CH_3), 60.8 (CH_2), 105.5 (C), 116.0 (CH), 117.7 (CH), 128.1 (CH), 144.7 (CH), 148.2 (C), 166.83 (C); *m/z* (ESI) 266.9628 (MNa^+, $C_9H_9{}^{79}BrNaO_3$ requires 266.9627), 242 (8%), 236 (36), 200 (4), 171 (4).

Ethyl (2*E*)-3-(2'-bromopyridin-3'-yl)prop-2-enoate (57i)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-vinylphenyl)prop-2-enoate (**50a**) using 2-bromopyridine-3-carboxaldehyde (**52i**) (0.500 g, 2.69 mmol). This gave ethyl (2*E*)-3-(2'-bromopyridin-3'-yl)prop-2-enoate (**57i**) (0.639 g, 93%) as a white solid. Mp 43–46 °C; ν_{max} (neat)/cm^{-1} 2980 (CH), 1709 (CO), 1636 (C=C), 1553, 1389, 1310, 1267, 1177, 1051, 972, 800; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.29 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 6.41 (1H, d, *J* 16.0 Hz, 2-H), 7.31 (1H, dd, *J* 7.7, 4.7 Hz, 5'-H), 7.86 (1H, dd, *J* 7.7, 1.9 Hz, 4'-H), 7.94 (1H, d, *J* 16.0 Hz, 3-H), 8.37 (1H, dd, *J* 4.7, 1.9 Hz, 6'-H); δ_C (101 MHz, $CDCl_3$) 14.4 (CH_3), 61.1 (CH_2), 123.2 (CH), 123.3 (CH), 132.3 (C), 135.7 (CH), 141.1 (CH), 144.4 (C), 150.9 (CH), 165.9 (C); *m/z* (ESI) 255.9961 (MH^+, $C_{10}H_{11}{}^{79}BrNO_2$ requires 255.9968), 228 (89%), 148 (100), 120 (19).

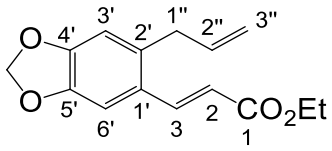
Ethyl (2*E*)-3-(2'-allylphenyl)prop-2-enoate (59a)[182]



Caesium fluoride (0.238 g, 1.57 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.032 g, 0.0392 mmol) and allylboronic acid pinacol ester (**58**) (0.147 mL, 0.784 mmol) were added to a degassed solution of ethyl (2*E*)-3-(2'-bromophenyl)prop-2-enoate (**57a**) (0.100 g, 0.392 mmol) in 1,4-dioxane (5 mL). The solution was heated to 85 °C for 18 h, cooled to room temperature and concentrated *in vacuo.* The reaction was purified by filtration through a pad of silica (elution with 20% diethyl ether:petroleum ether) to yield ethyl (2*E*)-3-(2'-allylphenyl)prop-2-enoate (**59a**) (0.0844 g, 100%) as a

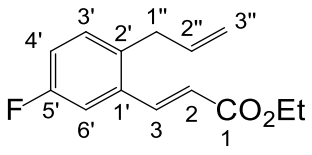
yellow oil. Spectroscopic data was in accordance with literature values.[182] ν_{max} (neat)/cm^{-1} 2980 (CH), 1712 (CO), 1635 (C=C), 1483, 1367, 1313, 1267, 1174, 1036, 980, 915, 764; δ_H (500 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.53 (2H, br d, *J* 6.2 Hz, 1''-H_2), 4.27 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.00 (1H, dq, *J* 17.1, 1.6 Hz, 3''-*H*H), 5.09 (1H, dq, *J* 10.1, 1.6 Hz, 3''-H*H*), 5.96 (1H, ddt, *J* 17.1, 10.1, 6.2 Hz, 2''-H), 6.36 (1H, d, *J* 15.8 Hz, 2-H), 7.20–7.27 (2H, m, 2 × ArH), 7.32 (1H, td, *J* 7.5, 1.3 Hz, ArH), 7.58 (1H, dd, *J* 7.5, 1.3 Hz, ArH), 7.99 (1H, d, *J* 15.8 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.4 (CH_3), 37.6 (CH_2), 60.6 (CH_2), 116.5 (CH_2), 119.8 (CH), 126.7 (CH), 127.0 (CH), 130.2 (CH), 130.4 (CH), 133.6 (C), 136.7 (CH), 139.4 (C), 142.3 (CH), 167.1 (C); *m/z* (EI) 216.1147 (M^+, $C_{14}H_{16}O_2$ requires 216.1150), 187 (24%), 171 (30), 143 (100), 142 (99), 128 (94), 115 (97), 84 (42).

Ethyl (2*E*)-3-(2'-allyl-4',5'-methylenedioxyphenyl)prop-2-enoate (59b)



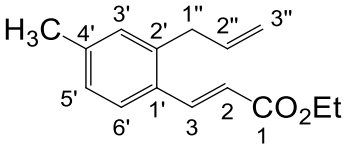
The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allylphenyl)prop-2-enoate (**59a**) using ethyl (2*E*)-3-(2'-bromo-4',5'-methylenedioxyphenyl)prop-2-enoate (**57b**) (0.270 g, 0.903 mmol). This gave ethyl (2*E*)-3-(2'-allyl-4',5'-methylenedioxyphenyl)prop-2-enoate (**59b**) (0.235 g, 100%) as a white solid. Mp 63–67 °C; ν_{max} (neat)/cm^{-1} 2982 (CH), 1694 (CO), 1499 (C=C), 1476, 1256, 1036, 974; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.45 (2H, dt, *J* 6.2, 1.5 Hz, 1''-H_2), 4.24 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.99 (1H, dq, *J* 17.0, 1.5 Hz, 3''-*H*H), 5.07 (1H, dq, *J* 10.1, 1.5 Hz, 3''-H*H*), 5.91 (1H, ddt, *J* 17.0, 10.1, 6.2 Hz, 2''-H), 5.97 (2H, s, OCH_2O), 6.21 (1H, d, *J* 15.7 Hz, 2-H), 6.68 (1H, s, 3'-H), 7.05 (1H, s, 6'-H), 7.89 (1H, d, *J* 15.7 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.5 (CH_3), 37.4 (CH_2), 60.5 (CH_2), 101.5 (CH_2), 105.8 (CH), 110.3 (CH), 116.4 (CH_2), 117.4 (CH), 126.8 (C), 134.9 (C), 136.7 (CH), 141.6 (CH), 146.9 (C), 149.6 (C), 167.3 (C); *m/z* (ESI) 283.0935 (MNa^+, $C_{15}H_{16}NaO_4$ requires 283.0941).

Ethyl (2*E*)-3-(2'-allyl-5'-fluorophenyl)prop-2-enoate (59c)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allylphenyl)prop-2-enoate (**59a**) using ethyl (2*E*)-3-(2'-bromo-5'-fluorophenyl)prop-2-enoate (**57c**) (0.254 g, 0.930 mmol). This gave ethyl (2*E*)-3-(2'-allyl-5'-fluorophenyl)prop-2-enoate (**59c**) (0.214 g, 98%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2982 (CH), 1711 (CO), 1636 (C=C), 1489, 1314, 1269, 1233, 1173, 1034, 976, 860; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, $OCH_2C\mathit{H_3}$), 3.48 (2H, br d, *J* 6.1 Hz, 1''-H_2), 4.27 (2H, q, *J* 7.1 Hz, $OC\mathit{H_2}CH_3$), 4.96 (1H, dq, *J* 17.1, 1.6 Hz, 3''-*H*H), 5.09 (1H, dq, *J* 10.1, 1.6 Hz, 3''-H*H*), 5.93 (1H, ddt, *J* 17.1, 10.1, 6.1 Hz, 2''-H), 6.33 (1H, d, *J* 15.8 Hz, 2-H), 7.02 (1H, td, *J* 8.3, 2.7 Hz, 4'-H), 7.18 (1H, dd, *J* 8.3, 5.8 Hz, 3'-H), 7.26 (1H, dd, *J* 9.8, 2.7 Hz, 6'-H), 7.90 (1H, dd, *J* 15.8, 1.6 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.5 (CH_3), 36.9 (CH_2), 60.8 (CH_2), 113.1 (d, $^2J_{CF}$ 22.1 Hz, CH), 116.7 (CH_2), 117.1 (d, $^2J_{CF}$ 21.2 Hz, CH), 120.9 (CH), 132.0 (d, $^3J_{CF}$ 7.9 Hz, CH), 135.1 (d, $^4J_{CF}$ 3.3 Hz, C), 135.3 (d, $^3J_{CF}$ 7.5 Hz, C), 136.5 (CH), 141.1 (d, $^4J_{CF}$ 2.2 Hz, CH), 161.7 (d, $^1J_{CF}$ 244.9 Hz, C), 166.8 (C); *m/z* (EI) 234.1053 (M^+, $C_{14}H_{15}FO_2$ requires 234.1056), 205 (12%), 189 (15), 161 (95), 146 (100), 133 (54), 84 (16), 69 (20).

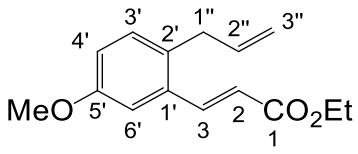
Ethyl (2*E*)-3-(2'-allyl-4'-methylphenyl)prop-2-enoate (59d)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allylphenyl)prop-2-enoate (**59a**) using ethyl (2*E*)-3-(2'-bromo-4'-methylphenyl)prop-2-enoate (**57d**) (0.050 g, 0.19 mmol). This gave ethyl (2*E*)-3-(2'-allyl-4'-methylphenyl)prop-2-enoate (**59d**) (0.042 g, 99%) as a colourless oil. ν_{max} (neat)/cm^{-1} 2980 (CH), 1709 (CO), 1632 (C=C), 1609, 1312, 1173, 1155; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1 Hz, $OCH_2C\mathit{H_3}$), 2.34 (3H, s, 4'-CH_3), 3.50 (2H, br d, *J* 6.2 Hz, 1''-H_2), 4.26 (2H, q, *J* 7.1 Hz, $OC\mathit{H_2}CH_3$), 5.00 (1H, dq, *J* 17.0, 1.6 Hz, 3''-*H*H), 5.08 (1H, dq, *J* 10.1, 1.6 Hz, 3''-H*H*), 5.95 (1H, ddt, *J* 17.0, 10.1, 6.2

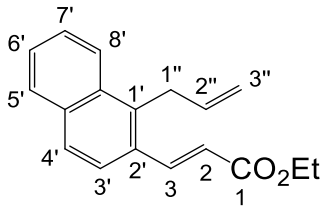
Hz, 2''-H), 6.33 (1H, d, *J* 15.8 Hz, 2-H), 7.03 (1H, s, 3'-H), 7.06 (1H, d, *J* 7.9 Hz, 5'-H), 7.49 (1H, d, *J* 7.9 Hz, 6'-H), 7.96 (1H, d, *J* 15.8 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.5 (CH_3), 21.5 (CH_3), 37.6 (CH_2), 60.5 (CH_2), 116.4 (CH_2), 118.6 (CH), 126.7 (CH), 127.8 (CH), 130.6 (C), 131.1 (CH), 136.8 (CH), 139.4 (C), 140.6 (C), 142.2 (CH), 167.3 (C); *m/z* (ESI) 253.1198 (MNa^+, $C_{15}H_{18}NaO_2$ requires 253.1199), 236 (8%), 157 (36), 142 (28).

Ethyl (2*E*)-3-(2'-allyl-5'-methoxyphenyl)prop-2-enoate (59e)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allylphenyl)prop-2-enoate (**59a**) using ethyl (2*E*)-3-(2'-bromo-5'-methoxyphenyl)prop-2-enoate (**57e**) (0.619 g, 2.17 mmol). This gave ethyl (2*E*)-3-(2'-allyl-5'-methoxyphenyl)prop-2-enoate (**59e**) (0.529 g, 99%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2980 (CH), 1709 (CO), 1634 (C=C), 1495, 1233, 1165, 1036; δ_H (500 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.46 (2H, br d, *J* 6.2 Hz, 1''-H_2), 3.81 (3H, s, OCH_3), 4.27 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.97 (1H, dq, *J* 17.1, 1.6 Hz, 3''-*H*H), 5.06 (1H, dq, *J* 10.0, 1.6 Hz, 3''-H*H*), 5.93 (1H, ddt, *J* 17.1, 10.0, 6.2 Hz, 2''-H), 6.34 (1H, d, *J* 15.8 Hz, 2-H), 6.89 (1H, dd, *J* 8.4, 2.7 Hz, 4'-H), 7.09 (1H, d, *J* 2.7 Hz, 6'-H), 7.12 (1H, d, *J* 8.4 Hz, 3'-H), 7.94 (1H, d, *J* 15.8 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 36.8 (CH_2), 55.5 (CH_3), 60.6 (CH_2), 111.4 (CH), 116.1 (CH_2), 116.4 (CH), 119.9 (CH), 131.5 (CH), 131.8 (C), 134.4 (C), 137.2 (CH), 142.3 (CH), 158.5 (C), 167.0 (C); *m/z* (ESI) 269.1141 (MNa^+, $C_{15}H_{18}NaO_3$ requires 269.1148).

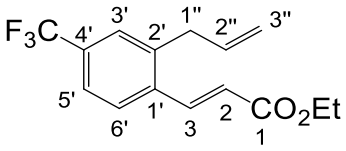
Ethyl (2*E*)-3-(1'-allylnaphthalen-2'-yl)prop-2-enoate (59f)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allylphenyl)prop-2-enoate (**59a**) using ethyl (2*E*)-3-(1'-

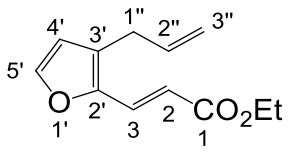
bromonaphthalen-2'-yl)prop-2-enoate (**57f**) (0.415 g, 1.36 mmol) and allylboronic acid pinacol ester (**58**) (0.636 mL, 3.41 mmol) at 100 °C. This gave ethyl (2*E*)-3-(1'-allylnaphthalen-2'-yl)prop-2-enoate (**59f**) (0.355 g, 98%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2978 (CH), 1707 (CO), 1626 (C=C), 1256, 1173, 1153, 1036, 812; δ_H (500 MHz, $CDCl_3$) 1.36 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.01 (2H, br d, *J* 5.6 Hz, 1''-H_2), 4.30 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.93 (1H, dq, *J* 17.1, 1.7 Hz, 3''-*H*H), 5.08 (1H, dq, *J* 10.2, 1.7 Hz, 3''-H*H*), 6.08 (1H, ddt, *J* 17.1, 10.2, 5.6 Hz, 2''-H), 6.48 (1H, d, *J* 15.8 Hz, 2-H), 7.48–7.56 (2H, m, 2 × ArH), 7.67 (1H, d, *J* 8.7 Hz, 4'-H), 7.74 (1H, d, *J* 8.7 Hz, 3'-H), 7.80–7.85 (1H, m, ArH), 8.08 (1H, d, *J* 8.1 Hz, ArH), 8.22 (1H, d, *J* 15.8 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 32.3 (CH_2), 60.7 (CH_2), 116.6 (CH_2), 120.5 (CH), 123.8 (CH), 125.1 (CH), 126.8 (CH), 126.8 (CH), 127.6 (CH), 128.8 (CH), 130.8 (C), 132.5 (C), 134.5 (C), 136.0 (CH), 136.1 (C), 142.7 (CH), 167.2 (C); *m/z* (ESI) 289.1190 (MNa^+, $C_{18}H_{18}NaO_2$ requires 289.1199), 236 (6%), 193 (3), 178 (2).

Ethyl (2*E*)-3-(2'-allyl-4'-trifluoromethylphenyl)prop-2-enoate (59g)



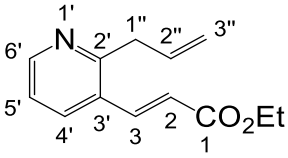
The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allylphenyl)prop-2-enoate (**59a**) using ethyl (2*E*)-3-(2'-bromo-4'-trifluoromethylphenyl)prop-2-enoate (**57g**) (0.321 g, 1.00 mmol). This gave ethyl (2*E*)-3-(2'-allyl-4'-trifluoromethylphenyl)prop-2-enoate (**59g**) (0.282 g, 100%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2984 (CH), 1715 (CO), 1638 (C=C), 1333, 1314, 1279, 1163, 1123, 1078; δ_H (500 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.56 (2H, br d, *J* 6.2 Hz, 1''-H_2), 4.28 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.01 (1H, dq, *J* 16.8, 1.5 Hz, 3''-*H*H), 5.14 (1H, dq, *J* 10.3, 1.5 Hz, 3''-H*H*), 5.94 (1H, ddt, *J* 16.8, 10.3, 6.2 Hz, 2''-H), 6.40 (1H, d, *J* 15.9 Hz, 2-H), 7.47 (1H, s, 3'-H), 7.50 (1H, d, *J* 8.2 Hz, 5'-H), 7.65 (1H, d, *J* 8.2 Hz, 6'-H), 7.95 (1H, d, *J* 15.9 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.4 (CH_3), 37.5 (CH_2), 60.9 (CH_2), 117.4 (CH_2), 122.2 (CH), 123.8 (CH, q, $^3J_{CF}$ 3.7 Hz), 124.0 (C, q, $^1J_{CF}$ 272.3 Hz), 127.1 (CH, q, $^3J_{CF}$ 3.8 Hz), 127.2 (CH), 131.8 (C, q, $^2J_{CF}$ 32.5 Hz), 135.6 (CH), 137.2 (C), 139.9 (C), 140.8 (CH), 166.5 (C); *m/z* (ESI) 307.0907 (MNa^+, $C_{15}H_{15}F_3NaO_2$ requires 307.0916), 301 (43%), 236 (36), 209 (72).

Ethyl (2*E*)-3-(3'-allylfuran-2'-yl)prop-2-enoate (59h)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allylphenyl)prop-2-enoate (**59a**) using ethyl (2*E*)-3-(3'-bromofuran-2'-yl)prop-2-enoate (**57h**) (0.230 g, 0.939 mmol). This gave ethyl (2*E*)-3-(3'-allylfuran-2'-yl)prop-2-enoate (**59h**) (0.193 g, 100%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2924 (CH), 1705 (CO), 1636 (C=C), 1304, 1258, 1165, 1042, 972; δ_H (500 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.29 (2H, br d, *J* 6.3 Hz, 1''-H_2), 4.24 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.06–5.11 (2H, m, 3''-H_2), 5.88 (1H, ddt, *J* 16.2, 10.0, 6.3 Hz, 2''-H), 6.27 (1H, d, *J* 15.6 Hz, 2-H), 6.35 (1H, d, *J* 1.6 Hz, 4'-H), 7.40 (1H, d, *J* 1.6 Hz, 5'-H), 7.47 (1H, d, *J* 15.6 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 29.4 (CH_2), 60.5 (CH_2), 113.9 (CH), 114.9 (CH), 116.5 (CH_2), 128.0 (C), 129.1 (CH), 135.6 (CH), 144.3 (CH), 147.1 (C), 167.5 (C); *m/z* (ESI) 229.0838 (MNa^+, $C_{12}H_{14}NaO_3$ requires 229.0835).

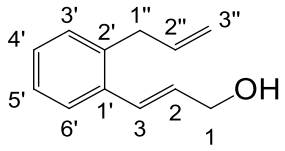
Ethyl (2*E*)-3-(2'-allylpyridin-3'-yl)prop-2-enoate (59i)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allylphenyl)prop-2-enoate (**59a**) using ethyl (2*E*)-3-(2'-bromopyridin-3'-yl)prop-2-enoate (**57i**) (0.346 g, 1.35 mmol). Purification by column chromatography (elution with 50% diethyl ether:petroleum ether) yielded ethyl (2*E*)-3-(2'-allylpyridin-3'-yl)prop-2-enoate (**59i**) (0.226 g, 77%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2980 (CH), 1713 (CO), 1636 (C=C), 1429, 1308, 1167; δ_H (500 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.74 (2H, br d, *J* 6.4 Hz, 1''-H_2), 4.27 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.08 (1H, dq, *J* 17.0, 1.5 Hz, 3''-*H*H), 5.13 (1H, dq, *J* 10.2, 1.5 Hz, 3''-H*H*), 6.03 (1H, ddt, *J* 17.0, 10.2, 6.4 Hz, 2''-H), 6.36 (1H, d, *J* 15.9 Hz, 2-H), 7.19 (1H, dd, *J* 7.9, 4.8 Hz, 5'-H), 7.82 (1H, dd, *J* 7.9, 1.6 Hz, 4'-H), 7.93 (1H, d, *J* 15.9 Hz, 3-H), 8.55 (1H, dd, *J* 4.8, 1.6 Hz, 6'-H); δ_C (126 MHz, $CDCl_3$) 14.4 (CH_3), 40.5 (CH_2), 60.9 (CH_2), 117.0 (CH_2), 121.7 (CH), 122.1 (CH),

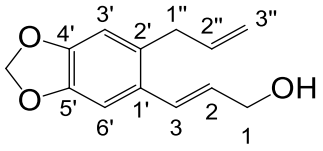
129.2 (C), 134.2 (CH), 135.0 (CH), 140.4 (CH), 150.6 (CH), 158.6 (C), 166.5 (C); *m/z* (ESI) 218.1185 (MH^+, $C_{13}H_{16}NO_2$ requires 218.1176), 190 (100%), 170 (10), 144 (78), 130 (54).

(2*E*)-3-(2'-Allylphenyl)prop-2-en-1-ol (61a)[183]



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(2'-allylphenyl)prop-2-enoate (**59a**) (0.700 g, 3.24 mmol). This gave (2*E*)-3-(2'-allylphenyl)prop-2-en-1-ol (**61a**) (0.456 g, 81%) as a colourless oil. Spectroscopic data was in accordance with literature values.[183] δ_H (400 MHz, $CDCl_3$) 1.48 (1H, t, *J* 5.4 Hz, OH), 3.45 (2H, dt, *J* 6.2, 1.7 Hz, 1''-H_2), 4.30–4.35 (2H, m, 1-H_2), 4.97 (1H, dq, *J* 17.1, 1.7 Hz, 3''-*H*H), 5.06 (1H, dq, *J* 10.1, 1.7 Hz, 3''-H*H*), 5.97 (1H, ddt, *J* 17.1, 10.1, 6.2 Hz, 2''-H), 6.26 (1H, dt, *J* 15.7, 5.7 Hz, 2-H), 6.85 (1H, dt, *J* 15.7, 1.5 Hz, 3-H), 7.14–7.23 (3H, m, ArH), 7.46–7.49 (1H, m, ArH); δ_C (101 MHz, $CDCl_3$) 37.6 (CH_2), 64.1 (CH_2), 116.0 (CH_2), 126.3 (CH), 126.8 (CH), 128.0 (CH), 128.9 (CH), 129.9 (CH), 130.4 (CH), 135.9 (C), 137.0 (CH), 137.3 (C); *m/z* (EI) 174 (M^+, 8%), 156 (31), 143 (62), 128 (100), 115 (70), 91 (23), 84 (12), 74 (5).

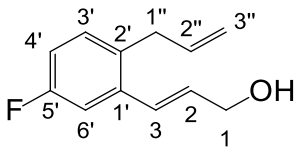
(2*E*)-3-(2'-Allyl-4',5'-methylenedioxyphenyl)prop-2-en-1-ol (61b)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(2'-allyl-4',5'-methylenedioxyphenyl)prop-2-enoate (**59b**) (1.14 g, 4.37 mmol). This gave (2*E*)-3-(2'-allyl-4',5'-methylenedioxyphenyl)prop-2-en-1-ol (**61b**) (0.920 g, 97%) as a white crystalline solid. Mp 45–49 °C; ν_{max} (neat)/cm^{-1} 3262 (OH), 2866 (CH), 1636 (C=C), 1503, 1481, 1244, 1165, 1044, 1017, 995; δ_H (400 MHz, $CDCl_3$) 3.30 (2H, dt, *J* 6.1, 1.5 Hz, 1''-H_2), 3.68 (1H, br s, OH), 4.25 (2H, br d, *J* 5.7 Hz, 1-H_2), 4.95 (1H, dq, *J* 17.0, 1.5 Hz, 3''-*H*H), 5.02 (1H, dq, *J* 10.1, 1.5 Hz, 3''-H*H*), 5.85 (2H, s,

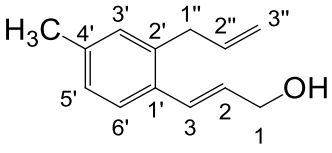
OCH_2O), 5.88 (2H, ddt, *J* 17.0, 10.1, 6.1 Hz, 2''-H), 6.08 (1H, dt, *J* 15.6, 5.7 Hz, 2-H), 6.60 (1H, s, ArH), 6.71 (1H, dt, *J* 15.6, 1.2 Hz, 3-H), 6.94 (1H, s, ArH); δ_C (101 MHz, $CDCl_3$) 37.4 (CH_2), 64.1 (CH_2), 101.1 (CH_2), 106.0 (CH), 109.9 (CH), 116.0 (CH_2), 128.6 (CH), 128.7 (CH), 129.2 (C), 131.4 (C), 137.0 (CH), 146.6 (C), 147.5 (C); *m/z* (EI) 218.0945 (M^+, $C_{13}H_{14}O_3$ requires 218.0943), 200 (20%), 173 (80), 160 (44), 149 (23), 115 (48), 103 (19), 83 (73), 77 (12).

(2*E*)-3-(2'-Allyl-5'-fluorophenyl)prop-2-en-1-ol (61c)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(2'-allyl-5'-fluorophenyl)prop-2-enoate (**59c**) (0.190 g, 0.812 mmol). This gave (2*E*)-3-(2'-allyl-5'-fluorophenyl)prop-2-en-1-ol (**61c**) (0.144 g, 92%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3300 (OH), 2857 (CH), 1609 (C=C), 1582, 1489, 1267, 1155, 964, 912, 870; δ_H (400 MHz, $CDCl_3$) 1.46 (1H, br t, *J* 5.8 Hz, OH), 3.41 (2H, br d, *J* 6.1 Hz, 1''-H_2), 4.34 (2H, td, *J* 5.8, 1.6 Hz, 1-H_2), 4.94 (1H, dq, *J* 17.0, 1.6 Hz, 3''-*H*H), 5.07 (1H, dq, *J* 10.1, 1.6 Hz, 3''-H*H*), 5.93 (1H, ddt, *J* 17.0, 10.1, 6.1 Hz, 2''-H), 6.25 (1H, dt, *J* 15.7, 5.8 Hz, 2-H), 6.80 (1H, dq, *J* 15.7, 1.6 Hz, 3-H), 6.90 (1H, td, *J* 8.3, 2.7, Hz, 4'-H), 7.10 (1H, dd, *J* 8.3, 5.9 Hz, 3'-H), 7.16 (1H, dd, *J* 10.2, 2.7 Hz, 6'-H); δ_C (101 MHz, $CDCl_3$) 36.8 (CH_2), 63.7 (CH_2), 112.6 (CH, d, $^2J_{CF}$ 21.9 Hz), 114.6 (CH, d, $^2J_{CF}$ 21.2 Hz), 116.2 (CH_2), 127.7 (CH, d, $^4J_{CF}$ 2.2 Hz), 131.4 (CH, d, $^3J_{CF}$ 8.7 Hz), 131.5 (CH), 132.9 (C, d, $^4J_{CF}$ 3.0 Hz), 136.8 (CH), 137.7 (C, d, $^3J_{CF}$ 7.5 Hz), 161.8 (C, d, $^1J_{CF}$ 243.7 Hz); *m/z* (CI) 175.0919 (MH^+-H_2O, $C_{12}H_{12}F$ requires 175.0923), 147 (25%), 113 (6), 85 (5), 73 (14).

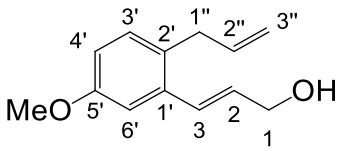
(2*E*)-3-(2'-Allyl-4'-methylphenyl)prop-2-en-1-ol (61d)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(2'-allyl-4'-

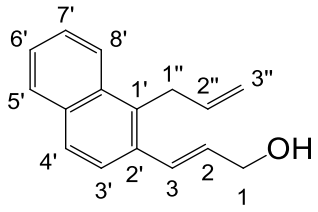
methylphenyl)prop-2-enoate (**59d**) (0.483 g, 2.10 mmol). This gave (2*E*)-3-(2'-allyl-4'-methylphenyl)prop-2-en-1-ol (**61d**) (0.348 g, 88%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3325 (OH), 2918 (CH), 1638 (C=C), 1611 (C=C), 1495, 1086, 995, 966; δ_H (500 MHz, $CDCl_3$) 1.39 (1H, t, *J* 5.9 Hz, OH), 2.32 (3H, s, 4'-CH_3), 3.42 (2H, dt, *J* 6.2, 1.6 Hz, 1''-H_2), 4.32 (2H, td, *J* 5.9, 1.5 Hz, 1-H_2), 4.98 (1H, dq, *J* 17.0, 1.6 Hz, 3''-*H*H), 5.06 (1H, dq, *J* 10.1, 1.6 Hz, 3''-H*H*), 5.95 (1H, ddt, *J* 17.0, 10.1, 6.2 Hz, 2''-H), 6.22 (1H, dt, *J* 15.7, 5.9 Hz, 2-H), 6.81 (1H, d, *J* 15.7 Hz, 3-H), 6.97 (1H, br s, 3'-H), 7.02 (1H, d, *J* 7.9 Hz, 5'-H), 7.38 (1H, d, *J* 7.9 Hz, 6'-H); δ_C (126 MHz, $CDCl_3$) 21.3 (CH_3), 37.6 (CH_2), 64.2 (CH_2), 115.9 (CH_2), 126.2 (CH), 127.6 (CH), 128.9 (CH), 129.4 (CH), 130.6 (CH), 133.0 (C), 137.1 (CH), 137.2 (C), 137.8 (C); *m/z* (ESI) 211.1096 (MNa^+, $C_{13}H_{16}NaO$ requires 211.1093), 190 (22%), 171 (29), 143 (100), 128 (46).

(2*E*)-3-(2'-Allyl-5'-methoxyphenyl)prop-2-en-1-ol (61e)



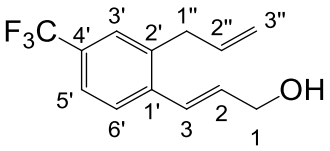
The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(2'-allyl-5'-methoxyphenyl)prop-2-enoate (**59e**) (0.461 g, 1.87 mmol). This gave (2*E*)-3-(2'-allyl-5'-methoxyphenyl)prop-2-en-1-ol (**61e**) (0.313 g, 82%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3228 (OH), 2909 (CH), 1605 (C=C), 1572, 1495, 1285, 1198, 1163, 1040, 964; δ_H (500 MHz, $CDCl_3$) 1.46 (1H, t, *J* 5.3 Hz, OH), 3.39 (2H, dt, *J* 6.2, 1.7 Hz, 1''-H), 3.81 (3H, s, OCH_3), 4.33 (2H, t, *J* 5.3 Hz, 1-H_2), 4.95 (1H, dq, *J* 16.9, 1.7 Hz, 3''-*H*H), 5.04 (1H, dq, *J* 10.2, 1.7 Hz, 3''-H*H*), 5.94 (1H, ddt, *J* 16.9, 10.2, 6.2 Hz, 2''-H), 6.25 (1H, dt, *J* 15.7, 5.3 Hz, 2-H), 6.78 (1H, dd, *J* 8.4, 2.8 Hz, 4'-H), 6.81 (1H, dt, *J* 15.7, 1.6 Hz, 3-H), 7.02 (1H, d, *J* 2.8 Hz, 6'-H), 7.07 (1H, d, *J* 8.4 Hz, 3'-H); δ_C (126 MHz, $CDCl_3$) 36.8 (CH_2), 55.4 (CH_3), 64.0 (CH_2), 111.4 (CH), 113.7 (CH), 115.7 (CH_2), 128.9 (CH), 129.7 (C), 130.5 (CH), 131.0 (CH), 136.9 (C), 137.4 (CH), 158.4 (C); *m/z* (EI) 204.1152 (M^+, $C_{13}H_{16}O_2$ requires 204.1150), 173 (100%), 159 (74), 158 (73), 115 (53), 103 (18), 91 (23), 77 (13), 51 (10).

(2*E*)-3-(1'-Allylnaphthalen-2'-yl)prop-2-en-1-ol (61f)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(1'-allylnaphthalen-2'-yl)prop-2-enoate (**59f**) (0.326 g, 1.23 mmol). This gave (2*E*)-3-(1'-allylnaphthalen-2'-yl)prop-2-en-1-ol (**61f**) (0.256 g, 93%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3320 (OH), 3055 (CH), 2859 (CH), 1636 (C=C), 1510, 1449, 1373, 1090, 966, 739; δ_H (400 MHz, $CDCl_3$) 1.58 (1H, br s, OH), 3.92 (2H, dt, *J* 5.5, 1.8 Hz, 1''-H_2), 4.40 (2H, d, *J* 5.7, 1-H_2), 4.91 (1H, dq, *J* 17.2, 1.8 Hz, 3''-*H*H), 5.06 (1H, dq, 10.2, 1.8 Hz, 3''-H*H*), 6.08 (1H, ddt, *J* 17.2, 10.2, 5.5 Hz, 2''-H), 6.39 (1H, dt, *J* 15.7, 5.7 Hz, 2-H), 7.07 (1H, d, *J* 15.7 Hz, 3-H), 7.45 (1H, ddd, *J* 8.0, 7.0, 1.1 Hz, ArH), 7.50 (1H, ddd, *J* 8.4, 7.0, 1.2 Hz, ArH), 7.63 (1H, d, *J* 8.7 Hz, ArH), 7.72 (1H, d, *J* 8.7 Hz, ArH), 7.81 (1H, dd, *J* 8.0, 1.2 Hz, ArH), 8.03 (1H, d, *J* 8.4 Hz, ArH); δ_C (101 MHz, $CDCl_3$) 32.3 (CH_2), 64.2 (CH_2), 116.1 (CH_2), 124.5 (CH), 124.6 (CH), 125.6 (CH), 126.4 (CH), 127.2 (CH), 128.6 (CH), 129.4 (CH), 131.2 (CH), 132.5 (C), 132.6 (C), 133.0 (C), 133.5 (C), 136.2 (CH); *m/z* (ESI) 247.1093 (MNa$^+$, $C_{16}H_{16}NaO$ requires 247.1093), 236 (49%), 227 (40), 207 (29), 179 (100), 166 (17), 159 (11).

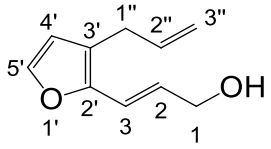
(2*E*)-3-(2'-Allyl-4'-trifluoromethylphenyl)prop-2-en-1-ol (61g)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(2'-allyl-4'-trifluoromethylphenyl)prop-2-enoate (**59g**) (0.326 g, 1.23 mmol). This gave (2*E*)-3-(2'-allyl-4'-trifluoromethylphenyl)prop-2-en-1-ol (**61g**) (0.256 g, 93%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3320 (OH), 2928 (CH), 1640 (C=C), 1616, 1420, 1332, 1160, 1118, 1091; δ_H (500 MHz, $CDCl_3$) 1.98 (1H, br s, OH), 3.48 (2H, dt, *J* 6.2, 1.5 Hz, 1''-H_2), 4.36 (2H, dd, *J* 5.4, 1.6 Hz, 1-H_2), 4.98 (1H, dq, *J* 16.7, 1.5 Hz,

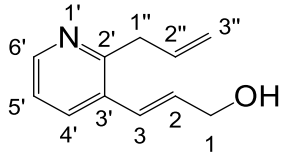
3''-*H*H), 5.11 (1H, dq, *J* 10.1, 1.5 Hz, 3''-H*H*), 5.94 (1H, ddt, *J* 16.7, 10.1, 6.2 Hz, 2''-H), 6.32 (1H, dt, *J* 15.8, 5.4 Hz, 2-H), 6.86 (1H, d, *J* 15.8 Hz, 3-H), 7.41 (1H, s, 3'-H), 7.44 (1H, d, *J* 8.2 Hz, 5'-H), 7.54 (1H, d, *J* 8.2 Hz, 6'-H); δ_C (126 MHz, $CDCl_3$) 37.4 (CH_2), 63.7 (CH_2), 117.0 (CH_2), 123.6 (CH, q, $^3J_{CF}$ 3.8 Hz), 124.4 (C, q, $^1J_{CF}$ 272.0 Hz), 126.6 (CH), 126.7 (CH, q, $^3J_{CF}$ 3.8 Hz), 127.3 (CH), 129.7 (C, q, $^2J_{CF}$ 32.3 Hz), 132.8 (CH), 135.9 (CH), 137.9 (C), 139.6 (C); *m/z* (CI) 225.0892 (MH^+-H_2O, $C_{13}H_{12}F_3$ requires 225.0891), 197 (12), 125 (3), 81 (13), 69 (15).

(2*E*)-3-(3'-Allylfuran-2'-yl)prop-2-en-1-ol (61h)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(3'-allylfuran-2'-yl)prop-2-enoate (**59h**) (0.235 g, 1.14 mmol). This gave (2*E*)-3-(3'-allylfuran-2'-yl)prop-2-en-1-ol (**61h**) (0.180 g, 96%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3323 (OH), 2924 (CH), 1640 (C=C), 1499, 1433, 1148, 1092, 1053, 993, 959; δ_H (500 MHz, $CDCl_3$) 1.37–1.44 (1H, m, OH), 3.20 (2H, br d, *J* 6.3 Hz, 1''-H_2), 4.31 (2H, td, *J* 5.6, 1.2 Hz, 1-H_2), 5.02–5.09 (2H, m, 3''-H_2), 5.88 (1H, ddt, *J* 16.7, 10.3, 6.3 Hz, 2''-H), 6.23–6.29 (2H, m, 2-H and 4'-H), 6.46 (1H, dt, *J* 15.7, 1.2 Hz, 3-H), 7.29 (1H, d, *J* 1.6 Hz, 5'-H); δ_C (126 MHz, $CDCl_3$) 29.2 (CH_2), 63.7 (CH_2), 113.1 (CH), 115.8 (CH_2), 117.6 (CH), 120.6 (C), 126.3 (CH), 136.4 (CH), 141.6 (CH), 148.0 (C); *m/z* (CI) 147.0807 (MH^+-H_2O, $C_{10}H_{11}O$ requires 147.0810), 137 (100%), 113 (6), 89 (22), 73 (12).

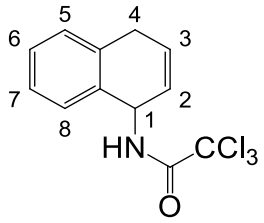
(2*E*)-3-(2'-Allylpyridin-3'-yl)prop-2-en-1-ol (61i)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-vinylphenyl)prop-2-en-1-ol (**51a**) using ethyl (2*E*)-3-(2'-allylpyridin-3'-yl)prop-2-enoate (**59i**) (0.100 g, 0.46 mmol). Purification by column chromatography (elution with 40–80% diethyl ether:petroleum ether) yielded (2*E*)-

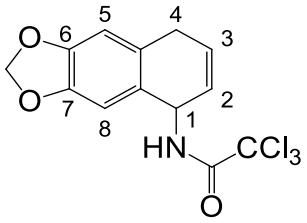
3-(2'-allylpyridin-3'-yl)prop-2-en-1-ol (**61i**) (0.066 g, 88%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3264 (OH), 2851 (CH), 1638 (C=C), 1572, 1429, 1091, 1018, 964; δ_H (500 MHz, $CDCl_3$) 1.71 (1H, t, *J* 5.5 Hz, OH), 3.67 (2H, dt, *J* 6.4, 1.6 Hz, 1''-H_2), 4.37 (2H, td, *J* 5.5, 1.5 Hz, 1-H_2), 5.05 (1H, dq, *J* 17.1, 1.6 Hz, 3''-*H*H), 5.11 (1H, dq, *J* 10.2, 1.6 Hz, 3''-H*H*), 6.05 (1H, ddt, *J* 17.1, 10.2, 6.4 Hz, 2''-H), 6.28 (1H, dt, *J* 15.8, 5.5 Hz, 2-H), 6.83 (1H, d, *J* 15.8 Hz, 3-H), 7.14 (1H, dd, *J* 7.8, 4.8 Hz, 5'-H), 7.73 (1H, dd, *J* 7.8, 1.7 Hz, 4'-H), 8.45 (1H, dd, *J* 4.8, 1.7 Hz, 6'-H); δ_C (126 MHz, $CDCl_3$) 40.4 (CH_2), 63.7 (CH_2), 116.6 (CH_2), 122.0 (CH), 126.7 (CH), 131.4 (C), 132.5 (CH), 133.8 (CH), 135.4 (CH), 148.5 (CH), 156.9 (C); *m/z* (CI) 176.1074 (MH^+, $C_{11}H_{14}NO$ requires 176.1075), 158 (33%), 130 (9), 118 (3), 81 (2), 69 (3).

1-(2',2',2'-Trichloromethylcarbonylamino)-1,4-dihydronaphthalene (65a)



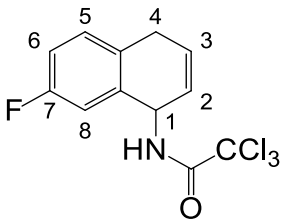
The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(2'-allylphenyl)prop-2-en-1-ol (**61a**) (0.049 g, 0.28 mmol). The RCM step was performed at room temperature. This gave 1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydronaphthalene (**65a**) (0.073 g, 89%) as a white solid. Mp 87–89 °C; ν_{max} (neat)/cm^{-1} 3271 (NH), 3032 (CH), 1682 (CO), 1520, 1250, 1018, 826, 741, 648; δ_H (500 MHz, $CDCl_3$) 3.39–3.54 (2H, m, 4-H_2), 5.71–5.77 (1H, m, 1-H), 5.93 (1H, ddt, *J* 10.0, 3.6, 2.2 Hz, 2-H), 6.20 (1H, dtd, *J* 10.0, 3.6, 1.8 Hz, 3-H), 6.83 (1H, br d, *J* 5.7 Hz, NH), 7.18–7.23 (1H, m, ArH), 7.27–7.31 (2H, m, 2 × ArH), 7.37–7.41 (1H, m, ArH); δ_C (126 MHz, $CDCl_3$) 29.5 (CH_2), 48.0 (CH), 92.9 (C), 124.4 (CH), 127.3 (CH), 128.1 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 133.2 (C), 134.1 (C), 161.6 (C); *m/z* (ESI) 311.9719 (MNa^+, $C_{12}H_{10}{}^{35}Cl_3NNaO$ requires 311.9720).

6,7-Methylenedioxy-1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydronaphthalene (65b)



The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(2'-allyl-4',5'-methylenedioxy phenyl)prop-2-en-1-ol (**61b**) (1.96 g, 8.99 mmol). Grubbs 2nd generation catalyst (0.114 g, 0.135 mmol) was added and the reaction was stirred at room temperature for 3 h before a second portion of Grubbs 2nd generation catalyst (0.0763 g, 0.0899 mmol) was added and allowed to stir for a further 17 h. This gave 6,7-methylenedioxy-1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydronaphthalene (**65b**) (2.43 g, 81%) as a white solid. Mp 114–116 °C; ν_{max} (neat)/cm^{-1} 3334 (NH), 2894 (CH), 1699 (CO), 1502, 1482, 1233, 1038, 819; δ_H (500 MHz, $CDCl_3$) 3.24–3.39 (2H, m, 4-H_2), 5.53–5.60 (1H, m, 1-H), 5.85 (1H, ddt, *J* 10.0, 3.9, 2.2 Hz, 2-H), 5.88 (1H, d, *J* 1.3 Hz, OC*H*HO), 5.89 (1H, d, *J* 1.3 Hz, OCH*H*O), 6.13 (1H, dtd, *J* 10.0, 3.5, 1.7 Hz, 3-H), 6.55 (1H, s, ArH), 6.75 (1H, s, ArH), 6.87 (1H, d, *J* 8.8 Hz, NH); δ_C (126 MHz, $CDCl_3$) 29.6 (CH_2), 48.2 (CH), 92.8 (C), 101.1 (CH_2), 107.5 (CH), 107.7 (CH), 123.8 (CH), 125.9 (C), 127.6 (C), 128.5 (CH), 146.8 (C), 147.5 (C), 161.4 (C); *m/z* (ESI) 355.9602 (MNa^+, $C_{13}H_{10}{}^{35}Cl_3NNaO_3$ requires 355.9618), 346 (7%), 242 (100), 236 (14), 184 (18), 173 (18), 142 (4).

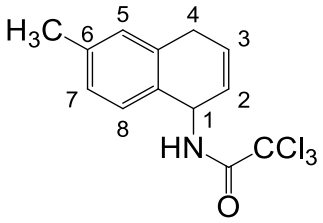
7-Fluoro-1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydronaphthalene (65c)



The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(2'-allyl-5'-

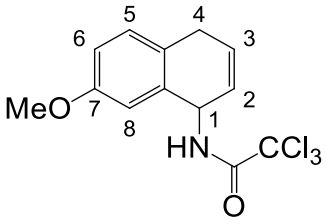
fluorophenyl)prop-2-en-1-ol (**61c**) (0.053 g, 0.28 mmol). The RCM step was performed at room temperature. This gave 7-fluoro-1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydronaphthalene (**65c**) (0.076 g, 76%) as a white solid. Mp 123–127 °C; ν_{max} (neat)/cm^{-1} 3268 (NH), 3040 (CH), 1687 (CO), 1503, 1249, 1226, 1023, 815; δ_H (500 MHz, $CDCl_3$) 3.34–3.50 (2H, m, 4-H_2), 5.66–5.73 (1H, m, 1-H), 5.80 (1H, ddt, *J* 10.1, 3.5, 1.9 Hz, 2-H), 6.21 (1H, dtd, *J* 10.1, 3.6, 1.9 Hz, 3-H), 6.84 (1H, br d, *J* 6.2 Hz, NH), 6.99 (1H, td, *J* 8.3, 2.6, Hz, 6-H), 7.09 (1H, dd, *J* 9.6, 2.6 Hz, 8-H), 7.17 (1H, dd, *J* 8.3, 5.7 Hz, 5-H); δ_C (126 MHz, $CDCl_3$) 28.9 (CH_2), 48.0 (CH, d, $^4J_{CF}$ 1.4 Hz), 92.8 (C), 114.5 (CH, d, $^2J_{CF}$ 21.6 Hz), 115.6 (CH, d, $^2J_{CF}$ 21.6 Hz), 123.8 (CH), 128.8 (CH), 129.7 (C, d, $^4J_{CF}$ 3.1 Hz), 130.2 (CH, d, $^3J_{CF}$ 7.8 Hz), 135.1 (C, d, $^3J_{CF}$ 7.0 Hz), 161.7 (C), 161.8 (C, d, $^1J_{CF}$ 245.5 Hz); *m/z* (ESI) 331.9588 (MNa^+, $C_{12}H_9{}^{35}Cl_2{}^{37}ClFNNaO$ requires 331.9597).

6-Methyl-1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydronaphthalene (65d)



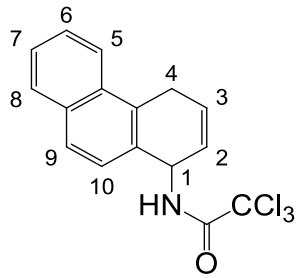
The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(2'-allyl-4'-methylphenyl)prop-2-en-1-ol (**61d**) (0.059 g, 0.31 mmol). The RCM step was performed at room temperature. This gave 6-methyl-1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydronaphthalene (**65d**) (0.078 g, 82%) as a white solid. Mp 118–122 °C; ν_{max} (neat)/cm^{-1} 3253 (NH), 3036 (CH), 1685 (CO), 1529, 1300, 1249, 1025, 823; δ_H (500 MHz, $CDCl_3$) 2.34 (3H, s, 6-CH_3), 3.33–3.49 (2H, m, 4-H_2), 5.65–5.73 (1H, m, 1-H), 5.92 (1H, ddt, *J* 10.1, 3.6, 2.2 Hz, 2-H), 6.18 (1H, dtd, *J* 10.1, 3.6, 1.8 Hz, 3-H), 6.82 (1H, br d, *J* 8.4 Hz, NH), 7.02 (1H, s, 5-H), 7.09 (1H, d, *J* 8.0 Hz, 7-H), 7.28 (1H, d, *J* 8.0 Hz, 8-H); δ_C (126 MHz, $CDCl_3$) 21.2 (CH_3), 29.4 (CH_2), 47.9 (CH), 93.0 (C), 124.4 (CH), 128.2 (CH), 128.3 (CH), 128.7 (CH), 129.0 (CH), 130.2 (C), 134.0 (C), 137.8 (C), 161.5 (C); *m/z* (ESI) 325.9864 (MNa^+, $C_{13}H_{12}{}^{35}Cl_3NNaO$ requires 325.9877), 319 (14%), 297 (6), 236 (10), 184 (14), 175 (14), 143 (36), 128 (7).

7-Methoxy-1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydronaphthalene (65e)



The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(2'-allyl-5'-methoxyphenyl)prop-2-en-1-ol (**61e**) (0.052 g, 0.26 mmol). The RCM step was performed at room temperature. This gave 7-methoxy-1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydronaphthalene (**65e**) (0.063 g, 76%) as a white solid. Mp 92–96 °C; ν_{max} (neat)/cm^{-1} 3293 (NH), 2935 (CH), 1704 (CO), 1613, 1501, 1261, 1241, 1033, 1021, 816; δ_H (500 MHz, $CDCl_3$) 3.31–3.46 (2H, m, 4-H_2), 3.77 (3H, s, OCH_3), 5.67–5.74 (1H, m, 1-H), 5.89 (1H, ddt, *J* 10.1, 3.6, 2.3 Hz, 2-H), 6.20 (1H, dtd, *J* 10.1, 3.6, 1.8 Hz, 3-H), 6.86 (1H, dd, *J* 8.4, 3.0 Hz, 6-H), 6.87–6.91 (2H, m, NH and 8-H), 7.10 (1H, d, *J* 8.4 Hz, 5-H); δ_C (126 MHz, $CDCl_3$) 28.7 (CH_2), 48.3 (CH_3), 55.5 (CH), 92.9 (C), 111.8 (CH), 115.4 (CH), 123.9 (CH), 126.1 (C), 129.1 (CH), 129.6 (CH), 134.1 (C), 158.6 (C), 161.6 (C); *m/z* (ESI) 341.9811 (MNa^+, $C_{13}H_{12}{}^{35}Cl_3NNaO_2$ requires 341.9826), 319 (83%), 307 (7), 297 (6), 236 (10), 218 (6), 184 (11), 159 (22), 144 (4).

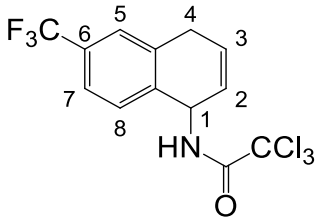
1-(2',2',2'-Trichloromethylcarbonylamino)-1,4-dihydrophenanthrene (65f)



The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(1'-allylnaphthalen-2'-yl)prop-2-en-1-ol (**61f**) (0.059 g, 0.31 mmol). The RCM step was performed at room temperature. This gave 1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydrophenanthrene (**65f**) (0.081 g, 84%) as a

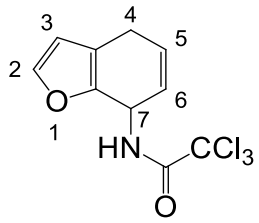
white solid. Mp 150–152 °C (decomposition); ν_{max} (neat)/cm^{-1} 3250 (NH), 3042 (CH), 1678 (CO), 1510, 1308, 1248, 1020, 818; δ_H (500 MHz, $CDCl_3$) 3.72–3.89 (2H, m, 4-H_2), 5.87–5.94 (1H, m, 1-H), 6.04 (1H, ddt, *J* 10.0, 3.6, 2.5 Hz, 2-H), 6.37 (1H, dtd, *J* 10.0, 3.6, 1.6 Hz, 3-H), 6.85 (1H, d, *J* 8.3 Hz, NH), 7.46 (1H, d, *J* 8.5 Hz, ArH), 7.52–7.61 (2H, m, 2 × ArH), 7.79 (1H, d, *J* 8.5 Hz, ArH), 7.86 (1H, dd, *J* 8.1, 0.9 Hz, ArH), 7.98 (1H, d, *J* 8.5 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 26.8 (CH_2), 48.7 (CH), 92.9 (C), 123.4 (CH), 123.7 (CH), 126.0 (CH), 126.4 (CH), 126.8 (CH), 128.0 (CH), 128.4 (CH), 128.7 (CH), 129.7 (C), 130.1 (C), 131.3 (C), 133.0 (C), 161.6 (C); *m/z* (ESI) 361.9866 (MNa^+, $C_{16}H_{12}{}^{35}Cl_3NNaO$ requires 361.9877), 320 (61%), 307 (10), 301 (7), 242 (7), 179 (100), 141 (3).

1-(2',2',2'-Trichloromethylcarbonylamino)-6-trifluoromethyl-1,4-dihydronaphthalene (65g)



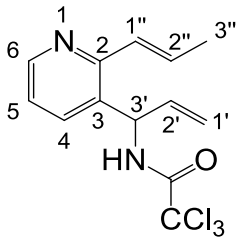
The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(2'-allyl-4'-trifluoromethylphenyl)prop-2-en-1-ol (**61g**) (0.061 g, 0.25 mmol). Grubbs 2nd generation catalyst (0.011 g, 0.013 mmol) was added and the reaction was stirred at 50 °C for 24 h before a second portion of Grubbs 2nd generation catalyst (0.011 g, 0.013 mmol) was added and allowed to stir at 50 °C for a further 24 h. This gave 1-(2',2',2'-trichloromethylcarbonylamino)-6-trifluoromethyl-1,4-dihydronaphthalene (**65g**) (0.065 g, 72%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3268 (NH), 2924 (CH), 1684 (CO), 1525, 1329, 1160, 1119, 822; δ_H (500 MHz, $CDCl_3$) 3.43–3.59 (2H, m, 4-H_2), 5.74–5.80 (1H, m, 1-H), 5.94 (1H, ddt, *J* 10.0, 3.5, 2.0 Hz, 2-H), 6.24 (1H, dtd, *J* 10.0, 3.5, 1.5 Hz, 3-H), 6.86 (1H, d, *J* 8.3 Hz, NH), 7.47 (1H, s, 5-H), 7.51–7.53 (2H, m, 7-H and 8-H); δ_C (126 MHz, $CDCl_3$) 29.4 (CH_2), 47.6 (CH), 92.7 (C), 124.0 (CH, q, $^3J_{CF}$ 3.6 Hz), 124.0 (C, q, $^1J_{CF}$ 272.3 Hz), 124.1 (CH), 125.6 (CH, q, $^3J_{CF}$ 3.8 Hz), 128.5 (CH), 129.0 (CH), 130.4 (C, q, $^2J_{CF}$ 32.5 Hz), 134.8 (C), 137.1 (C), 161.8 (C); *m/z* (ESI) 379.9581 (MNa^+, $C_{13}H_9{}^{35}Cl_3F_3NNaO$ requires 379.9594), 301 (19%), 236 (26), 199 (3), 136 (2).

7-(2',2',2'-Trichloromethylcarbonylamino)-4,7-dihydrobenzo[b]furan (65h)



The reaction was carried out according to the previously described procedure for 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (**54a**) using (2*E*)-3-(3'-allylfuran-2'-yl)prop-2-en-1-ol (**61h**) (0.055 g, 0.33 mmol). The RCM step was performed at room temperature. This gave 7-(2',2',2'-trichloromethylcarbonylamino)-4,7-dihydrobenzo[b]furan (**65h**) (0.052 g, 72%) as a white solid. Mp 102–104 °C; ν_{max} (neat)/cm^{-1} 3275 (NH), 2886 (CH), 1686 (CO), 1517, 1244, 1036, 821; δ_H (500 MHz, $CDCl_3$) 3.14–3.28 (2H, m, 4-H_2), 5.66–5.73 (1H, m, 7-H), 5.88 (1H, ddt, *J* 9.9, 3.7, 2.1 Hz, 6-H), 6.14 (1H, dtd, *J* 9.9, 3.4, 1.7 Hz, 5-H), 6.32 (1H, d, *J* 1.9 Hz, 3-H), 6.73 (1H, br s, NH), 7.42 (1H, d, *J* 1.9 Hz, 2-H); δ_C (126 MHz, $CDCl_3$) 25.1 (CH_2), 44.8 (CH), 92.7 (C), 109.6 (CH), 118.4 (C), 123.7 (CH), 129.2 (CH), 143.0 (CH), 145.3 (C), 161.5 (C); *m/z* (ESI) 301.9512 (MNa^+, $C_{10}H_8{}^{35}Cl_3NNaO_2$ requires 301.9513), 236 (10%), 218 (2), 184 (10).

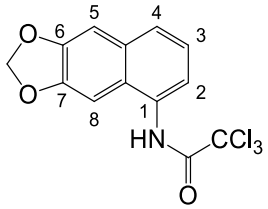
(1'*E*)-2-(Prop-1'-enyl)-3-(1''-(2''',2''',2'''-trichloromethylcarbonylamino)prop-2''-enyl)pyridine (65i)

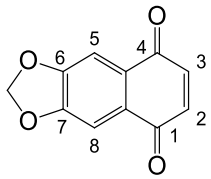


(2*E*)-3-(2'-Allylpyridin-3'-yl)prop-2-en-1-ol (**61i**) (0.055 g, 0.32 mmol) was dissolved in dry dichloromethane (8 mL) and cooled to 0 °C under argon with stirring. Trichloroacetonitrile (0.047 mL, 0.48 mmol) was added to the solution, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.024 mL, 0.16 mmol) and the reaction was allowed to return to room temperature over 1.5 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 **62i**

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 160 °C for 18 h. The reaction was allowed to cool to room temperature, Grubbs 2nd generation catalyst (0.013 g, 0.016 mmol) was added and the reaction was heated to 50 °C for 20 h. The reaction mixture was concentrated *in vacuo* and purified by silica column chromatography (elution with 20–100% diethyl ether/petroleum ether) to yield (1'*E*)-2-(prop-1'-enyl)-3-(1''-(2''',2''',2'''-trichloromethylcarbonylamino)prop-2''-enyl)pyridine (**65i**) (0.041 g, 40%) as a white solid. Mp 140–143 °C (decomposition); ν_{max} (neat)/cm^{-1} 3140 (NH), 2970 (CH), 1697 (CO), 1520, 1427, 927, 941, 826, 664; δ_H (500 MHz, $CDCl_3$) 1.95 (3H, dd, *J* 6.8, 1.7 Hz, 3'-H$_3$), 5.29 (1H, dd, *J* 17.2, 1.8 Hz, 3''-*H*H), 5.42 (1H, dd, *J* 10.5, 1.8 Hz, 3''-H*H*), 5.80–5.85 (1H, m, 1''-H), 6.06 (1H, ddd, *J* 17.2, 10.5, 4.4 Hz, 2''-H), 6.66 (1H, dq, *J* 14.4, 1.7 Hz, 1'-H), 6.87 (1H, br d, *J* 7.1 Hz, NH), 6.93 (1H, dq, *J* 14.4, 6.8 Hz, 2'-H), 7.15 (1H, dd, *J* 7.8, 4.7 Hz, 5-H), 7.56 (1H, dd, *J* 7.8, 1.5 Hz, 4-H), 8.52 (1H, dd, *J* 4.7, 1.5 Hz, 6-H); δ_C (126 MHz, $CDCl_3$) 18.9 (CH_3), 53.3 (CH), 92.5 (C), 118.0 (CH_2), 121.9 (CH), 126.3 (CH), 130.0 (C), 134.7 (CH), 134.9 (CH), 135.2 (CH), 149.3 (CH), 154.4 (C), 161.0 (C); *m/z* (ESI) 319.0155 (MH^+, $C_{13}H_{14}{}^{35}Cl_3N_2O$ requires 319.0166), 236 (6), 185 (8), 158 (4), 130 (3).

6,7-Methylenedioxy-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (68) and 6,7-methylenedioxy-1,4-naphthoquinone (69)

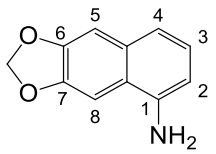




Manganese(IV) oxide (0.521 g, 5.99 mmol) was added to a solution of 6,7-methylenedioxy-1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydronaphthalene (**65b**) (0.200 g, 0.597 mmol) in chloroform (6 mL) and heated at 45 °C for 20 h. The crude reaction mixture was filtered through a short pad of Celite® with chloroform (100 mL) and then concentrated *in vacuo*. Purification by column chromatography (elution with 100% toluene) yielded 6,7-methylenedioxy-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (**68**) (0.143 g, 72%) as a white solid. Further elution gave 6,7-methylenedioxy-1,4-naphthoquinone (**69**) (0.019 g,

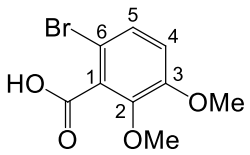
16%) as an orange solid. Data for **68**: Mp 139–140 °C; ν_{max} (neat)/cm^{-1} 3302 (NH), 2913 (CH), 1686 (CO), 1489, 1462, 1242, 1034, 849, 814; δ_H (500 MHz, $CDCl_3$) 6.05 (2H, s, OCH_2O), 7.05 (1H, s, ArH), 7.13 (1H, s, ArH), 7.32 (1H, t, *J* 7.9 Hz, 3-H), 7.55 (1H, d, *J* 7.9 Hz, 4-H), 7.60 (1H, d, *J* 7.9 Hz, 2-H), 8.47 (1H, br s, NH); δ_C (126 MHz, $CDCl_3$) 93.1 (C), 97.6 (CH), 101.6 (CH_2), 104.8 (CH), 121.4 (CH), 124.2 (CH), 125.3 (C), 127.0 (CH), 130.0 (C), 131.6 (C), 148.1 (C), 148.9 (C), 160.6 (C); *m/z* (ESI) 353.9452 (MNa^+, $C_{13}H_8{}^{35}Cl_3NNaO_3$ requires 353.9462), 301 (3%), 236 (7), 227 (4), 159 (1); Data for **69**: Mp 196–200 °C; ν_{max} (neat)/cm^{-1} 2928 (CH), 1655 (CO), 1586, 1485, 1316, 1026, 976, 833; δ_H (400 MHz, $CDCl_3$) 6.14 (2H, s, OCH_2O), 6.88 (2H, s, 5-H and 8-H), 7.45 (2H, s, 2-H and 3-H); δ_C (101 MHz, $CDCl_3$) 102.8 (CH_2), 106.0 (CH), 129.1 (C), 138.3 (CH), 152.5 (C), 184.1 (C); *m/z* (EI) 202.0264 (M^+, $C_{11}H_6O_4$ requires 202.0266), 174 (37%), 148 (22), 120 (29), 105 (20), 84 (41), 77 (19), 62 (24).

6,7-Methylenedioxy-1-aminonaphthalene (70)[184]



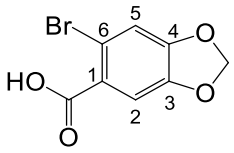
6 M Hydrochloric acid (15 mL) was added to a solution of 6,7-methylenedioxy-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (**68**) (0.330 g, 0.991 mmol) in methanol (20 mL) and heated with stirring to 90 °C for 60 h. The reaction mixture was cooled to room temperature then washed with dichloromethane (2 × 10 mL). The aqueous layer was basified to pH ~ 10 with 12 M sodium hydroxide solution and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield 6,7-methylenedioxy-1-aminonaphthalene (**70**) (0.182 g, 98%) as a white solid. Mp 151–152 °C (lit.[184] 152–154 °C); δ_H (500 MHz, $CDCl_3$) 3.85 (2H, s, NH_2), 6.03 (2H, s, OCH_2O), 6.69 (1H, dd, *J* 6.6, 1.9 Hz, 2-H), 7.09 (1H, s, ArH), 7.13 (1H, s, ArH), 7.14–7.18 (2H, m, 3-H and 4-H); δ_C (126 MHz, $CDCl_3$) 97.9 (CH), 101.2 (CH_2), 104.8 (CH), 109.7 (CH), 118.9 (CH), 120.3 (C), 125.0 (CH), 131.7 (C), 141.5 (C), 147.3 (C), 147.6 (C); *m/z* (ESI) 188 (MH^+, 100%), 158 (26), 146 (10), 130 (78).

6-Bromo-2,3-dimethoxybenzoic acid (72a)[101]



2,3-Dimethoxybenzoic acid (**71**) (0.20 g, 1.1 mmol) was added to a stirred solution of sodium hydroxide (0.048 g, 1.2 mmol) in water (1.7 mL) and the solution was cooled to 0 °C. Dibromodimethylhydantoin (0.19 g, 0.66 mmol) was added to the solution in small portions and the reaction mixture was allowed to return to room temperature over 20 h. The reaction was quenched with 1 M hydrochloric acid (3 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 6-bromo-2,3-dimethoxybenzoic acid (**72a**) (0.24 g, 82%) as a white solid. Mp 108–110 °C (lit.,[101] 110–112 °C); δ_H (500 MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.86 (1H, d, *J* 8.9 Hz, 5-H), 7.27 (1H, d, *J* 8.9 Hz, 4-H), 9.41 (1H, br s, CO_2H); δ_C (126 MHz, $CDCl_3$) 56.3 (CH_3), 62.0 (CH_3), 108.8 (C), 115.1 (CH), 128.3 (CH), 130.4 (C), 147.2 (C), 152.3 (C), 170.8 (C); *m/z* (CI) 261 (M^+, 13%), 183 (100), 165 (24), 153 (6), 133 (5), 85 (7), 69 (8).

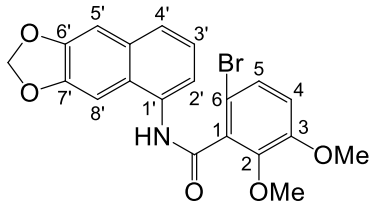
2-Bromo-4,5-methylenedioxybenzoic acid (72b)[102]



2-Methyl-but-2-ene (1.85 mL, 17.5 mmol), was added to a stirred solution of 2-bromo-4,5-methylenedioxybenzaldehyde (**52b**) (0.500 g, 2.18 mmol) in *tert*-butanol (10 mL). In a second flask, sodium chlorite (0.768 g, 8.73 mmol) and sodium dihydrogen phosphate (1.83 g, 15.3 mmol) were dissolved in water (10 mL) with stirring. The aqueous solution was added dropwise with vigorous stirring to the organic solution and stirred at room temperature for 3 h. The reaction was quenched with 6 M hydrochloric acid (5 mL), stirred for 0.25 h and then extracted with dichloromethane (3 × 20 mL). The combined organic layers were extracted with 6 M sodium hydroxide solution (2 × 30 mL). The resulting aqueous solution was acidified to pH ~ 2 with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine

(60 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 2-bromo-4,5-methylenedioxybenzoic acid (**72b**) (0.523 g, 98%) as a white solid. Mp 202–204 °C (lit.,[102] 205–208 °C); δ_H (500 MHz, $CDCl_3$) 6.08 (2H, s, OCH_2O), 7.14 (1H, s, 3-H), 7.51 (1H, s, 6-H), 11.20 (1H, br s, CO_2H); δ_C (126 MHz, $CDCl_3$) 102.8 (CH_2), 112.0 (CH), 115.0 (CH), 116.5 (C), 122.9 (C), 147.4 (C), 152.0 (C), 169.2 (C); *m/z* (EI) 244 (M^+, 100%), 227 (39), 199 (21), 165 (8), 143 (15), 107 (10), 79 (12), 62 (32).

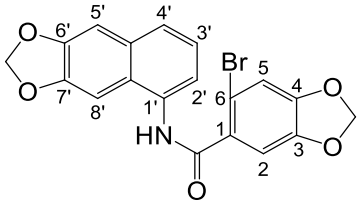
6-Bromo-2,3-dimethoxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (73a)



6-Bromo-2,3-dimethoxybenzoic acid (**72a**) (0.024 g, 0.10 mmol) was suspended in thionyl chloride (0.5 mL) and heated with stirring to 65 °C for 1 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to yield the acid chloride, which was used without further purification. In a second flask, *N,N*-diisopropylethylamine (0.14 mL, 0.80 mmol) was added to a solution of 6,7-methylenedioxy-1-aminonaphthalene (**70**) (0.015 g, 0.080 mmol) in dichloromethane (0.4 mL) and cooled to 0 °C. The crude acid chloride was dissolved in dichloromethane (0.4 mL) and added dropwise to the cooled, stirring solution of amines. The reaction mixture was stirred at 0 °C for 1 h and then allowed to return to room temperature over 1 h. The reaction was quenched with 1 M hydrochloric acid (1 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with a saturated solution of sodium hydrogen carbonate (20 mL) then brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting solid was washed with a minimal volume of ice cold chloroform to yield 6-bromo-2,3-dimethoxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**73a**) (0.031 g, 89%) as a white solid. Mp 227–229 °C; ν_{max} (neat)/cm^{-1} 3235 (NH), 2918 (CH), 1664 (CO), 1543, 1463, 1248, 1044, 997, 950, 805; δ_H (500 MHz, $CDCl_3$) 3.92 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.05 (2H, s, OCH_2O), 6.88 (1H, d, *J* 8.8 Hz, 4-H), 7.15 (1H, s, ArH), 7.34 (1H, d, *J* 8.8 Hz, 5-H), 7.38 (1H, t, *J* 7.8 Hz, 3'-H), 7.47–7.52 (2H, m, NH and ArH),

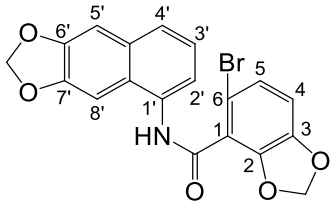
7.61 (1H, d, *J* 7.8 Hz, 4'-H), 7.69 (1H, d, *J* 7.8 Hz, 2'-H); δ_C (126 MHz, $CDCl_3$) 56.3 (CH_3), 62.5 (CH_3), 99.0 (CH), 101.4 (CH_2), 104.5 (CH), 110.0 (C), 114.6 (CH), 122.1 (CH), 124.4 (CH), 126.3 (C), 126.4 (CH), 128.6 (CH), 131.4 (C), 131.7 (C), 134.2 (C), 147.2 (C), 148.0 (C), 148.7 (C), 152.5 (C), 164.8 (C); *m/z* (ESI) 452.0090 (MNa^+, $C_{20}H_{16}{}^{79}BrNNaO_5$ requires 452.0104), 430 (1%), 413 (3), 243 (1).

2-Bromo-4,5-methylenedioxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (73b)



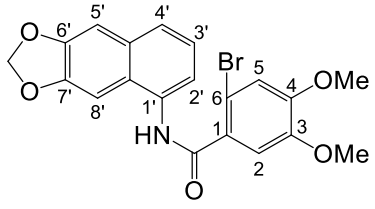
The reaction was carried out according to the previously described procedure for 6-bromo-2,3-dimethoxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**73a**) using 2-bromo-4,5-methylenedioxybenzoic acid (**72b**) (0.031 g, 0.13 mmol) and 6,7-methylenedioxy-1-aminonaphthalene (**70**) (0.020 g, 0.11 mmol). This gave 2-bromo-4,5-methylenedioxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**73b**) (0.039 g, 89%) as a white solid. Mp 236–238 °C; ν_{max} (neat)/cm^{-1} 3233 (NH), 2909 (CH), 1659 (CO), 1543, 1462, 1238, 1038, 934, 849; δ_H (500 MHz, DMSO-d_6) 6.15 (2H, s, OCH_2O), 6.16 (2H, s, OCH_2O), 7.31–7.38 (4H, m, 4 × ArH), 7.48 (1H, s, ArH), 7.52 (1H, d, *J* 7.7 Hz, 4'-H), 7.65 (1H, d, *J* 7.7 Hz, 2'-H), 10.24 (1H, s, NH); δ_C (126 MHz, DMSO-d_6) 99.7 (CH), 101.3 (CH_2), 102.3 (CH_2), 103.8 (CH), 108.9 (CH), 110.2 (C), 112.5 (CH), 121.6 (CH), 123.8 (CH), 125.2 (CH), 125.6 (C), 131.0 (2 × C), 132.6 (C), 146.9 (C), 147.3 (C), 147.6 (C), 148.8 (C), 166.2 (C); *m/z* (ESI) 435.9775 (MNa^+, $C_{19}H_{12}{}^{79}BrNNaO_5$ requires 435.9791), 413 (8%), 370 (4), 236 (7), 227 (8), 198 (3).

6-Bromo-2,3-methylenedioxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (73c)



The reaction was carried out according to the previously described procedure for 6-bromo-2,3-dimethoxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**73a**) using 6-bromo-2,3-methylenedioxybenzoic acid (**72c**) (0.13 g, 0.51 mmol) and 6,7-methylenedioxy-1-aminonaphthalene (**70**) (0.080 g, 0.43 mmol). This gave 6-bromo-2,3-methylenedioxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**73c**) (0.16 g, 89%) as a white solid. Mp 236–238 °C; ν_{max} (neat)/cm^{-1} 3237 (NH), 2905 (CH), 1655 (CO), 1543, 1493, 1451, 1238, 1038, 926, 849; δ_H (500 MHz, DMSO-d_6) 6.15 (2H, s, OCH_2O), 6.22 (2H, s, OCH_2O), 7.01 (1H, d, *J* 8.3 Hz, 4-H), 7.20 (1H, d, *J* 8.3 Hz, 5-H), 7.36 (1H, t, *J* 7.6 Hz, 3'-H), 7.37 (1H, s, ArH), 7.46 (1H, s, ArH), 7.47 (1H, d, *J* 7.6 Hz, 4'-H), 7.67 (1H, d, *J* 7.6 Hz, 2'-H), 10.52 (1H, s, NH); δ_C (126 MHz, DMSO-d_6) 99.3 (CH), 101.4 (CH_2), 102.6 (CH_2), 103.9 (CH), 110.0 (C), 110.2 (CH), 121.3 (C), 121.5 (CH), 123.9 (CH), 125.2 (CH), 125.4 (CH), 125.4 (C), 131.1 (C), 132.1 (C), 145.7 (C), 147.2 (C), 147.4 (C), 147.7 (C), 162.2 (C); *m/z* (ESI) 435.9792 (MNa^+, $C_{19}H_{12}{}^{79}BrNNaO_5$ requires 435.9791), 413 (13%), 335 (13), 289 (3), 236 (8), 159 (6).

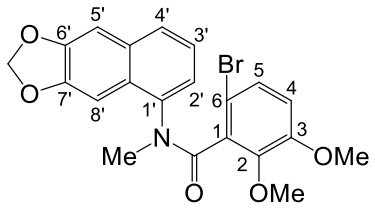
2-Bromo-4,5-dimethoxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (73d)



The reaction was carried out according to the previously described procedure for 6-bromo-2,3-dimethoxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**73a**) using 2-bromo-4,5-dimethoxybenzoic acid (**72d**) (0.084 g, 0.32 mmol) and 6,7-methylenedioxy-1-aminonaphthalene (**70**) (0.050 g, 0.27 mmol). This gave 2-bromo-4,5-dimethoxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**73d**)

(0.10 g, 88%) as a white solid. Mp 231–234 °C; ν_{max} (neat)/cm^{-1} 3217 (NH), 2934 (CH), 1627 (CO), 1534, 1459, 1243, 1040, 951, 837; δ_H (500 MHz, DMSO-d_6) 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.15 (2H, s, OCH_2O), 7.25 (1H, s, 3-H), 7.28 (1H, s, 6-H), 7.36 (1H, t, *J* 7.7 Hz, 3'-H), 7.36 (1H, s, ArH), 7.49 (1H, s, ArH), 7.54 (1H, d, *J* 7.7 Hz, 4'-H), 7.65 (1H, d, *J* 7.7 Hz, 2'-H), 10.22 (1H, s, NH); δ_C (126 MHz, DMSO-d_6) 56.0 (CH_3), 56.1 (CH_3), 99.8 (CH), 101.3 (CH_2), 103.8 (CH), 109.6 (C), 112.4 (CH), 115.7 (CH), 121.6 (CH), 123.9 (CH), 125.2 (CH), 125.6 (C), 131.1 (C), 131.1 (C), 132.8 (C), 147.3 (C), 147.6 (C), 148.0 (C), 150.1 (C), 166.4 (C); *m/z* (ESI) 452.0088 (MNa^+, $C_{20}H_{16}{}^{79}BrNNaO_5$ requires 452.0104), 413 (6%), 381 (10), 353 (10), 301 (3), 236 (3).

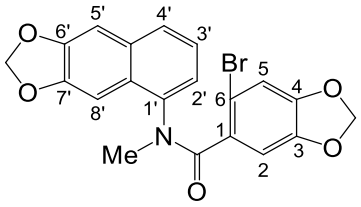
6-Bromo-2,3-dimethoxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (74a)[94]



Sodium hydride (60% dispersion in mineral oil, 0.020 g, 0.51 mmol) was washed with hexane (×3) under argon and dried under reduced pressure. *N*,*N*'-Dimethylformamide (1 mL) was added to the sodium hydride followed slowly by a solution of 6-bromo-2,3-dimethoxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**73a**) (0.087 g, 0.20 mmol) in *N*,*N*'-dimethylformamide (1 mL). The reaction mixture was stirred at room temperature for 0.1 h then methyl iodide (0.044 ml, 0.71 mmol) was added dropwise with vigorous stirring and the mixture was stirred for 18 h at room temperature. The reaction was quenched by the slow addition of 1 M hydrochloric acid solution (3 mL), diluted with 5% lithium chloride solution (3 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was washed with cold hexane (5 × 1 mL), to yield 6-bromo-2,3-dimethoxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74a**) (0.088 g, 98%) as a white solid. Mp 173–175 °C (lit.[94] mp 178–179 °C); the NMR spectra showed the presence of rotomers; for simplification, only signals for the major rotomer is reported: δ_H (500 MHz, DMSO-d_6) 3.20 (3H, s, NCH_3), 3.93 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 6.04 (1H, d, *J* 1.5

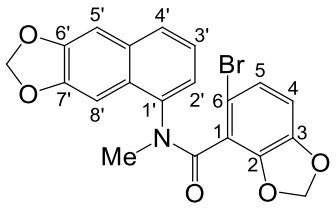
Hz, OC*H*HO), 6.05 (1H, d, *J* 1.5 Hz, OCH*H*O), 6.87 (1H, d, *J* 9.0 Hz, ArH), 7.17 (1H, s, ArH), 7.34 (1H, d, *J* 9.0 Hz, ArH), 7.38–7.42 (1H, m, ArH), 7.44–7.48 (1H, m, ArH), 7.53 (1H, s, ArH), 7.64–7.69 (1H, m, ArH); δ_C (126 MHz, DMSO-d_6) 39.6 (CH_3), 56.2 (CH_3), 61.9 (CH_3), 99.7 (CH), 101.3 (CH_2), 104.5 (CH), 109.4 (C), 114.0 (CH), 123.6 (CH), 124.7 (CH), 127.4 (CH), 128.2 (C), 128.5 (CH), 131.8 (C), 132.2 (C), 134.0 (C), 138.8 (C), 146.0 (C), 149.1 (C), 152.6 (C), 166.9 (C); *m/z* (ESI) 466 (MNa^+, 100%), 446 (1), 243 (1), 227 (1).

2-Bromo-4,5-methylenedioxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (74b)



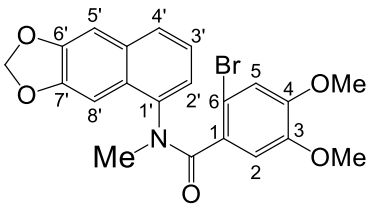
The reaction was carried out according to the previously described procedure for 6-bromo-2,3-dimethoxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74a**) using 2-bromo-4,5-methylenedioxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**73b**) (0.010 g, 0.024 mmol). This gave 2-bromo-4,5-methylenedioxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74b**) (0.010 g, 98%) as a white solid. Mp 193–196 °C; ν_{max} (neat)/cm^{-1} 2916 (CH), 1636 (CO), 1462, 1242, 1026, 934, 860; δ_H (500 MHz, $CDCl_3$) 3.48 (3H, s, NCH_3), 5.74 (1H, d, *J* 1.3 Hz, OC*H*HO), 5.78 (1H, d, *J* 1.3 Hz, OCH*H*O), 6.08 (1H, d, *J* 1.1 Hz, OC*H*HO), 6.11 (1H, d, *J* 1.1 Hz, OCH*H*O), 6.42 (1H, s, ArH), 6.80 (1H, s, ArH), 7.09 (1H, s, ArH), 7.15 (1H, dd, *J* 8.1, 7.5 Hz, 3'-H), 7.24 (1H, s, ArH), 7.34 (1H, dd, *J* 7.5, 1.0 Hz, 4'-H), 7.51 (1H, br d, *J* 8.1 Hz, 2'-H); δ_C (126 MHz, $CDCl_3$) 37.4 (CH_3), 99.2 (CH), 101.6 (CH_2), 101.9 (CH_2), 104.7 (CH), 107.2 (CH), 111.6 (C), 113.0 (CH), 124.2 (CH), 124.3 (CH), 127.3 (C), 127.7 (CH), 131.6 (C), 131.8 (C), 139.1 (C), 146.4 (C), 148.2 (C), 148.5 (C), 149.2 (C), 169.4 (C); *m/z* (ESI) 449.9935 (MNa^+, $C_{20}H_{14}{}^{79}BrNNaO_5$ requires 449.9948), 413 (4%), 301 (7), 257 (1), 236 (4), 199 (3).

6-Bromo-2,3-methylenedioxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (74c)



The reaction was carried out according to the previously described procedure for 6-bromo-2,3-dimethoxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74a**) using 6-bromo-2,3-methylenedioxy-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**73c**) (0.140 g, 0.338 mmol). This gave 6-bromo-2,3-methylenedioxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74c**) (0.138 g, 95%) as a white solid. Mp 161–163 °C; ν_{max} (neat)/cm^{-1} 2901 (CH), 1651 (CO), 1462, 1447, 1373, 1246, 1038, 934; the NMR spectra showed the presence of rotomers; for simplification, only signals for the major rotomer is reported: δ_H (500 MHz, $CDCl_3$) 3.52 (3H, s, NCH_3), 5.13 (1H, d, *J* 1.5 Hz, OC*H*HO), 5.79 (1H, d, *J* 1.5 Hz, OCH*H*O), 6.04 (1H, d, *J* 1.0 Hz, OC*H*HO), 6.08 (1H, d, *J* 1.0 Hz, OCH*H*O), 6.36 (1H, d, *J* 8.0 Hz, ArH), 6.82 (1H, d, *J* 8.0 Hz, ArH), 7.07 (1H, s, ArH), 7.13–7.17 (1H, m, ArH), 7.34 (1H, s, ArH), 7.51–7.55 (1H, m, ArH), 7.66–7.71 (1H, m, ArH); δ_C (126 MHz, $CDCl_3$) 37.3 (CH_3), 100.6 (CH), 101.4 (CH_2), 101.6 (CH_2), 104.3 (CH), 109.4 (CH), 111.2 (C), 121.1 (C), 124.2 (2 × CH), 125.3 (CH), 125.8 (C), 127.9 (CH), 138.7 (C), 144.9 (C), 146.6 (C), 146.7 (C), 147.9 (C), 148.1 (C), 162.X (C); *m/z* (ESI) 449.9935 (MNa^+, $C_{20}H_{14}{}^{79}BrNNaO_5$ requires 449.9948), 430 (1%), 413 (6), 236 (1), 227 (1).

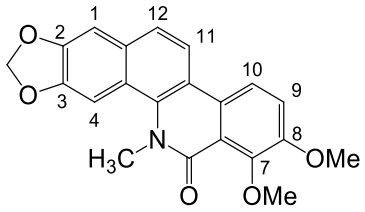
2-Bromo-4,5-dimethoxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (74d)



The reaction was carried out according to the previously described procedure for 6-bromo-2,3-dimethoxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74a**) using 2-bromo-4,5-dimethoxy-*N*-(6',7'-

methylenedioxynaphthalen-1-yl)benzamide (**73d**) (0.085 g, 0.20 mmol). This gave 2-bromo-4,5-dimethoxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74d**) (0.083 g, 94%) as a white solid. Mp 171–174 °C; ν_{max} (neat)/cm^{-1} 2901 (CH), 1646 (CO), 1507, 1462, 1247, 1212, 1162, 1035, 918, 855; δ_H (500 MHz, $CDCl_3$) 3.32 (3H, s, NCH_3), 3.52 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 6.07 (2H, s, OCH_2O), 6.46 (1H, s, ArH), 6.79 (1H, s, ArH), 7.09 (1H, s, ArH), 7.13 (1H, dd, *J* 8.1, 7.5 Hz, 3'-H), 7.29 (1H, dd, *J* 7.5, 1.1 Hz, 4'-H), 7.31 (1H, s, ArH), 7.49 (1H, br d, *J* 8.1 Hz, 2'-H); δ_C (126 MHz, $CDCl_3$) 37.2 (CH_3), 55.6 (CH_3), 56.1 (CH_3), 99.2 (CH), 101.6 (CH_2), 104.9 (CH), 110.6 (CH), 110.8 (C), 115.4 (CH), 124.4 (2 × CH), 127.5 (C), 127.7 (CH), 130.2 (C), 131.8 (C), 139.4 (C), 147.2 (C), 148.0 (C), 149.1 (C), 149.5 (C), 169.7 (C); *m/z* (ESI) 466.0238 (MNa^+, $C_{21}H_{18}{}^{79}BrNNaO_5$ requires 466.0261), 413 (1%), 381 (4), 353 (4), 236 (1), 227 (1).

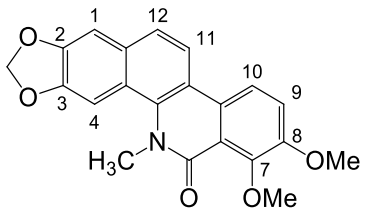
Oxychelerythrine (44)[185] ($Pd(OAc)_2$ method)



6-Bromo-2,3-dimethoxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74a**) (0.020 g, 0.045 mmol), palladium(II) acetate (0.0020 g, 0.0089 mmol), tri-*o*-tolylphosphine (0.0055 g, 0.018 mmol) and silver carbonate (0.025 g, 0.090 mmol) were combined with a stirred bar in a microwave vial and placed under argon. Degassed *N*,*N*'-dimethylformamide (1.2 mL) was added and the vial was sealed and heated to 160 °C for 3 h then cooled to room temperature. Additional palladium(II) acetate (0.0010 g, 0.0044 mmol) and tri-*o*-tolylphosphine (0.0025 g, 0.0082 mmol) were added and the reaction was resealed and heated to 160 °C for a further 18 h then cooled to room temperature. The reaction mixture was diluted with diethyl ether (4 mL) and filtered. The filtrate was the further diluted with diethyl ether (10 mL) and washed with 5% lithium chloride solution (3 × 15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (elution with 40% ethyl acetate:petroleum ether) yielded oxychelerythrine (**44**) (0.016 g, 97%) as a white solid. Mp 182–185 °C (lit.[185] 198−200 °C); δ_H (500 MHz, $CDCl_3$) 3.89 (3H, s, CH_3), 3.98 (3H, s, CH_3), 4.08 (3H, s, CH_3), 6.09 (2H, s, OCH_2O), 7.15 (1H, s, ArH), 7.38 (1H, d, *J* 9.0 Hz,

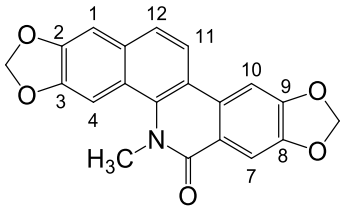
ArH), 7.52 (1H, d, *J* 9.0 Hz, ArH), 7.53 (1H, s, ArH), 7.97 (1H, s, ArH), 7.99 (1H, s, ArH); δ_C (126 MHz, $CDCl_3$) 40.9 (CH_3), 56.8 (CH_3), 61.9 (CH_3), 101.6 (CH_2), 102.6 (CH), 104.8 (CH), 117.3 (C), 117.9 (CH), 118.0 (CH), 118.6 (CH), 119.9 (C), 121.2 (C), 123.4 (CH), 129.1 (C), 131.8 (C), 135.8 (C), 147.2 (C), 147.6 (C), 150.3 (C), 152.9 (C), 162.8 (C); *m/z* (ESI) 386.0989 (MNa^+, $C_{21}H_{17}NNaO_5$ requires 386.0999), 371 (4%), 227 (6).

Oxychelerythrine (44)[185] (Herrmann-Beller catalyst method)



6-Bromo-2,3-dimethoxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74a**) (0.020 g, 0.045 mmol), *trans*-bis(acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (0.0042 g, 0.0045 mmol) and silver carbonate (0.025 g, 0.090 mmol) were combined with a stirred bar in a microwave vial and placed under argon. Degassed *N*,*N*'-dimethylformamide (1.2 mL) was added and the vial was sealed and heated to 160 °C for 22 h then cooled to room temperature. The reaction mixture was diluted with diethyl ether (4 mL) and filtered. The filtrate was then further diluted with diethyl ether (10 mL) and washed with 5% lithium chloride solution (3 × 15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (elution with 40% ethyl acetate:petroleum ether) and then washing of the resulting solid with hexane (3 × 1 mL) yielded oxychelerythrine (**44**) (0.016 g, 95%) as a white solid. Spectroscopic data as described above.

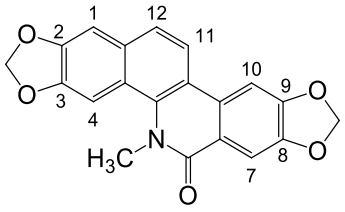
Oxyavicine (43)[185] ($Pd(OAc)_2$ method)



The reaction was carried out according to the previously described procedure for the synthesis of oxychelerythrine (**44**) ($Pd(OAc)_2$ method) using 2-bromo-4,5-

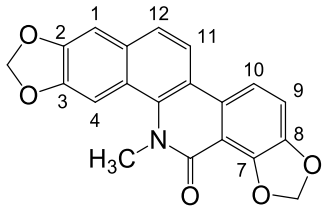
methylenedioxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74b**) (0.020 g, 0.047 mmol) and a single addition of palladium(II) acetate (0.0040 g, 0.018 mmol) and tri-*o*-tolylphosphine (0.010 g, 0.033 mmol). Purification by column chromatography (50% ethyl acetate:petroleum ether) and then washing the resulting solid with hexane (3 × 1 mL) yielded oxyavicine (**43**) (0.006 g, 23%) as a white solid. Mp 265−268 °C (lit.[185] 271−273 °C); δ_H (500 MHz, $CDCl_3$) 3.97 (3H, s, NCH_3), 6.10 (2H, s, OCH_2O), 6.13 (2H, s, OCH_2O), 7.17 (1H, s, ArH), 7.54 (1H, d, *J* 8.8 Hz, ArH), 7.60 (1H, s, ArH), 7.62 (1H, s, ArH), 7.89 (1H, s, ArH), 7.92 (1H, d, *J* 8.8 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 41.4 (CH_3), 100.8 (CH), 101.7 (CH_2), 102.1 (CH_2), 102.8 (CH), 104.9 (CH), 106.8 (CH), 117.0 (C), 118.7 (CH), 121.0 (C), 121.1 (C), 123.4 (CH), 131.2 (C), 132.1 (C), 136.0 (C), 147.2 (C), 147.7 (C), 148.3 (C), 152.6 (C), 164.2 (C); *m/z* (ESI) 370.0668 (MNa^+, $C_{20}H_{13}NNaO_5$ requires 370.0686), 357 (57%), 343 (100), 321 (6), 236 (6).

Oxyavicine (43)[185] (Herrmann-Beller catalyst method)



The reaction was carried out according to the previously described procedure for the synthesis of oxychelerythrine (**44**) (Herrmann-Beller catalyst method) using 2-bromo-4,5-methylenedioxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74b**) (0.040 g, 0.093 mmol). Purification was performed by washing with hexane (5 × 2 mL), then ice cold diethyl ether (3 × 1 mL) which yielded oxyavicine (**43**) (0.025 g, 78%) as a white solid. Spectroscopic data as above.

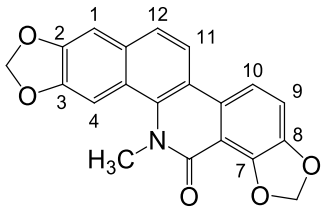
Oxysanguinarine (45)[185] ($Pd(OAc)_2$ method)



The reaction was carried out according to the previously described procedure for the synthesis of oxychelerythrine (**44**) ($Pd(OAc)_2$ method) using 6-bromo-2,3-

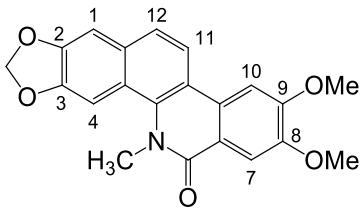
methylenedioxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74c**) (0.020 g, 0.047 mmol). Purification by column chromatography (40% ethyl acetate:petroleum ether) then a second column (eluted 1% methanol:dichloromethane) gave oxysanguinarine (**45**) (0.004 g, 22%) as an off white solid. Spectroscopic data as below with minor impurities.

Oxysanguinarine (45)[185] (Herrmann-Beller catalyst method)



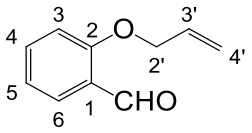
The reaction was carried out according to the previously described procedure for the synthesis of oxychelerythrine (**44**) (Herrmann-Beller catalyst method) using 6-bromo-2,3-methylenedioxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74c**) (0.020 g, 0.047 mmol). The reaction was complete after 3 h. Purification by column chromatography (20–100% ethyl acetate:petroleum ether then 1% methanol:dichloromethane) and then washing the resulting solid with hexane (3 × 1 mL) gave oxysanguinarine (**45**) (0.015 g, 90%) as a white solid. Mp 356−358 °C (lit.[185] 361−363 °C); δ_H (500 MHz, $CDCl_3$) 3.91 (3H, s, NCH_3), 6.10 (2H, s, OCH_2O), 6.27 (2H, s, OCH_2O), 7.16 (1H, s, 1-H), 7.24 (1H, d, *J* 8.7 Hz, ArH), 7.53 (1H, d, *J* 8.7 Hz, ArH), 7.57 (1H, s, 4-H), 7.76 (1H, d, *J* 8.7 Hz, ArH), 7.98 (1H, d, *J* 8.7 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 41.0 (CH_3), 101.7 (CH_2), 102.7 (CH), 103.0 (CH_2), 104.9 (CH), 111.1 (C), 113.3 (CH), 115.6 (CH), 117.4 (C), 118.9 (CH), 121.3 (C), 123.7 (CH), 129.0 (C), 132.0 (C), 135.7 (C), 147.3 (C), 147.7 (C), 147.8 (C), 147.9 (C), 162.8 (C); *m/z* (ESI) 370.0676 (MNa^+, $C_{20}H_{13}NNaO_5$ requires 370.0686), 354 (3%), 342 (3), 236 (6), 227 (1).

Oxynitidine (46)[185]



The reaction was carried out according to the previously described procedure for the synthesis of oxychelerythrine (**44**) (Herrmann-Beller catalyst method) using 2-bromo-4,5-dimethoxy-*N*-methyl-*N*-(6',7'-methylenedioxynaphthalen-1-yl)benzamide (**74d**) (0.019 g, 0.043 mmol) and *trans*-bis(acetato)bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) (0.0080 g, 0.0086 mmol). Purification was performed by washing with hexane (5 × 2 mL), then ice cold diethyl ether (3 × 1 mL), this yielded oxynitidine (**46**) (0.013 g, 83%) as a white solid. Mp 268−270 °C (lit.[185] 270−272 °C); δ_H (500 MHz, $CDCl_3$) 3.99 (3H, s, CH_3), 4.06 (3H, s, CH_3), 4.11 (3H, s, CH_3), 6.11 (2H, s, OCH_2O), 7.19 (1H, s, ArH), 7.57 (1H, d, *J* 8.7 Hz, ArH), 7.60 (1H, s, ArH), 7.65 (1H, s, ArH), 7.93 (1H, s, ArH), 8.00 (1H, d, *J* 8.7 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 41.4 (CH_3), 56.3 (CH_3), 56.4 (CH_3), 101.7 (CH_2), 102.8 (CH), 103.0 (CH), 104.9 (CH), 108.8 (CH), 116.9 (C), 118.5 (CH), 119.4 (C), 121.2 (C), 123.4 (CH), 129.1 (C), 132.0 (C), 136.1 (C), 147.2 (C), 147.7 (C), 149.9 (C), 153.7 (C), 164.4 (C); *m/z* (EI) 363.1109 (M^+, $C_{21}H_{17}NO_5$ requires 363.1107), 334 (17%), 305 (15), 290 (8), 262 (9), 182 (10), 84 (11).

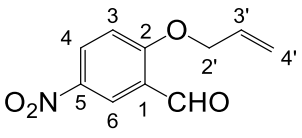
2-Allyloxybenzaldehyde (93a)[117]



Allyl bromide (0.98 mL, 1.3 mmol) was added to a stirred solution of 2-hydroxybenzaldehyde (**92a**) (0.10 mL, 0.94 mmol) and potassium carbonate (0.26 g, 1.9 mmol) in dimethylformamide (10 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 ($MgSO_4$), filtered and concentrated *in vacuo* to give 2-allyloxybenzaldehyde (**93a**) (0.15 g, 99%) as a colourless oil. Spectroscopic data

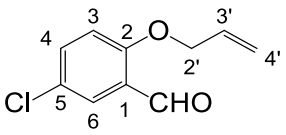
was in accordance with literature values.[117] δ_H (400 MHz, $CDCl_3$) 4.66 (2H, dt, *J* 5.1, 1.5 Hz, 2'-H_2), 5.34 (1H, dq, *J* 10.5, 1.5 Hz, 4'-*H*H), 5.45 (1H, dq, *J* 17.3, 1.5 Hz, 4'-H*H*), 6.08 (1H, ddt, *J* 17.3, 10.5, 5.1 Hz, 3'-H), 6.98 (1H, d, *J* 8.4 Hz, 3-H), 7.03 (1H, br t, *J* 7.5 Hz, 5-H), 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); δ_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-nitrobenzaldehyde (93b)[186]



The reaction was carried out according to the previously described procedure for 2-allyloxybenzaldehyde (**93a**) using 2-hydroxy-5-nitrobenzaldehyde (**92b**) (0.050 g, 0.32 mmol). Purification by column chromatography (elution with 40% diethyl ether in petroleum ether) gave 2-allyloxy-5-nitrobenzaldehyde (**93b**) (0.061 g, 98%) as a white solid. Mp 62–64 °C (lit.[186] 63–65 °C); δ_H (400 MHz, $CDCl_3$) 4.80 (2H, dt, *J* 5.3, 1.4 Hz, 2'-H_2), 5.41 (1H, ddt, *J* 10.7, 2.5, 1.4 Hz, 4'-*H*H), 5.48 (1H, ddt, *J* 17.3, 2.5, 1.4 Hz, 4'-H*H*), 6.08 (1H, ddt, *J* 17.3, 10.7, 5.3 Hz, 3'-H), 7.11 (1H, d, *J* 9.2 Hz, 3-H), 8.39 (1H, dd, *J* 9.2, 2.9 Hz, 4-H), 8.67 (1H, d, *J* 2.9 Hz, 6-H), 10.48 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 70.3 (CH_2), 113.5 (CH), 119.6 (CH_2), 124.7 (CH), 124.8 (C) 130.6 (CH), 131.1 (CH), 141.7 (C), 164.7 (C), 187.6 (CH); *m/z* (CI) 208 (MH^+, 100%), 178 (45), 168 (13), 138 (16), 113 (21), 97 (18), 81 (32), 69 (33).

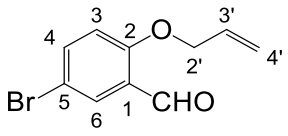
2-Allyloxy-5-chlorobenzaldehyde (93c)[187]



The reaction was carried out according to the previously described procedure for 2-allyloxybenzaldehyde (**93a**) using 2-hydroxy-5-chlorobenzaldehyde (**92c**) (0.500 g, 3.18 mmol). This gave 2-allyloxy-5-chlorobenzaldehyde (**93c**) (0.610 g, 96%) as a white solid. Mp 99–101 °C (lit.[187] 101–102 °C); δ_H (400 MHz, $CDCl_3$) 4.65 (2H,

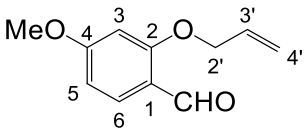
dt, *J* 5.2, 1.5 Hz, 2'-H_2), 5.35 (1H, dq, *J* 10.6, 1.5 Hz, 4'-*H*H), 5.44 (1H, dq, *J* 17.3, 1.5 Hz, 4'-H*H*), 6.06 (1H, ddt, *J* 17.3, 10.6, 5.2 Hz, 3'-H), 6.93 (1H, d, *J* 8.9 Hz, 3-H), 7.47 (1H, dd, *J* 8.9, 2.8 Hz, 4-H), 7.79 (1H, d, *J* 2.8 Hz, 6-H), 10.46 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 69.8 (CH_2), 114.7 (CH), 118.7 (CH_2), 126.1 (C), 126.7 (C), 128.1 (CH), 132.1 (CH), 135.4 (CH), 159.5 (C), 188.5 (CH); *m/z* (CI) 197 (MH^+, 100%), 169 (13), 157 (4), 81 (11), 69 (18).

2-Allyloxy-5-bromobenzaldehyde (93d)[187]



The reaction was carried out according to the previously described procedure for 2-allyloxybenzaldehyde (**93a**) using 2-hydroxy-5-bromobenzaldehyde (**92d**) (0.500 g, 2.49 mmol). This gave 2-allyloxy-5-bromobenzaldehyde (**93d**) (0.591 g, 99%) as a white solid. Mp 35–37 °C (lit.[187] 37–39 °C); δ_H (400 MHz, $CDCl_3$) 4.65 (2H, dt, *J* 5.2, 1.5 Hz, 2'-H_2), 5.35 (1H, dq, *J* 10.6, 1.5 Hz, 4'-*H*H), 5.44 (1H, dq, *J* 17.3, 1.5 Hz, 4'-H*H*), 6.05 (1H, ddt, *J* 17.3, 10.6, 5.2 Hz, 3'-H), 6.88 (1H, d, *J* 8.9 Hz, 3-H), 7.60 (1H, dd, *J* 8.9, 2.6 Hz, 4-H), 7.93 (1H, d, *J* 2.6 Hz, 6-H), 10.44 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 69.7 (CH_2), 113.8 (C), 115.1 (CH), 118.7 (CH_2), 126.6 (C), 131.2 (CH), 132.1 (CH), 138.3 (CH), 160.0 (C), 188.4 (CH); *m/z* (ESI) 263 (MNa^+, 75%), 236 (22), 219 (70), 201 (14), 184 (27).

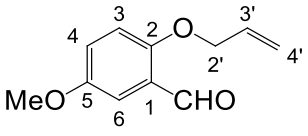
2-Allyloxy-4-methoxybenzaldehyde (93e)[188]



The reaction was carried out according to the previously described procedure for 2-allyloxybenzaldehyde (**93a**) using 2-hydroxy-4-methoxybenzaldehyde (**92e**) (0.500 g, 3.29 mmol). This gave 2-allyloxy-4-methoxybenzaldehyde (**93e**) (0.583 g, 92%) as a colourless oil. Spectroscopic data was in accordance with literature values.[188] δ_H (500 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 4.62 (2H, dt, *J* 5.1, 1.5 Hz, 2'-H_2), 5.33 (1H, dq, *J* 10.5, 1.5 Hz, 4'-*H*H), 5.45 (1H, dq, *J* 17.3, 1.5 Hz, 4'-H*H*), 6.06 (1H, ddt, *J* 17.3, 10.5, 5.1 Hz, 3'-H), 6.43 (1H, d, *J* 2.2 Hz, 3-H), 6.54 (1H, ddd, *J* 8.7, 2.2, 0.6 Hz, 5-H), 7.81 (1H, d, *J* 8.7 Hz, 6-H), 10.35 (1H, d, *J* 0.6 Hz, CHO); δ_C

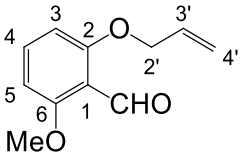
(126 MHz, $CDCl_3$) 55.8 (CH_3), 69.3 (CH_2), 99.2 (CH), 106.2 (CH), 118.2 (CH_2), 119.4 (C), 130.6 (CH), 132.4 (CH), 162.8 (C), 166.2 (C), 188.4 (CH); *m/z* (ESI) 215 (MNa^+, 100%), 187 (7), 174 (7), 159 (3).

2-Allyloxy-5-methoxybenzaldehyde (93f)[188]



The reaction was carried out according to the previously described procedure for 2-allyloxybenzaldehyde (**93a**) using 2-hydroxy-5-methoxybenzaldehyde (**92f**) (0.41 mL, 3.3 mmol). This gave 2-allyloxy-5-methoxybenzaldehyde (**93f**) (0.60 g, 96%) as a yellow oil. Spectroscopic data was in accordance with literature values.[188] δ_H (400 MHz, $CDCl_3$) 3.80 (3H, s, OCH_3), 4.61 (2H, d, *J* 5.2 Hz, 2'-H_2), 5.31 (1H, dd, *J* 10.6, 1.4 Hz, 4'-*H*H), 5.43 (1H, dd, *J* 17.1, 1.4 Hz, 4'-H*H*), 6.06 (1H, ddt, *J* 17.1, 10.6, 5.2 Hz, 3'-H), 6.93 (1H, d, *J* 9.1 Hz, 3-H), 7.11 (1H, dd, *J* 9.1, 3.3 Hz, 4-H), 7.33 (1H, d, *J* 3.3 Hz, 6-H), 10.49 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 56.0 (CH_3), 70.2 (CH_2), 110.4 (CH), 115.1 (CH), 118.1 (CH_2), 123.6 (CH), 125.6 (C), 132.8 (CH), 154.0 (C), 155.9 (C), 189.6 (CH); *m/z* (ESI) 215 (MNa^+, 40%), 206 (30), 174 (100).

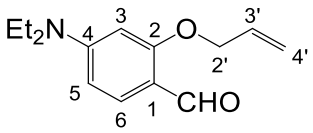
2-Allyloxy-6-methoxybenzaldehyde (93g)[188]



The reaction was carried out according to the previously described procedure for 2-allyloxybenzaldehyde (**93a**) using 2-hydroxy-6-methoxybenzaldehyde (**92g**) (0.500 g, 3.29 mmol). This gave 2-allyloxy-6-methoxybenzaldehyde (**93g**) (0.559 g, 88%) as a yellow oil. Spectroscopic data was in accordance with literature values.[188] δ_H (400 MHz, $CDCl_3$) 3.90 (3H, s, OCH_3), 4.63 (2H, dt, *J* 5.0, 1.4 Hz, 2'-H_2), 5.31 (1H, dq, *J* 10.4, 1.4 Hz, 4'-*H*H), 5.48 (1H, dq, *J* 17.3, 1.4 Hz, 4'-H*H*), 6.05 (1H, ddt, *J* 17.3, 10.4, 5.0 Hz, 3'-H), 6.56 (1H, d, *J* 8.5 Hz, ArH), 6.58 (1H, d, *J* 8.5 Hz, ArH), 7.42 (1H, t, *J* 8.5 Hz, 4-H), 10.56 (1H, s, CHO); δ_C (101 MHz, $CDCl_3$) 56.2 (CH_3), 69.7 (CH_2), 104.2 (CH), 105.3 (CH), 115.0 (C), 117.9 (CH_2), 132.6

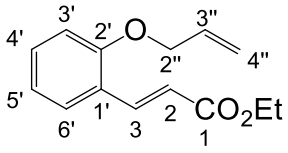
(CH), 135.8 (CH), 161.6 (C), 162.0 (C), 189.4 (CH); *m/z* (ESI) 215 (MNa^+, 100%), 187 (10), 174 (20), 137 (5).

2-(Allyloxy)-4-diethylaminobenzaldehyde (93h)[188]



The reaction was carried out according to the procedure described for 2-allyloxybenzaldehyde (**93a**) using 4-diethylamino-2-hydroxybenzaldehyde (**92h**) (0.520 g, 2.69 mmol). This gave 2-(allyloxy)-4-diethylaminobenzaldehyde (**93h**) (0.551 g, 88%) as an orange oil. Spectroscopic data was in accordance with literature values.[188] δ_H (400 MHz, $CDCl_3$) 1.11 (6H, t, *J* 7.1 Hz, $N(CH_2CH_3)_2$), 3.31 (4H, q, *J* 7.1 Hz, $N(CH_2CH_3)_2$), 4.53 (2H, dt, *J* 5.1, 1.5 Hz, 2'-H_2), 5.22 (1H, dq, *J* 10.6, 1.5 Hz, 4'-*H*H), 5.35 (1H, dq, *J* 17.3, 1.5 Hz, 4'-H*H*), 5.92–6.02 (2H, m, 3-H and 3'-H), 6.18 (1H, ddd, *J* 9.0, 2.3, 0.7 Hz, 5-H), 7.62 (1H, d, *J* 9.0 Hz, 6-H), 10.10 (1H, d, *J* 0.7 Hz, CHO); δ_C (101 MHz, $CDCl_3$) 12.8 (2 × CH_3), 45.0 (2 × CH_2), 69.1 (CH_2), 93.8 (CH), 104.6 (CH), 114.5 (C), 117.7 (CH_2), 130.5 (CH), 133.1 (CH), 153.8 (C), 163.3 (C), 187.2 (CH); *m/z* (ESI) 256.1312 (MNa^+. $C_{14}H_{19}NaNO_2$ requires 256.1308), 215, 200, 186, 178, 150.

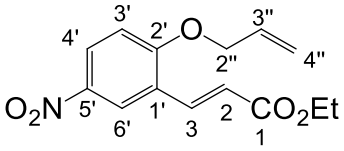
Ethyl (2*E*)-3-(2'-allyloxyphenyl)prop-2-enoate (94a)[183]



Lithium bromide (0.47 g, 5.4 mmol) was added to a solution of triethyl phosphonoacetate (**21**) (0.91 mL, 4.6 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.68 mL, 4.6 mmol) in acetonitrile (20 mL) and stirred at room temperature for 0.5 h. 2-Allyloxybenzaldehyde (**93a**) (0.22 g, 1.4 mmol) was added and the solution was stirred at room temperature for 18 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (30 mL), concentrated to half volume *in vacuo* and extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by filtration through a pad of silica

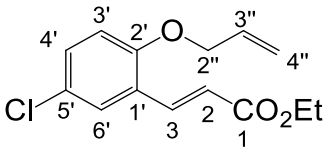
(elution with 20% diethyl ether in petroleum ether) gave ethyl (2*E*)-3-(2'-allyloxyphenyl)prop-2-enoate (**94a**) (0.30 g, 95%) as a yellow oil. Spectroscopic data was in accordance with literature values.[183] δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.26 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.62 (2H, dt, *J* 5.1, 1.5 Hz, 2''-H_2), 5.31 (1H, dq, *J* 10.6, 1.5 Hz, 4''-*H*H), 5.43 (1H, dq, *J* 17.3, 1.5 Hz, 4''-H*H*), 6.08 (1H, ddt, *J* 17.3, 10.6, 5.1 Hz, 3''-H), 6.53 (1H, d, *J* 16.2 Hz, 2-H), 6.90 (1H, d, *J* 8.3 Hz, 3'-H), 6.96 (1H, td, *J* 7.7, 0.5 Hz, 5'-H), 7.29–7.35 (1H, m, 4'-H), 7.52 (1H, dd, *J* 7.7, 1.7 Hz, 6'-H), 8.05 (1H, d, *J* 16.2 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.4 (CH_3), 60.3 (CH_2), 69.2 (CH_2), 112.5 (CH), 117.7 (CH_2), 118.8 (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^+, %), 187 (42), 158 (78), 144 (59), 129 (61), 118 (97), 84 (100), 77 (19), 49 (99).

Ethyl (2*E*)-3-(2'-allyloxy-5'-nitrophenyl)prop-2-enoate (94b)



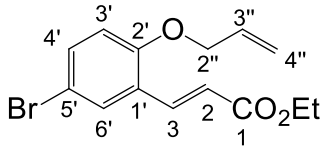
The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allyloxyphenyl)prop-2-enoate (**94a**) using 2-allyloxy-5-nitrobenzaldehyde (**93b**) (0.049 g, 0.24 mmol). This gave ethyl (2*E*)-3-(2'-allyloxy-5'-nitrophenyl)prop-2-enoate (**94b**) (0.060 g, 91%) as a white solid. Mp 64–65 °C; ν_{max} (neat)/cm^{-1} 2986 (CH), 1690 (CO), 1631 (C=C), 1580, 1512, 1341, 1273, 1150, 1032, 872; δ_H (500 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.29 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.74 (2H, dt, *J* 5.2, 1.5 Hz, 2''-H_2), 5.39 (1H, dq, *J* 10.6, 1.5 Hz, 4''-*H*H), 5.45 (1H, dq, *J* 17.3, 1.5 Hz, 4''-H*H*), 6.07 (1H, ddt, *J* 17.3, 10.6, 5.2 Hz, 3''-H), 6.61 (1H, d, *J* 16.2 Hz, 2-H), 6.98 (1H, d, *J* 9.2 Hz, 3'-H), 7.98 (1H, d, *J* 16.2 Hz, 3-H), 8.22 (1H, dd, *J* 9.2, 2.8 Hz, 4'-H), 8.43 (1H, d, *J* 2.8 Hz, 6'-H); δ_C (126 MHz, $CDCl_3$) 14.3 (CH_3), 60.7 (CH_2), 70.0 (CH_2), 112.2 (CH), 118.9 (CH_2), 121.5 (CH), 124.0 (CH), 124.3 (C), 126.6 (CH), 131.5 (CH), 137.3 (CH), 141.4 (C), 161.4 (C), 166.5 (C); *m/z* (ESI) 300.0829 (MNa^+, $C_{14}H_{15}NNaO_5$ requires 300.0842), 236 (16%), 218 (3), 210 (3).

Ethyl (2*E*)-3-(2'-allyloxy-5'-chlorophenyl)prop-2-enoate (94c)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allyloxyphenyl)prop-2-enoate (**94a**) using 2-allyloxy-5-chlorobenzaldehyde (**93c**) (0.595 g, 3.02 mmol). This gave ethyl (2*E*)-3-(2'-allyloxy-5'-chlorophenyl)prop-2-enoate (**94c**) (0.743 g, 92%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2982 (CH), 1705 (CO), 1632 (C=C), 1481, 1314, 1248, 1165, 1034, 984; δ_H (500 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1 Hz, $OCH_2C\mathit{H}_3$), 4.26 (2H, q, *J* 7.1 Hz, $OC\mathit{H}_2CH_3$), 4.60 (2H, dt, *J* 5.2, 1.4 Hz, 2''-H_2), 5.32 (1H, dq, *J* 10.5, 1.4 Hz, 4''-*H*H), 5.41 (1H, dq, *J* 17.3, 1.4 Hz, 4''-H*H*), 6.05 (1H, ddt, *J* 17.3, 10.5, 5.2 Hz, 3''-H), 6.49 (1H, d, *J* 16.2 Hz, 2-H), 6.83 (1H, d, *J* 8.9 Hz, 3'-H), 7.25 (1H, dd, *J* 8.9, 2.5 Hz, 4'-H), 7.48 (1H, d, *J* 2.5 Hz, 6'-H), 7.95 (1H, d, *J* 16.2 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 60.6 (CH_2), 69.7 (CH_2), 114.0 (CH), 118.2 (CH_2), 120.1 (CH), 125.4 (C), 126.1 (C), 128.3 (CH), 130.8 (CH), 132.6 (CH), 138.6 (CH), 155.8 (C), 167.2 (C); *m/z* (ESI) 289.0610 (MNa^+, $C_{14}H_{15}{}^{35}ClNaO_3$ requires 289.0602), 247 (1%), 236 (13), 218 (1).

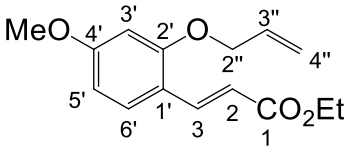
Ethyl (2*E*)-3-(2'-allyloxy-5'-bromophenyl)prop-2-enoate (94d)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allyloxyphenyl)prop-2-enoate (**94a**) using 2-allyloxy-5-bromobenzaldehyde (**93d**) (0.545 g, 2.26 mmol). This gave ethyl (2*E*)-3-(2'-allyloxy-5'-bromophenyl)prop-2-enoate (**94d**) (0.685 g, 97%) as a white solid. Mp <30 °C; ν_{max} (neat)/cm^{-1} 2986 (CH), 1688 (CO), 1628 (C=C), 1489, 1300, 1275, 1175, 986; δ_H (500 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1 Hz, $OCH_2C\mathit{H}_3$), 4.26 (2H, q, *J* 7.1 Hz, $OC\mathit{H}_2CH_3$), 4.60 (2H, dt, *J* 5.2, 1.4 Hz, 2''-H_2), 5.32 (1H, dq, *J* 10.6, 1.4 Hz, 4'-*H*H), 5.41 (1H, dq, *J* 17.3, 1.4 Hz, 4'-H*H*), 6.05 (1H, ddt, *J* 17.3, 10.6, 5.2 Hz, 3''-H), 6.49 (1H, d, *J* 16.2 Hz, 2-H), 6.78 (1H, d, *J* 8.8 Hz, 3'-H), 7.39 (1H, dd, *J* 8.8, 2.5 Hz, 4'-H), 7.62 (1H, d, *J* 2.5 Hz, 6'-H), 7.94 (1H, d, *J* 16.2 Hz, 3-H); δ_C (126

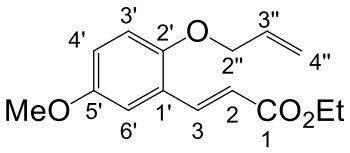
MHz, $CDCl_3$) 14.5 (CH_3), 60.6 (CH_2), 69.6 (CH_2), 113.3 (C), 114.4 (CH), 118.3 (CH_2), 120.2 (CH), 125.9 (C), 131.2 (CH), 132.6 (CH), 133.8 (CH), 138.5 (CH), 156.3 (C), 167.2 (C); *m/z* (ESI) 333.0090 (MNa^+, $C_{14}H_{15}{}^{79}BrNaO_3$ requires 333.0097), 236 (7%), 218 (1).

Ethyl (2*E*)-3-(2'-allyloxy-4'-methoxyphenyl)prop-2-enoate (94e)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allyloxyphenyl)prop-2-enoate (**94a**) using 2-allyloxy-4-methoxybenzaldehyde (**93e**) (0.580 g, 3.02 mmol). This gave ethyl (2*E*)-3-(2'-allyloxy-4'-methoxyphenyl)prop-2-enoate (**94e**) (0.79 g, 100%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2980 (CH), 1701 (CO), 1601 (C=C), 1505, 1300, 1252, 1155, 986; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.82 (3H, s, OCH_3), 4.24 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.60 (2H, dt, *J* 5.2, 1.5 Hz, 2''-H_2), 5.32 (1H, dq, *J* 10.5, 1.5 Hz, 4''-*H*H), 5.43 (1H, dq, *J* 17.3, 1.5 Hz, 4''-H*H*), 6.08 (1H, ddt, *J* 17.3, 10.5, 5.2 Hz, 3''-H), 6.43 (1H, d, *J* 16.1 Hz, 2-H), 6.44 (1H, d, *J* 2.4 Hz, 3'-H), 6.50 (1H, dd, *J* 8.6, 2.4 Hz, 5'-H), 7.46 (1H, d, *J* 8.6 Hz, 6'-H), 7.96 (1H, d, *J* 16.1 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 14.5 (CH_3), 55.6 (CH_3), 60.3 (CH_2), 69.3 (CH_2), 99.7 (CH), 105.6 (CH), 116.3 (C), 117.0 (CH_2), 118.1 (CH), 130.3 (CH), 132.9 (CH), 140.0 (CH), 158.8 (C), 162.6 (C), 168.0 (C); *m/z* (ESI) 285.1090 (MNa^+, $C_{15}H_{18}NaO_4$ requires 285.1097), 244 (4%), 236 (4), 215 (93), 210 (4), 187 (4), 174 (6).

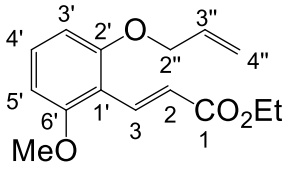
Ethyl (2*E*)-3-(2'-allyloxy-5'-methoxyphenyl)prop-2-enoate (94f)



The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allyloxyphenyl)prop-2-enoate (**94a**) using 2-allyloxy-5-methoxybenzaldehyde (**93f**) (0.580 g, 3.02 mmol). This gave ethyl (2*E*)-3-(2'-allyloxy-5'-methoxyphenyl)prop-2-enoate (**94f**) (0.792 g, 100%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2954 (CH), 1706 (CO), 1631 (C=C), 1494, 1214, 1165, 1042, 862;

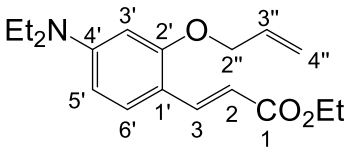
δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.79 (3H, s, OCH_3), 4.26 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.56 (2H, dt, *J* 5.2, 1.5 Hz, 2''-H_2), 5.29 (1H, dq, *J* 10.6, 1.5 Hz, 4''-*H*H), 5.41 (1H, dq, *J* 17.3, 1.5 Hz, 4''-H*H*), 6.06 (1H, ddt, *J* 17.3, 10.6, 5.2 Hz, 3''-H), 6.49 (1H, d, *J* 16.2 Hz, 2-H), 6.84 (1H, d, *J* 8.8 Hz, 3'-H), 6.88 (1H, dd, *J* 8.8, 2.9 Hz, 4'-H), 7.05 (1H, d, *J* 2.9 Hz, 6'-H), 8.02 (1H, d, *J* 16.2 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 55.9 (CH_3), 60.5 (CH_2), 70.2 (CH_2), 113.0 (CH), 114.4 (CH), 117.2 (CH), 117.8 (CH_2), 119.1 (CH), 124.7 (C), 133.3 (CH), 139.8 (CH), 151.9 (C), 153.8 (C), 167.5 (C); *m/z* (ESI) 285.1090 (MNa^+, $C_{15}H_{18}NaO_4$ requires 285.1097), 244 (64%), 236 (6), 217 (10), 189 (15), 176 (7).

Ethyl (2*E*)-3-(2'-allyloxy-6'-methoxyphenyl)prop-2-enoate (94g)



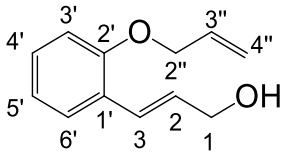
The reaction was carried out according to the previously described procedure for ethyl (2*E*)-3-(2'-allyloxyphenyl)prop-2-enoate (**94a**) using 2-allyloxy-6-methoxybenzaldehyde (**93g**) (0.531 g, 2.76 mmol). This gave ethyl (2*E*)-3-(2'-allyloxy-6'-methoxyphenyl)prop-2-enoate (**94g**) (0.594 g, 85%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2979 (CH), 1701 (CO), 1622 (C=C), 1593, 1473, 1308, 1254, 1160, 1093; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.88 (3H, s, OCH_3), 4.26 (2H, q, *J* 7.1 Hz,OCH_2CH_3), 4.62 (2H, dt, *J* 5.1, 1.5 Hz, 2''-H_2), 5.30 (1H, dq, *J* 10.5, 1.5 Hz, 4''-*H*H), 5.43 (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), 6.54 (1H, d, *J* 8.4 Hz, ArH), 6.56 (1H, d, *J* 8.4 Hz, ArH), 6.89 (1H, d, *J* 16.3 Hz, 2-H), 7.23 (1H, t, *J* 8.4 Hz, 4'-H), 8.17 (1H, d, *J* 16.3 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.4 (CH_3), 55.7 (CH_3), 60.1 (CH_2), 69.4 (CH_2), 103.8 (CH), 105.0 (CH), 112.5 (C), 117.6 (CH_2), 120.8 (CH), 131.1 (CH), 132.9 (CH), 135.4 (CH), 158.9 (C), 160.1 (C), 168.6 (C); *m/z* (ESI) 285.1088 (MNa^+, $C_{15}H_{18}NaO_4$ requires 285.1097), 271 (1%), 236 (3), 215 (2).

Ethyl (2*E*)-3-(2'-allyloxy-4'-diethylaminophenyl)prop-2-enoate (94h)



The reaction was carried out according to the procedure described for ethyl (2*E*)-3-(2'-allyloxyphenyl)prop-2-enoate (**94a**) using 2-(allyloxy)-4-diethylaminobenzaldehyde (**93h**) (0.562 g, 2.41 mmol). This gave ethyl (2*E*)-3-(2'-allyloxy-4'-diethylaminophenyl)prop-2-enoate (**94h**) (0.698 g, 95%) as a yellow oil. ν_{max} (neat)/cm^{-1} 2972 (CH), 1695 (CO), 1591 (C=C), 1514, 1144; δ_H (400 MHz, $CDCl_3$) 1.18 (6H, t, *J* 7.1 Hz, N($CH_2C\mathit{H}_3$)$_2$), 1.32 (3H, t, *J* 7.1 Hz, $OCH_2C\mathit{H}_3$), 3.37 (4H, q, *J* 7.1 Hz, N($C\mathit{H}_2CH_3$)$_2$), 4.23 (2H, q, *J* 7.1 Hz, $OC\mathit{H}_2CH_3$), 4.61 (2H, dt, *J* 5.2, 1.5 Hz, 2''-H_2), 5.30 (1H, dq, *J* 10.5, 1.5 Hz, 4''-*H*H), 5.44 (1H, dq, *J* 17.3, 1.5 Hz, 4''-H*H*), 6.05–6.14 (2H, m, 3'-H, 3''-H), 6.26 (1H, dd, *J* 8.8, 2.4 Hz, 5'-H), 6.31 (1H, d, *J* 16.0 Hz, 2-H), 7.37 (1H, d, *J* 8.8 Hz, 6'-H), 7.95 (1H, d, *J* 16.0 Hz, 3-H); δ_C (101 MHz, $CDCl_3$) 12.8 (2 × CH_3), 14.6 (CH_3), 44.7 (2 × CH_2), 60.0 (CH_2), 69.3 (CH_2), 95.5 (CH), 104.6 (CH), 111.5 (C), 112.4 (CH), 117.6 (CH_2), 130.6 (CH), 133.6 (CH), 140.7 (CH), 150.7 (C), 159.4 (C), 168.7 (C); *m/z* (CI) 304.1916 (MH^+. $C_{18}H_{26}NO_3$ requires 304.1913), 264 (4%), 218 (2), 138 (3), 71 (20).

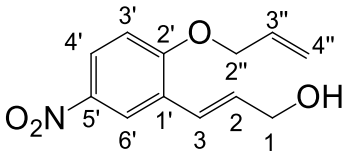
(2*E*)-3-(2'-Allyloxyphenyl)prop-2-en-1-ol (95a)[183]



Diisobutylaluminium hydride (3.21 mL, 1 M solution in hexanes) was added dropwise with stirring, to a solution of ethyl (2*E*)-3-(2'-allyloxyphenyl)prop-2-enoate (**94a**) (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 ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (elution with 30% diethyl ether in petroleum ether) gave (2*E*)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (**95a**) (0.211 g, 87%) as a white solid. Mp 44–46 °C. Spectroscopic data was in accordance with literature values.[183] δ_H (400

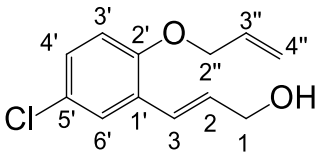
MHz, $CDCl_3$) 1.41 (1H, t, *J* 5.9 Hz, OH), 4.33 (2H, td, *J* 5.9, 0.8 Hz, 1-H_2), 4.58 (2H, dt, *J* 5.2, 1.5 Hz, 2''-H_2), 5.29 (1H, dq, *J* 10.5, 1.5 Hz, 4''-*H*H), 5.42 (1H, dq, *J* 17.3, 1.5 Hz, 4''-H*H*), 6.08 (1H, ddt, *J* 17.3, 10.5, 5.2 Hz, 3''-H), 6.40 (1H, dt, *J* 16.0, 5.9 Hz, 2-H), 6.87 (1H, dd, *J* 8.2, 0.8 Hz, 3'-H), 6.91–7.02 (2H, m, 3-H and 5'-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); δ_C (101 MHz, $CDCl_3$) 64.5 (CH_2), 69.4 (CH_2), 112.5 (CH), 117.6 (CH_2), 121.1 (CH), 126.2 (C), 126.4 (CH), 127.2 (CH), 128.8 (CH), 129.3 (CH), 133.5 (CH), 156.0 (C); *m/z* (EI) 190 (57%), 149 (59), 131 (92), 121 (60), 119 (46), 91 (100), 77 (40).

(2*E*)-3-(2'-Allyloxy-5'-nitrophenyl)prop-2-en-1-ol (95b)



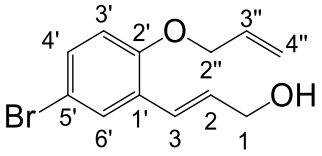
The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (**95a**) using ethyl (2*E*)-3-(2'-allyloxy-5'-nitrophenyl)prop-2-enoate (**94b**) (0.629 g, 2.27 mmol). This gave (2*E*)-3-(2'-allyloxy-5'-nitrophenyl)prop-2-en-1-ol (**95b**) (0.469 g, 88%) as a yellow solid. Mp 62–66 °C; ν_{max} (neat)/cm^{-1} 2864 (CH), 1611 (C=C), 1508, 1335, 1246, 1078, 990; δ_H (400 MHz, $CDCl_3$) 1.89 (1H, br s, OH), 4.37 (2H, dd, *J* 5.4, 1.7 Hz, 1-H_2), 4.67 (2H, dt, *J* 5.2, 1.5 Hz, 2''-H_2), 5.35 (1H, dq, *J* 10.6, 1.5 Hz, 4''-*H*H), 5.43 (1H, dq, *J* 17.3, 1.5 Hz, 4''-H*H*), 6.05 (1H, ddt, *J* 17.3, 10.6, 5.2 Hz, 3''-H), 6.49 (1H, dt, *J* 16.2, 5.4 Hz, 2-H), 6.88 (1H, d, *J* 9.2 Hz, 3'-H), 6.92 (1H, dt, *J* 16.2, 1.7 Hz, 3-H), 8.08 (1H, dd, *J* 9.2, 2.8 Hz, 4'-H), 8.30 (1H, d, *J* 2.8 Hz, 6'-H); δ_C (101 MHz, $CDCl_3$) 63.7 (CH_2), 69.8 (CH_2), 111.6 (CH), 118.8 (CH_2), 122.6 (CH), 123.6 (CH), 124.5 (CH), 127.0 (C), 132.0 (CH), 132.3 (CH), 141.5 (C), 160.3 (C); *m/z* (ESI) 258.0737 (MNa^+, $C_{12}H_{13}NNaO_4$ requires 258.0737), 243 (33%), 236 (11), 218 (3), 206 (3), 190 (1), 161 (1), 134 (1).

(2*E*)-3-(2'-Allyloxy-5'-chlorophenyl)prop-2-en-1-ol (95c)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (**95a**) using ethyl (2*E*)-3-(2'-allyloxy-5'-chlorophenyl)prop-2-enoate (**94c**) (0.126 g, 0.472 mmol). This gave (2*E*)-3-(2'-allyloxy-5'-chlorophenyl)prop-2-en-1-ol (**95c**) (0.101 g, 95%) as a yellow oil. ν_{max} (neat)/cm^{-1} 3336 (OH), 2918 (CH), 1592 (C=C), 1481, 1242, 1129, 1015, 970; δ_H (500 MHz, $CDCl_3$) 2.24 (1H, br s, OH), 4.30 (2H, dd, *J* 5.7, 1.5 Hz, 1-H_2), 4.51 (2H, dt, *J* 5.2, 1.4 Hz, 2''-H_2), 5.28 (1H, dq, *J* 10.6, 1.4 Hz, 4''-*H*H), 5.39 (1H, dq, *J* 17.3, 1.4 Hz, 4''-H*H*), 6.03 (1H, ddt, *J* 17.3, 10.6, 5.2 Hz, 3''-H), 6.34 (1H, dt, *J* 16.1, 5.7 Hz, 2-H), 6.74 (1H, d, *J* 8.8 Hz, 3'-H), 6.87 (1H, dt, *J* 16.1, 1.5 Hz, 3-H), 7.11 (1H, dd, *J* 8.8, 2.6 Hz, 4'-H), 7.37 (1H, d, *J* 2.6 Hz, 6'-H); δ_C (126 MHz, $CDCl_3$) 63.8 (CH_2), 69.6 (CH_2), 113.7 (CH), 117.8 (CH_2), 124.7 (CH), 126.0 (C), 126.7 (CH), 127.8 (C), 128.1 (CH), 130.7 (CH), 133.0 (CH), 154.3 (C); *m/z* (EI) 224.0606 (M^+, $C_{12}H_{13}{}^{35}ClO_2$ requires 224.0604), 183 (58%), 165 (89), 155 (78), 125 (86), 91 (36), 63 (12).

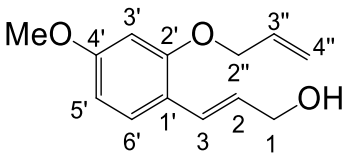
(2*E*)-3-(2'-Allyloxy-5'-bromophenyl)prop-2-en-1-ol (95d)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (**95a**) using ethyl (2*E*)-3-(2'-allyloxy-5'-bromophenyl)prop-2-enoate (**94d**) (0.075 g, 0.24 mmol). This gave (2*E*)-3-(2'-allyloxy-5'-bromophenyl)prop-2-en-1-ol (**95d**) (0.058 g, 90%) as a white solid. Mp <30 °C; ν_{max} (neat)/cm^{-1} 3297 (OH), 2857 (CH), 1588 (C=C), 1482, 1249, 1127, 1016, 974; δ_H (500 MHz, $CDCl_3$) 2.07 (1H, s, OH), 4.30 (2H, dd, *J* 5.7, 1.4 Hz, 1-H_2), 4.51 (2H, dt, *J* 5.2, 1.3 Hz, 2''-H_2), 5.28 (1H, dq, *J* 10.5, 1.3 Hz, 4''-*H*H), 5.38 (1H, dq, *J* 17.2, 1.3 Hz, 4''-H*H*), 6.03 (1H, ddt, *J* 17.2, 10.5, 5.2 Hz, 3''-H), 6.34 (1H, dt, *J* 16.1, 5.7 Hz, 2-H), 6.70 (1H, d, *J* 8.8 Hz, 3'-H), 6.86 (1H, dt, *J* 16.1, 1.4

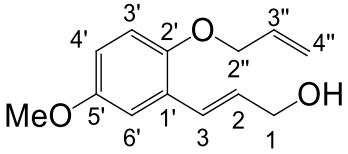
Hz, 3-H), 7.25 (1H, dd, *J* 8.8, 2.5 Hz, 4'-H), 7.52 (1H, d, *J* 2.5 Hz, 6'-H); δ_C (126 MHz, $CDCl_3$) 63.9 (CH_2), 69.5 (CH_2), 113.4 (C), 114.1 (CH), 117.9 (CH_2), 124.6 (CH), 128.3 (C), 129.6 (CH), 130.7 (CH), 131.1 (CH), 133.0 (CH), 154.8 (C); *m/z* (EI) 268.0101 (M^+, $C_{12}H_{13}{}^{79}BrO_2$ requires 268.0099), 229 (40%), 199 (50), 131 (20), 118 (100), 91 (27), 63 (11), 51 (8).

(2*E*)-3-(2'-Allyloxy-4'-methoxyphenyl)prop-2-en-1-ol (95e)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (**95a**) using ethyl (2*E*)-3-(2'-allyloxy-4'-methoxyphenyl)prop-2-enoate (**94e**) (0.676 g, 2.58 mmol). This gave (2*E*)-3-(2'-allyloxy-4'-methoxyphenyl)prop-2-en-1-ol (**95e**) (0.566 g, 100%) as a white solid. Mp <30 °C; ν_{max} (neat)/cm^{-1} 3379 (OH), 2914 (CH), 1609 (C=C), 1576, 1500, 1420, 1261, 1197, 1003; δ_H (500 MHz, $CDCl_3$) 1.89 (1H, s, OH), 3.78 (3H, s, OCH_3), 4.28 (2H, dd, *J* 6.1, 1.2 Hz, 1-H_2), 4.53 (2H, d, *J* 5.2 Hz, 2''-H_2), 5.28 (1H, dd, *J* 10.5, 1.5 Hz, 4''-*H*H), 5.41 (1H, dd, *J* 17.3, 1.5 Hz, 4''-H*H*), 6.06 (1H, ddt, *J* 17.3, 10.5, 5.2 Hz, 3''-H), 6.27 (1H, dt, *J* 16.0, 6.1 Hz, 2-H), 6.42 (1H, d, *J* 2.4 Hz, 3'-H), 6.47 (1H, dd, *J* 8.5, 2.4 Hz, 5'-H), 6.86 (1H, br d, *J* 16.0 Hz, 3-H), 7.35 (1H, d, *J* 8.5 Hz, 6'-H); δ_C (126 MHz, $CDCl_3$) 55.4 (CH_3), 64.5 (CH_2), 69.2 (CH_2), 99.7 (CH), 105.3 (CH), 117.7 (CH_2), 119.1 (C), 126.2 (CH), 127.1 (CH), 127.8 (CH), 133.2 (CH), 156.9 (C), 160.4 (C); *m/z* (CI) 221.1177 (MH^+, $C_{13}H_{17}O_3$ requires 221.1178), 203 (100%), 177 (3), 163 (2), 81 (5), 69 (7).

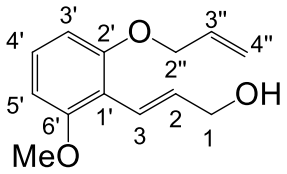
(2*E*)-3-(2'-Allyloxy-5'-methoxyphenyl)prop-2-en-1-ol (95f)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (**95a**) using ethyl (2*E*)-3-(2'-allyloxy-5'-methoxyphenyl)prop-2-enoate (**94f**) (0.126 g, 2.94 mmol). This gave (2*E*)-3-(2'-allyloxy-5'-methoxyphenyl)prop-2-en-1-ol (**95f**) (0.534 g, 83%) as a white solid. Mp

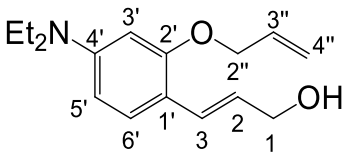
41–43 °C; ν_{max} (neat)/cm^{-1} 3387 (OH), 2915 (CH), 1585 (C=C), 1493, 1424, 1213, 1123, 1011; δ_H (500 MHz, $CDCl_3$) 1.48 (1H, br s, OH), 3.78 (3H, s, OCH_3), 4.33 (2H, br d, *J* 5.7 Hz, 1-H_2), 4.51 (2H, dt, *J* 5.2, 1.5 Hz, 2''-H_2), 5.27 (1H, dq, *J* 10.5, 1.5 Hz, 4''-*H*H), 5.40 (1H, dq, *J* 17.3, 1.5 Hz, 4''-H*H*), 6.06 (1H, ddt, *J* 17.3, 10.5, 5.2 Hz, 3''-H), 6.38 (1H, dt, *J* 16.0, 5.7 Hz, 2-H), 6.75 (1H, dd, *J* 8.9, 3.0 Hz, 4'-H), 6.81 (1H, d, *J* 8.9 Hz, 3'-H), 6.94 (1H, dt, *J* 16.0, 1.3 Hz, 3-H), 7.01 (1H, d, *J* 3.0 Hz, 6'-H); δ_C (126 MHz, $CDCl_3$) 55.9 (CH_3), 64.3 (CH_2), 70.3 (CH_2), 112.2 (CH), 114.0 (CH), 114.3 (CH), 117.5 (CH_2), 126.2 (CH), 127.2 (C), 129.6 (CH), 133.7 (CH), 150.4 (C), 154.0 (C); *m/z* (ESI) 243.0990 (MNa^+, $C_{13}H_{16}NaO_3$ requires 243.0992), 236 (19%), 202 (100), 175 (7).

(2*E*)-3-(2'-Allyloxy-6'-methoxyphenyl)prop-2-en-1-ol (95g)



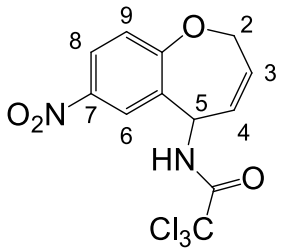
The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (**95a**) using ethyl (2*E*)-3-(2'-allyloxy-6'-methoxyphenyl)prop-2-enoate (**94g**) (0.569 g, 2.17 mmol). This gave (2*E*)-3-(2'-allyloxy-6'-methoxyphenyl)prop-2-en-1-ol (**95g**) (0.427 g, 90%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3372 (OH), 2953 (CH), 1584 (C=C), 1470, 1251, 1200, 1112, 1079; δ_H (500 MHz, $CDCl_3$) 1.41 (1H, t, *J* 5.9 Hz, OH), 3.85 (3H, s, OCH_3), 4.33 (2H, td, *J* 5.9, 1.0 Hz, 1-H_2), 4.58 (2H, dt, *J* 5.2, 1.5 Hz, 2''-H), 5.28 (1H, dq, *J* 10.5, 1.5 Hz, 4''-*H*H), 5.42 (1H, dq, *J* 17.3, 1.5 Hz, 4''-H*H*), 6.08 (1H, ddt, *J* 17.3, 10.5, 5.2 Hz, 3''-H), 6.55 (1H, d, *J* 8.3 Hz, ArH), 6.56 (1H, d, *J* 8.3 Hz, ArH), 6.82 (1H, dt, *J* 16.2, 5.9 Hz, 2-H), 6.92 (1H, br d, *J* 16.2 Hz, 3-H), 7.13 (1H, t, *J* 8.3 Hz, 4'-H); δ_C (126 MHz, $CDCl_3$) 55.8 (CH_3), 65.7 (CH_2), 69.6 (CH_2), 104.1 (CH), 105.4 (CH), 114.4 (C), 117.6 (CH_2), 122.0 (CH), 128.3 (CH), 132.8 (CH), 133.5 (CH), 157.6 (C), 158.7 (C); *m/z* (ESI) 243.0987 (MNa^+, $C_{13}H_{16}NaO_3$ requires 243.0992), 236 (4%), 227 (4), 215 (4), 202 (17), 171 (1), 161 (7), 149 (1), 137 (1).

(2*E*)-3-(2'-Allyloxy-4'-diethylaminophenyl)prop-2-en-1-ol (95h)



The reaction was carried out according to the previously described procedure for (2*E*)-3-(2'-allyloxyphenyl)prop-2-en-1-ol (**95a**) using ethyl (2*E*)-3-(2'-allyloxy-4'-diethylaminophenyl)prop-2-enoate (**94h**) (0.676 g, 2.23 mmol). Purification by filtration through a silica plug (elution with 40% diethyl ether in petroleum ether) yielded (2*E*)-3-(2'-allyloxy-4'-diethylaminophenyl)prop-2-en-1-ol (**95h**) (0.534 g, 92%) as an orange oil. δ_H (400 MHz, $CDCl_3$) 1.17 (6H, t, *J* 7.1 Hz, $N(CH_2C\mathit{H}_3)_2$), 1.31 (1H, t, *J* 5.6 Hz, OH), 3.35 (4H, q, *J* 7.1 Hz, $N(C\mathit{H}_2CH_3)_2$), 4.27 (2H, t, *J* 5.6 Hz, 1-H_2), 4.56 (2H, dt, *J* 5.2, 1.5 Hz, 2''-H_2), 5.29 (1H, dq, *J* 10.5, 1.5 Hz, 4''-*H*H), 5.43 (1H, dq, *J* 17.3, 1.5 Hz, 4''-H*H*), 6.09 (1H, ddt, *J* 17.3, 10.5, 5.2 Hz, 3''-H), 6.16 (1H, d, *J* 2.5 Hz, 3'-H), 6.21 (1H, dt, *J* 15.9, 5.6 Hz, 2-H), 6.28 (1H, dd, *J* 8.6, 2.5 Hz, 5'-H), 6.84 (1H, d, *J* 15.9 Hz, 3-H), 7.31 (1H, d, *J* 8.6 Hz, 6'-H); δ_C (101 MHz, $CDCl_3$) 12.8 (2 × CH_3), 44.7 (2 × CH_2), 65.1 (CH_2), 69.5 (CH_2), 96.6 (CH), 104.9 (CH), 113.6 (CH), 117.3 (CH_2), 124.1 (C), 127.3 (CH), 128.0 (CH), 134.0 (CH), 148.8 (C), 157.4 (C); *m/z* (EI) 261.1731 (M^+. $C_{16}H_{23}NO_2$ requires 261.1729), 246 (84%), 220 (32), 216 (27), 174 (65), 146 (11), 118 (7), 91 (6), 77 (4).

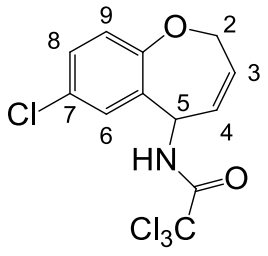
7-Nitro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (96b)



(2*E*)-3-(2'-Allyloxy-5'-nitrophenyl)prop-2-en-1-ol (**95b**) (0.050 g, 0.21 mmol) was dissolved in dry dichloromethane (8 mL) and cooled to 0 °C under argon with stirring. Trichloroacetonitrile (0.032 mL, 0.32 mmol) was added to the solution, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.016 mL, 0.11 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 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 59 h. The reaction was allowed to cool to room temperature before Grubbs 2nd generation catalyst (0.0090 g, 0.011 mmol) and *p*-xylene (21 mL) were added and the reaction was heated to 50 °C for 6 h. Grubbs 2nd generation catalyst (0.0040 g, 0.0055 mmol) was added and the reaction was continued at 50 °C for 17 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (elution with 50% diethyl ether in petroleum ether) to yield 7-nitro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96b**) (0.052 g, 71%) as a white solid. Decomposed at 170 °C; ν_{max} (neat)/cm^{-1} 3337 (NH), 2841 (CH), 1694 (CO), 1522 (C=C), 1491, 1344, 1236, 1047, 820; δ_H (500 MHz, $CDCl_3$) 4.50–4.59 (1H, m, 2-*H*H), 4.85–4.92 (1H, m, 2-H*H*), 5.57 (1H, t, *J* 7.5 Hz, 5-H), 5.78 (1H, ddd, *J* 11.6, 3.0, 2.4 Hz, 3-H), 6.09 (1H, ddt, *J* 11.6, 7.5, 2.4 Hz, 4-H), 7.24–7.30 (1H, m, 9-H), 7.45 (1H, br d, *J* 7.5 Hz, NH), 8.21 (1H, dd, *J* 9.5, 4.5 Hz, 8-H), 8.22 (1H, d, *J* 4.5 Hz, 6-H); δ_C (126 MHz, $CDCl_3$) 51.0 (CH), 71.4 (CH_2), 92.4 (C), 123.4 (CH), 123.8 (CH), 125.4 (CH), 125.9 (CH), 131.5 (CH), 136.4 (C), 144.6 (C), 161.1 (C), 162.4 (C); *m/z* (ESI) 372.9514 (MNa^+, $C_{12}H_9{}^{35}Cl_3N_2NaO_4$ requires 372.9520), 368 (3%), 320 (6), 312 (3), 301 (6), 242 (3), 236 (6), 218 (3), 199 (7), 190 (24), 149 (3), 144 (6).

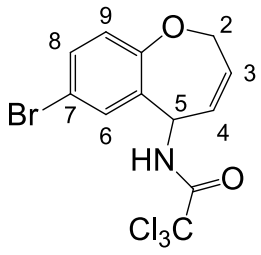
7-Chloro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (96c)



The reaction was carried out according to the previously described procedure for 7-nitro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96b**) using (2*E*)-3-(2'-allyloxy-5'-chlorophenyl)prop-2-en-1-ol (**95c**) (0.055 g, 0.25 mmol), except that the Overman rearrangement was heated at 140 °C for 60 h. This gave 7-chloro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-

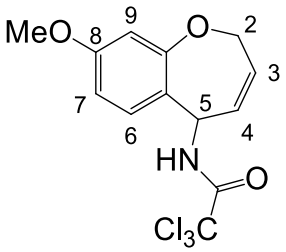
benzoxepine (**96c**) (0.058 g, 69%) as white solid. Mp 136–138 °C; ν_{max} (neat)/cm^{-1} 3260 (NH), 2943 (CH), 1708 (CO), 1687 (C=C), 1539, 1480, 1267, 1066, 825; δ_H (500 MHz, $CDCl_3$) 4.42 (1H, br d, *J* 17.7 Hz, 2-*H*H), 4.75–4.85 (1H, m, 2-H*H*), 5.36 (1H, t, *J* 7.9 Hz, 5-H), 5.72 (1H, ddd, *J* 11.7, 3.4, 2.0 Hz, 3-H), 6.07 (1H, ddt, *J* 11.7, 7.9, 2.3 Hz, 4-H), 7.07 (1H, d, *J* 8.3 Hz, 9-H), 7.23–7.30 (2H, m, 6-H and 8-H), 7.55 (1H, d, *J* 7.9 Hz, NH); δ_C (126 MHz, $CDCl_3$) 51.0 (CH), 71.3 (CH_2), 92.6 (C), 123.6 (CH), 125.6 (CH), 128.3 (CH), 130.0 (CH), 130.2 (C), 131.8 (CH), 136.6 (C), 155.9 (C), 160.8 (C); *m/z* (ESI) 361.9268 (MNa^+, $C_{12}H_9{}^{35}Cl_4NNaO_2$ requires 361.9280), 331 (1%), 312 (1), 301 (3), 236 (21), 218 (6), 179 (13), 164 (1).

7-Bromo-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (96d)



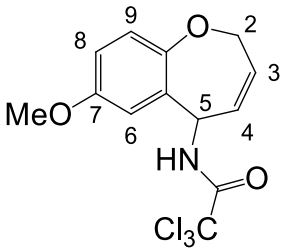
The reaction was carried out according to the previously described procedure for 7-nitro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96b**) using (2*E*)-3-(2'-allyloxy-5'-bromophenyl)prop-2-en-1-ol (**95d**) (0.10 g, 0.29 mmol), except that the Overman rearrangement was heated at 140 °C for 48 h. This gave 7-bromo-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96d**) (0.11 g, 79%) as white solid. Mp 147–149 °C; ν_{max} (neat)/cm^{-1} 3267 (NH), 2890 (CH), 1707 (CO), 1687 (C=C), 1535, 1478, 1267, 1067, 822; δ_H (500 MHz, $CDCl_3$) 4.37–4.46 (1H, m, 2-*H*H), 4.81 (1H, ddd, *J* 17.7, 3.3, 2.3 Hz, 2-H*H*), 5.36 (1H, t, *J* 8.2 Hz, 5-H), 5.71 (1H, ddd, *J* 11.7, 3.3, 2.0 Hz, 3-H), 6.07 (1H, ddt, *J* 11.7, 8.2, 2.3 Hz, 4-H), 7.01 (1H, d, *J* 8.2 Hz, 9-H), 7.42 (1H, dd, *J* 8.2, 2.5 Hz, 8-H), 7.43 (1H, d, *J* 2.5 Hz, 6-H), 7.54 (1H, d, *J* 8.2 Hz, NH); δ_C (126 MHz, $CDCl_3$) 51.0 (CH), 71.3 (CH_2), 92.6 (C), 117.8 (C), 124.0 (CH), 125.6 (CH), 131.2 (CH), 131.8 (CH), 133.0 (CH), 137.0 (C), 156.4 (C), 160.8 (C); *m/z* (ESI) 405.8764 (MNa^+, $C_{12}H_9{}^{79}Br^{35}Cl_3NNaO_2$ requires 405.8774), 394 (6%), 361 (3), 342 (4), 301 (7), 236 (18), 227 (10), 218 (6), 159 (3), 144 (3).

8-Methoxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (96e)



The reaction was carried out according to the previously described procedure for 7-nitro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96b**) using (2*E*)-3-(2'-allyloxy-4'-methoxyphenyl)prop-2-en-1-ol (**95e**) (0.048 g, 0.22 mmol), except that the Overman rearrangement was heated at 140 °C for 18 h. This gave 8-methoxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96e**) (0.051 g, 69%) as colourless oil. ν_{max} (neat)/cm^{-1} 3419 (NH), 2935 (CH), 1706 (CO), 1613 (C=C), 1496, 1156, 1122, 1032, 819; δ_H (500 MHz, $CDCl_3$) 3.79 (3H, s, OCH_3), 4.43 (1H, br d, *J* 17.6 Hz, 2-*H*H), 4.79 (1H, ddd, *J* 17.6, 3.6, 1.9 Hz, 2-H*H*), 5.33 (1H, t, *J* 8.3 Hz, 5-H), 5.69 (1H, ddd, *J* 11.5, 3.6, 1.9 Hz, 3-H), 6.09 (1H, ddt, *J* 11.5, 8.3, 1.9 Hz, 4-H), 6.64 (1H, dd, *J* 8.3, 2.6 Hz, 7-H), 6.68 (1H, d, *J* 2.6 Hz, 9-H), 7.20 (1H, d, *J* 8.3 Hz, 6-H), 7.53 (1H, d, *J* 8.3 Hz, NH); δ_C (126 MHz, $CDCl_3$) 51.3 (CH), 55.6 (CH_3), 71.2 (CH_2), 92.8 (C), 108.3 (CH), 110.0 (CH), 126.3 (CH), 127.1 (C), 129.3 (CH), 131.5 (CH), 158.4 (C), 160.7 (C), 161.1 (C); *m/z* (ESI) 357.9781 (MNa^+, $C_{13}H_{12}{}^{35}Cl_3NNaO_3$ requires 357.9775), 236 (3%), 215 (2), 175 (100), 160 (4), 147 (6).

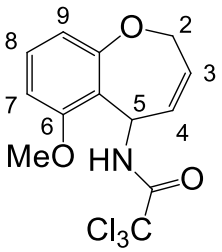
7-Methoxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (96f)



The reaction was carried out according to the previously described procedure for 7-nitro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96b**) using (2*E*)-3-(2'-allyloxy-5'-methoxyphenyl)prop-2-en-1-ol (**95f**) (0.064 g, 0.29

mmol), except that the Overman rearrangement was heated at 140 °C for 18 h. This gave 7-methoxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96f**) (0.075 g, 76%) as yellow oil. ν_{max} (neat)/cm^{-1} 3329 (NH), 2938 (CH), 1702 (CO), 1490, 1265, 1205, 1034, 818; δ_H (500 MHz, $CDCl_3$) 3.78 (3H, s, OCH_3), 4.34–4.44 (1H, m, 2-*H*H), 4.76 (1H, ddd, *J* 17.7, 3.3, 2.3 Hz, 2-H*H*), 5.34 (1H, t, *J* 8.0 Hz, 5-H), 5.68 (1H, ddd, *J* 11.6, 3.3, 2.0 Hz, 3-H), 6.09 (1H, ddt, *J* 11.6, 8.0, 2.3 Hz, 4-H), 6.79 (1H, dd, *J* 8.3, 3.0 Hz, 8-H), 6.81 (1H, d, *J* 3.0 Hz, 6-H), 7.05 (1H, d, *J* 8.3 Hz, 9-H), 7.66 (1H, d, *J* 8.0 Hz, NH); δ_C (126 MHz, $CDCl_3$) 51.6 (CH), 55.8 (CH_3), 71.5 (CH_2), 92.8 (C), 113.6 (CH), 114.7 (CH), 122.8 (CH), 126.0 (CH), 131.9 (CH), 135.8 (C), 150.9 (C), 156.5 (C), 160.8 (C); *m/z* (ESI) 357.9769 (MNa^+, $C_{13}H_{12}{}^{35}Cl_3NNaO_3$ requires 357.9775), 338 (1%), 236 (2), 218 (3), 175 (39), 147 (4).

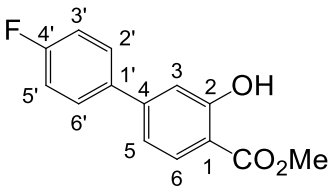
6-Methoxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (96g)



The reaction was carried out according to the previously described procedure for 7-nitro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96b**) using (2*E*)-3-(2'-allyloxy-6'-methoxyphenyl)prop-2-en-1-ol (**95g**) (0.049 g, 0.22 mmol), except that the Overman rearrangement was heated at 140 °C for 18 h. This gave 6-methoxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96g**) (0.046 g, 61%) as colourless oil. ν_{max} (neat)/cm^{-1} 3412 (NH), 2938 (CH), 1710 (CO), 1602 (C=C), 1471, 1278, 1088, 818; δ_H (500 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 4.36–4.43 (1H, m, 2-*H*H), 4.83 (1H, ddd, *J* 17.6, 3.6, 2.1 Hz, 2-H*H*), 5.65 (1H, ddd, *J* 10.7, 3.6, 1.9 Hz, 3-H), 6.00 (1H, t, *J* 8.1 Hz, 5-H), 6.17 (1H, dddd, *J* 10.7, 8.1, 2.6, 2.1 Hz, 4-H), 6.73 (1H, dd, *J* 8.2, 0.7 Hz, ArH), 6.75 (1H, dd, *J* 8.2, 0.7 Hz, ArH), 7.24 (1H, t, *J* 8.2 Hz, 8-H), 7.78 (1H, d, *J* 8.1 Hz, NH); δ_C (126 MHz, $CDCl_3$) 43.0 (CH), 56.3 (CH_3), 71.3 (CH_2), 93.0 (C), 108.2 (CH), 114.3 (CH), 123.9 (C), 126.7 (CH), 130.1 (CH), 131.3 (CH), 156.3 (C), 158.8 (C),

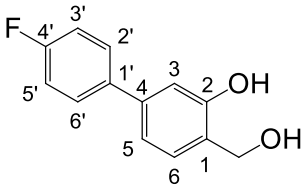
160.6 (C); *m/z* (ESI) 357.9766 (MNa^+, $C_{13}H_{12}{}^{35}Cl_3NNaO_3$ requires 357.9775), 301 (1%), 175 (15).

Methyl 4-(4'-fluorophenyl)-2-hydroxybenzoate (106)[121]



4-Fluorophenylboronic acid (0.378 g, 2.70 mmol), cesium carbonate (1.47 g, 4.50 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride (0.0735 g, 0.0899 mmol), were added to a degassed solution of methyl 2-hydroxy-4-iodobenzoate (**105**) (0.500 g, 1.80 mmol) in 1,4-dioxane (17 mL) and water (1 mL). The solution was heated to 80 °C for 18 h, cooled to room temperature and concentrated *in vacuo*. The reaction mixture was purified by filtration through a pad of silica (elution with 20% diethyl ether:petroleum ether) to yield methyl 4-(4'-fluorophenyl)-2-hydroxybenzoate (**106**) (0.442 g, 100%) as a white solid. Spectroscopic data was in accordance with literature values.[121] Mp 110–112 °C; ν_{max} (neat)/cm^{-1} 3146 (OH), 2925 (CH), 1666 (CO), 1624 (C=C), 1493, 1441, 1347, 1269, 1214, 1167, 1097, 840, 777, 703; δ_H (500 MHz, $CDCl_3$) 3.97 (3H, s, OCH_3), 7.06 (1H, dd, *J* 8.4, 1.0 Hz, 5-H), 7.10–7.17 (3H, m, 3-H, 2'-H and 6'-H), 7.57 (2H, dd, *J* 8.4, $^3J_{HF}$ 5.4 Hz, 3'-H and 5'-H), 7.87 (1H, d, *J* 8.4 Hz, 6-H), 10.82 (1H, br s, OH); δ_C (126 MHz, $CDCl_3$) 52.4 (CH_3), 111.3 (C), 115.7 (CH), 116.0 (2 × CH, d, $^2J_{CF}$ 21.6 Hz), 118.1 (CH), 129.0 (2 × CH, d, $^3J_{CF}$ 8.2 Hz), 130.5 (CH), 135.9 (C, d, $^4J_{CF}$ 3.2 Hz), 147.6 (C), 162.0 (C), 163.2 (C, d, $^1J_{CF}$ 248.3 Hz), 170.6 (C); *m/z* (EI) 246.0693 (M^+, $C_{14}H_{11}FO_3$ requires 246.0692), 214 (100%), 186 (45), 157 (30), 133 (10), 93 (9), 84 (30), 49 (34).

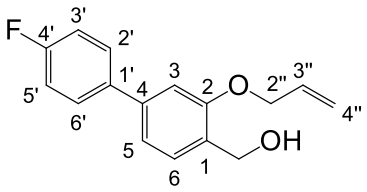
4-(4'-Fluorophenyl)-2-hydroxybenzyl alcohol (107)



Lithium aluminium hydride (0.663 g, 17.5 mmol) was added to a solution of methyl 4-(4'-fluorophenyl)-2-hydroxybenzoate (**106**) (1.72 g, 6.98 mmol) in

tetrahydrofuran (70 mL) and stirred at room temperature for 18 h. The reaction mixture was cooled to 0 °C and quenched by addition of 2 M hydrochloric acid (70 mL). The solution was extracted with dichloromethane (2 × 70 mL), washed with water (2 × 50 mL) and brine (70 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield 4-(4'-fluorophenyl)-2-hydroxybenzyl alcohol (**107**) (1.52 g, 100%) as a white solid. Mp 105–107 °C; ν_{max} (neat)/cm^{-1} 3441 (OH), 3395 (OH), 2918 (CH), 1491, 1241, 1184, 988, 822; δ_H (400 MHz, $CDCl_3$) 2.23 (1H, br s, 1-CH_2O*H*), 4.92 (2H, s, 1-CH_2), 7.03 (1H, dd, *J* 7.9, 1.6 Hz, 5-H), 7.06–7.16 (4H, m, 3-H, 6-H, 2'-H and 6'-H), 7.40 (1H, br s, 2-OH), 7.48–7.56 (2H, m, 3'-H and 5'-H); δ_C (126 MHz, $CDCl_3$) 64.6 (CH_2), 115.3 (CH), 115.8 (2 × CH, d, $^2J_{CF}$ 21.5 Hz), 118.8 (CH), 123.6 (C), 128.4 (CH), 128.7 (2 × CH, d, $^3J_{CF}$ 8.1 Hz), 136.7 (C), 141.9 (C), 156.6 (C), 162.7 (C, d, $^1J_{CF}$ 246.4 Hz); *m/z* (EI) 218.0742 (M^+, $C_{13}H_{11}FO_2$ requires 218.0743), 200 (68%), 172 (100), 133 (17), 120 (80), 85 (7).

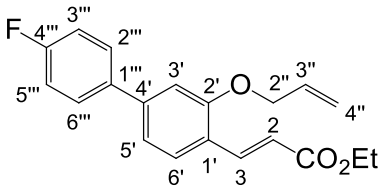
2-Allyloxy-4-(4'-fluorophenyl)benzyl alcohol (108)



Allyl bromide (0.79 mL, 9.2 mmol) was added to a solution of 4-(4'-fluorophenyl)-2-hydroxybenzyl alcohol (**107**) (1.0 g, 4.6 mmol), potassium carbonate (0.95 g, 6.9 mmol) and sodium iodide (0.041 g, 0.28 mmol) in dimethylformamide (31 mL) and stirred at room temperature for 24 h. The solution was diluted with diethyl ether (60 mL), washed with 5% lithium chloride solution (3 × 50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (elution with 20% diethyl ether:petroleum ether) gave 2-allyloxy-4-(4'-fluorophenyl)benzyl alcohol (**108**) (0.95 g, 80%) as a white solid. Mp 54–56 °C; ν_{max} (neat)/cm^{-1} 3354 (OH), 2853 (CH), 1610 (C=C), 1496, 1221, 1001, 819; δ_H (500 MHz, $CDCl_3$) 2.38 (1H, t, *J* 5.6 Hz, OH), 4.66 (2H, dt, *J* 5.2, 1.5 Hz, 2''-H_2), 4.75 (2H, d, *J* 5.6 Hz, 1-CH_2OH), 5.32 (1H, ddt, *J* 10.5, 2.9, 1.5 Hz, 4''-*H*H), 5.44 (1H, ddt, *J* 17.3, 2.9, 1.5 Hz, 4''-H*H*), 6.09 (1H, ddt, *J* 17.3, 10.5, 5.2 Hz, 3''-H), 7.02 (1H, d, *J* 1.5 Hz, 3-H), 7.06–7.15 (3H, m, 5-H, 2'-H and 6'-H), 7.34 (1H, d, *J* 7.7 Hz, 6-H), 7.44–7.65 (2H, m, 3'-H and 5'-H); δ_C (126 MHz, $CDCl_3$) 61.9 (CH_2), 69.0 (CH_2), 110.6 (CH), 115.8 (2 × CH, d, $^2J_{CF}$ 21.4 Hz), 118.0 (CH_2), 119.7 (CH), 128.6 (C), 128.8 (2 × CH, d, $^3J_{CF}$ 8.0 Hz), 129.3 (CH), 133.1 (CH), 137.3 (C, d,

$^{4}J_{CF}$ 3.2 Hz), 141.4 (C), 156.9 (C), 162.7 (C, d, $^{1}J_{CF}$ 246.6 Hz); *m/z* (EI) 258.1054 (M^{+}, $C_{16}H_{15}FO_2$ requires 258.1056), 228 (17%), 215 (27), 200 (57), 172 (70), 133 (17), 120 (6).

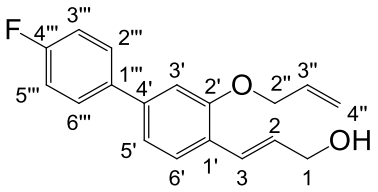
Ethyl (2*E*)-3-(2'-allyloxy-4'-[4'''-fluorophenyl]phenyl)prop-2-enoate (109)



Dimethyl sulfoxide (0.64 mL, 9.0 mmol) was added to a stirred solution of oxalyl chloride (0.40 mL, 4.5 mmol) in dichloromethane (15 mL) at −78 °C. The reaction mixture was stirred for 0.3 h then 2-allyloxy-4-(4'-fluorophenyl)benzyl alcohol (**108**) (0.78 g, 3.0 mmol) in dichloromethane (15 mL) was slowly added. The mixture was stirred for a further 0.3 h then triethylamine (2.1 mL, 15 mmol) was added. This reaction mixture was stirred for 0.5 h at −78 °C and then allowed to warm to room temperature and stirred for a further 2 h. Meanwhile, a solution of lithium bromide (1.0 g, 12 mmol), triethyl phosphonoacetate (**21**) (2.0 mL, 10 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5 mL, 10 mmol) in acetonitrile (30 mL) was prepared and stirred for 1 h. The Swern solution was concentrated *in vacuo* and the Horner–Wadsworth–Emmons solution was added. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was quenched by the addition of a saturated solution of ammonium chloride (20 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (2 × 30 mL). The organic layers were combined, washed with water (50 mL) and brine (50 mL) then dried ($MgSO_4$) and concentrated to give a yellow oil. Purification by column chromatography (elution with 5% diethyl ether:petroleum ether) gave ethyl (2*E*)-3-(2'-allyloxy-4'-[4'''-fluorophenyl]phenyl)prop-2-enoate (**109**) (0.83 g, 84%) as a white solid. Mp 75–76 °C; ν_{max} (neat)/cm^{-1} 2981 (CH), 1702 (CO), 1628 (C=C), 1604 (C=C), 1492, 1307, 1217, 1158, 986, 811; δ_H (500 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.27 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.69 (2H, d, *J* 5.2 Hz, 2''-H_2), 5.34 (1H, dd, *J* 10.5, 1.4 Hz, 4''-*H*H), 5.46 (1H, dd, *J* 17.2, 1.4 Hz, 4''-H*H*), 6.11 (1H, ddt, *J* 17.2, 10.5, 5.2 Hz, 3''-H), 6.56 (1H, d, *J* 16.2 Hz, 2-H), 7.04 (1H, d, *J* 1.3 Hz, 3'-H), 7.09–7.18 (3H, m, 5'-H, 2'''-H and 6'''-H), 7.48–7.55 (2H, m, 3'''-H and 5'''-H), 7.56 (1H, d, *J* 8.0 Hz, 6'-H), 8.06 (1H, d, *J* 16.2 Hz, 3-H); δ_C (126 MHz, $CDCl_3$) 14.5 (CH_3), 60.4 (CH_2), 69.4 (CH_2), 111.2 (CH), 115.9 (2 × CH, d, $^{2}J_{CF}$ 21.5

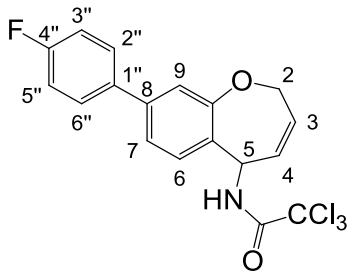
Hz), 118.0 (CH_2), 118.8 (CH), 119.7 (CH), 122.9 (C), 128.8 (2 × CH, d, $^{3}J_{CF}$ 8.1 Hz), 129.3 (CH), 132.9 (CH), 136.6 (C, d, $^{4}J_{CF}$ 3.2 Hz), 139.5 (CH), 143.4 (C), 157.9 (C), 162.9 (C, d, $^{1}J_{CF}$ 247.6 Hz), 167.6 (C); *m/z* (EI) 326.1316 (M^+, $C_{20}H_{19}FO_3$ requires 326.1318), 281 (23%), 252 (20), 238 (37), 225 (17), 212 (83), 183 (64), 165 (9), 157 (7), 133 (6), 113 (5).

(2*E*)-3-(2'-Allyloxy-4'-[4'''-fluorophenyl]phenyl)prop-2-en-1-ol (110)



Diisobutylaluminium hydride (6.1 mL, 1 M solution in hexanes) was added dropwise with stirring to a solution of ethyl (2*E*)-3-(2'-allyloxy-4'-[4'''-fluorophenyl]phenyl)prop-2-enoate (**109**) (0.79 g, 2.4 mmol), in diethyl ether (50 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 mixture was quenched with 10% aqueous potassium sodium tartrate solution (50 mL), extracted with diethyl ether (2 × 30 mL), washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield (2*E*)-3-(2'-allyloxy-4'-[4'''-fluorophenyl]phenyl)prop-2-en-1-ol (**110**) (0.63 g, 92%) as a white solid. Mp 84–86 °C; ν_{max} (neat)/cm^{-1} 3335 (OH), 2867 (CH), 1602 (C=C), 1519, 1493, 1392, 1220, 1014, 972, 827; δ_H (400 MHz, $CDCl_3$) 1.50 (1H, br s, OH), 4.36 (2H, dd, *J* 5.9, 1.1 Hz, 1-H_2), 4.65 (2H, dt, *J* 5.2, 1.5 Hz, 2''-H_2), 5.32 (1H, dq, *J* 10.5, 1.5 Hz, 4''-*H*H), 5.45 (1H, dq, *J* 17.3, 1.5 Hz, 4''-H*H*), 6.11 (1H, ddt, *J* 17.3, 10.5, 5.2 Hz, 3''-H), 6.45 (1H, dt, *J* 16.1, 5.9 Hz, 2-H), 6.99 (1H, dt, *J* 16.1, 1.1 Hz, 3-H), 7.02 (1H, d, *J* 1.7 Hz, 3'-H), 7.08–7.16 (3H, m, 5'-H, 2'''-H and 6'''-H), 7.47–7.57 (3H, m, 6'-H, 3'''-H and 5'''-H); δ_C (101 MHz, $CDCl_3$) 64.4 (CH_2), 69.5 (CH_2), 111.2 (CH), 115.8 (2 × CH, d, $^{2}J_{CF}$ 21.4 Hz), 117.8 (CH_2), 119.8 (CH), 125.2 (C), 125.9 (CH), 127.5 (CH), 128.6 (2 × CH, d, $^{3}J_{CF}$ 8.0 Hz), 129.5 (CH), 133.4 (CH), 137.1 (C, d, $^{4}J_{CF}$ 3.2 Hz), 140.9 (C), 156.2 (C), 162.7 (C, d, $^{1}J_{CF}$ 246.8 Hz); *m/z* (EI) 284.1214 (M^+, $C_{18}H_{17}FO_2$ requires 284.1213), 243 (49%), 225 (47), 215 (42), 196 (26), 183 (38), 165 (19), 133 (11), 107 (6), 55 (6).

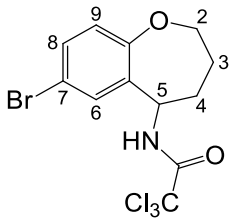
8-(4''-Fluorophenyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (99)



(2*E*)-3-(2'-allyloxy-4'-[4'''-fluorophenyl]phenyl)prop-2-en-1-ol (**110**) (0.200 g, 0.700 mmol) was dissolved in dry dichloromethane (32 mL) and cooled to 0 °C under argon with stirring. Trichloroacetonitrile (0.106 mL, 1.06 mmol) was added to the solution, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0530 mL, 0.350 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 (300 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 (60 mg, 3 mg/mL) to which degassed *p*-xylene (20 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 Grubbs 2nd generation catalyst (0.0300 g, 0.0350 mmol) and *p*-xylene (68 mL) were added. The reaction mixture was heated to 50 °C for 20 h. The reaction mixture was concentrated *in vacuo* and purified by column chromatography (elution with 20% diethyl ether in petroleum ether) to yield 8-(4''-fluorophenyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**99**) (0.277 g, 98%) as a white solid. Mp 115–117 °C; ν_{max} (neat)/cm^{-1} 3416 (NH), 2932 (CH), 1703 (CO), 1489, 1223, 907, 816, 729; δ_H (500 MHz, $CDCl_3$) 4.50 (1H, br d, *J* 17.7 Hz, 2-*H*H), 4.86 (1H, ddd, *J* 17.7, 3.3, 2.2 Hz, 2-H*H*), 5.45 (1H, t, *J* 8.2 Hz, 5-H), 5.74 (1H, ddd, *J* 11.6, 3.3, 1.9 Hz, 3-H), 6.13 (1H, ddt, *J* 11.6, 8.2, 2.2 Hz, 4-H), 7.09–7.15 (2H, m, 2''-H and 6''-H), 7.30 (1H, dd, *J* 7.8, 1.5 Hz, 7-H), 7.32 (1H, d, *J* 1.5 Hz, 9-H), 7.35 (1H, d, *J* 7.8 Hz, 6-H), 7.50–7.56 (2H, m, 3''-H and 5''-H), 7.63 (1H, d, *J* 8.2 Hz, NH); δ_C (126 MHz, $CDCl_3$) 51.4 (CH), 71.3 (CH_2), 92.8 (C), 115.9 (2 × CH, d, $^2J_{CF}$ 21.5 Hz), 120.8 (CH), 123.6 (CH), 126.1 (CH), 128.7 (2 × CH, d, $^3J_{CF}$ 8.1 Hz), 128.9 (CH), 131.8 (CH), 133.7 (C), 136.1 (C, d, $^4J_{CF}$ 3.2 Hz), 142.5 (C), 157.7 (C), 160.8 (C), 162.8 (C, d, $^1J_{CF}$ 247.2 Hz); *m/z* (EI) 398.9980 (M^+,

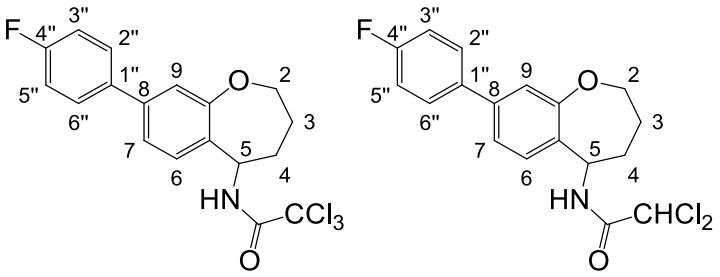
$C_{18}H_{13}{}^{35}Cl_3FNO_2$ requires 398.9996), 328 (59%), 294 (12), 282 (9), 252 (20), 238 (67), 225 (18), 209 (20), 196 (23), 183 (21), 157 (8), 133 (7), 120 (6).

7-Bromo-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (111)



7-Bromo-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96d**) (0.11 g, 0.29 mmol) was dissolved in ethyl acetate (6 mL) and a suspension of 10% palladium on carbon (0.022 g, 20% w/w) in ethyl acetate (5 mL) was added. The mixture was degassed, purged with hydrogen gas and left to stir at room temperature under a hydrogen atmosphere for 2 h. The suspension was filtered through Celite® with ethyl acetate (100 mL) and concentrated *in vacuo* to yield 7-bromo-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (**111**) (0.11 g, 100%) as a white solid. Mp 129–131 °C; ν_{max} (neat)/cm^{-1} 2921 (CH), 1709 (CO), 1530, 1476, 1223, 1165, 1038, 822; δ_H (500 MHz, $CDCl_3$) 1.74–1.93 (2H, m, 3-*H*H and 4-*H*H), 2.17–2.34 (2H, m, 3-H*H* and 4-H*H*), 3.72 (1H, td, *J* 11.9, 1.7 Hz, 2-*H*H), 4.39 (1H, dt, *J* 11.9, 3.2 Hz, 2-H*H*), 5.08 (1H, ddd, *J* 7.7, 6.5, 1.4 Hz, 5-H), 6.94 (1H, d, *J* 8.5 Hz, 9-H), 7.36 (1H, dd, *J* 8.5, 2.4 Hz, 8-H), 7.40 (1H, d, *J* 2.4 Hz, 6-H), 7.44 (1H, d, *J* 7.7 Hz, NH); δ_C (126 MHz, $CDCl_3$) 26.5 (CH_2), 29.7 (CH_2), 54.4 (CH), 74.1 (CH_2), 92.7 (C), 117.2 (C), 124.4 (CH), 132.2 (CH), 132.8 (CH), 135.6 (C), 158.7 (C), 160.9 (C); *m/z* (EI) 384.9042 (M^+, $C_{12}H_{11}{}^{79}Br^{35}Cl_3NO_2$ requires 384.9039), 352 (100%), 322 (17), 316 (17), 239 (11), 225 (17), 198 (10), 146 (32), 131 (14), 115 (12), 89 (6), 63 (5), 49 (4).

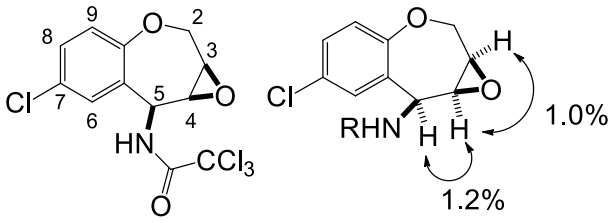
8-(4''-Fluorophenyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (112) and 8-(4''-fluorophenyl)-5-(2',2'-dichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (113)



p-Toluenesulfonyl hydrazide (0.030 g, 0.16 mmol) and potassium acetate (0.016 g, 0.16 mmol) were added to a stirred solution of 8-(4''-fluorophenyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**99**) (0.033 g, 0.082 mmol) in butan-1-ol (0.8 mL) at 50 °C. The reaction mixture was warmed to 100 °C and four additional portions of *p*-toluenesulfonyl hydrazide (0.030 g, 0.16 mmol) and potassium acetate (0.016 g, 0.16 mmol) were added at 1 h intervals. After 5 h, the reaction mixture was cooled to room temperature and diluted with diethyl ether (10 mL), then washed with 1 M sodium hydroxide (10 mL), water (10 mL) and brine (10 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (elution with 10% diethyl ether:petroleum ether) gave 8-(4''-fluorophenyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (**112**) (0.027 g, 81%) as a white solid. Further elution yielded 8-(4''-fluorophenyl)-5-(2',2'-dichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (**113**) (0.005 g, 17%) as a white solid. Data for 8-(4''-fluorophenyl)-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (**112**): Mp 128–130 °C; ν_{max} (neat)/cm^{-1} 3415 (NH), 2941 (CH), 1712 (CO), 1491, 1226, 817; δ_H (400 MHz, $CDCl_3$) 1.77–1.95 (2H, m, 3-*H*H and 4-*H*H), 2.22–2.42 (2H, m, 3-H*H* and 4-H*H*), 3.79 (1H, td, *J* 11.9, 1.7 Hz, 2-*H*H), 4.43–4.50 (1H, m, 2-H*H*), 5.18 (1H, ddd, *J* 8.1, 6.1, 1.7 Hz, 5-H), 7.09–7.17 (2H, m, 2''-H and 6''-H), 7.23–7.29 (2H, m, 7-H and 9-H), 7.33 (1H, d, *J* 8.5 Hz, 6-H), 7.45–7.56 (3H, m, NH, 3''-H and 5''-H); δ_C (126 MHz, $CDCl_3$) 26.6 (CH_2), 29.8 (CH_2), 54.9 (CH), 74.2 (CH_2), 92.9 (C), 115.9 (2 × CH, d, $^2J_{CF}$ 21.5 Hz), 121.1 (CH), 123.1 (CH), 128.7 (2 × CH, d, $^3J_{CF}$ 8.1 Hz), 130.2 (CH), 132.3 (C), 136.1 (C, d, $^4J_{CF}$ 3.3 Hz), 142.3 (C), 160.0 (C), 161.0 (C), 162.9 (C, d, $^1J_{CF}$ 247.2 Hz); *m/z* (EI) 401.0150 (M^+, $C_{18}H_{15}{}^{35}Cl_3FNO_2$ requires 401.0152), 366 (100%), 330 (27), 296 (15), 283 (12), 241 (38), 212 (24), 183 (22), 170 (16), 84 (61). Data for 8-(4''-fluorophenyl)-5-(2',2'-

dichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (**113**): Mp 154–156 °C; ν_{max} (neat)/cm^{-1} 3246 (NH), 2928 (CH), 1669 (CO), 1492, 1208, 806; δ_H (500 MHz, $CDCl_3$) 1.78–1.93 (2H, m, 3-*H*H and 4-*H*H), 2.23–2.34 (2H, m, 3-H*H* and 4-H*H*), 3.76–3.84 (1H, m, 2-*H*H), 4.44 (1H, dt, *J* 12.2, 3.4 Hz, 2-H*H*), 5.21 (1H, t, *J* 6.7 Hz, 5-H), 5.94 (1H, s, $CHCl_2$), 7.08–7.15 (2H, m, 2''-H and 6''-H), 7.22–7.29 (3H, m, NH, 7-H and 9-H), 7.31 (1H, d, *J* 8.0 Hz, 6-H), 7.49–7.55 (2H, m, 3''-H and 5''-H); δ_C (126 MHz, $CDCl_3$) 26.7 (CH_2), 30.1 (CH_2), 53.6 (CH), 66.8 (CH), 74.2 (CH_2), 115.9 (2 × CH, d, $^2J_{CF}$ 21.5 Hz), 121.0 (CH), 123.0 (CH), 128.7 (2 × CH, d, $^3J_{CF}$ 8.1 Hz), 130.0 (CH), 132.6 (C), 136.1 (C, d, $^4J_{CF}$ 3.1 Hz), 142.1 (C), 160.0(C), 162.8 (C, d, $^1J_{CF}$ 247.1 Hz), 163.2 (C); *m/z* (EI) 367.0545 (M^+, $C_{18}H_{16}{}^{35}Cl_2FNO_2$ requires 367.0542), 332 (100%), 296 (68), 256 (10), 241 (26), 212 (23), 183 (17), 170 (12), 133 (9), 84 (11).

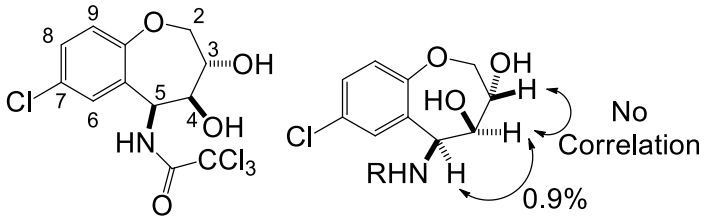
(3*R**,4*S**,5*S**)-3,4-Epoxy-7-chloro-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (115)



3-Chloroperbenzoic acid (0.10 g, 0.59 mmol) was added to a stirred solution of 7-chloro-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96c**) (0.050 g, 0.15 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 (0.10 g, 0.59 mmol) was added. The reaction mixture was stirred for a further 24 h, quenched by the addition of a saturated solution of sodium sulfite (5 mL) and extracted with dichloromethane (2 × 5 mL). The combined organic layers were washed with a saturated solution of sodium hydrogen carbonate (3 × 10 mL), water (10 mL) and brine (10 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (elution with 20% ethyl acetate:petroleum ether) gave an inseparable 12:1 mixture of (3*R**,4*S**,5*S**)-3,4-epoxy-7-chloro-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (**115**) and its anti-diastereomer (0.033 g, 62%) as a white solid which was used in the next step without further purification. Characterisation data for the major diastereomer **115**:

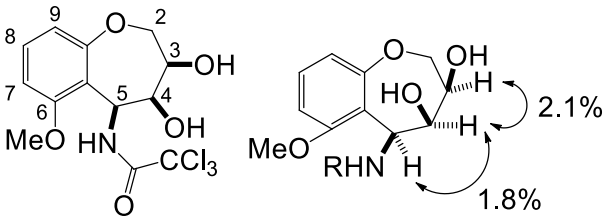
ν_{max} (neat)/cm^{-1} 3319 (NH), 2926 (CH), 1711 (CO), 1506, 1483, 1235, 1189, 1056, 835, 823; δ_H (500 MHz, $CDCl_3$) 3.19 (1H, dd, *J* 4.1, 1.4 Hz, 3-H), 3.72 (1H, dd, *J* 6.7, 4.1 Hz, 4-H), 4.05 (1H, dd, *J* 14.2, 1.4 Hz, 2-*H*H), 4.71 (1H, d, *J* 14.2 Hz, 2-H*H*), 5.38 (1H, dd, *J* 8.0, 6.7 Hz, 5-H), 7.04 (1H, d, *J* 8.5 Hz, 9-H), 7.29 (1H, dd, *J* 8.5, 2.5 Hz, 8-H), 7.37 (1H, d, *J* 2.5 Hz, 6-H), 7.76 (1H, d, *J* 8.0 Hz, NH); δ_C (126 MHz, $CDCl_3$) 50.2 (CH), 54.8 (CH), 55.6 (CH), 69.1 (CH_2), 92.5 (C), 123.8 (CH), 129.7 (CH), 130.7 (CH), 130.8 (C), 134.0 (C), 156.1 (C), 161.1 (C); *m/z* (ESI) 377.9213 (MNa^+, $C_{12}H_9{}^{35}Cl_4NNaO_3$ requires 377.9229), 227 (4%), 159 (1).

(3*S**,4*S**,5*S**)-3,4-Dihydroxy-7-chloro-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (116)



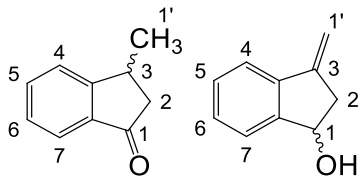
1.0 M Sulfuric acid (2 mL) was added to a solution of (3*R**,4*S**,5*S**)-3,4-epoxy-7-chloro-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (**115**) (0.017 g, 0.048 mmol) in 1,4-dioxane (2 mL) and stirred at room temperature for 48 h. The reaction was quenched by addition of a 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 ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by column chromatography (elution with 50% ethyl acetate:petroleum ether) gave (3*S**,4*S**,5*S**)-3,4-dihydroxy-7-chloro-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (**116**) (0.016 g, 91%) as a white foam. ν_{max} (neat)/cm^{-1} 3404 (NH and OH), 2927 (CH), 1696 (CO), 1507, 1482, 1228, 1081, 823; δ_H (400 MHz, $CDCl_3$) 2.70 (1H, d, *J* 3.7 Hz, OH), 3.33 (1H, d, *J* 5.3 Hz, OH), 3.76 (1H, dd, *J* 12.3, 8.4 Hz, 2-*H*H), 3.85–3.92 (1H, m, 4-H), 4.07 (1H, ddd, *J* 11.7, 8.4, 3.6 Hz, 3-H), 4.35 (1H, dd, *J* 12.3, 3.6 Hz, 2-H*H*), 5.33 (1H, dd, *J* 8.0, 1.5 Hz, 5-H), 7.02–7.10 (1H, m, 9-H), 7.27–7.31 (2H, m, 6-H and 8-H), 7.35 (1H, d, *J* 8.0 Hz, NH); δ_C (126 MHz, $CDCl_3$) 57.1 (CH), 71.1 (CH), 73.9 (CH_2), 75.8 (CH), 92.3 (C), 123.9 (CH), 129.7 (CH), 130.5 (C), 130.6 (C), 130.7 (CH), 157.3 (C), 163.2 (C); *m/z* (ESI) 395.9321 (MNa^+, $C_{12}H_{11}{}^{35}Cl_4O_4NNa$ requires 395.9334) 363 (3%), 301 (3), 283 (4), 274 (15), 227 (10), 159 (4).

(3*R,4*S**,5*S**)-3,4-Dihydroxy-6-methoxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (117)**



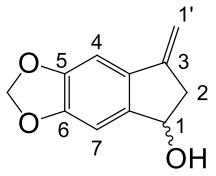
Tetramethylethylenediamine (0.019 mL, 0.13 mmol) was added to a solution of 6-methoxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,5-dihydro-1-benzoxepine (**96g**) (0.039 g, 0.12 mmol) in dichloromethane (2 mL) and cooled to −78 °C. After 0.2 h, a solution of osmium tetroxide (0.032 g, 0.13 mmol) in 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, then concentrated *in vacuo*. The residue was taken up in a solution of methanol (4 mL) and 12 M 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 (elution with 50% ethyl acetate:petroleum ether) to yield (3*R**,4*S**,5*S**)-3,4-dihydroxy-6-methoxy-5-(2',2',2'-trichloromethylcarbonylamino)-2,3,4,5-tetrahydro-1-benzoxepine (**117**) (0.032 g, 74%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3464 (OH), 3417 (NH), 2928 (CH), 1711 (CO), 1505, 1473, 1249, 1086, 820; δ_H (500 MHz, $CDCl_3$) 2.72 (1H, s, OH), 2.95 (1H, s, OH), 3.68 (1H, t, *J* 12.4 Hz, 2-*H*H), 3.85 (3H, s, OCH_3), 4.16–4.26 (2H, m, 2-H*H* and 3-H), 4.50 (1H, dd, *J* 6.6, 4.0 Hz, 4-H), 6.01 (1H, dd, *J* 8.4, 6.6 Hz, 5-H), 6.72 (1H, d, *J* 8.2 Hz, ArH), 6.75 (1H, d, *J* 8.2 Hz, ArH), 7.27 (1H, t, *J* 8.2 Hz, 8-H), 7.31 (1H, d, *J* 8.4 Hz, NH); δ_C (126 MHz, $CDCl_3$) 47.5 (CH), 56.4 (CH_3), 68.4 (CH), 69.0 (CH), 71.2 (CH_2), 92.5 (C), 107.9 (CH), 114.4 (CH), 117.3 (C), 130.8 (CH), 158.9 (C), 160.2 (C), 161.7 (C); *m/z* (ESI) 391.9818 (MNa^+, $C_{13}H_{14}{}^{35}Cl_3NNaO_5$ requires 391.9830), 381 (1%), 279 (1).

3-Methyl-2,3-dihydro-inden-1-one (127a)[189] and 2,3-dihydro-3-(methylene)inden-1-ol (126a)[150]



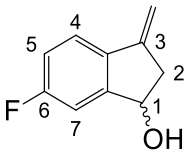
Allylboronic acid pinacol ester (**58**) (0.053 mL, 0.28 mmol) was added to a solution of 2-bromobenzaldehyde (**52a**) (0.031 mL, 0.27 mmol) and potassium carbonate (0.19 g, 1.4 mmol) in acetonitrile (2.7 mL) and water (0.019 mL, 1.1 mmol) at room temperature and stirred for 20 h. Bis(triphenylphosphine)palladium(II) dichloride (0.014 g, 0.020 mmol) was added to the solution followed by hydrazine monohydrate (0.0050 mL, 0.10 mmol). The reaction vessel was sealed and heated to 100 °C for 18 h then cooled to room temperature and diluted with diethyl ether (3 mL). The solution was filtered through a short pad of silica and concentrated *in vacuo*. Purification by column chromatography (elution with 20% diethyl ether:petroleum ether) yielded 3-methyl-2,3-dihydro-inden-1-one (**127a**) (0.002 g, 5%) as a yellow oil. Further elution yielded 2,3-dihydro-3-(methylene)inden-1-ol (**126a**) (0.030 g, 75%) as a white solid. Data for **127a**, spectroscopic data consistent with literature:[189] δ_H (500 MHz, $CDCl_3$) 1.41 (3H, d, *J* 7.3 Hz, CH_3), 2.28 (1H, dd, *J* 19.0, 3.6 Hz, 2-*H*H), 2.94 (1H, dd, *J* 19.0, 7.3 Hz, 2-H*H*), 3.44 (1H, quin.d, *J* 7.3, 3.6 Hz, 3-H), 7.37 (1H, t, *J* 7.7 Hz, ArH), 7.51 (1H, brd, *J* 7.7 Hz, ArH), 7.61 (1H, td, *J* 7.7, 1.2 Hz, ArH), 7.73 (1H, d, *J* 7.7 Hz, ArH); δ_C (126 MHz, $CDCl_3$) 21.5 (CH_3), 32.9 (CH), 45.5 (CH_2), 123.6 (CH), 125.4 (CH), 127.5 (CH), 134.9 (CH), 136.6 (C), 160.1 (C), 206.6 (C); *m/z* (EI) 146 (52%, M^+), 131 (64), 115 (34), 77 (31), 44 (10); Data for **126a**: Mp 72–73 °C (lit.,[150] 71–72 °C); δ_H (400 MHz, $CDCl_3$) 1.88 (1H, d, *J* 7.4 Hz, OH), 2.66 (1H, ddt, *J* 16.9, 3.8, 2.2 Hz, 2-*H*H), 3.20 (1H, ddt, *J* 16.9, 7.4, 2.2 Hz, 2-H*H*), 5.10 (1H, t, *J* 2.2 Hz, 1'-*H*H), 5.28 (1H, td, *J* 7.4, 3.8 Hz, 1-H), 5.53 (1H, t, *J* 2.2 Hz, 1'-H*H*), 7.29–7.37 (2H, m, ArH), 7.44–7.57 (2H, m, ArH); δ_C (101 MHz, $CDCl_3$) 42.7 (CH_2), 73.6 (CH), 104.5 (CH_2), 120.8 (CH), 125.2 (CH), 129.0 (CH), 129.1 (CH), 140.4 (C), 146.5 (C), 147.1 (C); *m/z* (EI) 146 (100%, M^+), 131 (80), 117 (57), 115 (47), 103 (28), 91 (28), 51 (20).

2,3-Dihydro-3-methylene-5,6-(methylenedioxy)inden-1-ol (126b)



The reaction was carried out according to the previously described procedure for 2,3-dihydro-3-(methylene)inden-1-ol (**126a**) using 2-bromo-4,5-methylenedioxybenzaldehyde (**52b**) (0.062 g, 0.27 mmol). Purification by column chromatography (elution with 30% diethyl ether:petroleum ether) gave 2,3-dihydro-3-methylene-5,6-(methylenedioxy)inden-1-ol (**126b**) (0.046 g, 89%) as a white solid. Mp 76–78 °C; ν_{max} (neat)/cm^{-1} 3306 (OH), 2897 (CH), 1638 (C=C), 1472, 1310, 1233, 1036, 939, 860; δ_H (500 MHz, $CDCl_3$) 1.95 (1H, d, *J* 7.0 Hz, OH), 2.63 (1H, ddt, *J* 16.8, 3.3, 2.0 Hz, 2-*H*H), 3.18 (1H, ddt, *J* 16.8, 7.0, 2.0 Hz, 2-H*H*), 4.94 (1H, t, *J* 2.0 Hz, 1'-*H*H), 5.13 (1H, td, *J* 7.0, 3.3 Hz, 1-H), 5.28 (1H, t, *J* 2.0 Hz, 1'-H*H*), 5.97 (2H, s, OCH_2O), 6.86 (1H, s, ArH), 6.89 (1H, s, ArH); δ_C (126 MHz, $CDCl_3$) 43.2 (CH_2), 73.2 (CH), 100.5 (CH), 101.6 (CH_2), 102.2 (CH_2), 104.9 (CH), 134.8 (C), 141.5 (C), 146.1 (C), 149.1 (C), 149.1 (C); *m/z* (EI) 190.0636 (M^+, $C_{11}H_{10}O_3$ requires 190.0630), 173 (28%), 162 (16), 143 (23), 131 (9), 115 (15), 103 (10), 77 (8), 63 (6), 51 (5).

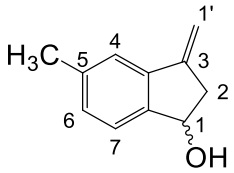
2,3-Dihydro-6-fluoro-3-(methylene)inden-1-ol (126c)[152]



The reaction was carried out according to the previously described procedure for 2,3-dihydro-3-(methylene)inden-1-ol (**126a**) using 2-bromo-5-fluorobenzaldehyde (**52c**) (0.055 g, 0.27 mmol). Purification by column chromatography (elution with 20% diethyl ether:petroleum ether) gave 2,3-dihydro-6-fluoro-3-(methylene)inden-1-ol (**126c**) (0.036 g, 80%) as a colourless oil. Spectroscopic data as reported in literature.[148] ν_{max} (neat)/cm^{-1} 3300 (OH), 2918 (CH), 1609 (C=C), 1479, 1325, 1252, 1130, 1088, 1042, 872, 827; δ_H (400 MHz, $CDCl_3$) 1.89 (1H, d, *J* 7.4 Hz, OH), 2.68 (1H, ddt, *J* 16.8, 4.3, 2.1 Hz, 2-*H*H), 3.23 (1H, ddt, *J* 16.8, 7.4, 2.1 Hz, 2-H*H*), 5.06 (1H, t, *J* 2.1 Hz, 1'-*H*H), 5.24 (1H, td, *J* 7.4, 4.3 Hz, 1-H), 5.43 (1H, t, *J* 2.1 Hz, 1'-H*H*), 7.02 (1H, ddd, $^3J_{HF}$ 8.5, *J* 8.5, 2.4 Hz, 5-H), 7.14 (1H, dd, $^3J_{HF}$ 8.5,

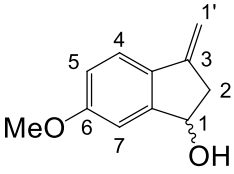
J 2.4 Hz, 7-H), 7.47 (1H, dd, *J* 8.5, $^{4}J_{HF}$ 5.0 Hz, 4-H); δ_C (126 MHz, $CDCl_3$) 43.0 (CH_2), 73.1 (CH, d, $^{4}J_{CF}$ 2.0 Hz), 104.0 (CH_2), 111.8 (CH, d, $^{2}J_{CF}$ 22.1 Hz), 116.5 (CH, d, $^{2}J_{CF}$ 23.4 Hz), 122.3 (CH, d, $^{3}J_{CF}$ 8.8 Hz), 136.3 (C, d, $^{4}J_{CF}$ 2.6 Hz), 145.2 (C), 149.1 (CH, d, $^{3}J_{CF}$ 7.6 Hz), 163.6 (C, d, $^{1}J_{CF}$ 248.0 Hz); *m/z* (EI) 164.0635 (M^+, $C_{10}H_9FO$ requires 164.0637), 149 (71%), 133 (31), 121 (19), 115 (12), 101 (12), 95 (6), 75 (5), 51 (3).

2,3-Dihydro-5-methyl-3-(methylene)inden-1-ol (126d)[152]



The reaction was carried out according to the previously described procedure for 2,3-dihydro-3-(methylene)inden-1-ol (**126a**) using 2-bromo-4-methylbenzaldehyde (**52d**) (0.054 g, 0.27 mmol). Purification by column chromatography (elution with 20% diethyl ether:petroleum ether) gave 2,3-dihydro-5-methyl-3-(methylene)inden-1-ol (**126d**) (0.032 g, 74%) as a white solid. Spectroscopic data as reported in literature.[152] Mp 98–100 °C; ν_{max} (neat)/cm^{-1} 3312 (OH), 2915 (CH), 1640 (C=C), 1439, 1335, 1049, 818; δ_H (400 MHz, $CDCl_3$) 1.93 (1H, d, *J* 6.1 Hz, OH), 2.39 (3H, s, CH_3), 2.64 (1H, ddt, *J* 16.9, 3.5, 2.1 Hz, 2-*H*H), 3.18 (1H, ddt, *J* 16.9, 7.2, 2.1 Hz, 2-H*H*), 5.07 (1H, t, *J* 2.1 Hz, 1'-*H*H), 5.17–5.26 (1H, m, 1-H), 5.50 (1H, t, *J* 2.1 Hz, 1'-H*H*), 7.14 (1H, d, *J* 7.6 Hz, 7-H), 7.30–7.39 (2H, m, 4-H and 6-H); δ_C (126 MHz, $CDCl_3$) 21.6 (CH_3), 43.0 (CH_2), 73.3 (CH), 104.1 (CH_2), 121.1 (CH), 124.9 (CH), 130.1 (CH), 138.8 (C), 140.5 (C), 144.5 (C), 146.5 (C); *m/z* (EI) 160.0883 (M^+, $C_{11}H_{12}O$ requires 160.0888), 145 (100%), 128 (30), 115 (40), 102 (5), 91 (19), 77 (10), 63 (8), 51 (7).

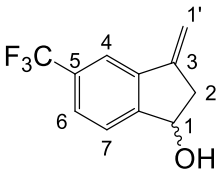
2,3-Dihydro-6-methoxy-3-(methylene)inden-1-ol (126e)[152]



The reaction was carried out according to the previously described procedure for 2,3-dihydro-3-(methylene)inden-1-ol (**126a**) using 2-bromo-5-

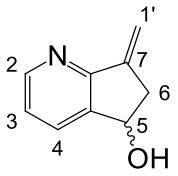
methoxybenzaldehyde (**52e**) (0.058 g, 0.27 mmol). Purification by column chromatography (elution with 20% diethyl ether:petroleum ether) gave 2,3-dihydro-6-methoxy-3-(methylene)inden-1-ol (**126e**) (0.034 g, 71%) as a white solid. Mp 60–62 °C (lit.[152] 64–66 °C); ν_{max} (neat)/cm^{-1} 3323 (OH), 2922 (CH), 1605 (C=C), 1487, 1331, 1288, 1260, 1148, 1024, 859, 816; δ_H (500 MHz, $CDCl_3$) 2.09 (1H, d, *J* 6.2 Hz, OH), 2.64 (1H, ddt, *J* 16.8, 4.1, 2.1 Hz, 2-*H*H), 3.18 (1H, ddt, *J* 16.8, 7.3, 2.1 Hz, 2-H*H*), 3.82 (3H, s, OCH_3), 4.95 (1H, t, *J* 2.1 Hz, 1'-*H*H), 5.17–5.23 (1H, m, 1-H), 5.35 (1H, t, *J* 2.1 Hz, 1-H*H*), 6.88 (1H, dd, *J* 8.5, 2.4 Hz, 5-H), 6.96 (1H, d, *J* 2.4 Hz, 7-H), 7.42 (1H, d, *J* 8.5 Hz, 4-H); δ_C (126 MHz, $CDCl_3$) 43.2 (CH_2), 55.6 (CH_3), 73.5 (CH), 102.1 (CH_2), 108.7 (CH), 116.5 (CH), 121.9 (CH), 133.2 (C), 145.9 (C), 148.8 (C), 160.8 (C); *m/z* (EI) 176.0840 (M^+, $C_{11}H_{12}O_2$ requires 176.0837), 148 (42%), 133 (31), 115 (22), 103 (9), 77 (9).

2,3-Dihydro-5-trifluoromethyl-3-(methylene)inden-1-ol (126g)



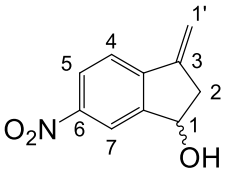
The reaction was carried out according to the previously described procedure for 2,3-dihydro-3-(methylene)inden-1-ol (**126a**) using 2-bromo-4-trifluoromethylbenzaldehyde (**52g**) (0.040 mL, 0.27 mmol). Purification by column chromatography (elution with 20% diethyl ether:petroleum ether) gave 2,3-dihydro-5-trifluoromethyl-3-(methylene)inden-1-ol (**126g**) (0.044 g, 78%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3322 (OH), 2962 (CH), 1650 (C=C), 1441, 1323, 1271, 1162, 1120, 1060, 897, 834; δ_H (400 MHz, $CDCl_3$) 1.91 (1H, d, *J* 7.4 Hz, OH), 2.72 (1H, ddt, *J* 16.9, 4.4, 2.2 Hz, 2-*H*H), 3.26 (1H, ddt, *J* 16.9, 7.4, 2.2 Hz, 2-H*H*), 5.20 (1H, t, *J* 2.2 Hz, 1'-*H*H), 5.32 (1H, td, *J* 7.4, 4.4 Hz, 1-H), 5.61 (1H, t, *J* 2.2 Hz, 1'-H*H*), 7.56 (1H, dd, *J* 8.4, 1.6 Hz, 6-H), 7.59 (1H, d, *J* 8.4 Hz, 7-H), 7.75 (1H, br s, 4-H); δ_C (126 MHz, $CDCl_3$) 42.8 (CH_2), 73.2 (CH), 106.4 (CH_2), 118.0 (CH, q, $^3J_{CF}$ 4.0 Hz), 124.3 (C, q, $^1J_{CF}$ 272.5 Hz), 125.8 (CH), 125.8 (CH, q, $^3J_{CF}$ 3.0 Hz), 131.5 (C, q, $^2J_{CF}$ 32.1 Hz), 141.0 (C), 145.1 (C), 150.3 (C); *m/z* (EI) 214.0597 (M^+, $C_{11}H_9F_3O$ requires 214.0605), 199 (100%), 195 (25), 186 (19), 177 (13), 171 (13), 165 (18), 151 (18), 145 (34), 128 (11), 117 (35), 115 (31), 91 (3).

6,7-Dihydro-7-(methylene)cyclopenta[b]pyridin-5-ol (126i)[150]



The reaction was carried out according to the previously described procedure for 2,3-dihydro-3-(methylene)inden-1-ol (**126a**) using 2-bromopyridine-3-carboxaldehyde (**52i**) (0.050 g, 0.27 mmol). Purification by column chromatography (elution with 40% ethyl acetate:petroleum ether) gave 6,7-dihydro-7-(methylene)cyclopenta[b]pyridin-5-ol (**126i**) (0.033 g, 84%) as a white solid. Spectroscopic data as reported in literature.[1] Mp 101–103 °C; δ_H (500 MHz, $CDCl_3$) 2.69 (1H, ddt, *J* 17.1, 4.0, 2.1 Hz, 6-*H*H), 3.19–3.23 (1H, m, OH), 3.23 (1H, ddt, *J* 17.1, 7.5, 2.1 Hz, 6-H*H*), 5.19 (1H, t, *J* 2.1 Hz, 1'-*H*H), 5.23–5.30 (1H, m, 5-H), 5.99 (1H, t, *J* 2.1 Hz, 1'-H*H*), 7.17 (1H, dd, *J* 7.7, 4.8 Hz, 3-H), 7.77 (1H, ddd, *J* 7.7, 1.5, 0.7 Hz, 4-H), 8.47 (1H, dd, *J* 4.8, 1.5 Hz, 2-H); δ_C (126 MHz, $CDCl_3$) 40.9 (CH_2), 71.1 (CH), 108.2 (CH_2), 123.4 (CH), 133.7 (CH), 140.4 (C), 145.0 (C), 150.6 (CH), 158.3 (C); *m/z* (EI) 147 (M^+, 78%), 130 (18), 118 (100), 104 (12), 91 (13), 79 (12).

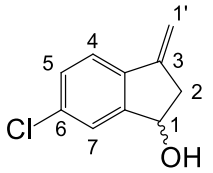
2,3-Dihydro-3-methylene-6-(nitro)inden-1-ol (126j)



The reaction was carried out according to the previously described procedure for 2,3-dihydro-3-(methylene)inden-1-ol (**126a**) using 2-bromo-5-nitrobenzaldehyde (**52j**) (0.062 g, 0.27 mmol) and hydrazine monohydrate (0.0020 mL, 0.040 mmol). Purification by column chromatography (elution with 50% diethyl ether:petroleum ether) gave 2,3-dihydro-3-methylene-6-(nitro)inden-1-ol (**126j**) (0.042 g, 83%) as an orange solid. Mp 72–74 °C, ν_{max} (neat)/cm^{-1} 3357 (OH), 2916 (CH), 1590 (C=C), 1515, 1334, 1054, 900; δ_H (400 MHz, $CDCl_3$) 2.17 (1H, d, *J* 6.8 Hz, OH), 2.77 (1H, br d, *J* 16.9 Hz, 2-*H*H), 3.30 (1H, dd, *J* 16.9, 7.3 Hz, 2-H*H*), 5.28–5.40 (2H, m, 1-H, 1'-*H*H), 5.72 (1H, br s, 1'-H*H*), 7.62 (1H, d, *J* 8.5 Hz, 4-H), 8.20 (1H, dd, *J* 8.5, 1.4 Hz, 5-H), 8.32 (1H, d, *J* 1.4 Hz, 7-H); δ_C (126 MHz, $CDCl_3$) 42.7

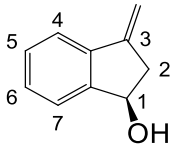
(CH_2), 72.6 (CH), 109.4 (CH_2), 121.1 (CH), 121.4 (CH), 124.5 (CH), 144.6 (C), 146.4 (C), 148.2 (C), 148.4 (C); *m/z* (EI) 191.0585 (M^+, $C_{10}H_9NO_3$ requires 191.0582), 176 (100%), 144 (31), 127 (18), 115 (63), 102 (10), 91 (17), 84 (12), 77 (10).

6-Chloro-2,3-dihydro-3-(methylene)inden-1-ol (126k)[152]



The reaction was carried out according to the previously described procedure for 2,3-dihydro-3-(methylene)inden-1-ol (**126a**) using 2-bromo-5-chlorobenzaldehyde (**52k**) (0.059 g, 0.27 mmol) and bis(triphenylphosphine)palladium(II) dichloride (0.019 g, 0.027 mmol). Purification by column chromatography (elution with 20% diethyl ether:petroleum ether) gave 6-chloro-2,3-dihydro-3-(methylene)inden-1-ol (**126k**) (0.034 g, 69%) as a white solid. Spectroscopic data as reported in literature.[152] Mp 85–87 °C; ν_{max} (neat)/cm^{-1} 3321 (OH), 2923 (CH), 1641 (C=C), 1470, 1334, 1175, 1070, 1040, 883, 826; δ_H (400 MHz, $CDCl_3$) 2.02 (1H, d, *J* 7.4 Hz, OH), 2.66 (1H, ddt, *J* 16.9, 4.1, 2.2 Hz, 2-*H*H), 3.20 (1H, ddt, *J* 16.9, 7.4, 2.2 Hz, 2-H*H*), 5.10 (1H, t, *J* 2.2 Hz, 1'-*H*H), 5.23 (1H, td, *J* 7.4, 4.1 Hz, 1-H), 5.49 (1H, t, *J* 2.2 Hz, 1'-H*H*), 7.28 (1H, ddd, *J* 8.3, 1.9, 0.4 Hz, 4-H), 7.41–7.45 (2H, m, 5-H and 7-H); δ_C (101 MHz, $CDCl_3$) 42.9 (CH_2), 73.1 (CH), 105.2 (CH_2), 122.0 (CH), 125.4 (CH), 129.3 (CH), 134.7 (C), 138.9 (C), 145.3 (C), 148.7 (C); *m/z* (EI) 180.0338 (M^+, $C_{10}H_9{}^{35}ClO$ requires 180.0342), 165 (43%), 152 (29), 145 (21), 115 (57), 84 (55), 75 (13), 49 (42), 44 (100).

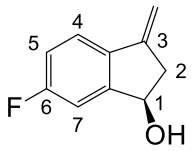
(1*R*)-2,3-Dihydro-3-methylene-inden-1-ol ((*R*)-126a)[150]



Allylboronic acid pinacol ester (**58**) (29 µL, 0.15 mmol) was added in a single portion to a solution of 2-bromobenzaldehyde (**52a**) (15 µL, 0.13 mmol) and (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (0.0050 g, 0.0066 mmol) in dry toluene (1.9 mL) at −50 °C and stirred for 22 h at

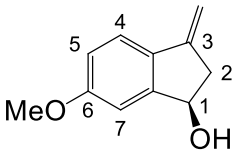
this temperature. The solution was allowed to slowly warm to room temperature over 1 h then potassium carbonate (0.11 g, 0.77 mmol) and water (23 µL, 1.3 mmol) were added and stirred for 1 h. Bis(triphenylphosphine)palladium(II) dichloride (0.0070 g, 0.0097 mmol) was added to the solution followed by hydrazine monohydrate (1.9 µL, 0.039 mmol). The reaction mixture was heated to 100 °C for 20 h then cooled to room temperature and diluted with hexane (3 mL). The solution was filtered through a short pad of silica with first hexane (20 mL) then diethyl ether (100 mL). The diethyl ether fraction was concentrated *in vacuo* then purified by column chromatography (elution with 20% diethyl ether:petroleum ether) to yield (*R*)-2,3-dihydro-3-methylene-inden-1-ol (**(*R*)-126a**) (0.017 g, 91%) as a white solid. Spectroscopic data as for (**126a**). Enantiomeric excess was determined by HPLC analysis of the crude, pre-column product with a chiracel OD-H column (hexane:^{i}PrOH 95:5, flow rate 1.0 mL min^{-1}), t_{minor} = 6.57 min, t_{major} = 7.85 min; e.r. = 86:14. $[\alpha]_D^{24}$ +3.2 (c 0.8, $CHCl_3$).

(1*R*)-2,3-Dihydro-6-fluoro-3-(methylene)inden-1-ol ((*R*)-126c)



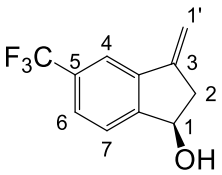
The reaction was carried out according to the previously described procedure for (1*R*)-2,3-dihydro-3-(methylene)inden-1-ol (**(*R*)-126a**) using 2-bromo-5-fluorobenzaldehyde (**52c**) (0.027 g, 0.13 mmol). Purification by column chromatography (elution with 20% diethyl ether:petroleum ether) gave (1*R*)-2,3-dihydro-6-fluoro-3-(methylene)inden-1-ol (**(*R*)-126c**) (0.019 g, 85%) as a colourless oil. Spectroscopic data as for (**126c**). Enantiomeric excess was determined by HPLC analysis of the crude, pre-column product with a chiracel OD-H column (hexane:^{i}PrOH 98:2, flow rate 1.5 mL min^{-1}), t_{minor} = 7.27, t_{major} = 8.46 min min; e.r. = 92:8. $[\alpha]_D^{24}$ +8.5 (c 1.3, $CHCl_3$).

(1*R*)-2,3-Dihydro-6-methoxy-3-(methylene)inden-1-ol ((*R*)-126e)



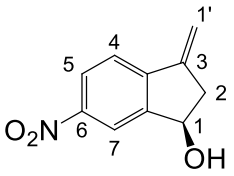
The reaction was carried out according to the previously described procedure for (1*R*)-2,3-dihydro-3-(methylene)inden-1-ol (**(*R*)-126a**) using 2-bromo-5-methoxybenzaldehyde (**52e**) (0.028 g, 0.13 mmol). Purification by column chromatography (elution with 20% diethyl ether:petroleum ether) gave (1*R*)-2,3-dihydro-6-methoxy-3-(methylene)inden-1-ol (**(*R*)-126e**) (0.022 g, 96%) as a white solid. Spectroscopic data as for (**126e**). Enantiomeric excess was determined by HPLC analysis of the crude, pre-column product with a chiracel OD-H column (hexane:^{i}PrOH 95:5, flow rate 1.0 mL min^{-1}), t_{minor} = 8.47, t_{major} = 9.41 min min; e.r. = 90:10. $[\alpha]_D^{24}$ −25.4 (c 0.8, $CHCl_3$).

(1*R*)-2,3-Dihydro-5-trifluoromethyl-3-(methylene)inden-1-ol ((*R*)-126g)



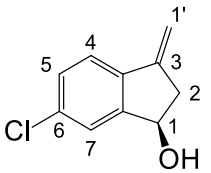
The reaction was carried out according to the previously described procedure for (1*R*)-2,3-dihydro-3-(methylene)inden-1-ol (**(*R*)-126a**) using 2-bromo-4-trifluoromethylbenzaldehyde (**52g**) (20 µL , 0.13 mmol). Purification by column chromatography (elution with 20% diethyl ether:petroleum ether) gave (1*R*)-2,3-dihydro-5-trifluoromethyl-3-(methylene)inden-1-ol (**(*R*)-126g**) (0.022 g, 76%) as a colourless oil. Spectroscopic data as for (**126g**). Enantiomeric excess was determined by HPLC analysis of the crude, pre-column product with a chiracel AD-H column (hexane:^{i}PrOH 98:2, flow rate 1.5 mL min^{-1}), t_{minor} = 5.86 min, t_{major} = 6.68 min; e.r. = 66:34. $[\alpha]_D^{24}$ −3.9 (c 1.3, $CHCl_3$).

(1*R*)-2,3-Dihydro-3-methylene-6-(nitro)-inden-1-ol ((*R*)-126j)



The reaction was carried out according to the previously described procedure for (1*R*)-2,3-dihydro-3-(methylene)inden-1-ol (**(*R*)-126a**) using 2-bromo-5-nitrobenzaldehyde (**52j**) (0.030 g, 0.13 mmol). Purification by column chromatography (elution with 40% diethyl ether:petroleum ether) gave (1R)-2,3-dihydro-3-methylene-6-(nitro)-inden-1-ol (**(*R*)-126j**) (0.022 g, 87%) as a white solid. Spectroscopic data as for (**126j**). Enantiomeric excess was determined by HPLC analysis of the crude, pre-column product with a chiracel AD-H column (hexane:^{i}PrOH 95:5, flow rate 2.0 mL min^{-1}), t_{minor} = 6.46 min, t_{major} = 8.37 min; e.r. =98:2. $[\alpha]_D^{24}$ −18.2 (c 1.1, $CHCl_3$).

(1*R*)-6-Chloro-2,3-dihydro-3-(methylene)inden-1-ol ((*R*)-126k)



The reaction was carried out according to the previously described procedure for (1*R*)-2,3-dihydro-3-(methylene)inden-1-ol (**(*R*)-126a**) using 2-bromo-5-chlorobenzaldehyde (**52k**) (0.029 g, 0.13 mmol). Purification by column chromatography (elution with 20% diethyl ether:petroleum ether) gave (1*R*)-2,3-dihydro-6-chloro-3-(methylene)inden-1-ol (**(*R*)-126k**) (0.022 g, 92%) as a white solid. Spectroscopic data as for (**126k**). Enantiomeric excess was determined by HPLC analysis of the crude, pre-column product with a chiracel OD-H column (hexane:^{i}PrOH 95:5, flow rate 1.5 mL min^{-1}), t_{minor} = 3.57 min, t_{major} = 4.05 min; e.r. = 94:6. $[\alpha]_D^{24}$ −14.7 (c 0.7, $CHCl_3$).

Chapter 6 References

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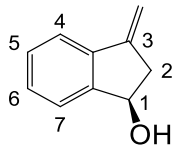
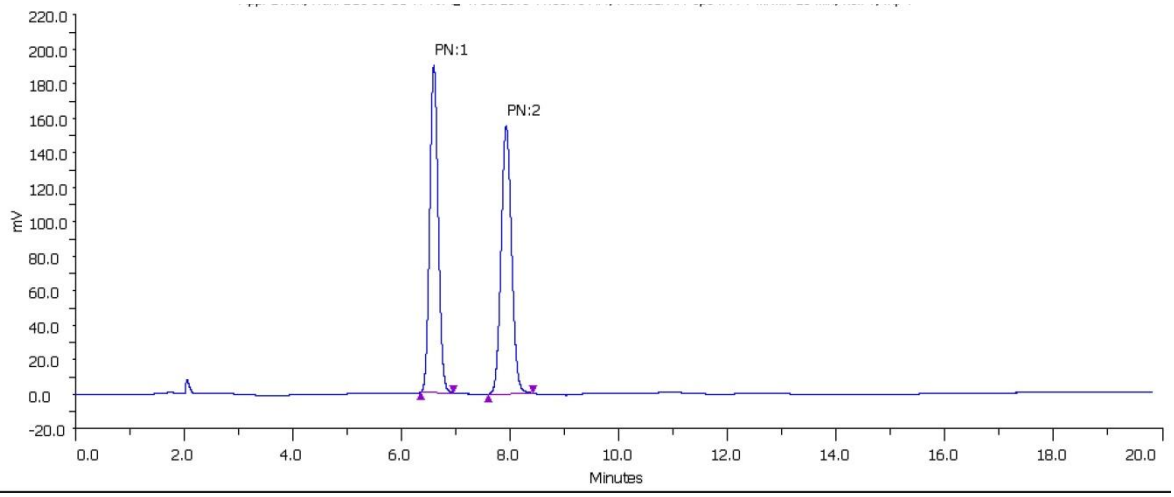
Appendices

Appendix 1: Chiral HPLC traces:

(1*R*)-2,3-Dihydro-3-methylene-inden-1-ol (**(*R*)-126a**)



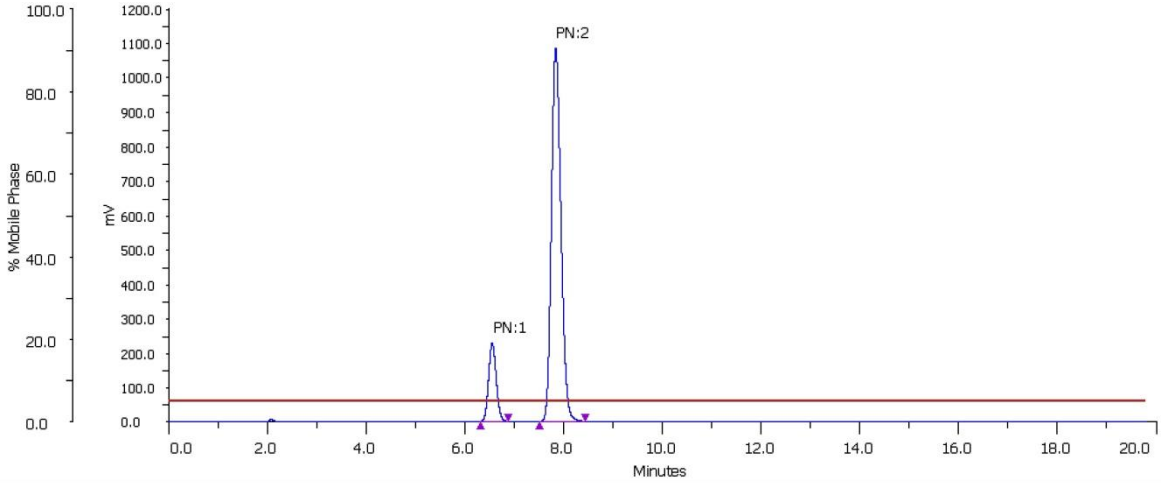
Racemic:



Sample Table

Sample Name	Retention Time (min)	Height (mV)	Area (uVmin x100)	Area %				
EC8-53	6.607	189.63	3413632.5762	49.631				
EC8-53	7.941	155.055	3464355.8985	50.369				

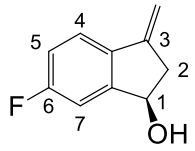
Enantioselective:



Sample Table

Peak Name	Sample Name	Height (mV)	Retention Time (min)	Area (uVmin x100)	Area %			
1	EC8-69	227.105	6.566	4083372.1282	14.379			
2	EC8-69	1084.853	7.854	24315761.2504	85.621			

(1*R*)-2,3-Dihydro-6-fluoro-3-(methylene)inden-1-ol (**(*R*)-126c**)



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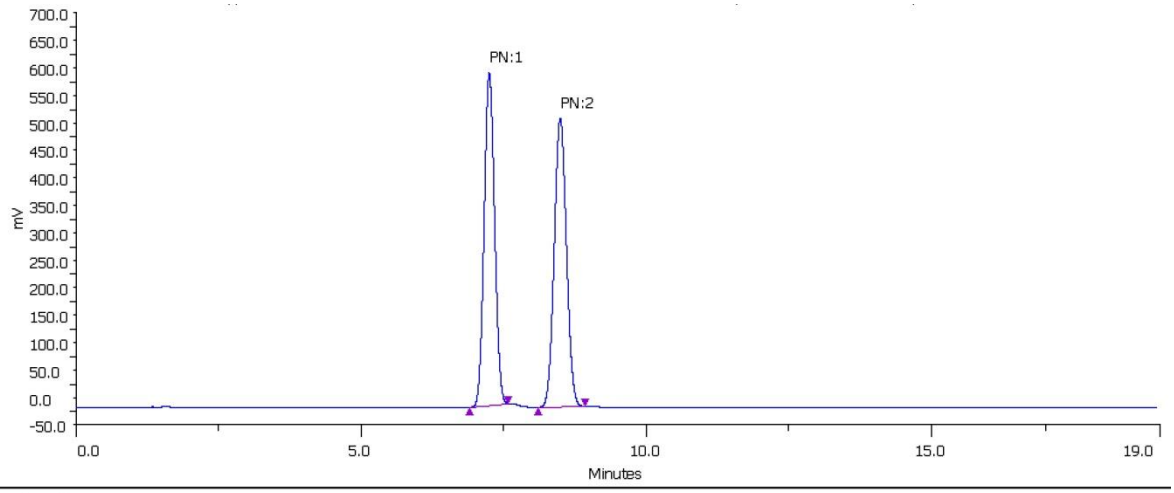
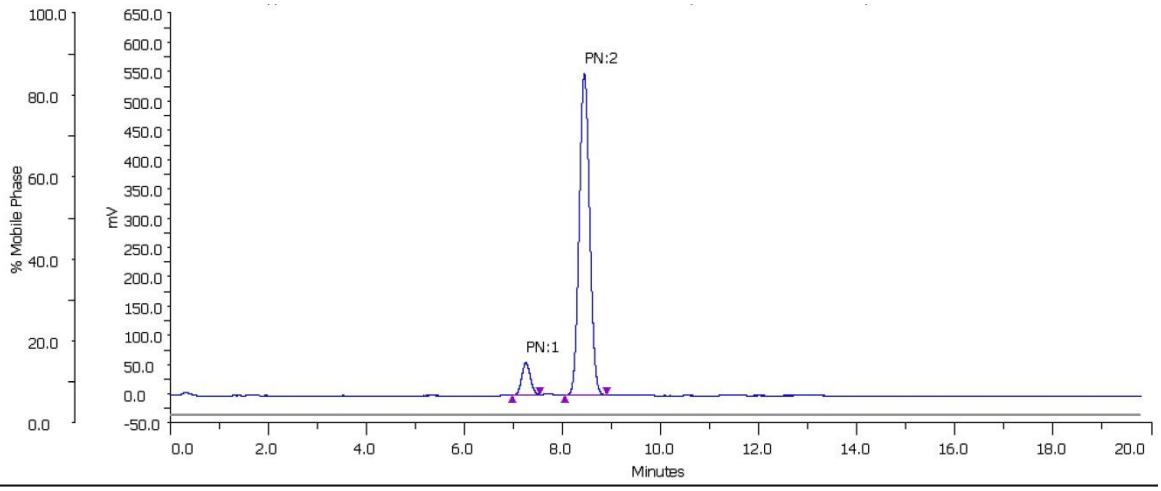


Sample Table

Sample Name	Retention Time (min)	Height (mV)	Area (uVmin x100)	Area %				
EC8-50	7.259	605.321	12903474.9095	49.682				
EC8-50	8.505	525.803	13068660.4574	50.318				

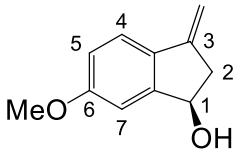
Enantioselective:



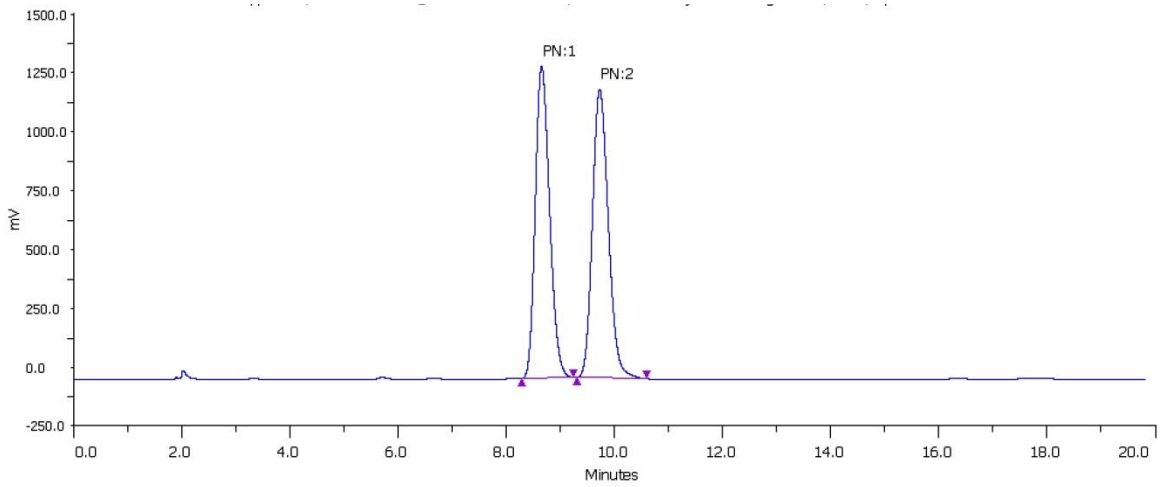
Sample Table

Sample Name	Retention Time (min)	Height (mV)	Area (uVmin x100)	Area %				
EC8-71	7.266	54.856	1122480.1115	7.662				
EC8-71	8.457	548.947	13526613.7528	92.338				

(1*R*)-2,3-Dihydro-6-methoxy-3-(methylene)inden-1-ol (**(*R*)-126e**)



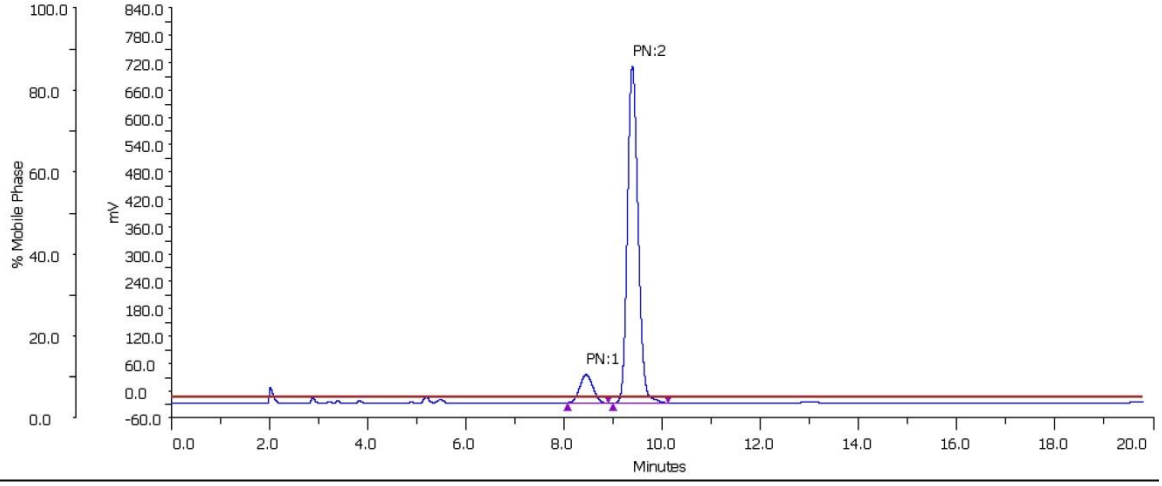
Racemic:



Sample Table

Sample Name	Retention Time (min)	Height (mV)	Area (uVmin x100)	Area %				
Ec8-17	8.668	1326.205	40670042.4778	49.295				
Ec8-17	9.743	1225.8	41833094.6884	50.705				

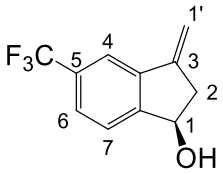
Enantioselective:



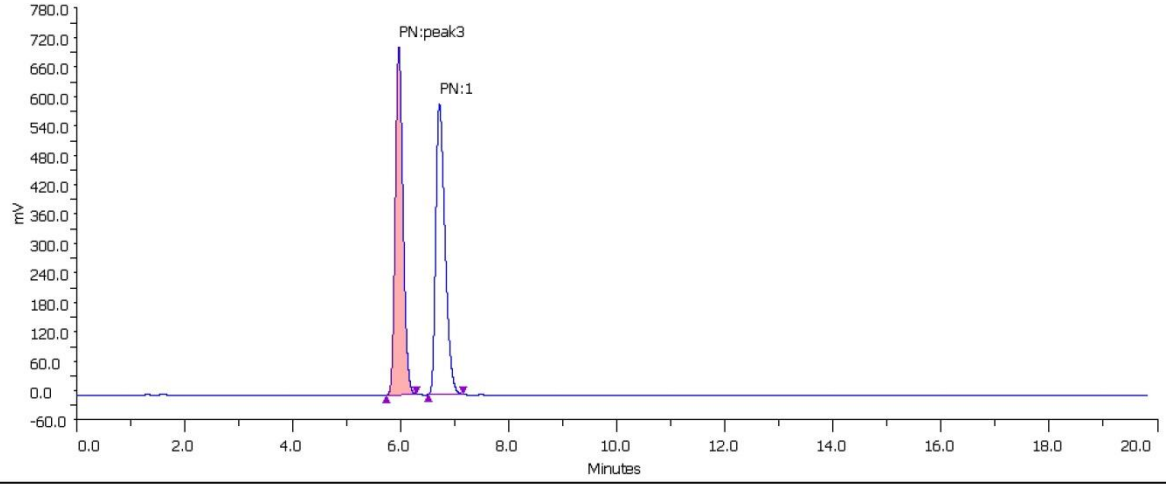
Sample Table

Sample Name	Peak Name	Height (mV)	Retention Time (min)	Area (uVmin x100)	Area %			
EC8-64	1	62.022	8.465	1964344.5205	9.52			
EC8-64	2	740.947	9.406	18669610.3533	90.48			

(1*R*)-2,3-Dihydro-5-trifluoromethyl-3-(methylene)inden-1-ol (**(*R*)-126g**)



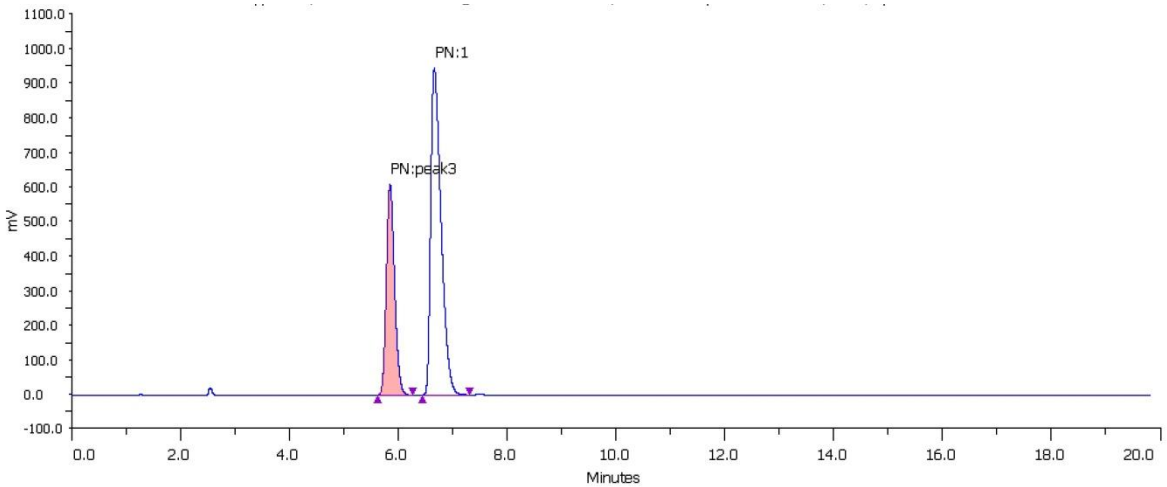
Racemic:



Sample Table

Sample Name	Retention Time (min)	Height (mV)	Area (uVmin x100)	Area %				
EC8-49	5.976	708.536	11762822.9243	50.078				
EC8-49	6.728	592.798	11726407.9203	49.922				

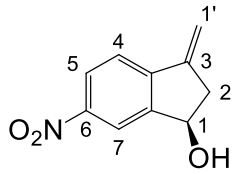
Enantioselective:



Sample Table

Sample Name	Retention Time (min)	Height (mV)	Area (uVmin x100)	Area %				
EC8-70	5.861	609.739	10660361.7414	33.864				
EC8-70	6.677	946.295	20819741.6707	66.136				

(1*R*)-2,3-Dihydro-3-methylene-6-(nitro)-inden-1-ol (**(*R*)-126j**)



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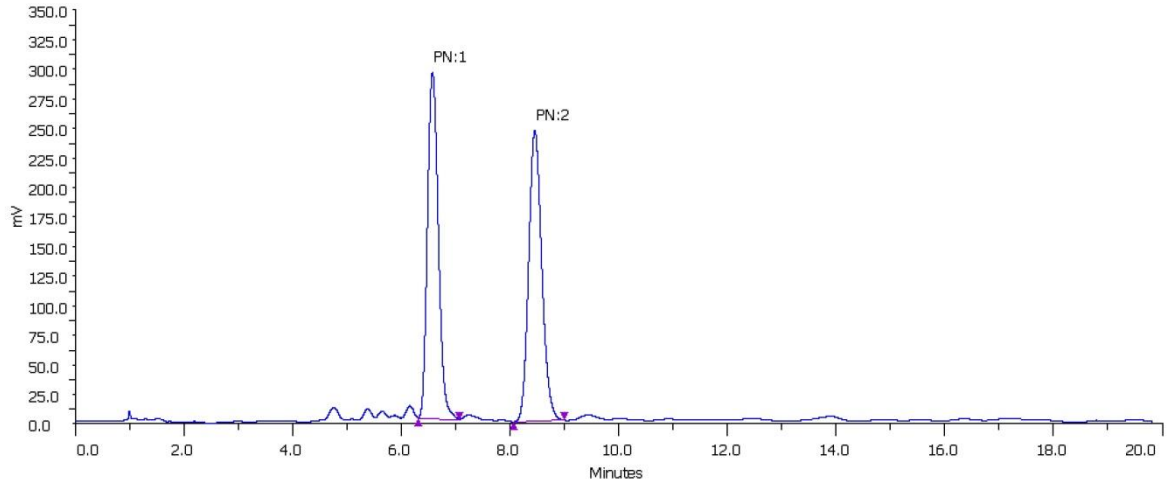
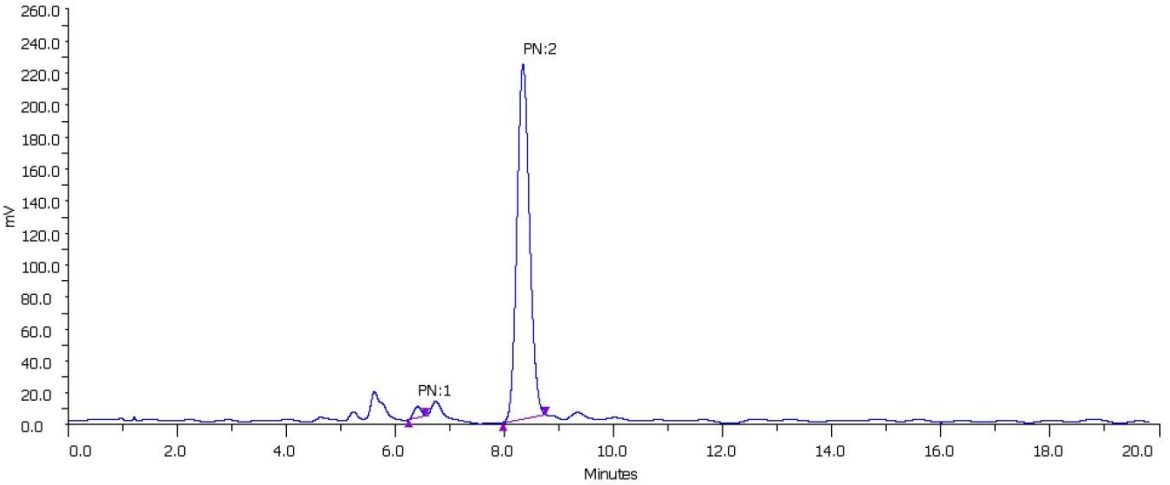


Sample Table

Sample Name	Retention Time (min)	Height (mV)	Area (uVmin x100)	Area %			
EC8-40	6.585	292.551	6788437.5998	49.639			
EC8-40	8.469	246.193	6887157.9122	50.361			

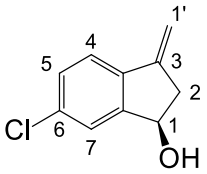
Enantioselective:



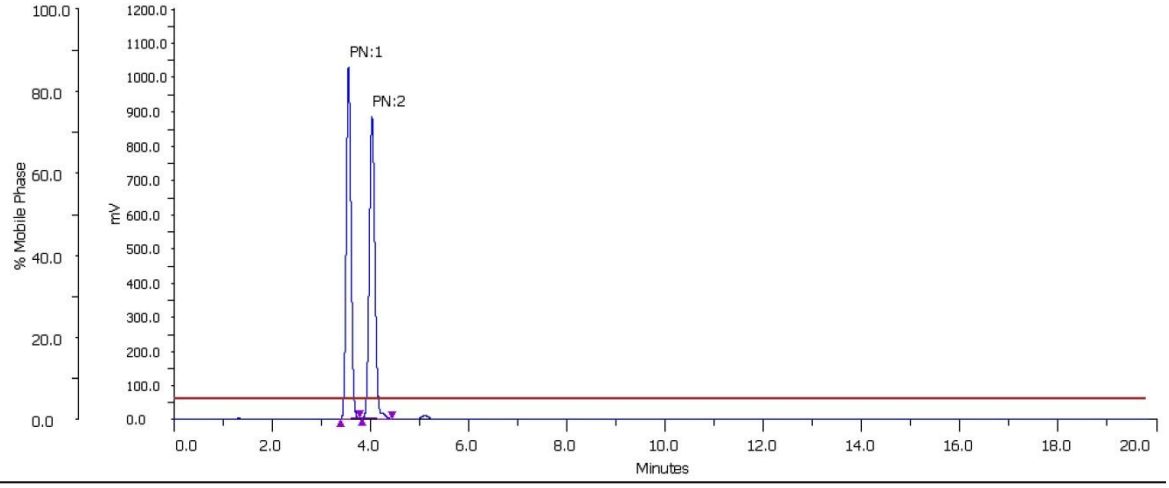
Sample Table

Sample Name	Retention Time (min)	Height (mV)	Area (uVmin x100)	Area %			
EC8-73	6.415	7.133	113310.005	1.874			
EC8-73	8.352	221.971	5932734.1661	98.126			

(1*R*)-6-Chloro-2,3-dihydro-3-(methylene)inden-1-ol (**(*R*)-126k**)



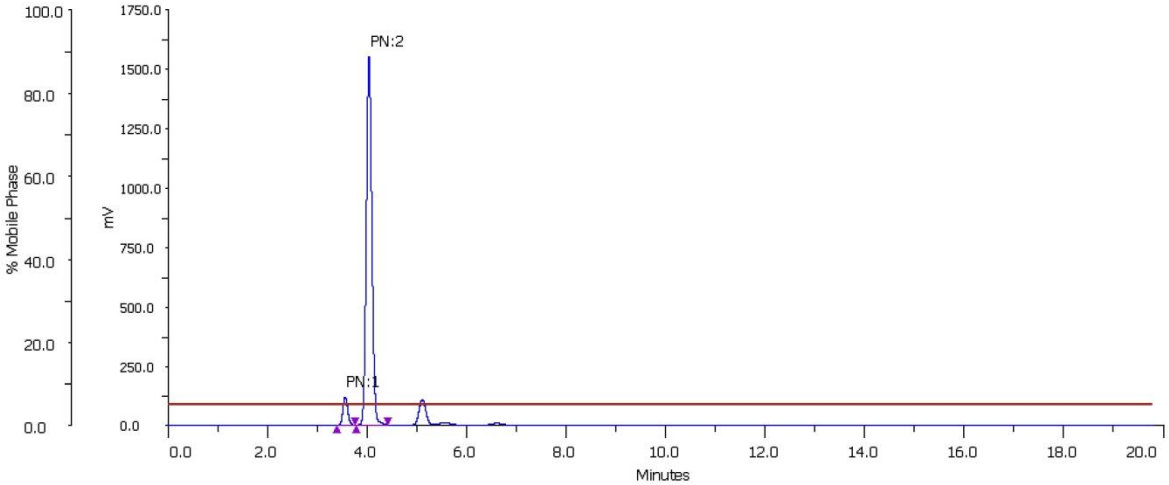
Racemic:



Sample Table

Peak Name	Sample Name	Height (mV)	Retention Time (min)	Area (uVmin x100)	Area %			
1	EC8-57	1027.028	3.565	11504697.4982	49.42			
2	EC8-57	883.49	4.043	11774503.6879	50.58			

Enantioselective:



Sample Table

Sample Name	Height (mV)	Retention Time (min)	Area (uVmin x100)	Area %				
EC8-72	118.021	3.571	1285859.5817	6.033				
EC8-72	1549.515	4.049	20027551.2491	93.967				