Atom Transfer Radical Cyclisation Reactions in Organic Synthesis

A Thesis submitted to The University Manchester for the degree of Doctor of Philosophy in the Faculty of Engineering and Physical Sciences

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CONTENTS

ABSTRACT

A new method for the synthesis of naphthalenes has been recently discovered. The **A**tom **T**ransfer **R**adical **C**yclisation (**ATRC**) of diverse 2−allylphenyl 2',2',2'−trichloroacetates in the presence of a Cu complex affords chloronaphthalenes in good yields using either microwave or thermolytic methods of activation. A mechanism for the benzannulation reaction is proposed and experiments presented in order to validate this hypothesis. The use of 1,3−*bis*(2,6−diisopropylphenyl)imidazolium copper(I) chloride [(IPr)CuCl)] along with other metal carbenes is compared to the already reported CuCl/ligand system.

Since the scope and synthetic utility of this new benzannulation reaction is restricted due to the use of the MW reactor, a solvent in which the thermal reaction can take place is reported, proving its efficiency in the synthesis of a range of substituted naphthalenes.

The potential and versatility of the benzannulation reaction has been investigated. Studies towards the synthesis of gilvocarcin M which contains a tetracyclic aromatic core are presented. Gilvocarcins have potential use as anti−cancer agents and represent a member of the *C*−aryl glycosides found in natural products. Gilvocarcin M is a challenging target because there are a sparse number of total syntheses reported in the literature.

The ATRC reaction of (vinyl)phenyl trichloroacetate has also been investigated, affording the synthesis of functionalised coumarins. The mechanism of this reaction has also been investigated, establishing that, in some cases, a retro−Kharasch reaction is observed.

DECLARATION

No portion of the work referred to in this thesis has been submitted in the support of an application for another degree or qualification of this or any other university or other institute of learning.

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Para mi familia y amigos que tanto me han apoyado

ACKNOWLEDGMENTS

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I owe a great deal to University of Manchester Technical Staff who helped me since the very beginning of my PhD always with a smile; it was a pleasure working with all of you.

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Per finalitzar: David, Pol, Jan, Joel, Marc i Aniol vosaltres sou massa petits per adonar-vos que he estat tant de temps lluny de casa, però no sabeu com de feliç em feu cada cop que hi torno i correu a llençar-vos als meus braços.

ABBREVIATIONS

AIBN	2,2'–Azobis(2–propionitrile)
Ar	General aromatic group
ATRC	Atom transfer radical cyclisation
BDE	Bond dissociation energy
BHQ reaction	**B**ull **H**utchings **Q**uayle reaction
bipy	2,2'–Bipyridyl
BTPPC	Benzyltriphenylphosphonium chloride
cat.	Catalytic
conc.	Concentrated
COSY	^{1}H–^{1}H correlation spectroscopy
Cp_2	Dicyclopentadiene
d	Doublet
δ	Chemical shift
DBU	1,8-Diazabicyclo[5.4.0]undecene
DCE	1,2–Dichloroethane
DBE	1,2–Dibromoethane
de	Diastereomeric excess
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Di–*iso*–butylaluminium hydride
DCC	*N*,*N'*–Dicyclohexylcarbodiimide
Diglyme	Bis(2–methoxyethyl) ether
DMA	Dimethylamine
DMAP	4–Dimethylaminopyridine
DMF	*N*,*N*–Dimethylformamide
DMSO	Dimethylsulfoxide
Dppp	1,3–Bis(diphenylphosphino)propane
DReM	Direct remote metallation
ee	Enantiomeric excess
EI	Electron impact ionisation
ES+/-	Electrospray (positive *or* negative mode)
GC	Gas chromatography
GC/MS	Gas chromatography mass spectrometry
HMPA	Hexamethylphosphoramide
IMes	1,3–Bis–(2,4,6–trimethylphenyl)imidazolium
IPr	1,3–Bis–(diisopropyl)imidazolium
IR	Infrared

LDA	Lithium diisopropylamide
LG	General leaving group
m	Multiplet
M^+	Molecular ion
MOM	Methoxymethyl ether
MS	Molecular sieve
m/z	mass–to–charge ratio
MW	Microwave
Nu	Nucleophile
ND	Not done
NHC	*N*–Heterocyclic carbenes
NMP	*N*–Methyl–2–pyrrolidone
o–	*ortho*–
p–	*para*–
Petrol	Petroleum ether (40 – 60 ºC)
PEPPSI™	Pyridine–Enhanced Precatalyst Preparation Stabilisation and Initiation
PG	General protecting group
Prod.	Product
Py	Pyridine
q	Quartet
qn	Quintet
quant.	Quantitative
R	General alkyl group
R_f	Retention factor
rt	Room temperature
s	Singlet
satd. aq.	Saturated aqueous
SIPr	1,3–Bis–(2,6–Diisopropylphenyl)imidazolidene
SM	Starting material
t	Triplet
TBAB	Tetrabutylammonium bromide
TBS	*tert*–Butyldimethylsilyl
TBTH	Tributyltin hydride
Tf	Triflate
TFA	Trifluoroacetic acid
TFA–d	Deuterotrifluoro acetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TM	Transition metal

TMAP	Phenyltrimethylammonium tribromide
TMS	Trimethylsilyl
Tp	Tris(1–pyrazolyl)borate
X	General leaving group

PART I: INTRODUCTION AND RESULTS AND DISCUSSION

CHAPTER 1: INTRODUCTION

1.1 ATRC REACTIONS

Atom transfer reactions include a large range of radical reactions in which a C–heteroatom or heteroatom–heteroatom bond is added across a multiple bond.[1] The first example of an atom transfer radical addition reaction was reported by Kharasch *et al*.[2] in 1945 in which CCl_4 was found to react with 1–octene in the presence of radical initiators. Kharasch suggested a free radical process for these reactions which proceed *via* initial homolysis of the C–Cl bond in CCl_4 (Figure 1.1).

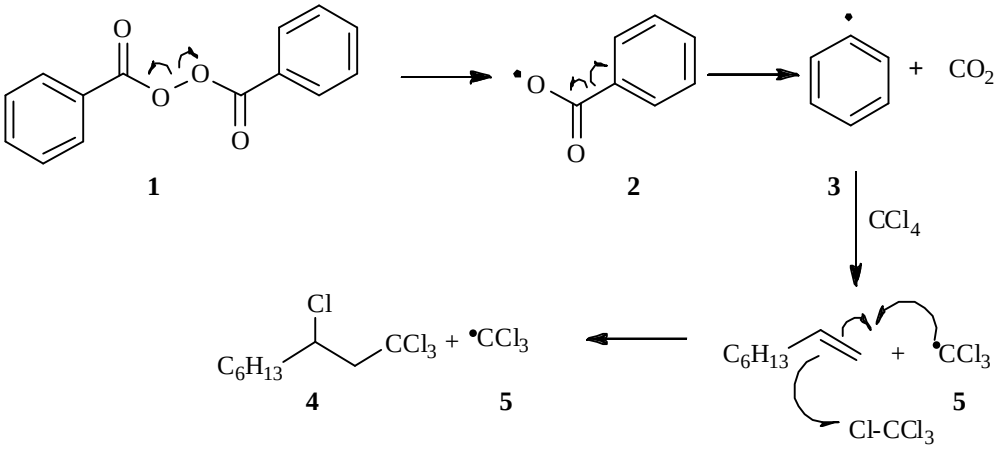
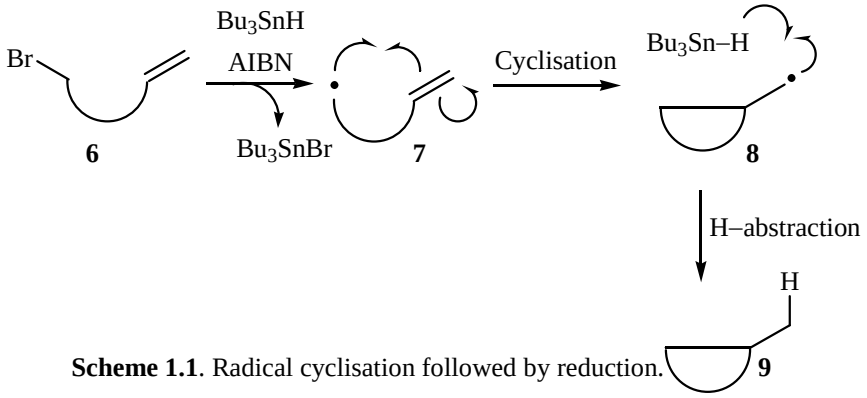


Figure 1.1. Proposed radical mechanism for the addition of CCl_4 to 1–octene.

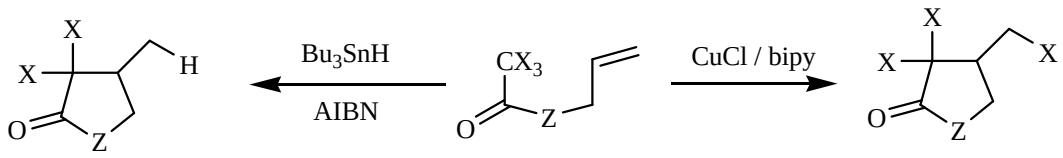
In the intervening years free radical reactions have been widely adapted by the synthetic chemist where their application to the synthesis of carbocyclic and heterocyclic systems is now commonplace. The most commonly adopted procedures involve a radical chain reaction which utilises either tin (TBTH) or silicon hydrides in the initial radical–generating step. Radical generation followed by cyclisation and termination *via* H–abstraction from the hydride reagent results in the overall reductive cyclisation of the substrate **6** (Scheme 1.1).[3]



Scheme 1.1. Radical cyclisation followed by reduction.

A potentially more versatile variant of this process involves radical halogen abstraction rather than hydrogen abstraction in the propragation step – a process which constitutes an **A**tom **T**ransfer **R**adical **C**yclisation (**ATRC)** reaction. Previous work within the Quayle group sought to establish the potential benefits, if any, of **ATRC** cycles where simple transition metal complexes (*e.g.* based on Cu(I)) were employed in both the radical initiation and propagation steps of the cyclisation reaction. The potential advantages of the metal–catalysed **ATRC** reactions over standard TBTH mediated cycles include:

- the reduction of the substrate in copper catalysed reactions is less pronounced than in the case of TBTH–mediated reactions. This consideration is especially important where the rate of addition of the radical intermediate to the alkene is slow;
- only catalytic quantities of inexpensive copper(I) chloride are required;
- unlike in the case of TBTH–mediated reactions where (stoichiometric) quantities of difficult to remove organo–tin by–products are produced, TM catalysts can be more easily sequestered or even recycled;
- compared to the TBTH–mediated cycles, **ATRC** reactions result in the generation of functionalised products which may be used in subsequent transformations[4] (Scheme 1.2, *i.e.* **ATRC** reactions are "atom economical");
- the use of stoichiometric and lipophilic tin reagents is minimised due to their toxicity.



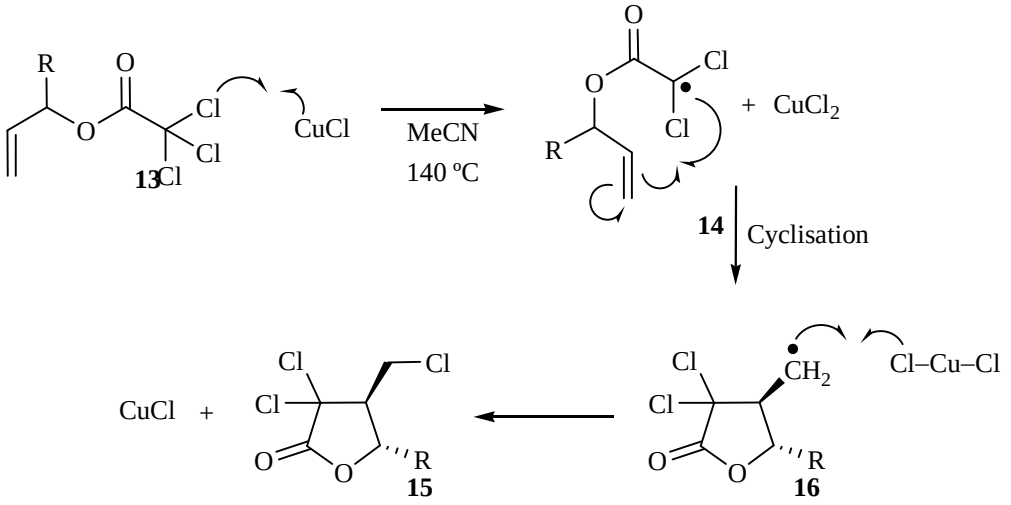
X = halogen, Z = O, NR

10 **11** **12**

Scheme 1.2. Radical reaction with Bu_3SnH versus CuCl.

The use of Cu(I) complexes in **ATRC** reactions implies a redox process which cycles between copper(I) and copper(II) species. In these reactions the metal has high affinity towards atom/group X but low affinity for H or alkyl radicals.

Although **ATRC** reactions of 2',2',2'–trichlorinated carbonyl compounds have been reported using a variety of different transition metal complexes,[5] those employing copper–based catalysts are most common.[6] A generalised mechanism for copper(I) chloride catalysed **ATRC** reactions is depicted in Scheme 1.3. Reaction of trichloroacetate **13** with copper(I) initiates a radical cascade, generating the radical species **14** with concomitant formation of copper(II) chloride. Cyclisation of secondary radical **14** to the primary radical **16** followed by halogen abstraction from copper(II) chloride regenerates copper(I) chloride and also results in the formation of lactone **15**. Such cyclisation reactions can take place with high levels of diastereoselectivity.[7] These cyclisation reactions are very attractive because they offer the possibility of transforming structurally simple compounds into more complex products in a single operation.



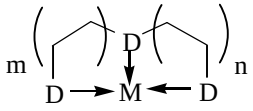
SM	R	Product	Yield
13a	Me	**15a**	78%
13b	*i*–Pr	**15b**	96%

Scheme 1.3. Radical cyclisation of trichloroacetate **13**.

A wide range of copper complexes of general structure **17** have been used, with variable success, in **ATRC** reactions (Figure 1.2). As part of a programme of research aimed at defining the structural parameters required to facilitate **ATRC** with Cu catalysts, we have recently shown that the ligand **18** with CuCl (see Figure 1.3) enables *in situ* generation of lipophilic Cu(I) complexes **17** which are soluble in organic solvents such DCE and are active in promoting **ATRC** reactions.

D = donor

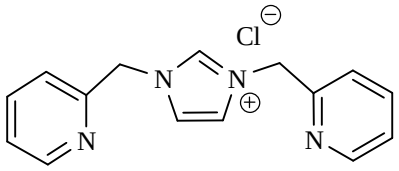
M = metal centre



17

Figure 1.2. Tridentate skeleton generated with pincer ligands.

To date, we have been unable to determine the structure of the complex generated from the reaction between ligand **18** and copper(I) chloride (Figure 1.3) but we mused whether the active catalytic entity in such reactions was in fact a NHC–Cu complex such as **19** rather than a simple pyridyl–Cu σ–complex.



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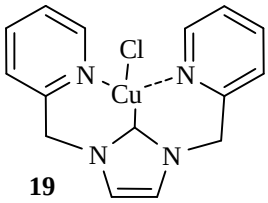
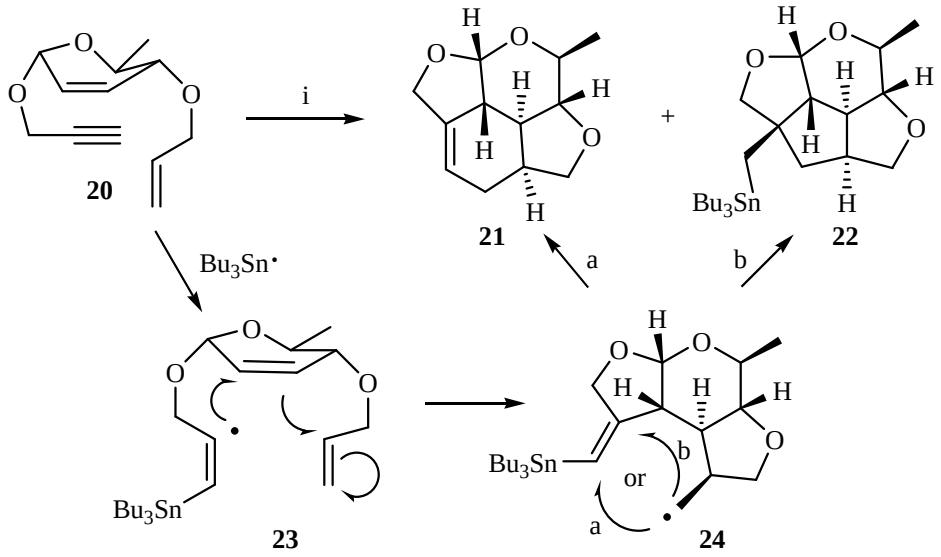


19

Figure 1.3. Suggested coordination between ligand **18** and CuCl.

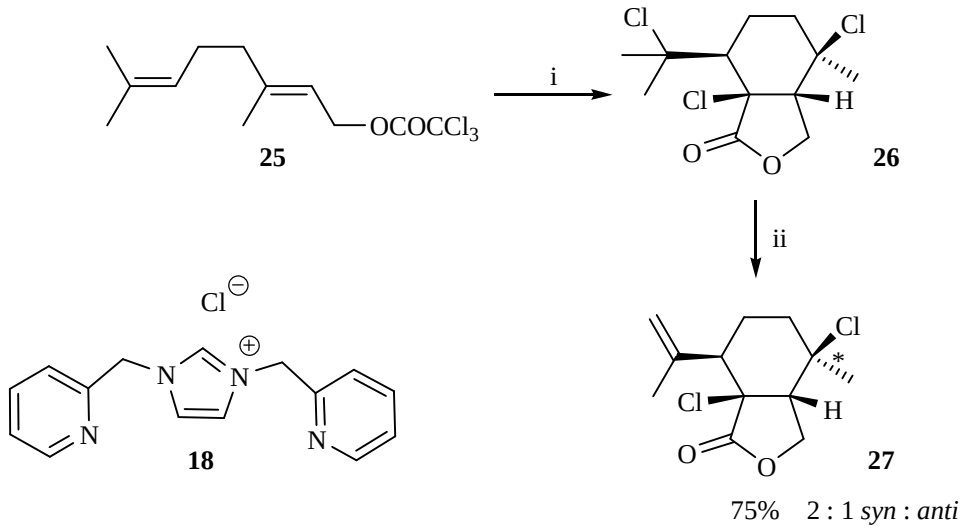
1.1.1. APPLICATION OF ATRC REACTIONS

The use of radical cyclisation reactions for the synthesis of heterocycles is now a well established and a frequently used methodology. Radical cyclisation reactions are particularly useful in this regard as they usually permit the cyclisation of functionalised substrates with high levels of chemoselectivity; frequently such reactions also proceed with useful levels of stereoselectivity. These characteristics together with the use tandem radical reactions enable the rapid synthesis of complex intermediates from simple acyclic substrates. For example, the TBTH–initiated radical cascade reaction of **20** (Scheme 1.4) afforded tetracycles **21** and **22** in a single synthetic operation.[8] This reaction proceeds *via* the generation of a vinyl radical **23** by addition of $Bu_3Sn^{\cdot}$ to the alkyne moiety of **20**. Subsequent tandem 5–*exo*–*trig* cyclisation of vinyl radical **23** generates the primary radical **24** which affords a mixture of tetracycles **21** and **22** *via* competing 5–*exo*–*trig* or 6–*endo*–*trig* cyclisation pathways (**21** : **22** in a 56 : 44 ratio).



Scheme 1.4. Radical cyclisation of alkene **20**. i. Bu_3SnH (syringe pump addition), AIBN, toluene, reflux, 38% (**21** : **22**, 56 : 44 ratio).

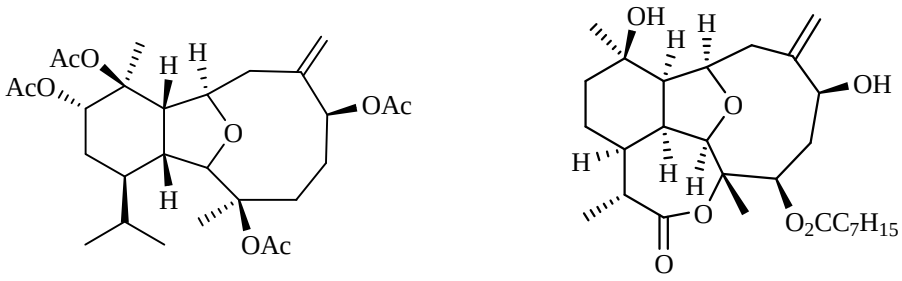
The application of **ATRC** reactions to the synthesis γ–butyrolactams is reasonably well established. However, the synthesis of γ–butyrolactones and medium–sized rings by this methodology remains something of a curiosity. Previously the Quayle group[9] had demonstrated that **ATRC** reaction of the readily available trichloroacetate **25** with CuCl and ligand **18** undergoes cyclisation to the 2–oxabicyclo [4.3.0]nonane **26** in 75% isolated yield *via* a tandem 5–*exo*–*trig*–6–*exo*–*trig* cyclisation–elimination sequence, obtaining lactone **27** (Scheme 1.5).



75% 2 : 1 *syn* : *anti*

Scheme 1.5. ATRC reaction of trichloroacetate **25** with ligand **18**. i. CuCl (5 mol%), ligand **18** (5 mol%), DCE, 90 ºC, 3.5 h. ii. SiO_2.

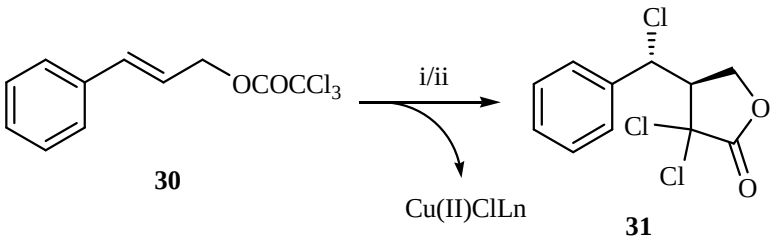
A diverse family of natural products are known to contain the 2–oxabicyclo [4.3.0]nonane ring system and many of these such as eunicellin (**28**) and briarellin A (**29**), Figure 1.4) exhibit interesting biological profiles.[10]



eunicellin **28** briarellin A **29**

Figure 1.4. Natural products containing the 2–oxabicyclo[4.3.0]nonane ring systems.

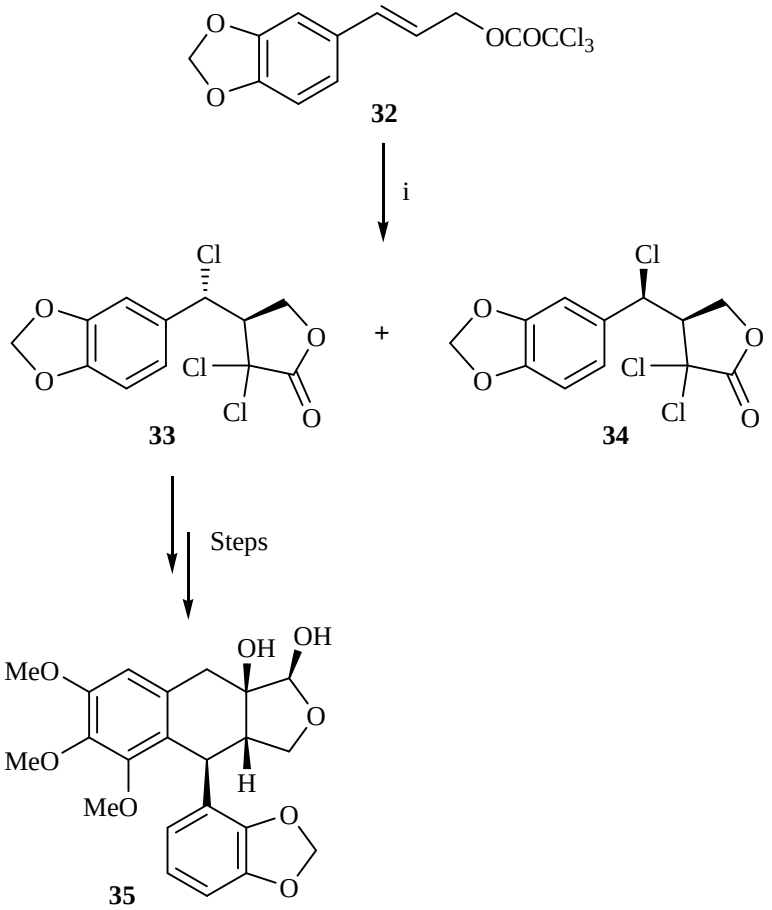
Previously, the Quayle group[11] had demonstrated that the 1st generation Grubbs' catalyst promotes cyclisation of trichloroacetate **30** into lactone **31** with high stereoselectivity, affording the *threo*–isomer **31** as a single product in a 54% yield (Scheme 1.6).[12] Subsequent investigations showed that this stereochemical outcome was independent of the catalyst used for the cyclisation; the same result is achieved with CuCl (Scheme 1.6). The **ATRC** reaction proceeds with good levels of stereocontrol, a feature that may be of use in subsequent synthetic investigations.



30 **31**

Scheme 1.6. Reagents and conditions for the cyclisation of trichloroacetate **30**. i. Grubbs' 1 (5 mol%), toluene, 3.5 h, reflux, 54%. ii. CuCl (5 mol%), dHbipy (5 mol%), DCE, 80 ºC, 89%, (*dr* > 95 : 5).

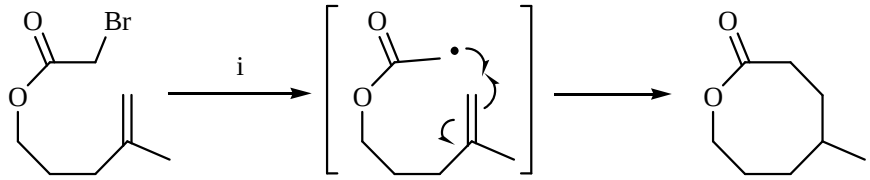
The trichloroacetate **32**, which is readily accessible from piperonal in three steps, affords lactones **33** and **34**, as a 19 : 1 mixture of diastereoisomers, when treated with CuCl.dHbipy in DCE at reflux (Scheme 1.7). Lactone **33** proves to be a useful synthetic intermediate and can, for example, be converted into lactol **35** using standard methodology.[13]



32 **33** **34** **35**

Scheme 1.7. Obtaining *anti* and *syn* trichloroacetates **33** and **34**. i. CuCl (5 mol%), dHbipy (5 mol%), DCE, 3.5 h, reflux.

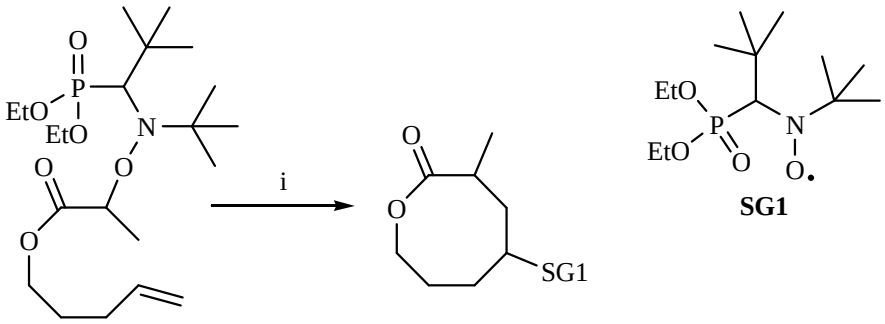
The synthesis of medium ring lactones and lactams by *endo* cyclisation (8– to 12–membered rings) continues to be an active area of research due to the large number of natural products that contain these structural motifs. In the example shown below (Scheme 1.8), α–bromoester **36** leads to lactone **38** *via* an 8–*endo* cyclisation of α–ester radical **37**.[14]



36 **37** **38**

Scheme 1.8. Radical cyclisation of lactone **36**. i. Bu_3SnH (syringe pump addition), AIBN, benzene, reflux, 38% (uncyclised reduced product 18%).

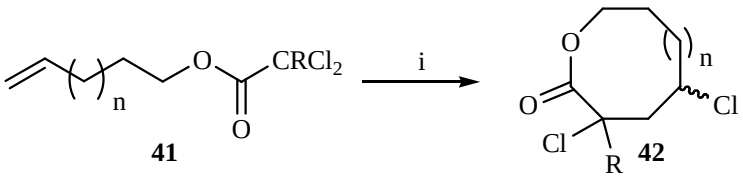
Gigmes *et al.*[15] have developed monocomponent initiators for the synthesis of lactones and lactams which utilise the homolysis of alkoxyamines such as SG1 in the key initiation step. This mode of initiation is "tin–free" and has been applied successfully to the synthesis of 8–membered ring lactones such as **40** (Scheme 1.9).



39 **40** **SG1**

Scheme 1.9. Synthesis of 8–membered ring lactone **40**. ^{t}BuOH, N_2, 110 °C, 12 h.

Medium–size lactones have also been prepared from trichloroacetates using CuCl–bipy catalysed **ATRC** reactions (Scheme 1.10).[16] In all cases examined, cyclisation *via* an *endo*–mode addition was observed.

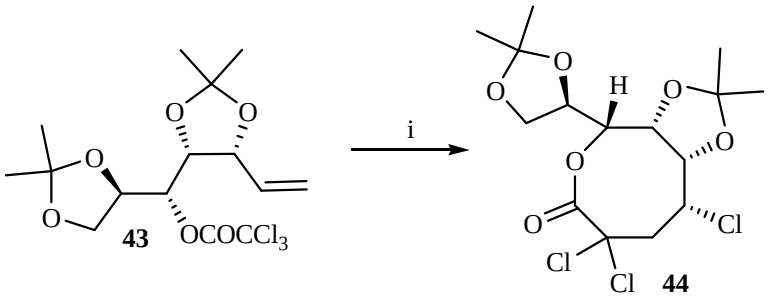


i. CuCl (30 mol%), bipy (30 mol%), DCE (0.1 M), reflux.

SM	R	n	Prod.	Yield
41a	Cl	1	**42a**	60%
41b	Cl	2	**42b**	59%
41c	H	1	**42c**	75%
41d	H	2	**42d**	57%

Scheme 1.10. Synthesis of lactones *via* radical reaction.

A variety of 8–membered ring lactones were prepared using this methodology. Most significantly, the diastereoselective synthesis of highly functionalised lactones such as **44** from the carbohydrate precursor **43** is possible using this approach (Scheme 1.11). It should be noted however that good yields of lactone **44** were only obtained using relatively high catalyst loadings (30 mol%) and at elevated reaction temperatures.

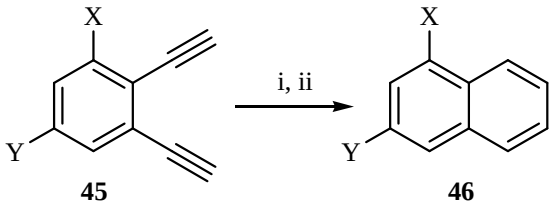


Scheme 1.11. Synthesis of highly functionalised lactone **44**. i. CuCl (30 mol%), bipy (30 mol%), DCE (0.1 M), reflux.

1.2 SYNTHESIS OF AROMATIC COMPOUNDS

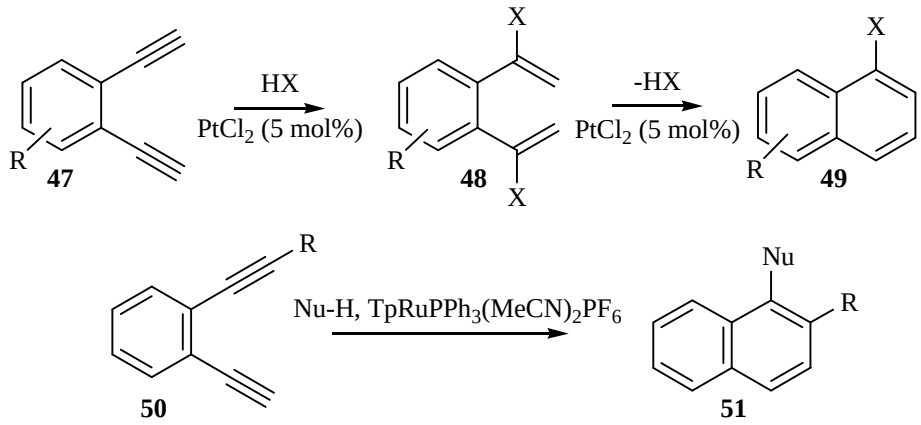
The development of new synthetic routes to aromatic compounds has recently been the subject of intense investigation as these structural motifs are prevalent in new materials, the design of molecular devices, and the synthesis of natural products and scaffolds.

A biologically inspired synthesis of substituted naphthalenes (such as is reported here) utilises the Bergman cyclisation of 1,2–bis(ethynyl)benzenes (Scheme 1.12).[17] The use of the Bergman cyclisation has been largely under–developed but has much potential for the synthesis of highly functionalised aromatics[18] and provides a complementary route to the more traditional Friedel–Crafts[19] approach to substituted naphthalenes.



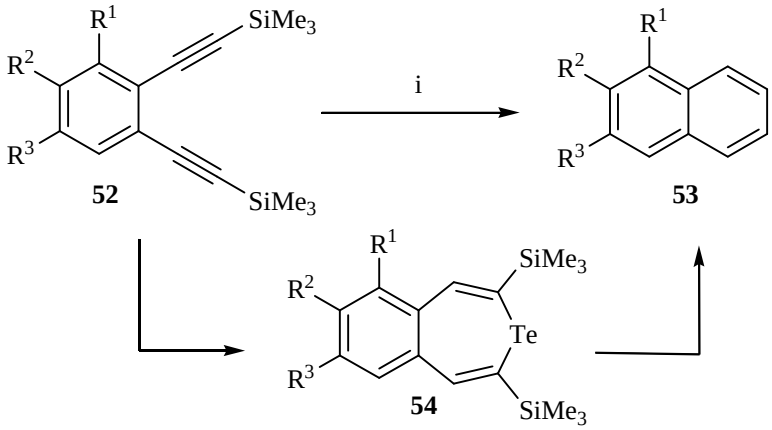
Scheme 1.12. Bergmann reaction**..** i. Heat. ii. 1,4-Cyclohexadiene.

For example Liu *et al.* reported the use of a Bergman cyclisation in the synthesis of a variety of substituted naphthalenes in high yields,[20] as briefly outlined below (Scheme 1.13).



Scheme 1.13. Substituted naphthalenes *via* the Bergman cyclisation

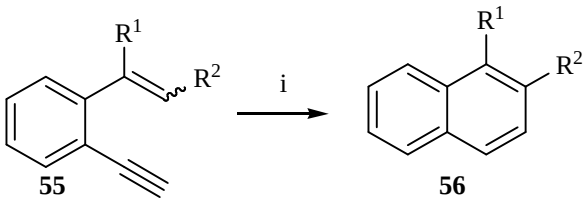
A variation on this theme includes the cycloaromatisation of *bis*–acetylenes mediated by tellurium.[21] This reaction is compatible with some of the more common functional groups, enabling the synthesis of functionalised aromatics, suitable for further manipulation. Of note is the observation that this sequence is devoid of side reactions (*e.g.* polymerisation reactions), even when reactions are performed at relatively high concentrations (>4 M, Scheme 1.14).



Entry	R^1	R^2	R^3	Yield
1	H	n–Hexyl	n–Hexyl	65%
2	H	OEt	OEt	62%
3	Br	H	^{t}Bu	66%

Scheme 1.14. Tellurium mediated cyclisation. i. Benzene, Te^o (1.1 equiv.), NaOH (10% aqueous), N_2H_4 (2 equiv.), $NaBH_4$ (1.1 equiv.), Aliquat 464, 40 ^{o}C, sonication, 8 h.

Cycloisomerisation of ene–ynes has also been effected by the use of $W(CO)_5$·THF. Again this methodology provides a simple and potentially general approach to polyfunctionalised aromatic systems[22] (Scheme 1.15) although, to date, applications in a synthetic context have not been reported.

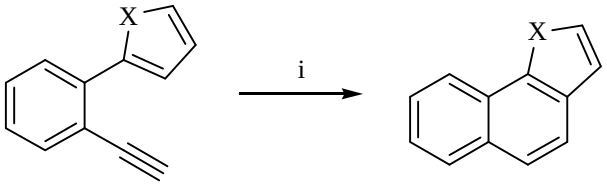


55 **56**

i. $W(CO)_5$·THF (5 mol %), THF (0.1 M), 3–5 days.

Entry	R^1	R^2	Yield
1	OTBS	H	100%
2	H	H	68%[a]
3	Me	COOEt	100%

a. 30 mol % catalyst was used.



57 **58**

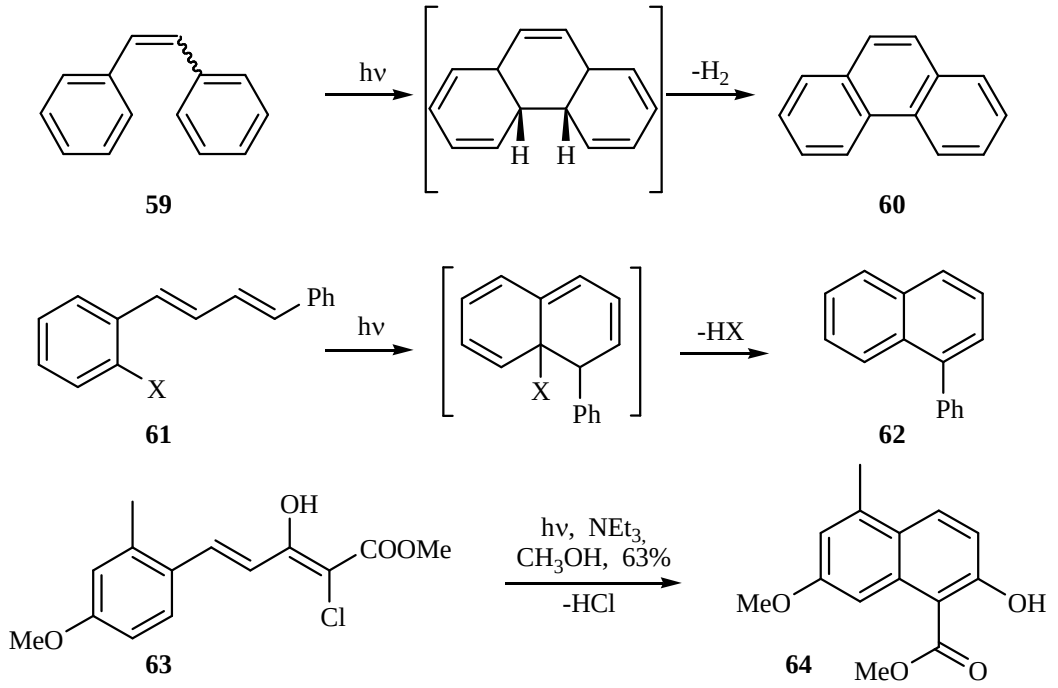
X = O 82%[a]

X = S 82%

i. $W(CO)_5$·THF (5 mol %), THF (0.1 M), 3–5 days. a. 100 mol% of $W(CO)_5$·THF was used.

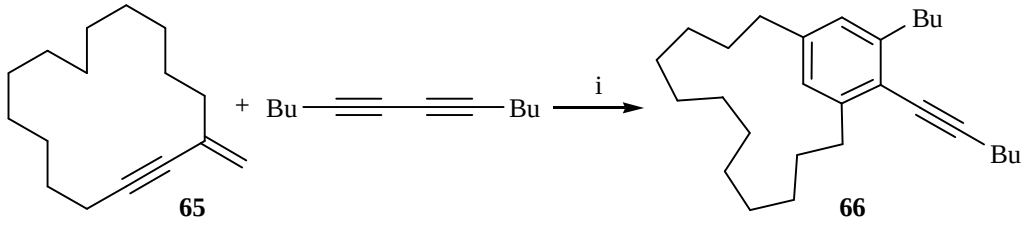
Scheme 1.15. Synthesis of naphthalenes and polyaromatic compound using $W(CO)_5$·THF as catalyst.

The synthesis of extended polycyclic aromatic compounds has been extensively reviewed by Hopf *et al.*[23] These workers have shown the wide range of synthetic strategies successfully employed in the preparation of aromatic structures from readily available starting materials. Benzannulation approaches to bi– and tri–cyclic systems have undergone much development over the last decade. The well–established photocyclisation of stilbenes[24] to form anthracenes[25] **60** and biaryl–naphthyls[26] (Scheme 1.16) was employed by Myers *et al.* in the synthesis of naphthalene **64**,[27] a key intermediate in the synthesis of the chromophoric core of the natural chromoprotein antitumor agent neocarzinostatin.



Scheme 1.16. Stilbene photocyclisation

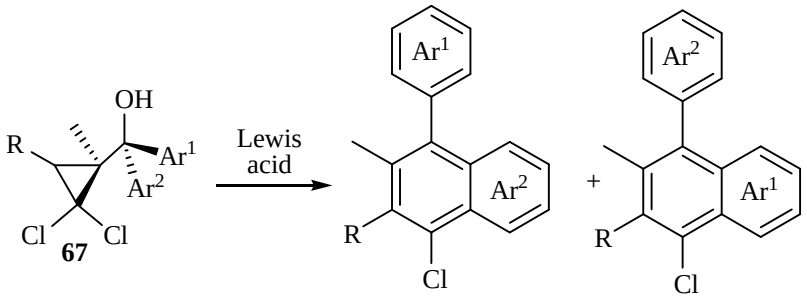
The ongoing work of Gevorgyan *et al.* on the palladium catalysed enyne–diyne cross–benzannulation reaction have provided a new stratagem for the preparation of both alkyne–substituted aromatics like benzene **66**, and novel cyclophanes, by an intramolecular process (Scheme 1.17).[28] Gevorgyan *et al.* have written a comprehensive review of the recent advances in transition metal–catalysed annulations.[29]



Scheme 1.17. Palladium catalysed benzannulation reaction. i. $Pd(PPh_3)_4$ (5 mol%), THF (1 M), 100 °C, overnight, 78%.

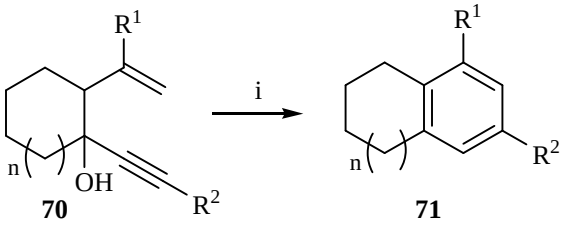
Tanabe and co–workers have reported an efficient synthesis of highly substituted arylnaphthalenes using a Lewis acid–promoted regioselective benzannulation of dichlorocyclopropane **67** (Scheme 1.18).[30] The choice of Lewis acid is critical in controlling the regiochemical outcome of the reaction. Hence, by judicious

selection of the Lewis acid promoter (either $TiCl_4/SnCl_4$ or silyltriflates), unsymmetrical arylnaphthalenes **68** and **69** can be prepared with excellent regiocontrol and in moderate to good yields (40 – 91%).



Scheme 1.18. Tanabe's regiocontrolled benzannulation.

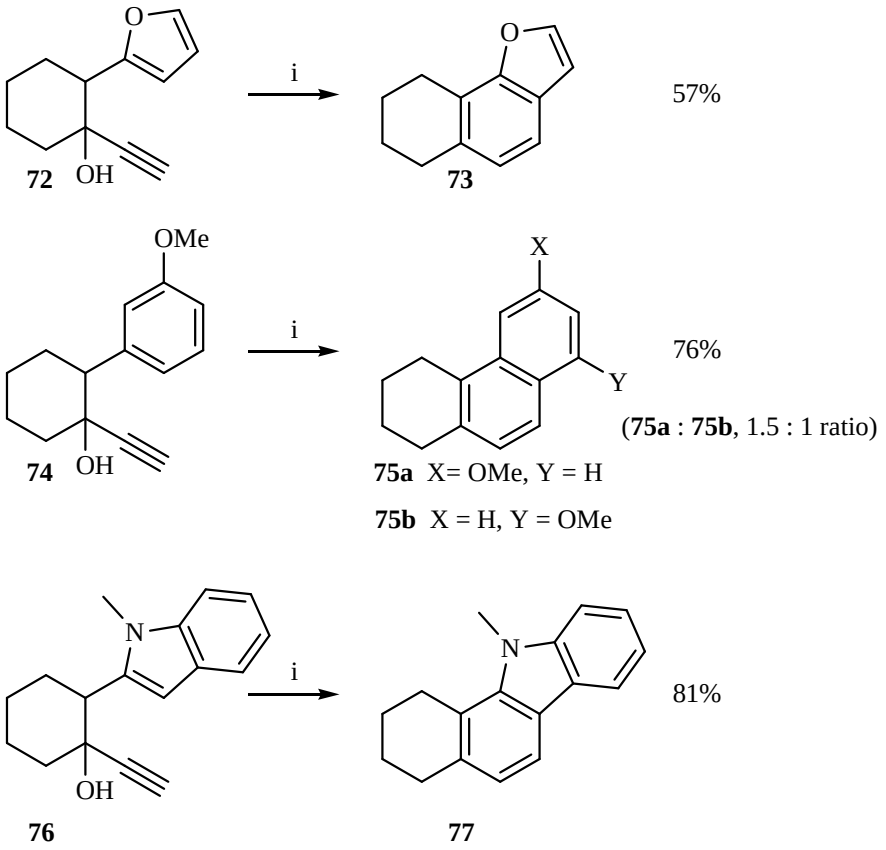
More recently, the burgeoning use of gold catalysis in organic synthesis has resulted in the development of a novel gold(I)–catalysed benzannulation reaction sequence starting from propargylic alcohols **70**.[31] These reactions proceed under mild conditions and provide a very general method for the synthesis of *meta*–substituted aromatic rings **71** in good overall yields (Scheme 1.19).



Entry	R^1	R^2	n	Yield
1	Me	H	0	28%
2	Ph	H	1	84%
3	OEt	H	1	12%
4	Me	Ph	2	65%
5	Me	Me	1	77%

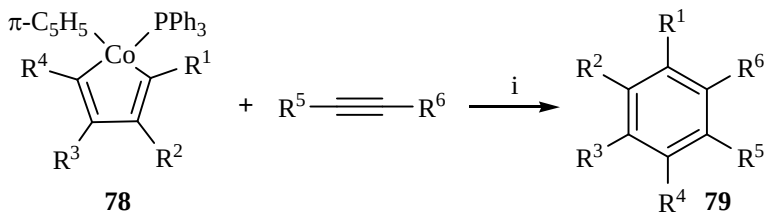
Scheme 1.19. Gold catalysis for the synthesis of aromatic compounds. i. $Au(PPh_3)Cl$ (2.5 mol%), AgOTf (2.5 mol%), CH_2Cl_2, 23 ºC, 18 h.

The conditions employed in this particular reaction sequence are also compatible with electron–rich aromatics such as furans *e.g.* **72** and indoles *e.g.* **76** enabling the rapid synthesis of functionalised scaffolds (Scheme 1.20).



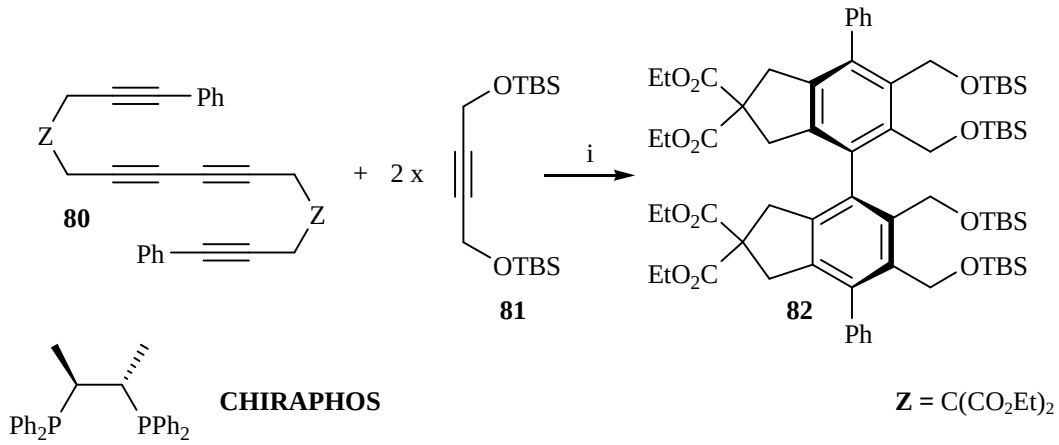
Scheme 1.20. Synthesis of electron–rich aromatics in the presence of silver(I). i. AgOTf (2.5 mol%), $Au(PPh_3)Cl$ (2.5 mol%), CH_2Cl_2, 23 ºC, 18 h.

In 1948, the Ni–mediated cycloisomerisation of acetylene was reported. In this reaction benzene is prepared *via* a formal [2+2+2] cycloaddition reaction.[32] Subsequently the Co–mediated cyclotrimerisation of diphenylacetylene was disclosed, an observation which constituted the first *practical* example of a [2+2+2] cycloaddition process leading to the synthesis of substituted aromatics (Scheme 1.21).[33]



Scheme 1.21. Co–mediated cyclotrimerisation. i. Benzene, 70 – 100 ºC, 16 – 59%.

Since this pioneering work, the synthesis of substituted aromatic rings using variations of the basic metal–mediated "[2+2+2] cycloaddition" concept have been widely developed. Recently Shibata *et al.* have demonstrated that chiral iridium complexes can catalyse a consecutive and enantioselective [2+2+2] cycloaddition of polyynes to give axially chiral compounds (Scheme 1.22).[34]



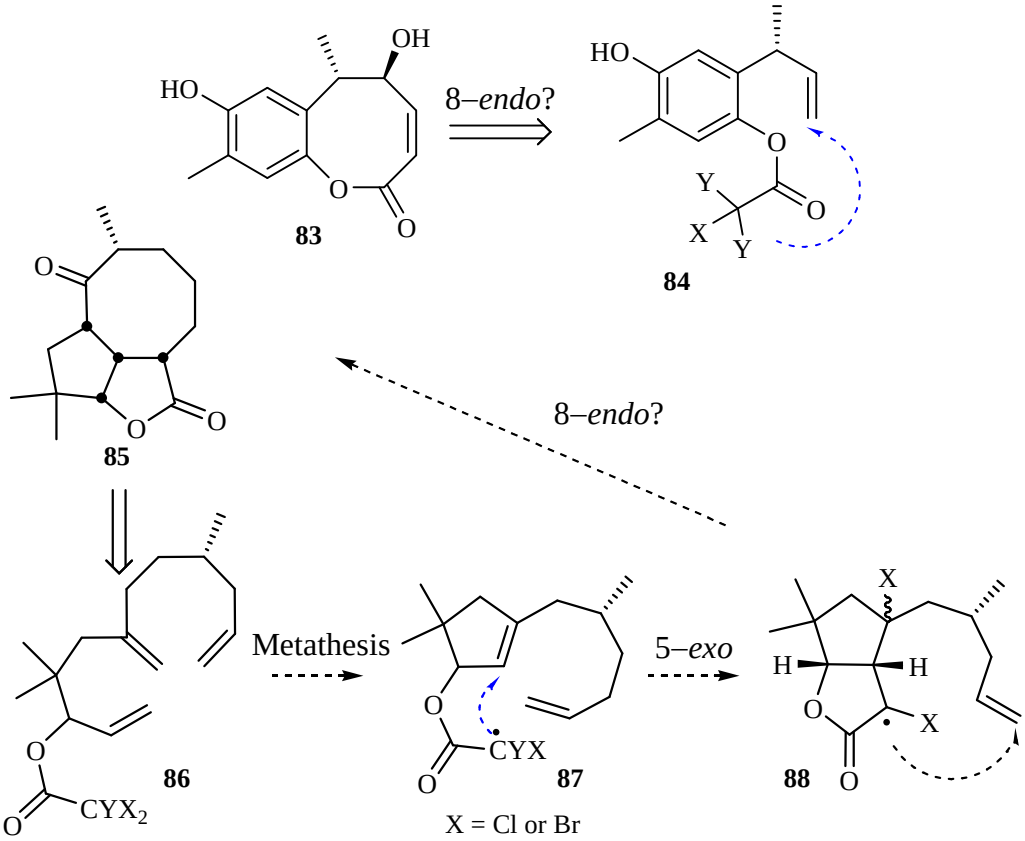
Scheme 1.22. Synthesis of axially chiral compounds. i. $[IrCl(cod)]_2$ + 2CHIRAPHOS (20 mol%), xylene, 100 ºC – reflux, 3 h, 49% (89% *ee*). (Z = $C(CO_2Et)_2$).

Although there are now a variety of procedures for the synthesis of aromatics from acyclic precursors, many of these are not general or require expensive catalysts or even stoichiometric promoters. It is in this context that the development of new synthetic procedures for the (regiocontrolled) synthesis of functionalised aromatics should be framed.

CHAPTER 2: STUDIES OF THE BHQ REACTION

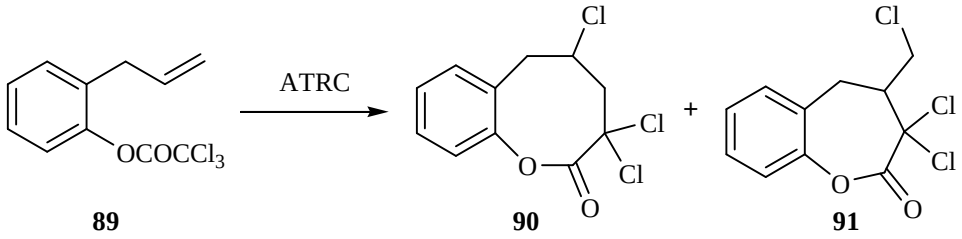
2.1 DISCOVERY OF A NEW BENZANNULATION REACION: The "BHQ" Reaction

As a continuation of our interest in the application of **ATRC** reactions in organic synthesis we wished to investigate whether such processes could be of use in the synthesis of oxocine–based natural products. This entailed the synthesis of an 8–membered ring lactone **83** *via* the 8–*endo* cyclisation of the acetate **84**. Furthermore, we wished to determine if more complex structures such as lactone **85** could be accessed *via* a tandem metathesis–**ATRC** sequence using our recently disclosed studies on "catalysis economy" (Scheme 2.1).[13,35]



Scheme 2.1. Project outline: Potential synthetic applications of **ATRC** and tandem metathesis–**ATRC** sequences.

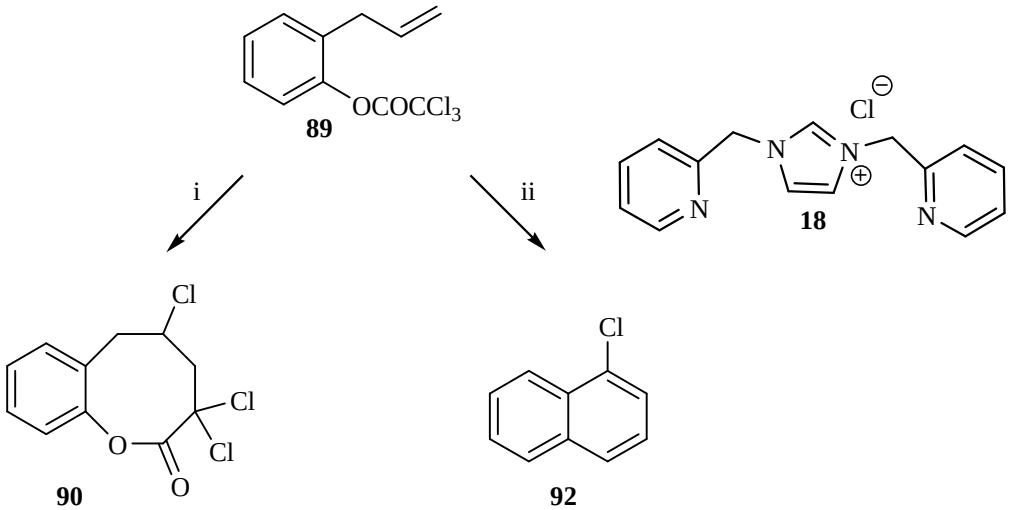
In order to validate the viability of these reactions the radical cyclisation of **89** was attempted. In principle the **ATRC** reaction of trichloroacetate **89** could proceed by way of a 7–*exo* or 8–*endo* pathway to give lactams **91** and **90** respectively (Scheme 2.2).[36] We also believed that trichloroacetate **89** would be a good substrate with which to screen potential catalysts for **ATRC** reactions.



89 **90** **91**

Scheme 2.2. 8–*endo*–*trig vs* 7–*exo*–*trig* mode of cyclisation of aryl trichloroacetates.

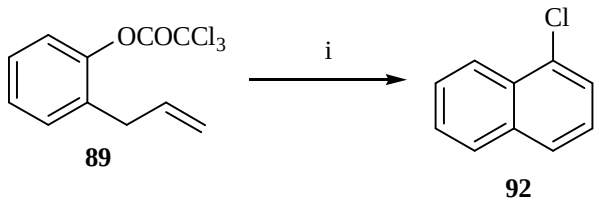
When attempted, the copper–catalysed **ATRC** reaction of the readily available trichloroacetate **89**, proved to be quite sluggish (CuCl (5 mol%), ligand **18** (5 mol%), toluene, reflux, 48 h, 95%).[37] However, after prolonged reaction times lactone **90** could be isolated in a good overall yield together with the formation of a wholly aromatic by–product, which was later identified as 1–chloronaphthalene (**92**). We presumed that lactone **90** was the product of an 8–*endo*–*trig* reaction[38] whereas the mode of formation of naphthalene **92** was more contentious. Subsequent studies revealed that conducting the **ATRC** reaction of trichloroacetate **89** for 120 h in refluxing toluene afforded 1–chloronaphthalene (**92**) as the sole product in a 23% yield (Scheme 2.3).



Scheme 2.3. Cyclisation reaction of trichloroacetate **89** after 48 h and 120 h. i. CuCl (5 mol%), ligand **18** (5 mol%), toluene, reflux, 48 h, 95%. ii. CuCl (5 mol%), ligand **18** (5 mol%), toluene, reflux, 120 h, 23%.

After much experimentation we observed that the reaction time for transformation of trichloroacetate **89** into naphthalene **92** could be drastically reduced (to 2 h) when the reaction was conducted under microwave irradiation at 200 ºC using

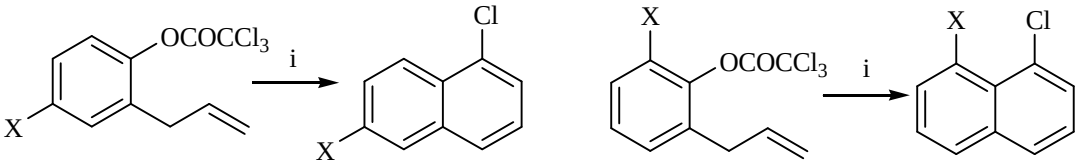
DCE as solvent. In this particular case the isolated yield of naphthalene **92** also rose to 84% (Scheme 2.4).



89 **92**

Scheme 2.4. Benzannulation reaction of trichloroacetate **89** under MW irradiation. i. CuCl (5 mol%), ligand **18** (5 mol%), DCE, MW, 220 ºC, 2 h, 84%.

Subsequent investigations validated the generality of this new naphthalene synthesis. This new benzannulation reaction (the **BHQ** reaction) appeared to be tolerant of many of the more common functional groups (esters, aldehydes, nitro *etc*.), enabling the highly regiospecific synthesis of functionalised aromatic systems from readily available intermediates (Scheme 2.5).



89a X = F
89b X= CO_2Me
89c X = OMe
89d X = COMe
89e X = NO_2
89f X = Me

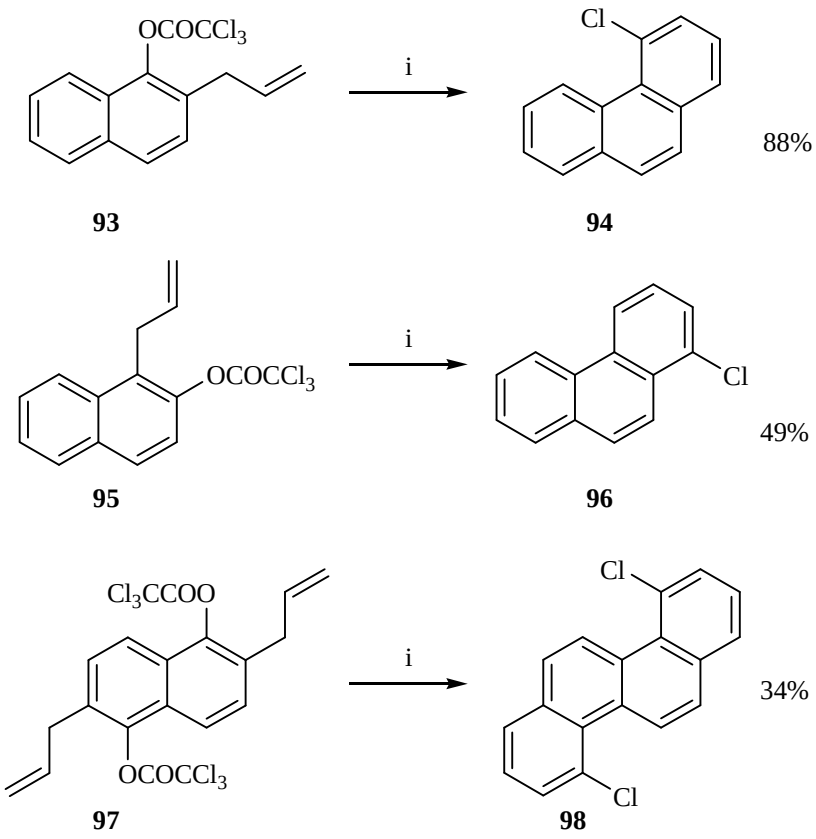
92a 62%
92b 91%
92c 67%
92d 89%
92e 55%
92f 81%

89g X =Me
89h X= OMe
89i X = Ph
89j X = CHO
89k X = NO_2

92g 76%
92h 74%
92i 78%
92j 59%
92k 36%

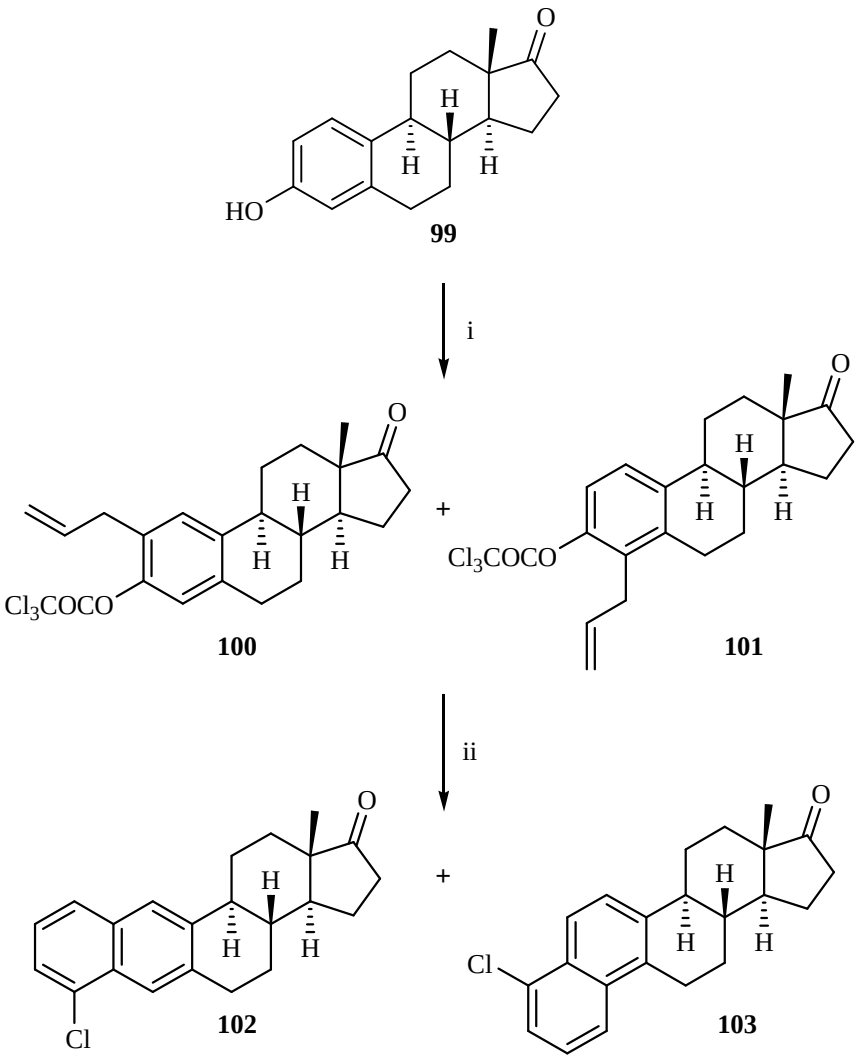
Scheme 2.5. Benzannulation reactions of substituted aryl trichloroacetates. i. CuCl (5 mol%), ligand **18** (5 mol%), DCE, MW, 200 ºC, 2 h.

Further experiments indicated that even sterically encumbered systems, for example chlorophenanthrenes **94** and **96** and 4,10−dichlorochrysene (**98**), could be prepared using this methodology. The latter case is particularly striking as it utilised a two−directional benzannulation reaction starting from bistrichloroacetate **97** (Scheme 2.6).



Scheme 2.6. Benzannulation sequences: synthesis of more complex aromatic systems. i. CuCl (5 mol%), ligand **18** (5 mol%), DCE, MW, 200 ºC, 2 h.

The synthetic potential of the **BHQ** benzannulation sequence was further exemplified by the synthesis of the novel steroids **102** and **103** from estrone **99** using a four–step route (Scheme 2.7).

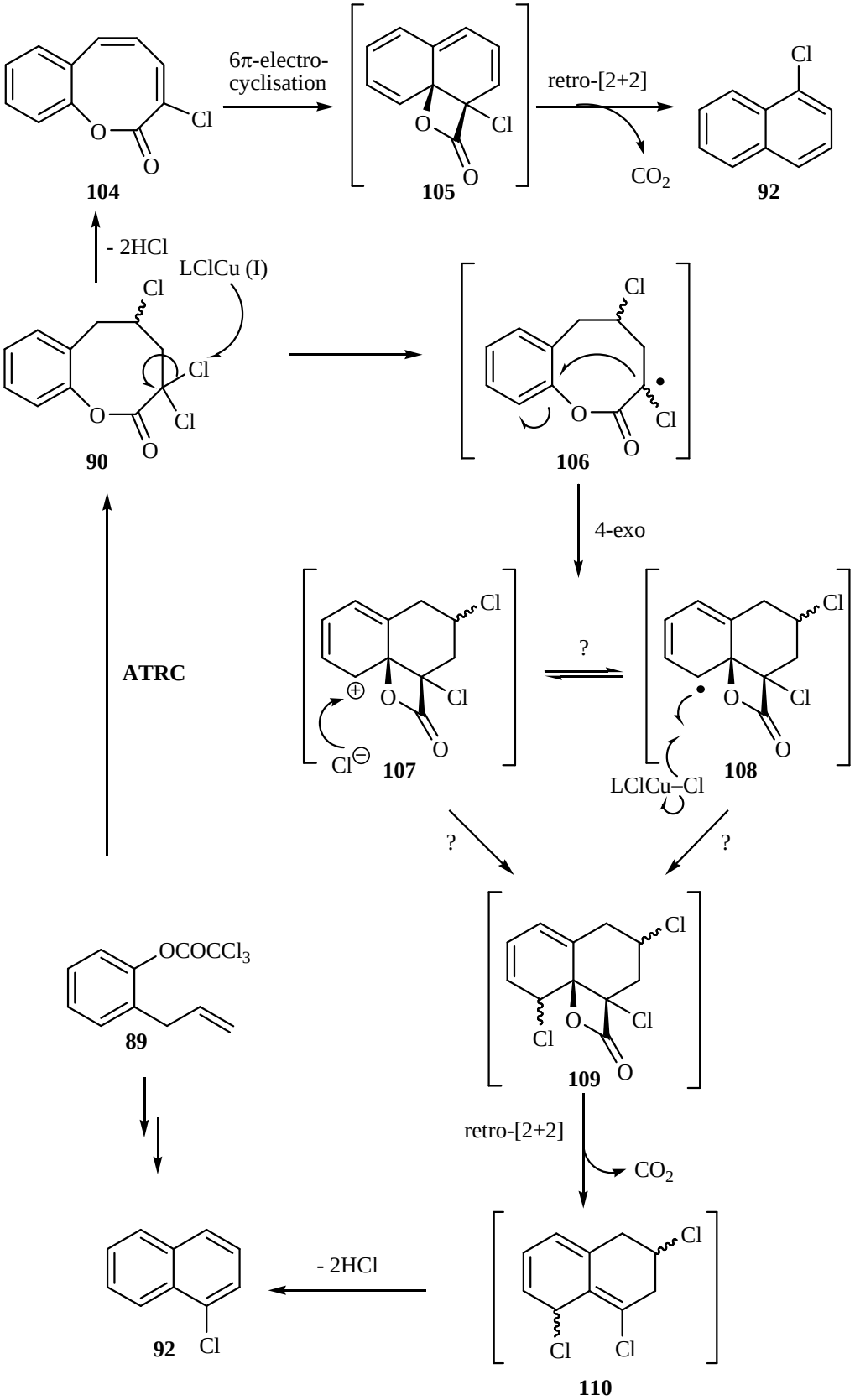


Scheme 2.7. Application of the **BHQ** benzannulation reaction. i. a. Allyl bromide (1.2 equiv.), K_2CO_3 (1.2 equiv.), 56 ºC. b. MW, 215 ºC. c. Et_3N (1.2 equiv.), Cl_3CCOCl (1.2 equiv.), Et_2O, 0 ºC, 80%; (3 steps). ii. CuCl (5 mol%), ligand **18** (5 mol%), DCE, MW, 200 ºC, 2 h, 67% (naphthalenes **102** + **103**).

2.1.1. MECHANISM OF THE "BHQ" BENZANNULATION REACTION

We have alumbrated a mechanistic pathway for the **BHQ** benzannulation reaction[37] which is initiated by an 8–*endo*–*trig* **ATRC** reaction of trichloroacetate **89** to afford the isolable lactone **90**. Lactone **90** could then be converted into the product **92** by one of several pathways (Scheme 2.8). For example, double dehydrochlorination of lactone **90**, affording diene **104**, followed by 6π–electrocyclisation and then extrusion of CO_2 would lead to 1–chloronaphthelene (**92**). The observation that lactone **90** is stable towards *simple thermolysis* militates against this fragmentation pathway. This outcome is to be compared with the observation that lactone **90** is converted into 1–chloronaphthalene (**92**) upon thermolysis in the *presence* of Cu(I) catalysts.

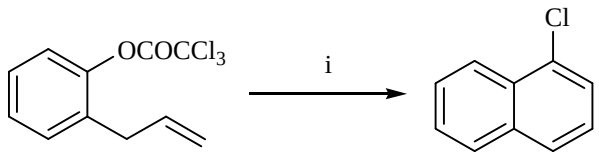
These observations are in accordance with an alternative decomposition pathway which involves a separate **ATRC** of lactone **90** onto the aromatic ring (**108** or **109**), followed by extrusion of CO_2, giving intermediate **110** and finally rearomatisation by double dehydrochlorination.



Scheme 2.8. Proposed mechanism for the conversion of trichloroacetate **89** to naphthalene **92**.

2.2. AIM OF THE PROJECT

Given the unprecedented nature of the transformation of *o*-allylphenyl trichloroacetates into halonaphthalenes (Scheme 2.9), the initial aim of this project was three–fold:



89 **92**

Scheme 2.9. Benzannulation reaction of trichloroacetate **89** under MW irradiation. i. CuCl (5 mol%), ligand **18** (5 mol%), DCE, MW, 220 ºC, 2 h, 84%.

- to define an optimum set of conditions for this "decarboxylative benzannulation reaction" (the "**BHQ** Reaction");[37]

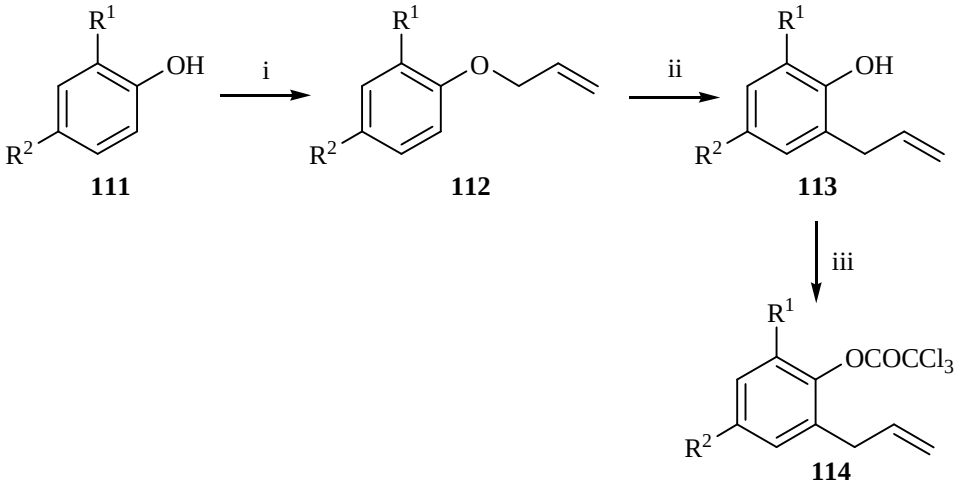
- to delineate the scope and limitations of this new reaction sequence (*e.g.* with regards to functional group compatibility and maintaining stereochemical integrity of stereogenic centres prone to epimerisation);

- to provide insights into the mechanism of the transformation, and to apply this benzannulation reaction to targets of biological interest.

2.3. PREPARATION OF SUBSTRATES FOR THE BHQ SEQUENCE

One appealing aspect of the **BHQ** benzannulation reaction is its potential generality especially given the fact it utilises trihaloacetate esters of phenols and these substrates are themselves readily available by classical *ortho*–Claisen rearrangement chemistry.

In order to test the generality of the **BHQ** reaction a series of 2–allylaryl trichloroacetates were prepared and their benzannulation in the presence of Cu(I) catalysts was investigated. The requisite 2–allylaryl trichloroacetates **114** were readily accessible from phenyl allyl ethers **112** *via* an *ortho*–Claisen rearrangement followed by trichloroacylation (Scheme 2.10).

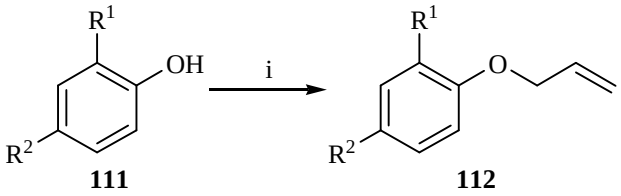


Scheme 2.10. Synthetic route for obtaining trichloroacetates. i. Allyl bromide (0.93 equiv.), K_2CO_3 (1.26 equiv.), acetone, 16 h. ii. Claisen rearrangement. iii. Cl_3CCOCl (1.20 equiv.), base (Et_3N or py, 1.20 equiv.), Et_2O.

In this way it was possible to prepare a large range of substrates in order to elucidate the mechanism of the reaction and to help define the scope and limitations of the benzannulation reaction.

2.3.1 *O*–ALLYLATION REACTIONS

A general procedure for the *O*–allylation of a range of phenols was adopted whereby the phenol was reacted with 1.6 equiv. of allyl bromide in the presence of a mild base (usually K_2CO_3) in acetone at ambient temperature (Scheme 2.11). This procedure afforded uniformly high yields of the desired ethers, except in the case of 2,4–dibromophenol (**112f**), where the reaction did not proceed to completion.

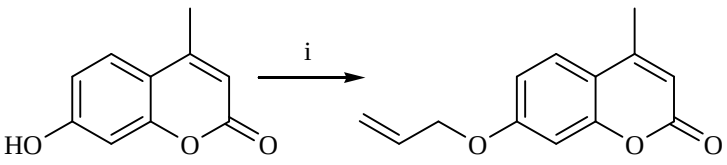


111 **112**

Entry	Product	R^1	R^2	Yield
1	**112a**	H	Br	98%
2	**112b**	Br	H	100%
3	**112c**	H	Cl	89%
4	**112d**	Cl	H	96%
5	**112e**	Cl	Cl	82%
6	**112f**	Br	Br	56%
7	**112g**	H	F	82%

Scheme 2.11. Ether synthesis. i. Allyl bromide (0.93 equiv.), K_2CO_3 (1.26 equiv.), acetone, rt, 16 h.

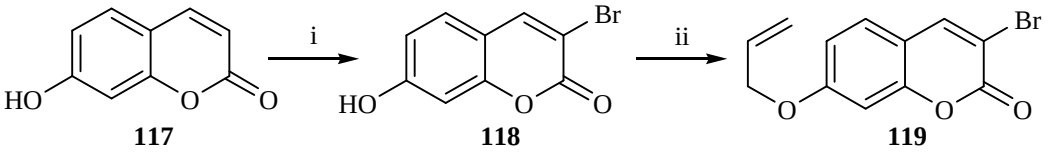
The allylation of 4–methylumbelliferone (**115**) was also sluggish under these conditions but did afford a quantitative yield of the desired product in refluxing acetone (Scheme 2.17).[39]



115 **116**

Scheme 2.12. Synthesis of 7–allyloxy–4–methylumbelliferone (**116**). i. Allyl bromide (1.2 equiv.), K_2CO_3 (2.0 equiv.), acetone, 16 h, reflux, quant.

7–(Allyloxy)–3–bromo–2*H*–1–benzopyran–2–one (**119**) was readily prepared in a two–step sequence from umbelliferone (Scheme 2.13). Bromination of coumarin **117** (TMAP (1.45 equiv.), 1,4–dioxane, 5 days, 25 ºC, 98%)[40] followed by allylation of the purified phenol with allyl bromide in refluxing acetone using K_2CO_3 as base afforded the desired allyl ether **119** in acceptable yield.

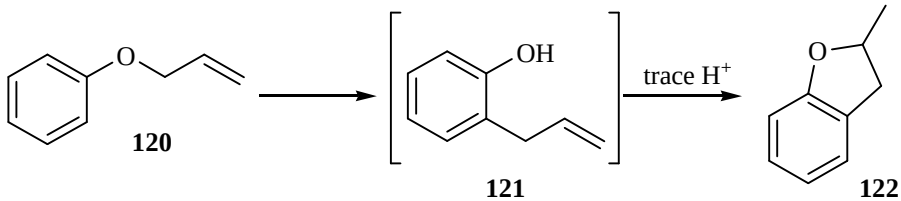


117 **118** **119**

Scheme 2.13. Synthesis of 7–(allyloxy)–3–bromo–2*H*–1–benzopyran–2–one (**119**). i. TMAP (1.5 equiv.), 1,4–dioxane, 25 ºC, 5 days, 98%. ii. Allyl bromide (1.2 equiv.), K_2CO_3 (1.2 equiv.), acetone, 16 h, reflux, 51%.

2.3.2 *ortho*–CLAISEN REARRANGEMENTS

The *ortho*–Claisen rearrangement has been employed extensively for the preparation of *o*–allyl phenols since its discovery almost a century ago.[41,42] Previous work in the group has shown that many *ortho*–Claisen rearrangements proceed more efficiently when irradiated by microwave radiation,[43,44] although this may not be generally the case. The thermal reaction took place between 210 and 220 ºC.[45] Thermolysis for extended reaction times (> 6 h) is generally to be avoided as secondary reaction processes tend to occur, usually resulting in the isolation of dihydrobenzofurans (*e.g.* furan **122**, Scheme 2.14).[46] In certain cases these cyclisation reactions take place rapidly and may be catalysed by (Lewis) acid impurities present in the reagents, solvents or on the surface of the glassware used for the reaction.

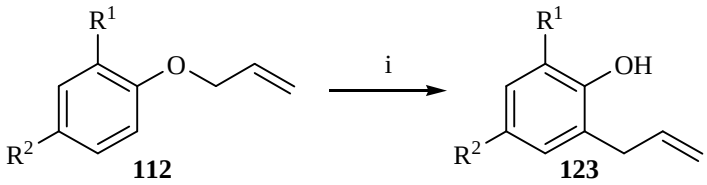


120 **121** **122**

Scheme 2.14. Formation of benzofuran post *ortho*–Claisen rearrangement.

Adopting this general set of reaction conditions (6 h at 210 – 220 ºC and under nitrogen) for the *ortho*–Claisen rearrangement of simple monocyclic substrates

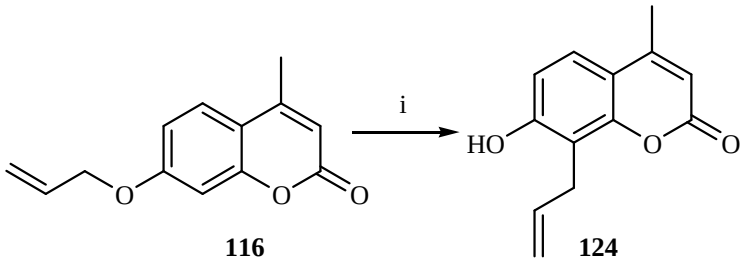
afforded high yields of the rearranged product except in the case of 1–(allyloxy)–2,4–dibromobenzene (**123f**). A maximum yield of 68% of the desired product could not be improved upon due the increasing competitive formation of the corresponding furan derivative (Scheme 2.15).



Entry	Compound	R^1	R^2	Yield
1	**123a**	H	Br	75%
2	**123b**	Br	H	79%
3	**123c**	H	Cl	100%
4	**123d**	Cl	H	74%
5	**123e**	Cl	Cl	79%
6	**123f**	Br	Br	68%
7	**123g**	H	F	99%[a]

Scheme 2.15. Claisen rearrangement results. i. 210 – 220 ºC, 6 h. a. Longer reaction time was required (10 h).

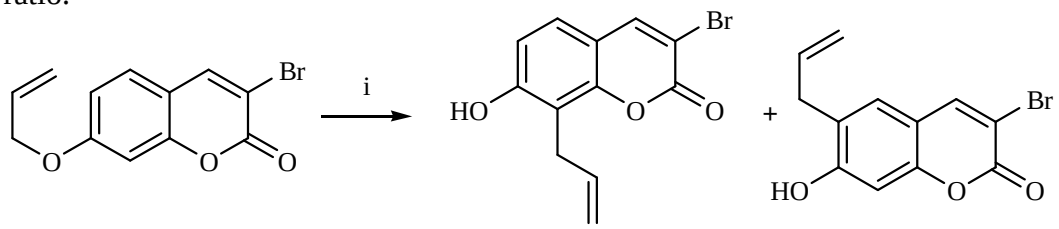
The optimisation of the *ortho*–Claisen rearrangement of more heavily functionalised substrates sometimes proved difficult to achieve, as exemplified by the case of umbelliferone **116**, which when performed solvent free at 210 – 220 ºC afforded variable quantities of the dihydrofuran by–product. In this case, cyclisation of the initial rearranged product took place rapidly making it difficult to successfully optimise the reaction. Dilution of the allyl ether in *N*,*N*–diethylaniline helped to prevent the formation of the dihydrofuran by–product and led to a 76% yield of umbelliferone **124** (Scheme 2.16). In this case, the reaction was wholly regioselective and resulted in the formation of umbelliferone **124**.



116 **124**

Scheme 2.16. Claisen rearrangement of umbelliferone **116**. i. Et_2NPh, reflux, 6 h, 76%.

Claisen rearrangement of bromoumbelliferone **119** also proved to be problematic. When conducted in *N*,*N*–diethylaniline at reflux for 12 h the reaction only went to 40% conversion. However when the same reaction was conducted in a microwave reactor complete conversion to product was achieved after 16 h at 220 ºC in toluene (Scheme 2.17). Unfortunately, this reaction was not wholly regioselective and afforded a mixture of the 8– and 6–allyl coumarins **125** and **126** in a 3.7 : 1 ratio.[47]

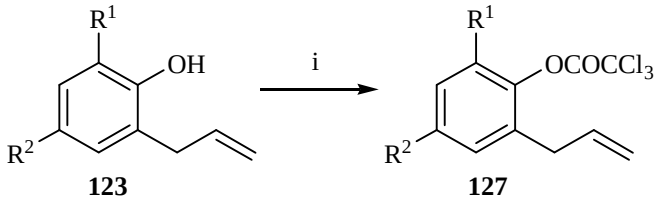


119 **125** **126**

Scheme 2.17. Claisen rearrangement of umbelliferone **119**. i. Toluene, 220 ºC, MW, 12 h, 37%.

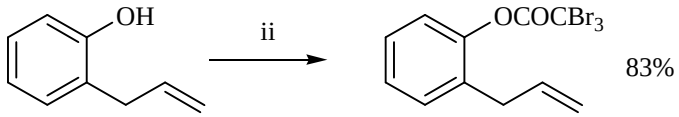
2.3.3. TRIHALOACYLATION

Acylation of the phenols prepared above was readily achieved using standard methodology (1.2 equiv. trichloroacetyl chloride or tribromoacetyl chloride, 1.2 equiv. Et_3N, 0 ºC, 3 h). In most cases, the resulting activated esters were used without further purification as they had a tendency to undergo hydrolysis upon column chromatography (Scheme 2.18).



123 **127**

Entry	Compound	R^1	R^2	Yield[a]
1	**89**	H	H	93%
2	**89a**	H	F	63%
3	**127a**	H	Br	84%
4	**127b**	Br	H	74%
5	**127c**	H	Cl	70%
6	**127d**	Cl	H	88%
7	**127e**	Cl	Cl	82%
8	**127f**	Br	Br	54%

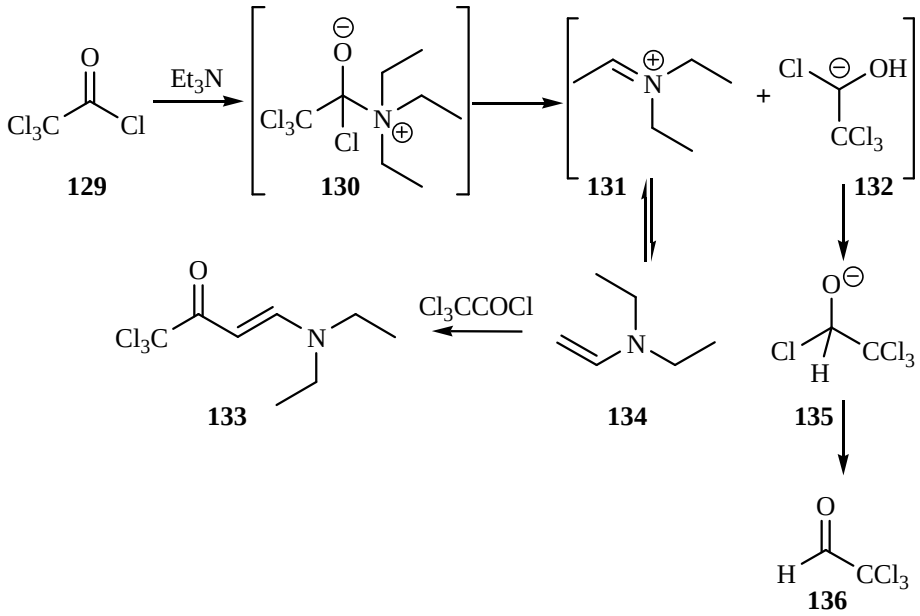


121 **128**

Scheme 2.18. Acylation results. i. $ClCOCCl_3$ (1.2 equiv.), Et_3N (1.2 equiv.), Et_2O, 0 ºC, 3 h. ii. $ClCOCBr_3$ (1.2 equiv.), Et_3N (1.2 equiv.), Et_2O, 0 ºC, 3 h. a. Yields of crude reaction mixtures.

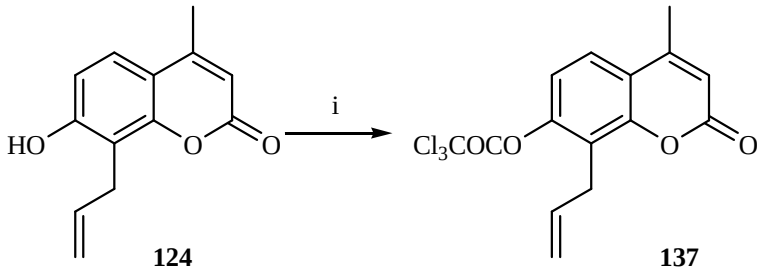
Acylation of umbelliferone **124** with $ClCOCCl_3$ and Et_3N gave trichloroacetate **137** but the reaction was hampered by the formation of $Cl_3CCOCHCHNEt_2$[48] (**133**) in a 1.1 : 1 ratio respectively (Figure 2.1). There was a 67% conversion of umbelliferone **124** into trichloroacetate **137**; unfortunately isolation of trichloroacetate **137** from the vinylogous amide **133** formed proved to be difficult.

In those cases where acylation of the phenol is slow, competing functionalisation of the base is seen, which leads to the formation of amide **133** (Scheme 2.19).[49] The proposed mechanism of the reaction goes through an initial addition of Et_3N to Cl_3CCOCl followed by proton abstraction to give enamine **134**. Cl_3CCOCl reacts with enamine **134** to afford vinylogous amide **133**.



Scheme 2.19. $Cl_3CCOCHCHNEt_2$ formation.

However, acylation of coumarin **124** in the presence of pyridine at rt for 16 h achieved the formation of trichloroacetate **137** in a 75% yield (Scheme 2.20).[50]



Scheme 2.20. Acylation of coumarin **124**. i. $ClCOCCl_3$ (1.2 equiv.), py (1.2 equiv.), CH_2Cl_2, rt, 16 h, 75% (crude yield).

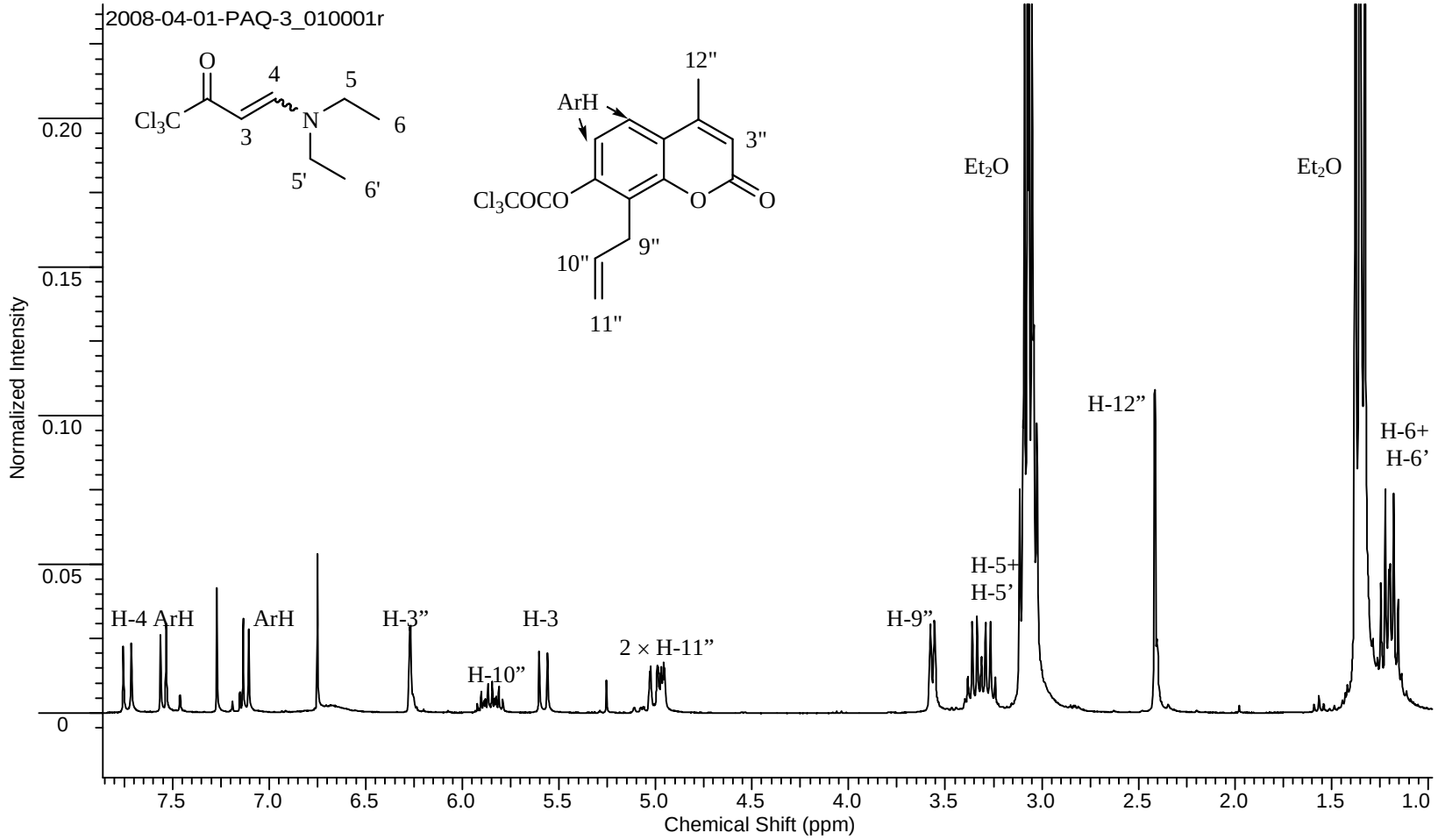
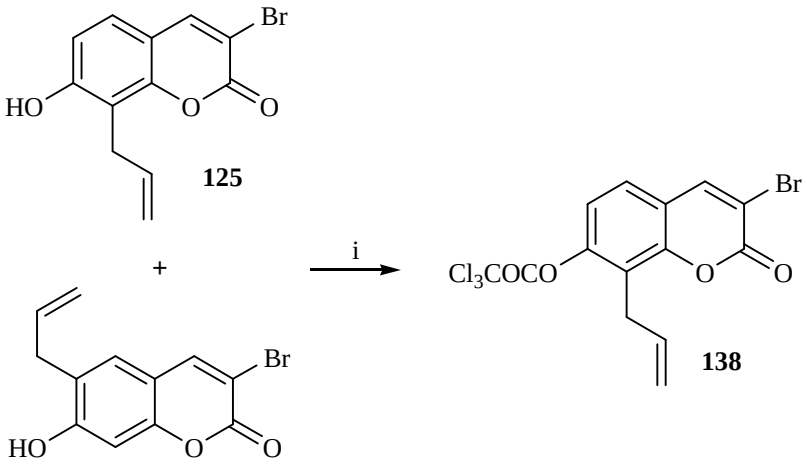


Figure 2.1. $Cl_3COCHCHNEt_2$ and coumarin **135** ^1H NMR of the crude product ($CDCl_3$).

Acylation of coumarins **125** and **126** also proved to be sluggish but afforded trichloroacetate **138** in 80% yield after a reaction time of 16 h at rt (Scheme 2.21). Fortuitously the minor isomer **126** was lost upon purification.

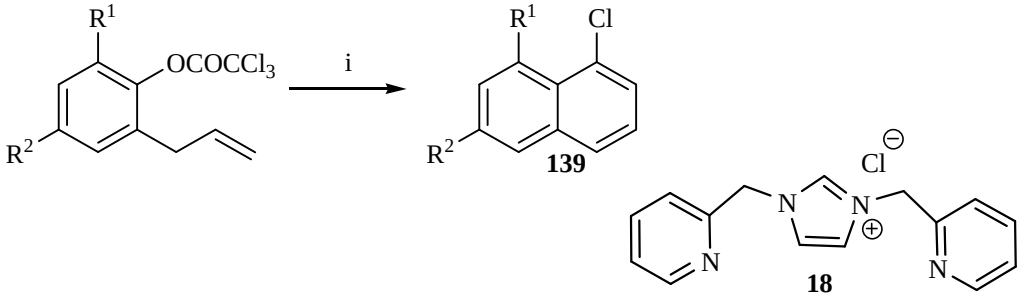


Scheme 2.21. Acylation of coumarins **125** and **126**. i. $ClCOCCl_3$ (1.2 equiv.), Et_3N (1.2 equiv.), Et_2O, 16 h, rt, 80% (crude yield).

2.4. BENZANNULATION REACTION

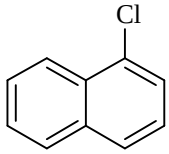
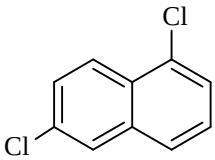
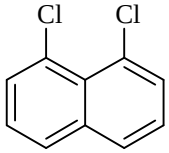
Having prepared a range of substrates their benzannulation chemistry was investigated.

The benzannulation reaction of the trichloroacetates proceeded smoothly in the presence of 5 mol% of ligand **18** and 5 mol% of CuCl in DCE at 200 ºC in the microwave for 2 h under N_2 (Scheme 2.22).



Scheme 2.22. Benzannulation reaction. i. CuCl (5 mol%), ligand **18** (5 mol%), DCE, 2 h, MW.

Benzannulation of trichloroacetates derived from fluoro− and chloro−substituted phenols proceeded cleanly and afforded single regioisomeric products in good yields (Table 2.1).

Entry	SM	R^1	R^2	Product	Yield
1	**89**	H	H	 **92**	71%
2	**127c**	H	Cl	 **139c**	72%
3	**127d**	Cl	H	 **139d**	59%

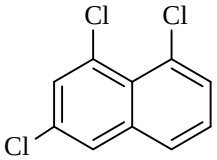
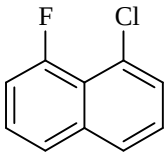
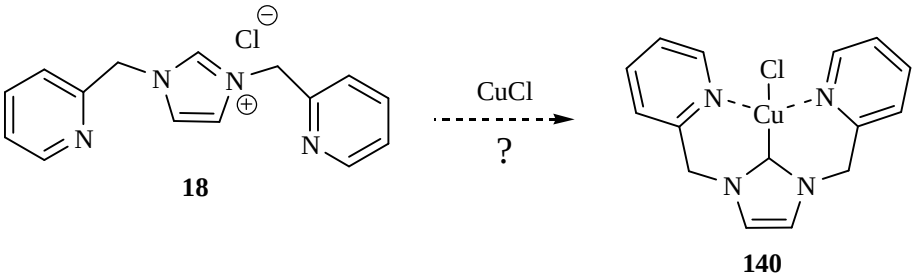
4	**127e**	Cl	Cl	 **139e**	61%
5	**127h**	F	H	 **139h**	68%

Table 2.1. Results of benzannulation sequences of derivatives of fluoro− and chloro−phenols.

Up to this stage the catalyst system of choice for the **BHQ** reaction was the ligand **18** in the presence of CuCl. Given the possibility for NHC−carbene formation under these reaction conditions we wondered whether the actual catalyst species was in fact the carbene complex **140** (Figure 2.2).



18 **140**

Figure 2.2. Attempt to prepare complex **138**.

Unfortunately, all attempts to prepare complex **140** from ligand **18** (Figure 2.2) were unsuccessful and we have been unable to prove whether this complex is the actual catalytic species in our reaction. We have reported that carbenes can promote radical reactions.[11] Therefore, we wondered if the catalytic complex **140** created during the **BHQ** reaction could be a carbene and if preformed carbenes could improve the results for our benzannulation reaction.

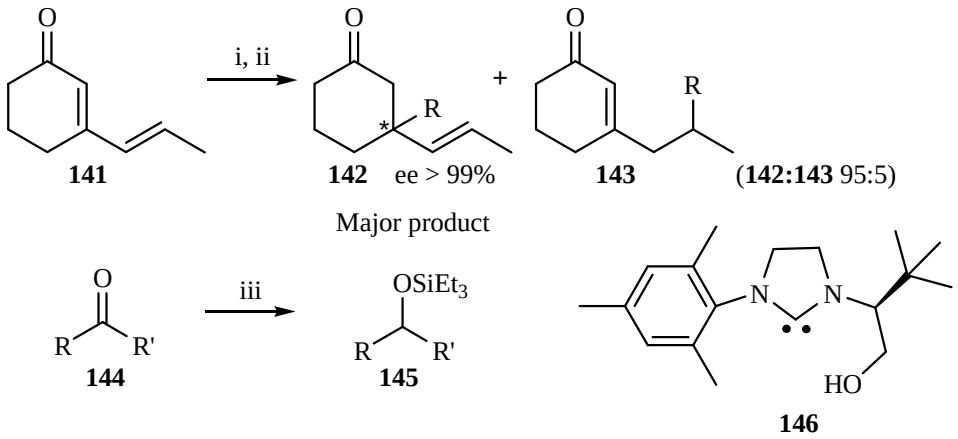
2.4.1. PREFORMED NHC–Cu CARBENES AS CATALYST FOR BENZANNULATION REACTIONS

2.4.1.1. INTRODUCTION

During the last 10 years *N*–heterocyclic carbenes (NHC) have emerged as efficient ligands in metal–mediated reactions for homogeneous catalysis. As electron–rich σ–donors and poor π–acceptors[51] these ligands have a strong interaction with the metal centre generating stable organometallic species that prevent decomposition of the catalyst, at the same time they are sterically hindered nucleophilic carbene ligands.

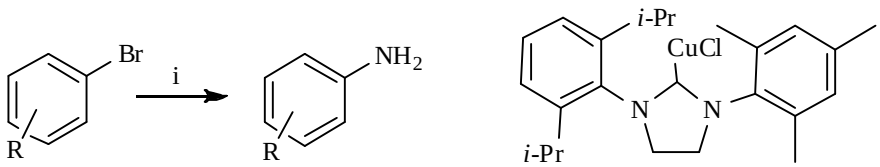
The first NHC–copper complex derived from imidazolium salt and copper triflate was reported by Arduengo in 1993.[52] Since then their applications in synthetic chemistry for homogeneous catalysis have been widely studied.

Such *N*–heterocyclic carbene complexes have been used to catalyse a variety of reactions such as the selective 1,4– over 1,6–conjugate addition of Grignard reagents[53] and the reduction of ketones.[54] It is important to notice that in the core of 1,4– addition, an all–carbon bearing stereogenic centre is generated with high enantioselectivity (Scheme 2.23).



Scheme 2.23. Selective 1,4–conjugated addition and ketone reduction catalysed by *N*–heterocycles. i. RMgBr, CH_2Cl_2, –10 ºC, $Cu(OTf)_2$ (6 mol%), **146** (9 mol%). ii. NH_4Cl, then DBU. iii. (IPr)CuCl (**156**, 3 mol%), NaO^tBu (6 – 12 mol%), Et_3SiH, toluene, rt, 0.75 – 3 h, 82 – 96%.

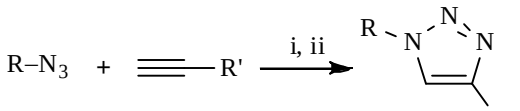
The preparation of aziridines by a carbene transfer reaction and anilines *via* coupling of aromatic and heteroaromatic bromides with ammonia is also possible (Scheme 2.24a).



147 **148** **149**

Scheme 2.24a. Preparation of anilines promoted by *N*–heterocyclic carbenes. i. Catalyst **149** (5 mol%), NH_3 (excess), K_2CO_3 (2.0 equiv.), MeOH/NMP, 90 ºC, 66 – 97%.

More recently, the "click" reaction between azides and alkynes was also been found to be promoted by Cu–NHC complexes. The reason for the good yields could be due to the efficiency of the formed azolium salt to protonate the copper triazole intermediate (Scheme 2.24b).



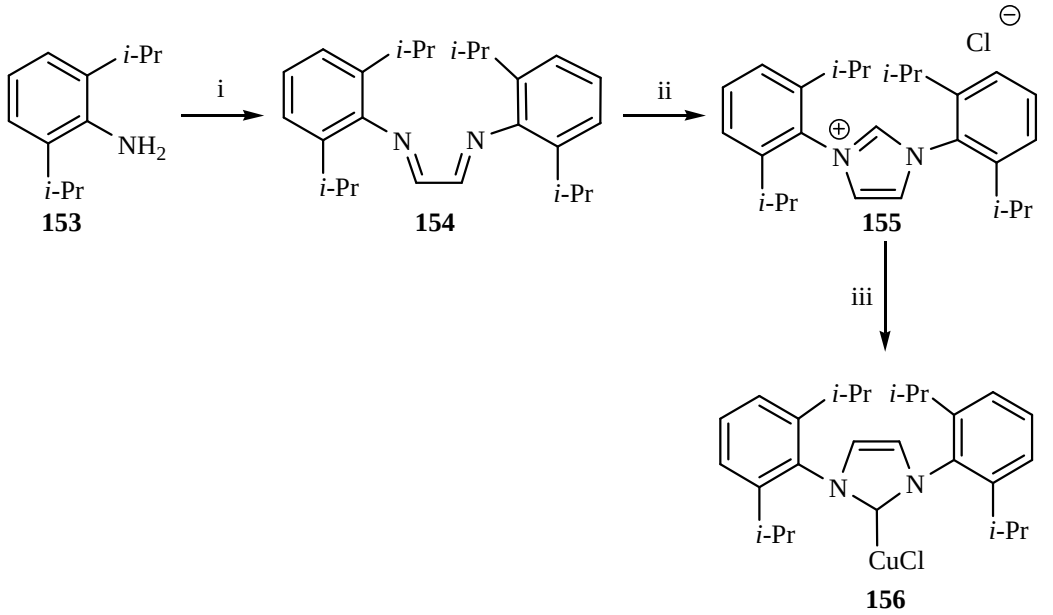
150 **151** **152**

Scheme 2.25b. Preparation of aziridines promoted by *N*–heterocyclic carbenes. i. [(SIPr)CuCl] (2 mol%), DMSO, rt, 1 week. ii. H_2O, 60 ºC, 83 – 98%.

Until our investigations, the use of these copper carbenes in radical–mediated reactions had not been reported. However, recent reports from the Nolan group concerning the isolation of stable Cu–NHC complexes[54,55] led us to examine their utility in our benzannulation reaction.

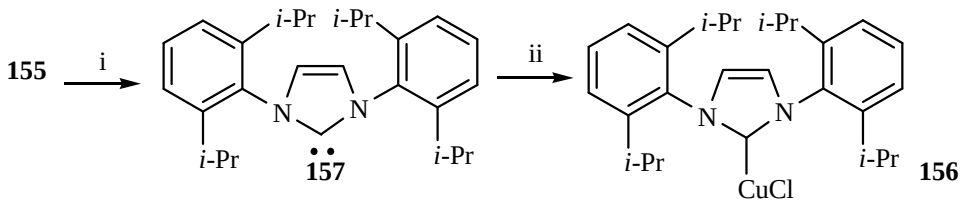
2.4.1.2 USE OF THE NOLAN CARBENE FOR THE BHQ REACTION

Initially we chose 1,3–bis–(2,6–diisopropylphenyl)–imidazolium chloride IPr.HCl (**155**) for the preparation of the copper adduct. IPr.HCl (**155**) was prepared by addition of glyoxal to 2,6–diisopropylaniline (**153**) in ethanol in the presence of a catalytic amount of formic acid leading firstly to the formation of the diazabutadiene **154** in good yield (Scheme 2.25). This compound reacts with paraformaldehyde and HCl in dioxane to form IPr.HCl (**155**) in a moderate yield.[55] Finally, the air and moisture–stable NHC–copper(I) catalyst **156** was readily prepared by deprotonation of IPr.HCl with NaO^{t}Bu in the presence of CuCl (Scheme 2.25).[56]



Scheme 2.26. Synthesis of Nolan catalyst **156**. i. Glyoxal 40% in water (0.5 equiv.), formic acid (cat.), EtOH, 2 days, rt, 84%. ii. Paraformaldehyde (1.0 equiv.), HCl/dioxane (~ 4 M, 1.0 equiv.), toluene, 48%. iii. CuCl (1.0 equiv.), NaO^{t}Bu (1.06 equiv.), THF, 20 h, rt, 90%.

We also prepared and isolated the free carbene IPr (**157**) by treating IPr.HCl with NaO^{t}Bu in dry THF.[32] Subsequent reaction of IPr **157** with CuCl in dry THF afforded (IPr)CuCl (**156**) in a reasonable yield (Scheme 2.25).

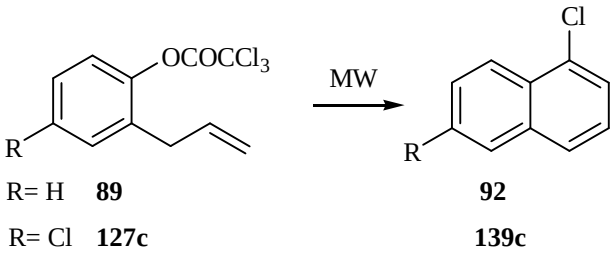


Scheme 2.27. Generation of carbene **157** and formation of (IPr)CuCl (**156**). i. Na^{t}OBu (1.07 equiv.), THF, 65%; ii. CuCl (1.0 equiv.), THF, 4 h, rt.

Having prepared a sample of carbene complex **156**, its efficiency in our benzannulation reactions was investigated.

2.4.1.3 BENZANNULATION REACTION WITH THE NOLAN CARBENE

The efficacy of the carbene complex **156** was tested in our benzannulation reaction. A series of experiments were undertaken with a range of substrates in order to optimise the reaction conditions (Scheme 2.27).



Scheme 2.28. Benzannulation reaction of **89** and **127c**.

The benzannulation reaction under the standard conditions (DCE, 200 ºC, MW, 2 h) adding 5 mol% of (IPr)CuCl (**156**) to the mixture proved the efficiency of the catalyst (entries 1 and 3, Table 2.2).[57]

Earlier work in the group had shown that the **BHQ** reaction could be carried out in a microwave reactor at 200 ºC. Such reactions were complete after shorter reaction times than when they were reacted thermally but precluded scale–up.

As part of an optimisation process we tried to reduce the reaction temperature from 200 to 150 ºC (entries 4 and 5, Table 2.2). After 2 h at 150 ºC some benzannulation product was observed but starting material and lactone **158c** (~ 1 :

1 ratio, Figure 2.3) were the major components. Repeating this reaction for 4 h afforded some benzannulation product in a 2 : 1 : 1 ratio with starting material **127c** and lactone **158c**, with 1,6–dichloronaphthalene (**139c**) also being obtained in 20% yield. The reaction time was also reduced to 1 h but maintaining the standard temperature of 200 ºC a reasonable yield of 34% was obtained, around half of that obtained under the standard conditions with (IPr)CuCl (**156**, entry 6, Table 2.2). When the reaction was carried out in the presence of (IPr) (**157**) and without CuCl, starting material was recovered. This proved that the presence of CuCl in the reaction mixture is essential for the outcome of the reaction.

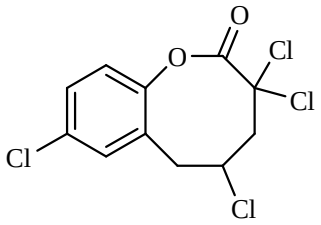


Figure 2.3. Structure of lactone **158c**.

Finally, in an attempt to reproduce the conditions established for the benzannulation reaction with the ligand **18**/CuCl system a reaction with 5 mol% of IPr.HCl (**155**) and 5 mol% of CuCl was performed in DCE (entry 2, Table 2.2). 1–Chloronaphthalene was obtained in a 57% yield, this was slightly lower than for the previous system but this was attributed to the volatile of the product.

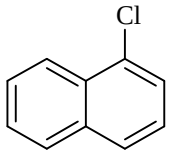
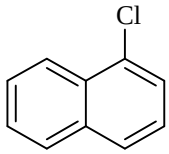
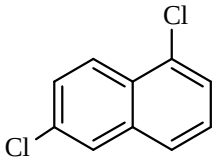
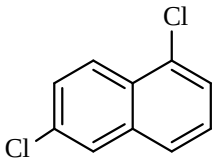
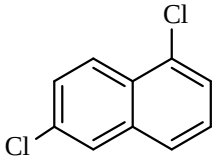
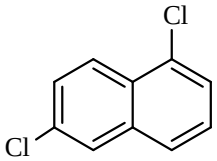
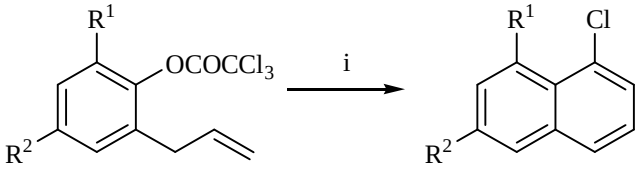
Entry	SM	Product	Conditions	Yield
1	**89**	 **92**	(IPr)CuCl (5 mol%), 200 ºC, 2 h	47%
2	**89**	 **92**	IPr.HCl (5 mol%), CuCl (5 mol%), 200 ºC, 2 h	57%
3	**127c**	 **139c**	(IPr)CuCl (5 mol%), 200 ºC, 2 h	62%
4	**127c**	 **139c**	(IPr)CuCl (5 mol%), 150 ºC, 2 h	~ 0% + SM[a] + Lactone **158c**[a]
5	**127c**	 **139c**	(IPr)CuCl (5 mol%), 150 ºC, 4 h	20% + SM[a] + Lactone **158c**[a]
6	**127c**	 **139c**	(IPr)CuCl (5 mol%), 200 ºC, 1 h	34% + Lactone **158c**[a]

Table 2.2. Reaction optimisation results. a. Components determined by ^{1}H NMR studies of the reaction mixture.

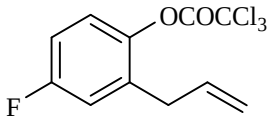
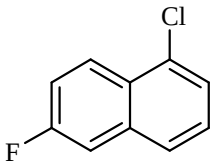
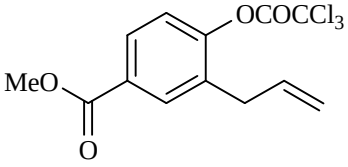
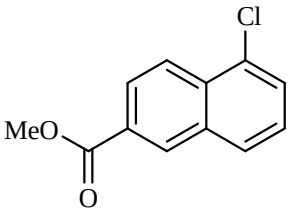
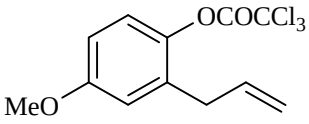
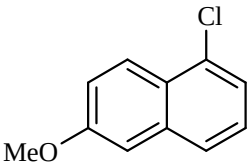
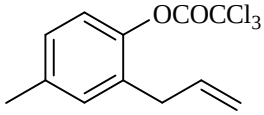
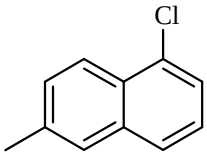
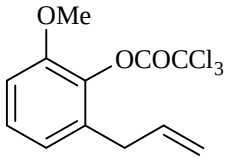
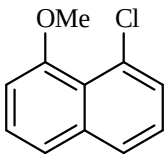
After some experimentation, the optimal conditions for the benzannulation reaction were found to require 5 mol% of (IPr)CuCl (**156**) in DCE for 2 h at 200 ºC under conditions of microwave activation. The optimised methodology was then tested by submitting a representative range of trichloroacetates to these conditions (Scheme 2.28, Table 2.3). We were happy to see that in most of the cases the results obtained with the Nolan carbene were comparable to, if not better than those using the CuCl/ligand **18** catalyst system. The only exception was the formation of methyl 5–chloronaphthalene–2–carboxylate (**92b**, entry 2, Table 2.3)

which afforded a lower yield than when the reaction was promoted by CuCl/ligand **18**.

It is important to mention that the reactions catalysed by carbene **156** were much cleaner than those promoted by CuCl/ligand **18**. In the case of this ligand system, reactions invariably led to the formation of an intractable black–coloured residue, which made purification/isolation difficult.



Scheme 2.29. Optimal benzannulation reaction. i. (IPr)CuCl (**156**, 5 mol%), DCE, 2 h, 200 ºC, MW.

Entry	SM	Product	Yield
1	 **89a**	 **92a**	58% (60%)
2	 **89b**	 **92b**	67% (91%)
3	 **89c**	 **92c**	79% (67%)
4	 **89f**	 **92f**	79% (81%)
5	 **89h**	 **92h**	82% (74%)

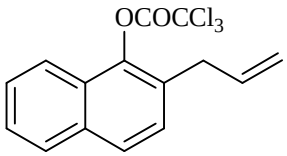
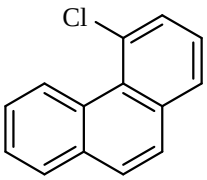
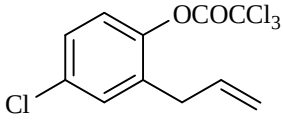
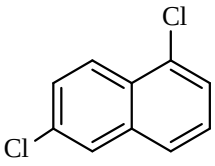
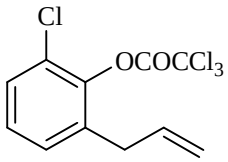
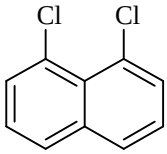
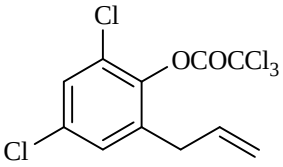
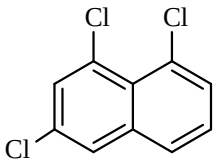
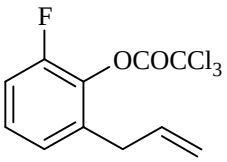
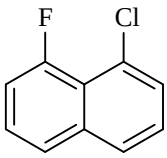
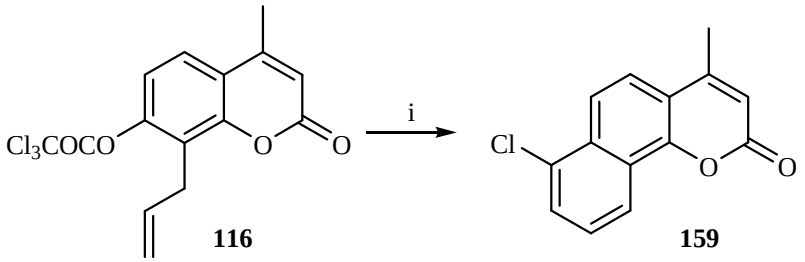
6	 **93**	 **94**	90% (88%)
7	 **127c**	 **139c**	66% (61%)
8	 **127d**	 **139d**	76% (59%)
9	 **127e**	 **139e**	76% (61%)
10	 **127h**	 **139h**	60% (68%)

Table 2.3. Benzannulation reaction catalysed by (IPr)CuCl (**156**). Yields in parenthesis are those obtained using CuCl/ligand **18** as catalyst [CuCl (5 mol%), ligand **18** (5 mol%), DCE, 200 ºC, MW, 2 h].

Taking into account the fact that there are relatively few general approaches for the synthesis of carbocyclic aromatics from simple acyclic precursors we wanted to test our methodology on the synthesis of benzo−fused coumarin derivatives, a structural motif common to a variety of natural products. We were happy to see that when trichloroacetate **116** was submitted to the benzannulation reaction a 41% yield of coumarin **159** was achieved (*vide supra*, Scheme 2.29).

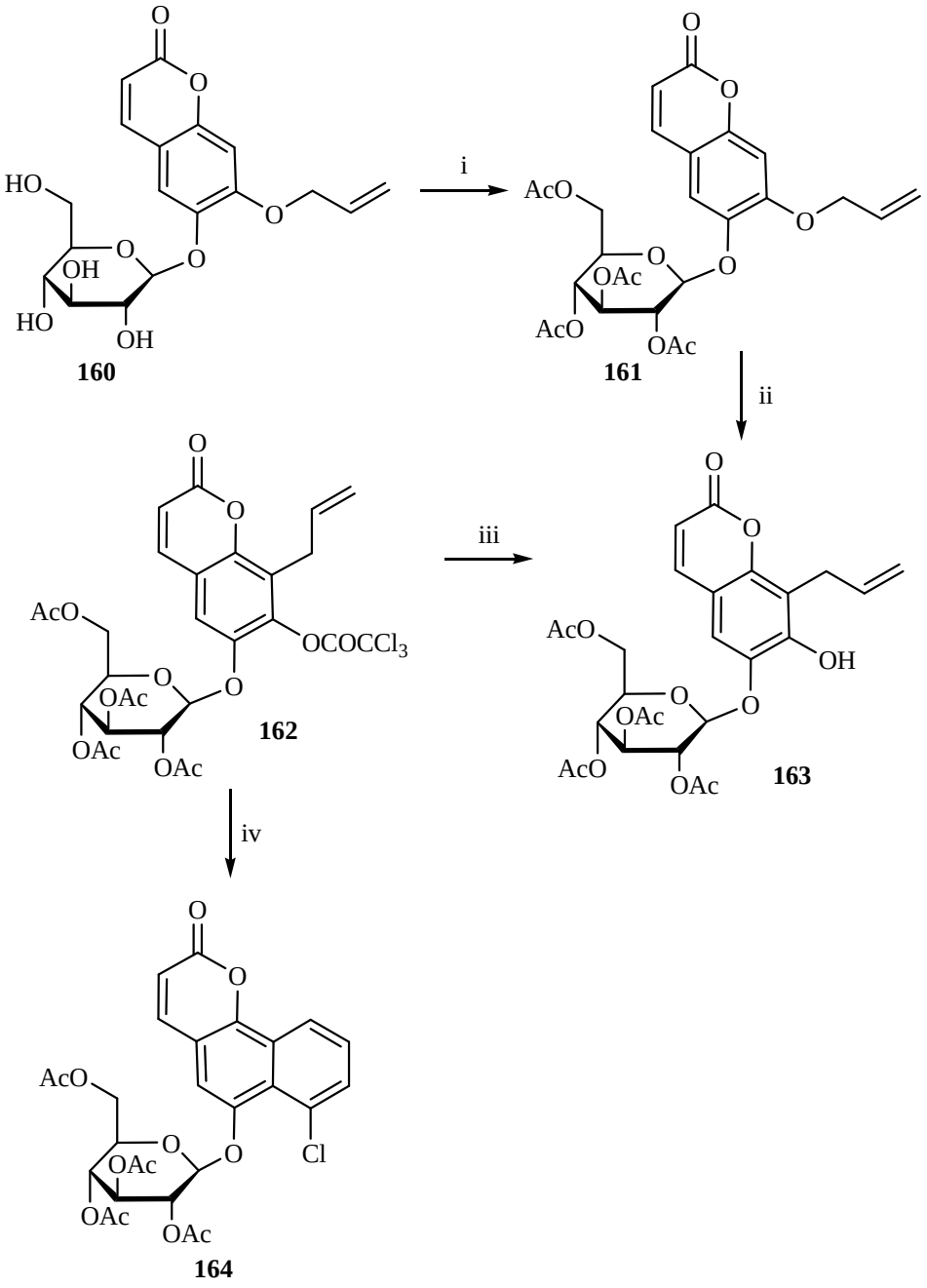


116 **159**

Scheme 2.30. Benzannulation reaction of trichloroacetate **116**. i. (IPr)CuCl (**156**, 5 mol%), DCE, 200 ºC, MW, 2 h, 41%.

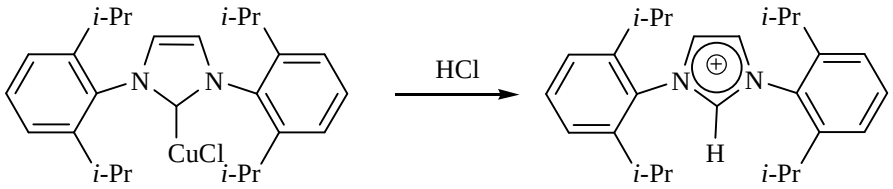
Most notably, we were able to demonstrate that the esculine derivative **162** underwent the **BHQ** reaction without cleavage of the labile *o*–glysoside bond.

The synthesis of the trichloroacetate **162** precursor for the benzannulation reaction followed our standard procedure (Scheme 2.30).[58] Acetate protection[59] of glycoside **160**[60] followed by *ortho* Claisen rearrangement (**163**, 94% yield) and acylation (**162**, 60%) of allyl esculin **163** gave trichloroacetate **162**. Radical cyclisation of acetate **162** afforded the novel fused coumarin **164** in a modest 21% yield.



Scheme 2.31. Study of the benzannulation reaction of the esculin derivative **160**. i. Ac_2O (11.2 equiv.), py, rt, 17 h, 54%. ii. 210 – 220 ºC, 5 h. iii. $ClCOCCl_3$ (1.2 equiv.), Et_3N (1.2 equiv.), Et_2O, 0 ºC, 3 h, 60%. iv. (IPr)CuCl (**156**, 5 mol%), DCE, 200 ºC, 2 h, MW, 21%.

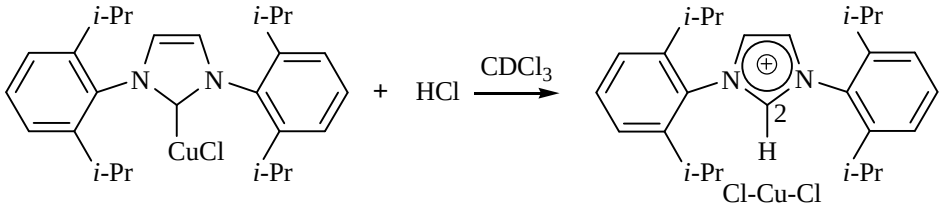
Boyle *et al.*[61] demonstrated that in the presence of strong protic acids such as HCl, Cu–NHC complexes suffer protonation forming complexes such as **165** (Scheme 2.31).



156 **165**

Scheme 2.32. Protonation of Nolan catalyst **156**.

In accordance with this report we indeed found that reaction of carbene **156** with HCl (11 M aq. HCl) in $CDCl_3$ after 48 h at rt afforded the imidizolium complex **165** (Scheme 2.32).[61] This blank reaction underscores the potential instability of the Nolan carbene **156** to the BHQ reaction conditions and brings into question the true catalytic species which participates in the reaction.

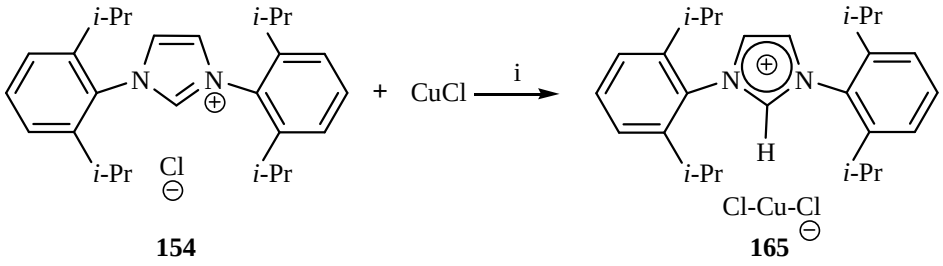


156 **165**

Scheme 2.33. Spectroscopic studies of the protonation of (IPr)CuCl (**156**) in the presence of HCl.

Given the fact that HCl is generated during the benzannulation reaction the question arose as to whether complex **165** is produced during the course of these reactions. Indeed an examination of the ^1H NMR of the crude reaction mixtures showed the presence of a low field resonance at 9.3 ppm, which could be attributed to H–2 in complex **165** (Figure 2.4). The question was if the benzannulation reaction was catalysed by the Nolan carbene **156** or the CuCl–imidazolium complex **165** which is produced during the benzannulation reaction.

The CuCl–imidazolium complex **165** was easily prepared by combining stoichiometric amounts of IPr.HCl (**154**) and CuCl in CH_2Cl_2 (Scheme 2.33).[61]



154 **165**

Scheme 2.34. (IPr.HCl)CuCl (**165**) synthesis. i. IPr.HCl (**154**, 1.0 equiv.), CuCl (1.0 equiv.), CH_2Cl_2, 25 ºC, 2 h, 75%.

The radical cyclisation was then performed using (IPr.HCl)CuCl (**165**) as the catalyst system in order to compare the results obtained with the CuCl–carbene **156**. Remarkably reasonable the products were obtained with both carbene catalyst **156** and (IPr.HCl)CuCl (**165**) in the cyclisation of trichloroacetates **127d** and **89a**. Only slightly lower yields were observed for the (IPr.HCl)CuCl (**165**) system and as a result we were unable to conclude which was the active catalyst (Table 2.4).

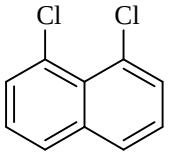
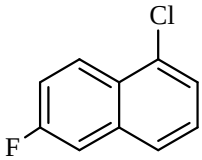
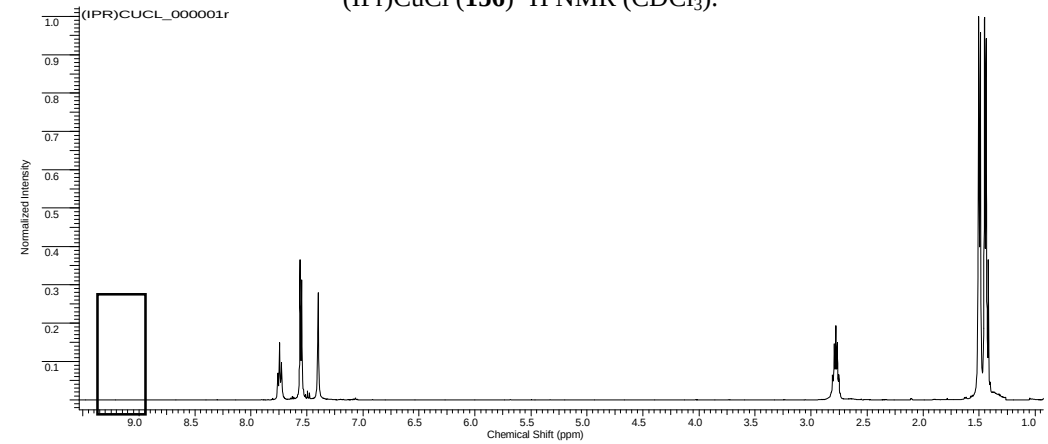
Entry	SM	Product	Conditions	Yield[a]	Yield[b]
1	**127d**	 **139d**	catalyst (5 mol %), DCE, 2 h, 200 ºC	66%	76%
2	**89a**	 **92a**	catalyst (5 mol %), DCE, 2 h, 200 ºC	51%	58%

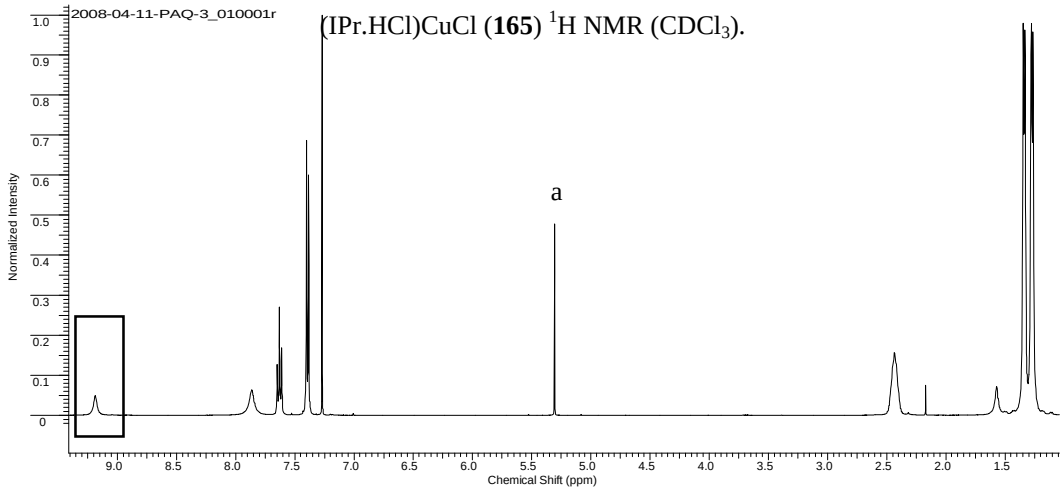
Table 2.4. Benzannulation reaction with complex **165** under MW radiation. a. (IPr.HCl)CuCl (**165**). b. (IPr)CuCl (**156**).

Repeating the benzannulation reaction to form 1–chloronaphthalene (**92**) using 10 mol % of the Nolan carbene **156** clearly concluded the formation of (IPr.HCl)CuCl (**165**, Figure 2.4).

(IPr)CuCl (**156**) ^{1}H NMR ($CDCl_3$).



(IPr.HCl)CuCl (**165**) ^{1}H NMR ($CDCl_3$).



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^{1}H NMR ($CDCl_3$) of the benzannulation reaction mixture of trichloroacetate **89** with 10 mol% (IPr)CuCl (**156**). a. DCM.

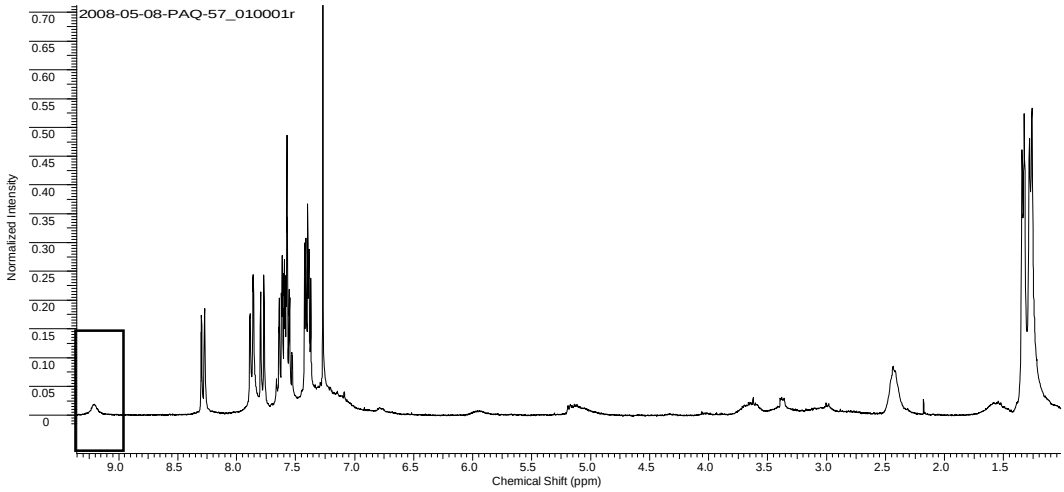


Figure 2.4. Spectroscopic data of the (IPr)CuCl's protonation studies.

2.4.1.4 CARBENE SCREENING STUDIES

Having demonstrated that CuCl carbenes can promote **ATRC** reactions very successfully we wished to test other transition metal–NHC complexes in our benzannulation reactions. Six catalysts were selected out of which five were commercially available (**167**, **168**, **169**, **170** and **171**) and only one **166** was synthesised (Figure 2.5).[57]

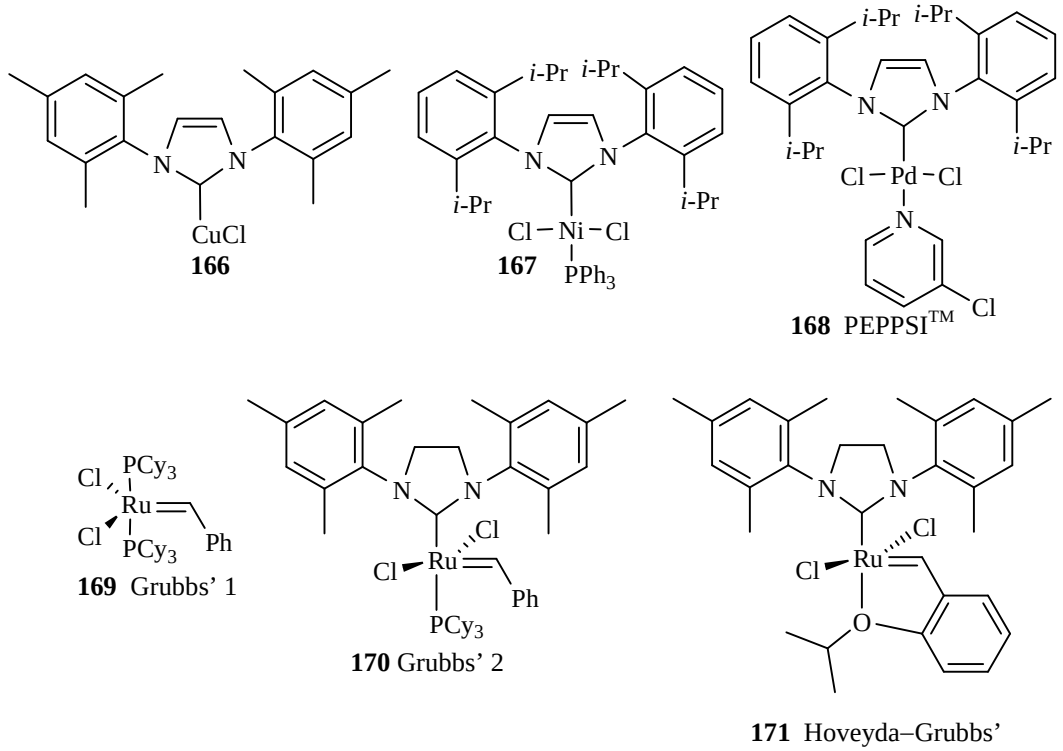
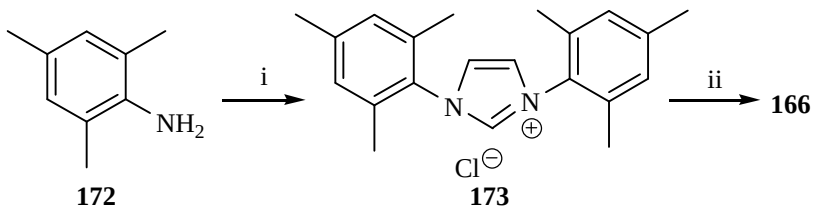


Figure 2.5. Carbene **c**atalysts tested in the benzannulation reaction.

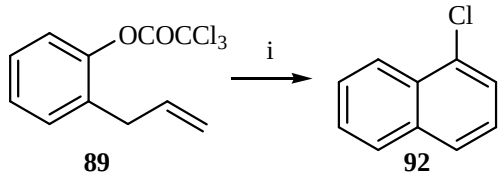
Synthesis of 1,3–bis–(2,4,6–trimethylphenyl)imidazolium copper chloride (**166**)[62] followed a modification of the procedure reported by Arduengo to synthesise 1,3–bis–(4–methylphenyl)imidazolium copper(I) chloride (**166**, Scheme 2.34).[63]



Scheme 2.35. Synthesis of carbene **166**. i. 2,4,6–Trimethylaniline (2.0 equiv.), paraformaldehyde (1.0 equiv.), toluene, 100 ºC, 1 h, cool to 40 ºC, HCl (1.0 equiv.), glyoxal (1.0 equiv.), then reflux, 1.5 h, 31%. ii. CuCl (1.0 equiv.), Na^{t}OBu (1.0 equiv.), THF, 4 h, rt, 88%.

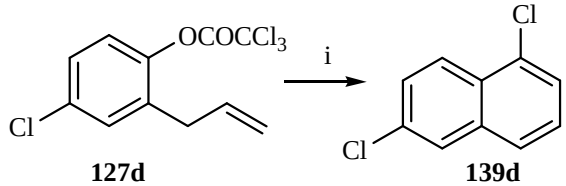
Replacing carbene **156** with a similar NHC carbene **166** did not have any significant effect on the yields obtained in the benzannulation reaction of trichloroacetates **89**, **127d** and **127c**, while the Ni complex **167** had a negative effect. Starting material was recovered for the reaction with trichloroacetates **89** and **127c** and a low yield for acetate **127d** was obtained (Scheme 2.35). The recently described PEPPSI™ palladium complex **168**[64] did promote the conversion of trichloroacetate **127c** to naphthalene **139c** but required longer reaction times (8 h); further studies were not conducted.

Previously in the group[11] it was demonstrated that Grubbs' 1 catalyst (**169**) is efficient at promoting **ATRC** reactions, an observation which has been extended to our benzannulation reaction. The benzannulation reaction using Grubbs' 1 catalyst (**169**) under the standard conditions afforded yields ranging from 46 to 55% (Scheme 2.35). Yields were also lower as the stability of the catalyst (or precatalyst) increased.[65] The mixture of catalysts **156** and **169** also proved to be unfavourable on the effectiveness of the benzannulation reaction.



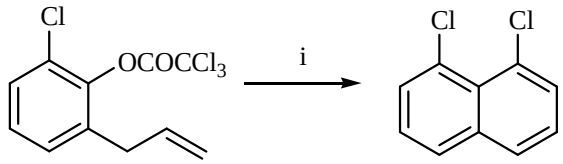
89 **92**

Entry	Catalyst	Yield
1	**166**	69%
2	**167**	SM
3	**168**	ND
4	**169**	49%
5	**170**	23%
6	**171**	ND
7	**156** + **169**	ND



127d **139d**

Entry	Catalyst	Yield
1	**166**	52%
2	**167**	36%
3	**168**	ND
4	**169**	46%
5	**170**	11%
6	**171**	ND
7	**156** + **169**	ND



127c **139c**

Entry	Catalyst	Yield
1	**166**	79%
2	**167**	SM
3	**168**[a]	18%
4	**169**	55%
5	**170**	38%
6	**171**	16%
7	**156** + **169**[b]	73%

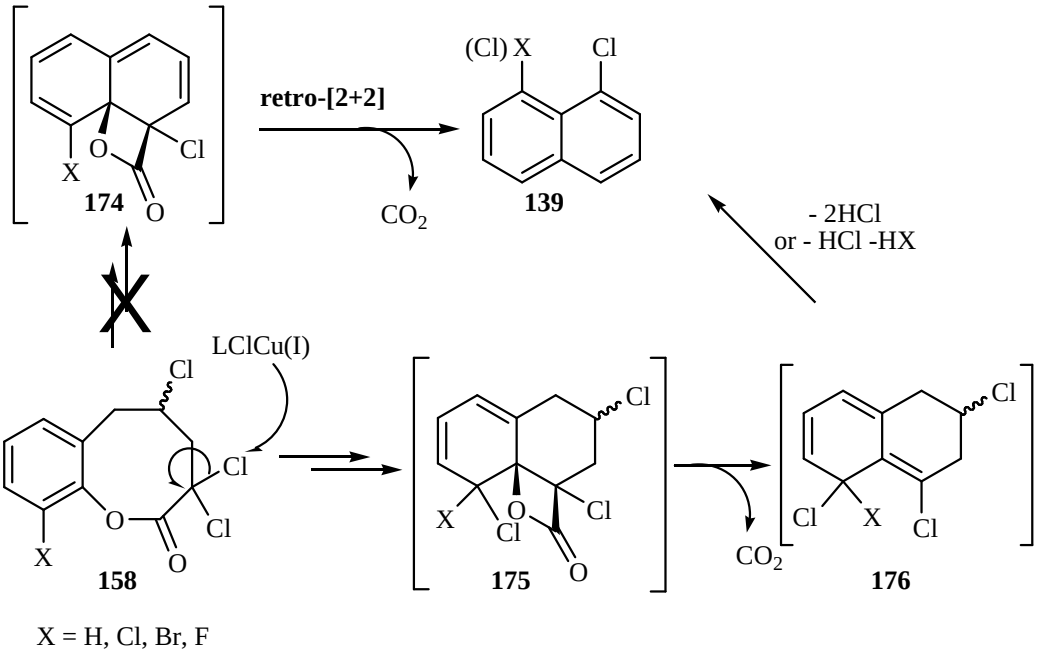
Scheme 2.36. Benzannulation reaction with different NHC catalysts. i. SM (500 mg), catalyst (5 mol%), DCE (6 mL), MW, 200 ºC, 2 h. a. 8 h at 200 ºC. b. Catalyst comprising 5 mol% of carbene **156** and 5 mol% of carbene **167**.

We were very pleased to see that the reaction can be promoted by a range of different carbene complexes. However, the good results obtained with (IPr)CuCl (**156**) are more consistent, therefore further studies of the benzannulation reaction were conducted with this carbene system.

2.4.2. FURTHER STUDIES OF THE BHQ MECHANISM

Even though the benzannulation reaction seemed to be very promising for the trichloroacetates tested before, when the bromosubstituted trichloroacetates **127a**, **127b** and **127f** were submitted to the standard benzannulation conditions bromine–chlorine exchange was observed (Table 2.6).

In view of the reaction mechanism proposed (*vide supra*) the electrocyclisation path would not explain the observed halogen exchange. On the other hand, the radical pathway would lead to intermediate **174** which would rearomatise by the loss of either HCl or HX leading to a possible halogen scrambling (Scheme 2.36).



Scheme 2.37. Proposed mechanism for the benzannulation reaction.

Halogen exchange can be expected on the grounds of the BDE's of the respective C–X bonds (Table 2.5). In particular, in the case of the fluorosubstituted starting material **89a** as this would necessitate the loss of HF instead of HCl from the intermediate **174**. This exchange is less likely to happen. On the other hand, exchange cannot be observed in the chlorine substituted arylacetates. However, we cannot be certain that it did not take place.

Halogen exchange in starting material **127a**, **127b** and **127f** would however be more likely to happen considering the relative C – X bond enthalpies (Table 2.5).

Bond	**Bond enthalpy / kJ mol^{-1}**
C – F	485
C – Cl	327
C – Br	285

Table 2.5. Tabulated C–halogen bond energies.

On inspection of Table 2.6, we note (entry 1 and 2) that conversion is good, but unfortunately the by–product formed by halogen exchange is also observed. However, when trichloroacetate **127f** was tested none of the expected 6,8–dibromo–1–chloronaphthalene (**139f**) was formed, instead, a mixture of the two exchange components **177** and **139e** were isolated. Analysis of the mixtures by GC/MS suggested that the major compound had a molecular formula of $C_{10}H_5BrCl_2$; and most likely to be naphthalene **177**. The minor product was obtained as a result of the exchange of both bromines giving 1,6,8–trichloronaphthalene (**139e**). Further investigations will be performed to elucidate the structure of the major product.

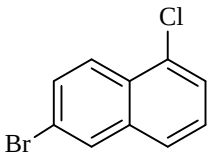
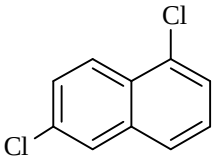
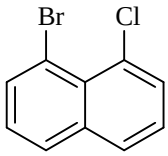
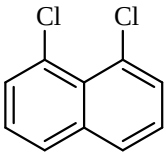
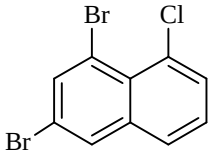
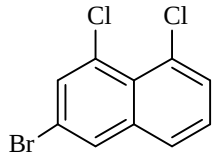
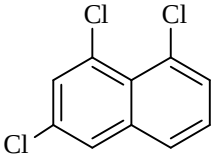
Entry	SM	Product	By–product	Ratio[a]	Yield
1	**127a**	 **139a**	 **139c**	> 132 : 1 (**139a** : **139c**)	42%
2	**127b**	 **139b**	 **139d**	1 : 1.6 (**139b** : **139d**)	65%
3	**127f**	 **139f**	 **177**  **139e**	0 : 17 : 1 (**139f** : **175** : **139e**)	53%

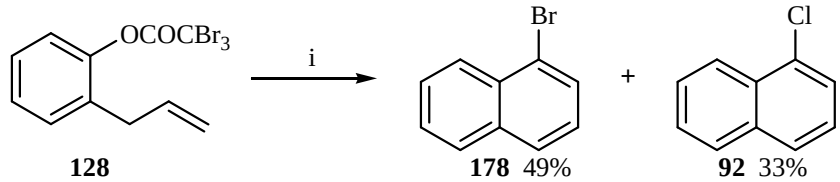
Table 2.6. Results of benzannulation sequences of derivatives of bromo–substituted trichloroacetates. a. Ratio and determined by GC/MS.

There are two essential points to mention about the cyclisation of trichlorocacetates **127a** and **127b**:

1. It is important to notice that halogen exchange is not the same for entries 1 and 2 (Table 2.6), and what is more significant, when **BHQ** of acetate **127b** was repeated the ratio of the product **139b** and by−product **139d** changed from 1.6 : 1 to 1 : 1. It seems to be that radical exchange is not a controlled process, in other words, it is not a repeatable reaction.

2. The amount of by−product obtained for the **BHQ** of acetate **127b** (entry 2, Table 2.6) is higher than that expected if the exchange was due to the copper catalyst. The only way that more chlorine could be incorporated into the molecule is from the solvent (DCE). Thus, we can conclude that the solvent plays an important role in this radical process.

Benzannulation reaction of 2−allylphenyl 2',2',2'−tribromoacetate (**128**) in DCE under the usual conditions gave two products 1−bromonaphthalene (**178**) and 1−chloronaphthalene (**92**) in a ratio of 1.5 : 1 respectively. Thus, halogen exchange cannot only take place on the aromatic ring of the starting material, but also in other positions of the naphthalene product especially in the case of bromine (Scheme 2.37). Obtaining multiple examples of bromine substituted naphthalenes is very important for future synthetic applications due to its high reactivity.



Scheme 2.38. Benzannulation of 2−allylphenyl 2',2',2'−tribromoacetate. i. CuCl (5 mol%), ligand **18** (5 mol%), DCE, 2 h, MW.

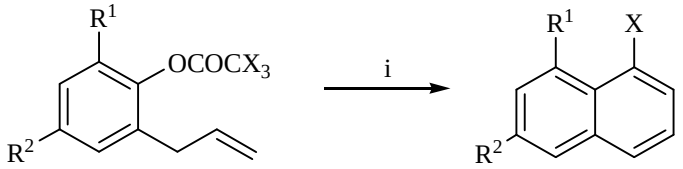
The influence of the solvent in the benzannulation reaction has proved enormously intriguing to us, as a result we focussed our work on investigating the influence of different solvents on this reaction.

2.5 SOLVENT SCREENING STUDIES

In order to optimise the **BHQ** reaction and minimise or avoid the halogen scrambling processes different solvent system were investigated.

2.5.1. BENZANNULATION REACTION IN DBE

Since halogen exchange (Br – Cl) was observed with DCE, DBE was chosen as a solvent so that halogen swap in acetates **127a**, **127b**, **127f** and **128** would not be observed.



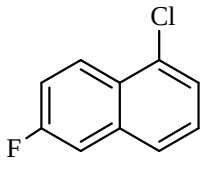
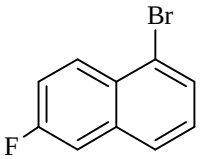
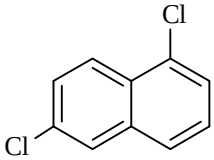
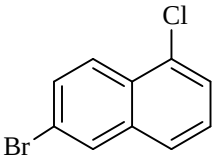
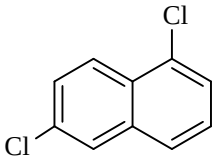
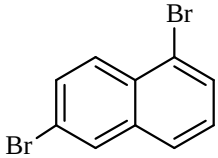
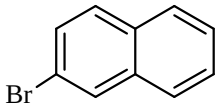
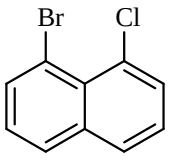
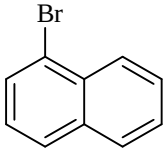
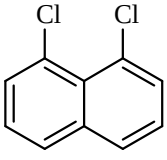
X = Cl or Br ; R = Br or H

Scheme 2.39. Benzannulation reaction in DBE. i. SM (500 mg), CuCl (5 mol%), ligand **18** (5 mol%), DBE (2 – 2.5 mL), MW, 2 h.

We started with fluorine–substituted acetate **89a** to check if the reaction could work with this solvent. Surprisingly when the product mixture of the reaction was analysed by GC/MS it was found to contain three different compounds. Chlorine – bromine exchange was observed along with a very small amount of fluorine – chlorine exchange, presumably from CuCl, giving naphthalene **179** (Table 2.7). Even though the yield is lower than with DCE (62%), it is a remarkable result because it was the first observation of radical substitution of fluorine in the benzannulation reaction, albeit to a small extent.

Benzannulation reaction of 2–allyl–4–chlorophenyl 2',2',2'–trichloroacetate (**127c**) did not lead to the anticipated chlorine–bromine exchange (entry 4, Table 2.7). Instead, exchange of chlorine with hydrogen was observed giving naphthalene **180**. In this particular case the solvent acted as a hydrogen atom donor, giving a compound with molecular formula $C_{10}H_6Cl$, 4–chloronaphthalene (**180**), as a by–product. Hydrogen atom donation by DBE is common to the reactions depicted in Table 2.7.

When the same reaction was attempted with 2–allylphenyl 2',2',2' –tribromoacetate (**128**, entry 5, Table 2.7) the main component was 1–bromonaphthalene (**178**) along with by–products due to proton (from DBE) and chlorine exchange giving naphthalene (**181**) and 1–chloronaphthalene (**92**) respectively in a ratio of 94 : 16 : 1. For entries 4 and 5 in Table 2.7 the desired product was formed in reasonable yield but, again, by–products were obtained due to bromine, proton and chlorine exchange.

Entry	SM	Product	By–product	Ratio	Yield
1	**89a**	 **92a**	 **179**  **139c**	> 99 : 1[b] [**92a** : (**179** + **139c**)]	50%
2	**127a**	 **139a**	 **139c**  **180**  **181**	> 99 : 1[b] [**139a** : (**139b** + **182** + **183**)]	46%
3	**127b**	 **139b**	 **178**  **139d**	45 : 53 < 1[b] : < 1[b] (**139b** : **176** : **127d** : **184**)	58%

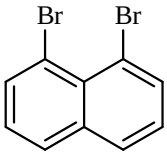
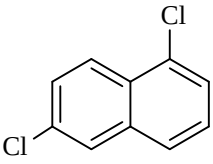
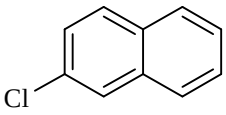
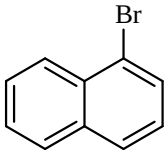
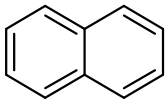
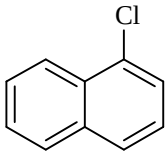
			 **182**		
4	**127c**	 **139c**	 **183**	80 : 20[b] (**139** : **180**)	73%
5	**128**	 **178**	 **184**  **92**	94 : 16 :1[b] (**178** : 1**81** : **92**)	44%[c]

Table 2.7. Results of benzannulation sequences in DBE. a. Products ratio were determined by ^{1}H NMR, traces of impurities are determined by GC/MS. b. Impurities obtained in the ^{1}H NMR.

Although we wished to perform more experiments in this solvent, reactions in DBE proved to be violently exothermic. Such was the violence of the reaction that it was deemed unsafe to conduct further work in this solvent.

2.5.2 BENZANNULATION REACTION IN DMSO

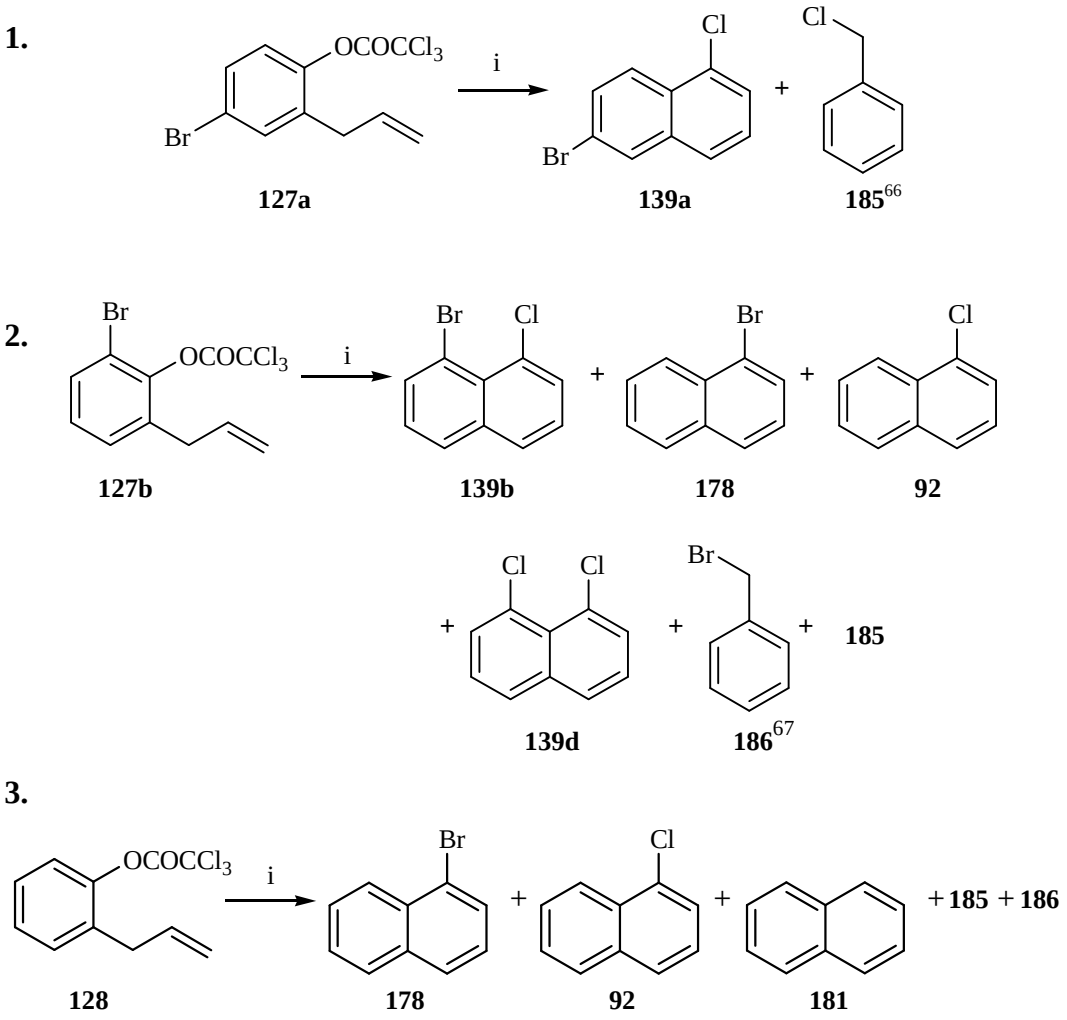
DMSO is very polar and it would be easy to reach high reaction temperatures in the MW reactor. However, in the microwave reactor the reaction became overpressurised resulting in the reaction vial exploding. To this end no further experiments were conducted.

2.5.3 BENZANNULATION REACTION IN TOLUENE

When the reaction was first discovered, the solvent used was toluene. Although the thermal reaction in toluene was sluggish,[37] we decided to test this solvent in the MW reactor to investigate if MW irradiation would afford better yields.

As we had predicted the MW reaction was more efficient (than the thermal one), however, halogen exchange was prominent. When trichloroacetates **127a**, **127b** and **128** were submitted to the benzannulation reaction in toluene, benzyl chloride

(**185**) or benzyl bromide (**186**) were obtained as by–products along with several substituted naphthalenes resulting from Br–Cl exchange (Scheme 2.39). Though the solvent proved to be a hydrogen donor in some cases product yields were not diminished compared to those obtained with DCE (Table 2.8), the formation of by–products was commonplace, therefore, excluding toluene as the preferred solvent for the **BHQ** reaction.



Scheme 2.40. Benzannulation reaction in toluene. i. SM (500 mg), CuCl (5 mol%), ligand **18** (5 mol%), toluene (2.5 mL), 200 ºC, MW, 2 h.

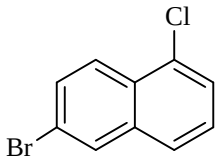
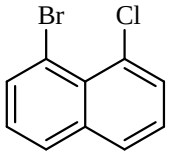
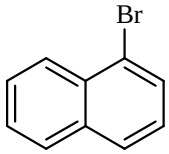
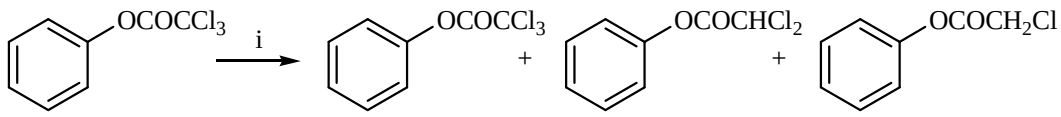
Entry	SM	Product	Ratio	Yield
1	**127a**		1 : 0.11[a] (**139a** : **185**)	54%
2	**127b**		1 : 0.08 : < 1% : < 1% : 8% : 0.25[b] (**139b** : **178** : **92** : **139d** : **186** : **185**)	53%
3	**128**		1 : 9% : 0.68 : 0.88 : < 1%[b] (**178** : **92** : **181** : **185** : **186**)	15%

Table 2.8. Benzannulation reaction results in toluene. Reaction conditions: SM (500 mg), CuCl (5 mol%), ligand **18** (5 mol%), toluene, 2 h, 200 ºC, MW. a. Ratio determined by ^{1}H NMR. b. Ratio determined by GC/MS.

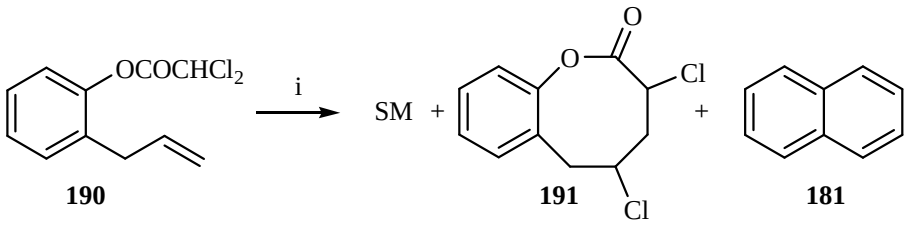
In an attempt to deduce whether the exchange had taken place before the benzannulation reaction started or during the radical cyclisation process, we submitted trichloroacetate **187** to the benzannulation conditions in toluene (2 h, 200 ºC, MW). A mixture of inseparable products was obtained containing starting material, monohydrogenated acetate and dihydrogenated acetate (Scheme 2.40). The exchange was a very favoured process and took place even after 20 min of reaction.



187 **187** **188** **189**

Scheme 2.41. Blank reaction results. i. CuCl (5 mol%), pincer ligand **18** (5 mol%), toluene, 2 h, 200 ºC, MW.

Dichloroacetate **190** was also subjected to the benzannulation conditions ((IPr)CuCl (**156**, 5 mol%), DCE, MW; Scheme 2.41). After 6 h in the MW reactor at 200 ºC starting material was recovered along with lactone **191** and naphthalene (**181**, Scheme 2.41).



Scheme 2.42. Benzannulation reaction of dichloroacetate **190**. i. (IPr)CuCl (**156**, 5 mol%), DCE, 6 h, 200 ºC, MW.

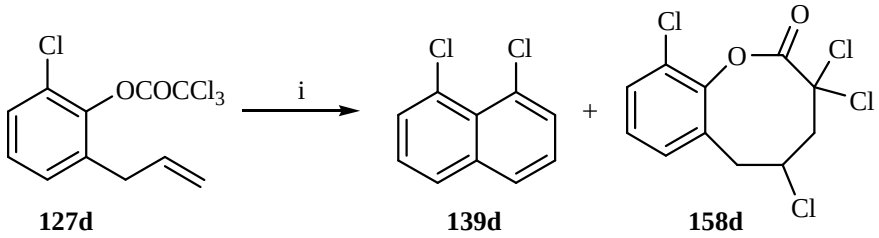
Considering the mixture of products obtained in the benzannulation reaction in toluene we can venture to say that if the exchange had taken place before the benzannulation reaction the lactone intermediate **191** and dichloroacetate **190** should have been isolated along with the other by–products. However, we cannot prove for certain when the exchange takes place.

2.5.4 THERMAL BENZANNUATION REACTION STUDIES

The choice of solvent for the benzannulation reaction is very important due to the side effects observed previously. One of the aims of the project was to be able to promote the reaction under thermal conditions in order to increase its versatility. Therefore we set a double goal of discovering a solvent that would promote the benzannulation reaction thermally and with minimum halogen exchange (Scheme 2.42).

We decided to test solvents with similar boiling points to toluene. α,α,α–Trifluorotoluene, cyclopentyl methyl ether, 1,4–dioxane and pyridine were selected and although they had similar boiling points, results were incredibly different. After 16 h in refluxing α,α,α–trifluorotoluene no conversion was observed and starting material **127d** was recovered. The reaction in cyclopentyl methyl ether showed some conversion and analysis of the crude reaction mixture showed the presence of starting material **127d**, the corresponding lactone **158d** and 1,8–dichloronaphthalene (**139d**, Scheme 2.42; entries 2 and 3, Table 2.9). These results proved that there was an obvious solvent effect on the reaction. On the other hand, the reactions in dioxane and pyridine were left to reflux for longer to allow the reaction to reach completion, however, in both cases yields were low (entries 4 and 5, Table 2.9).

It was obvious after these results that a higher boiling point solvent was necessary. Diglyme seemed to be the perfect choice; halogen exchange was not expected and its miscibility in water would facilitate isolation of the crude product. A 61% isolated yield was achieved (entry 6, Table 2.9). These encouraging results prompted further investigations with this solvent.



127d **139d** **158d**

Scheme 2.43. Benzannulation reaction in different solvents. i. **127d** (250 mg), (IPr)CuCl (**156**, 5 mol%), solvent, reflux.

Entry	Solvent	bp (ºC)[a]	Time	Yield of 139d
1	Toluene	100 – 110	2 days	40%
2	α,α,α–trifluorotoluene	100 – 103	16 h	SM
3	cyclopentyl methyl ether	106	16 h	SM + lactone **158d** + **139d**
4	1,4–Dioxane	100 – 102	3 days	16%
5	Pyridine	115	7 h	18%
6	Diglyme	162	16 h	61%

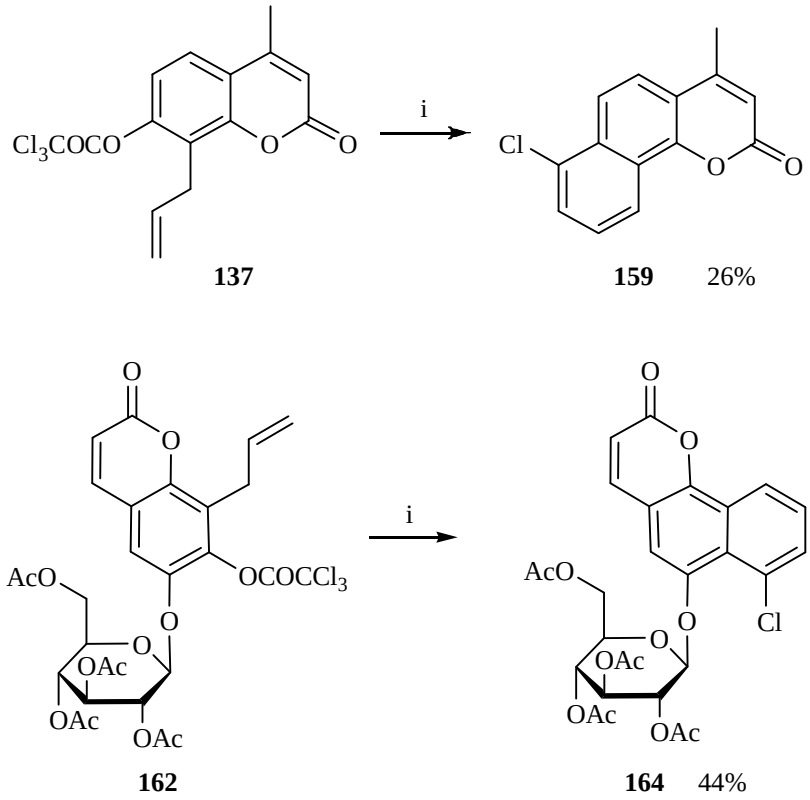
Table 2.9. Results of the thermal benzannulation reaction in different solvents. a. At 760 mm Hg.

2.5.4.1. THERMAL BENZANNULATION REACTION IN DIGLYME

The benzannulation reaction in diglyme afforded a good yield of benzannulation product **139d**. Reducing the reaction time from 16 h to 7 h gave a similar yield (59%), however with shorter times yields were lower than 59% (yield after 2 h refluxing in 1 mL of diglyme was 51%). Despite these good results, diglyme was a difficult solvent to work with due to mechanical losses.

Unfortunately these milder reaction conditions revealed a low reaction yield of the benzannulation reaction of trichloroacetate **137** to naphthalene **159** obtaining a

modest 26% yield (Scheme 2.43). However, glycoside **162** which seemed to be sensitive to the harsh benzannulation conditions in the MW, mainly decomposing during the course of the reaction, afforded a better yield of glycoside **164** (44%) and a cleaner crude reaction mixture after refluxing for 2 h in diglyme (Scheme 2.43 and Figure 2.6).



Scheme 2.44. Benzannulation reaction of trichloroacetates **137** and **162**. i. (IPr)CuCl (**156**, 5 mol%), diglyme, reflux, 2 h, 44%.

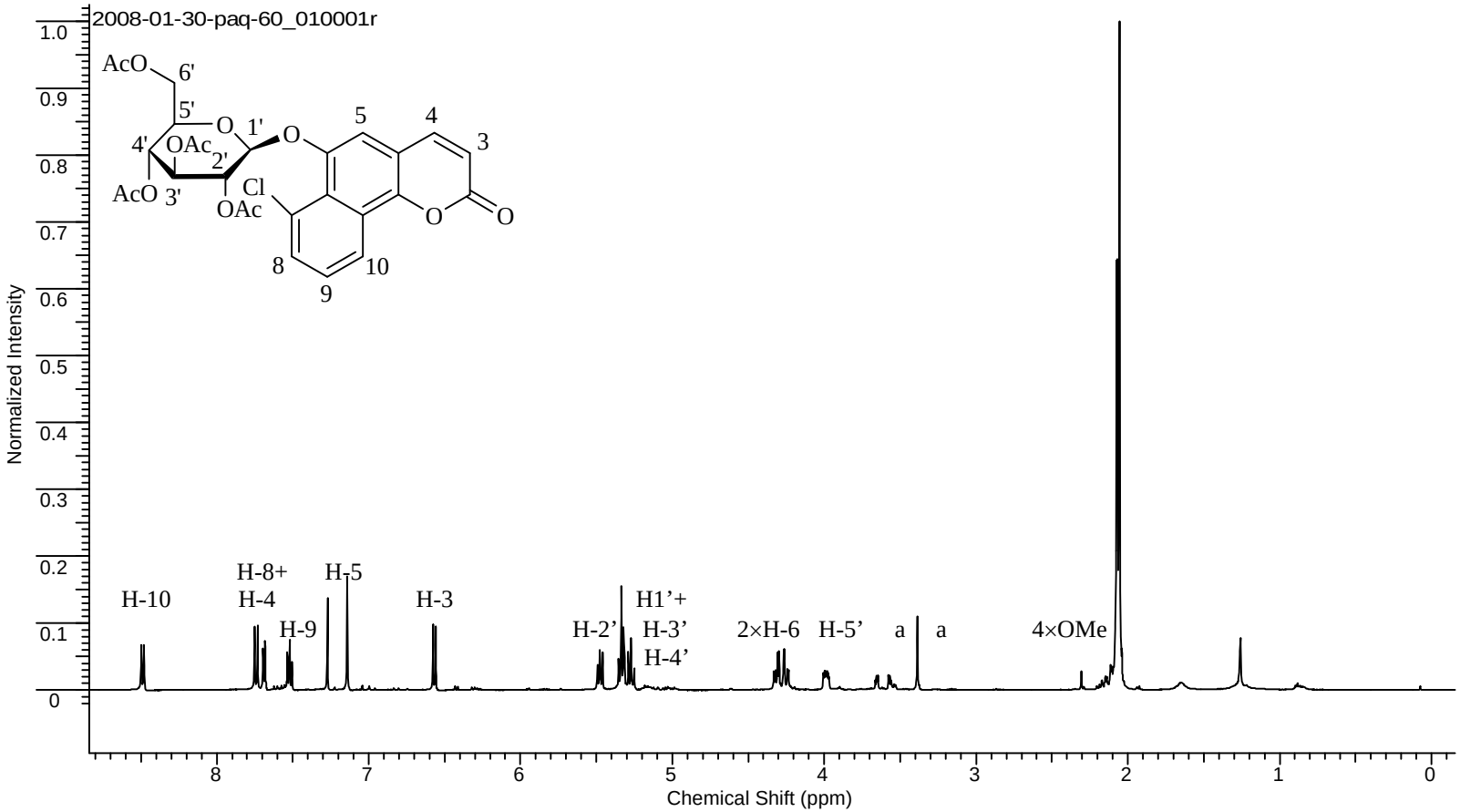
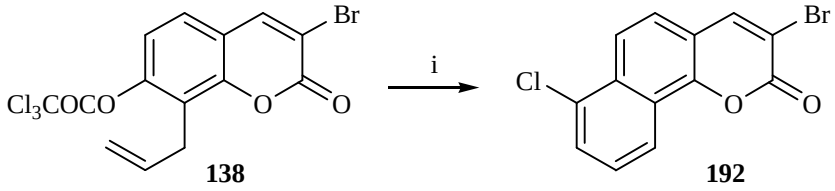


Figure 2.6. ^{1}H NMR of glycoside **162**. a. Peaks due to diglyme.

Benzannulation of coumarin **138** in refluxing diglyme for 7 h afforded coumarin **192** in a 41% yield (Scheme 2.44). No starting material or by–products were observed in the ^{1}H NMR of the crude mixture suggesting that decomposition of the starting material had taken place during the reaction. It is also important to note that bromine–hydrogen exchange was not observed. The presence of the bromine in the coumarin ring opens a door for future modifications in the synthesis of more complex molecules.

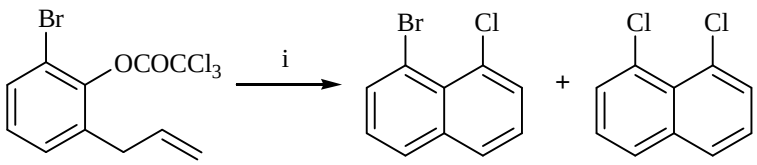


138 **192**

Scheme 2.45. Benzannulation of umbelliferone **138**. i. (IPr)CuCl (**156**, 5 mol%), diglyme, refluxed, 7 h, 41%.

Our first goal had therefore been achieved; we have found a solvent which can promote the thermal benzannulation reaction in moderate yields and under mild conditions.

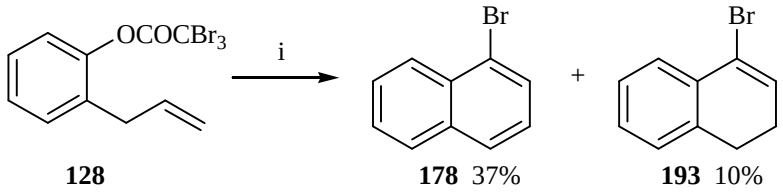
However, when *ortho*–bromotrichloroacetate **127b** was refluxed in diglyme in the presence of (IPr)CuCl (**156**) for 7 h (Scheme 2.45) halogen exchange was observed and an inseparable mixture of 1–bromo–8–chloronaphthalene (**139b**) and 1,8–dichloronaphthalene (**92**) was obtained in a 1 : 4.6 ratio respectively. The solvent was obviously not involved in the exchange, thus the chlorine responsible of the exchange must have come from the trichloroacetate starting material **127b** and the CuCl catalyst **156**.



127b **139b** 12% **92** 54%

Scheme 2.46. Benzannulation reaction of **127b** in diglyme. i. **127b** (250 mg), (IPr)CuCl (**156**, 5 mol%), diglyme, reflux, 7 h.

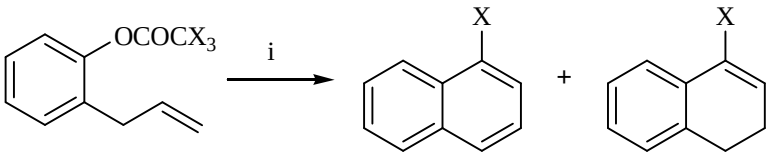
In order to eliminate any kind of chlorine source in the reaction mixture with the purpose of avoiding any halogen exchange, 2–allylphenyl 2',2',2'–tribromoacetate (**128**) was refluxed in diglyme in the presence of CuBr and ligand **18**. The desired product **178** was isolated as a inseparable mixture together with vinyl bromide **193**[68] in a ratio 3.4 : 1 respectively (Scheme 2.46).



128 **178** 37% **193** 10%

Scheme 2.47. 2–Allylphenyl 2',2',2'–tribromoacetate (**128**) benzannulation reaction. i. Tribromoacetate **128** (500 mg), CuBr (5 mol%), ligand **18** (5 mol%), diglyme (5 mL), reflux, 7 h.

It was the first time that this kind of reduction had been observed, we wondered if the reduction was as a result of the catalytic system (CuBr and ligand **18**) used in the reaction or due to the solvent. To have a comparable result, trichloroacetate **89** was submitted to the same reaction conditions (Scheme 2.47). The reduced product was also observed but to a lower extent; 1–chloronaphthalene (**92**) and 4–chloro–1,2–dihydronaphthalene (**195**) were obtained in a 200 : 1 ratio (entry 1, Table 2.10) concluding that the catalytic system of CuBr and ligand **18** was the reason for the reduction, when the ligand **18** was changed to IPr.HCl (**155**), reduction of 1–bromonaphthalene (**178**) increased to 50 : 1 ratio. We then synthesised (IPr)CuBr (**194**) from IPr.HCl (**155**) and CuBr[69] and when applied to the benzannulation reaction reduction was observed at a 20 : 1 ratio (entry 3 in Table 2.10). It was obvious that the formation of vinyl chloride **195** was related to diglyme but also the catalyst used to promote the cyclisation.



89 X = Cl **92** **195**

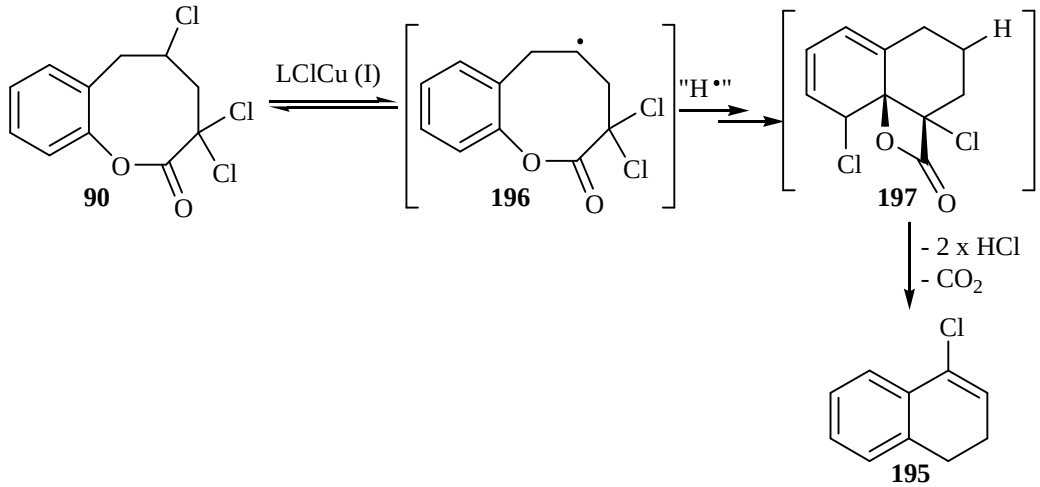
128 X = Br **178** **193**

Scheme 2.48. i. SM (500 mg), catalyst (5 mol%), diglyme (5 mL), reflux, 7h.

Entry	SM	Catalyst	Product	Ratio	Yield (%)
1	**89**	CuBr : ligand **18**	**92 : 195**	200 : 1	51 : 0.3
2	**128**	CuBr + IPr.HCl	**178 : 193**	50 : 1	41 : 0.8
3	**128**	(IPr)CuBr	**178 : 193**	20 : 1	43 : 2

Table 2.10. Benzannulation thermal results in diglyme for trichloroacetates **89** and **128**.

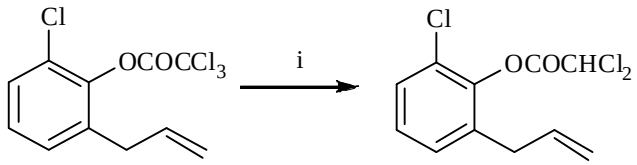
The suggested mechanism for the reductive formation of vinyl chloride **195** implies a radical hydrogen abstraction once radical lactone **196** has been formed (Scheme 2.48).



Scheme 2.49. Possible mechanism for the synthesis of vinyl chloride **193**.

The hydrogen source seems to come from the solvent so we submitted the benzannulation reaction in the presence of a possible reductive solvent like 1,4–cyclohexadiene (bp = 88 – 89 °C). Unfortunately, no benzannulated product was obtained after 16 h refluxing in 1,4–cyclohexadiene. Trichloroacetate **127d**

had only been reduced to dichloroacetate **198** with no radical cyclisation product observed (Scheme 2.49).



127d **198**

Scheme 2.50. Reduction obtained in the benzannulation reaction in cyclohexadiene. i. Trichloroacetate **127d** (250 mg), (IPr)CuCl (**156**, 5 mol%), 1,4–cyclohexadiene, 16 h, reflux.

2.5.5. MW BENZANNULATION REACTION IN DIGLYME

Cyclisation of a range of trichloroacetates in DCE with the Nolan catalyst **156** afforded products after 2 h in a MW reactor, irradiation of the reaction mixture was the key to promoting the radical process. Whereas the thermal benzannulation reaction was possible in diglyme achieving good yields and in reasonable reaction times, nevertheless we wondered if the influence of MW radiation could induce better results as we had seen with DCE.

To achieve this objective we tried to reduce the temperature of our benzannulation reaction from 200 ºC in DCE to 90 ºC in diglyme and in the presence of the Nolan catalyst **156** (entry 1 in Table 2.11). After 2 h at 90 ºC just starting material **127d** was recovered. When the reaction was repeated at 140 ºC starting material and lactone **158d** were the only compounds observed. The reaction temperature was further increased to 170 ºC (diglyme bp = 162 ºC) and a reasonable 67% yield was obtained (entry 3 in Table 2.11) comparable to that obtained in DCE with (IPr)CuCl (**156**, entry 1 in Table 2.11). When the reaction was concentrated to in 1 mL (entry 4 Table 2.11) instead of 4 mL of diglyme the yield increased to 79% and in addition the pressure build up in the reactor observed with DCE was not a problem. In the case of diglyme the MW irradiation does not have detrimental effects on the yield. Finally, when the reaction times were reduced to 10 min and 30 min the reaction yields were negatively affected decreasing to 51% and 53% respectively (entries 5 and 6 in Table 2.11).

Heating trichloroacetate **162** (250 mg) and (IPr)CuCl (**156**) in the MW reactor for 2 h in diglyme at 170 ºC, a 50% yield of glycoside **164** was obtained. For the first time, traces of sugar cleavage were observed giving coumarin **199** but unfortunately it was not possible to fully isolated this material.

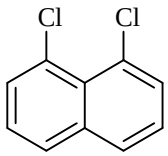
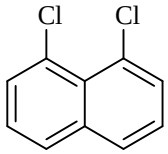
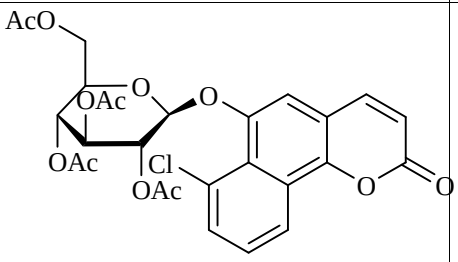
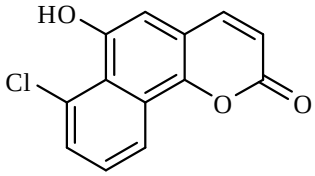
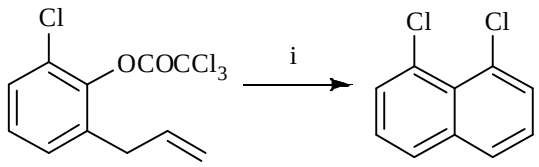
Entry	Diglyme	T (ºC)	Time	Product	Yield
1	4 mL	90	2 h	SM **127d**	–
2		140	2 h	SM **127d** + Lactone **156d**	–
3		170	2 h	 **139d**	67%
4	1 mL	170	2 h	 **139d**	79%
5			10 min		51%
6			30 min		53%
7	1 mL	170	2 h	 **164**	50%
				 **199**[70]	12%[a]

Table 2.11. Benzannulation results in diglyme under MW irradiation. a. Impure sample.

2.6. BENZANNULATION REATION IN THE PRESENCE OF REDUCING AGENTS

One of the key factors for the development of the benzannulation reaction was the ability of Cu to reduce from Cu(II) to Cu(I) during the course of the reaction. The addition of a reducing agent to the reaction could encourage the reduction of Cu(II) (Scheme 2.50). Metals with good reducing properties were added in excess to our reaction (Table 2.12). Alas the addition of the metals to the reaction did not increase the reaction yield, generally lower yields were obtained, copper dust being the only metal that did not have an adverse effect on the **BHQ** reaction.



127d **139d**

Scheme 2.51. Benzannulation reaction in the presence of reducing agents. i. Acetate **127d** (500 mg), catalyst (5 mol%), metal (excess), diglyme (0.5 mL), 2 h, reflux.

Entry	Catalyst	Metal additive (excess)	Yield
1	(IPr)CuCl	Zn	12%
2		Fe	39%
3		Cu	51%
4		In	5%
5	CuCl, ligand **18**	Cu	39%

Table 2.12. Benzannulation results of the addition of reducing metals to the mixture.

Ongoing work within the group is exploring the possible benefits of the addition of reducing agents to the reaction mixture.

CHAPTER 3: APPLICATIONS OF THE BHQ REACTION

3.1 SYNTHESIS OF SELECTIVE DEUTERIUM–LABELLED COMPOUNDS

Deuterium–labelled compounds have been used widely as research tools in biological, environmental and other sciences.[71] Important uses include:

1. internal standards in mass spectrometry;[72]

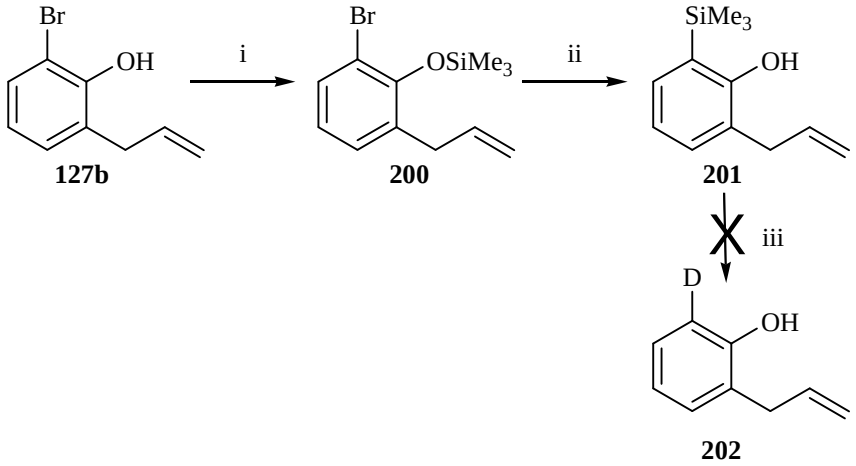
2. elucidation and detailed mechanistic studies of many chemical reactions;[73]

3. tools to investigate pharmacokinetics;[74]

4. compounds facilitating signal assignment and structure determination in NMR spectroscopy.[75,76]

The regioselectivity observed in the **BHQ** reaction potentially enables selective deuteration of aromatic systems. We submitted some deuterated trichloroacetates to the benzannulation conditions to investigate the potential of the **BHQ** reaction for the synthesis of labelled analogues.

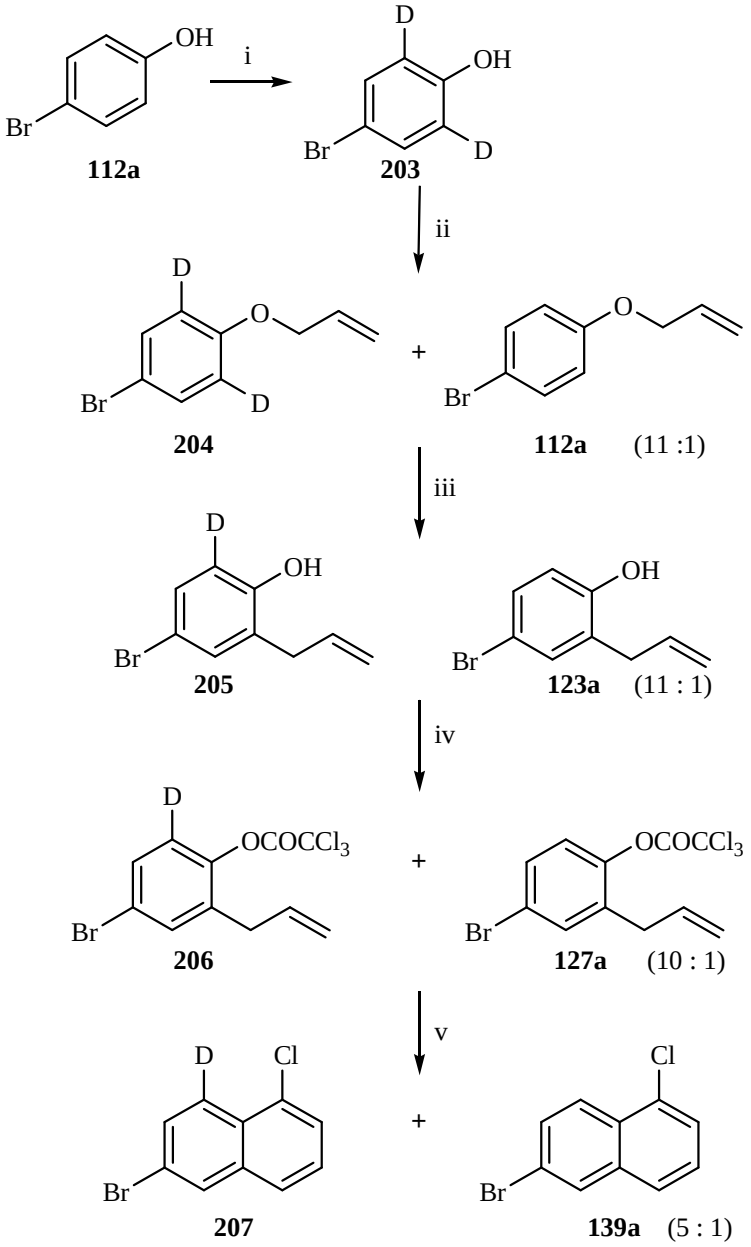
The first substrate introduced the deuterium label in the original aromatic ring. Our first attempt to synthesise phenol **202** the deuterium analogue of 2–allylphenol (**121**), was *via* silicon deuterium–substitution. The formation of (2–allyl–6–bromophenoxy)trimethylsilane (**200**) occurred very smoothly after the addition of hexamethyldisilazane to bromophenol **127b** at 170 ºC (Scheme 3.1).[77] Halogen–lithium exchange on silylether **200** triggered a spontaneous *retro*–Brook rearrangement to give 2–allyl–6–(trimethylsilyl)phenol (**201**) in good yield. Unfortunately, Si–D exchange using deuterated–TFA resulted in an inseparable mixture of two products. The phenol moiety was also likely to be deuterated under the reaction conditions, however, attempts to protect the phenol met with little or no success. An alternative route to the deuterated analogue **202** was sought.



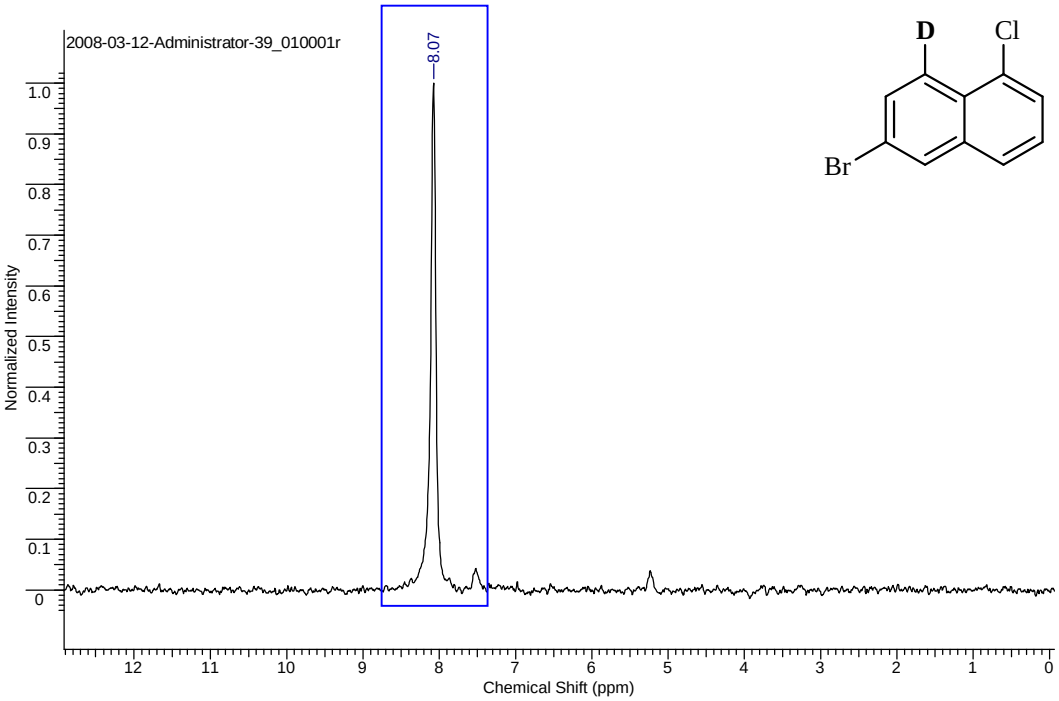
Scheme 3.1. Attempt to synthesise the deuterium analogue **202**. i. $(Me_3Si)_2NH$ (0.55 equiv.), 170 ºC, 2 h, 63%. ii. ^{n}BuLi (1.1 equiv., 1.6 M in hexane), THF, −78 to 0 ºC, 77%. iii. d-TFA (2.0 equiv.), CH_2Cl_2, 36 h, 25 ºC.

Literature procedures suggest that phenols can be deuterated with D_2O in the presence of Na[78] by a repeating a D_2O/NaOD cycle. 4−Bromo−2,6−dideuterophenol (**203**) was easily obtained by following the described literature procedure by Williams (Scheme 3.2). Allylation of the phenol **203** and Claisen rearrangement were not as efficient as in the non−deuterated analogue **123a**, so the standard procedures for this chemistry were modified slightly [higher reaction temperature for allylation (refluxing instead than rt) and longer reaction times for the Claisen rearrangement (9 h instead of 6 h)]. Unfortunately, some D–H exchange was observed in the allylation product affording ethers **204** and **112a** in a 11 : 1 ratio respectively. Finally, trichloroacetate **206** was prepared in moderate yield (61%) giving the deuterated and the non−deuterated trichloroacetates **206** and **127a** in a 10 : 1 ratio respectively.

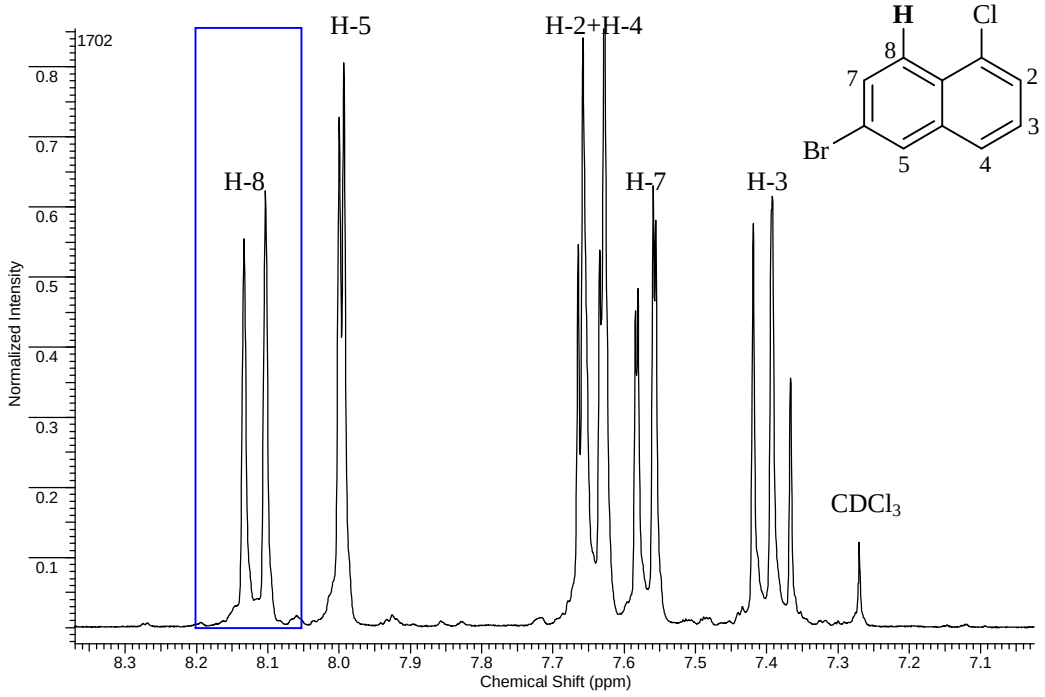
Trichlorophenols **206** and **127a** were then submitted to the standard benzannulation conditions ((IPr)CuCl (**156**, 5 mol%), DCE, 200 ºC, MW, 2 h) obtaining naphthalene **207**. During the radical cyclisation a very small amount of D–H exchange occurred and a 5 : 1 ratio (68%) of naphthalenes **207** and **139a** was observed by ^{1}H NMR (Figure 3.1).



Scheme 3.2. Synthetic route of naphthalene **207**. i. Na, D_2O, 100 ºC, 5 days (change of the solvent every 24 h is required until ^1H NMR results show that the reaction had reached completion), 65%. ii. Allyl bromide (1.2 equiv.), K_2CO_3 (1.2 equiv.), acetone, reflux, 16 h, 72%. iii. 210 – 220 ºC, 9 h, 25%. iv. $ClCOCCl_3$ (1.2 equiv.), Et_3N (1.2 equiv.), Et_2O, 0 ºC, 3 h, 61%. v. (IPr)CuCl (**156**, 5 mol%), DCE, 200 ºC, MW, 2 h, 68%.



^{2}H NMR (CH_2Cl_2) of naphthalene **207**.

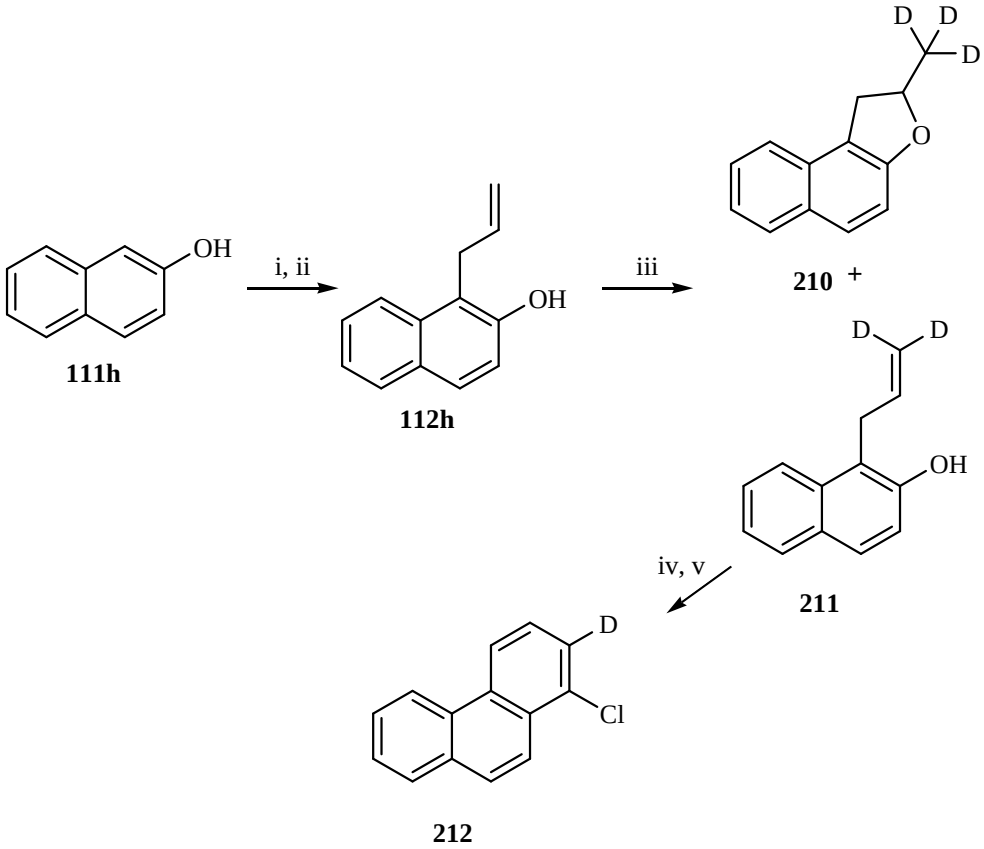


^{1}H NMR ($CDCl_3$) of naphthalene **139a**.

Figure 3.1. Deuterium studies spectroscopic data.

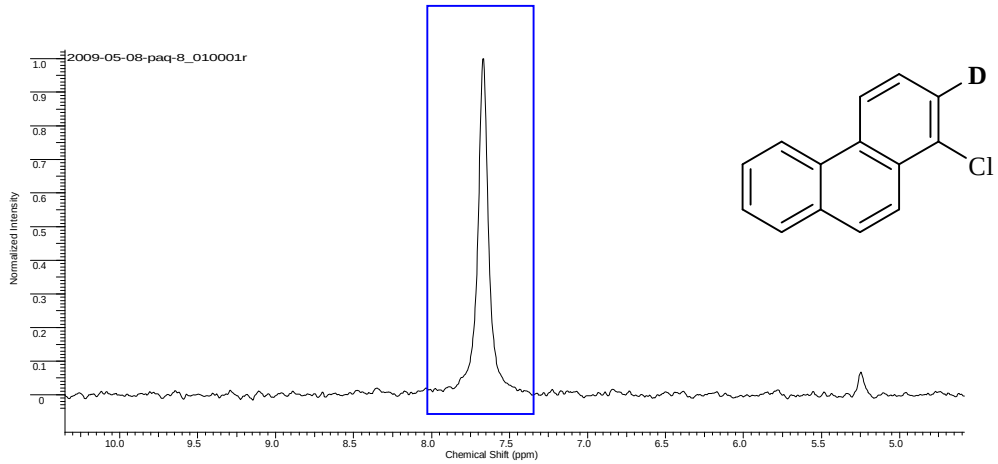
It is also reported in the literature that deuterium could also be introduced into the terminal carbon of the allyl group of 1–allylnaphthalen–2–ol (**112h**) when irradiated in the presence of D_2O.[79]

1–Allylnaphthalen–2–ol (**112h**) was obtained from allylation (ether **208**) of 2–naphthol under standard conditions followed by the Claisen rearrangement in toluene at 200 ºC in the MW reactor (Scheme 3.3). The naphthol was then heated in the MW reactor at 200 ºC for 3 h in the presence of D_2O, replacing the D_2O after 1.5 h. Unfortunately, two products were obtained, the desired deuterated naphthol **211** and furan **210** in a 4 : 1 ratio. The pure deuterated naphthol **211** was acylated with $ClCOCCl_3$ in the presence of Et_3N (trichloroacetate **209**) and submitted to the benzannulation conditions [(IPr)CuCl (**156**, 5 mol%), DCE, 200 ºC, MW, 2 h] affording the required 1–chloro–2–deuterophenanthrene (**212**) in a reasonable 42% yield.

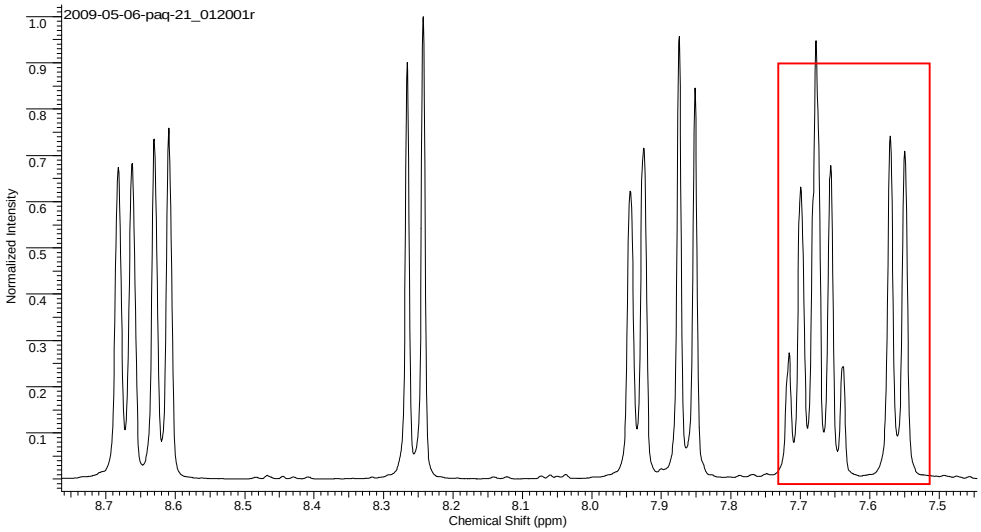


111h **112h** **211** **212**

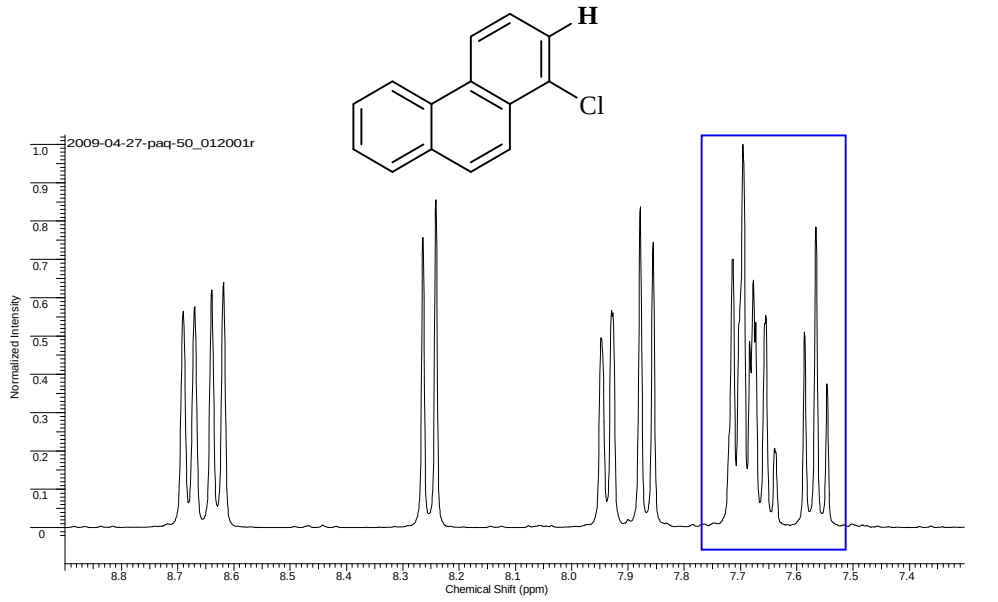
Scheme 3.3. Synthesis of deuterophenanthrene **212**. i. Allyl bromide (1.2 equiv.), K_2CO_3 (1.2 equiv.), acetone, reflux, 5 h, 99%. ii. Toluene, 200 ºC, MW, 11 h, 75%. iii. D_2O, 200 ºC, MW, 1.5 h and exchange of the solvent then 200 ºC, MW, 1.5 h, 66%. iv. $ClCOCCl_3$ (1.25 equiv.), Et_3N (1.25 equiv.), Et_2O, rt, 16 h, 90%. v. (IPr)CuCl (**156**, 5 mol%), DCE, 200 ºC, MW, 2 h, 42%.



1–Chloro–2–deuterophenanthrene **212** ^{2}H NMR (CH_2Cl_2).



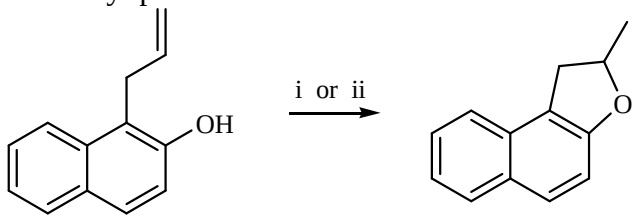
1–Chloro–2–deuterophenanthrene (**212**) ^{1}H NMR ($CDCl_3$).



1–Chloronanthrene (**96**) ^{1}H NMR ($CDCl_3$).

Figure 3.2. Deuterium studies spectroscopic results.

We wondered whether formation of the furan **210** during the deuteration step had been caused by traces of acid in the reaction mixture. Thus, we heated 1–allylnaphthalen–2–ol (**112h**) in H_2O for 2 h but no cyclisation took place. However, if a crystal of *p*–toluene sulfonic acid was added to the mixture and heated at 200 ºC for 2h 2–methyl–1,2–dihydronaphthol[2,1–*b*]furan (**213**) was afforded in 67% yield (Scheme 3.4). This indicated that the presence of a trace of acid in the deuteration of the allyl naphthol **112h** was responsible for the formation of the furan by–product.



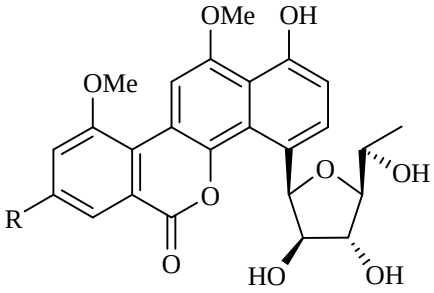
112h **213**

Scheme 3.4. Studies on the formation of furan **213**. i. H_2O, 200 ºC, 2 h, 0%. ii. *p*–toluenesulfonic acid, H_2O, 200 ºC, 2 h, 63%.

3.2 STUDIES TOWARDS THE SYNTHESIS OF GILVOCARCIN M

3.2.1 INTRODUCTION

Gilvocarcin M (**214**, Figure 3.3) is the minor analogue of a complex *C*–glycoside isolated 1981[80] from a *Streptomyces*. Gilvocarcins show significant antibacterial, antifungal, antiviral and antitumor activity with exceptionally low toxicity.[81] The anticancer gilvocarcins belong to one of four classes of naturally occurring *C*–aryl glycosides to which various rare sugar units are connected through a C–C bond.

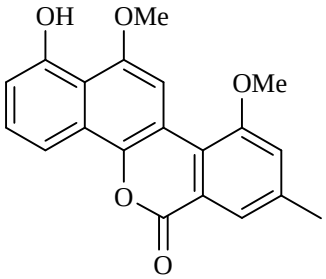


R = Me (M) **214**
R = Et (E) **215**
R = Vinyl (V) **216**

Figure 3.3. gilvocarcin structure.

The gilvocarcins locate the sugar unit *para* to a phenolic hydroxyl group. They share a common tetracyclic aromatic nucleus, 6*H*–benzo[*d*]–naphtho[1,2–*b*] pyran–6–one to which rare sugars are attached as a *C*–glycoside at the C(4) position. Fucose, in the furanosyl form, is the sugar unit present in the gilvocarcins M, E and V, and there are three congeners which differ in the C(8) substituent in the tetracyclic core (methyl (M) **214**, ethyl (E) **215** and vinyl (V) **216**). Gilvocarcin M contains a methyl group in the 8–position. These compounds have stimulated considerable interest in their syntheses, due to the challenge presented by the unusual *C*–glycoside structures linked to the highly functionalised aromatic skeleton.

Approaches to the aglycons and defucogilvocarcins such as **217** (Figure 3.4),[82] have been extensively studied, and as many as ten successful routes have been documented so far. However, total syntheses of the gilvocarcin natural products have remained a challenge because of the potential difficulty of the *C*–glycoside formation.



217

Figure 3.4. defucogilvocarcin **217**.

Snieckus *et al.*[83] have recently reported the latest synthesis of defucogilvocarcin M. The C–(8) methyl group is incorporated by using metal–catalysed coupling reaction with the triflate **219**. The key step for this synthesis is the DReM (directed remote metalation)–carbamoyl migration of carbamate **219** followed by standard lactonisation. Biaryl **219** is disconnected to carbamate **222** and arene **221** *via* a cross coupling reaction (Figure 3.5).

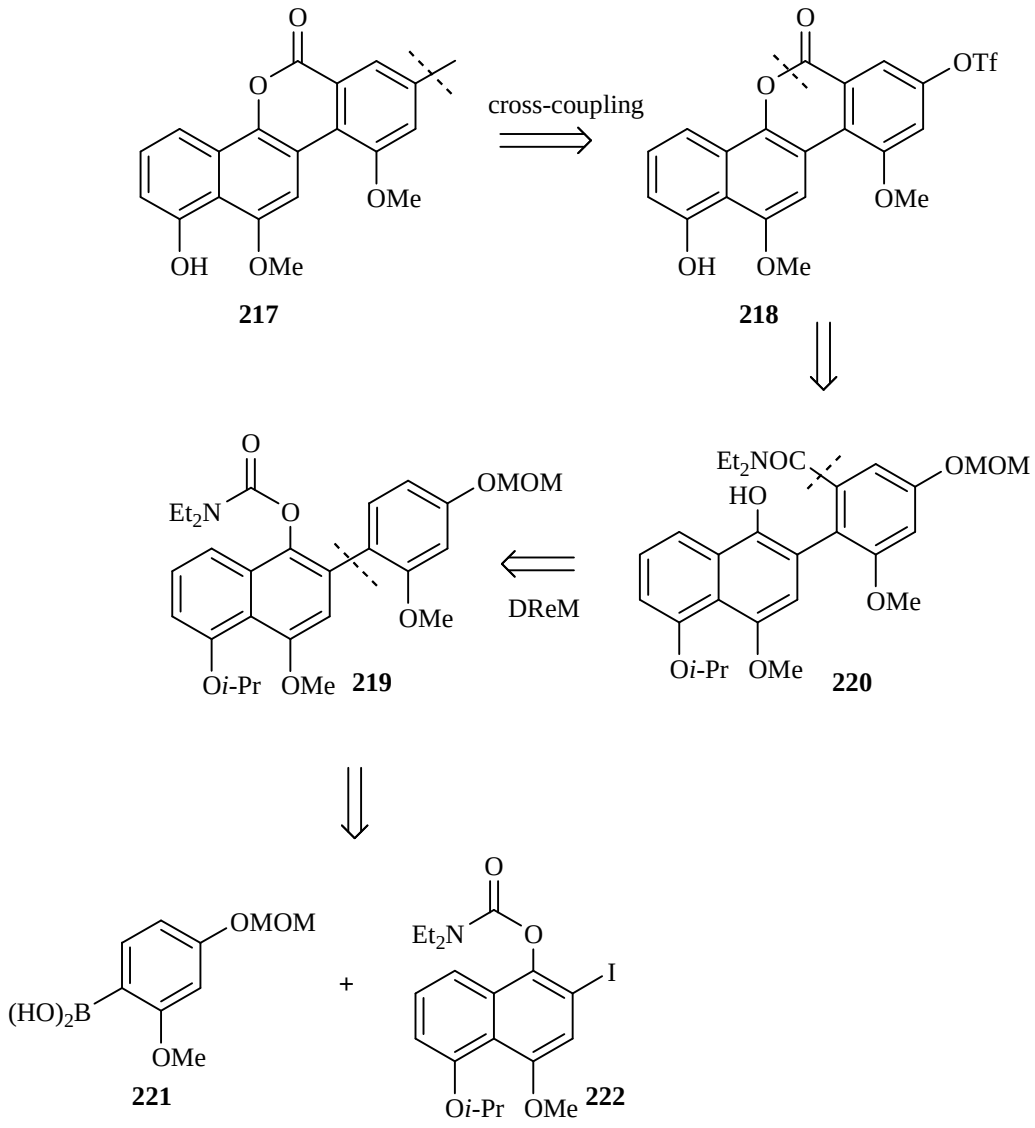
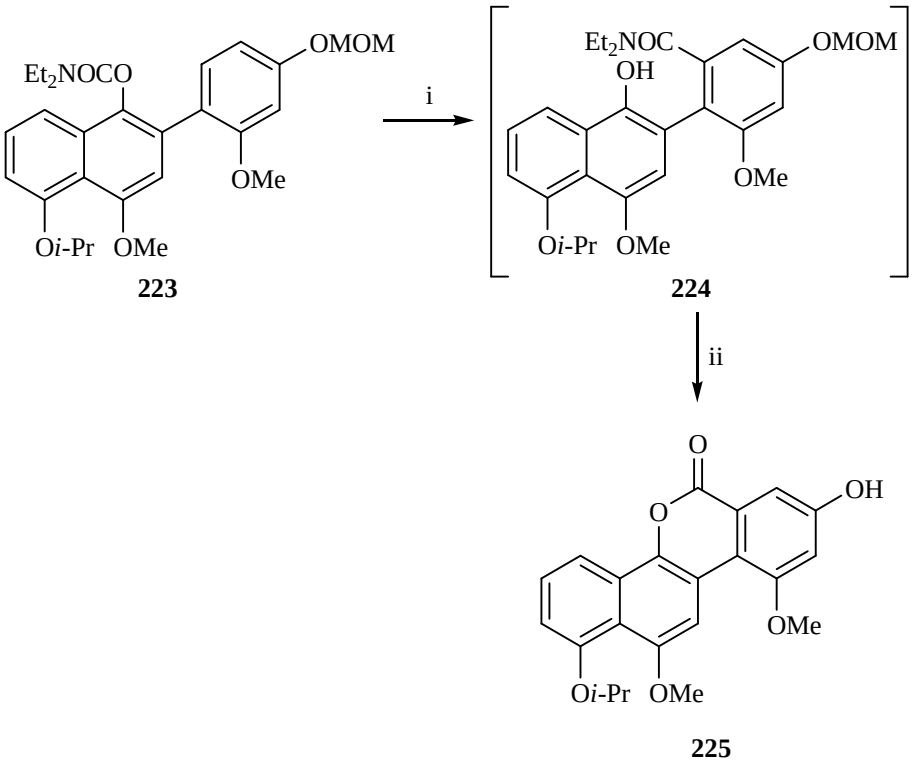


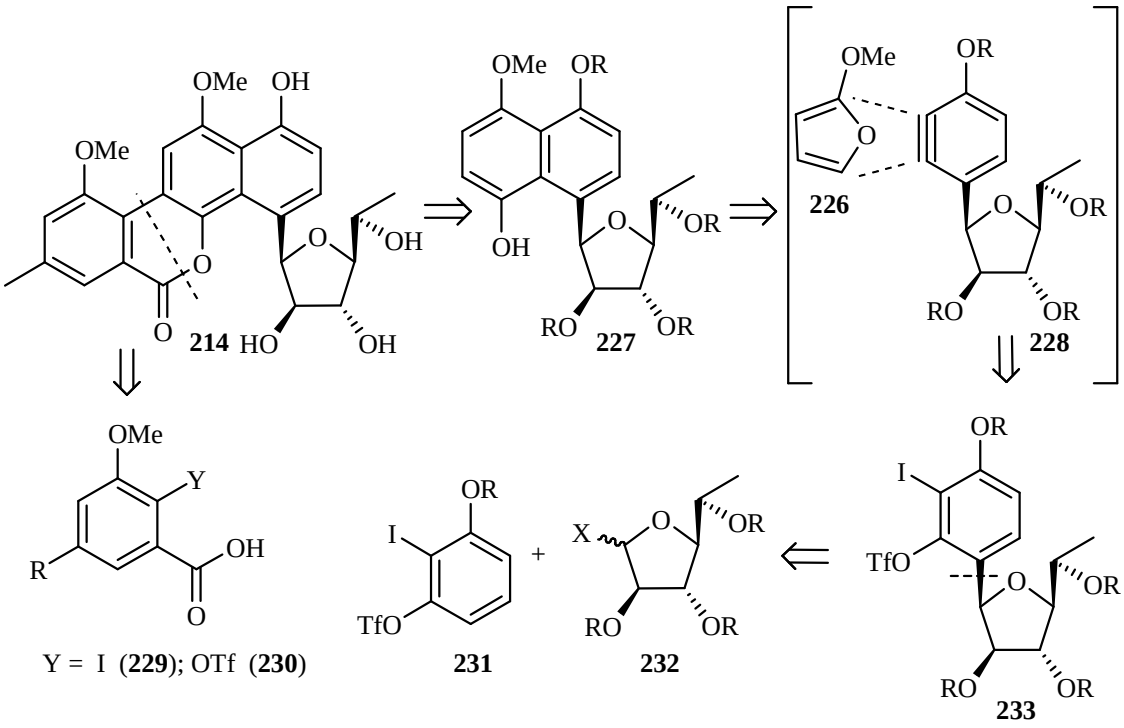
Figure 3.5. Snieckus retrosynthetic analysis of defucogilvocarcin M (**217**).

A DReM–carbomyl migration completed the tetracyclic ring system **225** in the presence of LDA affording 70% yield. Low concentration of the base in the reaction mixture was required to avoid possible side reactions induced by base–cleavage of the isopropoxy and carbamoyl groups.



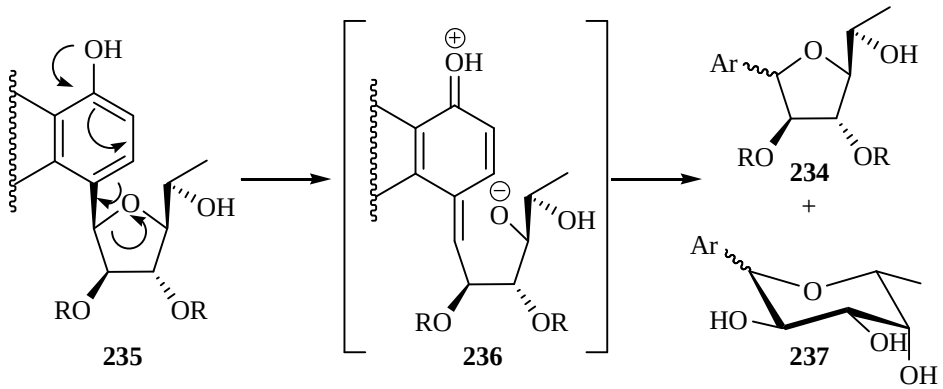
Scheme 3.5. DReM–carbomyl migration for the synthesis tetracyclic ring system. i. LDA, THF, reflux, 1 h. ii. HOAc/H_2O, reflux, 70%.

The first total synthesis of optically pure gilvocarcin M was thought to be reported in 1992 by Suzuki *et al.*[84] Unfortunately, the sign of the optical rotation was opposite to the one reported in the literature.[85] Two years later they reported the total synthesis of the naturally occurring enantiomer.[86] The strategy chosen was based on the initial glycosylation of a simple aromatic precursor because they considered that there could be some potential difficulty in the regio and stereocontrolled connection of a carbohydrate to the complex and fully elaborated aromatic system. A linear synthesis for the elaboration of the aromatic skeleton followed (Scheme 3.6). The key intermediate was the naphthol **227** with the sugar unit attached. One of the challenges for the synthesis of this fragment was the installation of the sugar in the correct position and the differential protection of hydroxyl groups to allow selective manipulations. The second challenge was the formation of a benzyne intermediate with the sugar substituent attached.



Scheme 3.6. Suzuki retrosynthetic analysis of gilvocarcin M.

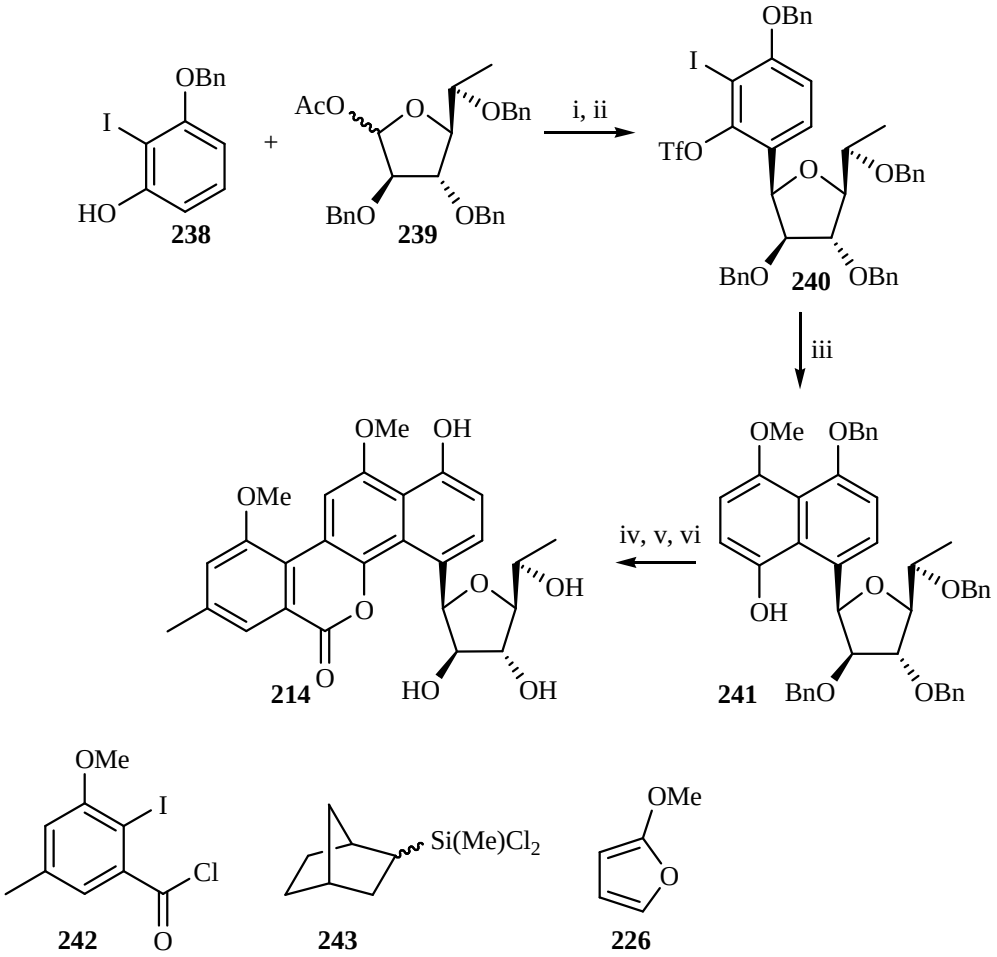
A major concern for Suzuki was the apparently unfavourable disposition of the aryl *C*–glycoside bond as it was likely to suffer anomerisation and/or ring enlargement reactions probably *via* quinone methide species **236**, to give an equilibrium mixture of the furanoside/pyranoside anomers **234** and **237** respectively (Scheme 3.7).



Scheme 3.7. Possible anomerisation of the furanoside.

As mention above the most challenging step was the aryl C–glycoside bond formation. The key C–C bond forming step was heavily dependent on the Lewis acid promoter. Different catalysts were screened and silane **243** gave the best selectivity (Scheme 3.8). The resulting phenol was converted to the

corresponding triflate **240** and treatment with ^{n}BuLi in THF in the presence of 2–methoxyfuran (**226**) formed the benzyne *in situ*. A [4 + 2] cycloaddition with the furan followed by aromatisation gave naphthol **241**. Acylation with iodide **242** followed by intramolecular biaryl coupling gave gilvocarcin M **214** after deprotective hydrogenation.



Scheme 3.8. Synthesis of gilvocarcin M. i. **243**–$AgClO_4$, CH_2Cl_2 (–78 to –20 ºC), 91%. ii. Tf_2O, $^{i}Pr_2NEt/CH_2Cl_2$, –78 ºC, 1 h, 99%. iii. ^{n}BuLi, **226**/THF, –78 ºC, 10 min, 88%. iv. **242**, *i*–Pr_2NEt, DMAP (cat.), THF, rt, 2 h, 91%. v. $(Ph_3P)_2PdC1_2$ (26 mol%), NaOAc/DMA, 125 ºC, 5 h, 90%. vi. H_2, 10% Pd–C/MeOH–THF, rt, 5 h, 90%.

3.2.2. TOWARDS THE SYNTHESIS OF GILVOCARCIN M

Our approach to gilvocarcin M was by formation of the C(1)–C(2) bond using the **BHQ** reaction (Figure 3.6).

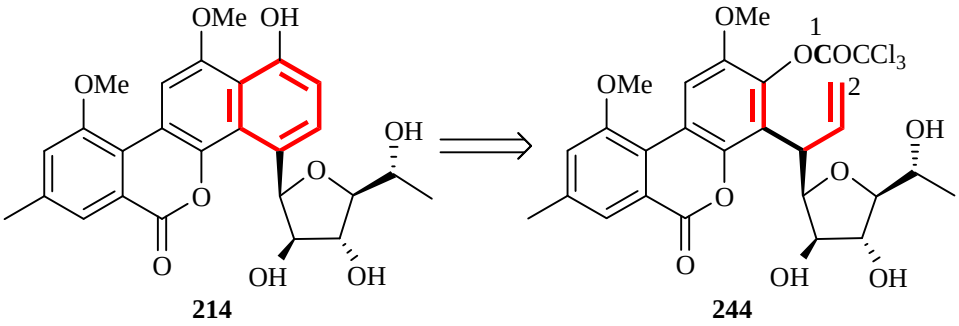


Figure 3.6. Proposed synthesis of gilvocarcin M by **BHQ** reaction.

In order to obtain the necessary trichloroacetate **244** for the **BHQ** reaction it was necessary to synthesise carbohydrate **245**. Allyl ether **245** would undergo a Claisen rearrangement followed by acylation of the phenol **246** affording trichloroacetate **244** (Figure 3.7).

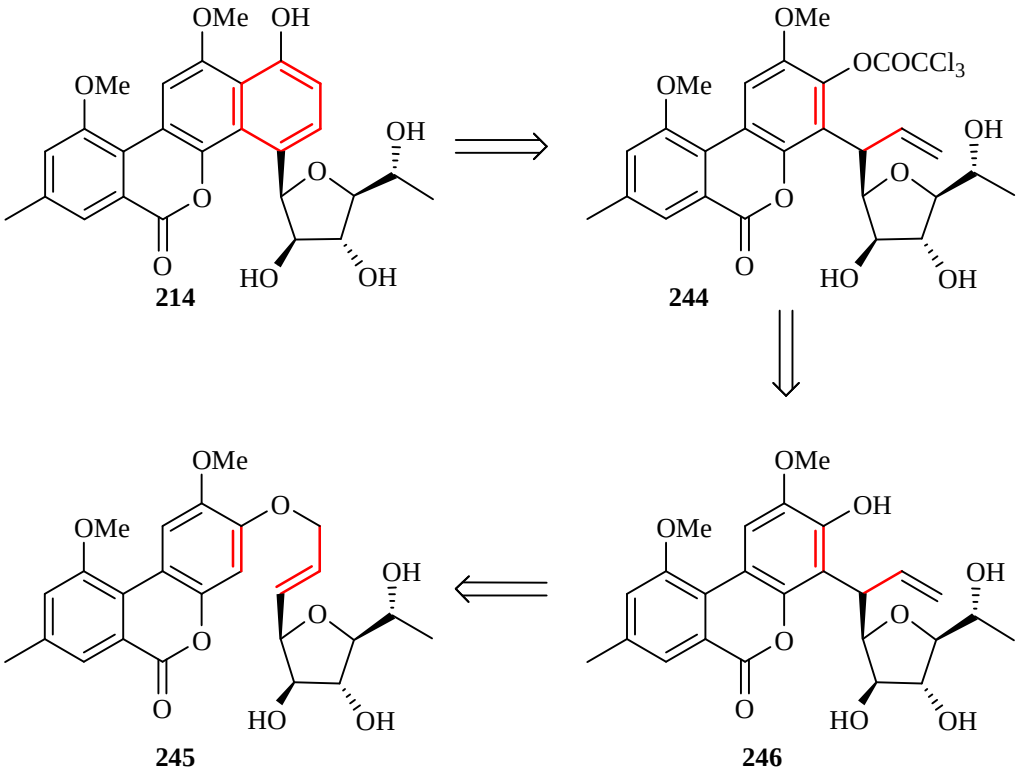
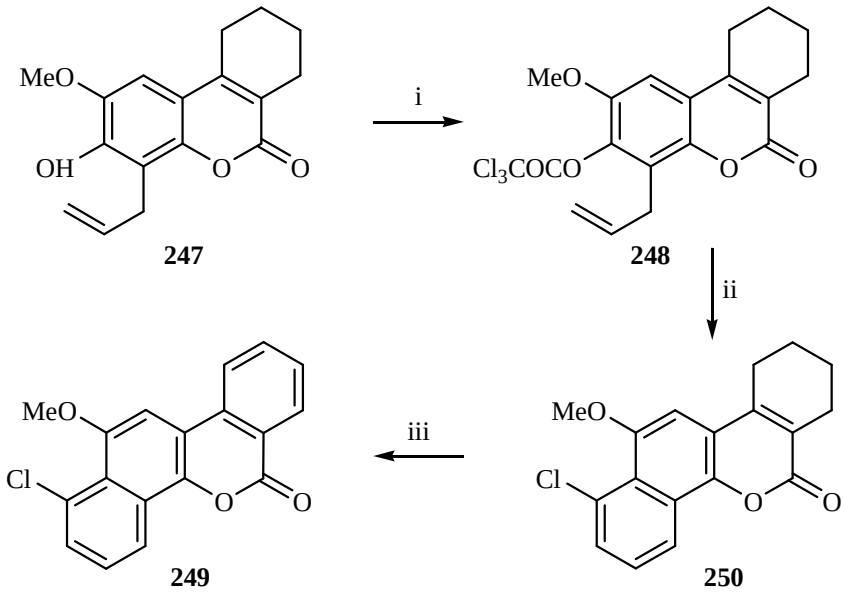


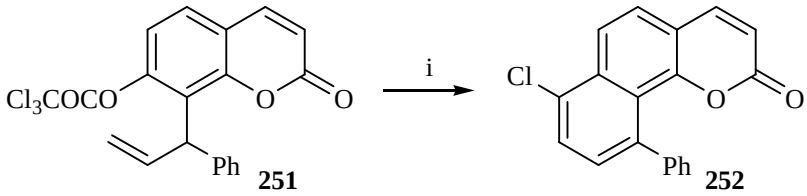
Figure 3.7. Proposed retrosynthetic route for the synthesis of gilvocarcin M.

Model studies within the group showed that the benzannulation reaction could take place with a coumarin ring[37] in an excellent 92% yield (Scheme 3.9).



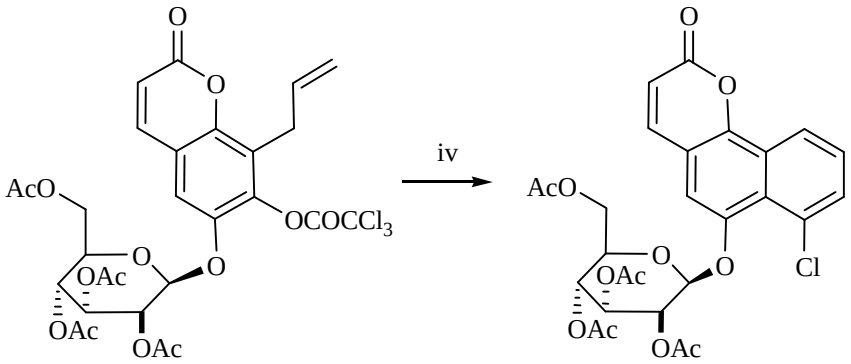
Scheme 3.9. Benzannulation reaction of coumarin **248**. i. Cl_3CCOCl, py, CH_2Cl_2, 0 ºC, 62%. ii. CuCl (5 mol%), ligand **18** (5 mol%), DCE, 200 ºC, MW, 2 h, 92%. iii. 10% Pd–C, Ph_2O, 259 ºC, N_2, 48 h, then in air 24 h, 62%.

Model studies have also shown that the benzannulation reaction proceeds to afford sterically congested aromatic systems as in the case of trichloroacetate **251** where the reaction takes place with a phenyl group on the allylic substituent (Scheme 3.10).[37]



Scheme 3.10. BHQ reaction of sterically congested trichloroacetate **251**. i. CuCl (5 mol%), ligand **18** (5 mol%), DCE, 200 ºC, 2 h, MW, 62%.

Finally, we also know that the reaction also allows for the presence of acid labile groups in the trichloroacetate (*vida supra*). The labile carbohydrate derivative **162** survives the benzannulation sequence (Scheme 3.11).



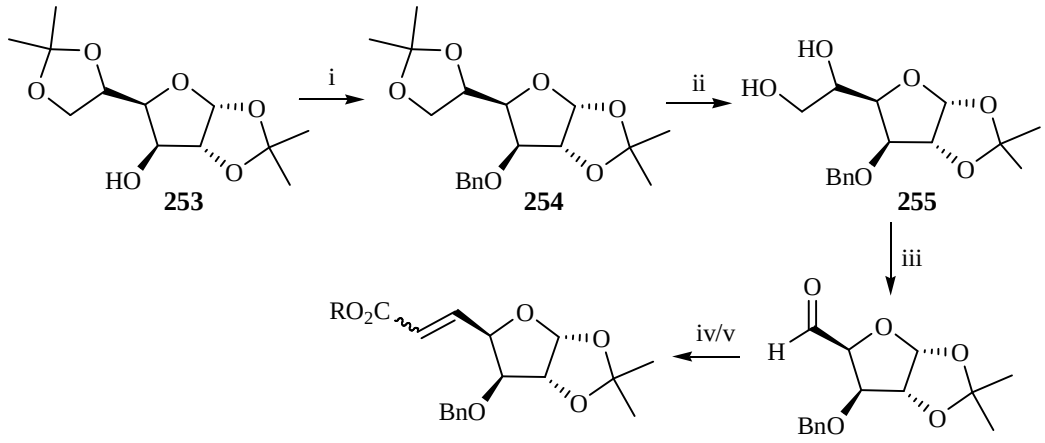
162 **164**

Scheme 3.11. Benzannulation reaction in the presence of acid labile groups. i. (IPr)CuCl (**156**, 5 mol%), diglyme, 170 ºC, 2 h, 50%.

3.2.3. MODEL STUDIES

Our model studies focused upon the Claisen rearrangement of an allyl phenol containing a sugar substituent attached to it. A literature search indicated that this was an unprecedented reaction and our initial efforts centred on the development of this methodology. Commercially available 1,2:5,6–di–*O*–isopropylidene–α–D–glucofuranose (**253**) was modified by standard chemistry to a substrate required to test the Claisen rearrangement and the **BHQ** reaction sequence.

Benzyl protection of furanose **253** followed by selective acetonide deprotection afforded diol **255** which upon oxidative cleavage and Wittig reaction led to the conjugated esters **256**, **257**, **259** and **260** (Scheme 3.13).[87]



R = Et *cis* **256** *trans* **257** (1 : 4) 68%

R = Me *cis* **259** *trans* **260** 26% : 50%

Scheme 3.12. Synthetic sequence for the synthesis of the unsaturated carbohydrate. i. BnCl (1.1 equiv.), NaH (1.5 equiv.), DMF, 0 ºC → rt, 16 h, 99%. ii. AcOH and H_2O, 40 ºC, 20 h, 99%. iii. $NaIO_4$ (1.2 equiv.), 1,4−dioxane/H_2O, rt, 99%. vi. Ph_3PCHCO_2Et (1.1 equiv.), CH_2Cl_2, rt, 16 h, 68% (1 : 4 *cis*/*trans* mixture). v. PPh_3CHCO_2Me (1.0 equiv.), THF, rt, 16 h, 81% combined yield (50% pure *trans* isomer and 26% pure *cis* isomer).

Alternatively, we also believed that naphthalene **261** could be prepared from known alkene **263**[88] using a cross−metathesis reaction (Figure 3.8).

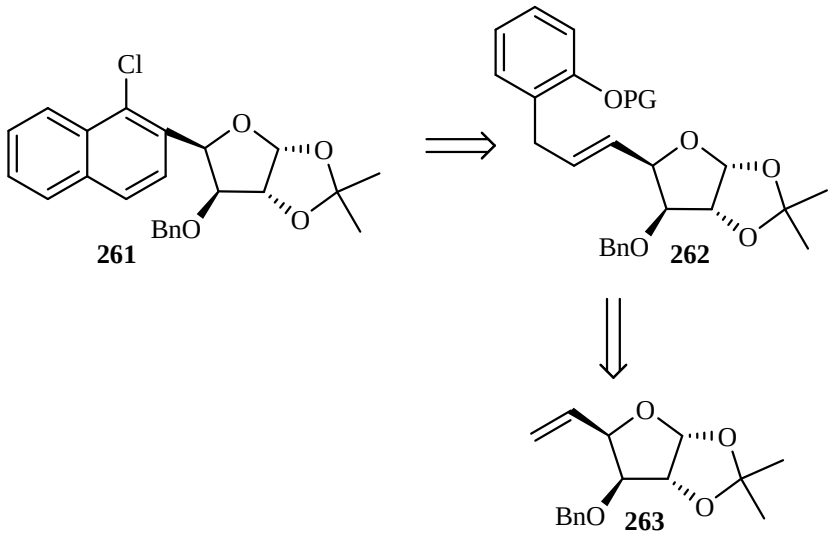
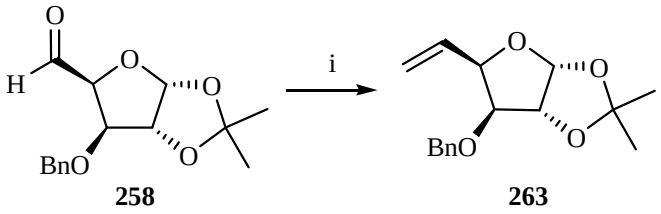


Figure 3.8. Proposed model studies.

Our first attempt to synthesise of furanose **263** was from the aldehyde **258**. We hoped that the Wittig reaction of aldehyde **258** with methyltriphosphonium bromide would give the desired vinyl carbohydrate **258**.[89] Unfortunately, after several attempts we discarded this route because the crude reaction mixture

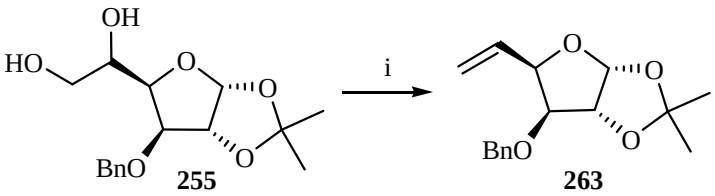
showed a complex mixture of starting material, product and by–products. Yields were never better than 31% (Scheme 3.13).



258 **263**

Scheme 3.13. Vinyl carbohydrate synthesis attempt through cross metathesis. i. $Ph_3PCMeBr$ (1.5 equiv.), KO^{t}Bu (1.5 equiv.), THF, 0 ºC, 30 min, addition of **258** then rt, 12 h, 31%.

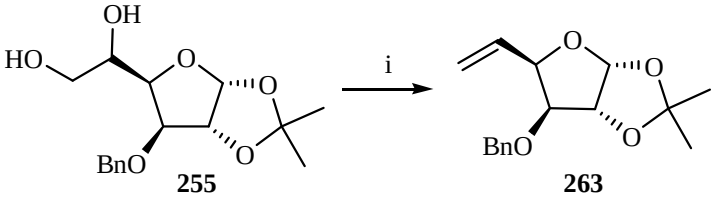
Samuelsson *et al.*[90] reported a synthesis of vinyl sugar **263** from diol **255** (Scheme 3.14). Firstly diol **255** would form a diphenylphosphinate after the addition of chlorodiphenylphosphine in the presence of imidazole. Then reductive elimination in the presence of iodine and zinc powder would afford olefin **263**. Unfortunately, the insoluble by–products formed by the addition of Zn made this method incompatible with scaling up.



255 **263**

Scheme 3.14. Diol reductive elimination for the synthesis of alkene **263**. i. Ph_2PCl (2.2 equiv.), imidazole (4.0 equiv.), 80 ºC, toluene, then I_2 (2.2 equiv.), 1.5 h, 100 ºC, then Zn powder (9.9 equiv.), reflux, 1.5 h, 63%.

Fortunately, the method of Turner *et al.*[91] afforded alkene **263** in 96% yield in the presence of triphenylphosphine and iodine (Scheme 3.15).

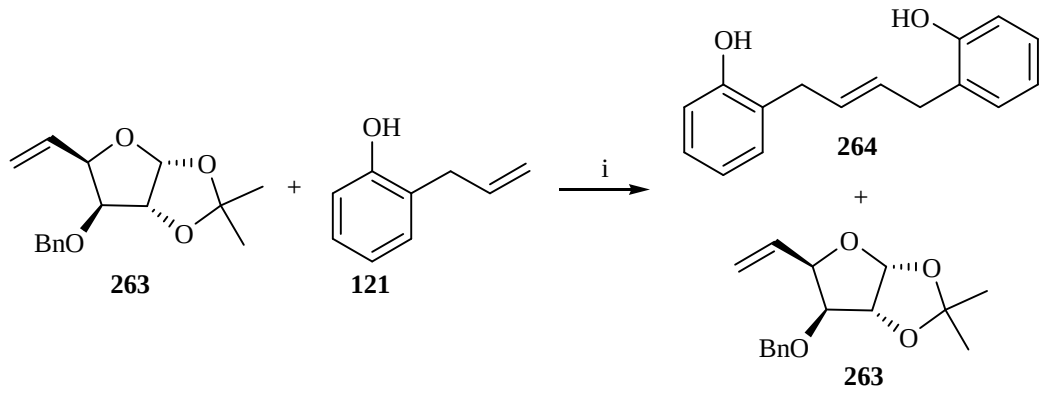


255 **263**

Scheme 3.15. Vinyl group formation reaction. i. Imidazole (4.0 equiv.), triphenylphosphine (4.0 equiv.), toluene, 50 °C, then I_2 (4.0 equiv.), reflux, 24 h. Then rt, AcOEt (0.08 equiv.) and iodine (4.0 equiv.), 15 min, 96 %.

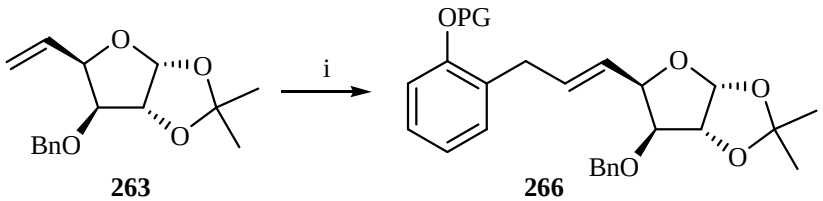
Attempted cross–metathesis of alkene **263** with allylphenol **121** afforded a complex mixture of products, none of which incorporated the sugar residue,

suggesting that self metathesis of allyl phenol **121** was the dominant process in this reaction (Scheme 3.16).



Scheme 3.16. Cross–metathesis reaction of vinyl **263** and phenol **121**. i. Grubbs' 1 (5 mol%), CH_2Cl_2, 24 h, reflux.

In order to determine the effect of the phenol protecting group on the course of the metathesis reaction, TBS ether **265b** and acetate **265a** were investigated. The TBS protected phenol **265b** in the presence of 1st generation Grubbs–Hoveyda catalyst gave some conversion to the desired product after 30 h refluxing in CH_2Cl_2. Sadly, after several attempts and longer reaction times the reaction did not go to completion. However, in the presence of the 2nd generation Grubbs' catalyst, the TBS phenol **265b** gave a 44% yield of **266b** as a single *trans* isomer[92] (entry 4, Table 3.1). For scale up purposes we reduced the amount of catalyst from 5 to 1 mol% and we were very pleased to see that the reaction yield did not decrease (entry 5, Table 3.1).



Scheme 3.17. Cross–metathesis reaction conditions. i. Allyl phenol (1.0 equiv.), catalyst, CH_2Cl_2, reflux.

Entry	SM	PG	Catalyst	Time	Yield
1	**121**	None	Grubbs' 1 (5 mol%)	24 h	0%[a]
2	**121**	None	Grubbs' 2 (5 mol%)	24 h	0%[a]
3	**265a**	Ac	Grubbs' 2 (5 mol%)	24 h	0%[a]
4	**265b**	TBS	Grubbs' 2 (5 mol%)	20 h	44%
5	**265b**	TBS	Grubbs' 2 (1 mol%)	20 h	44%

Table 3.1. Cross−metathesis results. a. Complex mixture of products, no product observed by ^{1}H NMR.

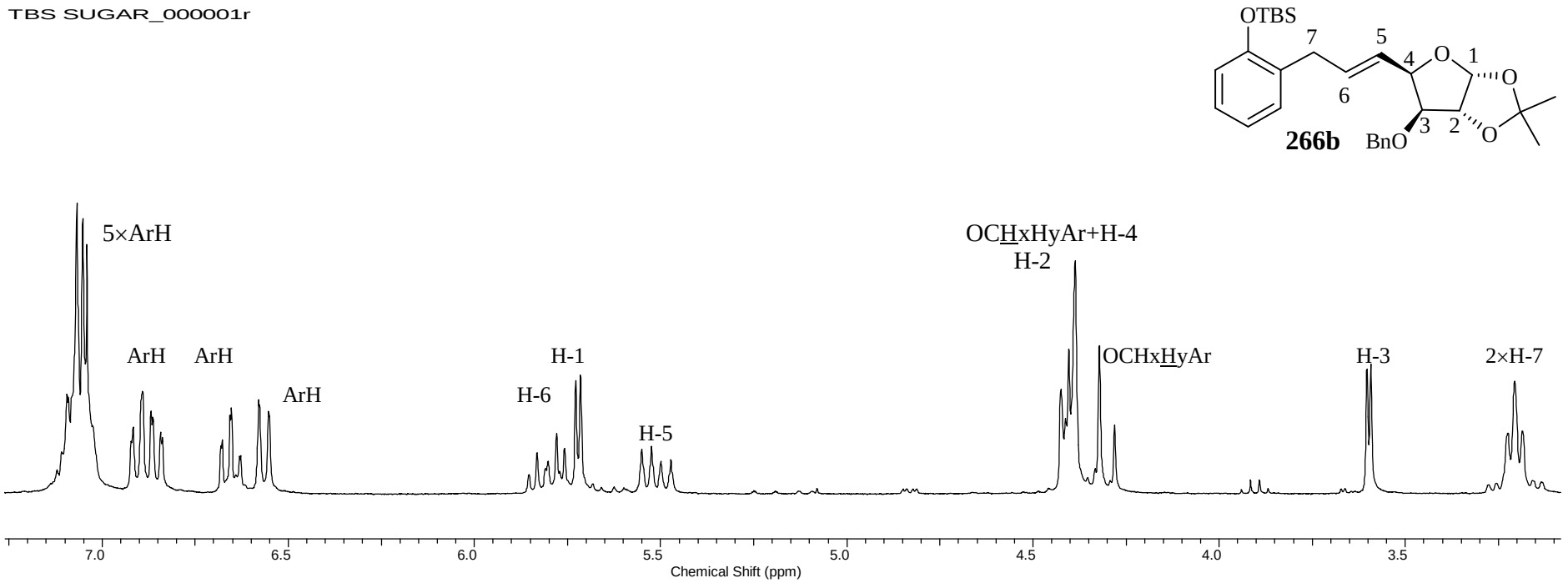
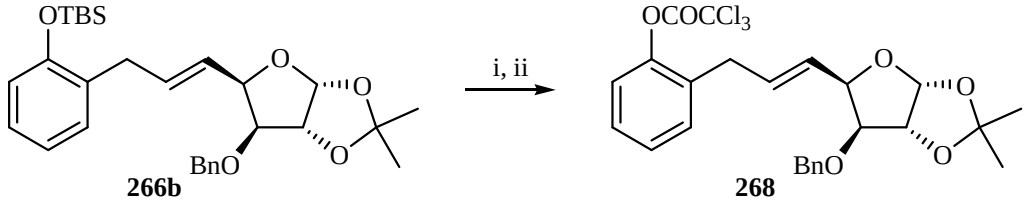


Figure 3. 9. Main 1H NMR peaks of carbohydrate **266b**.

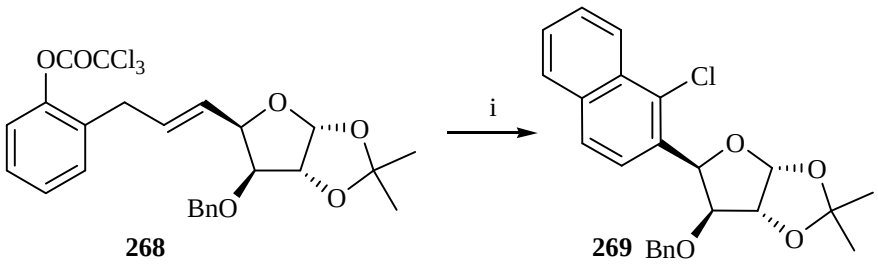
Deprotection to afford phenol **267** under mild conditions in the presence of potassium hydroxide[93] followed by acylation with excess of $ClCOCCl_3$ (3.8 equiv.) and Et_3N (3.8 equiv.) afforded the desired trichloroacetate **268** (Scheme 3.18). This trichloroacetate was stable to purification by flash chromatography column with no deacylated product isolated.



266b **268**

Scheme 3.18. Deprotection and acylation reaction conditions. i. KOH (1.5 equiv.), EtOH, 25 ºC, 16 h, 91%. ii. $ClCOCCl_3$ (3.8 equiv.), Et_3N (3.8 equiv.), Et_2O, 25 ºC, 16 h, 88%.

Unfortunately, when trichloroacetate **268** was submitted to the standard benzannulation conditions in the MW reactor neither starting material **268** nor desired benzannulation product **269** were recovered. The harsh acid conditions due to the formation of HCl during the course of the reaction could be the cause of the observed decomposition. Future work in the group would be to introduce a buffer solution to the reaction mixture in order to be able to work with acid sensitive substrates.



268 **269**

Scheme 3.19. Benzannulation reaction attempt. i. (IPr)CuCl (**156**, 5 mol%), DCE, 200 ºC, 2 h, MW.

Even though the benzannulation reaction was unsuccessful we decided use acetate **270** as an alternative model system (Figure 3.10).

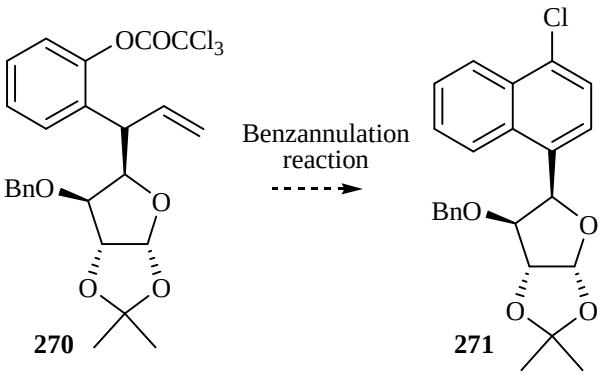


Figure 3.10. Model studies of benzannulation reaction of **270**.

3.2.3.1. CLAISEN REARRANGEMENT APPROACH

We envisaged that the synthesis of model substrate **270** would proceed *via* phenol **272**, which could be prepared *via* Claisen rearrangement of phenol ether **273** (Figure 3.11).

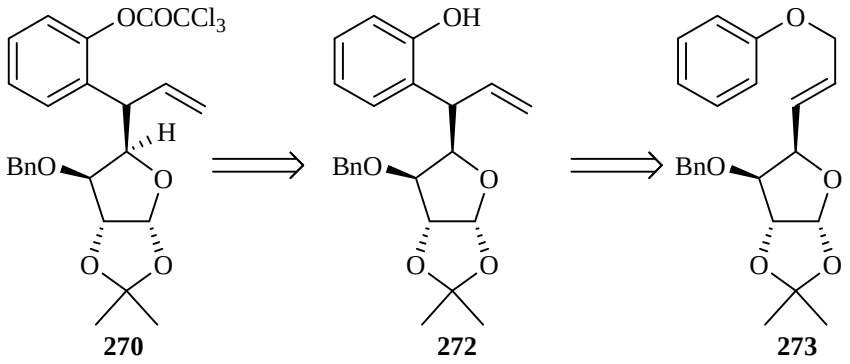
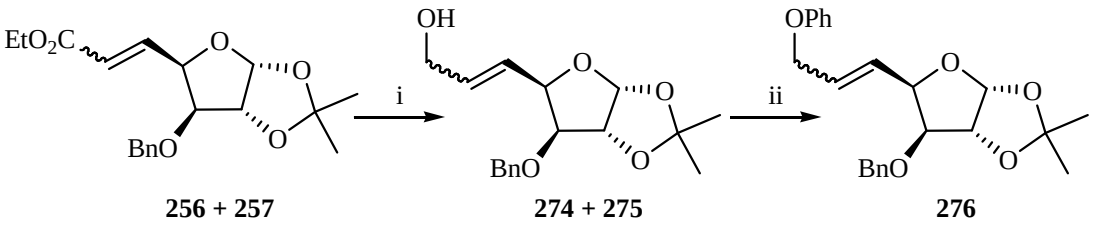


Figure 3.11. Retrosynthetic approach to acetate **270**.

The synthesis of allyl phenol **273** was achieved using standard chemistry. Reduction of the isomeric esters **256** and **257** to the alcohol in the presence of DIBAL–H in very good yield gave a *cis* and *trans* mixture of alcohols **274** and **275**. Carbohydrates **274** and **275** were converted to the allyl phenol **276** by a Mitsunobu reaction in the presence of Et_3N and DIAD in THF in moderate 49% yield (Scheme 3.20).

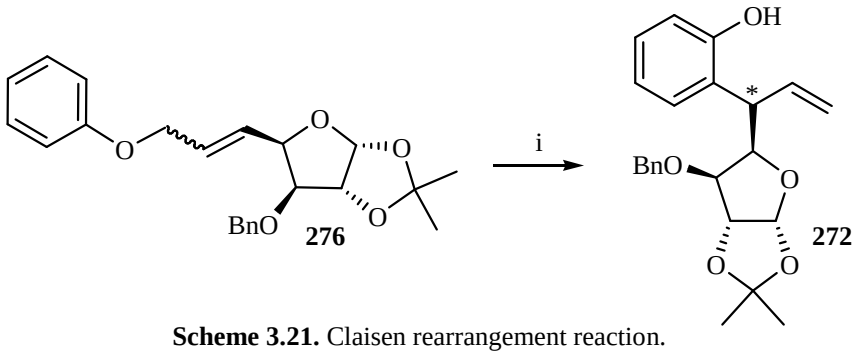


256 + 257 **274 + 275** **276**

Scheme 3.20. Synthesis of allyl phenol **276**. i. DIBAL–H (1M in hexane, 2.5 equiv.), CH_2Cl_2, –78 ºC, 95%. ii. Phenol (1.0 equiv.), PPh_3 (1.0 equiv.), Et_3N (1.0 equiv.), DIAD (1.0 equiv.), THF, rt, 16 h, 49%.

Previously in the group the rearrangement of **276** had been achieved in a low 11% conversion by thermolysis at 220 ºC in a microwave reactor for 16 h.[94] Unfortunately, this result was irreproducible and only starting material was recovered after 16 h heating in the MW reactor at 220 ºC in toluene (Table 3.2).

Other high boiling point solvents were also tested (Et_2NPh, diglyme, Ph_2O) and in some cases under MW radiation. The Claisen rearrangement took place after 16 h in refluxing Ph_2O affording a single allyl phenol diastereomer **272** in 8% yield (Table 3.2, figures 3.12 and 3.13). Sadly, the result was not reproducible with the recovery of starting material in every case.



Scheme 3.21. Claisen rearrangement reaction.

Entry	Solvent	T (ºC)	MW	Time (h)	Yield
1	Toluene	220	Y	16	SM
2	Et_2NPh	217	N	6	SM
3	Diglyme	220	Y	16	SM
4	Ph_2O	220	N	16	8%[a]

Table 3.2. Claisen rearrangement results. a. Single diastereomer.

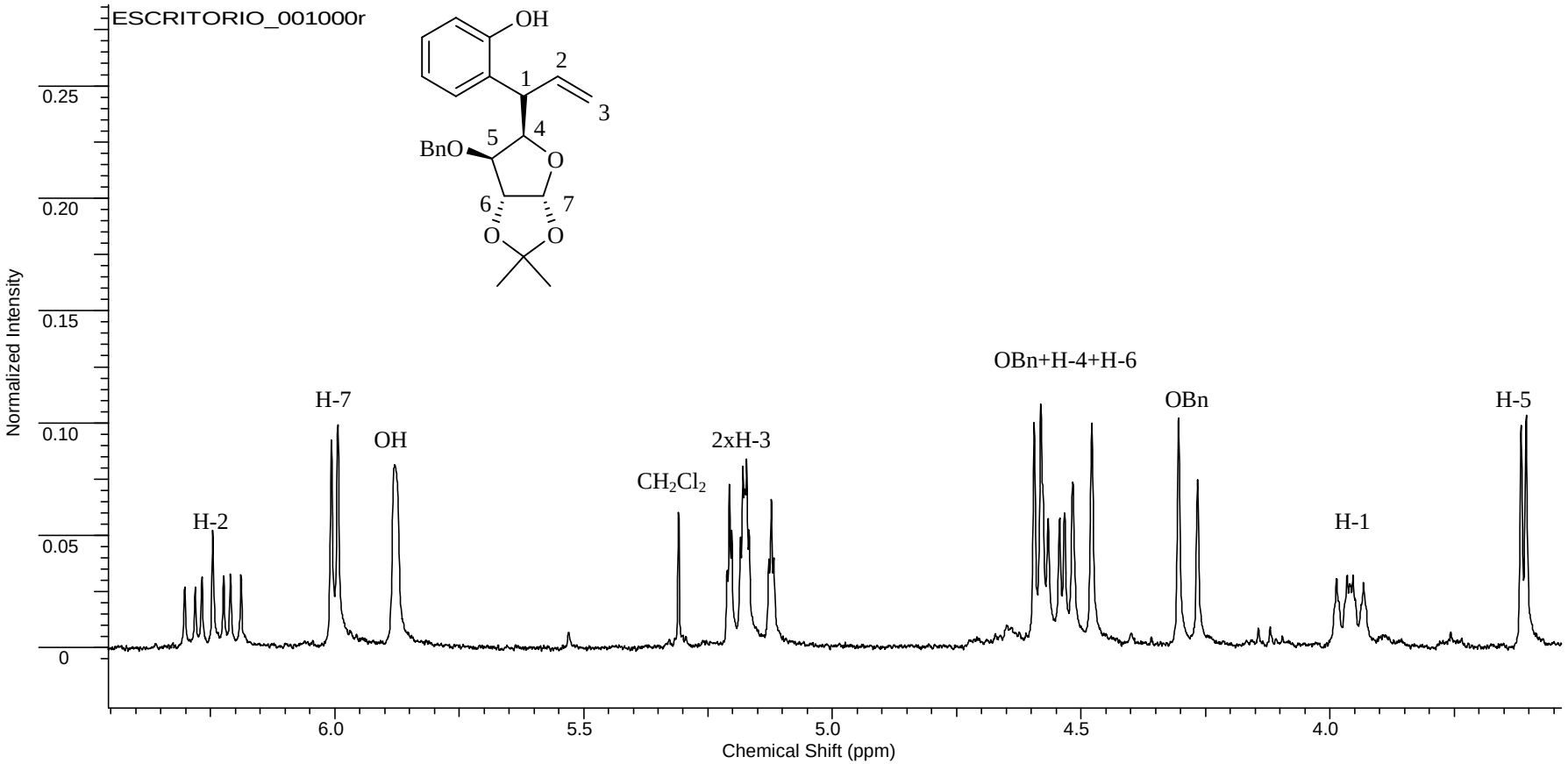


Figure 3.12. Characteristic peaks of the carbohydrate allyl phenol **272** ^{1}H NMR ($CDCl_3$).

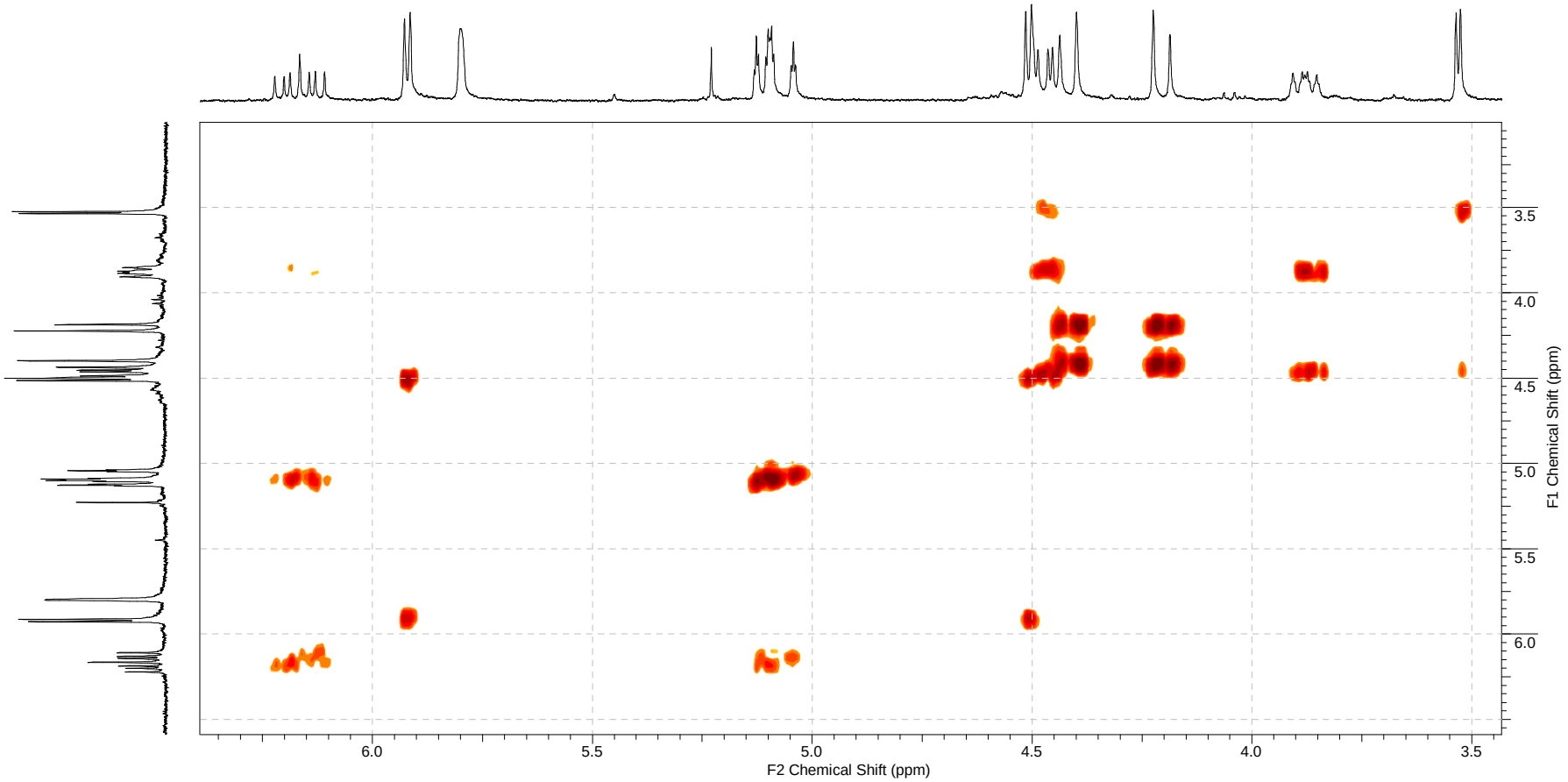


Figure 3.13. Carbohydrate allyl phenol **272** COSY NMR ($CDCl_3$).

The addition of Lewis acid catalysts to the reaction was also investigated in this Claisen rearrangement (Table 3.3). Unfortunately, none of the desired product was observed in the crude mixture of these reactions, only SM was recovered.

Entry	Solvent	Catalyst	T (ºC)	MW	Time (h)	Result
1	CH_3CN	$Bi(OTf)_3$[95]	82	Y	20	SM
2	CH_3CN	$Bi(OTf)_3$	150	Y	2	SM
3	Ph_2O	$Bi(OTf)_3$	220	N	16	SM
4	CH_2Cl_2	BCl_3[96]	–78	N	6	SM
5	CH_2Cl_2	$SnCl_4$[97]	20	N	1	SM

Table 3.3. Claisen rearrangement results in the presence of catalysts.

Claisen rearrangement for the synthesis of **272** proved to be sluggish so different alternatives routes were then explored.

3.2.3.2. S_N2' ADDITION

Given that the Claisen rearrangement approach was unsuccessful a different strategy, involving an S_N2' displacement leading to a substrate such as **278**, was employed. The introduction of a good leaving group adjacent to the alkene would lead to a cascade of reactions whereby a nucleophilic attack of the alkene would displace the LG placing the double bond at the terminal position (Figure 3.13).

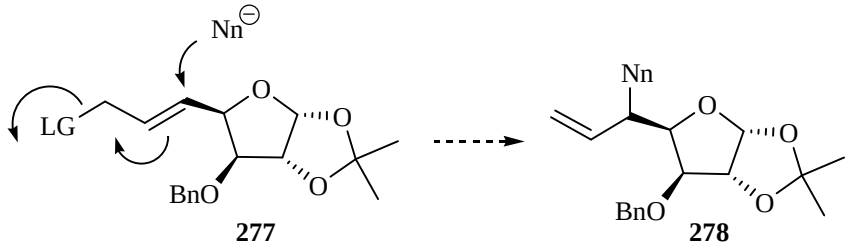
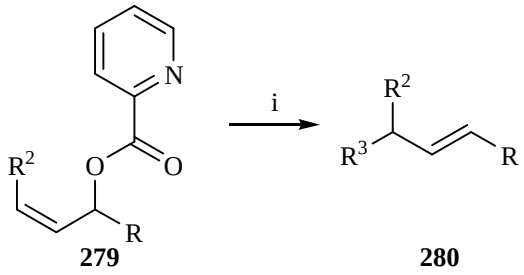


Figure 3.14. Alternative approach to the allyl phenol **278**.

Kobayashi *et al.*[98] reported that the use of allylic picolinates **279** and copper reagents derived from RMgBr can promote an anti–S_N2 displacement reaction (Scheme 3.22). Double activation of the allyl group is caused, first of all by the

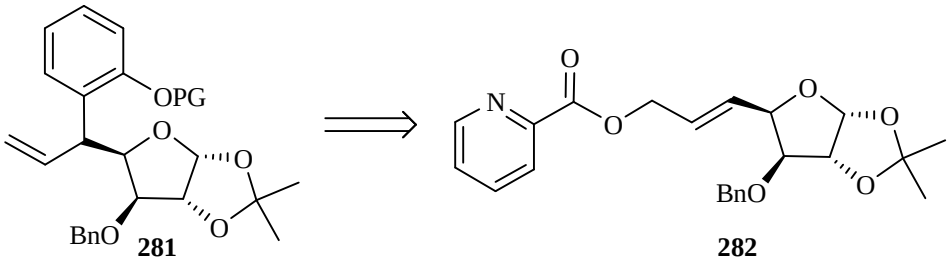
electron withdrawing pyridyl group and secondly by chelation of the carbonyl oxygen and the pyridyl nitrogen to $MgBr_2$ that is generated *in situ* from R_3MgBr and CuBr.



279 **280**

Scheme 3.22. Anti S_N2 stereoselective substitution. i. R_3–MgBr/CuBr

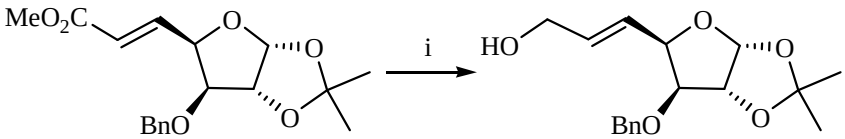
We envisaged that the synthesis of sugar **281** may be possible *via* an S_N2' reaction of picolinate **282** with a phenyl Grignard reagent (Figure 3.15).



281 **282**

Figure 3.15. Synthesis of phenol **281** from allylic picolinate **282**.

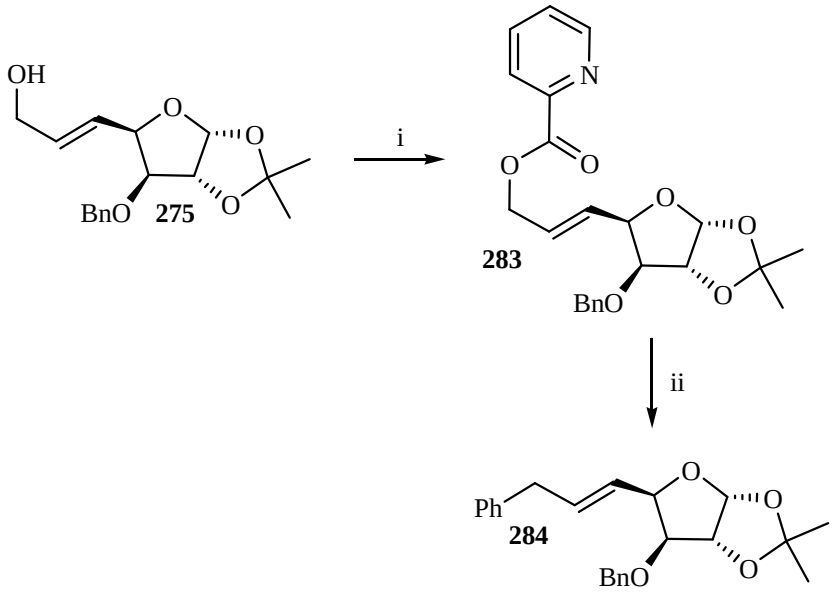
Thus, reduction of the isomerically pure *trans* methyl ester **260** in the presence of DIBAL–H at −78 ºC gave the respective alcohol **275** in very good yield (Scheme 3.23).



260 **275**

Scheme 3.23. Methyl ester **260** reduction. i. DIBAL–H (1M in hexane, 2.5 equiv.), CH_2Cl_2, −78 ºC, 89%.

The *trans* picolinate **281** was easily obtained by treating alcohol **273** with 2–picolinic acid in the presence of DMAP and DCC in CH_2Cl_2 (65% yield). Unfortunately, picolinate **281** in the presence of phenyl magnesium bromide and $CuBr.Me_2S$ underwent a direct S_N2 displacement, affording allylphenyl **284**[99] in a 56% yield (Scheme 3.24).



Scheme 3.24. S_N2' substitution of picolinate **283**. i. 2–Picolinic acid (1.2 equiv.), DMAP (1.0 equiv.), DCC (1.0 equiv.), CH_2Cl_2, 0 ºC, 1.5 h, 65%. ii. PhMgBr (2.0 equiv.), CuBr.Me_2S (1.0 equiv.), THF, –40 ºC to –60 ºC, 0%.

Given the problems associated with this approach another alternative method for the synthesis of **281** was sought.

3.2.3.3. HECK APPROACH

A possible alternative approach to allyl phenol **281** was *via* a Heck reaction. Although this approach would not generate sugar **281** in a single step it would enable the synthesis of the required carbon skeleton. The alkene and ester functions of carbohydrate **285** should eventually be reduced, and formed by elimination of the hydroxyl group, affording the desired alkene **281** (Figure 3.16).

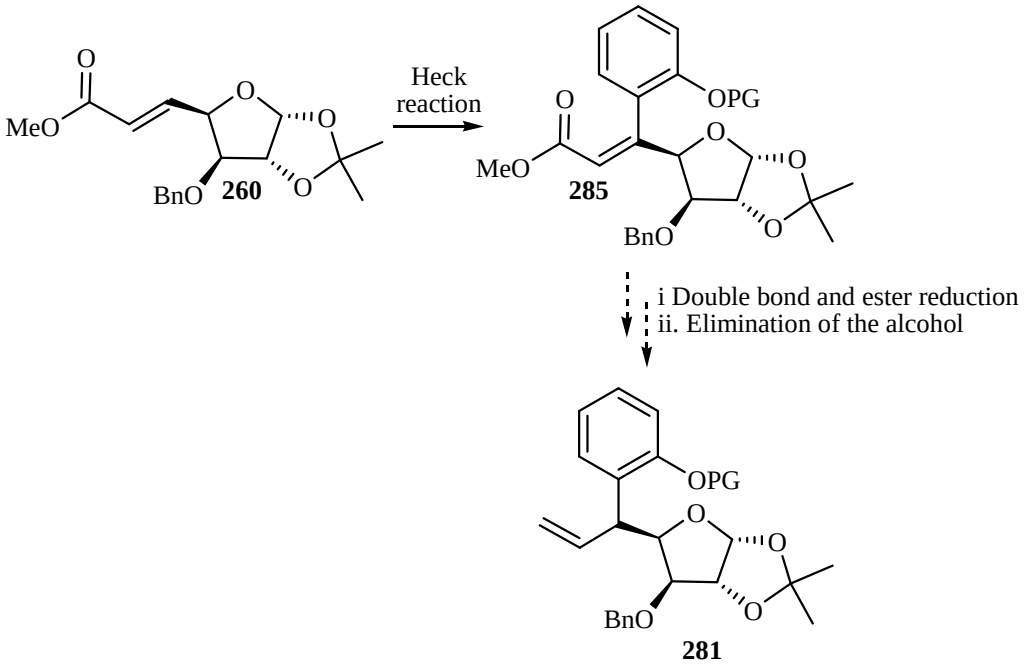
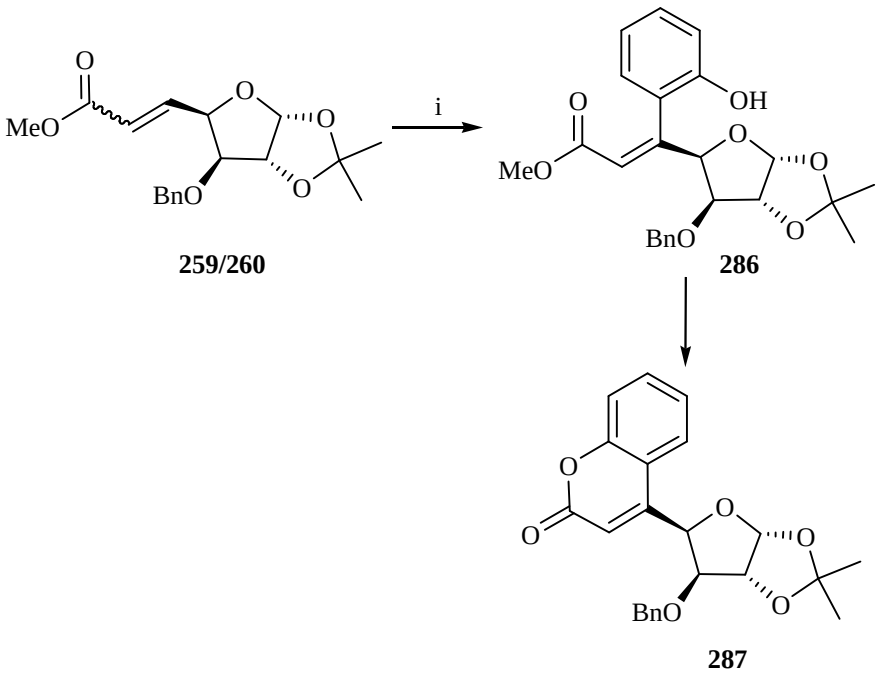


Figure 3.16. Approach to the allyl phenol **281** *via* a Heck reaction.

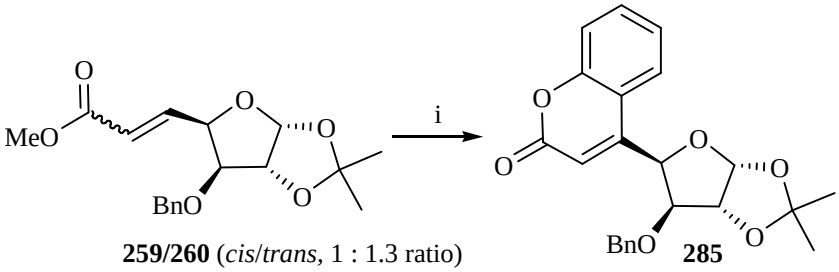
This approach would introduce the phenolic group for subsequent transformations along with the required carbon skeleton. But in reality, reaction of the isomeric mixture **259**/**260** with 2–iodophenol afforded the coumarin **287**, in a 37% yield, presumably *via* cyclisation of the intermediate Heck–product **286** (Scheme 3.25).



Scheme 3.25. Heck reaction reaction. i. *o*–Iodophenol (1.0 equiv.), Et_3N (3.4 equiv.), TBAB (3.4 equiv.), $Pd(OAc)_2$ (0.1 equiv.), DMF, 100 ºC, 48 h, 37%.

The yield of this reaction was improved to 42% and the reaction time reduced to 24 h when the solvent was changed to acetonitrile (entry 2, Table 3.4). Use of sodium bicarbonate (1.8 equiv.) as base afforded a mixture of phenol **284** and coumarin **285** (30% isolated yield). Unfortunately, the yield did not improve even when the reaction was left for 48 h refluxing in acetonitrile (entry 3, Table 3.4).

Since the double bond geometry has to be *Z* to allow the cyclisation to the coumarin we tested the reaction with geometrically pure esters. The reaction yield showed an expected improvement with the *cis* isomer **259** (49%) and was poor in the case of the *trans* isomer **260** (24%) meaning double bond isomerisation must have occurred. We thought that addition of formic acid would generate "Pd–H" species which in principle could isomerise the double bond of the *E*–isomer **260**. Thus, formic acid was added after the Heck addition had taken place 24 h to give coumarin **285** in 41% yield. The addition of formic acid to promote the isomerisation of the double bond did not affect the reaction yield.



259/260 (*cis*/*trans*, 1 : 1.3 ratio) **285**

Scheme 3.26. Heck reaction conditions. i. *o*–Iodophenol (1.0 equiv.), base, TBAB (3.4 equiv.), $Pd(OAc)_2$ (0.1 equiv.), solvent, reflux.

Entry	Ester	Base	Solvent	T (ºC)	time	Additives	Yield
1	*cis*/*trans*	Et_3N	DMF	100	48 h	–	37%
2	*cis*/*trans*	Et_3N	MeCN	82	24 h	–	42%
3	*cis*/*trans*	$NaHCO_3$	MeCN	82	24 h	–	30%
3	*cis*/*trans*	$NaHCO_3$	MeCN	82	48 h	–	24%
5	*cis*	Et_3N	MeCN	82	24 h	–	49%
6	*trans*	Et_3N	MeCN	82	24 h	–	24%
7	*cis*/*trans*	Et_3N	MeCN	82	48 h	HCO_2H	41%

Table 3.4. Heck reaction results.

The main concern about obtaining coumarin **287** was the reduction of the double bond present in the ring (Figure 3.17). Dihydrocoumarin **288** should be ring opened and the resulting ester group transformed into alkene **286**.

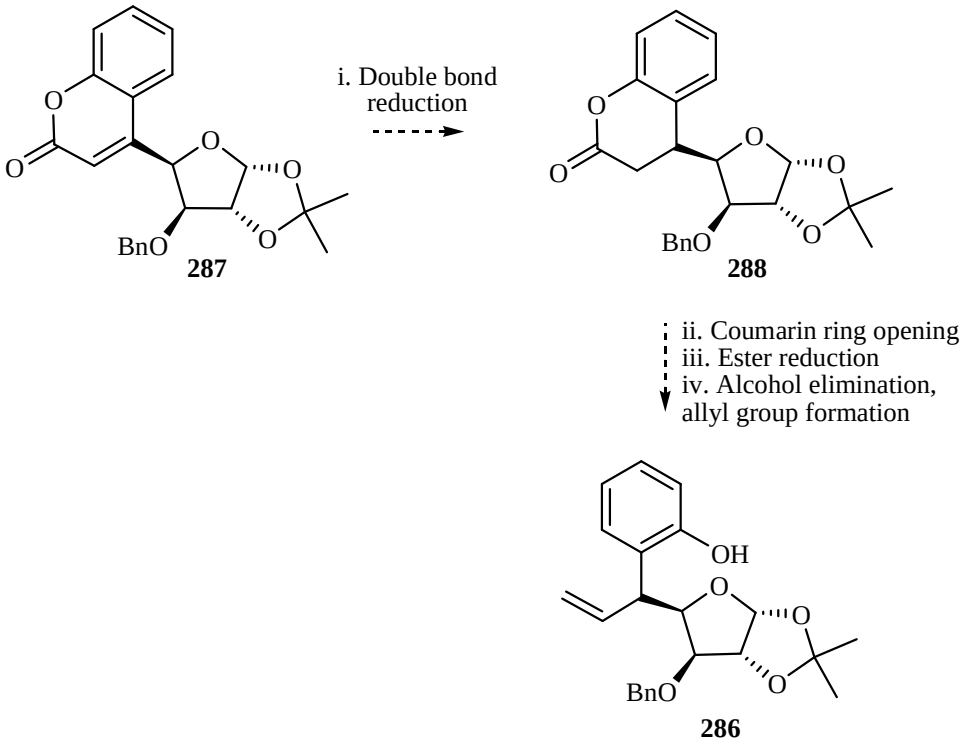
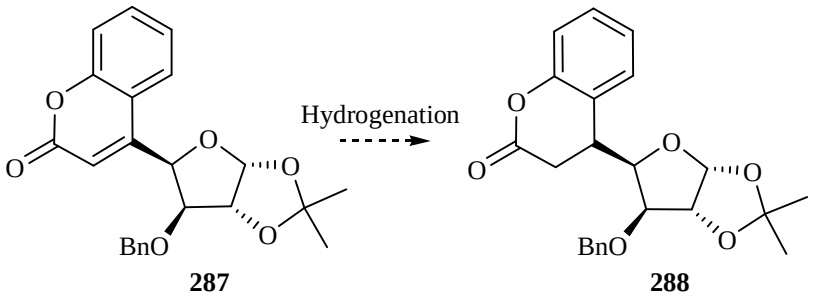


Figure 3.17. Suggested route to afford allyl phenol **286** from coumarin **287**.

The most common method in the literature for furnishing the corresponding dihydrocoumarin is by catalytic hydrogenation.[100] The main concern was hydrogenation of the benzylic protecting group during the course of the reaction.

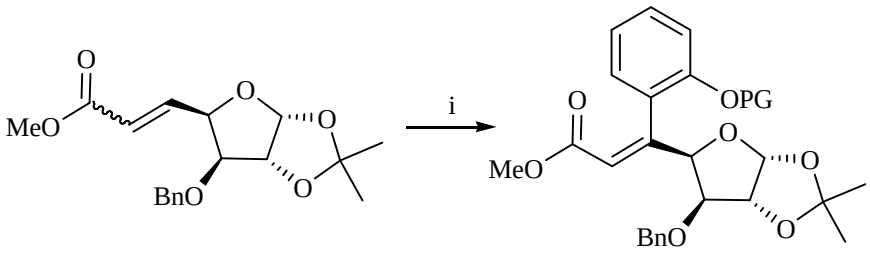
The reduction of the double bond of coumarin **287** was attempted in ethanol using a H–cube (Scheme 3.27).[101] Unfortunately, along with the non–desired benzyl deprotection a large number of by–products were obtained in the crude reaction mixture. The synthesis of the dihydrocoumarin **288** by hydrogenation was not feasible. An alternative strategy to prevent the observed deprotection would be to change the benzyl protecting group for one not sensitive to hydrogenation, such as a TBS ether.



287 **288**

Scheme 3.27. Dihydrocoumarin **288** synthesis from coumarin **287**.

Also the use of a protected 2–iodophenol would prevent coumarin formation after the Heck addition, as well as circumventing the problem of reducing the double bond in the coumarin ring. To this end, 2–iodophenol was protected as the acetate[102] and TBS ether, two protective groups that could be removed under mild conditions without affecting the carbohydrate. The Heck reaction of the acetate **290** (entry 1 Table 3.5) gave a very messy crude mixture, no starting material remained but isolation of the product was not achieved. In the case of the TBS protected phenol **291**, coumarin **287** (33%) was isolated. Thus, the TBS group was too labile for the reaction conditions.



259 and **260** **289**

Scheme 3.28. Heck reaction with protected phenols **290** and **291**. i. Et_3N (3.4 equiv.), TBAB (3.4 equiv.), $Pd(OAc)_2$ (0.1 equiv.), CH_3CN, reflux, 24 h.

Entry	Ester	PG	Yield
1	*cis*/*trans*	Ac, **290**	0%
2	*cis*/*trans*	TBS, **291**	0%

Table 3.5. Heck reaction results.

Different protecting groups will be screened in future to optimise the Heck reaction towards the synthesis of gilvocarcin M.

3.2.3.4. MICHAEL Cu ADDITION

We also considered that cuprate–type chemistry may serve as a possible alternative to the Heck reaction for the synthesis of the required homologated carbohydrate nucleus **292**. It was envisaged that 1,4–addition[103] of aryl–metal species to the ester **260**, followed by reduction of the ester and Grieco elimination[104,105] of the alcohol would give the desired alkene **281** (Figure 3.18).

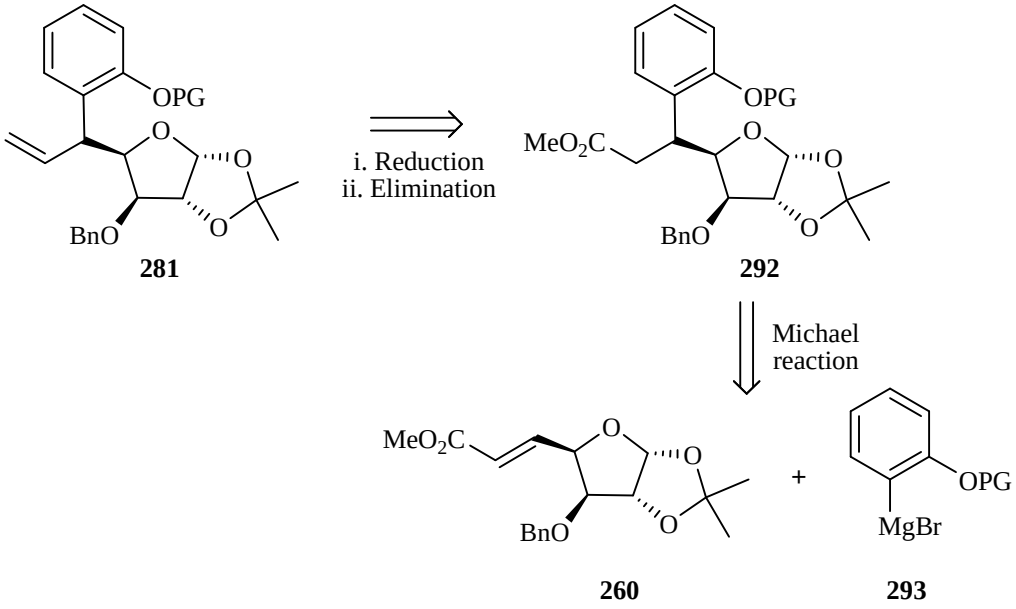
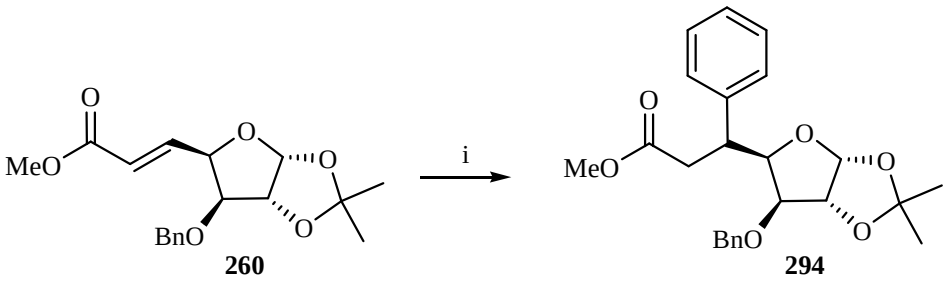


Figure 3.18. Michael addition approach for the synthesis of allyl phenol **281**.

In order to simplify the Michael addition studies we began our investigations with phenyl magnesium bromide. When methyl ester **260** was treated with PhMgBr in the presence of CuI, a single isomer was obtained in 31% yield. Increasing the quantity of CuI in the reaction from 0.1 to 1.5 equivalents improved the yield to 50% (Scheme 3.29 and Table 3.6).

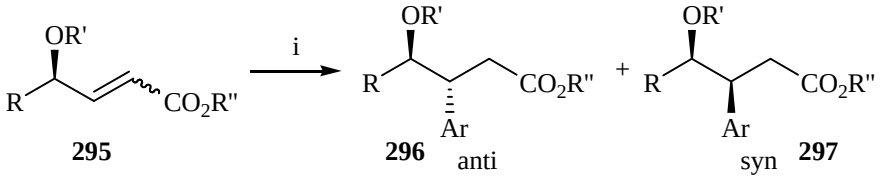


Scheme 3.29. Michael addition to methyl ester **260**. i. CuI, PhMgBr (1.0 equiv.), –78 ºC to rt, THF.

Entry	CuI (equiv.)	PhMgBr	Yield
1	0.1	1.5	31%
2	1.5	1.5	50%

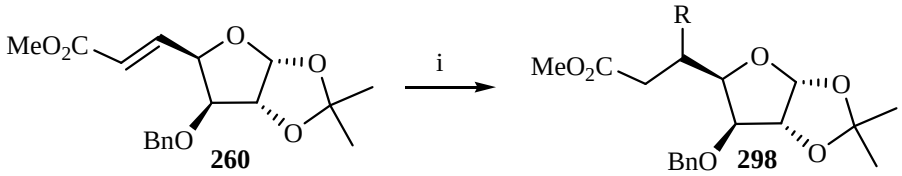
Table 3.6. Michael addition results.

Kornienko *et al.*[106] reported 1,4–additions with good yields and stereoselectivity in γ–oxosubstituted compounds **295** (Scheme 3.30). The addition of TMSCl to the reaction mixture is beneficial in terms of rate and overall yield of the reaction.



Scheme 3.30. 1,4–addition in γ–oxosubstituted compounds.

Subsequent studies have in fact shown that this conjugate addition reaction is general, resulting in the synthesis of different carbohydrates with high levels of diastereocontrol (*de* > 95: 5, Table 3.7).[107]



Scheme 3.31. Michael addition reaction conditions in the presence of TMSCl. i. CuI (1.0 equiv.), RMgBr (1M in THF, 5.0 equiv.), −78 ºC, THF, 40 min, TMSCl (15 equiv.), methyl ester (0.31M in THF, 1.0 equiv.), −78 ºC, then rt, 3 h, *de* > 95 : 5.

Entry	R	Yield
1	Phenyl	84%
2	Vinyl	80%
3	Ethyl	78%
4	Isopropenyl	65%
5	Methyl	SM + Product

Table 3.7. Michael addition results.

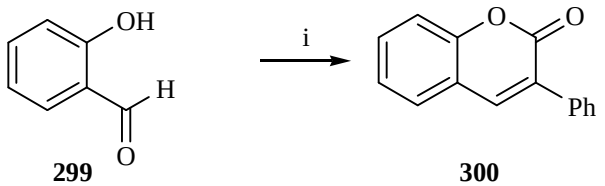
Further studies will be carried out within the group to improve this methodology.

CHAPTER 4: SYNTHESIS OF COUMARINS

4.1 INTRODUCTION

Coumarins are widely distributed among plants and more than 1800 different natural coumarins have been discovered and described to date.[108] They are known to exhibit numerous interesting biological activities. They are unwittingly experienced on a routine basis by most living organisms and so it is astonishing, due to their sheer abundance, that there have been realtively few successful attempts to effectively construct a usable synthetic pathway.[109]

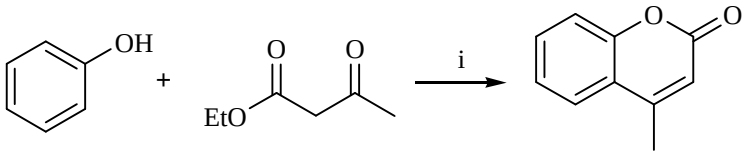
There are a number of classic syntheses of coumarins and their derivatives, unfortunately they are often not synthetically useful due to the harsh conditions required or the low yields obtained. Coumarins can be prepared in the laboratory by a Perkin reaction[110] between salicylaldehyde and acetic anhydride. Crawford *et al.*[111] demonstrated years later how this classic reaction could be utilised (Scheme 4.1).



299 **300**

Scheme 4.1. Perkin reaction for the synthesis of coumarin **300**. i. Ac_2O (0.5 equiv.), 180 ºC, 2 h, 69%.

The Pechmann condensation[112] allows the synthesis of coumarins by reaction of phenols with β–keto esters (Scheme 4.2).

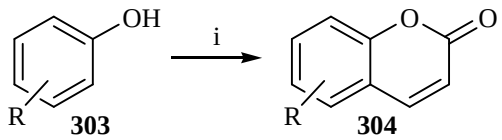


111 **301** **302**

Scheme 4.2. Pechmann condensation. i. $AlCl_3$, $PhNO_2$, 130 ºC, 85%.

De *et al.*[113] have recently reported using $BiCl_3$ as an efficient catalyst in the Pechmann condensation reaction of phenols with β–keto esters leading to the

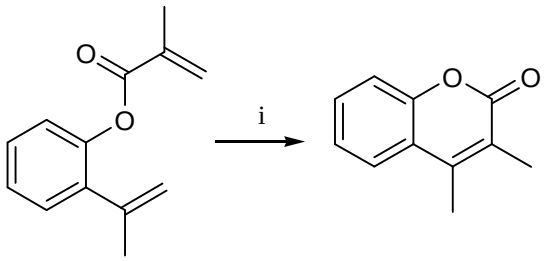
formation of coumarin derivatives in excellent yields under solvent free conditions (Scheme 4.3).



303 **304**

Scheme 4.3. Pechmann condensation in the presence $BiCl_3$. i. Ethyl acetoacetate (1.0 equiv.), $BiCl_3$ (5 mol%), 75 ºC, 1 – 4 h, 66 – 92%.

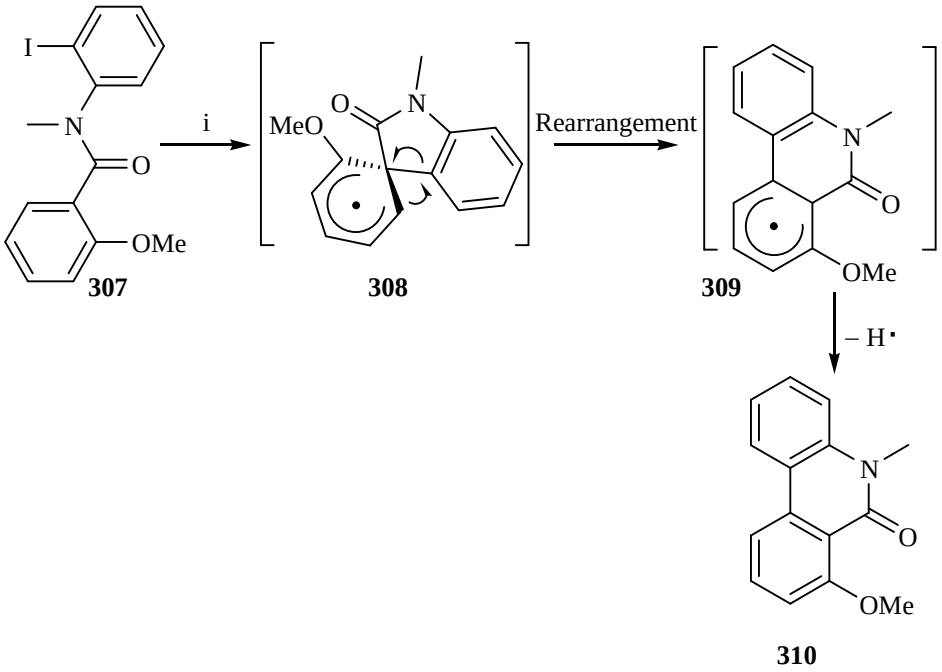
Another general method for the synthesis of coumarins is by ring closing metathesis.[114] This method allows for convenient access to a variety of coumarins substituted at both the 3– and 4–positions, as well as the tetrasubstituted example below (Scheme 4.4).



305 **306**

Scheme 4.4. Ring closing metathesis for the formation of coumarin **306**. i. Grubbs' 2 (5 mol%), toluene, 80 ºC, 12 h, 45%.

The synthesis of coumarins *via* the **ATRC** reaction has not been reported in the literature. However amide analogues (quinolines) have been reported by radical chemistry. Aryl halides such as **307** undergo spirocyclisation in the presence of samarium(II) iodide. In the absence of a proton source the product obtained is the fused heterocycle **310**. Quinoline **310** is presumably formed *via* rearrangement of the spirocyclohexadienyl radical (Scheme 4.5).[115]



307 **308** **309** **310**

Scheme 4.5. Synthesis of quinolines *via* rearrangement of spirocyclohezadienyl radicals. i. SmI_2 (5.0 equiv.), HMPA (18 equiv.), THF, 0 ºC, 89%.

4.2 DISCOVERY OF A NEW COUMARIN SYNTHESIS

During the initial studies of the benzannulation reaction it was observed that in some cases, during the Claisen rearrangement of 2–bromophenyl allyl ether (**112b**), isomerisation of the double bond was a minor side reaction. The inseparable mixture of phenols **123b** and **312** was acetylated (Figure 4.1) and after submitting the mixture to the benzannulation conditions [CuCl (5 mol%), ligand 18 (5 mol%), DCE, MW, 200 ºC, 2 h] two products **139b** and **313** were obtained. The isomerised trichloroacetate **311** had undergone a 6–*exo* ATRC reaction giving coumarin **313**.[43]

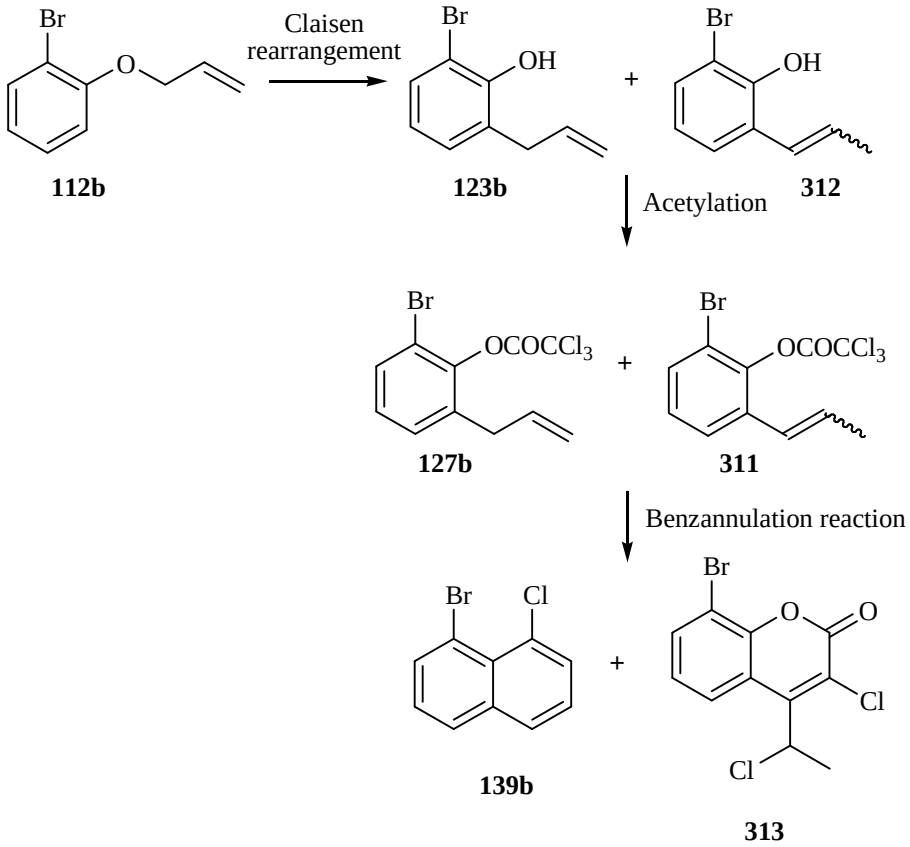
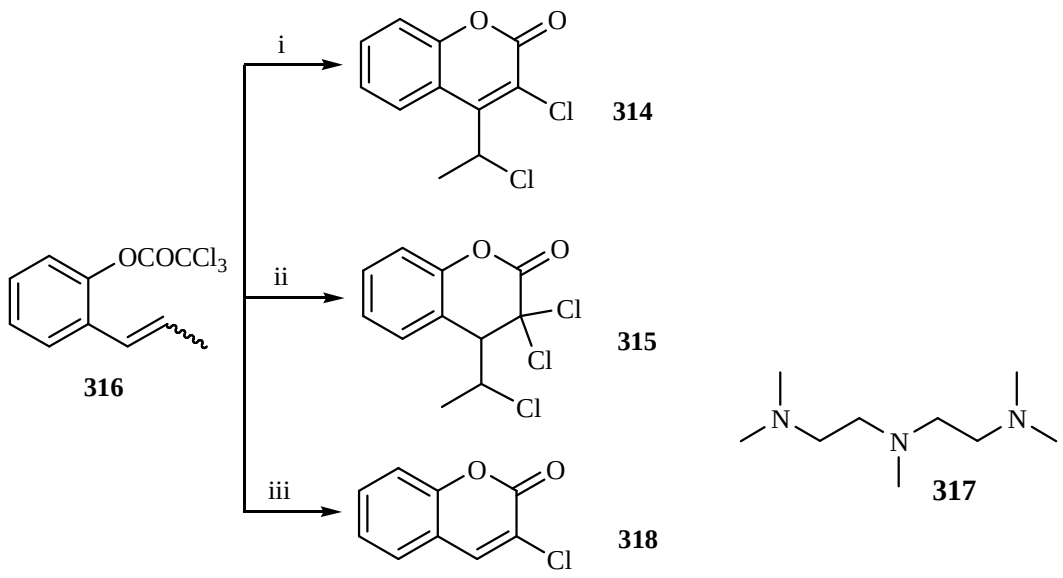


Figure 4.1. Discovery of the formation of coumarin **313** from trichloroacetate **311** under the benzannulation conditions [CuCl (5 mol%), ligand **18** (5 mol%), DCE, MW, 200 ºC, 2 h].

Earlier studies within the group,[116] led to an optimisation in yield from 34% to 92% when the reaction temperature was reduced from 200 to 190 ºC in the microwave reactor (Scheme 4.6). At lower temperatures (130 ºC) lactone **315** was isolated in 12% yield. In all these reactions coumarin **318** was found as a minor product, however, when the reaction was performed at 200 ºC for 6 h dihydrocoumarin **315** was isolated in 40% yield (Scheme 4.6).



Scheme 4.6. Influence of the temperature on the course of the radical cyclisation of trichloroacetate **311**. i. (IPr)CuCl (**156**, 5 mol%), DCE, MW, 190 ºC, 2 h, 92%. ii. CuCl (5 mol%), ligand **317** (5 mol%), DCE, MW, 130 ºC, 36 h, 12%. iii. CuCl (5 mol%), ligand **18** (5 mol%), DCE, MW, 200 ºC, 6 h, 40%.

We suggest that the reaction leading to the formation of the coumarins proceeds *via* an initial 6*–exo–trig* radical cyclisation, leading to isolable lactone **315** (Figure 4.2), followed by either elimination of HCl or 1,1–dichloroethane in a competitive process, resulting in the isolation of coumarins **314** and **318** respectively. The ratio of coumarins **314** and **318** can be controlled by changing the temperature and the ligand system leading to the exclusive formation of coumarin **314** along with the minor product **318** in a 4 : 1 ratio respectively.

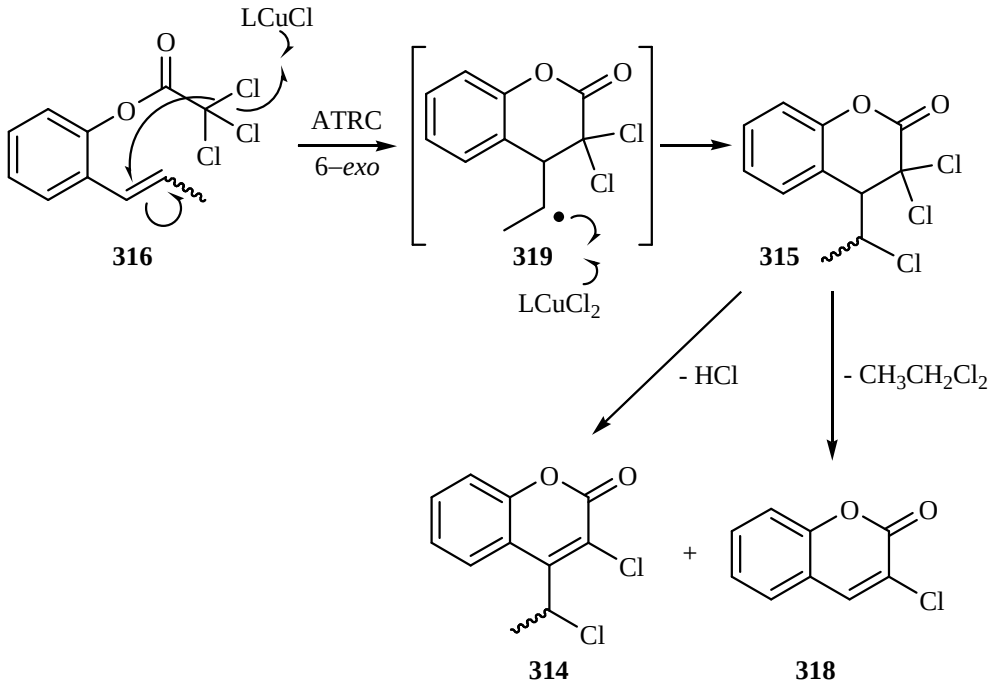


Figure 4.2. Proposed radical mechanism for the formation of coumarins **314** and **318**.

4.3 SYNTHESIS OF BENZANNULATION PRECURSORS

We envisaged that a diverse family of 1–propenyl trichloroacetates could be prepared from alkene isomerisation of readily available allyl phenols which we had been used previously in the **BHQ** reaction (Figure 4.3). Alternatively, the same substrates could also be available using standard Wittig chemistry with the appropriate benzaldehyde component.

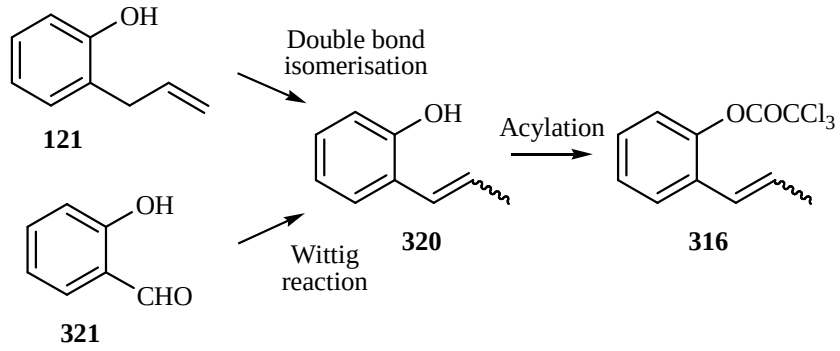
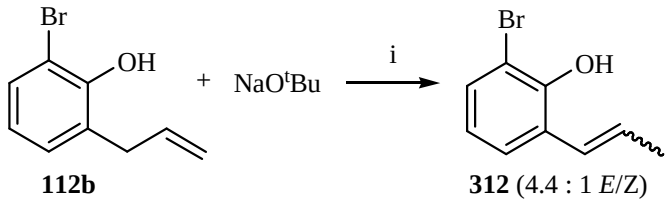


Figure 4.3. Proposed synthesis for the differents propenyl trichloroacetates.

For our studies just a few propenyl phenyl trichloroacetates examples were required.

4.3.1 ALLYL PHENOL ISOMERISATION

A standard literature procedure[117] for the isomerisation of the allyl group was followed, in which phenol **112b** and NaO^tBu were stirred at rt for 16 h. However, ^1H NMR of the crude mixture showed that there was still 26% of starting material unreacted. After some experimentation, conditions for this isomerisation reaction were optimised to reflux in THF for 24 h (Scheme 4.7). Under these conditions a 4.4 : 1 *E*/*Z* mixture of **312** was obtained in 86% yield.



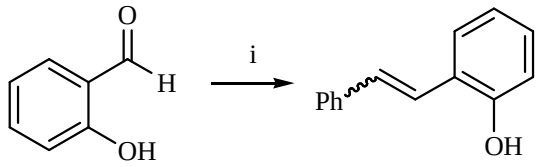
112b **312** (4.4 : 1 *E*/Z)

Scheme 4.7. Isomerisation of the double bond. i. THF, reflux, 24 h, 86%.

4.3.2 WITTIG REACTION

The Wittig reaction has become a popular method for alkene synthesis precisely because of its wide applicability. A large variety of ketones and aldehydes are effective in the reaction.

The Wittig reagent itself is usually derived from a primary alkyl halide, because with most secondary halides the phosphonium salt is formed in poor yield. However in our case the readily available BTPPC was successfully used (Scheme 4.8). One limitation of this method is the lack of selectivity in the stereochemistry of the product **322**. A mixture of *E* and *Z*–isomers **322** in a near 1 : 1 ratio was obtained in 69% yield after refluxing salicylaldehyde **299** and BTPPC for 12 h in acetonitrile in the presence of DBU.[118]

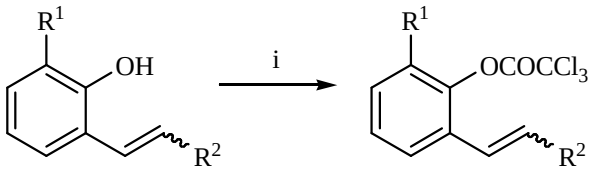


299 **322** (*E*/*Z* 1 : 1)

Scheme 4.8. Wittig reaction results. i. BTPPC (1.1 equiv.), DBU (1.1 equiv.), acetonitrile, reflux, 12 h, 69%.

4.3.3 ACYLATION

Acylation of the phenols **312**, **322** and 2–propenylphenol (**320**) was performed using standard methodology (trichloroacetyl chloride (1.2 equiv.), Et_3N (1.2 equiv.), 0 ºC, 3 h, Scheme 4.9, Table 4.1). The resulting activated esters were used usually without further purification as they had the tendency to undergo hydrolysis upon column chromatography.



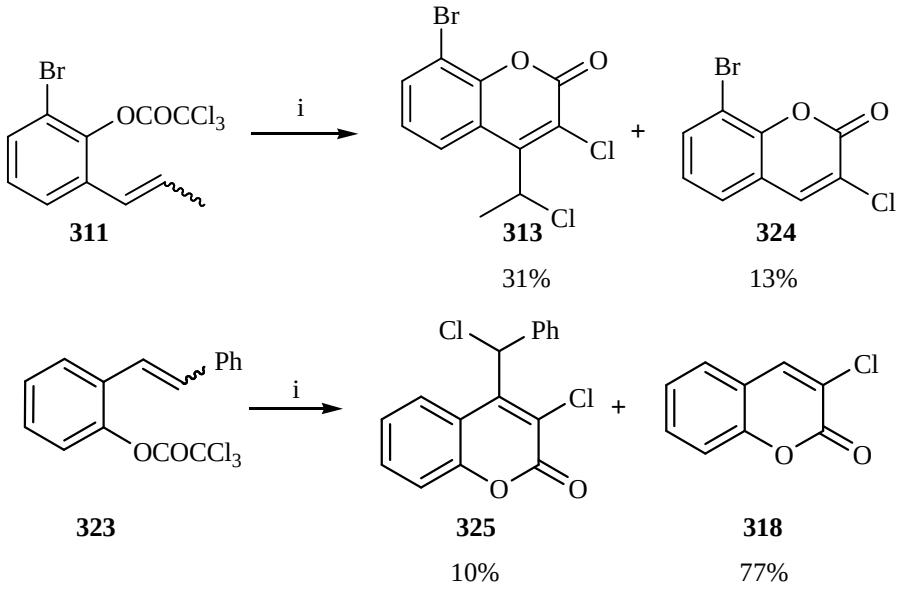
Scheme 4.9. Acylation conditions. i. Cl_3CCOCl (1.2 equiv.), Et_3N (1.2 equiv.), Et_2O, 0 ºC, 3 h.

Entry	SM	R^1	R^2	Product	Yield[a]
1	**312**	Br	H	**311**	92%
2	**320**	H	H	**316**	100%
3	**322**	H	Ph	**323**	82%

Table 4.1. Acylation results. a. Yields of crude products.

4.3.4 ATRC REACTIONS

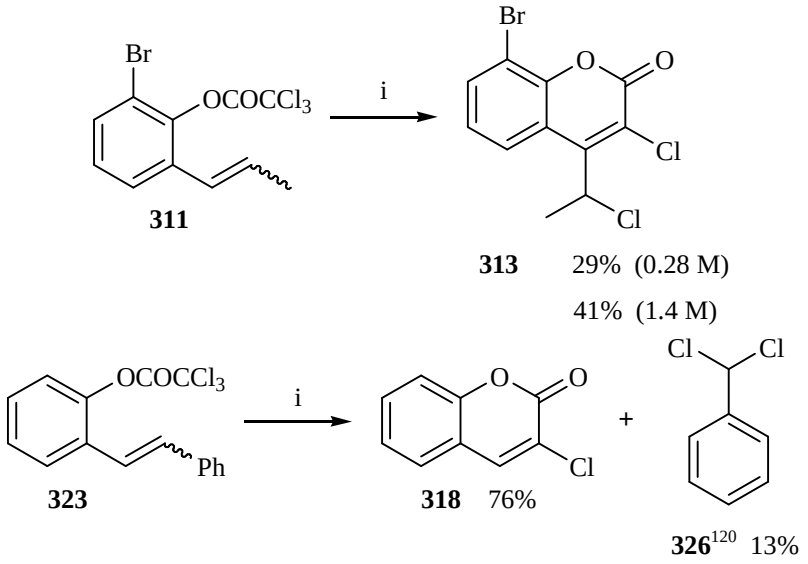
Initial **ATRC** reactions were conducted using trichloroacetates **311** and **323** under our optimised reaction conditions ((IPr)CuCl (**156**, 5 mol%), DCE, 190 ºC, 2 h, MW). Unfortunately, in both cases, further reactions took place after the initial **ATRC** reaction, leading to the isolation of the dealkylated coumarins **324** and **318** in 13% and 77% yields (Scheme 4.10).



Scheme 4.10. Coumarin formation results under standard cyclisation conditions. i. (IPr)CuCl (**156**, 5 mol%), DCE, 190 ºC, 2 h, MW.

It was thought that the dealkyllation reaction could in some way be affected by the temperature at which the reaction was performed or related to some intrinsic property of the solvent employed. Therefore we decided to screen the use of different solvents in this reaction. Repeating both **ATRC** reactions under purely thermal conditions ((IPr)CuCl (**156**, 5 mol%), diglyme, reflux, 7 h) gave an unanticipated outcome. Whereas cyclisation of trichloroacetate **311** afforded the desired coumarin **313** as the sole product, cyclisation of trichloroacetate **323** under identical conditions resulted in the isolation of coumarin **318** (76%) together with the eliminated fragment, α,α–dichlorotoluene (**326**, 13%, Scheme 4.10).[119]

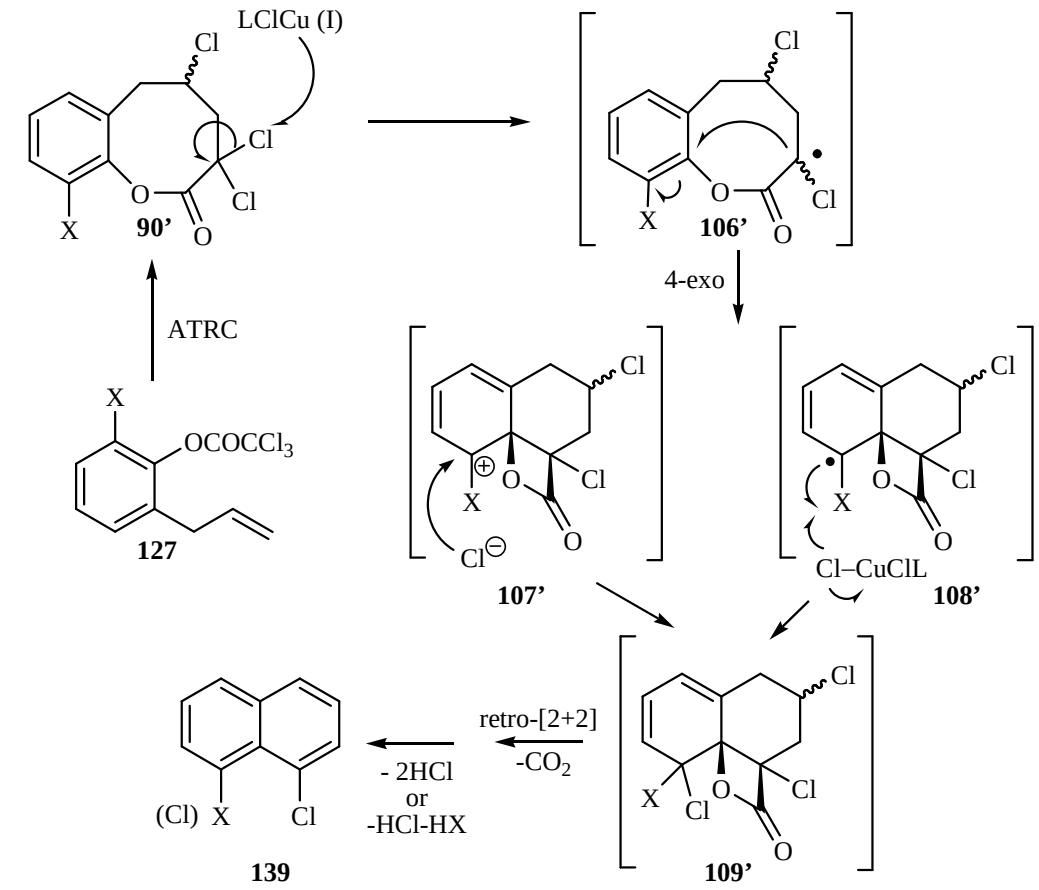
Another important aspect of this sequence is that when the reaction concentration of trichloroacetate **311** was increased from 0.28 M to 1.4 M yields also improved from 29% to 41% (Scheme 4.11).



Scheme 4.11. Cyclisation results at higher substrate concentration. i. (IPr)CuCl (**156**, 5 mol%), diglyme, reflux, 7 h.

It is important to notice that after the radical cyclisation of trichloacetate **319** there is no Br–Cl exchange in the molecule as observed in the past formation of bromo–substituted naphthalenes (*vida supra*).

If we compare both radical mechanisms (Figure 4.4) the initial **ATRC** reaction generates lactones **90'** and **328**, which can be identified by ^{1}H NMR but in the case of the 8–membered ring lactone **90'** its instability makes it impossible to isolate in good yields. Radical cyclisation of **90'** on to the aromatic ring allows for the halogen exchange observed before. However, this second radical cyclisation does not take place in coumarin **313** formation therefore no halogen exchange is possible, leading to a single product.



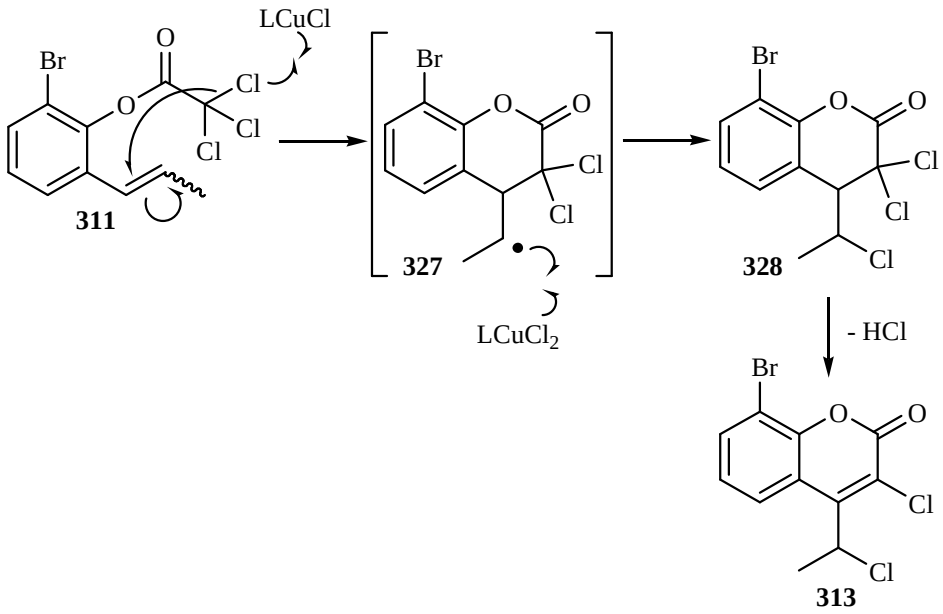
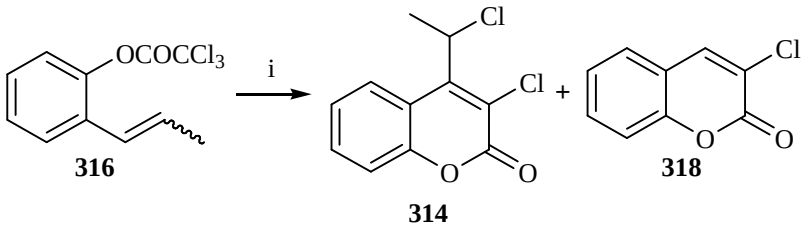


Figure 4.4. Mechanisms of the **ATRC** formation of naphthalenes and coumarins.

The thermal cyclisation reaction conditions in diglyme were then applied to the radical cyclisation of trichloroacetate **316**, after 7 h refluxing in diglyme two products were isolated. Coumarins **314** and **318** were obtained in a 1 : 2 ratio respectively and in poor yield (Scheme 4.12). As we had previously seen (Scheme 4.5, *vide supra*), temperature is an important factor in the formation of coumarins **314** and **318** so we tried the reaction in the presence of 5 mol% CuCl/ligand **18** (entry 2 in Table 4.2) and 5 mol% (IPr)CuCl (**156**, entry 3 in Table 4.2) in refluxing DCE for 24 h. Unfortunately, the lower temperature did not promote the radical cyclisation and starting material was recovered.



316 **314** **318**

Scheme 4.12. Cyclisation reaction conditions. i. Catalyst (5 mol%), solvent, reflux.

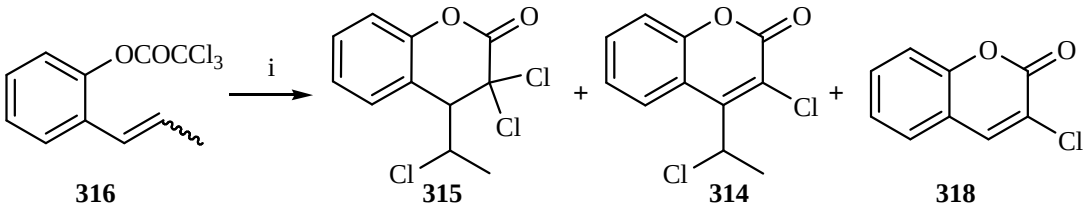
Entry	Catalyst	Solvent	Time	Yield (**314 : 318**)	Ratio (**314 : 318**)
1	(IPr)CuCl	Diglyme	7 h	7% : 13%	1 : 2
2	CuCl/ligand **18**	DCE	24 h	0%	–
3	(IPr)CuCl	DCE	24 h	0%	–

Table 4.2. Studies of the thermal radical cyclisation of **316**.

We have observed that the radical cyclisations of both (*E*,*Z*)–2–(prop–1–enyl) phenyl 2',2',2'–trichloroacetate (**316**) and (*E*/*Z*)–2–styrylphenyl 2',2',2'–trichlo–roacetate (**323**) gave 3–chlorocoumarin (**318**) as the major product. The radical cyclisation of trichloroacetate **316** was studied in order to elucidate the radical process in which the synthesis of by–product **318** is more favourable.

We had previously observed that after refluxing trichloroacetate **316** for 7 h in diglyme, coumarins **314** and **318** were isolated in 7% and 13% yields respectively (Scheme 4.13) with no starting material observed in the crude reaction mixture. We reduced the reaction time from 7 h to 2 h (Table 4.3) and ^{1}H NMR analysis

showed a 68% conversion to lactone **315**. Coumarins **314** and **318** were not observed. Unfortunately purification of the crude reaction mixture was not possible due to the instability of the coumarin and starting material on the silica column. Increasing the reaction time to 4 h to drive the reaction to completion, coumarin **314** was obtained in a 53% yield (entry 2, Table 4.3) along with an inseparable mixture of 1–chloronaphthalene (**92**) and 7–membered ring lactones **329** and **330** in a 1 : 7.8 : 1.3 ratio respectively (Table 4.3).[121]



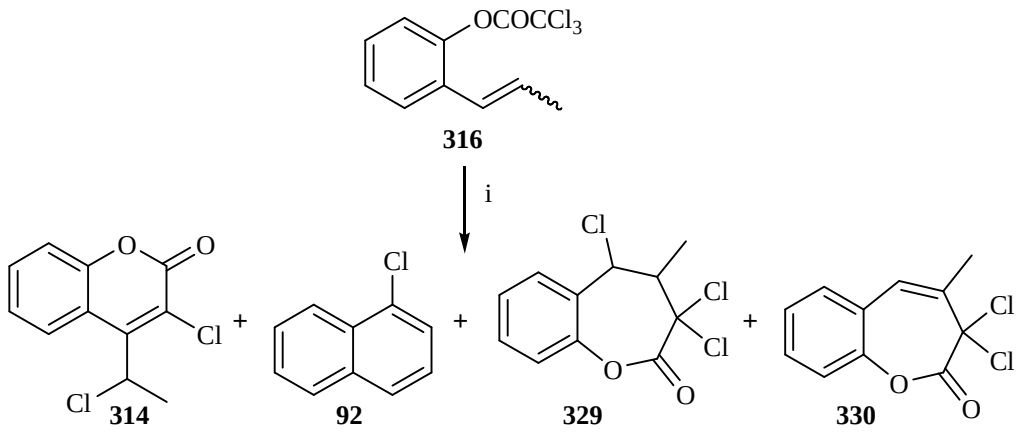
316 **315** **314** **318**

Scheme 4.13. Cyclisation products of trichloroacetate **314 ATRC** reaction. i. (IPr)CuCl (**156**, 5 mol%), diglyme, reflux.

Entry	Time (h)	315	314	318
1	2	68%[a]	–	–
2	4	0%	53%[b]	0%
3	7	0%	7%[b]	13%[b]

Table 4.3. Cyclisation results. a. Conversion yield. b. Isolated yield.

1–Chloronaphthalene (**92**) is obtained as a result of the isomerisation of the double bond to give 2–allylphenyl 2',2',2'–trichloroacetate (**89**) which undergoes the benzannulation process. On the other hand, a 7–*endo* radical cyclisation leads to lactone **329** which, by elimination of HCl, gives lactone **330**. These analogues (naphthalene **92** and lactones **329** and **330** in a 1 : 1.3 : 7.8 ratio) were determined by ^{1}H NMR analysis of the crude reaction mixture (Scheme 4.14).



Scheme 4.14. Products obtained of the cyclisation of trichloroacetate **314**. i. (IPr)CuCl (**156**, 5 mol%), diglyme, 4 h, reflux.

However, having been satisfied with the isolation of a single major product the result was not reproducible. Repeating this reaction several times afforded a variable mixture of coumarins **314**, **315** and **318**. On these occasions we were unable to isolate the by−products (napthalene **92** and coumarins **329** and **330**) formed previously, suggesting that there was either a further elimination of CH_3CHCl_2 after formation of coumarin **314** (pathway *a* Figure 4.5); or a competitive process for the formation of coumarins **314** and **318** once **314** has been formed (pathway *b* Figure 4.5).

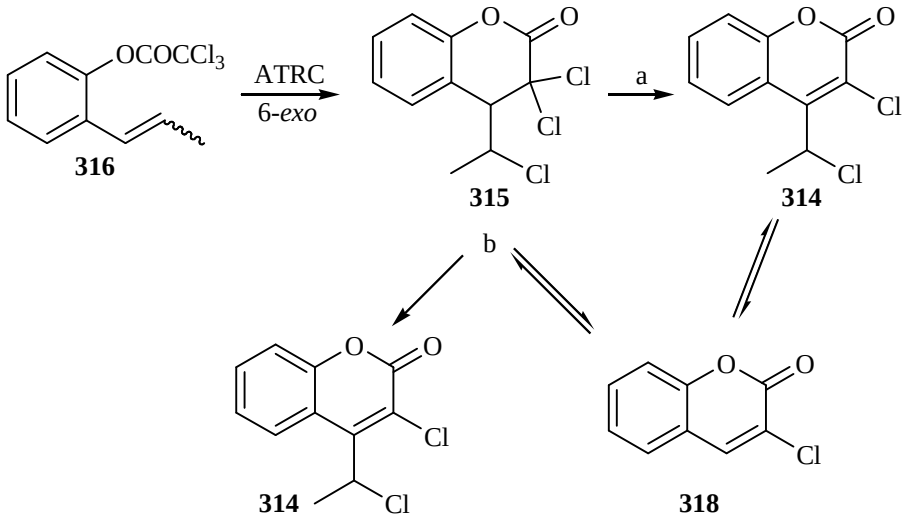
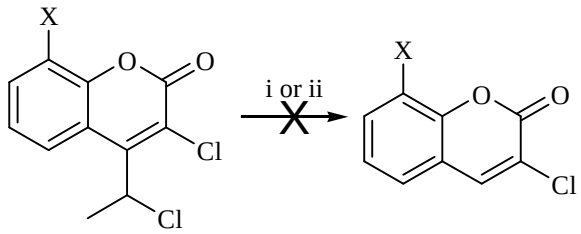


Figure 4.5. Proposed synthetic mechanism for the synthesis of the different coumarins.

First of all, we considered that coumarins **324** and **318** could result from the thermal decomposition of coumarins **313** and **314** respectively during the course

of the reaction (Scheme 4.15). However, blank experiments indicated that the isolated samples of coumarins **313** and **314** were stable to the reaction conditions (thermolysis in diglyme for 20 h and 3 h respectively with and without the presence of the Nolan carbene). In all the cases the isolation of unreacted starting material demonstrated that coumarins **313** and **314** were not the progenitors of coumarins **324** and **318** (Scheme 4.15).



X = Br **313** **324**

X = H **314** **318**

Scheme 4.15. Elimination experiments. a. X = Br i. Diglyme (1.0 mL), 20 h, reflux. ii. (IPr)CuCl (**156**, 5 mol%), diglyme (1.0 mL), 20 h, reflux. b. X = H i. Diglyme (0.1 mL), 3 h, reflux. ii. (IPr)CuCl (**156**, 5 mol%), diglyme (0.1 mL), 3 h, reflux.

4.3.5 DE–AKYLATIVE KHARASCH REACTION: MECHANISTIC STUDIES

In an attempt to gain information about the mechanism of this de–alkylative *retro*–Kharasch reaction, we investigated the cyclisation pathway starting from a specifically deuterated substrate. Based on our previous results cyclisation of the deuterated analogue of trichloroacetate **323** (deuterated trichloroacetate **331**) was investigated. If the final product contained deuterium at C(4), this would mean that the reaction pathway proceeds through radical elimination of α,α–dichlorotoluene (**326**, pathway *a* in Figure 4.6). On the other hand, if the final coumarin did not contain the deuterium label at C(4) an alternate fragmentation mechanism would have to be considered such as pathway *b* (Figure 4.6).

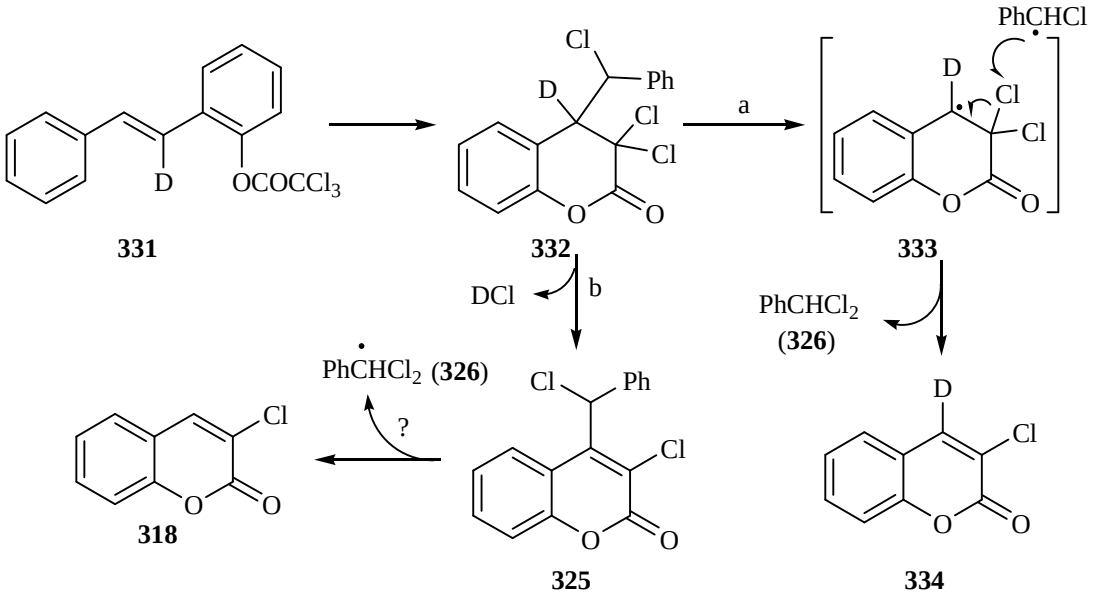


Figure 4.6. Proposed deuterated experiment.

(*E*/*Z*)–1–Deutero–2–styrylphenyl 2',2',2'–trichloroacetate (**331**) was readily available from the acylation of 2–[(*E*/*Z*)–2–deuterophenylvinyl]phenol (**335**), which itself was obtained from the Wittig reaction of α–deutero–2–hydroxybenzaldehyde (**336**, Figure 4.7). The deuterated aldehyde **336** synthesis had been reported in the literature by trapping of the dianion derived from *ortho*–bromophenol with d_7–*N*,*N*–dimethylformamide.

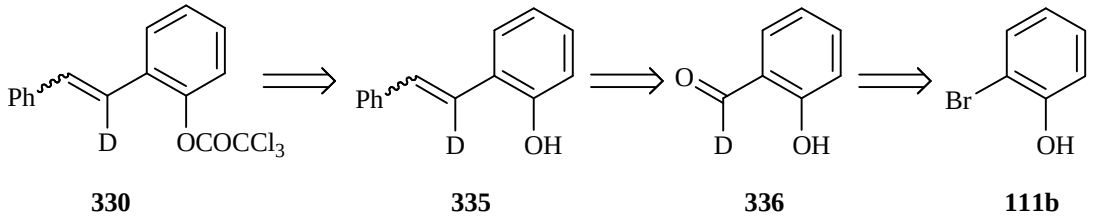
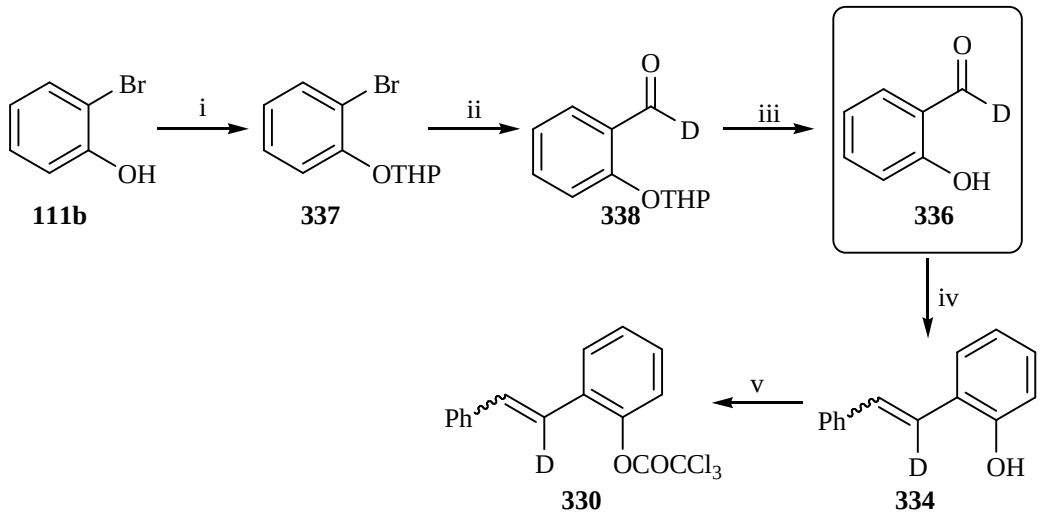


Figure 4.7. Retrosynthesis of (*E*/*Z*)–1–deutero–2–styrylphenyl 2',2',2'–trichloroacetate **330** synthesis.

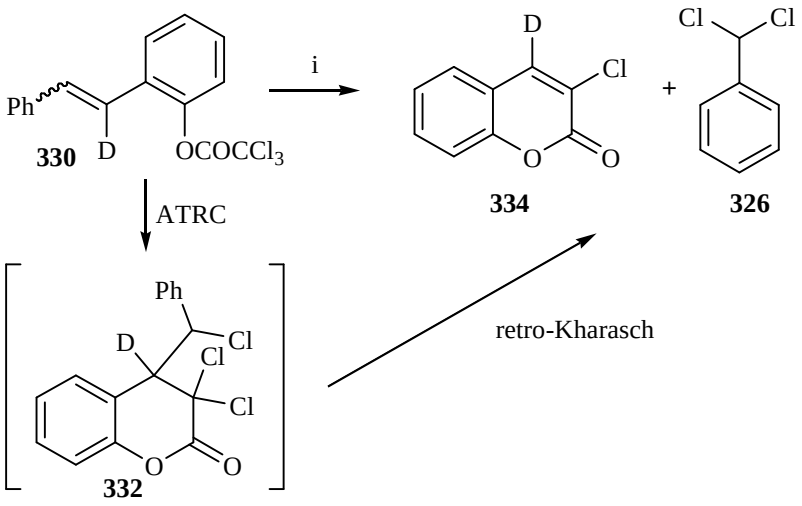
Initial attempts to prepare salicylaldehyde **320** starting fom 2–bromophenol (2 equiv. of ^{n}BuLi followed by the addition of *N*,*N*–dimethylformamide) were largely unsuccessful and resulted in low isolated yields of the desired product. However adoption of the route reported by Woggon *et al.*,[122] which involved the halogen–metal exchange of the protected phenol **337**, followed by trapping of the lithio anion with d_7–DMF afforded the deuterated aldehyde **336** in 46% overall yield after removal of the protecting group (Scheme 4.16). Wittig olefination of

aldehyde **336** (1 : 1.6 *E*/*Z* ratio) followed by the acylation afforded trichloroacetate **330** (96% yield over two steps).

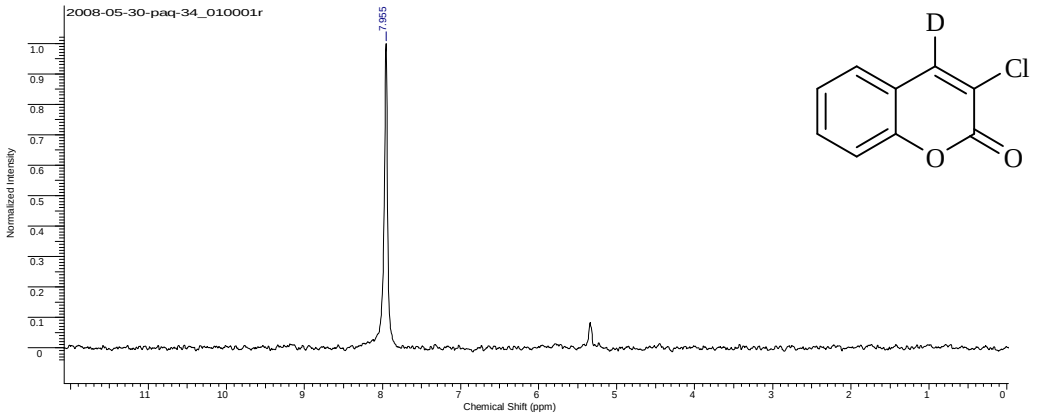


Scheme 4.16. Synthesis of deuterated trichloroacetate **330**. i. DHP (1.1 equiv.), CF_3CO_2H (cat.), 0 ºC to rt, 71%. ii. ^{n}BuLi (1.5 equiv.), d_7–DMF (1.1 equiv.), 0 ºC to rt, 86%. iii. HCl (1N) excess, THF, 16 h, rt, 46%. iv. DBU (1.1 equiv.), acetonitrile, reflux, 12 h, 54%. v. Cl_3CCOCl (1.2 equiv.), Et_3N (1.2 equiv.), Et_2O, 0 ^{o}C, 3 h, 96%.

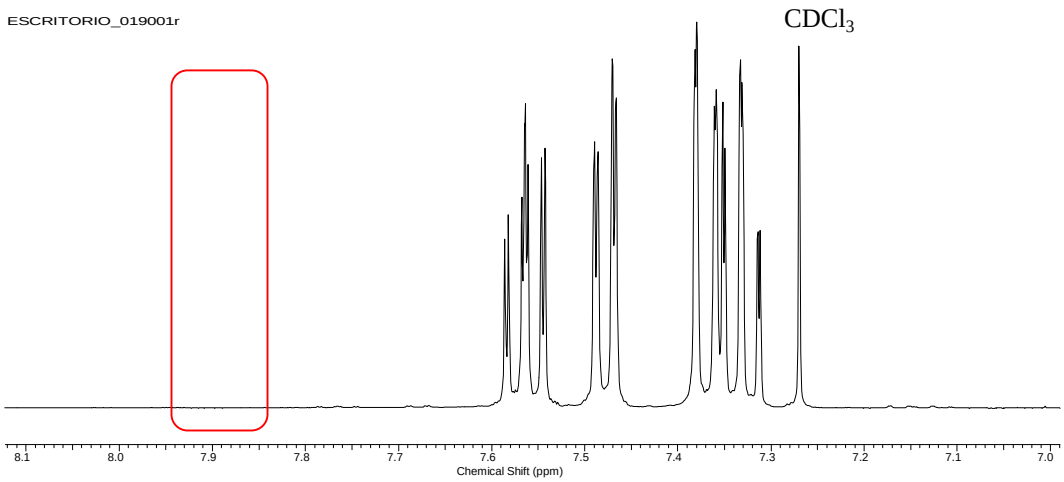
Finally, cyclisation of trichloroacetate **330** was attempted in the presence of 5 mol% (IPr)CuCl (**156**) in DCE at 190 ºC for 2 h in a microwave reactor. After purification two products were isolated: 3–chloro–2*H*–chromen–2–one–d–1 (**334**, 61%) and α,α–dichlorotoluene (**326**, 52%, Scheme 4.16), ^{1}H NMR analysis showed the absence of the hydrogen at C(4) and further ^{2}H NMR analysis (Figure 4.18) proved the presence of deuterium. We can conclude therefore that the formation of coumarin **334** is the result of an initial 6–*exo*–trig **ATRC** reaction, affording intermediate **332**, which then suffers a *retro*–Kharsach reaction, ultimately leading to the isolation of coumarin **334** and toluene **326**.



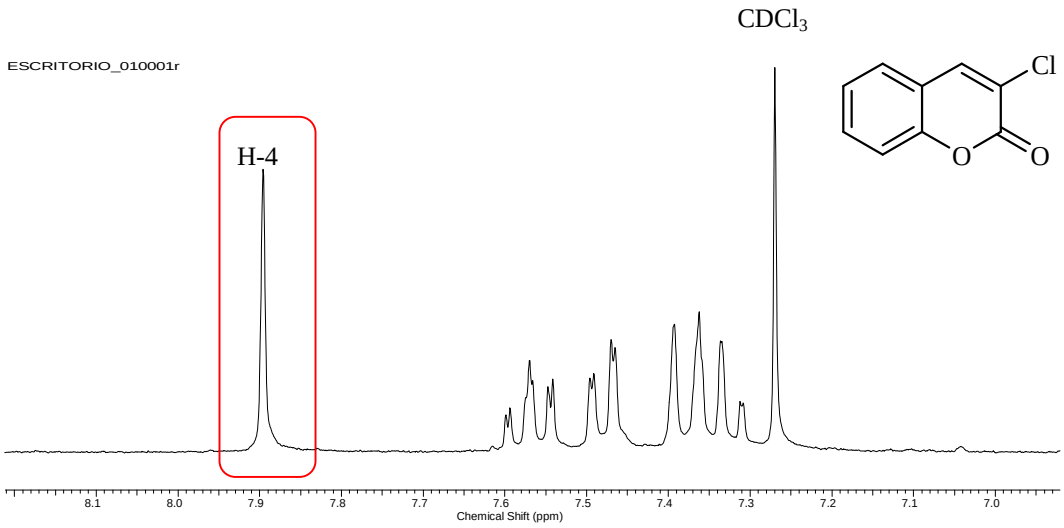
Scheme 4.17. Benzannulation reaction of **330**. i. (IPr)CuCl (**156**, 5 mol%), DCE, 190 ºC, MW, 2 h, 61%.



^{2}H NMR (CH_2Cl_2) of 3–Chloro–2*H*–chromen–2–one–d–1 (**331**)



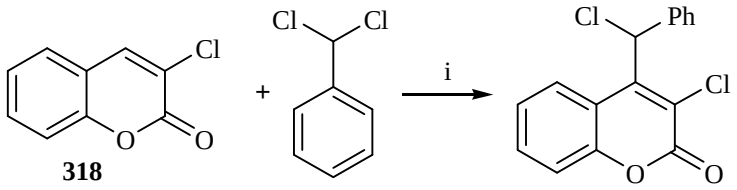
^{1}H NMR ($CDCl_3$) of 3–chloro–2*H*–chromen–2–one–d–1 (**331**)



^{1}H NMR ($CDCl_3$) of coumarin **318**

Figure 4.8. Deuterium studies spectroscopic results.

The reverse fragmentation of coumarin **318** to **325** was also investigated (Scheme 4.18). However, attempted Kharasch reaction of coumarin **318** into coumarin **325** under our standard reaction conditions did not afford any detectable amount of the adduct **325**. Presumably the thermodynamic products of the equilibrium in this reaction are coumarin **318** and toluene **326**.



318 **326** **325**

Scheme 4.18. i. (IPr)CuCl (**156**, 5 mol%), DCE, 190 ºC, MW, 2 h, 61%.

CHAPTER 5: RELATED ATRC REACTIONS

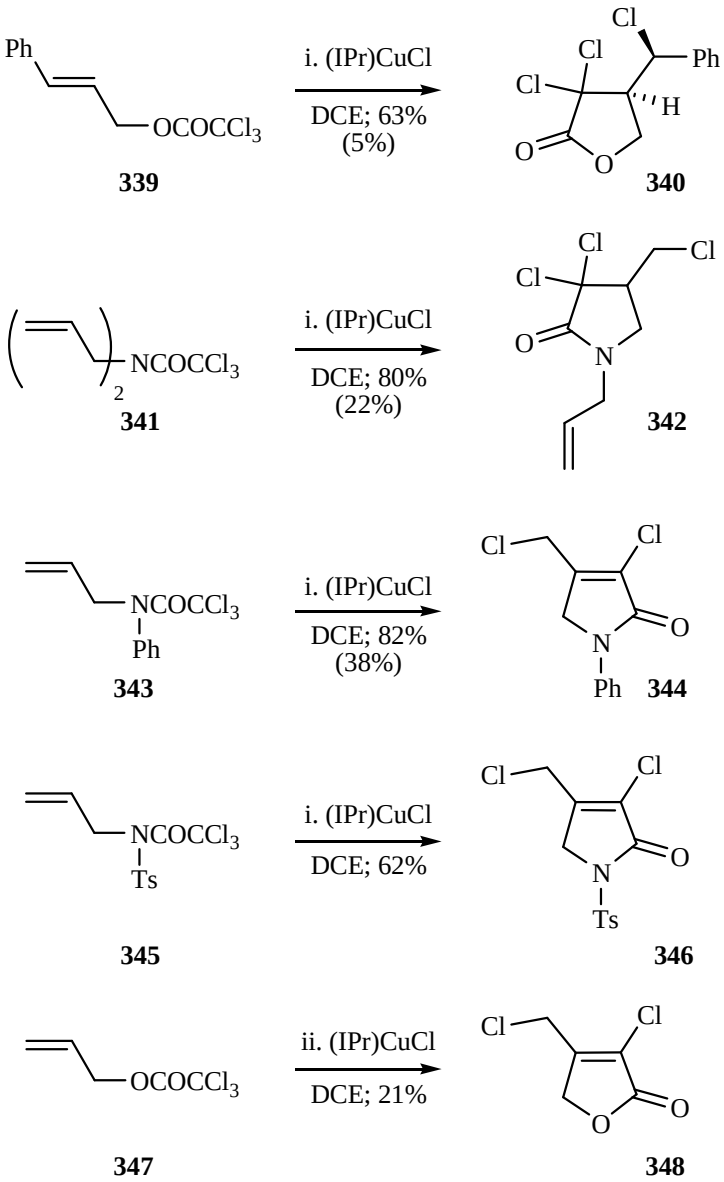
5. RELATED ATRC REACTIONS

Finally, we briefly investigated the efficacy of TM–NHC carbene complexes in other, related, **ATRC** reactions. Unfortunately, thermolysis of trichloroacetates **339**, **341** and **343** in DCE to in the presence of (IPr)CuCl (**156**) afforded the lactone **340** and lactams **342** and **344** in very low yields (Scheme 5.1) with no starting material recovered.

Since the first report of the use of microwave irradiation in 1986 by the groups of Gedye and Guiguere[123,124] the application of microwaves in organic synthesis has been widely studied. Microwave heating in organic synthesis can accelerate the transformations if the compounds or the solvents can absorb the MW radiation.[125] Our previous observation concerning the beneficial effects of microwave irradiation on the cyclisation of 2–allyl phenyl 2',2',2'–trichloroacetates [(IPr)CuCl (**156**, 5 mol%), DCE, 200 ºC, MW, 2 h] encouraged us to attempt these **ATRC** reactions in a microwave reactor. Fortunately, adopting this experimental regime resulted in a vast improvement in the product yield (Scheme 5.1). There is obviously a microwave effect which is beneficial to the reaction yields.

The lack of recovered starting material after the thermal reaction was due to the capacity of the microwave reactor to heat the reaction mixture rapidly over the DCE boiling point. This was the key factor in promoting the cyclisation before the decomposition of the trichloroacetate takes place.

The temperature required for the cyclisation of trichloroacetates **339** – **347** was 110 ºC. At lower temperatures the reaction was sluggish whereas at temperatures above 150 ºC extensive decomposition of either product or starting material led to the isolation of the desired product in reduced yields. Similarly, reduction of the catalyst loadings (from 5 to 1 mol%) resulted in diminished yields (from 82% to 63% of **346**) when conducting the reaction in the microwave reactor at 110 ºC for 17 h.



Scheme 5.1. **ATRC** reactions catalysed by (IPr)CuCl (**156**). i. (IPr)CuCl (5 mol%), DCE, 3 h, 110 ºC, MW. ii. (IPr)CuCl (5 mol%), DCE, 17 h, 110 ºC, MW. Yields in parentheses are those obtained by the thermolysis of the substrate in the presence of (IPr)CuCl (**156**, 5 mol%) refluxing in DCE for 3 h.

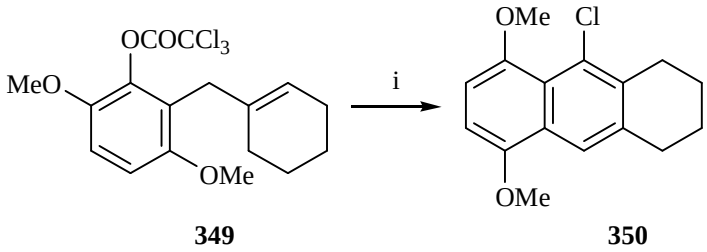
CHAPTER 6: CONCLUSION

6. CONCLUSION

An investment into the scope and limitations of a new decarboxylative benzannulation reaction has been undertaken. These studies point to a mechanism which involves initial **A**tom **T**ransfer **R**adical **C**yclisation (**ATRC**) of an appropriate *ortho*–allylphenyl trichloroacetate to an eight–membered ring lactone followed by extrusion of carbon dioxide; finally loss of hydrogen chloride leads to the observed aromatic product. Both halogen and hydrogen scrambling studies support a radical cyclisation process in the key carbon-carbon bond-forming step.

Methodological studies have also shown that a variety of transition metal carbene complexes can serve as catalysts, with varying degrees of efficiency, for this reaction. Significantly 1,3–*bis*(2,6–diisopropylphenyl)imidazolium copper(I) chloride [(IPr)CuCl)] can successfully promote the **BHQ** reaction affording naphthalenes in similar or better yields than the CuCl/ligand **8** system. Reaction crude mixtures are also cleaner resulting in a simple methodology for the synthesis of naphthalenes.

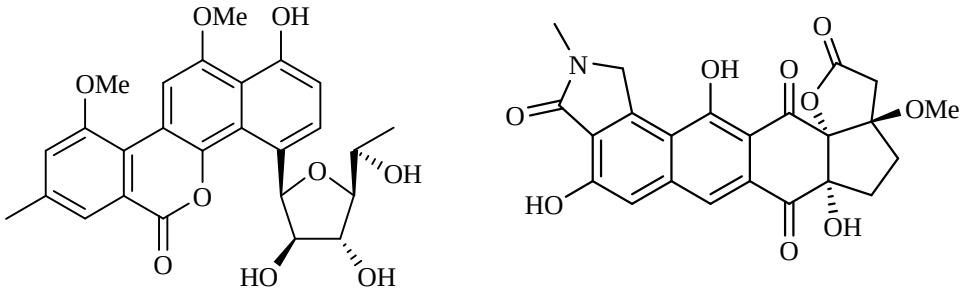
The synthetic potential of this reaction (the "**BHQ** reaction") has been further augmented by demonstrating that this transformation can be effectively carried out in diglyme at reflux. Although the reaction conditions are now less harsh some acid sensitive compounds still suffer side reactions. Future work will involve the introduction of buffer solutions to the **BHQ** reaction mixture. Studies within the group concerning the synthesis of more complex naphthalenes such as **350** indicate the potential of this transformation in natural product synthesis and is an area which is under active investigation (Scheme 6.1).



349 **350**

Scheme 6.1. i. (IPr)CuCl (**156**, 5 mol%), diglyme, reflux, 15 h, 78%.

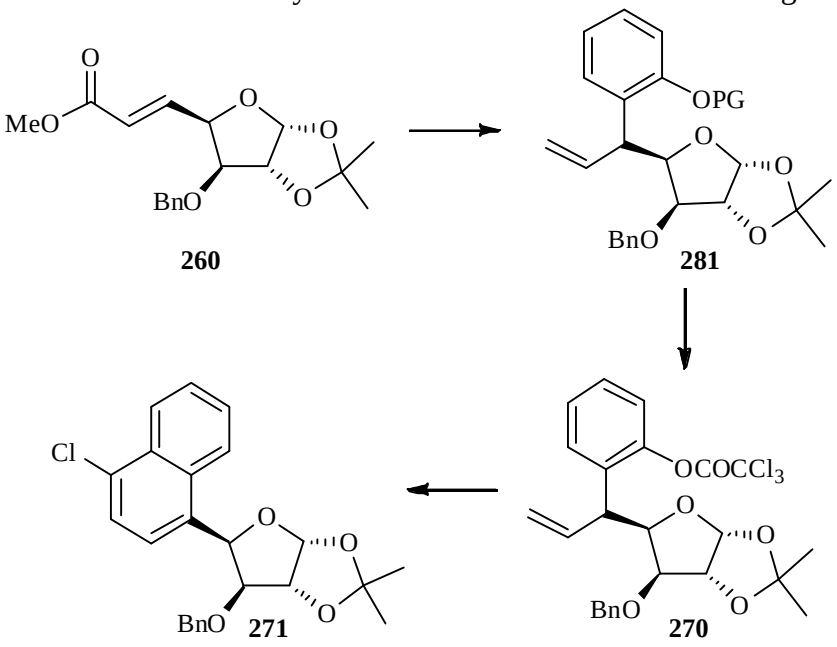
Current synthetic objectives include the development of new approaches to the synthesis of gilvocarcin M **214** and lactonamycin **351**.



Gilcovarcin M **214** lactonamycin **351**

Figure 6.1. Gilcovarcin M and lactonamycin.

Model studies directed towards the synthesis of gilvocarcin M **214** have shown that the BHQ benzannulation reaction allows sterically hindered and acid labile systems to be synthesised from readily available intermediates. Unfortunately attempts to promote the Claisen rearrangement of glycoside substituted allyl phenol have so far been unsuccessful. Model studies have shown that the synthesis of key intermediates such as **281** which are required for this approach can addressed using a hitherto unknown cuprate addition to unsaturated sugar derivatives such as **260**. The synthetic potential of this highly diastereoselective 1,4-addition reaction is currently the focus of further work within the group.



Scheme 6.2. Michael addition approach to the synthesis of carbohydrate **271**.

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PART II: EXPERIMENTAL

GENERAL EXPERIMENTAL

All reactions were carried out under an atmosphere of dry nitrogen unless stated otherwise. Temperatures quoted are for the external heating/cooling source and are given in degrees Celsius (ºC). Where a temperature is not quoted, the reaction in question was carried out at rt.

Melting points were performed on a Sanyo Gallenkamp melting point apparatus and are uncorrected.

Optical rotations were measured using an Optical Activity Ltd. AA–100 Polarimeter with a 0.25 dm cell. The concentration is measured in g/cm^3.

Infrared spectra were recorded on a Genesis FTIR as evaporated films on sodium chloride plates and are quoted in cm^{-1}.

Nuclear magnetic resonance (NMR) spectra were recorded using deuterated chloroform as solvent unless otherwise stated. Proton NMR spectra (^{1}H NMR) were recorded on Bruker Avance Ultrashield 500 (500 MHz), Bruker Avance Ultrashield 400 (400 MHz), Bruker Avance Ultrashield 300 (300 MHz) and Varian INOVA Unity 300 (300 MHz) spectrometers. Residual non–deuterated solvent was used as internal standard. Chemical shifts (δ_H) are quoted in parts per million (ppm) downfield from tetramethyl silane (TMS). Signal splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), broad singlet (broad s) or multiplet (m). Coupling constants (*J*) are quoted in Hz. Carbon NMR spectra (^{13}C NMR) were recorded on a Bruker Avance Ultrashield 500 (125 MHz), Bruker Avance Ultrashield 400 (100 MHz), Bruker Avance Ultrashield 300 (75 MHz) and Varian INOVA Unity 300 (75 MHz) spectrometers, again with residual deuterated solvent resonance as the internal standard. Chemical shifts (δ_C) are quoted in ppm downfield from TMS. Fluorine NMR spectra (^{19}F NMR) were recorded on a Varian INOVA unity 300 spectrometer at 75 MHz. Deuterium NMR spectra (^{2}H NMR) were recorded in CH_2Cl_2 on a Bruker Avance Ultrashield 400 (61 MHz).

Low resolution mass spectra were recorded on a Micromass Trio 200 spectrometer. High resolution mass spectra were recorded on a Kratos Concept IS spectrometer. Modes of ionisation were electron impact (EI), chemical ionisation (CI) using ammonia or electrospray in positive mode (ES^+).

Microanalysis was performed on a Carlo Erba EA1108 Elemental Analyzer for the determination of % levels of carbon, hydrogen and nitrogen a Metrohm 686 Titroprocessor + 665 Dosimat Autotitrator for chlorine.

Flash column chromatography was carried out using Davisil silica gel LC60 Å 40-60 micron purschased from Fluorochem. Thin layer chromatography (TLC) was carried out using plastic plates coated with Polygram® SIL G/UV_{254} silica gel from Macherey–Nagel GmbH & Co. Detection was by ultraviolet absorption and/or treatment with either basic potassium permanganate, ethanolic phosphomolybdic acid or acidic ninhydrin solutions followed by heating.

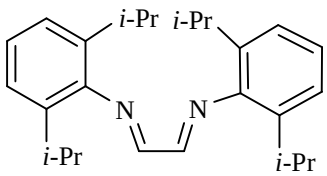
'Petrol' refers to the fraction of petroleum ether that boils between 40 ºC and 60 ºC at atmospheric pressure. 'Ether' refers to diethyl ether, which was used without further purification. THF was dried over sodium benzophenone ketyl and distilled under a dry nitrogen atmosphere prior to use. CH_2Cl_2 was dried over calcium hydride and distilled under an atmosphere of dry nitrogen prior to use. Anhydrous toluene (99.8%) was used as supplied from Aldrich. DCE was distilled over CaH_2 prior to use. Anhydrous CuCl was purchased from Aldrich (≥ 99.99% trace metals basis). All other reagents and solvents were used as purchased, from commercial sources, unless otherwise stated.

Experiments using MW radiation were conducted in a Biotage Initiator™ microwave reactor (maximum power output of 300 W; operating frequency 2450 MHz).

Tricloroacetates **89a – 89c**, **89f**, **89h**, **93** and 7–(allyloxy)–6–(tetrahydro–3,4,5–trihydroxy–6–(hydroxymethyl)–2*H*–pyran–2–yloxy)–2*H*–chromen–2–one (**160**) were supplied by Dr. James Bull (preparation as described in his PhD Thesis, *University of Manchester*, **2008**)

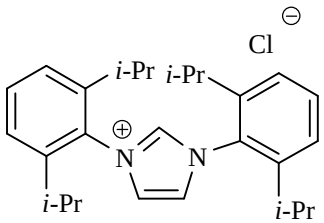
1. SYNTHESIS OF THE CATALYSTS

Bis–(2,6–diisopropylphenyl)–diazabutadiene (154):[126]



A few drops of formic acid (> 96%) were added to a solution of 2,6–diisopropylaniline (13.3 mL, 70.5 mmol) in EtOH (40 mL). After 10 min stirring glyoxal (2.6 mL of a 40% v/v aqueous solution, 35.3 mmol) was added dropwise. The mixture was left stirring for 2 days at rt. The resulting yellow solid was isolated by filtration and washed with cold MeOH to afford the *title compound* (**154**, 10.51 g, 27.9 mmol, 84%) as a yellow solid. **Mp**: 106 ºC (lit.[126] Mp: 105 ºC). **IR** ν_{max}(film): 3062, 2964, 2924, 2871, 1918, 1670, 1626, 1589, 1465, 1436, 1360, 1290, 1176, 1109, 924 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.19 (2H, s, NCH), 7.27 (6H, m, ArH), 3.03 (4H, sep, *J* = 7, C<u>H</u>$(CH_3)_2$), 1.28 (24H, d, *J* = 7, CH(C<u>H</u>$_3)_2$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.09, 147.97, 136.70, 125.10, 123.16, 28.01, 26.67 ppm. *m/z* **EI:** 377 [M+]. **Accurate Mass:** $C_{26}H_{36}N_2$ requires 377.2951; found 377.2956.

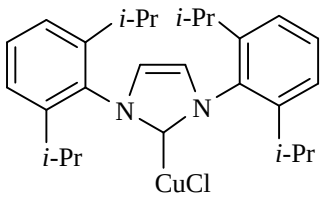
1,3–*Bis*(2,6–diisopropylphenyl)imidazolium chloride (IPr.HCl, 155):[127]



To a solution of bis–(2,6–diisopropylphenyl)–diazabutadiene (**154**, 13.95 g, 37.0 mmol) in toluene (280 mL) was added solid paraformaldehyde (1.11 g, 37.0 mmol). The mixture was heated at 100 ºC until most of paraformaldehyde was dissolved. On cooling to 40 ºC HCl (9.3 mL of a 4 M solution in dioxane, 37.0 mmol) was then added slowly added slowly by a syringe and the reaction mixture was heated to 70 ºC for a further period of 5 h. The resulting heterogeneuous mixture was then allowed to stir at rt for 36 h after which time the precipitate

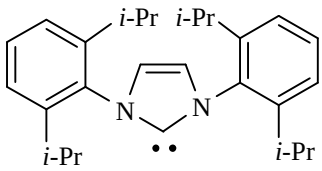
which had formed was isolated by filtration and washed with THF (T = 0 ºC). Trituration of the the pink–coloured powder with Et_2O (at ambient temperature) afforded the *title compound* (**155**, 7.58 g, 17.8 mmol, 48%) as an off–white coloured solid. **Mp:** 260 ºC (lit.[127] Mp: 260 – 262 ºC). **IR** ν_{max}(film): 3155, 2961, 2869, 1752, 2730, 1532, 1469, 1442, 1365, 1332, 1207, 1062 cm^{-1}. **^{1}H NMR** (300 MHz, DMSO–d_6) δ 11.24 (1H, s, NC(H̲C–l)N), 7.86 (2H, app s, NCH), 7.70 (2H, t, *J* = 8, *p*–C_6H_3), 7.47 (4H, d, *J* = 8, *m*–C_6H_3), 2.42 (4H, sep, *J* = 7, C̲H$(CH_3)_2$), 1.36 (12H, d, *J* = 7, CH(C̲$H_3)_2$), 1.33 (12H, d, *J* = 7, CH(C̲$H_3)_2$) ppm. **^{13}C NMR** (75 MHz, CD_2Cl_2) δ 145.38, 140.77, 132.26, 130.28, 125.79, 124.92, 29.42, 24.69, 23.60 ppm. *m/z* **EI:** 389 [M – Cl]. **Accurate Mass:** $C_{27}H_{37}N_2$ requires 389.2951; found 389.2962.

1,3–*Bis*(2,6–diisopropylphenyl)imidazolium copper(I) chloride ((IPr)CuCl), 156):[128]



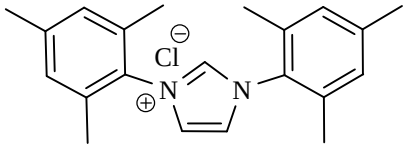
THF (12 mL) was added to a flask containing IPr.HCl (**155**, 1.30 g, 3.1 mmol), CuCl (302 mg, 3.1 mmol) and NaO^tBu (294 mg, 3.1 mmol) under nitrogen. The heterogenous mixture was stirred for 4 h at rt and then filtered through Celite® in order to remove the inorganic salts. The filtrate was concentrated *in vacuo* to afford the *title compound* (**156**, 1.34 g, 2.7 mmol, 90%) as an off–white solid in an essentially pure state. Mp: > 300 ºC (lit.[128] Mp: > 300 ºC). **IR** ν_{max}(film): 3160, 3133, 2964, 2870, 1684, 1592, 1545, 1469, 1457, 1405, 1363, 1272, 806, 761, 736 cm^{-1}. **^{1}H NMR** (300 MHz, acetone–d_6) δ 7.26 (2H, s, NCH), 7.49 (2H, dd, *J* = 15.5, *J* = 8, ArH), 7.42 (4H, d, *J* = 8, ArH), 2.70 – 2.65 (4H, m, C̲H$(CH_3)_2$), 1.32 (12H, d, *J* = 7, CH(C̲$H_3)_2$), 1.26 (12H, d, *J* = 7, CH(C̲$H_3)_2$) ppm. **^{13}C NMR** (75 MHz, acetone–d_6) δ 180.23, 146.05, 135.12, 130.61, 124.17, 24.44, 23.29 ppm. **Scan ES+:** 511/509 [M + Na]. **Accurate Mass:** $C_{27}H_{36}{}^{35}ClCuN_2Na$ requires 509.1770; found 509.1755.

1,3–*Bis*(2,6–diisopropylphenyl)imidazol–2–ylidene (IPr, 157):[129]



To a mixture of IPr.HCl (**155**, 1.00 g, 2.4 mmol) and NaO^{t}Bu (242 mg, 2.5 mmol) was added THF (10 mL). The brown–coloured heterogeneous mixture was left for 4 h at ambient temperature and the solvent was then removed *in vacuo*. The residue was taken up in hot toluene (70 ºC), the toluene extracts were filtered through Celite® and the filtrate concentrated *in vacuo* to afford the *title compound* (**157**, 594 mg, 1.5 mmol, 65%) as a brown solid. **Mp**: 212 ºC (lit.[129] Mp: 213 – 217 ºC). **IR** ν_{max}(film): 3136, 3063, 2964, 2869, 1677, 1617, 1539, 1464, 1384, 1319, 802, 754 cm^{-1}. **^{1}H NMR** (300 MHz, C_6D_6) δ 7.22 (2H, m, *p*–ArH), 7.11 (4H, m, *m*–ArH), 6.57 (2H, s, NCH), 2.91 (4H, sep, *J* = 9, C<u>H</u>(CH$_3$)$_2$), 1.23 (12H, d, *J* = 9, CH(C<u>H</u>$_3$)$_2$), 1.13 (12H, d, *J* = 9, CH(C<u>H</u>$_3$)$_2$) ppm. **^{13}C NMR** (75 MHz, C_6D_6) δ 146.16, 128.97, 123.60, 121.47, 28.66, 24.70, 23.54 ppm. **Scan ES+:** 389 [M+]. **Accurate Mass:** $C_{27}H_{37}N_2$ requires 389.2947; found 389.2951.

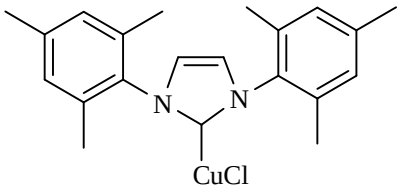
1,3–*Bis*(2,4,6–trimethylphenyl)–imidazolium chloride (IMes.HCl, 173):[127]



A mixture of 2,4,6–trimethylaniline (3.9 mL, 28.0 mmol) and paraformaldehyde (420 mg, 14.0 mmol) in toluene (14 mL) was heated at 100 ºC for 1 h under nitrogen. After cooling to 40 ºC, HCl (1.2 mL, 14.0 mmol, 37% in H_2O) was added dropwise. To the resulting suspension was added glyoxal (1.6 mL, 14.0 mmol, 40% in H_2O) and the reaction mixture was brought to reflux for 1.5 h. On cooling to rt the volatiles were removed *in vacuo* leaving a sticky black solid. The reaction crude was dissolved in the minimum amount of hot CH_2Cl_2 and it was recrystalised by the addition of Et_2O to afford the *title compound* (**173**, 1.47 g, 4.3 mmol, 31%) as a brown powder. **Mp**: > 240 ºC (lit.[127] Mp: 351 – 352 ºC). **IR**

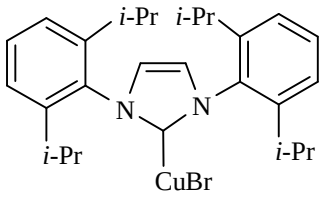
ν_{max}(film): 3629, 3292, 3196, 3150, 2899, 1607, 1535, 1482, 1459, 1234, 868, 782 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.58 (1H, s, NC(HCl)N), 7.64 (2H, s, NCH), 7.00 (4H, s, ArH), 2.32 (6H, s, *p*–CH_3), 2.16 (12H, s, *o*–CH_3) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.26, 134.04, 130.54, 129.83, 129.51, 124.44, 21.08, 17.59 ppm. **Scan ES+:** 305 [M – Cl^-]. **Accurate Mass:** $C_{21}H_{25}N_2$ requires 305.2012; found 305.2022.

1,3–*Bis*(2,4,6–trimethylphenyl)imidazolium copper (I) chloride (166):[130]



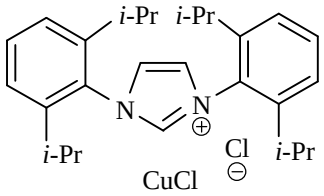
THF (80 mL) was added to a flask containing IMes.HCl (**173**, 500 mg, 1.5 mmol), CuCl (145 mg, 1.5 mmol) and NaO^tBu (141 mg, 1.5 mmol) under nitrogen. The mixture was stirred for 4 h at rt and then filtered through Celite®. The filtrate was concentrated *in vacuo* to afford the crude product as a brown solid. Trituration of this material with Et_2O afforded the *title compound* (**166**, 520 mg, 1.3 mmol, 88%) as a brown solid in an essentially pure state. **Mp**: > 240 ºC (lit.[131] Mp: 273 – 277 ºC). **IR** ν_{max}(film): 3160, 3136, 2979, 2950, 2914, 2850, 1607, 1485, 1400, 1238, 1076, 931, 864, 742 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.98 (2H, app s, NCH), 6.92 (4H, s, ArH), 2.27 (6H, s, *p*–CH_3), 2.03 (12H, s, *o*–CH_3) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 178.95, 139.44, 135.01, 134.50, 129.42, 122.20, 21.04, 17.69 ppm. **Scan ES+:** 428/426 [M + Na]. **Accurate Mass:** $C_{21}H_{25}{}^{35}ClCuN_2Na$ requires 426.4254; found 426.4260.

1,3–*Bis*(2,6–diisopropylphenyl)imidazolium copper(I) bromide (194):[132]



THF (12 mL) was added to a flask containing IPr.HCl (**155**, 200 mg, 0.5 mmol), CuBr (67 mg, 0.5 mmol) and Na^{t}OBu (48 mg, 0.5 mmol) under nitrogen. The mixture was stirred for 20 h at rt. The mixture was filtered through Celite® and the filtrate concentrated *in vacuo* to afford the *title compound* (**194**, 113 mg, 0.21 mmol, 45%) as a white solid. **Mp:** > 240 ºC. **IR** ν_{max}(film): 3159, 3136, 2966, 2925, 1495, 1455, 1407, 1365, 1328, 1265, 1058, 808, 763, 742 cm^{-1}. **^{1}H NMR** (300 MHz, acetone–d_6) δ 7.89 (2H, broad s, NCH), 7.54 (2H, dd, *J* = 16, *J* = 8, ArH), 7.40 (4H, d, *J* = 8, ArH), 2.55 – 2.47 (4H, m, C<u>H</u>(CH$_3$)$_2$), 1.21 (24H, d, *J* = 7, CH(C<u>H</u>$_3$)$_2$) ppm. **^{13}C NMR** (75 MHz, acetone–d_6) δ 180.21, 146.04, 135.07, 130.63, 124.23, 24.36, 23.28 ppm. **Scan ES+:** 555/553 [M + Na], 389 [M – CuBr]. **Accurate Mass:** $C_{27}H_{36}N_2{}^{79}BrCuNa$ requires 553.1250; found 553.1263.

(IPr.HCl)CuCl complex (165):[133]



CH_2Cl_2 (10 mL) was added to a flask containing IPr.HCl (**155**, 300 mg, 0.7 mmol) and CuCl (75 mg, 0.7 mmol) under nitrogen. The pale brown solution was stirred for 2 h at rt and filtered through Celite®. The filtrate was concentrated *in vacuo* and the residue was dissolved in the minimum amount of CH_2Cl_2. Careful addition of pentane initiated crystallisation to afford the *title compound* (**165**, 278 mg, 0.5 mmol, 75%) as a yellow crystalline solid. **Mp**: 171 ºC. **IR** ν_{max}(film): 2968, 1535, 1456, 1367, 1329, 1203, 1062, 805, 757 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.22 (1H, broad s, N(C<u>H</u>)N), 7.86 (2H, broad s, NC<u>H</u>C<u>H</u>N), 7.63 (2H, t, *J* = 8, ArH), 7.39 (4H, d, *J* = 8, ArH), 2.43 (4H, m, C<u>H</u>(CH$_3$)$_2$), 1.33 (12H, d, *J* =

7, $CH(C\underline{H}_3)_2$), 1.26 (12H, d, *J* = 7, $CH(C\underline{H}_3)_2$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.86, 132.60, 129.43, 126.15, 124.99, 29.22, 24.89, 24.05 ppm. **Scan ES+:** 524 [M+]. **Accurate Mass:** $C_{27}H_{37}Cl_2CuN_2$ requires 524.0481; found 524.0421.

2. GENERAL PROCEDURES

General procedure A:

To a stirred mixture of 1.3 equiv. of K_2CO_3 and 1.06 equiv. of phenol in acetone was added 1 equiv. of allylbromide at rt and under dry nitrogen. The mixture was left stirring at rt for 18 h. The mixture was filtered and the solvent was concentrated *in vacuo*. The crude product was dissolved in AcOEt (75 mL) and washed with H_2O (3 × 75 mL). The layers were separated and the organic layer was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to give the crude product. The crude product was purified by flash column chromatography (SiO_2; petrol 100%).

General procedure B:

The arylallylether obtained following procedure A was heated, without solvent, to 210 – 220 ºC for 6 h under dry nitrogen. The residue was diluted with Et_2O (50 mL) and washed with 1.0 M NaOH (50 mL). The layers were separated and the aqueous extracts were acidified to pH 4 (2.0 M HCl) and extracted (CH_2Cl_2 2 × 75 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; gradient elution starting from petrol and progressing to petrol : AcOEt 7 : 3).

General procedure C1:

Trichloroacetylchloride (1.2 equiv.) was added dropwise to a solution of the *ortho*–allylphenol (1.0 equiv.) and Et_3N (1.2 equiv.) in Et_2O at 0 °C under nitrogen. The reaction mixture was left at 0 °C for 3 h and then quenched by the addition of H_2O (20 mL). The quenched reaction mixture was diluted with Et_2O (75 mL) and the organic layer separated, washed (satd. aq. $NaHCO_3$ 2 × 75 mL) dried ($MgSO_4$) and concentrated *in vacuo*.

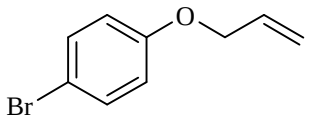
General procedure C2:

Tribromoacetylchloride (1.2 equiv.) was added dropwise to a solution of the *ortho*–allylphenol (1.0 equiv.) and Et_3N (1.2 equiv.) in Et_2O at 0 ºC under nitrogen. The reaction mixture was left at 0 °C for 3 h and then quenched by the addition of H_2O (20 mL). The quenched reaction mixture was diluted with Et_2O (25 mL) and the organic layer separated, washed (satd. aq. $NaHCO_3$ 2 × 25 mL) dried ($MgSO_4$) and concentrated *in vacuo*.

3. SYNTHESIS OF STARTING MATERIALS

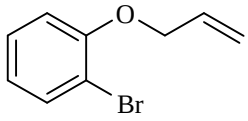
3.1 SYNTHESIS OF THE ALLYLETHERS

1–(Allyloxy)–4–bromobenzene (112a):[134]



Was prepared using general procedure A [4–bromophenol (7.00 g, 40.5 mmol), allyl bromide (3.32 mL, 39.3 mmol) and K_2CO_3 (6.84 g, 49.5 mmol) in acetone (35 mL)] to afford the *title compound* (**112a**, 8.20 g, 38.4 mmol, 98%) as a colourless oil. **Rf** (petrol 100%): 0.34. **IR** ν_{max}(film): 3084, 3020, 2918, 2869, 1590, 1489, 1286, 1242, 1172, 999, 928 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 (2H, dd, *J* = 8, *J* = 2, ArH), 6.82 (2H, dd, *J* = 8, *J* = 2, ArH), 6.06 (1H, ddt, *J* = 17, *J* = 10, *J* = 5, C<u>H</u>CH_2), 5.44 (1H, dd, *J* = 17, *J* = 2, CHC<u>H</u>xHy), 5.32 (1H, dd, *J* = 10, *J* = 2, CHCHx<u>H</u>y), 4.65 (2H, dt, *J* = 5, *J* = 2, ArOCH_2) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.24, 132.85, 130.50, 127.78, 123.18, 121.68, 118.00, 113.94, 69.80 ppm. *m/z* **EI+:** 214/212 [M+], 174/172 [M – CH_2CHCH_2], 132 [M – Br]. **Accurate Mass:** $C_9H_9{}^{79}BrO$ requires 211.9831; found 211.9824.

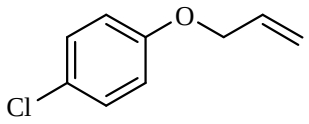
1–(Allyloxy)–2–bromobenzene (112b):[135]



Was prepared using general procedure A [2–bromophenol (7.36 g, 42.6 mmol), allyl bromide (3.5 mL, 41.3 mmol) and K_2CO_3 (7.20 g, 52.1 mmol) in acetone (20 mL)] to afford the *title compound* (**112b**, 8.81 g, 41.3 mmol, 100%) as a colourless oil. **Rf** (petrol 100%): 0.17. **IR** ν_{max}(film): 1649, 1477, 1276, 1050, 1030, 995, 744 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 (1H, dd, *J* = 8, *J* = 2, ArH), 7.29 (1H, td, *J* = 8, *J* = 2, ArH), 6.91 (2H, m, ArH), 6.14 (1H, ddt, *J* = 17, *J* = 10.5, *J* = 5, CH_2C<u>H</u>), 5.54 (1H, ddd, *J* = 17, *J* = 3, *J* = 1, CHC<u>H</u>xHy), 5.37 (1H, ddd, *J* = 10.5, *J* = 3, *J* = 1, CHCHx<u>H</u>y), 4.64 (2H, dt, *J* = 5, *J* = 1, ArOCH_2) ppm.

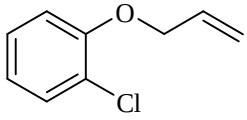
^{13}C NMR (75 MHz, $CDCl_3$) δ 154.95, 133.34, 132.68, 128.48, 122.05, 117.72, 113.81, 112.29, 69.59 ppm. *m/z* **EI+:** 214/212 [M+], 174/172 [M – CH_2CHCH_2], 132 [M – Br]. **Accurate Mass:** $C_9H_9{}^{79}BrO$ requires 211.9831; found 211.9824.

1–(Allyloxy)–4–chlorobenzene (112c):[136]



Was prepared using general procedure A [4–chlorophenol (5.59 g, 43.5 mmol), allyl bromide (3.5 mL, 41.3 mmol) and K_2CO_3 (7.42 g, 53.7 mmol) in acetone (14 mL)] to afford the *title compound* (**112c**, 6.20 g, 36.7 mmol, 94%) as a colourless oil. **Rf** (petrol 100%): 0.24. **IR** ν_{max}(film): 1489, 1239, 1170, 1091, 996, 928, 821 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 (2H, dd, *J* = 7, *J* = 2, ArH), 6.85 (2H, dd, *J* = 7, *J* = 2, ArH), 6.05 (1H, ddt, *J* = 17, *J* = 11, *J* = 5, C<u>H</u>CH_2), 5.44 (1H, ddd, *J* = 17, *J* = 3, *J* = 2, CHC<u>H</u>xHy), 5.31 (1H, ddd, *J* = 11, *J* = 3, *J* = 2, CHCHx<u>H</u>y), 4.52 (2H, dq, *J* = 5, *J* = 2, OCH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.30, 133.23, 129.54, 125.91, 118.14, 116.24, 69.28 ppm. *m/z* **EI:** 168/170 [M+], 133 [M – Cl], 127/129 [M – CH_2CHCH_2]. **Accurate Mass:** $C_9H_9{}^{35}ClO$ requires 168.0336; found 168.0338.

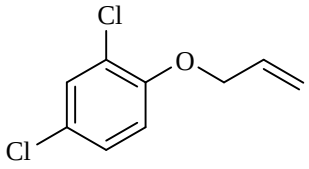
1–(Allyloxy)–2–chlorobenzene (112d):[134]



Was prepared using general procedure A [6–chlorophenol (5.59 g, 43.5 mmol), allyl bromide (3.5 mL, 41.3 mmol) and K_2CO_3 (7.42 g, 53.7 mmol) in acetone (14 mL)] to afford the *title compound* (**112d**, 6.69 g, 39.9 mmol, 96%) as a colourless oil. **Rf** (petrol 100%): 0.48. **IR** ν_{max}(film): 1483, 1277, 1234, 1060, 996, 928 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 (1H, dd, *J* = 8, *J* = 2, ArH), 7.25 (1H, dd, *J* = 8, *J* = 2, ArH), 7.22 (1H, dd, *J* = 8, *J* = 2, ArH), 6.98 – 6.93 (1H, m, ArH), 6.12

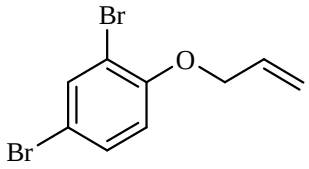
(1H, ddt, *J* = 17, *J* = 10.5, *J* = 5, C<u>H</u>CH_2), 5.52 (1H, ddd, *J* = 17, *J* = 3, *J* = 2, CHC<u>H</u>xHy), 5.36 (1H, ddd, *J* = 10.5, *J* = 3, *J* = 1, CHCHx<u>H</u>y), 4.66 (2H, ddd, *J* = 5, *J* = 2, *J* = 1, ArOCH_2) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.24, 130.60, 132.96, 127.89, 128.88, 121.78, 118.10, 114.05, 69.80 ppm. *m/z* **EI+:** 168/170 [M+], 133 [M – Cl]. **Accurate Mass:** $C_9H_9{}^{35}ClO$ requires 168.0336; found 168.0338.

1–(Allyloxy)–2,4–dichlorobenzene (112e):[137]



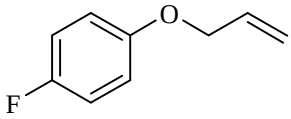
Was prepared using general procedure A [2,4–dichlorophenol (5.00 g, 30.7 mmol), allyl bromide (2.52 mL, 29.8 mmol) and K_2CO_3 (5.19 g, 37.5 mmol) in acetone (15 mL)] to afford the *title compound* (**112e**, 4.98 g, 24.5 mmol, 82%) as a colourless oil. **Rf** (petrol 100%): 0.53. **IR** ν_{max}(film): 1483, 1286, 1265, 1104, 1060, 995, 928, 753 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (1H, d, *J* = 2.5, ArH), 7.17 (1H, dd, *J* = 9, *J* = 2.5, ArH), 6.84 (1H, d, *J* = 9, ArH), 6.05 (1H, ddt, *J* = 17, *J* = 11, *J* = 5, OCH_2C<u>H</u>), 5.47 (1H, ddd, *J* = 17, *J* = 3, *J* = 1.5, CHC<u>H</u>xHy), 5.32 (1H, ddd, *J* = 11, *J* = 3, *J* = 1.5, CHCHx<u>H</u>y), 4.60 (2H, dt, *J* = 5, *J* = 1.5, ArOCH_2) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.92, 132.26, 130.03, 127.48, 125.85, 123.85, 118.17, 114.46, 69.96 ppm. *m/z* **EI+:** 202/204/206 [M+], 161/163/165 [M – CH_2CHCH_2], 133 [M – 2 × Cl]. **Accurate Mass:** $C_9H_8{}^{35}Cl_2O$ requires 201.9947; found 201.9944.

1–(Allyloxy)–2,4–dibromobenzene (112f):[137]



Was prepared using general procedure A [2,4–dibromophenol (5.00 g, 19.9 mmol), allyl bromide (1.58 mL, 18.7 mmol) and K_2CO_3 (3.37 g, 24.4 mmol) in acetone (10 mL)] to afford the *title compound* (**112f**, 3.11 g, 10.6 mmol, 56%) as a colourless oil. **Rf** (petrol 100%): 0.56. **IR** ν_{max}(film): 3086, 2988, 2924, 2867, 1578, 1474, 1426, 1286, 1245, 1046, 995 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.68 (1H, d, *J* = 2.5, ArH), 7.36 (1H, dd, *J* = 8.5, *J* = 2.5, ArH), 6.77 (1H, d, *J* = 8.5, ArH), 6.04 (1H, ddt, *J* = 17, *J* = 11, *J* = 5, $OCH_2C\underline{H}$), 5.48 (1H, ddd, *J* = 17, *J* = 3, *J* = 2, CHC<u>H</u>xHy), 5.33 (1H, ddd, *J* = 11, *J* = 3, *J* = 1.5, CHCHx<u>H</u>y), 4.60 (2H, ddd, *J* = 5, *J* = 2, *J* = 1.5, $ArOCH_2$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.27, 135.56, 135.01, 132.16, 131.12, 118.09, 114.70, 113.19, 113.12, 69.90 ppm. *m/z* **EI+:** 294/292/290 [M+], 254/252 [M – CH_2CHCH_2], 213/211 [M – Br], 132 [M – 2 × Br]. **Accurate Mass:** $C_9H_8{}^{79}Br_2O$ requires 289.8936; found 289.8932.

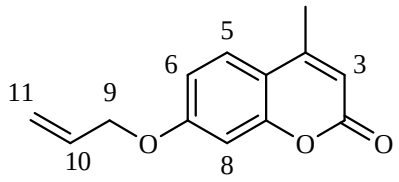
1–(Allyloxy)–4–fluorobenzene (112g):[138]



Was prepared using general procedure A [4–fluorophenol (10.00 g, 89.2 mmol), allyl bromide (7.33 mL, 86.6 mmol) and K_2CO_3 (14.72 g, 106.5 mmol) in acetone (45 mL)] to afford the *title compound* (**112g**, 10.83 g, 71.1 mmol, 82%) as a colourless oil. **Rf** (petrol/AcOEt 5%): 0.22. **IR** ν_{max}(film): 3084, 3004, 2985, 2865, 1650, 1602, 1506, 1255, 1212, 1097, 1024, 997, 929, 828 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.87 – 6.80 (2H, m, ArH), 6.75 – 6.79 (2H, m, ArH), 5.91 (1H, ddt, *J* = 17, *J* = 10, *J* = 5, C<u>H</u>CH_2), 5.28 (1H, ddd, *J* = 17, *J* = 3, *J* = 1, CHC<u>H</u>xHy), 5.16 (1H, ddd, *J* = 10, *J* = 3, *J* = 1, CHCHx<u>H</u>y), 4.36 (2H, dt, *J* = 5, *J* = 1, ArOC<u>H_2</u>) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.21 (d, *J* = 238), 154.64 (d,

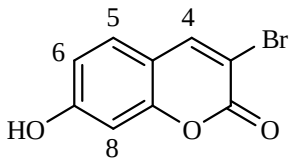
J = 2), 133.13 (d, *J* = 1), 117.55 (d, *J* = 2), 115.82, 115.68, 115.57, 115.52, 69.28 ppm. **^{19}F NMR** (75 MHz, $CDCl_3$) δ – 124.2 ppm. *m/z* **EI+:** 152 [M+], 112 [M – CH_2CHCH_2]. **Accurate Mass:** C_9H_9FO requires 152.0632; found 152.0629.

7–(Allyloxy)–4–methyl–2*H*–chromen–2–one (116):[139]



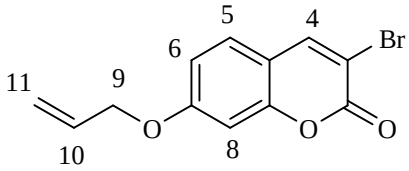
A mixture of 4–methylumbelliferone (2.00 g, 11.4 mmol), allyl bromide (1.2 mL, 13.6 mmol) and K_2CO_3 (3.15 g, 22.8 mmol) in acetone (16 mL) was refluxed for 16 h under nitrogen. The reaction mixture was diluted with AcOEt (50 mL) and water (50 mL). The layers were separated and the organic layer was washed with H_2O (3 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography column (SiO_2; eluent petrol: AcOEt, 1:1) to afford the *title compound* (**116**, 2.41 g, 11.2 mmol, 98%) as a white solid. **Rf** (petrol/AcOEt 50%): 0.49. **Mp:** 86 ºC (lit.[139] Mp: 87 – 89 ºC). **IR** ν_{max}(film): 1736, 1620, 1391, 1284, 1262, 1207, 1142, 1069, 994 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 (1H, d, *J* = 9, ArH), 6.85 (1H, dd, *J* = 9, *J* = 3, ArH), 6.78 (1H, d, *J* = 3 ArH), 6.10 (1H, s, H–3), 6.02 (1H, ddt, *J* = 17, *J* = 11, *J* = 5, H–10), 5.42 (1H, dd, *J* = 17, *J* = 1, HxHy–11), 5.42 (1H, dd, *J* = 11, *J* = 1, HxHy–11), 4.57 (2H, d, *J* = 5, 2 × H–9), 3.4 (3H, s, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.43, 161.14, 155.03, 152.48, 132.08, 125.45, 118.37, 113.54, 112.61, 111.84, 101.59, 69.09, 18.56 ppm. *m/z* **EI+:** 216 [M+], 174 [M – CO_2], 119 [M – CO_2 – OCH_2CHCH_2]. **Accurate Mass:** $C_{13}H_{13}O_3$ ([M + H]$^+$) requires 217.0859; found 217.0859.

3–Bromoumbelliferone (118):[140]



A mixture of umbelliferone (2.00 g, 12.7 mmol) and TMAP (6.96 g, 18.5 mmol) in dry 1,4–dioxane (120 mL) was stirred for 5 days under nitrogen at rt. Et_2O (300 mL) was added to precipitate the excess of TMAP. The mixture was filtered and the solvent evaporated to afford the *title compound* (**118**, 3.00 g, 12.4 mmol, 98%) as an off–white solid. **Rf** (EtOAc/petroleum ether 40%): 0.20. **Mp:** > 230 ºC (lit.[141] Mp: 235 – 236 ºC). **IR** ν_{max}(film): 3247, 1682, 1619, 1552, 1440, 1361, 1260 cm^{-1}. **^{1}H NMR** (300 MHz, DMSO–d_6) δ 10.73 (1H, s, OH), 8.46 (1H, s, H–4), 7.51 (1H, d, *J* = 9, H–5), 6.81 (1H, dd, *J* = 9, *J* = 2, H–6), 6.73 (1H, d, *J* = 2, H–8) ppm. **^{13}C NMR** (100 MHz, DMSO–d_6) δ 161.66, 156.87, 154.74, 145.54, 129.26, 113.69, 111.91, 105.25, 102.07 ppm. *m/z* **EI+:** 240/241 [M+], 105 [M – COCBrCH], 91 [M – CO_2CBrCH], 77 [M – CO_2CBrCH – OH]. **Accurate Mass Measurement** $C_9H_5{}^{79}BrO_3$ requires 239.9417; found 239.9423.

7–(Allyloxy)–3–bromo–2*H*–1–benzopyran–2–one (119):

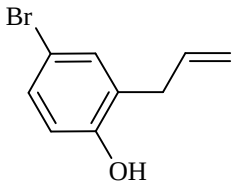


Allylbromide (0.63 mL, 7.4 mmol) was added dropwise to a mixture of 3–bromoumbelliferone (**118**, 1.49 g, 6.2 mmol) and K_2CO_3 (945.2 mg, 7.4 mmol) in acetone (29 mL) at rt. The reaction mixture was then brought to reflux under nitrogen for 16 h. Upon cooling to ambient temperature the inorganic material was removed by filtration and the filtrate concentrated *in vacuo*. The crude product was redissolved in AcOEt (20 mL) and washed (H_2O; 3 × 20 mL). The layers were separated and the organic layer was dried ($MgSO_4$) and reconcentrated *in vacuo*. Purification of the residue by flash chromatography

(SiO_2; eluent petrol : AcOEt; gradient elution starting from 0.5 : 9.5 and progressing to 1.5 : 8.5) to afforded the *title compound* (**119**, 891.1 mg, 3.2 mmol, 51%) as a yellow solid. **Rf** (EtOAc/petroleum ether 40%): 0.32. **Mp:** 93 – 94 ºC. **IR** ν_{max}(film): 3082, 2915, 2862, 1727, 1759, 1503, 1460, 1354, 1217, 1127 cm^{-1}. **^{1}H NMR** (300 MHz, acetone–d_6) δ 8.16 (1H, s, H–4), 7.43 (1H, d, *J* = 9, H–5), 6.82 (1H, dd, *J* = 9, *J* = 2, H–6), 6.77 (1H, d, *J* = 2, H–8), 5.95 (1H, ddt, *J* = 16, *J* = 10.5, *J* = 5, H–10), 5.32 (1H, *J* = 17, *J* = 1.5, HxHy–11), 5.16 (1H, dd, *J* = 10.5, *J* = 1.5, HxHy–11), 4.56 (2H, d, *J* = 5, 2 × H–9) ppm. **^{13}C NMR** (100 MHz, acetone–d_6) δ 206.22, 163.02, 157.43, 156.06, 145.76, 133.77, 129.71, 118.38, 114.29, 108.01, 102.20, 70.07 ppm. *m/z* **EI+:** 280/282 [M+], 238/241 [M – CH_2CHCH_2]. **Accurate Mass Measurement** $C_{12}H_9{}^{79}BrO_3$ requires 279.9730; found 279.9733.

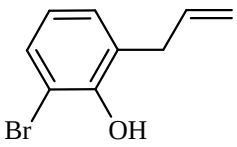
3.2 CLAISEN REARRANGEMENTS

2–Allyl–4–bromophenol (123a):[142]



Was prepared using general procedure B [1–(allyloxy)–4–bromobenzene (**112a**, 3.07 g, 23.1 mmol)] to afford the *title compound* (**123a**, 2.31 g, 10.8 mmol, 75%) as an orange oil. **Rf** (petrol/AcOEt 20%): 0.31. **IR** ν_{max}(film): 3449, 3006, 2979, 2912, 1637, 1583, 1491, 1413, 1264, 1211, 1165, 1111, 920, 810 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.12 (2H, m, 2 × ArH), 6.73 (1H, dd, *J* = 6, *J* = 3, ArH), 5.89 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, C<u>H</u>CH_2), 5.23 (1H, ddd, *J* = 10, *J* = 2.5, *J* = 1, CHC<u>H</u>xHy), 5.21 (1H, ddd, *J* = 17, *J* = 2.5, *J* = 2, CHCHx<u>H</u>y), 4.86 (1H, s, OH), 3.14 (2H, ddd, *J* = 6, *J* = 2, *J* = 1, ArCH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.21, 134.27, 132.96, 130.56, 129.70, 128.61, 126.41, 112.89, 34.76 ppm. *m/z* **EI+:** 212/214 [M+], 133 [M – Br]. **Accurate Mass:** $C_9H_9{}^{79}BrO$ requires 211.9831; found 211.9831.

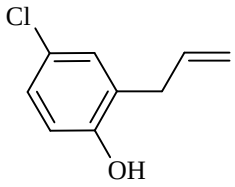
2–Allyl–6–bromophenol (123b):[142]



Was prepared using general procedure B [1–(allyloxy)–2–bromobenzene (**112b**, 4.40 g, 20.6 mmol)] to afford the *title compound* (**123b**, 3.48 g, 16.3 mmol, 79%) as a colourless oil. **Rf** (petrol 100%): 0.22. **IR** ν_{max}(film): 3510, 3077, 2978, 2912, 1639, 1598, 1451, 1327, 1239, 1197, 1121, 916, 766 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (1H, dd, *J* = 8, *J* = 2, ArH), 7.13 (1H, ddd, *J* = 7, *J* = 2, *J* = 1, ArH), 6.81 (1H, dd, *J* = 8, *J* = 7, ArH), 6.05 (1H, ddt, *J* = 17.5, *J* = 10, *J* = 7, C<u>H</u>CH_2), 5.66 (1H, s, OH), 5.19 – 5.12 (2H, m, $CHCH_2$), 3.50 (2H, d, *J* = 7, ArCH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.13, 135.94, 129.89, 129.59,

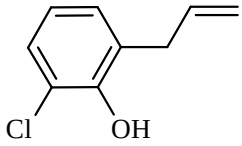
127.71, 121.41, 116.08, 110.43, 34.85 ppm. *m/z* **EI+:** 212/214 [M+], 133 [M – Cl]. **Accurate Mass:** $C_9H_9{}^{79}BrO$ requires 211.9831; found 211.9831.

2–Allyl–4–chlorophenol (123c):[134]



Was prepared using general procedure B [1–(allyloxy)–4–chlorobenzene (**112c**, 4.36 g, 26.0 mmol)] to afford the *title compound* (**123c**, 4.35 g, 25.8 mmol, 100%) as a brown oil. **Rf** (petrol/AcOEt 20%): 0.39. **IR** ν_{max}(film): 2443, 3080, 2979, 2914, 1489, 1419, 1261, 1212, 1167, 1113, 998, 921, 813 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 – 7.08 (2H, m, ArH), 6.78 (1H, dd, *J* = 8, *J* = 1, ArH), 5.98 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, C<u>H</u>CH_2), 5.19 (1H, ddd, *J* = 10, *J* = 3, *J* = 1, CHC<u>H</u>xHy), 5.16 (1H, ddd, *J* = 17, *J* = 3, *J* = 2, CHCHx<u>H</u>y), 4.96 (1H, s, OH), 3.55 (2H, broad d, *J* = 6, $ArCH_2$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.54, 135.49, 130.04, 129.66, 128.53, 127.48, 126.37, 116.90, 34.64 ppm. *m/z* **EI+:** 168/170 [M+], 133 [M – Cl], 125/127 [M – CH_2CHCH_2]. **Accurate Mass:** $C_9H_9{}^{35}ClO$ requires 168.0336; found 168.0336.

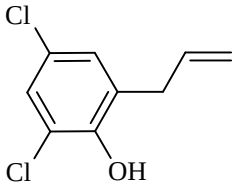
2–Allyl–6–chlorophenol (123d):[134]



Was prepared using general procedure B [1–(allyloxy)–2–chlorobenzene (**112d**, 6.32 g, 38.0 mmol)] to afford the *title compound* (**123d**, 4.67 g, 27.6 mmol, 74%) as a yellow oil. **Rf** (petrol 100%): 0.24. **IR** ν_{max}(film): 3528, 3078, 2979, 2913, 1639, 1602, 1453, 1330, 1240, 1198, 1132, 916, 771, 735 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.06 (1H, dd, *J* = 8, *J* = 1, ArH), 6.91 (1H, dd, *J* = 8, *J* = 1, ArH), 6.67 (1H, dd, *J* = 8, *J* = 1, ArH), 5.57 (1H, ddt, *J* = 18, *J* = 9, *J* = 7, C<u>H</u>CH_2), 5.53

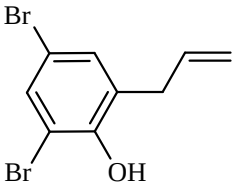
(1H, s, OH), 5.00 – 4.96 (2H, m, CHC$\underline{H}_2$), 3.31 (2H, d, *J* = 7, ArC$\underline{H}_2$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 149.25, 136.00, 128.90, 127.84, 126.87, 120.81, 119.91, 116.05, 34.54 ppm. *m/z* **EI+:** 168/170 [M+], 133 [M – Cl], 125/127 [M – CH_2CHCH_2]. **Accurate Mass:** $C_9H_9{}^{35}ClO$ requires 168.0336; found 168.0336.

2–Allyl–4,6–dichlorophenol (123e):[143]



Was prepared using general procedure B [2–allyl–4,6–dichlorophenol (**112e**, 3.00 g 14.8 mmol)] to afford the *title compound* (**123e**, 2.24 g, 11.0 mmol, 75%) as a yellow oil. **Rf** (petrol/AcOEt 2.5%): 0.14. **IR** ν_{max}(film): 3530, 3082, 2980, 2915, 1640, 1594, 1579, 1465, 1413, 1323, 1235, 1160, 995, 921, 855 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.12 (1H, d, *J* = 2.5, ArH), 6.95 (1H, d, *J* = 2.5, ArH), 5.87 (1H, ddt, *J* = 17, *J* = 10, *J* = 7, C$\underline{H}CH_2$), 5.51 (1H, s, OH), 5.05 (1H, *J* = 17, *J* = 3, *J* = 1.5, CHC$\underline{H}$xHy), 5.03 (1H, ddd, *J* = 10, *J* = 3, *J* = 1.5, CHCHx$\underline{H}$y), 3.31 (2H, broad d, *J* = 7, ArC$\underline{H}_2$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 148.04, 135.07, 129.14, 126.21, 125.09, 123.99, 120.21, 116.91, 34.39 ppm. *m/z* **EI+:** 201/203/205 [M+], 166/168 [M – Cl], 131 [M – Cl]. **Accurate Mass:** $C_9H_8{}^{35}Cl_2O$ requires 201.9947; found 201.9943.

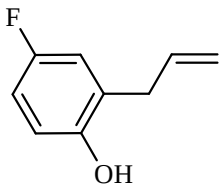
2–Allyl–4,6–dibromophenol (123f):[144]



Was prepared using general procedure B [1–(allyloxy)–4,6–dibromobenzene (**112f**, 2.00 g, 6.90 mmol)] to afford the *title compound* (**123f**, 1.36 g, 4.64 mmol, 68%) as a yellow solid. Mp: 34.5 ºC. **Rf** (petrol/AcOEt 2.5%): 0.18. **IR** ν_{max}(film): 3507, 3078, 2979, 2916, 1459, 1319, 1235, 1194, 1141, 995, 856 cm^{-1}.

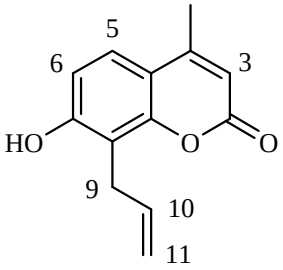
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (1H, d, *J* = 2, ArH), 7.14 (1H, d, *J* = 2, ArH), 5.87 (1H, ddt, *J* = 17.5, *J* = 10.5, *J* = 6.5, C<u>H</u>CH_2), 5.50 (1H, s, OH), 5.07 – 5.03 (2H, m, CHC<u>H</u>$_2$), 3.33 (2H, d, *J* = 6.5, $ArCH_2$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.99, 135.25, 131.93, 131.43, 129.11, 116.55, 112.02, 110.41, 34.26 ppm. ***m/z*** **EI+:** 290/292/294 [M+], 211/213 [M – Br], 131 [M – 2 × Br]. **Accurate Mass:** $C_9H_8{}^{79}Br_2O$ requires 289.8936; found 289.8938.

2–Allyl–4–fluorophenol (123g):[145]



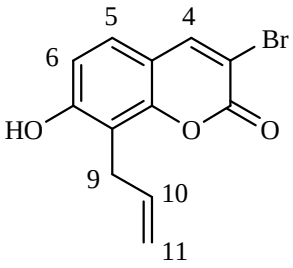
Was prepared using general procedure B for 10 h [1–(allyloxy)–4–fluorobenzene (**112g**, 10.20 g, 64.4 mmol)] to afford the *title compound* (**123g**, 10.15 g, 63.8 mmol, 99%) as a yellow oil. **Rf** (petrol/AcOEt 5%): 0.17. **IR** ν_{max}(film): 3429, 3082, 2982, 2964, 1706, 1639, 1505, 1441, 1336, 1180, 998, 964, 869 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.12 (2H, m, 2 × ArH), 6.73 (1H, dd, *J* = 6, *J* = 3, ArH), 5.89 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, CH_2C<u>H</u>), 5.19 (1H, ddd, *J* = 10, *J* = 3, *J* = 1, CHC<u>H</u>xHy), 5.16 (1H, ddd, *J* = 10, *J* = 3, *J* = 2, CHC<u>H</u>xHy), 4.86 (1H, s, OH), 3.14 (2H, broad d, *J* = 6, $ArCH_2$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.9 (d, *J* = 236), 149.84 (d, *J* = 2), 135.64, 127.53 (d, *J* = 7), 116.16 (d, *J* = 7), 116.01, 116.46 (d, *J* = 8), 113.40 (d, *J* = 23), 34.35 ppm. **^{19}F NMR** (75 MHz, $CDCl_3$) δ – 124.5 ppm. ***m/z*** **EI+:** 152 [M+], 137 [M – OH]. **Accurate Mass:** C_9H_9F requires 152.0632; found 152.0627.

8–Allyl–7–hydroxy–4–methyl–2*H*–chromen–2–one (124):[146]



7–(Allyloxy)–4–methyl–2*H*–chromen–2–one (**116**, 1.00 g, 4.6 mmol) in *N*,*N*–diethylaniline (12 mL) was refluxed for 6 h under nitrogen. Then it was let to cool down to 25 ºC and petrol was added to the solution. The *title compound* crystallised out (**124**, 761 mg, 3.5 mmol, 76%) as a white solid. **Mp:** 194 ºC (lit.[146] Mp: 198 – 199 ºC). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 (1H, d, *J* = 9, ArH), 6.86 (1H, d, *J* = 9, ArH), 6.16 (1H, broad d, *J* = 1, ArH), 6.01 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, H–10), 5.87 (1H, app s, H–3), 5.20 (1H, ddd, *J* = 17, *J* = 3, *J* = 1, HxHy–11), 5.17 (1H, ddd, *J* = 10, *J* = 3, *J* = 1, HxHy–11), 3.69 (2H, dt, *J* = 6, *J* = 1, 2 × H–9), 2.41 (3H, broad d, *J* = 1, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.32, 158.76, 153.82, 152.61, 135.40, 123.98, 115.04, 112.64, 112.07, 111.98, 109.97, 26.53, 18.22 ppm. *m/z* **EI+:** 216 [M+], 201 [M – O], 188 [M – CO], 172 [M – CO_2], 145 [M – $OCOCHCCH_3$], 90 [M – $OCOCHCCH_3$ – CH_2CHCH_2 – OH]. **Accurate Mass:** $C_{13}H_{13}O_3$ ($[M+H]^+$) requires 217.0859; found 217.0854.

8–Allyl–3–bromoumbelliferone (125):

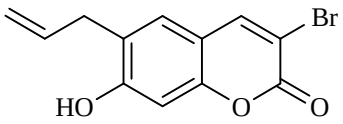


A solution of 7–(allyloxy)–3–bromo– umbelliferone (**119**, 500 mg, 1.8 mmol) in toluene (5 mL) was heated in a microwave reactor at 170 ºC for 16 h under nitrogen. Upon cooling to ambient temperature the solvent was removed *in vacuo* and the crude product was purified by flash chromatography (SiO_2; gradient

elution petrol : AcOEt 9.5 : 0.5 to 8 : 2) to afford an inseparable mixture of the *title compound* (**125**) together with the isomeric coumarin **126** (**125 : 126** = 3.7 : 1) as a yellow oil (183.9 mg, 0.67 mmol, 37% overall yield). **Rf** (EtOAc/petroleum ether 30%): 0.44. **IR** ν_{max}(film): 2973, 2929, 2855, 1727, 1700, 1601, 1442, 1442, 1256, 1241, 1024, 903 cm^{-1}. *m/z* **EI+:** 280/282 [M+], 238/241 [M – CH_2CHCH_2]. **Accurate Mass:** $C_{12}H_9{}^{79}BrO_3$ requires 279.9730; found 279.9733.

8–Allyl–3–bromoumbelliferone (125): ^{1}H NMR (300 MHz, acetone–d_6) δ 9.53 (1H, s, OH), 8.25 (1H, s, H–4), 7.37 (1H, d, *J* = 8, H–5), 6.92 (1H, d, *J* = 8, H–6), 5.95 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, H–10), 5.01 (1H, *J* = 17, *J* = 1, HxHy–11), 4.94 (1H, broad d, *J* = 10, HxHy–11), 3.52 (2H, d, *J* = 6, 2 × H–9) ppm. **^{13}C NMR** (100 MHz, acetone–d_6) δ 206.45, 159.87, 157.65, 153.93, 146.33, 135.94, 127.52, 115.69, 114.50, 113.75, 106.80, 27.47 ppm.

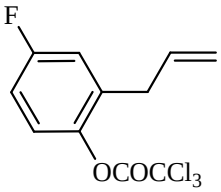
6–Allyl–3–bromoumbelliferone (126):



^{1}H NMR (300 MHz, acetone–d_6) δ 6.77 (1H, d, *J* = 2, H–8), 3.37 (2H, d, *J* = 6, $ArCH_2$) ppm.

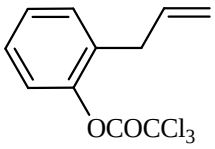
3.3 ACYLATION

2–Allyl–4–fluorophenyl 2',2',2'–trichloroacetate (89a):



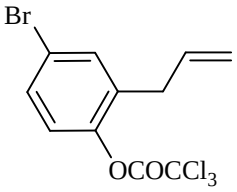
Was prepared using procedure C1 [2–allyl–4–fluorophenol (**123g**, 5.00 g, 32.8 mmol), trichloroacetylchloride (4.6 mL, 39.4 mmol) and triethylamine (5.4 mL, 39.4 mmol) in Et_2O (40 mL)] to afford the *title compound* (**89a**, 6.17 g, 20.7 mmol, 63%) as a yellow oil. **IR** ν_{max}(film): 3084, 2983, 2918, 1782, 1642, 1622, 1593, 1492, 1435, 1213, 1165, 994, 957, 923, 865, 827 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.04 (1H, dd, *J* = 8, *J* = 5, ArH), 6.93 – 6.85 (2H, m, ArH), 5.79 (1H, ddt, *J* = 17, *J* = 10, *J* = 6.5, C<u>H</u>CH_2), 5.06 – 4.97 (2H, m, CHC<u>H_2</u>), 3.26 (2H, d, *J* = 6.5, ArCH_2) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.69 (d, *J* = 245), 160.05, 160.04, 143.94 (d, *J* = 3), 133.91, 133.73 (d, *J* = 8), 122.09 (d, *J* = 9), 117.22, 117.23 (d, *J* = 24), 114.38 (d, *J* = 24), 33.53 (d, *J* = 1) ppm. **^{19}F NMR** (75 MHz, $CDCl_3$) δ –114.87 ppm.

2–Allylphenyl 2',2',2'–trichloroacetate (89):



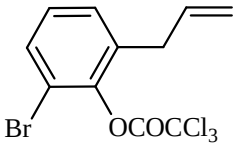
Was prepared using procedure C1 [2–allylphenol (**121**, 18.58 g, 138.6 mmol), trichloroacetylchloride (19.4 mL, 166.3 mmol) and triethylamine (22.6 mL, 166.3 mmol) in Et_2O (300 mL)] to afford the *title compound* (**89**, 36.07 g, 128.9 mmol, 93%) as a yellow oil. **IR** ν_{max}(film): 3082, 2982, 2916, 1777, 1641, 1582, 1489, 1453, 1222, 1165, 994, 962, 919, 824 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 – 7.27 (3H, m, ArH), 7.23 – 7.21 (1H, m, ArH), 6.00 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, C<u>H</u>CH_2), 5.19 – 5.11 (2H, m, CHC<u>H_2</u>), 3.47 (2H, dd, *J* = 6, *J* = 1, ArC<u>H_2</u>) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.68, 148.94, 135.51, 132.04, 131.16, 128.07, 127.67, 121.34, 117.11, 89.52, 34.01 ppm.

2–Allyl–4–bromophenyl 2',2',2'–trichloroacetate (127a):



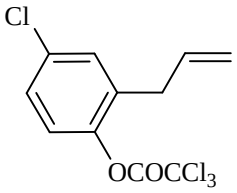
Was prepared using procedure C1 [2–allyl–4–bromophenol (**123a**, 2.95 g, 13.6 mmol), trichloroacetylchloride (1.9 mL, 16.3 mmol) and triethylamine (2.2 mL, 16.3 mmol) in Et_2O (20 mL)] to afford the *title compound* (**127a**, 3.78 g, 11.4 mmol, 84%) as a colourless oil. **IR** ν_{max}(film): 3087, 2984, 2916, 1780, 1644, 1572, 1484, 1218, 1162, 1095, 993, 960, 922, 822 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.34 (1H, m, ArH), 7.28 – 7.15 (1H, m, ArH), 6.99 (1H, d, *J* = 9, ArH), 5.81 (1H, ddt, *J* = 17, *J* = 10, *J* = 7, $CHCH_2$), 5.06 (1H, ddd, *J* = 10, *J* = 3, *J* = 1, CHC<u>H</u>xHy), 5.02 (1H, ddd, *J* = 17, *J* = 3, *J* = 1.5, CHCHx<u>H</u>y), 3.27 (2H, broad d, *J* = 7, $ArCH_2$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): 160.15, 147.64, 134.27, 129.69, 128.61, 126.40, 122.69, 120.57, 117.63, 89.33, 33.75 ppm.

2–Allyl–6–bromophenyl 2',2',2'–trichloroacetate (127b):



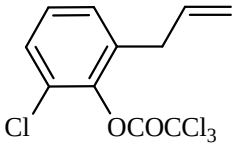
Was prepared using procedure C1 [2–allyl–6–bromophenol (**123b**, 3.00 g, 14.1 mmol), trichloroacetylchloride (2.0 mL, 16.9 mmol) and triethylamine (2.3 mL, 16.9 mmol) in Et_2O (25 mL)] to afford the *title compound* (**127b**, 3.74 g, 10.4 mmol, 74%) as a colourless oil. **IR** ν_{max}(film): 3082, 2982, 2887, 1783, 1641, 1576, 1443, 1214, 1126, 994, 955, 922, 873 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.17 (1H, d, *J* = 3, ArH), 7.14 (1H, dd, *J* = 9, *J* = 7, ArH), 6.99 (1H, d, *J* = 9, ArH), 5.76 (1H, ddt, *J* = 17, *J* = 10, *J* = 4, C<u>H</u>CH_2), 5.02 (1H, app d, *J* = 17, CHC<u>H</u>xHy), 4.98 (1H, dd, *J* = 10, *J* = 1, CHCHx<u>H</u>y), 3.23 (2H, broad d, *J* = 7, Ar<u>C</u>H_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.96, 147.46, 134.15, 133.96, 133.53, 130.65, 122.66, 120.46, 117.58, 89.27, 33.66 ppm.

2–Allyl–4–chlorophenyl 2',2',2'–trichloroacetate (127c):



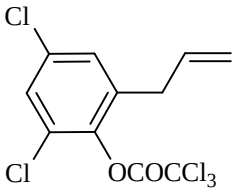
Was prepared using procedure C1 [2–allyl–4–chlorophenol (**123c**, 5.18 g, 30.7 mmol), trichloroacetylchloride (4.3 mL, 36.8 mmol) and triethylamine (5.0 mL, 36.8 mmol) in Et_2O (30 mL)] to afford the *title compound* (**127c**, 6.78 g, 21.6 mmol, 70%) as a colourless oil. **IR** ν_{max}(film): 3083, 2982, 2918, 1781, 1641, 1579, 1223, 1163, 1109, 994, 961, 923, 857, 827 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 – 7.14 (2H, m, ArH), 7.04 (1H, d, *J* = 8, ArH), 5.81 (1H, ddt, *J* = 17, *J* = 10, *J* = 7, C<u>H</u>CH_2), 5.07 (1H, ddd, *J* = 10, *J* = 3, *J* = 1, CHC<u>H</u>xHy), 5.02 (1H, ddd, *J* = 17, *J* = 3, *J* = 1.5, CHCHx<u>H</u>y), 3.28 (2H, broad d, *J* = 7, Ar<u>C</u>H_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.23, 147.06, 134.27, 133.76, 132.77, 129.69, 128.61, 127.77, 126.41, 89.40, 33.80 ppm.

2–Allyl–6–chlorophenyl 2',2',2'–trichloroacetate (127d):



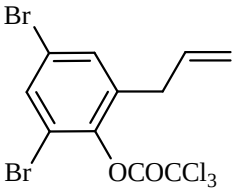
Was prepared using procedure C1 [2–allyl–6–chlorophenol (**123d**, 2.00 g, 11.9 mmol), trichloroacetylchloride (1.7 mL, 14.3 mmol) and triethylamine (1.9 mL, 14.3 mmol) in Et_2O (20 mL)] to afford the *title compound* (**127d**, 3.30 g, 10.5 mmol, 88%) as a colourless oil. **IR** ν_{max}(film): 3083, 2983, 2918, 1781, 1641, 1579, 1482, 1435, 1404, 1223, 1163, 1109, 994, 961, 923, 827 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (1H, dd, *J* = 7, *J* = 3, ArH), 7.08 – 7.06 (2H, m ArH), 5.75 (1H, ddt, *J* = 17, *J* = 10.5, *J* = 7, C<u>H</u>CH_2), 4.99 (1H, dd, *J* = 10.5, *J* = 1.5, CHC<u>H</u>xHy), 4.97 (1H, dd, *J* = 17, *J* = 1.5, CHCHx<u>H</u>y), 3.25 (2H, broad d, *J* = 7, $ArCH_2$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.01, 144.65, 134.41, 130.25, 129.02, 128.60, 127.91, 127.02, 117.29, 89.22, 34.24 ppm.

2–Allyl–4,6–dichlorophenyl 2',2',2'–trichloroacetate (127e):



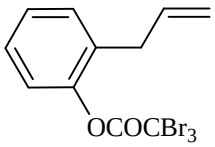
Was prepared using procedure C1 [2–allyl–4,6–dichlorophenol (**123e**, 2.10 g, 10.3 mmol), trichloroacetylchloride (1.5 mL, 12.4 mmol) and triethylamine (1.7 mL, 12.4 mmol) in Et_2O (15 mL)] to afford the *title compound* (**127e**, 2.94 g, 8.4 mmol, 82%) as a yellow oil. **IR** ν_{max}(film): 3084, 2984, 2920, 1789, 1641, 1591, 1571, 1453, 1247, 1199, 1156, 993, 954, 822 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (1H, d, *J* = 2.5, ArH), 7.21 (1H, d, *J* = 2.5, ArH), 5.86 (1H, ddt, *J* = 17, *J* = 10, *J* = 7, C<u>H</u>CH_2), 5.18 (1H, ddd, *J* = 10, *J* = 3, *J* = 1, CHC<u>H</u>xHy), 5.13 (1H, ddd, *J* = 17, *J* = 3, *J* = 1.5, CHCHx<u>H</u>y), 3.36 (2H, ddd, *J* = 7, *J* = 1.5, *J* = 1, Ar<u>CH_2</u>) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.01, 143.35, 135.73, 133.62, 133.12, 129.09, 128.45, 127.96, 118.27, 88.98, 34.18 ppm.

2–Allyl–4,6–dibromophenyl 2',2',2'–trichloroacetate (127f):



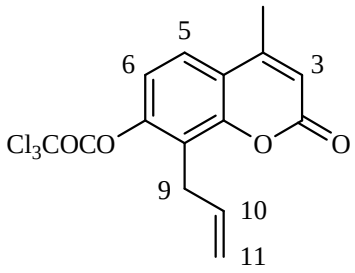
Was prepared using procedure C1 [2–allyl–4,6–dibromophenol (**123f**, 600 mg, 2.1 mmol), trichloroacetylchloride (288 μl, 2.5 mmol) and triethylamine (335 μL, 2.5 mmol) in Et_2O (5 mL)] to afford the *title compound* (**127f**, 483 mg, 1.1 mmol, 54%) as a yellow oil. **IR** ν_{max}(film): 3080, 2982, 2920, 1787, 1640, 1585, 1559, 1446, 1393, 1198, 1143, 993, 953, 926, 858 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 (1H, d, *J* = 2, ArH), 7.40 (1H, d, *J* = 2, ArH), 5.85 (1H, ddt, *J* = 17, *J* = 10, *J* = 7, ArH), 5.19 (1H, ddd, *J* = 10, *J* = 3, *J* = 1, CHC<u>H</u>xHy), 5.13 (1H, ddd, *J* = 17, *J* = 3, *J* = 1, CHCHx<u>H</u>y), 3.35 (2H, broad d, *J* = 7, Ar<u>CH_2</u>CH) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.80, 145.04, 136.07, 134.07, 132.67, 121.60, 120.96, 118.31, 117.00, 89.37, 34.27 ppm.

2–Allylphenyl 2',2',2'–tribromoacetate (128):



Was prepared using procedure C2 [2–allylphenol (**121**, 0.20 mL, 1.6 mmol), tribromoacetylchloride (0.30 mL, 1.6 mmol) and triethylamine (0.20 mL, 1.6 mmol) in Et_2O (21 mL)] to afford the *title compound* (**128**, 532 mg, 1.3 mmol, 83%) as a yellow oil. **IR** ν_{max}(film): 3079, 2980, 2915, 1773, 1639, 1581, 1488, 1453, 1165, 1197, 994, 951, 920, 772 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 – 7.18 (3H, m, ArH), 7.10 – 7.08 (1H, m, ArH), 5.88 (1H, ddt, *J* = 17, *J* = 10, *J* = 7, C<u>H</u>CH_2), 5.03 (1H, dq, *J* = 10, *J* = 3, *J* = 2, CHC<u>H</u>xHy), 5.02 (1H, ddd, *J* = 17, *J* = 3, *J* = 2, CHCHx<u>H</u>y), 3.36 (2H, broad d, *J* = 7, ArCH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.40, 148.94, 134.55, 131.93, 130.79, 127.68, 127.23, 120.93, 116.74, 34.01, 27.93 ppm.

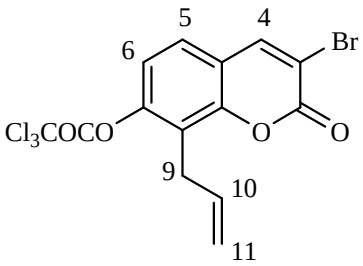
8–Allyl–2–oxo–2*H*–chromen–7–yl 2',2',2'–trichloroacetate (137):



Trichloroacetylchloride (0.30 mL, 2.8 mmol) was added dropwise to a solution of *o*–allylphenol **124** (500 mg, 2.3 mmol) and pyridine (0.2 mL, 2.8 mmol) in CH_2Cl_2 (27 mL). The resulting mixture was then stirred at rt for 20 h under nitrogen and then quenched by the addition of H_2O (20 mL). The quenched reaction mixture was diluted with Et_2O (75 mL) and the organic layer separated, washed (satd. aq. $NaHCO_3$ 2 × 75 mL) dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* (**137**, 640 mg, 1.8 mmol, 77%) as an off–white solid. **Mp:** 65 ºC. **IR** ν_{max}(film): 1689, 1601, 1449, 1427, 1386, 1210, 1047, 831 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59 (1H, d, *J* = 9, ArH), 7.18 (1H, d, *J* = 9, ArH), 6.33 (1H, app broad d, *J* = 1, H–3), 5.93 (1H, ddt, *J* = 17, *J* = 9, *J* = 6, H–10),

5.09 (1H, ddd, *J* = 17, *J* = 3, *J* = 1, HxHy–11), 5.04 (1H, ddd, *J* = 9, *J* = 3, *J* = 1, HxHy–11), 3.69 (2H, dt, *J* = 6, *J* = 1, H–9), 2.47 (3H, d, *J* = 1, CH_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.05, 159.96, 152.36, 151.93, 150.65, 133.55, 123.35, 121.12, 118.92, 117.07, 116.70, 115.07, 89.21, 27.63, 18.86 ppm.

8–Allyl–3–bromo–2–oxo–2*H*–chromen–7–yl 2',2',2'–trichloroacetate (138):



Trichloroacetylchloride (0.09 mL, 0.79 mmol) was added dropwise to a solution of the allylphenols **125** and **126** (184 mg, 0.65 mmol) and Et_3N (0.1 mL, 0.79 mmol) in Et_2O (3 mL) at 0 °C under nitrogen. The reaction mixture was left stirring at rt for 16 h. The reaction was quenched by the addition of Et_2O (10 mL) and H_2O (10 mL). The organic layer was separated, washed (satd. aq. $NaHCO_3$ 2 × 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* (**138**, 188.0 mg, 0.52 mmol, 80%) as an orange thick oil. **IR** ν_{max}(film): 1686, 1597, 1560, 1496, 1301, 1240, 1030 cm^{-1}. **^{1}H NMR** (300 MHz, acetone–d_6) δ 8.36 (1H, s, H–4), 7.62 (1H, d, *J* = 8, ArH), 7.27 (1H, d, *J* = 8, ArH), 5.82 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, H–10), 4.95 – 4.89 (2H, m, 2 × H–11), 3.49 (2H, broad d, *J* = 6, H–9) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.18, 177.46, 164.53, 158.30, 152.56, 145.07, 134.44, 126.29, 116.86, 113.75, 113.39, 107.32, 42.69, 26.98 ppm.

4 BENZANNULATION REACTION

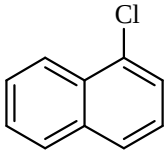
4.1 EXPERIMENTS IN DCE

General procedure D:

A solution of the trihaloester (1.0 equiv.), CuCl (5 mol%), ligand **18** (5 mol%) in DCE (6 mL) was heated in a microwave reactor at 200 ºC under nitrogen for 2 h. Upon cooling to ambient temperature the solvent was removed *in vacuo* and the crude product purified by flash column chromatography (SiO_2; eluent petrol).

Benzannulation reaction of 2–allylphenyl 2',2',2'–trichloroacetate (89): was accomplished using procedure D [Trichloroacetate **89** (1.00 g, 3.6 mmol), CuCl (17 mg, 0.18 mmol) and ligand **18** (52 mg, 0.18 mmol) in DCE (2 mL)] to afford naphthalene **92** (413 mg, 2.6 mmol, 71%) as a yellow oil.

1–Chloronaphthalene (92):[147]

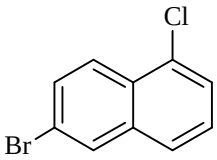


Rf (petrol): 0.49. **IR** ν_{max}(film): 1504, 1379, 1255, 1201, 968, 789, 770, 664 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.35 (1H, d, *J* = 8.5, ArH), 7.90 (1H, d, *J* = 8, ArH), 7.80 (1H, d, *J* = 8, ArH), 7.67 – 7.57 (3H, m, ArH), 7.42 (1H, dd, *J* = 8, *J* = 8, ArH) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.47, 131.84, 130.72, 128.14, 127.09, 126.96, 126.60, 126.08, 125.64, 124.32 ppm. *m/z* **EI+**: 162/164 [M+]. **Accurate Mass:** $C_{10}H_7{}^{35}Cl$ requires 162.0231, found 162.0229.

Benzannulation reaction of 2–allyl–4–bromophenyl 2',2',2'–trichloroacetate (127a): was accomplished using procedure D [Trichloroacetate **127a** (400 mg, 1.1 mmol), CuCl (5.5 mg, 0.06 mmol) and ligand **18** (16.0 mg, 0.06 mmol) in DCE (6 mL)] to afford a white solid (104 mg, 0.46 mmol, 42%) which was a inseparable mixture of 6–bromo–1–chloronaphthalene (**139a**) and 1,6–dichloronaphthalene

(**139c**, ^{1}H NMR and ^{13}C NMR spectra as above) in a 132 : 1 ratio.[148] **Rf** of the mixture (petrol): 0.80.

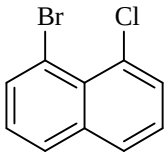
6–Bromo–1–chloronaphthalene (139a):



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (1H, d, *J* = 9, ArH), 8.03 (1H, d, *J* = 2, ArH), 7.67 (1H, d, *J* = 8, ArH), 7.67 (1H, dd, *J* = 9, *J* = 2, ArH), 7.58 (1H, dd, *J* = 7.5, *J* = 1, ArH), 7.11 (1H, dd, *J* = 8, *J* = 7.5, ArH) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.50, 132.08, 130.38, 130.33, 129.33, 126.92, 126.54, 126.29, 126.21, 120.97 ppm. *m/z* **EI/CI**: 240/242/244 [M+], 161/163 [M – Br], 126 [M – Br – Cl]. **Accurate mass:** $C_{10}H_6{}^{79}Br^{35}ClO$ requires 239.9336; found 239.9332.

Benzannulation reaction of 2–allyl–6–bromophenyl 2',2',2'–trichloroacetate (127b): was accomplished using procedure D [Trichloroacetate **127b** (400 mg, 1.1 mmol), CuCl (5.5 mg, 0.06 mmol) and ligand **18** (16.0 mg, 0.06 mmol) in DCE (6 mL)] to afford a white solid (154 mg, 0.72 mmol, 65%) which was a inseparable mixture of 8–bromo–1–chloronaphthalene (**139b**) and 1,8–dichloronaphthalene (**139d**, ^{1}H NMR and ^{13}C NMR spectra as above) in a 1 : 1.6 ratio.[149] **Rf** of the mixture (petrol): 0.80.

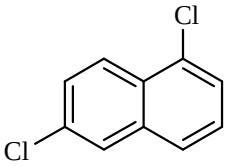
1–Bromo–8–chloronaphthalene (139b):[149]



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (1H, dd, *J* = 8, *J* = 1, ArH), 7.70 (1H, d, *J* = 8, ArH), 7.67 (1H, app t, *J* = 8, ArH), 7.56 (1H, dd, *J* = 8, *J* = 1, ArH), 7.77 (1H, app t, *J* = 8, ArH), 7.19 (1H, d, *J* = 8, ArH) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.18, 130.99, 129.22, 128.75, 128.11, 126.44, 125.95, 118.08 137.00, 135.18 ppm. *m/z* **EI+:** 242/244/246 [M+], 196/198 [M – Cl], 163/165 [M – Br], 128 [M – Br – Cl]. **Accurate mass:** $C_{10}H_6{}^{79}Br^{35}ClO$ requires 239.9336; found 239.9344.

Benzannulation reaction of 2–allyl–4–chlorophenyl 2',2',2'–trichloroacetate (127c): was accomplished using procedure D [Trichloroacetate **127c** (250 mg, 0.8 mmol), CuCl (3.9 mg, 0.06 mmol) and ligand **18** (11.4 mg, 0.06 mmol) in DCE (6 mL)] to afford naphthalene **139d** (112 mg, 0.58 mmol, 72%) as white solid.

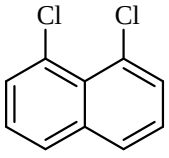
1,6–Dichloronaphthalene (139c):[148]



Mp: 46.7 – 47.7 ºC (lit.[150] Mp: 49 ºC). **Rf** (petrol): 0.80. **IR** ν_{max}(film): 1597, 1553, 1496, 1195, 1153, 1079, 970, 887, 810 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08 (1H, d, *J* = 8.5, ArH), 7.71 (1H, d, *J* = 2, ArH), 7.54 (1H, d, *J* = 8.5, ArH), 7.44 (1H, dd, *J* = 7.5, *J* = 2.5, ArH), 7.40 (1H, dd, *J* = 7.5, *J* = 2.5, ArH), 7.28 (1H, t, *J* = 7.5, ArH) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.10, 132.73, 132.4, 129.14, 127.92, 126.98, 126.84, 126.43, 126.30, 126.28 ppm. *m/z* **EI+**: 196/198 [M+], 161/163 [M – Cl], 126 [M – 2 × Cl]. **Accurate Mass:** $C_{10}H_6{}^{35}Cl_2O$ requires 195.9841; found 195.9844.

Benzannulation reaction of 2–allyl–6–chlorophenyl 2',2',2'–trichloroacetate (127d): was accomplished using procedure D [Trichloroacetate (**127d**, 400 mg, 1.3 mmol), CuCl (6.3 mg, 0.06 mmol) and ligand **18** (18.2 mg, 0.06 mmol) in DCE (6 mL)] to afford naphthalene **139d** (147 mg, 0.77 mmol, 59%) as a white solid.

1,8–Dichloronaphthalene (139d):[147]

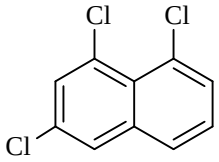


Mp: 88 ºC (lit.[151] Mp: 89 ºC). **Rf** (petrol): 0.46. **IR** ν_{max}(film): 1597, 1553, 1502, 1360, 1325, 1195, 1153, 971, 887 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (2H, dd, *J* = 8, *J* = 1, ArH), 7.57 (2H, dd, *J* = 7.5, *J* = 1, ArH), 7.37 (2H, dd, *J* = 8, *J* =

7.5, ArH) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$): 137.20, 130.85, 130.44, 128.54, 127.53, 126.15 ppm. *m/z* **EI+:** 195/197/199 [M+], 161/163 [M – Cl], 125 [M – 2 × Cl]. **Accurate Mass:** $C_{10}H_6{}^{35}Cl_2O$ requires 195.9841; found 195.9844.

Benzannulation reaction of 2–allyl–4,6–dichlorophenyl 2',2',2'–trichloroa–cetate (127e): was accomplished using procedure D [Trichloroacetate **127e** (400 mg, 1.3 mmol), CuCl (6.3 mg, 0.06 mmol) and ligand **18** (18.3 mg, 0.06 mmol) in DCE (6 mL)] to afford naphthalene **139e** (153 mg, 0.79 mmol, 61%) as a white solid.

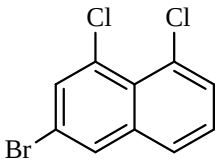
1,6,8–Trichloronaphthalene (139e):[152]



Mp: 89 ºC (lit.[151] Mp: 89 ºC). **Rf** (petrol 100%): 0.71. **IR** ν_{max}(film): 1587, 1553, 1501, 1360, 1325, 1195, 1153, 970 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 (1H, d, *J* = 2), 7.67 (1H, dd, *J* = 8, *J* = 1, ArH), 7.60 (2H, dd, *J* = 8, *J* = 2, ArH), 7.35 (1H, t, *J* = 8, ArH) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.28, 131.71, 131.25, 131.01, 130.97, 130.82, 127.70, 127.26, 127.05, 126.02 ppm. *m/z* **EI+:** 230/232/234/236 [M+], 196/198/200 [M – Cl], 160/162 [M – 2 × Cl], 125 [M – 3 × Cl]. **Accurate Mass:** $C_{10}H_5{}^{35}Cl_3$ requires 229.9451; found 229.9456.

Benzannulation reaction of 2–allyl–4,6–bromophenyl 2',2',2'–trichloro acetate (127f): was accomplished using procedure D [Trichloroacetate **127f** (300 mg, 0.7 mmol), CuCl (3.4 mg, 0.03 mmol) and ligand **18** (9.7 mg, 0.03 mmol) in DCE (6 mL)] to afford a white solid (99.7 mg, 0.37 mmol, 53%) which was a inseparable mixture of 6–bromo–1,8–dicholoronaphthalene (**177**) and 1,6,8–trichloronaphthalene (**139e**, ^{1}H NMR and ^{13}C NMR spectra as above) in a 17 : 1 ratio.[149] **Rf** of the mixture (petrol): 0.81.

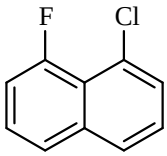
6–Bromo–1,8–dicholoronaphthalene (177):



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* = 2, ArH), 7.75 (1H, dd, *J* = 7, *J* = 2.5, ArH), 7.64 (1H, d, *J* = 2, ArH), 7.56 (1H, brd. dd, *J* = 7, *J* = 2.5, ArH), 7.30 (1H, distorted triplet, *J* = 8, ArH) ppm.

Benzannulation reaction of 2–allyl–6–fluorophenyl 2',2',2'–trichloroacetate (127h): was accomplished using procedure D [Trichloroacetate **127h** (400 mg, 1.3 mmol), CuCl (6.7 mg, 0.07 mmol) and ligand **18** (19.2 mg, 0.07 mmol) in DCE (6 mL)] to afford naphthalene **139h** (164 mg, 0.88 mmol, 68%) as a yellow solid.

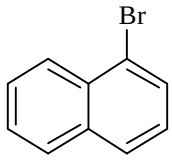
1–Chloro–8–fluoronaphthalene (139h):[153]



Mp: 43 ºC (lit.[152] Mp: 44 ºC). **Rf** (petrol): 0.64. **IR** ν_{max}(film): 1631, 1598, 1572, 1458, 1365, 1356, 1247, 1198, 1024, 940 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 (1H, ddd, *J* = 8, *J* = 1.5, *J* = 1, ArH), 7.48 (1H, brd. d, *J* = 8, ArH), 7.41 (1H, dd, *J* = 8, *J* = 1, ArH), 7.28 (1H, td, *J* = 8, *J* = 5, ArH), 7.23 (1H, app t, *J* = 8, ArH), 7.07 (1H, ddd, *J* = 13, *J* = 8, *J* = 1, ArH) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.43 (d, *J* = 257), 136.91 (d, *J* = 3), 128.81, 128.08 (d, *J* = 2), 126.96 (d, *J* = 4), 126.45, 126.39, 126.38, 124.58, 121.19 (d, *J* = 9), 112.34 (d, *J* = 23) ppm. **^{19}F NMR** (75 MHz, $CDCl_3$) δ –112.5 ppm. *m/z* **EI+:** 180/182 [M+], 161/163 [M – F], 144 [M – Cl], 125 [M – F – Cl]. **Accurate Mass:** $C_{10}H_6{}^{35}ClFO$ requires 180.0140; found 180.0138. **Microanalysis $C_{10}H_6ClF$** requires: C: 66.50, H: 3.35, Cl: 19.63%. Found: C: 66.50, H: 3.50, Cl: 19.22%.

Benzannulation reaction of 2–allylphenyl 2',2',2'–tribromoacetate (128): was accomplished using procedure D [Tribromoacetate **128** (250 mg, 0.6 mmol), CuCl (3.0 mg, 0.03 mmol) and ligand **18** (8.6 mg, 0.03 mmol) in DCE (3 mL)] to afford a yellow solid (93 mg) as an inseparable mixture of 1–bromonaphthalene (**178**, 61 mg, 49%) and 1–chloronaphthalene (**92**, 32 mg, 33%, NMR spectra as above) in a 1.5 : 1 ratio.[154]

1–Bromonaphthalene (178):[155]



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (1H, d, *J* = 8, ArH), 7.85 (3H, m, ArH), 7.60 (2H, m, ArH), 7.38 (1H, t, *J* = 7, ArH) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 134.62, 132.00, 129.75, 128.18, 127.79, 127.01, 126.99, 126.41, 125.87, 122.96 ppm. *m/z* **EI+**: 208/207 [M+]. **Accurate Mass:** $C_{10}H_7{}^{79}Br$ requires 207.0666, found 207.0687.

4.2 BENZANNULATION REACTIONS USING NHC–Cu CATALYST 156

1–Chloronaphthalene (92): A mixture of (IPr)CuCl (**156**, 52 mg, 0.11 mmol) and 2–allylphenyl 2',2',2'–trichloroacetate (**89**, 600 mg, 2.2 mmol) in DCE (6 mL) was heated in a microwave at 200 ºC under dry nitrogen for 2 h. Upon cooling to ambient temperature the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (SiO_2; eluent petrol) afforded the *title compound* (**92**, 166 mg, 1.0 mmol, 47%) as a colourless oil (NMR spectra as above).

1,6–Dichloronaphthalene (139c): A mixture of (IPr)CuCl (**156**, 39 mg, 0.08 mmol) and 2–allyl–4–chlorophenyl 2',2',2'–trichloroacetate (**127c**, 500 mg, 1.6

mmol) in DCE (6 mL) was heated in a microwave at 200 ºC under dry nitrogen for 2 h. Upon cooling to ambient temperature the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (SiO_2; eluent petrol) afforded the *title compound* (**139c**, 194 mg, 0.99 mmol, 62%) as a white solid (NMR spectra as above).

1,6–Dichloronaphthalene (139e): A mixture of (IPr)CuCl (**156**, 78 mg, 0.16 mmol) and 2–allyl–4–chlorophenyl 2',2',2'–trichloroacetate (**127e**, 1.00 g, 3.2 mmol) in DCE (6 mL) was heated in a microwave at 200 ºC under dry nitrogen for 1 h. Upon cooling to ambient temperature the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (SiO_2; eluent petrol) afforded the *title compound* (**139e**, 214 mg, 1.1 mmol, 34%) as a white solid (NMR spectra as above).

1–Chloronaphthalene (92): A mixture of CuCl (11 mg, 0.11 mmol), IPr.HCl (**155**, 46 mg, 0.11 mmol) and 2–allylphenyl 2',2',2'–trichloroacetate (**89**, 600 mg, 2.2 mmol) in DCE (6 mL) was heated in a microwave at 200 ºC under dry nitrogen for 2 h. Upon cooling to ambient temperature the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (SiO_2; eluent petrol) afforded the *title compound* (**92**, 201 mg, 1.0 mmol, 47%) as a white solid (NMR spectra as above).

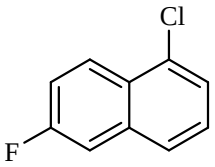
General procedure E:

A solution of the trihaloester (1.0 equiv.), (IPr)CuCl (**156**, 5 mol%) in DCE (6 mL) was heated in a microwave reactor at 200 ºC under nitrogen for 2 h. Upon cooling to ambient temperature the solvent was removed *in vacuo* and the crude product purified by flash column chromatography (SiO_2; eluent petrol).

Benzannulation reaction of 2–allylphenyl 2',2',2'–trichloroacetate (89): The preparation of naphthalene **92** was accomplished using procedure E [Acetate **89** (500.0 mg, 1.8 mmol) and (IPr)CuCl (**156**, 43.9 mg, 0.09 mmol) in DCE (6 mL)] to afford naphthalene **92** (138 mg, 0.84 mmol, 47%) as a yellow oil.

Benzannulation reaction of 2–allyl–4–fluorophenyl 2',2',2'–trichloroacetate (89a): The preparation of naphthalene **92a** was accomplished using procedure E [Acetate **89a** (500 mg, 1.7 mmol) and (IPr)CuCl (**156**, 41 mg, 0.09 mmol) in DCE (6 mL)] to afford naphthalene **92a** (179 mg, 0.99 mmol, 58%) as a yellow oil.

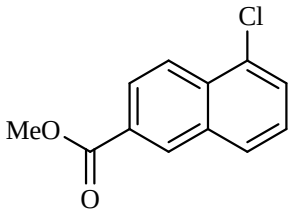
1–Chloro–6–fluoronaphthalene (92a):



Rf (petrol): 0.60. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.28 (1H, dd, *J* = 9, *J* = 5, ArH), 7.70 (1H, d, *J* = 8.5, ArH), 7.54 (1H, d, *J* = 7, ArH), 7.47 (1H, dd, *J* = 9.5, *J* = 2.5, ArH), 7.38 (1H, distorted triplet, *J* = 8, ArH), 7.37 (1H, td, *J* = 9, *J* = 2.5, ArH) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.02 (d, *J* = 247), 135.39 (d, *J* = 9), 128.14, 127.29, 127.17, 126.92 (d, *J* = 1), 126.48 (d, *J* = 5), 125.42 (d, *J* = 2), 117.30 (d, *J* = 25), 111.27 (d, *J* = 21) ppm. **^{19}F NMR** (75 MHz, $CDCl_3$) δ – 114.32 ppm. ***m/z* EI+:** 180/182 [M+], 125 [M – Cl – F]. **Accurate Mass:** $C_{10}H_6{}^{35}Cl^{19}FO$ requires 180.0140; found 180.0139. **Microanalysis $C_{10}H_6ClFO$ requires:** C: 66.50; H: 3.35; Cl: 19.63%. Found: C: 66.46; H: 3.42; Cl: 19.38%.

Benzannulation reaction of methyl 4–(2',2',2'–trichlororoacetoyloxy)–3–allylbenzoate (89b): The preparation of naphthalene **92b** was accomplished using procedure E [Acetate **89b** (500 mg, 1.5 mmol) and (IPr)CuCl (**156**, 36 mg, 0.07 mmol) in DCE (6 mL)] to afford naphthalene **92b** (221 mg, 1.0 mmol, 67%) as a white solid.

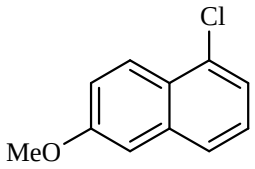
Methyl 5–chloronaphthalene–2–carboxylate (92b):[156]



Rf (petrol/AcOEt 20%): 0.59. **Mp:** 61 ºC. **IR** ν_{max}(film): 1729, 1627, 1596, 1566, 1463, 1429, 1282, 1201, 1104, 768 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.60 (1H, s, ArH), 8.30 (1H, d, *J* = 9, ArH), 8.15 (1H, d, *J* = 9, ArH), 7.86 (1H, d, *J* = 8, ArH), 7.66 (1H, d, *J* = 8, ArH), 7.44 (1H, app t, *J* = 8, ArH), 3.81 (3H, s, C$\underline{H}_3$OAr) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.82, 133.67, 132.80, 131.99, 131.19, 128.52, 128.40, 128.23, 126.58, 126.35, 124.85, 52.40 ppm. *m/z* **EI+:** 222/221/220 [M+], 191/189 [M – OCH_3], 163/161 [M – CO_2Me], 126 [M – CO_2Me – Cl]. **Accurate Mass:** $C_{12}H_9{}^{35}ClO_2$ requires 220.0286; found 220.0288.

Benzannulation reaction of 2–allyl–4–methoxyphenyl 2',2',2'–trichloroace–tate (89c): The preparation of naphthalene **92c** was accomplished using procedure E [Acetate **89c** (500 mg, 1.6 mmol) and (IPr)CuCl (**156**, 38 mg, 0.08 mmol) in DCE (6 mL)] to afford naphthalene **92c** (235 mg, 1.2 mmol, 79%) as a yellow oil.

1–Chloro–6–methoxynaphthalene (92c):[157]

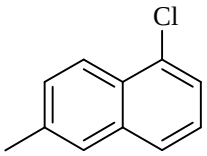


Rf (petrol): 0.17. **IR** ν_{max}(film): 1629, 1571, 1428, 1361, 1264, 1032, 968, 817 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (1H, d, *J* = 9, ArH), 7.49 (1H, d, *J* = 8, ArH), 7.28 (1H, dd, *J* = 7, *J* = 0.9, ArH), 7.18 (1H, t, *J* = 8, ArH), 7.11 (1H, dd, *J* = 9, *J* = 2.5, ArH), 6.98 (1H, d, *J* = 2.5, ArH), 3.77 (3H, s, C$\underline{H}_3$OAr) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 158.19, 135.92, 131.89, 126.41, 126.25, 126.09, 125.99, 123.92, 119.77, 106.08, 55.40 ppm. *m/z* **EI+:** 192/194 [M+], 126 [M – OCH_3 – Cl]. **Accurate Mass:** $C_{11}H_9{}^{35}ClO$ requires 192.0336; found 192.0341.

Microanalysis $C_{11}H_9ClO$ requires: C: 68.58; H: 4.71; Cl: 18.40%. Found: C: 68.44; H: 4.76; Cl: 18.40%.

Benzannulation reaction of 2–allyl–4–methylphenyl 2',2',2'–trichloroacetate (89f): The preparation of naphthalene **92f** was accomplished using procedure E [Acetate **89f** (500 mg, 1.7 mmol) and (IPr)CuCl (**156**, 44 mg, 0.09 mmol) in DCE (6 mL)] to afford naphthalene **92f** (236 mg, 1.3 mmol, 79%) as a yellow oil.

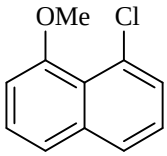
1–Chloro–6–methylnaphthalene (92f):[158]



Rf (petrol): 0.51. **IR** ν_{max}(film): 1922, 1862, 1771, 1632, 1598, 1565, 1503, 1416, 1356, 1258, 972 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.23 (1H, d, *J* = 9, ArH), 7.71 (1H, d, *J* = 8, ArH), 7.65 (1H, brd. s, ArH), 7.55 (1H, d, *J* = 8, ArH), 7.47 (1H, dd, *J* = 9, *J* = 2, ArH), 7.38 (1H, dd, *J* = 8, *J* = 8, ArH), 2.58 (3H, s, C$\underline{H}_3$Ar) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.40, 134.72, 131.72, 129.22, 129.02, 127.10, 126.43, 125.67, 125.17, 124.16, 21.46 ppm. *m/z* **EI+:** 178/176 [M+], 141 [M – Cl], 126 [M – Cl – CH_3]. **Accurate Mass:** $C_{11}H_9{}^{35}Cl$ requires 176.0387; found 176.0390. **Microanalysis $C_{11}H_9Cl$ requires:** C: 74.79; H: 5.14; Cl: 20.07%. Found: C: 74.14; H: 5.29; Cl: 19.74%.

Benzannulation reaction of 2–allyl–6–methoxyphenyl 2',2',2'–trichloroacetate (89h): The preparation of naphthalene **92h** was accomplished using procedure E [Acetate **89h** (500 mg, 1.6 mmol) and (IPr)CuCl (**156**, 38 mg, 0.08 mmol) in DCE (6 mL)] to afford naphthalene **92h** (244 mg, 1.3 mmol, 82%) as a yellow oil.

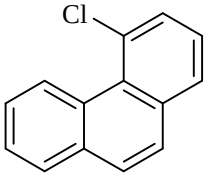
1–Chloro–8–methoxynaphthalene (92h):[159]



Rf (petrol 100%): 0.13. **IR** ν_{max}(film): 1617, 1571, 1458, 1370, 1265, 1114, 1056, 813 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (1H, dd, *J* = 8, *J* = 1, ArH), 7.37 (1H, dd, *J* = 8, *J* = 1, ArH), 7.28 (1H, dd, *J* = 8, *J* = 1, ArH), 7.24 (1H, app t, *J* = 8, ArH), 7.15 (1H, app t, *J* = 8, ArH), 6.74 (1H, broad. dd, *J* = 8, *J* = 1, ArH), 3.81 (3H, s, C$\underline{H_3}$OAr) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.36, 137.16, 129.75, 128.88, 127.31, 126.62, 125.97, 122.94, 121.33, 107.27, 56.03 ppm. *m/z* **EI+:** 192/194 [M+], 157 [M – Cl]. **Accurate Mass:** $C_{11}H_9{}^{35}ClO$ requires 192.0336; found 192.0337.

Benzannulation reaction of 2–allylnaphthalen–1–yl 2',2',2'–trichloroacetate (93): The preparation of naphthalene **94** was accomplished using procedure E [Acetate **93** (500 mg, 1.5 mmol) and (IPr)CuCl (**156**, 37 mg, 0.08 mmol) in DCE (6 mL)] to afford anthrene **94** (288 mg, 1.4 mmol, 90%) as a white solid.

4–Chlorophenanthrene (94):[160]



Rf (petrol): 0.34. **Mp:** 52 ºC (lit.[161] Mp: 57 – 58 ºC). **IR** ν_{max}(film): 3050, 2922, 1560, 1450, 1428, 1292, 1187 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.97 (1H, d, *J* = 8, ArH), 7.93 (1H, dd, *J* = 9, *J* = 2, ArH), 7.82 (1H, dd, *J* = 8, *J* = 1, ArH), 7.77 (1H, d, *J* = 9, ArH), 7.76 (1H, dd, *J* = 8, *J* = 1, ArH), 7.71 (1H, d, *J* = 9, ArH), 7.67 (1H, dd, *J* = 8, *J* = 2, ArH), 7.66 (1H, dd, *J* = 8, *J* = 2, ArH), 7.49 (1H, app t, *J* = 8, ArH) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.06, 133.35, 131.61, 130.66, 129.67, 128.57, 128.26, 128.21, 127.33, 127.18, 127.12, 126.88, 126.19, 125.92 ppm. *m/z* **EI+:** 214/212 [M+], 176 [M – Cl]. **Accurate Mass:** $C_{14}H_9{}^{35}Cl$ requires 212.0387; found 212.0381.

Benzannulation reaction of 2–allyl–4–chlorophenyl 2',2',2'–trichloroacetate (127c): The preparation of naphthalene **139c** was accomplished using procedure E [Acetate **127c** (500 mg, 1.6 mmol) and (IPr)CuCl (**156**, 39 mg, 0.08 mmol) in DCE (6 mL)] to afford naphthalene **139c** (208 mg, 1.1 mmol, 66%) as a white solid (data identical as above).

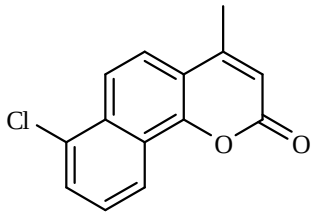
Benzannulation reaction of 2–allyl–6–chlorophenyl 2',2',2'–trichloroacetate (127d): The preparation of naphthalene **139d** was accomplished using procedure E [Acetate **127d** (500 mg, 1.6 mmol) and (IPr)CuCl (**156**, 39 mg, 0.08 mmol) in DCE (6 mL)] to afford naphthalene **139d** (240 mg, 1.2 mmol, 76%) as a yellow solid (data identical as above).

Benzannulation reaction of 2–allyl–4,6–dichlorophenyl 2',2',2'–trichloroa–cetate (127e): The preparation of naphthalene **139e** was accomplished using procedure E [Acetate **127e** (500 mg, 1.4 mmol) and (IPr)CuCl (**156**, 35 mg, 0.07 mmol) in DCE (6 mL)] to afford naphthalene **139e** (244 mg, 1.1 mmol, 76%) as a white solid (data identical as above).

Benzannulation reaction of 2–allyl–6–fluorophenyl 2',2',2'–trichloroacetate (127h): The preparation of naphthalene **139h** was accomplished using procedure E [Acetate **127h** (500 mg, 1.7 mmol) and (IPr)CuCl (**156**, 41 mg, 0.09 mmol) in DCE (6 mL)] to afford naphthalene **139h** (185 mg, 1.0 mmol, 60%) as an off–white solid (data identical as above).

Benzannulation reaction of 8–allyl–2–oxo–2*H*–chromen–7–yl 2',2',2'–trichloroacetate (116): The preparation of naphthalene **159** was accomplished using procedure E [Acetate **116** (250 mg, 0.7 mmol) and (IPr)CuCl (**156**, 17 mg, 0.03 mmol) in DCE (5 mL)] to afford coumarin **159** (69 mg, 0.29 mmol, 41%) as a white solid.

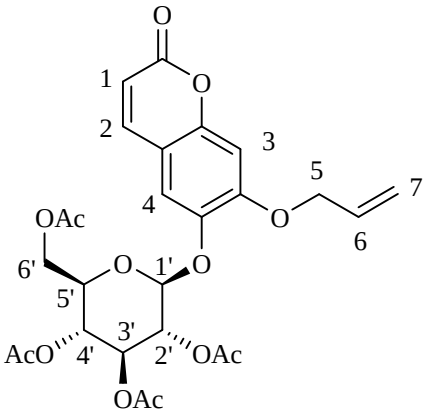
7–Chloro–4–methyl–2*H*–benzo[*H*]chromen–2–one (159):



Mp: 163 ºC. **IR** ν_{max}(film): 1725, 1608, 1382 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.47 (1H, d, *J* = 8, ArH), 8.01 (1H, d, *J* = 9, ArH), 7.69 (1H, d, *J* = 8, ArH), 7.68 (1H, d, *J* = 9, ArH), 7.52 (1H, app t, *J* = 8, ArH), 6.41 (1H, s, H), 2.54 (3H, s, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.41, 153.08, 150.27, 131.92, 128.74, 126.98, 125.37, 124.37, 121.70, 121.40, 120.43, 115.62, 115.00, 19.18 ppm. **GC/MS:** 246/244 [M+], 216/218 [M – CO]. **Accurate Mass:** $C_{14}H_9{}^{35}ClO_2$ requires 244.0286; found 244.0286.

4.2.1. APPLICATION TO CARBOHYDRATES: SYNTHESIS AND BENZANNULATION REACTION

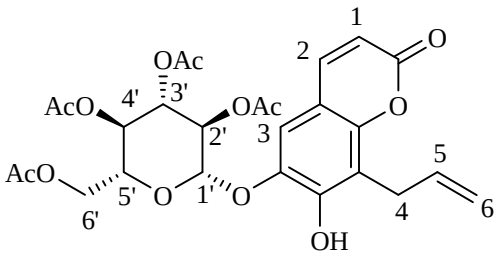
7–(2–Propen–1–yloxy)–6–[(2,3,4,6–tetra–*O*–acetyl–β–D–glucopyranosyl)oxy]–2*H*–1–benzopyran–2–one (161):[162]



Acetic anhydride (5.6 mL, 7.6 mmol) was added dropwise, with stirring, to a solution of 7–(allyloxy)–6–(tetrahydro–3,4,5–trihydroxy–6–(hydroxymethyl)–2*H*–pyran–2–yloxy)–2*H*–chromen–2–one (**160**, 2.00 g, 1.0 mmol) in pyridine (30 mL) at 0 ºC under nitrogen. The reaction mixture was kept at rt for 17 h followed by quenching with AcOEt (30 mL) and H_2O (30 mL). The organic layer was separated, washed (H_2O; 3 × 25 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (SiO_2; eluent petrol : AcOEt, 9 : 1) to afford the *title compound* (**161**, 1.93 g, 0.54 mmol, 54%) as a yellow solid. **Rf** (petrol/AcOEt 90%): 0.55. **Mp:** 110 ºC. **IR** ν_{max}(film): 3084, 2958, 2887, 1755, 1616, 1561, 1513, 1436, 1377, 1282, 1234, 1044 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 9, H–2), 7.22 (1H, s, H–4), 6.82 (1H, s, H–3), 6.27 (1H, d, *J* = 9, H–1), 6.02 (1H, ddt, *J* = 17, *J* = 11, *J* = 5, allyl H–6), 5.45 (1H, broad dd, *J* = 17, *J* = 1, allyl HxHy–7), 5.33 (1H, broad dd, *J* = 11, *J* = 1, allyl HxHy–7), 5.28 – 5.26 (2H, ddm, H–1' + H–2'), 5.17 (1H, ddd, *J* = 10, *J* = 6, *J* = 3, H–4'), 4.96 (1H, dd, *J* = 5, *J* = 2, H–3'), 4.60 (2H, d, *J* = 5, allyl H–5), 4.26 (1H, dd, *J* = 12, *J* = 5, HxHy–6'), 4.16 (1H, dd, *J* = 12, *J* = 2, HxHy–6'), 3.76 (1H, ddd, *J* = 10, *J* = 5, *J* = 3, H–5´), 2.06 (3H, s, $OCOCH_3$), 2.05 (3H, s, $OCOCH_3$), 2.03 (6H, s, $OCOCH_3$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.41, 170.19, 169.34, 169.27, 160.90, 153.12, 151.88, 143.00, 142.39, 131.68, 118.76, 118.66, 113.86, 111.56, 101.66, 100.44, 72.36, 71.97, 70.95, 69.79, 68.20, 61.69,

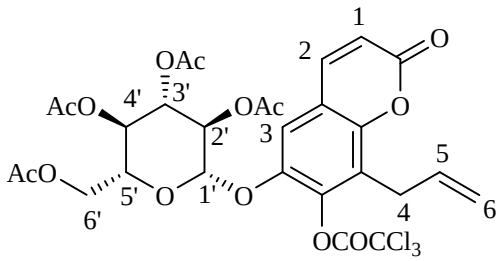
20.69, 20.56, 20.54 ppm. *m/z* **EI+:** 548 [M+], 509 [M – CH_2CHCH_2], 218 [M – sugar]. **Accurate Mass:** $C_{26}H_{29}O_{13}$ requires 548.1524; found 548.1529.

7–Hydroxy–8–(2–propen–1–yl)–6–[(2,3,4,6–tetra–*O*–acetyl–β–D–glucopyranosyl)oxy]–2*H*–1–benzopyran–2–one (163):



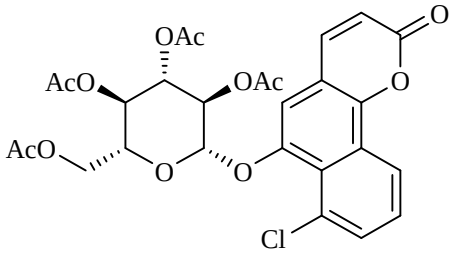
Glycoside **161** (1.87 g, 3.4 mmol) was heated without solvent at 210 – 220 ºC for 5 h under nitrogen. Purification of the crude product by flash chromatography (SiO_2; eluent petrol : AcOEt, 9 : 1) afforded the *title compound* (**163**, 1.30 g, 2.3 mmol, 69%) as a pale yellow solid. **Rf** (petrol:AcOEt, 9:1): 0.40. **Mp:** 72 ºC. **IR** ν_{max}(film): 3422, 1740, 1735, 1731, 1577, 1490, 1212, 1031 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 10, H–2), 6.96 (1H, s, H–3), 6.57 (1H, s, OH), 6.29 (H, d, *J* = 10, H–1), 5.97 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, H–5), 5.33 (1H, d, *J* = 9, H–1'), 5.27 (1H, dd, *J* = 9, *J* = 8, H–2'), 5.18 (1H, t, *J* = 10, H–4'), 5.11 (1H, dd, *J* = 17, *J* = 2, HxHy–6), 5.02 (1H, dd, *J* = 10, *J* = 2, HxHy–6), 4.99 (1H, broad d, *J* = 8, H–3'), 4.31 (1H, dd, *J* = 12, *J* = 5, HxHy–6'), 4.21 (1H, dd, *J* = 12, *J* = 2, HxHy–6'), 3.89 (1H, ddd, *J* = 10, *J* = 5, *J* = 2.5, H–5'), 3.62 (2H, broad d, *J* = 6, H–4), 2.14 (3H, s, OCH_3), 2.11 (3H, s, OCH_3), 2.07 (3H, s, OCH_3), 2.06 (3H, s, OCH_3) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.44, 170.11, 170.05, 169.33, 161.03, 150.01, 149.00, 143.24, 141.00, 134.28, 115.89, 115.70, 113.70, 112.90, 111.36, 101.53, 72.36, 71.92, 71.34, 67.91, 61.62, 27.13, 20.78, 20.67, 20.55, 20.53 ppm. *m/z* **EI+:** 548 [M+], 218 [M – multiple fragment lost]. **Accurate Mass:** $C_{26}H_{29}O_{13}$ requires 548.1603; found 548.1593.

2–oxo–8–(2–propen–1–yl)–6–[(2,3,4,6–tetra–*O*–acetyl–β–D–glucopyranosyl) oxy]–2*H*–1–benzopyran–7–yl 2',2',2'–trichloroacetate (162):



Trichloroacetylchloride (0.30 mL, 2.5 mmol) was added dropwise to a solution of the allylphenol **163** (1.15 g, 2.1 mmol) and Et_3N (0.34 mL, 2.5 mmol) in Et_2O (30 mL) at 0 °C under nitrogen. The reaction mixture was left stirring for 3 h at 0 ºC and at rt for 16 h. Water (20 mL) and Et_2O (20 mL) were added and the organic layer separated, washed (satd. aq. $NaHCO_3$, 2 × 25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* (**162**, 1.23 g, 1.8 mmol, 84%) as a golden coloured solid. **Mp:** 59 ºC. **IR** ν_{max}(film): 1788, 1747, 1583, 1480, 1436, 1370, 1293, 1220, 1135, 1042, 991, 907 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (1H, d, *J* = 10, H–2), 7.06 (1H, s, H–3), 6.28 (1H, d, *J* = 10, H–1), 5.89 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, H–5), 5.33 (1H, d, *J* = 7, H–1), 5.30 (1H, broad d, *J* = 7, H–2), 5.20 (1H, dd, *J* = 10, *J* = 5, HxHy–6'), 5.18 (1H, dd, *J* = 10, *J* = 3, HxHy–6'), 5.08 (1H, dd, *J* = 17, *J* = 1, HxHy–6), 5.06 (1H, dd, *J* = 10, *J* = 1.5, HxHy–6), 4.30 (1H, dd, *J* = 13, *J* = 6, H–4'), 4.18 (1H, dd, *J* = 13, *J* = 2.5, H–3'), 3.95 (1H, ddd, *J* = 10, *J* = 5, *J* = 2, H–5'), 3.62 (2H, d, *J* = 6, H–4) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.68, 170.52, 169.55, 144.91, 142.85, 133.29, 123.66, 117.90, 117.85, 117.45, 98.52, 73.09, 72.61, 71.41, 68.11, 62.23, 28.00, 21.00, 20.97, 20.85 ppm.[163]

Benzannulation reaction of 2–oxo–8–(2–propen–1–yl)–6–[(2,3,4,6–tetra–*O*–acetyl–β–D–glucopyranosyl)oxy]–2*H*–1–benzopyran–7–yl 2',2',2'–trichloroacetate (162):



It was followed general procedure E [Acetate **162** (150 mg, 0.21 mmol) and (IPr)CuCl (**156**, 4.2 mg, 0.01 mmol) in DCE (2.5 mL)]. The crude product was purified by flash column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting from 0.5 : 9.5 and progressing to AcOEt) to afford glycoside **164** (25.3 mg, 0.04 mmol, 21%) as a yellow solid. **Rf** (AcOEt 100%): 0.60. **Mp:** 185 ºC. **IR** ν_{max}(film): 1746, 1560, 1459, 1424, 1367, 1318, 1234, 1042, 912 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.47 (1H, dd, *J* = 11, *J* = 2, H–10), 7.75 (1H, d, *J* = 12, H–4), 7.68 (1H, dd, *J* = 9, *J* = 2, H–8), 7.51 (1H, dd, *J* = 10, *J* = 10, H–9), 7.13 (1H, s, H–5), 6.56 (1H, d, *J* = 12, H–3), 5.48 (1H, dd, *J* = 11, *J* = 10, H–2'), 5.33 (2H, app t, *J* = 9, H–3'), 5.32 (1H, d, *J* = 8, H–1'), 5.27 (1H, app t, *J* = 9, H–4'), 4.32 (1H, dd *J* = 15, *J* = 7, HxHy–6'), 4.24 (1H, dd, *J* = 15, *J* = 3, HxHy–6'), 3.98 (1H, ddd, *J* = 10, *J* = 7, *J* = 3, H–5'), 2.08 (3H, s, $OCOCH_3$), 2.06 (3H, s, $OCOCH_3$), 2.06 (6H, s, 2 × $OCOCH_3$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 170.40, 170.30, 169.38, 169.31, 160.27, 149.23, 146.82, 143.12, 132.38, 130.03, 127.52, 126.35, 124.32, 121.42, 117.46, 114.06, 108.29, 99.32, 72.97, 72.23, 71.11, 68.07, 62.06, 20.76, 20.72, 20.60, 20.58 ppm. **Scan ES+:** 599/601 [M + Na]. **Accurate mass:** $C_{27}H_{25}{}^{35}ClONa$ requires 599.0927; found 599.0930.

4.3 SOLVENT SCREENING STUDIES

4.3.1 BENZANNULATION REACTION IN DBE

General procedure F:

A solution of the trihaloester (1.0 equiv.), CuCl (5 mol%), ligand **18** (5 mol%) in DBE (2.5 mL) was heated in a microwave reactor at 200 ºC under nitrogen for 2 h. Upon cooling to ambient temperature the crude product was purified by flash column chromatography (SiO_2; eluent petrol).

Benzannulation reaction of 2–allyl–4–fluorophenyl 2',2',2'–trichloroacetate (89a): The benzannulation reaction was carried out using procedure F [Acetate **89a** (500 mg, 1.7 mmol), CuCl (8.3 mg, 0.08 mmol) and ligand **18** (23 mg, 0.08 mmol) in DBE (2 mL)] to afford a white solid (106 mg, 50%) as an inseparable mixture of three products 1–chloro–6–fluoronaphthalene (**92a**, NMR spectra as above), 1–bromo–6–fluoronaphthalene (**179**) and 1,6–dichloronaphthalene (**139c**) in a ratio > 99 : 1. **Rf** (petrol) of the mixture: 0.80.

Benzannulation reaction of 2–allyl–4–bromophenyl 2',2',2'–trichloroacetate (127a): This benzannulation reaction was carried out using procedure F [Acetate **127a** (500 mg, 1.4 mmol), CuCl (6.9 mg, 0.07 mmol) and ligand **18** (20 mg, 0.07 mmol) in DBE (2 mL)] to afford a white solid (162 mg, 46%) as an inseparable mixture of four products 6–bromo–1–chloronaphthalene (**139a**, NMR spectra as above), 1,6–dichlonaphthalene (**139c**), 1,6–dibromonaphthalene (**182**) and 6–bromonaphthalene (**183**) in a > 99 : 1 ratio.[149]

Benzannulation reaction of 2–allyl–6–bromophenyl 2',2',2'–trichloroacetate (127b): The benzannulation reaction was carried out using procedure F [Acetate **127b** (500 mg, 1.4 mmol), CuCl (6.9 mg, 0.07 mmol) and ligand **18** (20 mg, 0.07

mmol) in DBE (2 mL)] to afford a yellow solid (181 mg, 58%) as an inseparable mixture of four products 8–bromo–1–chloronaphthalene (**157b**), 1–bromonaphthalene (**178**, NMR's spectra as above), 1,6–dichloronaphthalene (**137d**) and 1,6–dibromonaphthalene (**184**) in a 45 : 53 < 1 : < 1 ratio.[149]

Benzannulation reaction of 2–allyl–4–chlorophenyl 2',2',2'–trichloroacetate (127c): The benzannulation reaction was carried out using procedure F [Acetate **127c** (500 mg, 1.6 mmol), CuCl (7.9 mg, 0.08 mmol) and ligand **18** (23 mg, 0.08 mmol) in DBE (2 mL)] to afford a yellow oil (231.3 mg, 73%) as an inseparable mixture of two products 1,6–dichloronaphthalene (**139c**, NMR's spectra as above) and 6–chloronaphthalene (**180**, GC/MS molecular *m/z* 242) in a 8 : 2 ratio.[149] **Rf** (petrol): 0.8.

Benzannulation reaction of 2–allylphenyl 2',2',2'–tribromoacetate (128): The benzannulation reaction was carried out using procedure F [Acetate **128** (500 mg, 1.2 mmol), CuCl (6.0 mg, 0.06 mmol) and ligand **18** (17 mg, 0.06 mmol) in DBE (2 mL)] to afford a yellow solid (105 mg, 47%) as an inseparable mixture of 1–bromonaphthalene (**178**), naphthalene (**181**) and 1–chloronaphthalene (**91**, NMR's spectra as above) in a 94 : 16 : 1 ratio.[149] **Rf** of the mixture (petrol): 0.49.

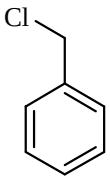
4.3.2. BENZANNULATION REACTION IN TOLUENE

General procedure G:

A solution of the trihaloester (1.0 equiv.), CuCl (5 mol%), ligand **18** (5 mol%) in toluene was heated in a microwave reactor at 200 ºC under nitrogen for 2 h. Upon cooling to ambient temperature the crude product was purified by flash column chromatography (SiO_2; eluent petrol).

Benzannulation reaction of 2–allyl–4–bromophenyl 2'2'2'–trichloroacetate (127a): It was followed general procedure G [Acetate **127a** (500 mg, 1.4 mmol), CuCl (6.9 mg, 0.07 mmol) and ligand **18** (20 mg, 0.07 mmol) in toluene (2 mL)] to afford a white solid (213 mg, 54%) as an inseparable mixture of 6–bromo–1–chloronaphthalene (**139a**, NMR spectra as above) and 1–(chloromethyl)benzene (**185**) in a 1 : 0.11 ratio.[154]

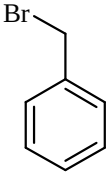
Benzyl chloride (185):[164]



^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (2H, s, CH_2Cl) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 46.34 ppm.

Benzannulation reaction of 2–allyl–6–bromophenyl 2',2',2'–trichloroacetate (127b): It was followed general procedure G [Acetate **127b** (500 mg, 1.4 mmol), CuCl (6.9 mg, 0.07 mmol) and ligand **18** (20 mg, 0.07 mmol) in toluene (2.5 mL)] to afford a white solid (223 mg, 53%) as an inseparable mixture of 8–bromo–1–chloronaphthalene (**139b**), 1–bromonaphthalene (**178**), 1–chloronaphthalene (**92**), 1,8–dichloronaphthalene (**139d**), 1–(chloromethyl)benzene (**185**, NMR spectra as above) and 1–(bromomethyl)benzene (**186**) in a 1 : 0.08 : < 1% : < 1% : 0.08 : 0.25 ratio.[149]

Benzenyl bromide (186):[165]



^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (2H, s, CH_2Br) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 21.52 ppm.

Benzannulation reaction of 2–allylphenyl 2',2',2'–tribromoroacetate (128): It was followed general procedure G [Acetate **128** (500 mg, 1.2 mmol), CuCl (6.0 mg, 0.06 mmol) and ligand **18** (17 mg, 0.06 mmol) in toluene (2.5 mL)] to afford a yellow oil (70.3 mg, 15%) as an inseparable mixture of 1–bromonaphthalene (**178**), 1–chloronaphthalene (**92**), naphthalene (**181**, **GC/MS:** 128 [M+]. **Accurate Mass:** $C_{10}H_8$ requires 128.0621, found 128.0622), 1–(bromomethyl)benzene (**186**) and 1–(chloromethyl)benzene (**185**, NMR spectra as above) in a 1 : 0.09 : 0.68 : 0.88 : < 1% ratio.[149]

4.3.3. THERMAL BENZANNULATION REACTION IN DIGLYME

Benzanulation reaction of 2–allyl–6–chlororophenyl 2',2',2'–trichloroacetate (127d): Acetate **127d** (500 mg, 1.5 mmol) and (IPr)CuCl (**156**, 38 mg, 0.08 mmol) were refluxed in diglyme (5 mL) for 7 h. The crude product was purified by flash column chromatography (SiO_2; eluent petrol) to afford 1,8–dichloronaphthalene (**139d**, 182 mg, 0.89 mmol, 59%) as a white solid (NMR spectra as above).

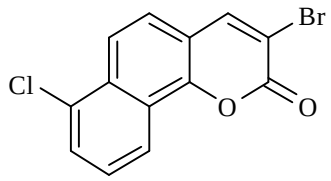
Benzanulation reaction of 2–allyl–6–chlororophenyl 2',2',2'–trichloroacetate (127d): Acetate **127d** (500 mg, 1.5 mmol) and (IPr)CuCl (**156**, 38 mg, 0.08 mmol) were refluxed in diglyme (1 mL) for 7 h. The crude product was purified by flash column chromatography (SiO_2; eluent petrol) to afford 1,8–dichloronaphthalene (**139d**, 158 mg, 0.77 mmol, 51%) as a white solid (NMR spectral data as above).

Benzannulation reaction of 8–allyl–2–oxo–2*H*–chromen–7–yl 2',2',2'–trichloroacetate (137): Acetate **137** (250 mg, 0.7 mmol) and (IPr)CuCl (**156**, 17 mg, 0.03 mmol) were refluxed in diglyme (0.5 mL) for 7 h. The crude product was purified by flash column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting from 9 : 1 and progressing to AcOEt) to afford

7–chloro–4–methyl–2*H*–benzo[*H*]chromen–2–one (**159**, 44 mg, 0.18 mmol, 26%) as a colourless oil (NMR spectra as above).

Benzannulation reaction of 2–oxo–8–(2–propen–1–yl)–6–[(2,3,4,6–tetra–*O*–acetyl–β–D–glucopyranosyl)oxy]–2*H*–1–benzopyran–7–yl 2',2',2'–trichloroacetate (162): Acetate **162** (250 mg, 0.36 mmol) and (IPr)CuCl (**156**, 8.7 mg, 0.02 mmol) were refluxed in diglyme (1 mL) for 2 h. The crude product was purified by flash column chromatography (SiO_2; eluent (SiO_2; eluent petrol : AcOEt; gradient elution starting from 7 : 3 and progressing to AcOEt) to afford coumarin **164** (91 mg, 0.16 mmol, 44%) as a yellow solid (NMR spectral data as above).

Benzannulation reaction of 8–Allyl–3–bromo–2–oxo–2*H*–chromen–7–yl 2',2',2'–trichloroacetate (192):

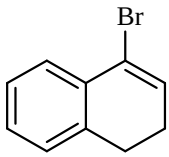


A solution of acetate **138** (100 mg, 0.23 mmol) and (IPr)CuCl (**156**, 5.7 mg, 5 mol%) in diglyme (1 mL) was brought to reflux for 7 h. After cooling to ambient temperature the solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2; eluent petrol : AcOEt; (SiO_2; eluent petrol : AcOEt; gradient elution starting from 1 : 0 and progressing to 8.3 : 1.5)) to afford coumarin **192** (28 mg, 0.09 mmol, 41%) as a colourless oil. **Rf** (EtOAc/petroleum ether 10%): 0.16. **IR** ν_{max}(film): 1732, 1721, 1705, 1634, 1596, 1553, 1321, 113, 943 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.48 (1H, brd. d, *J* = 8, ArH), 8.24 (1H, s, H–4), 8.16 (1H, d, *J* = 9, ArH), 7.78 (1H, app t, *J* = 8, ArH), 7.58 (1H, app t, *J* = 8, ArH), 7.53 (1H, d, *J* = 9, ArH) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.96, 150.26, 144.76, 132.35, 132.04, 129.27, 127.51, 124.17, 123.76, 121.62, 121.29, 115.32, 112.28 ppm. *m/z* **EI+:** 311/310/309 [M+], 284/282/280 [M – Cl], 231/229

[M – Br]. **Accurate Mass:** [$C_{13}H_6{}^{79}Br^{35}Cl\ NaO_2$ – 1] requires 330.9123; found 330.9197.

Benzannulation reaction of 2–allylphenyl 2',2',2'–tribromoacetate (128): Acetate **128** (250 mg, 0.61 mmol) was refluxed in diglyme (1 mL) in the presence of CuBr (4.3 mg, 0.03 mmol) and ligand **18** (8.6 mg, 0.03 mmol) to afford a yellow oil as an inseparable mixture of 1–bromonaphthalene (**178**, 47 mg, 0.22 mmol, 37%) and 4–bromo–1,2–dihydronaphthalene (**193**, 12.8 mg, 0.06 mmol, 10%).[154]

4–Bromo–1,2–dihydronaphthalene (193):[166]



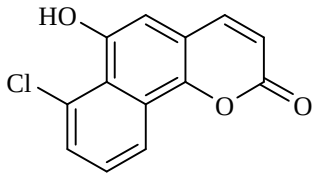
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (1H, t, *J* = 5, H–2), 2.86 (2H, t, *J* = 8, 2 × H–4), 2.39 (2H, dt, *J* = 8, *J* = 5, 2 × H–3) ppm.

4.3.4. MW BENZANNULATION REACTION IN DIGLYME

Benzannulation reaction of 2–allyl–6–chlororophenyl 2',2',2' –trichloroace–tate (127d): Acetate **127d** (250 mg, 0.8 mmol) and (IPr)CuCl (**156**, 19 mg, 0.04 mmol) and diglyme (1 mL) were heated in a MW reactor at 170 ºC for 2 h. The crude product was purified by flash column chromatography (SiO_2; eluent petrol) to afford 1,8–dichloronaphthalene (**139d**, 123 mg, 0.63 mmol, 79%) as a white solid.

Benzannulation reaction of 2–oxo–8–(2–propen–1–yl)–6–[(2,3,4,6–tetra–*O*–acetyl–β–D–glucopyranosyl)oxy]–2*H*–1–benzopyran–7–yl 2',2',2'–trichloroacetate (162): Acetate **162** (200 mg, 0.29 mmol) and (IPr)CuCl (**156**, 7.0 mg, 0.01 mmol) and diglyme (1 mL) were heated in a MW reactor at 170 ºC for 2 h. The crude product was purified by flash column chromatography (SiO_2; eluent (SiO_2; eluent petrol : AcOEt; gradient elution starting from 7 : 3 and progressing to AcOEt)) to afford napthalene **164** (84 mg, 0.14 mmol, 50%, NMR data as above) as a yellow solid and coumarine **199** (8.6 mg, 0.03 mmol, 12%) as a yellow oil.

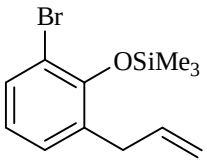
7–Chloro–6–hydroxy–2*H*–naphtho[1,2–*b*]pyran–2–one (199):



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (1H, d, *J* = 8.5, H–10), 8.02 (1H, s, H–5), 7.75 (1H, d, *J* = 9, H–4), 7.62 (1H, d, *J* = 8, H–8), 7.57 (1H, app t, *J* = 8, H–9), 7.02 (1H, s, OH), 6.56 (1H, d, *J* = 9, H–3) ppm.

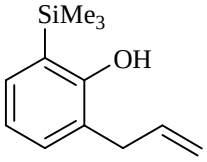
5. APPLICATIONS OF THE BHQ

(2–Allyl–6–bromophenoxy)trimethylsilane (200):



Hexamethyldisilazane (1.7 mL, 8.12 mmol) was added dropwise (**CARE** – ammonia generated!) to 2–allyl–6–bromophenol (3.20 g, 15.1 mmol) at 170 ºC. The homogeneous solution was maintained at 170 ºC for 2 h and then allowed to cool to ambient temperature. Purification of the crude product by vacuum distillation afforded the *title compound* (**200**, 2.70 g, 9.5 mmol, 63%) as a colourless mobile oil. **IR** ν_{max}(film): 3057, 2955, 2899, 1636, 1596, 1576, 1490, 1423, 1253, 918, 870, 760 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (1H, dd, *J* = 8, *J* = 2, ArH), 7.08 (1H, dd, *J* = 8, *J* = 2, ArH), 6.81 (1H, app t, *J* = 8, ArH), 5.94 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, C<u>H</u>CH_2), 5.10 (1H, ddd, *J* = 10, *J* = 3, *J* = 1, CHC<u>H</u>xHy), 5.04 (1H, ddd, *J* = 17, *J* = 3, *J* = 1.5, CHCHx<u>H</u>y), 3.38 (2H, broad d, *J* = 6, $ArCH_2$), 0.33 (9H, s, $Si(CH_3)_3$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.89, 136.22, 132.65, 131.12, 129.16, 122.61, 116.25, 115.66, 35.00, 1.10 ppm. **GC/MS**: 286/284 [M+], 271/269 [M – CH_2], 243/241 [M – CH_2CHCH_2], 115 [M – Br – $OSiMe_3$]. **Accurate Mass:** $C_{12}H_{17}{}^{79}BrO^{28}Si$ requires 284.0227; found 284.0225.

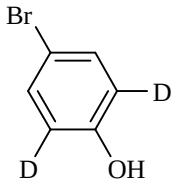
2–Allyl–6–(trimethylsilyl)phenol (201):



A solution of silane **200** (2.50 g, 8.8 mmol) in THF (3 mL) was added dropwise to a stirred solution of ^{n}BuLi (6.0 mL, 9.6 mmol, 1.6 M in hexanes) in THF (3 mL) at −78 ºC under nitrogen. The resulting mixture was stirred at −78 ºC for 5 h. The mixture was allowed to warm up to 0 ºC and stirred for a further1 h. Upon

recooling to −78 ºC the reaction was quenched by the addition of H_2O (0.5 mL) and stirred for 16 h at rt. The mixture was extracted with AcOEt (3 × 15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* (**201**, 1.40 g, 6.8 mmol, 77%) as a brown oil. **IR** ν_{max}(film): 3536, 3056, 2954, 2898, 1635, 1596, 1576, 1423, 1244, 918, 870 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 (1H, dd, *J* = 7, *J* = 2, ArH), 7.02 (1H, dd, *J* = 7, *J* = 2, ArH), 6.82 (1H, app t, *J* = 7, ArH), 5.92 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, C<u>H</u>CH_2), 5.19 (1H, s, OH), 5.13 (1H, dq, *J* = 17, *J* = 2, CHC<u>H</u>xHy), 5.13 (1H, dq, *J* = 10, *J* = 2, CHCHx<u>H</u>y), 3.29 (2H, broad d, *J* = 6, $ArCH_2$), 0.25 (9H, s, $Si(CH_3)_3$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 159.49, 136.21, 133.78, 131.68, 126.11, 123.24, 120.62, 117.07, 35.96, 0.89 ppm. *m/z* **EI+:** 206 [M+]. **Accurate Mass:** $C_{12}H_{18}O^{28}Si$ requires 206.1121; found 206.1126.

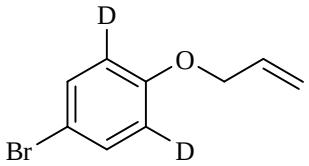
4–Bromo–2,6–dideuterophenol (203):



Sodium (272 mg, 11.9 mmol) was added to a mixture of *p*–bromophenol (**112a**, 5.00 g, 28.9 mmol) and D_2O (99.99% D content; 11 mL) in a Schlenk flask under nitrogen (CARE!: violent reaction; D_2 evolved). After effervescence had subsided the reaction mixture was brought to reflux. After 16 h the solvent was removed and a fresh sample of D_2O (11 mL) was added. The reaction mixture was brought to reflux for a further period of 24 h. This solvent exchange process was repeated a further four times (total reaction time +96 h). Upon cooling to ambient temperature the reaction mixture was acidified to pH 3 (2 M HCl) and extracted with Et_2O (20 mL × 3). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* (**203**, 3.31 g, 18.8 mmol, 65%) as a brown oil which was sufficiently pure to be used without further purification (> 99.9% D incorporation by ^{1}H NMR). **IR** ν_{max}(film): 3340, 1796, 1702, 1656, 1614, 761 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 (2H, s, ArH) ppm; **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.45, 132.31, 116.88 (t, *J* = 23.75, ArC–D), 112.70 ppm.

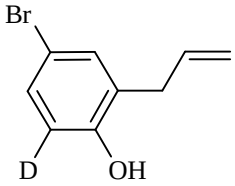
m/z **EI+:** 174/176 [M+], 95 [M – Br]. **Accurate Mass:** $C_6H_3{}^2H_2{}^{79}BrO$ requires 173.9638; found 173.9644.

1–(Allyloxy)–4–bromo–2,6–dideuterobenzene (204):



To a stirred mixture of K_2CO_3 (2.67 g, 16.1 mmol) and dideutereophenol **203** (2.37 g, 13.4 mmol) in acetone (15 mL) was added allylbromide (1.9 mL, 16.1 mmol) at rt. The mixture was refluxed for 18 h, filtered and the solvent removed *in vacuo*. The crude product was dissolved in AcOEt (20 mL) and washed with H_2O (3 × 20 mL). The layers were separated, the organic layer dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; eluent petrol 100%) to afford a colourless oil (2.86 g, 72%) as an inseparable mixture of 1–(allyloxy)–4–bromo–2,6–dideutereobenzene (**204**) and 1–(allyloxy)–4–bromo–benzene (**112a**, **204** : **112a**; 11 : 1 ratio). **Rf** (petrol 100%): 0.28. **IR** ν_{max}(film): 3083, 2984, 2859, 1648, 1579, 1563, 1442, 1238, 1007, 927, 889 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (2H, s, ArH), 6.06 (1H, ddt, *J* = 17, *J* = 10, *J* = 5, C<u>H</u>CH_2), 5.47 (1H, dd, *J* = 17, *J* = 1, CHC<u>H</u>xHy), 5.36 (1H, dd, *J* = 10, *J* = 2, CHCHx<u>H</u>y), 4.55 (2H, broad d, *J* = 5, ArOCH_2) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.46, 132.74, 132.00, 117.74, 116.14 (t, *J* = 24.7, ArC–D) 112.80, 68.81 ppm. *m/z* **EI+:** 214/216 [M+], 173/175 [M – CH_2CHCH_2], 136 [M – Br], 94 [M – CH_2CHCH_2 – Br], 78 [M – OCH_2CHCH_2 – Br]. **Accurate Mass:** $C_9H_7{}^2H_2{}^{79}BrO$ requires 213.9957; found 213.9951.

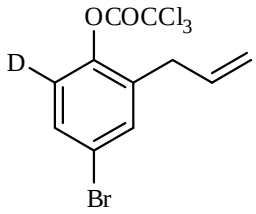
2–Allyl–4–bromo–3–deutereophenol (205):



Was prepared using general procedure B for 9 h [Ethers **204** and **112a** (1.48 g, 6.9 mmol)] to afford a yellow oil (732 mg, 50%) as an inseparable mixture of deuterophenol **205** and phenol **123a** in a 11 : 1 ratio. **Rf** (petrol/AcOEt 20%): 0.18. **IR** ν_{max}(film): 3435, 3078, 2976, 2912, 1638, 1598, 1461, 1320, 1236, 1124, 1006 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.05 (1H, d, *J* = 3, ArH), 6.96 (1H, d, *J* = 3, ArH), 5.84 (1H, ddt, *J* = 18, *J* = 9, *J* = 7, C<u>H</u>CH_2), 4.91 (2H, m, CHC<u>H_2</u>), 3.12 (1H, d, *J* = 7, ArCH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.10, 135.41, 132.91, 130.71 (t, *J* = 23), 130.52, 130.43, 117.48, 117.16, 34.75 ppm. *m/z* **EI+:** 213/215 [M+], 134 [M – Br]. **Accurate Mass:** $C_9H_8{}^2H_2{}^{79}BrO$ requires 213.9816; found 213.9823.

2–Allyl–4–bromophenol (123a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (1H, dd, *J* = 6, *J* = 3, ArH) ppm.

2–Allyl–4–bromo–3–deuterophenyl 2'2'2'–trichloroacetate (206):

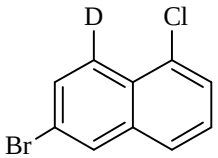


Was prepared using general procedure C [Phenols **205** and **123a** (500 mg, 2.3 mmol), trichloroacetylchloride (0.33 mL, 2.8 mmol) and triethylamine (0.38 mL, 2.8 mmol) in Et_2O (2 mL)] to afford a yellow oil (546 mg, 65%) which corresponds to an inseparable mixture of 2–allyl–4–bromo–3–deuterophenyl–2'2'2'–trichloroacetate (**207**) and 2–allyl–4–bromophenyl 2'2'2'–trichloroacetate (**137a**) in a 11 : 1 ratio. **IR** ν_{max}(film): 3087, 2984, 2916, 1780, 1644, 1572, 1484, 1162 cm^{-1}. **^{1}H NMR** (500

MHz, $CDCl_3$) δ 7.47 – 7.44 (2H, m, ArH), 5.89 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, C<u>H</u>CH_2), 5.15 (1H, dq, *J* = 10, *J* = 1, CHC<u>H</u>xHy), 5.11 (1H, dq, *J* = 17, *J* = 1, CHCHx<u>H</u>y), 3.36 (2H, broad d, *J* = 6, Ar<u>C</u>H_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.14, 147.53, 134.26, 134.09, 132.72, 130.66, 11.46 (t, *J* = 28), 120.55, 117.65, 34.74 ppm.[163]

Benzannulation reaction of 2–allyl–4–bromo–3–deuterophenyl 2'2'2'–trichloroacetate (206): The benzannulation reaction was carried out using procedure E [Acetates **206** and **127a** (206 mg, 0.57 mmol) and (IPr)CuCl (**156**, 14 mg, 0.03 mmol) in DCE (6 mL)] to afford a white solid (93.4 mg, 68%) as an inseparable mixture of naphthalenes **207** and **139a** in a 1 : 0.19 ratio.

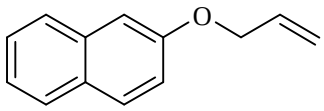
6–Bromo–1–chloro–8–deuteronaphthalene (207):



Rf (petrol): 0.53. **Mp:** 42 ºC. **IR** ν_{max}(film): 1615, 1582, 1556, 1483, 1330, 1201, 965 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (1H, s, ArH), 7.66 (1H, d, *J* = 7, ArH), 7.65 (1H, s, ArH), 7.58 (1H, d, *J* = 7, ArH), 7.41 (1H, app t, *J* = 7, ArH) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.45, 132.05, 132.02, 130.24, 130.24, 130.08, 129.23, 126.50 (1C, t, *J* = 47, ArC–D), 126.24, 120.95 ppm. *m/z* **EI+**: 241/243/245/246 [M+], 162/164 [M – Br], 127 [M – Cl – Br]. **Accurate mass:** $C_{10}H_5{}^2H_2{}^{79}Br^{35}ClO$ requires 240.9399; found 240.9396.

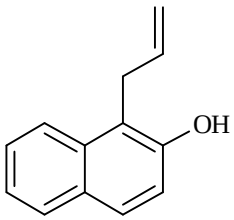
6–Bromo–1–chloronaphthalene (139a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (1H, d, *J* = 8.8, ArH) ppm.

2–(Allyloxy)–naphthalene (208):[167]



Was accomplished using general procedure A [2–naphthol (2.00 g, 13.9 mmol), allyl bromide (1.4 mL, 16.6 mmol) and K_2CO_3 (2.30 g, 16.6 mmol) in acetone (40 mL)] to afford the *title compound* (**208**, 2.55 g, 13.7 mmol, 99%) as a yellow oil. **Rf** (petrol 100%): 0.22. **IR** ν_{max}(film): 1732, 1628, 1599, 1510, 1462, 1390, 1256, 1214, 1180 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.75 – 7.54 (3H, m, ArH), 7.34 (1H, dt, *J* = 8, *J* = 1, ArH), 7.19 (1H, dd, *J* = 9, *J* = 2, ArH), 7.06 (1H, dd, *J* = 8, *J* = 2, ArH), 7.00 (1H, s, H–1), 6.14 (1H, ddt, *J* = 16, *J* = 10.5, *J* = 5, C<u>H</u>CH_2), 5.49 (1H, dq, *J* = 17, *J* = 2, CHC<u>H</u>xHy), 5.35 (1H, dq, *J* = 10.5, *J* = 1, CHCHx<u>H</u>y), 4.68 (2H, dt, *J* = 5, *J* = 1, OCH_2) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.52, 134.51, 133.19, 129.38, 129.02, 127.61, 126.73, 126.31, 123.62, 118.94, 117.68, 107.04, 68.78 ppm. **GC/MS:** 184 [M+], 169 [M – CH_2], 143 [M – CH_2CHCH_2], 115 [M – $CHCOCH_2CHCH_2$]. **Accurate Mass:** $C_{13}H_{12}O$ requires 184.0883; found 184.0883.

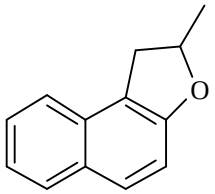
1–Allylnaphthalen–2–ol (112h):[168]



A solution of 2–(allyloxy)–naphthalene (**208**, 1.00 g, 5.4 mmol) in toluene (3.5 mL) was heated at 200 °C in a MW reactor for 11 h under nitrogen. The crude was purified by flash chromatography column (SiO_2; eluent petrol : AcOEt, 9 : 1) to afford the *title compound* (**112h**, 753 mg, 4.1 mmol, 75%) as a colourless oil. **Rf** (EtOAc/petroleum ether 30%): 0.31. **IR** ν_{max}(film): 3412, 1626, 1597, 1514, 1437, 1390, 1354, 1261 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82 (1H, d, *J* = 8, ArH), 7.70 (1H, d, *J* = 8, ArH), 7.59 (1H, d, *J* = 9, ArH), 7.39 (1H, ddd, *J* = 8, *J* = 7, *J* = 1, ArH), 7.25 (1H, ddd, *J* = 8, *J* = 7, *J* = 1, ArH), 7.00 (1H, d, *J* = 9, ArH),

5.99 (1H, ddt, *J* = 16, *J* = 10, *J* = 6, C<u>H</u>CH$_2$), 5.05 – 4.90 (2H, m, CHC<u>H$_2$</u>), 3.75 (2H, dt, *J* = 4, *J* = 2, ArC<u>H$_2$</u>) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.21, 135.74, 133.23, 129.41, 129.30, 128.55, 128.29, 126.46, 123.12, 122.98, 117.92, 115.89, 29.15 ppm. **GC/MS:** 184 [M+], 169 [M – CH_2], 141 [M – CH_2CHCH_2]. **Accurate Mass:** $C_{13}H_{12}O$ requires 184.0883; found 184.0882.

2–Methyl–1,2–dihydronaphthol[2,1–*b*]furan (213):[169]

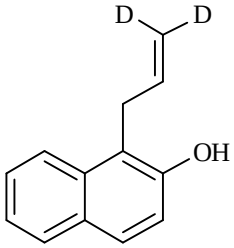


A mixture of 1–allylnaphthalen–2–ol (**112h**, 143 mg, 0.77 mmol) and one crystal of *p*–toluenesulfonic acid in H_2O (1.4 mL) was heated in a MW reactor at 200 °C for 2 h under nitrogen. Upon cooling to ambient temperature the solvent was removed *in vacuo* and the crude was purified by column chromatography (SiO_2; petrol : AcOEt, 8.5 : 1.5) to afford the racemic *title compound* (**213**, 89 mg, 0.49 mmol, 63%) as a yellow oil. **Rf** (EtOAc/petroleum ether 30%): 0.60. **IR** ν_{max}(film): 1629, 1578, 1520, 1465, 1379, 1241 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 8, ArH), 7.69 (1H, d, *J* = 9, ArH), 7.58 (1H, d, *J* = 8, ArH), 7.48 (1H, ddd, *J* = 8, *J* = 7, *J* = 1, ArH), 7.31 (1H, ddd, *J* = 8, *J* = 7, *J* = 1, ArH), 7.11 (1H, d, *J* = 9, ArH), 5.15 (1H, ddq, *J* = 9, *J* = 7, *J* = 6, OC<u>H</u>CH$_3$), 3.62 (1H, dd, *J* = 15, *J* = 9, C<u>H</u>xHyCH), 3.10 (1H, dd, *J* = 15, *J* = 7, CHx<u>H</u>yCH), 1.57 (3H, d, *J* = 6, OCHC<u>H$_3$</u>) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.00, 131.00, 128.98, 128.87, 128.65, 126.65, 123.83, 122.74, 118.44, 112.20, 80.31, 35.98, 22.22 ppm. *m/z* **GC/MS:** 184 [M+], 169 [M – CH_3], 141 [M – CH_2CHCH_3]. **Accurate Mass:** $C_{13}H_{12}O$ requires 184.0883; found 184.0890.

1–Allyl–3',3'–dideuteronaphthalen–2–ol (211): A mixture of 2–(allyloxy)naphthalene (**112h**, 524 mg, 2.8 mmol) in D_2O (99.9 % D content; 5.5 mL) was heated at 200 °C in a MW reactor. After 1.5 h the deuterated water was exchange and the mixture was heated again in a MW reactor. After 1.5 h the

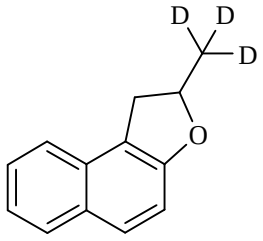
crude product was purified by flash chromatography (SiO_2; petrol : AcOEt; 9 : 1) to afford the deuterated furan **210** (80 mg, 0.50 mmol, 18%) as a colourless oil. Further elution afforded the *title compound* (**211**, 348 mg, 1.8 mmol, 66%) as a colourless oil.

1–Allyl–3',3'–dideuteronaphthalen–2–ol (211):



Colourless oil (> 99.9% D incorporation by ^{1}H NMR). **Rf** (EtOAc/petroleum ether 30%): 0.30. **IR** ν_{max}(film): 3415, 1721, 1625, 1596, 1437, 1391, 1260 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 9, ArH), 7.80 (1H, d, *J* = 8, ArH), 7.69 (1H, d, *J* = 9, ArH), 7.50 (1H, ddd, *J* = 8, *J* = 7, *J* = 1, ArH), 7.36 (1H, ddd, *J* = 8, *J* = 7, *J* = 1, ArH), 7.12 (1H, d, *J* = 9, ArH), 6.08 (1H, broad s, C<u>H</u>CH_2), 5.08 (1H, br s, OH), 3.85 (2H, d, *J* = 6, ArC<u>H</u>$_2$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 151.19, 135.48, 133.20, 129.42, 128.56, 128.33, 126.48, 123.16, 122.97, 117.91, 116.76, 29.17 ppm. **^{2}H NMR** (61.42 MHz, CH_2Cl_2) δ 5.05 ppm. **GC/MS:** 186 [M+], 169 [M – OH], 141 [M – CH_2CHCD_2]. **Accurate Mass:** $C_{13}H_{10}{}^2H_2O$ requires 186.1008; found 186.1010.

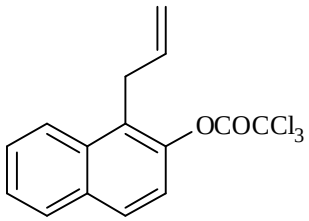
2–(Trideuteromethyl)–1,2–dihydronaphthol[2,1–*b*]furan (210):



Yellow oil. **Rf** (EtOAc/petroleum ether 30%): 0.60. **IR** ν_{max}(film): 1630, 1578, 1520, 1465, 1379, 1241 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 8, ArH), 7.69 (1H, d, *J* = 9, ArH), 7.58 (1H, d, *J* = 8, ArH), 7.48 (1H, ddd, *J* = 8, *J* = 7, *J* = 1, ArH), 7.31 (1H, ddd, *J* = 8, *J* = 7, *J* = 1, ArH), 7.11 (1H, d, *J* = 9, ArH), 5.15 (1H, ddq, *J* = 9, *J* = 7, *J* = 6, OC<u>H</u>CH_3), 3.62 (1H, dd, *J* = 15, *J* = 9,

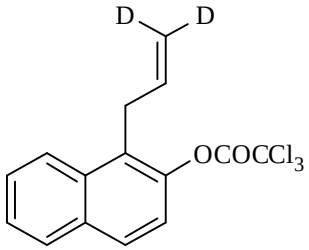
C<u>H</u>xHyCH), 3.10 (1H, dd, *J* = 15, *J* = 7, CHx<u>H</u>yCH) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.97, 130.96, 129.13, 128.89, 128.68, 126.67, 126.56, 122.65, 118.36, 112.12, 80.11, 35.86 ppm.[170] **^{2}H NMR** (61.42 MHz, CH_2Cl_2) δ 1.13 ppm. *m/z* **GC/MS:** 187 [M], 169 [M – CD_3], 141 [M – CH_2CHCD_3]. **Accurate Mass:** $C_{13}H_9{}^2H_2O_1$ requires 187.1076; found 187.1042.

1–Allylnaphthalen 2',2',2'–trichloroacetate (95):



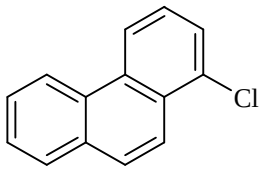
Trichloroacetylchloride (0.19 mL, 1.6 mmol) was added dropwise to a solution of 1–allylnaphthalen–2–ol (**112h**, 250 mg, 1.4 mmol) and Et_3N (0.22 mL, 1.6 mmol) in Et_2O (6 mL) at 0 °C under nitrogen. The reaction mixture was left stirring for 16 h at rt and then quenched by the addition of H_2O (20 mL). The quenched reaction mixture was diluted with Et_2O (15 mL) and the organic layer separated, washed (satd. aq. $NaHCO_3$ 2 × 15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* (**95**, 397 mg, 1.2 mmol, 89%) as a yellow oil. **IR** ν_{max}(film): 1716, 1463, 1164, 1073, 1024 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 (1H, d, *J* = 8, ArH), 7.91 – 7.83 (2H, m, ArH), 7.62 – 7.51 (2H, m, ArH), 7.30 (1H, d, *J* = 7, ArH), 5.99 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, C<u>H</u>CH_2), 5.07 (1H, dt, *J* = 10, *J* = 2, CHC<u>H</u>xHy), 5.07 (1H, dt, *J* = 17, *J* = 2, CHCHx<u>H</u>y), 3.86 (2H, dt, *J* = 6, *J* = 2, Ar<u>C</u>H_2) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.05, 134.82, 132.67, 132.46, 128.73, 128.60, 126.96, 126.36, 126.04, 124.40, 119.67, 116.48, 29.73 ppm.

1–(3,3–Dideuteroallyl)naphthalen–2–yl 2',2',2'–trichloroacetate (209):



Trichloroacetylchloride (0.22 mL, 2.0 mmol) was added dropwise to a solution of naphthol **211** (300 mg, 1.6 mmol) and Et_3N (0.27 mL, 2.0 mmol) in Et_2O (7 mL) at 0 °C under nitrogen. The reaction mixture was left stirring for 16 h at rt and then quenched by the addition of H_2O (20 mL). The quenched reaction mixture was diluted with Et_2O (15 mL) and the organic layer separated, washed (satd. aq. $NaHCO_3$ 2 × 15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* (**209**, 486 mg, 1.4 mmol, 90%) as a yellow oil. **IR** ν_{max}(film): 1716, 1463, 1163, 1073, 1024 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.05 (1H, d, *J* = 8, ArH), 7.90 (1H, d, *J* = 6, ArH), 7.85 (1H, d, *J* = 9, ArH), 7.60 (1H, td, *J* = 6, *J* = 1, ArH), 7.55 (1H, td, *J* = 6, *J* = 1, ArH), 7.30 (1H, d, *J* = 9, ArH), 6.00 (1H, m, C<u>H</u>CD_2), 3.86 (2H, d, *J* = 6, ArC<u>H_2</u>) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.02, 134.61, 132.64, 132.42, 128.73, 128.60, 126.96, 126.0, 124.40, 119.67, 29.65 ppm.[171] **^{2}H NMR** (61.42 MHz, CH_2Cl_2) δ 5.01 ppm.

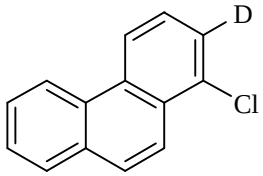
1–Chlorophenanthrene (96):[172]



Was accomplished using procedure D [Trichloroacetate **95** (138 mg, 0.46 mmol) and (IPr)CuCl (**156**, 4.1 mg, 0.008 mmol) in DCE (2 mL)] to afford the *title compound* (**96**, 33 mg, 0.18 mmol, 39%) as a white solid. **Mp:** 119 – 120 ºC (lit.[172] Mp: 120 – 121 ºC). **IR** ν_{max}(film): 1592, 1494, 1440, 1294, 1204, 1110, 1043, 1019 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.68 (1H, d, *J* = 9, ArH), 8.63 (1H, d, *J* = 8, ArH), 8.25 (1H, d, *J* = 9, ArH), 7.93 (1H, d, *J* = 8, ArH), 7.87 (1H,

d, *J* = 9, ArH), 7.71 – 7.64 (3H, m, 3 × ArH), 7.57 (1H, t, *J* = 8, ArH, H–3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 132.67, 131.85, 129.89, 129.29, 128.67, 128.18, 127.14, 127.03, 126.40, 122.92, 122.46, 121.59 ppm. **GC/MS:** 212/213 [M+], 176 [M – Cl]. **Accurate Mass:** $C_{14}H_9{}^{35}Cl$ requires 212.0387; found 212.0380.

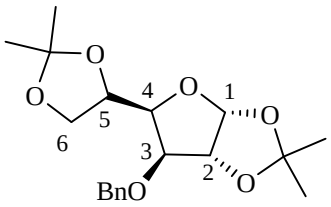
Benzannulation reaction of 1–(3,3–dideuteroallyl)–naphthalene–2–yl 2',2',2'–trichloroacetate (212):



Was accomplished using procedure D [Trichloroacetate **209** (150 mg, 0.45 mmol) and (IPr)CuCl (**156**, 11 mg, 0.02 mmol) in DCE (4 mL)] to afford the *title compound* (**212**, 40 mg, 0.19 mmol, 42%) as a white solid. **Mp:** 120 – 121 ºC. **IR** ν_{max}(film): 1584, 1426, 1367, 1291, 1258, 1104, 1042 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (1H, d, *J* = 8, ArH), 8.62 (1H, d, *J* = 8, ArH), 8.25 (1H, d, *J* = 9, ArH), 7.94 (1H, d, *J* = 8, ArH), 7.87 (1H, d, *J* = 9, ArH), 7.70 (1H, app t, *J* = 7, ArH), 7.66 (1H, d, *J* = 7, ArH) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 132.57, 131.84, 129.89, 129.28, 128.66, 128.17, 127.13, 127.02, 126.60 (t, *J* = 26), 126.28, 122.91, 122.43, 121.58 ppm. **^{2}H NMR** (61.42 MHz, CH_2Cl_2) δ 7.67 ppm. **GC/MS:** 213/214 [M+], 177 [M – Cl]. **Accurate Mass:** $C_{14}H_7{}^2H_2{}^{35}Cl$ requires 212.0372; found 212.0374.

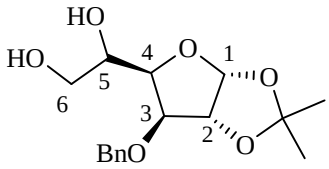
5.1 STUDIES TOWARDS THE SYNTHESIS OF GILVOCARCIN M

3–*O*–Benzyl–1,2:5,6–di–*O*–isopropylidene–α–D–glucofuranose (254):[173]



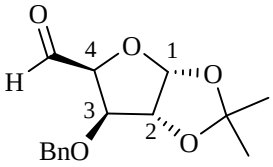
A solution of 1,2:5,6–di–*O*–isopropylidene–α–D–glucofuranose (10.00 g, 38.4 mmol) in dimethylformamide (26 mL) was added dropwise at 0 ºC to a suspension of sodium hydride (1.38 g, 57.6 mmol) in dimethylformamide (26 mL). The resulting mixture was stirred for fifteen minutes at 0 ºC and then it was allowed to warm up to rt and stirred for one hour. Benzyl bromide (5.01 mL, 42.2 mmol) was added dropwise at 0 ºC to this mixture. The resulting reaction mixture was then stirred for 16 h at rt. The mixture was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted using Et_2O (3 × 30 mL). The combined organic extracts were washed with water (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2; eluent (SiO_2; eluent petrol : AcOEt, 9.5 : 0.5) to afford the *title compound* (**254**, 13.41 g, 38.0 mmol, 99%) as a white oil. **$[\alpha]_D$** (c = 11.2 x 10^{-3}, $CHCl_3$) = –9.4 (lit $[\alpha]_D$ (c = 1.06 x 10^{-3}, $CHCl_3$, T = 20 ºC)[173] = –29.8). **Rf** (petrol/AcOEt 30%): 0.53. **IR** ν_{max}(film): 3064, 3032, 1728, 1381, 1371, 11252, 1070, 1020 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 – 7.23 (5H, m, ArH), 5.83 (1H, d, *J* = 4, H–1), 4.70 (1H, d, *J* = 12, CHxHyAr), 4.64 (1H, d, *J* = 12, CHxHyAr), 4.60 (1H, d, *J* = 4, H–2), 4.38 (1H, dt, *J* = 8, *J* = 6, H–5), 4.16 (1H, dd, *J* = 7.5, *J* = 3, H–3), 4.13 (1H, dd, *J* = 7.5, *J* = 6, H–4), 4.04 – 3.99 (2H, m, H–6), 1.50 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.32 (3H, s, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.65, 128.38, 127.81, 127.63, 111.77, 108.96, 105.29, 82.66, 81.70, 81.32, 72.51, 72.38, 67.40, 26.83, 26.77, 26.22, 25.43 ppm. *m/z* ES+: 351 [M+], 108 [M – OBn – $(CH_3)_2C$ – $(CH_3)_2CO_2CH_2CH$]. **Accurate Mass** $C_{19}H_{26}NaO_6$ requires 373.1622; found 373.1618.

3–*O*–Benzyl–1,2–*O*–isopropylidene–*α*–*D*–glucofuranose (255):[174]



Acetic acid (39.5 mL) and water (21.6 mL) were added dropwise at rt to glucofuranose **254** (13.39 g, 20.3 mmol). The resulting reaction mixture was stirred for 20 h at 40 ºC. The mixture was then neutralised with saturated aqueous Na_2CO_3 and extracted using CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed with water (75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2; eluent petroleum ether : EtOAc, 7 : 3) to afford the *title compound* (**255**, 11.85 g, 20.0 mmol, 99%) as a colourless oil. **Rf** (AcOEt): 0.49. **$[\alpha]_D$** (c = 10.5 x 10^{-3}, $CHCl_3$) = –21.0 (lit. $[\alpha]_D$ (c = 1.0 x 10^{-3}, T = 20 ºC, $CHCl_3$)[175] = –39.4). **IR** ν_{max}(film): 3424, 2985, 2935, 1712, 1454, 1374, 1249, 1215, 1018, 1015 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 – 7.31 (5H, m, ArH), 5.93 (1H, d, *J* = 4, H–1), 4.72 (1H, d, *J* = 12, CHxHyAr), 4.62 (1H, d, *J* = 4, H–2), 4.57 (1H, d, *J* = 12, CHxHyAr), 4.13 (1H, m, H–4), 4.13 (1H, s, OH), 4.11 (1H, s, OH), 4.10 (1H, d, *J* = 4 Hz, H–3), 4.05 – 4.02 (1H, m, H–5), 3.81 (1H, dd, *J* = 12, *J* = 3, HxHy–6), 3.69 (1H, dd, *J* = 12, *J* = 6, HxHy–6), 1.49 (3H, s, CH_3), 1.32 (3H, s, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.00, 128.45, 128.14, 127.62, 110.89, 104.90, 81.87, 79.74, 71.90, 69.02, 64.14, 60.17, 26.48, 25.97, 20.78, 13.93 ppm. **Scan ES+:** 333 [M + Na], 328 [M + NH_4^+]. **Accurate Mass** $C_{16}H_{22}NaO_6$ requires 333.1309, found 333.1302.

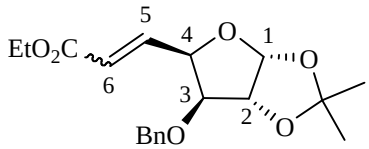
3–*O*–Benzyl–1,2–*O*–isopropylidene–*α*–D–xylo–pentadialdo–1,4–furanose (258):[176]



Diol **255** (11.86 g, 38.2 mmol) was dissolved in dioxane (99 mL) and a solution of sodium metaperiodate (9.80 g, 45.8 mmol) in water (99 mL) was added. The

reaction mixture was stirred for 16 h at rt and then filtered. The filtrate was extracted with CH_2Cl_2 (80 mL). The combined organic fractions were washed with water (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the *title compound* (**258**, 10.55 g, 37.8 mmol, 99%) as a yellow oil. **$[\alpha]_D$** (c = 27.2 x 10^{-3}, EtOH) = –45.4 (lit $[\alpha]_D$ (c = 2.7 x 10^{-3}, $CHCl_3$)[177] = –86.5). **IR** ν_{max}(film): 1719, 1456, 1405, 1200, 1163, 1073, 1001 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.62 (1H, d, *J* = 1.5, CHO), 7.32 – 7.17 (5H, m, ArH), 6.07 (1H, d, *J* = 3, H–1), 4.59 (1H, d, *J* = 3, H–2), 4.56 (1H, d, *J* = 12, CHxHyAr), 4.52 (1H, dd, *J* = 4, *J* = 1.5, H–4), 4.43 (1H, d, *J* = 12, CHxHyAr), 4.28 (1H, d, *J* = 4, H–3), 1.14 (3H, s, CH_3), 1.13 (3H, s, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.88, 136.59, 128.51, 128.13, 127.69, 112.53, 106.17, 84.57, 83.69, 82.16, 72.35, 26.94, 26.31 ppm. *m/z* **EI+**: 278 [M+], 263 [M – O], 249 [M – CO], 174 [M – OBn]. **Accurate Mass** $C_{15}H_{18}O_5Na$ requires 301.1046; found 301.1045.

(*E*,*Z*)–Ethyl 3–*O*–Benzyl–5,6–dideoxy–1,2–*O*–isopropylidene–α–D–xylo–hept–5–enfuranuronate (256 and **257):**[178]



To a solution of the crude aldehyde **258** (10.55 g, 37.9 mmol) in CH_2Cl_2 (200 mL) was added (ethoxycarbonylmethylene)triphenylphosphorane (14.50 g, 41.7 mmol) at rt. After stirring for 16 h the solvent was evaporated and the crude product was purified by column chromatography (silica gel; eluent petroleum ether : EtOAc, 8 : 2) to afford the *title compound* (**256** and **257**, 8.96 g, 25.8 mmol, 68%) as a colourless oil. The elution gave a *cis* and *trans* ester 1 : 4 mixture. **IR** ν_{max}(film): 2985, 2935, 2870, 1716, 1663, 1373, 1259, 1072, 1022 cm^{-1}. **Scan ES+:** 371 [M + Na], 366 [M + NH_4^+], 349 [M+]. **Accurate Mass** $C_{19}H_{25}NaO_6$ requires 371.1465; found 371.1469.

Z–isomer:

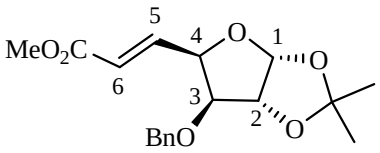
Rf (EtOAc/petroleum ether 20%): 0.45. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.24 (5H, m, ArH), 6.39 (1H, dd, *J* = 12, *J* = 7, H–5), 6.01 (1H, d, *J* = 4, H–1),

5.92 (1H, dd, *J* = 12, *J* = 2, H–6), 5.63 (1H, ddd, *J* = 7, *J* = 3, *J* = 2, H–4), 4.64 (1H, d, *J* = 4, H–2), 4.62 (1H, d, *J* = 13, C<u>H</u>xHyAr), 4.45 (1H, d, *J* = 13, CHx<u>H</u>yAr), 4.28 (1H, d, *J* = 3, H–3), 4.16 – 4.07 (2H, m, $CH_3C\underline{H}_2O$), 1.52 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.26 (3H, t, *J* = 7, $C\underline{H}_3CH_2O$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.50, 145.17, 137.46, 128.37, 127.85, 127.73, 121.19, 111.78, 105.15, 83.79, 83.12, 78.17, 72.18, 60.38, 26.94, 26.42, 14.19 ppm.

E–isomer:

Rf (EtOAc/petroleum ether 20%): 0.43. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 – 7.22 (5H, m, ArH), 6.92 (1H, dd, *J* = 16, *J* = 5, H–5), 6.12 (1H, dd, *J* = 16, *J* = 2, H–6), 5.95 (1H, d, *J* = 4, H–1), 4.75 (1H, ddd, *J* = 5, *J* = 3, *J* = 2, H–4), 4.59 (1H, d, *J* = 4, H–2), 4.58 (1H, d, *J* = 12, C<u>H</u>xHyAr), 4.45 (1H, d, *J* = 12, CHx<u>H</u>yAr), 4.17 (2H, q, *J* = 7, $CH_3C\underline{H}_2O$), 3.93 (1H, d, *J* = 3, H–3), 1.44 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.23 (3H, t, *J* = 7, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.97, 141.39, 137.17, 128.51, 128.05, 127.80, 123.34, 111.94, 105.14, 82.97, 82.84, 79.50, 72.25, 60.42, 26.83, 26.22, 14.21 ppm.

(*E*,*Z*)–Methyl 3–*O*–benzyl–5,6–dideoxy–1,2–*O*–isopropylidene–α–D–xylo–hept–5–enfuranuronate (259 and **260):**[87c]



To a solution of the crude aldehyde **258** (15.55 g, 55.7 mmol) in THF (75 mL) was added methoxycarbonylmethylene)triphenylphosphorane (18.62 g, 55.7 mmol) at rt. After stirring for 16 h the solvent was evaporated and the crude product was purified by column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting from 1 : 0 and progressing to 9 : 1) to afford the (*E*)–methyl ester (9.22 g, 27.5 mmol, 50%) and the (*Z*)–methyl ester (4.75 g, 14.5 mmol, 26%) both as colourless oils (1 : 3 *Z*/*E* crude mixture ratio).

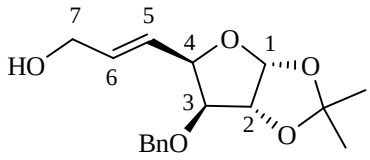
Z–isomer**:**

[α]$_D$ (c = 16.0 x 10^{-3}, $CHCl_3$) = –70.9. **Rf** (EtOAc/petroleum ether 20%): 0.27. **IR** ν_{max}(film): 1721, 1510, 1379, 1213, 1164, 1072, 1018 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 – 7.25 (5H, m, ArH), 6.41 (1H, dd, *J* = 9, *J* = 5, H–5), 6.02 (1H, d, *J* = 3, H–1), 5.94 (1H, dd, *J* = 9, *J* = 1, H–6), 5.65 (1H, ddd, *J* = 5, *J* = 2, *J* = 1, H–4), 4.65 (1H, d, *J* = 3, H–2), 4.62 (1H, d, *J* = 9, CHxHyAr), 4.46 (1H, d, *J* = 9, CHxHyAr), 4.30 (1H, d, *J* = 2, H–3), 4.68 (3H, s, OCH_3), 1.53 (3H, s, CH_3), 1.34 (3H, s, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.85, 145.65, 137.42, 128.31, 127.79, 127.69, 120.59, 111.79, 105.13, 83.77, 83.10, 78.07, 72.13, 51.35, 26.91, 26.41 ppm. **Scan ES+:** 335.0 [M+] (91%), 352.1 [M + NH_4^+] (9%). **Accurate Mass** $C_{18}H_{22}O_6$ requires 335.1489; found 335.1488.

E–isomer:

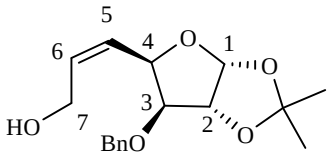
[α]$_D$ (c = 9.9 x 10^{-3}, $CHCl_3$) = –18.2 (lit. $[\alpha]_D$ (c = 1.5 x 10^{-3}, $CHCl_3$)[179] = –165.5). **Rf** (EtOAc/petroleum ether 20%): 0.21. **IR** ν_{max}(film): 1720, 1458, 1383, 1200, 1072, 1002 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.25 (5H, m, ArH), 6.96 (1H, dd, *J* = 12, *J* = 4, H–5), 6.17 (1H, d, *J* = 12, H–6), 5.98 (1H, d, *J* = 3, H–1), 4.78 (1H, broad s, H–4), 4.62 (1H, d, *J* = 3, H–2), 4.60 (1H, d, *J* = 9, CHxHyAr), 4.48 (1H, d, *J* = 9, CHxHyAr), 3.96 (1H, d, *J* = 2, H–3), 3.74 (3H, s, OCH_3), 1.47 (3H, s, CH_3), 1.31 (3H, s, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.35, 141.67, 137.04, 128.44, 127.97, 127.72, 122.74, 111.84, 104.95, 82.86, 82.74, 79.38, 72.16, 51.55, 26.74, 26.13 ppm. **GC/MS:** 334 [M+]. **Accurate Mass** $C_{18}H_{22}O_6$ requires 334.1411; found 334.1417.

(*Z*)–3–*O*–Benzyl–5,6–dideoxy–1,2–*O*–isopropylidene–α–D–xylo–hept–5–enfuranose (275):[181]



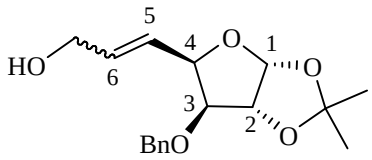
To a cooled solution (–78 ºC) of the (*Z*)–methyl ester **260** (3.27 g, 9.8 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise a 1 M solution of diisobutylaluminium hydride (DIBAL–H) in heptane (24.4 mL, 24.4 mmol) was added dropwise and the mixture was stirred for 2 h at –78 ºC. The excess of hydride was decomposed by the addition of ethyl acetate (3.5 mL) at –78 ºC followed by water (18 mL) at rt. The insoluble material was filtered off by suction and the filtrate dried, concentrated *in vacuo*. The crude product was isolated by column chromatography (SiO_2; eluent petroleum ether : EtOAc, 6 : 4) to afford the *title compound* (**275**, 2.66 g, 8.7 mmol, 89%) as a colourless oil. **Rf** (EtOAc/petroleum ether 50%): 0.16. **$[\alpha]_D$** (c = 12.3 x 10^{-3}, $CHCl_3$) = –27.9 (lit $[\alpha]_D$ (c = 1.22 x 10^{-3}, $CHCl_3$)[181] = –60.9). **IR** ν_{max}(film): 3441, 3031, 2987, 2934, 1384, 1212, 1163, 1071, 1007 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.28 (5H, m, ArH), 6.01 (1H, dt, *J* = 16, *J* = 5, H–6), 5.90 (1H, d, *J* = 4, H–1), 5.82 (1H, dd, *J* = 16, *J* = 7, H–5), 4.65 – 4.63 (3H, m, CHxHyAr + H–2 + H–4), 4.53 (1H, d, *J* = 12, CHxHyAr), 4.16 (2H, d, *J* = 5, 2 × H–7), 3.87 (1H, d, *J* = 3, H–3), 1.50 (3H, s, CH_3), 1.32 (3H, s, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.41, 134.13, 128.44, 127.90, 127.67, 125.52, 111.63, 104.79, 83.41, 82.84, 80.64, 72.19, 62.85, 60.40, 26.77, 26.20, 21.03 ppm. **Scan ES+:** 329 [M + Na] (86%), 324 [M + NH_4^+] (14%). **Accurate Mass:** $C_{17}H_{22}NaO_5$ requires 329.1359; found 329.1373.

(*E*)–3–*O*–Benzyl–5,6–dideoxy–1,2–*O*–isopropylidene–α–D–xylo–hept–5–enfuranose (274):[181]



To a cooled −78 ºC solution of the (*E*)–methyl ester **259** (4.00 g, 12.0 mmol) in dry CH_2Cl_2 (50 mL) a 1 M solution of DIBAL–H in heptane (29.9 mL, 29.9 mmol) was added dropwise and the mixture was stirred for 2 h at −78 ºC. The excess of hydride was decomposed by the addition of ethyl acetate (5 mL) at −78 ºC followed by water (25 mL) at rt. The insoluble material was filtered off by suction and the filtrate dried, concentrated *in vacuo*. The crude product was isolated by column chromatography (SiO_2; eluent petroleum ether : EtOAc, 6 : 4) to afford the *tittle compound* (**274**, 3.46 g, 11.3 mmol, 94%) as a colourless oil. **Rf** (EtOAc/petroleum ether 50%): 0.17. **$[\alpha]_D$** (c = 11.4 x 10^{-3}, $CHCl_3$) = –20.9 (lit $[\alpha]_D$ (c = 1.10 x 10^{-3}, $CHCl_3$)[180] = –92.9). **IR** ν_{max}(film): 3431, 2986, 2932, 2868, 1374, 1213, 1163, 1072, 1015 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 – 7.19 (5H, m, ArH), 5.90 (1H, d, *J* = 4, H–1), 5.84 (1H, broad dd, *J* = 11, *J* = 7, H–6), 5.71 (1H, broad dd, *J* = 11, *J* = 7.5, H–5), 4.87 (1H, broad dd, *J* = 7.5, *J* = 3, H–4), 4.59 (1H, d, *J* = 12, CHxHyAr), 4.56 (1H, d, *J* = 4, H–2), 4.45 (1H, d, *J* = 12, CHxHyAr), 4.20 (2H, ddd, *J* = 13, *J* = 7, *J* = 1, 2 × H–7), 3.78 (1H, d, *J* = 3, H–3), 1.43 (3H, s, CH_3), 1.24 (3H, s, CH_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.51, 134.07, 128.43, 127.86, 127.65, 125.11, 111.57, 104.80, 83.39, 82.91, 80.55, 72.18, 62.90, 26.75, 26.18 ppm. **Scan ES+:** 329 [M + Na], 324 [M + NH_4^+], 307 [M+]. **Accurate Mass:** $C_{17}H_{22}NaO_5$ requires 329.1359; found 329.1366.

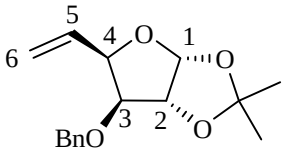
(*Z*/*E*)–3–*O*–Benzyl–5,6–dideoxy–1,2–*O*–isopropylidene–α–D–xylo–hept–5–enfuranose (274 and **275):**[181]



To a cooled solution (−78 ºC) of the (*E*/*Z*)–ethyl ester **256** and **257** (3.87 g, 11.1 mmol) in dry CH_2Cl_2 was added dropwise a 1 M solution diisobutylaluminium hydride (DIBAL–H) in heptane (27.8 mL, 27.8 mmol). The resulting mixture was stirred for 2 h at −78 ºC. The excess of hydride was decomposed by the addition of ethyl acetate (4 mL) at −78 ºC followed by water (20 mL) at rt. The insoluble material was filtered off by suction and the filtrate dried, concentrated *in vacuo*. The crude product was isolated by column chromatography (SiO_2; eluent petroleum ether : EtOAc, 6 : 4) to afford a colourless oil (1.56 g, 9.1 mmol, 82%) as a *cis* : *trans* mixture in a 1 : 4 ratio (NMR data as above). **Scan ES+:** 329 [M + Na], 324 [M + NH_4^+]. **Accurate Mass:** $C_{17}H_{22}NaO_5$ requires 329.1359; found 329.1351.

5.1.1 MODEL STUDIES

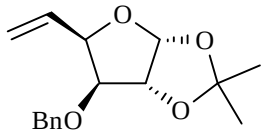
5,6–Dideoxy–1,2–*O*–(1–methylethylidene)–3–*O*–(phenylmethyl)–α–D–ribo–hex–5–enofuranose (263):[181]



Iodine (720.3 mg, 2.8 mmol) was added portionwise to a solution of 3–*O*–benzyl–1,2–*O*–isopropylidene–α–D–glucofuranose (**255**, 400 mg, 1.3 mmol), imidazole (354 mg, 5.2 mmol) and chlorodiphenylphosphine (0.5 mL, 2.8 mmol) in toluene (24 mL) at 80 °C. The reaction mixture was stirred at 100 °C for 1.5 h followed by the addition of Zn powder (844 mg, 12.9 mmol) in one portioin. The reaction was then maintained at a gentle reflux for 1.5 h and then allowed to

cool to ambient temperature. The reaction mixture was diluted by the addition of AcOEt (10 mL) and the organic extracts were washed [NaOH (1 M, 10 mL) and then H_2O (10 mL)], dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by by column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting from 1 : 0 and progressing to 9.5 : 0.5) afforded the *title compound* (**263**, 224 mg, 3.3 mmol, 63%) as colourless oil. **Rf** (petrol/AcOEt 10%): 0.20. **$[\alpha]_D$** (c = 2.08 x 10^{-3}, EtOH) = –59 (lit $[\alpha]_D$ (c = 2.13 x 10^{-3}, T = 20 ^oC, EtOH)[181] = –61). **IR** ν_{max}(film): 2987, 2930, 2863, 1455, 1373, 1214, 1164, 1072, 1024 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 – 7.30 (5H, m, ArH), 6.03 (1H, ddd, *J* = 17, *J* = 10, *J* = 7, H–5), 5.98 (1H, d, *J* = 4, H–1), 5.45 (1H, broad dt, *J* = 17, *J* = 1, HxHy–6), 5.34 (1H, broad dt, *J* = 10, *J* = 1, HxHy–6), 4.66 (1H, d, *J* = 12, CHxHyAr), 4.64 – 4.63 (2H, m, H–4 + H–2), 4.56 (1H, d, *J* = 12, CHxHyAr), 3.89 (1H, d, *J* = 3, H–3), 1.51 (3H, s, CH_3), 1.34 (3H, s, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 137.50, 132.21, 128.42, 127.84, 127.54, 119.11, 111.52, 104.82, 83.34, 82.83, 81.55, 72.05, 26.75, 26.19 ppm. **GC/MS:** 276 [M+], 261 [M – CH_2], 91 [M – OBn – $(O)_2C(CH_3)_2$]. **Accurate Mass:** $C_{16}H_{20}O_4$ requires 276.1356; found 276.1356.

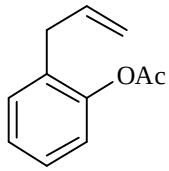
5,6–Dideoxy–1,2–*O*–(1–methylethylidene)–3–*O*–(phenylmethyl)–α–D–ribo–hex–5–enofuranose (263):



Iodine (6.548 g, 25.8 mmol) was added slowly portionwise to a stirred mixture of 3–*O*–benzyl–1,2–*O*–isopropylidene–α–D–glucofuranose (**255**, 2.00 g, 6.4 mmol), imidazole (1.76 g, 25.8 mmol) and triphenylphosphine (6.77 g, 25.8 mmol) in toluene (58 mL) at 50 °C. The mixture was refluxed for 24 h and then allowed to marm to rt. AcOEt (48 mL) and iodine (5.76 g) were added and the mixture then stirred for 15 min at rt. The reaction was quenched by the addition of 5% aqueous solution of NaOH solution (20 mL). The layers were separated and the aqueous layer was extracted with AcOEt (2 × 30 mL). The organic extracts were combined and washed with H_2O (3 × 30 mL), saturated aqueous solution of

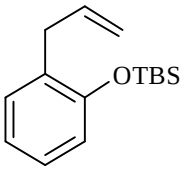
$Na_2S_2O_3$ (2 × 30 mL) and H_2O (2 × 30 mL). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting from 1 : 0 and progressing to 9 : 1) to afford the *title compound* (**263**, 1.71 g, 6.1 mmol, 96%) as colourless oil. (NMR data as above)

2–Allylphenyl acetate (265a):[182]



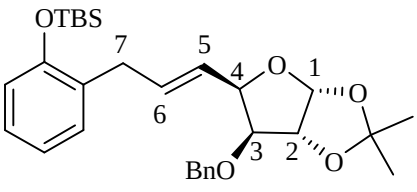
A mixture of 2–allylphenol (0.5 mL, 3.7 mmol) and Ac_2O (0.7 mL, 7.5 mmol) in pyridine (17 mL) was stirred at rt for 2 d under nitrogen. The solvent was removed under *vacuum* and the crude product was purified by column chromatography (SiO_2; eluent petrol) to afford the *title compound* (**265a**, 626 mg, 3.5 mmol, 95%) as a colourless oil. **Rf** (petrol): 0.32. **IR** ν_{max}(film): 3078, 2979, 2915, 1757, 1639, 1487, 1368, 1198, 1169 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49 – 7.38 (3H, m, ArH), 7.26 – 7.24 (1H, m, ArH), 6.12 (1H, ddt, *J* = 18, *J* = 9, *J* = 7, C<u>H</u>CH_2), 5.32 – 5.31 (1H, m, CHC<u>H</u>xHy), 5.28 – 5.25 (1H, m, CHCHx<u>H</u>y), 3.52 (2H, d, *J* = 7, ArC<u>H_2</u>), 2.52 (3H, s, $COCH_3$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.36, 148.98, 135.90, 131.91, 130.40, 127.44, 126.19, 122.39, 116.19, 34.69, 20.94 ppm. **GC/MS:** 176 [M+], 134 [M – CH_2CHCH_2], 119 [M – CH_2CHCH_2 – CH_3], 115 [M – CH_2CHCH_2 – OCH_3], 91 [M – CH_2CHCH_2 – OAc]. **Accurate Mass:** $C_{11}H_{12}O_2$ requires 176.0832; found 176.0837.

(2–Allylphenoxy)(*tert*–butyl)dimethylsilane (265b):[183]



tert–Butyl dimethylsilyl chloride (1.39 g, 9.2 mmol) was added in one portion to a mixture of 2–allylphenol (1.0 mL, 7.7 mmol) and imidazole (626 mg, 9.2 mmol) in acetonitrile (34 mL) under nitrogen. The mixture was stirred for 3 d at rt. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2; eluent petrol) to afford the *title compound* (**265b**, 1.76 g, 7.1 mmol, 92%) as colourless oil. **Rf** (petrol): 0.50. **IR** ν_{max}(film): 2956, 2929, 2896, 2858, 1489, 1452, 917 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (1H, d, *J* = 8, ArH), 7.13 (1H, td, *J* = 8, *J* = 1.5, ArH), 6.94 (1H, t, *J* = 7, ArH), 6.84 (1H, d, *J* = 8, ArH), 6.03 (1H, ddt, *J* = 17, *J* = 9, *J* = 7, C<u>H</u>CH_2), 5.12 – 5.10 (1H, m, CHC<u>H</u>xHy), 5.08 – 5.06 (1H, m, CHC<u>H</u>xHy), 3.42 (2H, broad d, *J* = 7, $ArCH_2$), 1.06 (9H, s, $SiC(CH_3)_3$), 0.29 (6H, s, $Si(CH_3)_2$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.32, 137.04, 130.66, 130.11, 127.02, 121.06, 118.39, 115.43, 34.43, 25.79, 18.24, –4.16 ppm. **GC/MS:** 248/249 [M+], 191/192 [M – $C(CH_3)_3$], 163/164 [M – $C(CH_3)_3$ – 2 × CH_3], 135 [M – TBS], 115 [M – OTBS]. **Accurate Mass:** $C_{15}H_{24}O^{28}Si$ requires 248.1591; found 248.1586.

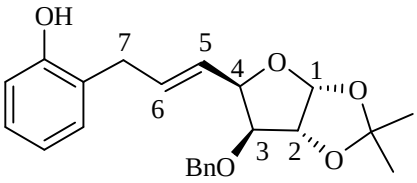
(2–((*E*)–3–((3a*R*,5*R*,6*S*,6a*R*)–6–(benzyloxy)–tetrahydro–2,2–dimethylfuro[2,3–*d*][1,3]dioxol–5–yl)allyl)phenoxy)(*tert*–butyl)dimethylsilane (266b):



A mixture of the vinyl furanose **263** (500 mg, 1.8 mmol), (2–allylphenoxy)(*tert*–butyl)dimethylilane (**265b**, 477 mg, 1.8 mmol) and Grubbs' catalayst 2nd generation (15 mg, 0.02 mmol) in CH_2Cl_2 (6 mL) was brought to reflux for 20 h under nitrogen. The solvent was then removed *in vacuo*

and the residue purified by column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting from 9.5 : 0.5 and progressing to 9 : 1) to afford the *title compound* (**266b**, 391 mg, 0.79 mmol, 44%) as colourless oil. **Rf** (petrol : AcOEt, 7 : 3): 0.30. **IR** ν_{max}(film): 3031, 2954, 2886, 1489, 1452, 1252, 1074, 1023, 975 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.11 – 7.02 (5H, m, ArH), 6.91 (1H, broad d, *J* = 9, ArH), 6.80 – 6.90 (1H, m, ArH), 6.65 (1H, td, *J* = 7.5, *J* = 1, ArH), 6.56 (1H, dd, *J* = 8, *J* = 1, ArH), 6.00 (1H, dt, *J* = 16, *J* = 6, H–6), 5.92 (1H, d, *J* = 4, H–1), 5.71 (1H, broad dd, *J* = 16, *J* = 8, H–5), 4.60 – 4.58 (3H, m, CHxHyAr + H–4 + H–2), 4.50 (1H, d, *J* = 12, CHxHyAr), 3.80 (1H, d, *J* = 3, H–3), 3.44 (1H, dd, *J* = 16, *J* = 6, HxHy–7), 3.42 (1H, dd, *J* = 16, *J* = 6, HxHy–7), 1.27 (3H, s, CH_3), 1.10 (3H, s, CH_3), 0.79 (9H, s, $C(CH_3)_3$), 0.00 (6H, s, $Si(CH_3)_2$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.25, 137.63, 134.43, 130.38, 130.21, 128.39, 127.73, 127.50, 127.10, 125.01, 121.15, 118.49, 111.38, 104.72, 83.46, 82.98, 81.36, 72.05, 32.98, 26.74, 26.20, 25.81, 18.26, 4.11, 4.18 ppm. **Scan ES+:** 519.2 [M + Na] (100%). **Accurate Mass:** $C_{29}H_{40}O_5NaSi$ requires 519.2537; found 519.2537.

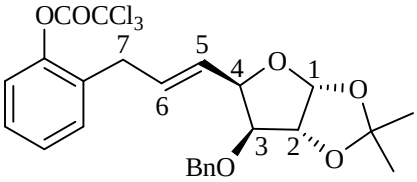
2–((*E*)–3–((3a*R*,5*R*,6*S*,6a*S*)–6–(benzyloxy)–tetrahydro–2,2–dimethylfuro[2,3–*d*][1,3]dioxol–5–yl)allyl)phenol (267):



A mixture of glucofuranose **266b** (391 mg, 0.78 mmol) and potassium hydroxide (66 mg, 1.2 mmol) in EtOH (0.8 mL) was stirred for 16 h at 25 ºC. The solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 (5 mL) and H_2O (5 mL). The layers were separated and the aqueous layer neutralised by the addition of dilute HCl (0.1 M solution) and extracted with CH_2Cl_2 (5 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting from 9 : 1 and progressing to 8 : 2) to afford the *title compound* (**267**, 273 mg, 0.71 mmol, 91%) as yellow solid. **Mp:** 103 – 104 ºC. **IR**

ν_{max}(film): 3446, 2995, 2930, 2901, 2856, 1591, 1502, 1453, 1375, 1246, 1255, 1080 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.28 (5H, m, ArH), 7.15 – 7.10 (2H, m, ArH), 6.88 (1H, dt, *J* = 7, *J* = 1, ArH), 6.79 (1H, d, *J* = 8, ArH), 6.07 (1H, dtd, *J* = 16, *J* = 7, *J* = 1, H–6), 5.95 (1H, d, *J* = 4, H–1), 5.72 (ddt, *J* = 16, *J* = 7, *J* = 1, H–5), 4.97 (1H, broad s, OH), 4.67 – 4.63 (3H, m, H–4 + H–2 + CHxHyAr), 4.52 (1H, d, *J* = 12, CHxHyAr), 3.84 (1H, d, *J* = 4, H–3), 3.47 (1H, dd, *J* = 16, *J* = 6, HxHy–7), 3.45 (1H, dd, *J* = 16, *J* = 6, HxHy–7), 1.50 (3H, s, CH_3), 1.32 (3H, s, CH_3) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 153.91, 137.41, 133.00, 130.53, 128.43, 121.90, 127.84, 127.67, 125.55, 125.33, 120.94, 115.86, 111.49, 104.70, 83.06, 82.74, 80.84, 71.94, 33.60, 26.72, 26.18 ppm. **Scan ES+:** 405 [M + Na], 400 $[M + NH_4]^+$. **Accurate Mass:** $C_{23}H_{26}NaO_5$ requires 405.1680; found 405.1697.

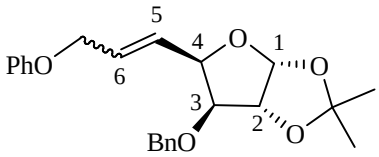
2–((*E*)–3–((3a*R*,5*R*,6*S*,6a*R*)–6–(benzyloxy)–tetrahydro–2,2–dimethylfuro[2,3–*d*][1,3]dioxol–5–yl)allyl)phenyl 2',2',2'–trichloroacetate (268):



Trichloroacetylchloride (0.22 mL, 1.9 mmol) was added dropwise to a solution of phenol **267** (200 mg, 0.52 mmol) and Et_3N (0.26 mL, 1.9 mmol) in Et_2O (6 mL) at 0 °C under nitrogen. The reaction mixture was left to stir for 20 h at r.t and then quenched by the addition of H_2O (3 mL). The quenched reaction mixture was diluted with Et_2O (3 mL) and the layers separated. The organic layer was washed (satd. aq. $NaHCO_3$ 2 × 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2; eluent petrol : AcOEt, 9 : 1) to afford the *title compound* (**268**, 240 mg, 0.44 mmol, 88%) as a yellow oil. **IR** ν_{max}(film): 2987, 2931, 2864, 1774, 1488, 1453, 1373, 1216, 1073, 1022 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 – 7.16 (8H, m, ArH), 7.09 (1H, d, *J* = 8, ArH), 5.96 (1H, dt, *J* = 16, *J* = 7, H–6), 5.91 (1H, d, *J* = 4, H–1), 5.70 (1H, dd, *J* = 16, *J* = 8, H–5), 4.56 – 4.53 (2H, m, H–2 + H–4), 4.54 (1H, d, *J* = 12, ArCHxHy), 4.44 (1H, d, *J* = 12, ArCHxHy), 3.80 (1H, d, *J* = 3, H–3), 3.39 (1H,

dd, *J* = 16, *J* = 7, HxHy–7), 3.37 (1H, dd, *J* = 16, *J* = 7, HxHy–7), 1.42 (3H, s, CH_3), 1.24 (3H, s, CH_3) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.42, 148.44, 137.51, 132.37, 131.45, 130.95, 130.43, 128.44, 128.39, 127.80, 127.79, 127.55, 127.50, 127.42, 126.27, 120.98, 111.47, 104.71, 83.24, 82.79, 80.88, 71.99, 32.42, 26.72, 26.16 ppm.

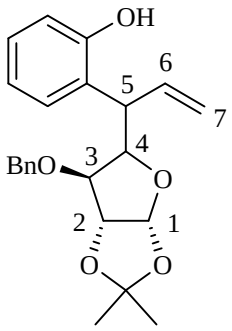
3–*O*–Benzyl–5,6–dideoxy–1,2–*O*–isopropylidene–*α*–D–xylo–hept–5–enfuranosephenyl ether (276):



Phenol (998 mg, 10.6 mmol), furanoses **274** and **275** (3.25 g, 10.6 mmol), triphenylphosphine (2.78 g, 10.6 mmol) and triethylamine (1.50 mL, 10.6 mmol) were stirred in dry THF (31 mL) under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and DIAD (2.1 mL, 10.6 mmol) added dropwise. The resulting solution was allowed to warm up to rt and stirred for 12 h. The reaction was quenched with 5% HCl (4.5 mL) and extracted with Et_2O (3 × 20 mL). The layers were separated and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2; eluent petroleum ether : EtOAc, 6 : 4). The elution gave a mixture of the *cis* and *trans* alkene 1 : 0.80 alkene **276** (1.99 g, 5.2 mmol, 49%) as a colourless oil. **Rf** (EtOAc/petroleum ether 40%): 0.50. **IR** ν_{max}: 2987, 2932, 2914, 2888, 1598, 1497, 1454, 1378, 1074, 1009 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 – 7.11 (12H, m, ArH), 6.88 – 6.78 (7H, m, ArH), 6.73 (1H, m, ArH), 6.07 (1H, dt, *J* = 16, *J* = 5, H_{trans}–6), 5.98 (1H, broad dd, *J* = 11, *J* = 6, H_{cis}–6), 5.91 (1H, d, *J* = 4, H_{cis}–1), 5.86 (1H, d, *J* = 4, H_{trans}–1), 5.95 (1H, dtd, *J* = 16, *J* = 6, *J* = 1, H_{trans}–5), 5.88 (1H, ddt, *J* = 11, *J* = 7, *J* = 1, H_{cis}–5), 4.99 (1H, dd, *J* = 7, *J* = 3, H_{cis}–4), 4.68 (1H, dd, *J* = 6, *J* = 3, H_{trans}–4), 4.63 – 4.54 (8H, m, 4 × H–7 + 2 × H–2 + CH_2Ar), 4.50 (1H, d, *J* = 12, OCHxHyAr), 4.48 (1H, d, *J* = 12, OCHxHyAr), 3.88 (1H, d, *J* = 3, H_{cis}–3), 3.86 (1H, d, *J* = 3, H_{trans}–3), 1.48 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.31 (6H, s, 2 × CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$)

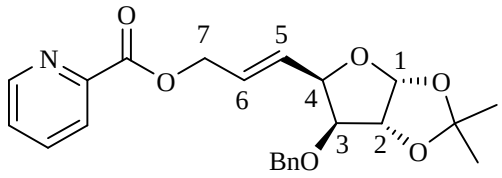
δ 158.42, 158.22, 155.75, 137.34, 137.31, 129.78, 129.55, 129.52, 129.42, 129.39, 128.39, 128.38, 127.84, 127.82, 127.60, 127.05, 126.89, 120.87, 120.79, 120.37, 115.25, 114.63, 114.62, 111.58, 111.56, 104.76, 104.73, 83.31, 83.13, 82.84, 82.78, 80.48, 76.54, 72.09, 67.43, 64.28, 26.73, 26.69, 26.14, 26.10 ppm. **Scan ES+:** 405 [M + Na] (100%). **Accurate Mass:** $C_{23}H_{26}NaO_5$ requires 405.1672; found 405.1673.

2–(1–((3a*R*,6*S*,6a*R*)–6–Benxyloxy)–2,2–dimethyltetrahydrofuro[2,3–*d*][1,3]dioxol–5–yl)allyl)phenol (272):



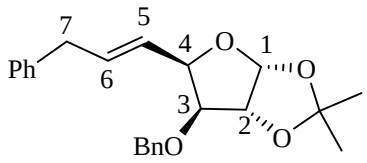
Allyl ether **276** (50 mg, 0.13 mmol) was heated in diphenylether (75 mL) at 220 °C under nitrogen for 16 h in a MW reactor. The crude product was purified by column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting from 1 : 0 and progressing to 9 : 1) to afford the *title compound* (**272**, 3.9 mg, 0.01 mmol, 8%) as a yellow oil. **Rf** (petrol/AcOEt 30%): 0.29. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 – 7.29 (5H, m, ArH), 7.16 – 7.12 (2H, m, ArH), 6.92 – 6.88 (2H, m, ArH), 6.25 (1H, ddd, *J* = 17, *J* = 10.5, *J* = 6, H–6), 6.00 (1H, d, *J* = 4, H–1), 5.88 (1H, broad s, OH), 5.19 (1H, dt, *J* = 9, *J* = 1, HxHy–7) 5.14 (1H, dt, *J* = 17, *J* = 1, HxHy–7), 4.59 (1H, d, *J* = 4, H–2), 4.56 (1H, dd, *J* = 10, *J* = 3, H–4), 4.50 (1H, d, *J* = 11, ArCHxHy), 4.28 (1H, d, *J* = 11, ArCHxHy), 3.95 (1H, dd, *J* = 10, *J* = 6, H–5), 3.61 (1H, d, *J* = 3, H–3), 1.52 (3H, s, CH_3), 1.31 (3H, s, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.53, 137.87, 129.49, 128.54, 128.20, 128.16, 127.95, 126.37, 121.03, 117.38, 116.47, 111.64, 105.03, 82.44, 82.28, 81.39, 77.22, 71.82, 42.15, 30.93, 26.76, 26.24 ppm.

(*E*)–3–((3a*R*,5*R*,6*S*,6a*R*)–6(Benxyloxy)2,2–dimethyltetrahydrofuro[2,3–*d*][1,3]dioxol–5–yl)allyl picolinate (283):



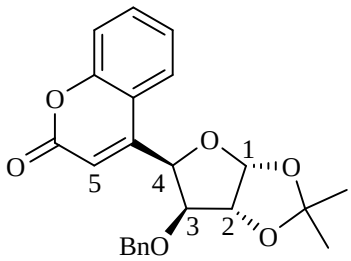
DMAP (794 mg, 6.5 mmol) and DCC (990 mg, 8.5 mmol) were added to a suspension of picolinic acid (960 mg, 7.8 mmol) in CH_2Cl_2 (10 mL) under nitrogen. After 20 min at rt, furanose **275** (2.00 g, 6.5 mmol) in CH_2Cl_2 (10 mL) was added at 0 °C under nitrogen. The reaction was left to stir at rt for 8 h. Petrol (20 mL) was added to the reaction mixture, which was then filtered through Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting from 7 : 3 and progressing to 2.5 : 7.5) to afford the *title compound* (**283**, 1.73 g, 4.2 mmol, 65%) as a yellow oil. **Rf** (petrol/AcOEt 80%): 0.41. **$[\alpha]_D$** (c = 10.3 x 10^{-3}, $CHCl_3$) = –20.2. **IR** ν_{max}(film): 2986, 2933, 2867, 1718, 1583, 1454, 1374, 1304, 1243, 1071 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.75 (1H, dq, *J* = 5, *J* = 1, ArH), 8.10 (1H, d, *J* = 8, ArH), 7.81 (1H, td, *J* = 8, *J* = 2, ArH), 7.47 (1H, ddd, *J* = 8, *J* = 5, *J* = 1, ArH), 7.40 – 7.24 (4H, m, ArH), 6.12 (1H, dt, *J* = 16, *J* = 6, H–6), 5.98 (1H, dd, *J* = 16, *J* = 6, H–5), 5.95 (1H, d, *J* = 4, H–1), 4.97 (1H, dd, *J* = 16, *J* = 6, HxHy–7), 4.92 (1H, dd, *J* = 16, *J* = 6, HxHy–7), 4.61 (1H, dd, *J* = 7, *J* = 3, H–4), 4.56 (1H, d, *J* = 12, OCHxHyAr), 4.56 (1H, d, *J* = 4, H–2), 4.44 (1H, d, *J* = 12, OCHxHyAr), 3.87 (1H, d, *J* = 3, H–3), 1.48 (3H, s, CH_3), 1.30 (3H, s, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.71, 149.88, 147.85, 137.33, 136.96, 128.94, 128.38, 128.18, 127.81, 127.56, 126.91, 125.17, 111.60, 104.78, 83.11, 82.78, 80.26, 72.09, 65.41, 26.71, 26.16 ppm. **Scan ES+:** 412.0 [M+] (100%). **Accurate Mass:** $C_{23}H_{26}NO_6$ requires 412.1755; found 412.1744.

3a*R*,5*R*,6*S*,6a*R*)–6–(Benzyloxy)–2,2–dimethyl–5–((*E*)–3–phenylprop–1–enyl) tretahydrofuro[2,3–*d*][1,3]dioxole (284):



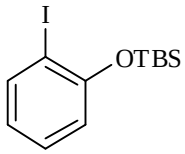
To an ice cold suspension of CuBr·DMS (22 mg, 0.36 mmol) in THF (12 mL) was added 1M solution of phenylmagnesium bromide in THF (0.72 mL, 0.72 mmol) under nitrogen. After 30 mins of stirring the resulting mixture was cooled to –60 °C and picolinate **283** (150 mg, 0.36 mmol) in THF (4 mL) was added dropwise. It was allowed to warm up to –40 °C and left to stir for 1.5 h. The reaction was quenched by the addition of a saturated solution of NH_4Cl (2 mL) and diluted with petroleum ether (5 mL). The layers were separated and the aqueous layer extracted with petrol (2 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$) and the solvent concentrate *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting with 9.5 : 0.5 and progressing to 7 : 3) to afford the *title compound* (**284**, 132 mg, 0.20 mmol, 56%) as a yellow oil. **Rf** (petrol/AcOEt 80%): 0.41. **$[\alpha]_D$** (c = 11.2 x 10^{-3}, $CHCl_3$) = –6.6. **IR** ν_{max}(film): 3030, 2987, 2934, 1723, 1601, 1585, 1452, 1375, 1070, 1016 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.16 (10H, m, ArH), 6.00 (1H, dt, *J* = 15, *J* = 7, H–6), 5.93 (1H, d, *J* = 4, H–1), 5.71 (1H, ddt, *J* = 15, *J* = 8, *J* = 1.5, H–5), 4.65 – 4.61 (3H, m, OCHxHyAr + H–4 + H–3), 4.50 (1H, d, *J* = 12, OCHxHyAr), 3.81 (1H, d, *J* = 3, H–3), 3.42 (2H, d, *J* = 6, 2 × H–7), 1.47 (3H, s, CH_3), 1.30 (3H, s, CH_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.59, 137.57, 134.65, 128.68, 128.42, 128.40, 127.77, 127.50, 126.12, 125.22, 111.41, 104.72, 83.38, 82.90, 81.14, 72.00, 38.81, 26.73, 26.19 ppm. **GC/MS:** 366 [M+], 275 [M – CH_2Ph]. **Accurate Mass:** $C_{23}H_{26}O_4$ requires 366.1826; found 366.1828.

4–((3a*R*,5*R*,6*S*,6a*R*)–6–(Benzyloxy)–tetrahydro–2,2–dimethylfuro[2,3–*d*][1,3]dioxol–5–yl)–2*H*–chromen–2–one (287):



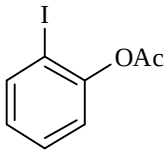
A mixture of TBAB (3.39 g, 10.2 mmol), Et_3N (1.4 mL, 10.2 mmol), palladium acetate (67 mg, 0.3 mmol), and the (*E*,*Z*)–methyl ester (**259** and **260**, 1.00 g, 3.0 mmol) in acetonitrile (22 mL) was refluxed under nitrogen for 20 h. The crude mixture was filtered through Celite® and the solvent was concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting from 9 : 1 and progressing to 7 : 3) to afford the *title compound* (**287**, 476 mg, 1.2 mmol, 40%) as a yellow solid. **Rf** (petrol/AcOEt 30%): 0.10. **Mp:** 86 – 87 ºC. **$[\alpha]_D$** (c = 9.9 x 10^{-3}, $CHCl_3$) = –58.0. **IR** ν_{max}(film): 2986, 2933, 2871, 1722, 1606, 1450, 1375, 1074, 1021 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 (1H, dt, *J* = 7, *J* = 1, ArH), 7.28 (1H, dt, *J* = 8, *J* = 1, ArH), 7.22 (1H, dt, *J* = 8, *J* = 1, ArH), 7.05 (1H, dt, *J* = 8, *J* = 1, ArH), 7.03 – 6.94 (4H, m, 3 × ArH), 6.74 (1H, d, *J* = 7, ArH), 6.70 (1H, d, *J* = 1, H–5), 6.06 (1H, d, *J* = 4, H–1), 5.40 (1H, dd, *J* = 3, *J* = 1, H–4), 4.67 (1H, d, *J* = 4, H–2), 4.35 (1H, d, *J* = 12, OCHxHyAr), 4.21 (1H, d, *J* = 3, H–3), 4.11 (1H, d, *J* = 12, OCHxHyAr), 1.50 (3H, s, CH_3), 1.32 (3H, s, CH_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.45, 153.45, 149.03, 136.10, 131.41, 128.19, 127.92, 127.58, 124.11, 122.84, 117.37, 114.51, 112.27, 104.54, 82.76, 81.72, 77.67, 71.97, 26.90, 26.18 ppm. **GC/MS:** 394 [M+], 266 [M – CO_2CH – Ph], 175 [M – CO_2CH – Ph – $OC(CH_3)_2CO$)]. **Accurate Mass:** $C_{23}H_{22}O_6$ requires 394.1411; found 394.1403. **Anal. Calcd for $C_{23}H_{22}O_6$:** requires C: 70.04, H: 5.90%. Found: C: 69.83, H: 5.90%.

***tert*–Butyl(2–iodophenoxy)dimethylsilane (291)**:[184]



TBSCl (822 mg, 5.5 mmol) was added in one portion to a solution of 2–iodophenol (1.00 g, 4.5 mmol) and imidazole (374 mg, 5.5 mmol) in acetonitrile (20 mL) under nitrogen. The mixture was stirred for 3 days at rt. The solvent was concentrated *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; eluent petrol : AcOEt, 9 : 1) to afford the *title compound* (**291**, 1.43 g, 4.3 mmol, 96%) as a yellow oil. **Rf** (petrol/AcOEt 20%): 0.67. **IR** ν_{max}(film): 2954, 2928, 2886, 2857, 1280, 1469, 1286, 1253, 1019, 914 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 (1H, dd, *J* = 8, *J* = 2, ArH), 7.20 (1H, td, *J* = 8, *J* = 1.5, ArH), 6.83 (1H, dd, *J* = 8, *J* = 1.5, ArH), 6.69 (1H, td, *J* = 8, *J* = 1.5, ArH), 1.07 (9H, s, $C(C\underline{H}_3)_3$, 0.29 (6H, s, 2 × CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.15, 139.55, 129.20, 122.71, 118.52, 90.53, 25.85, 18.36, –4.02 ppm. **GC/MS:** 334/335 [M+], 277/278 [M – CCH_3], 150 [M – I – CCH_3], 135 [M – I – $C(CH_3)_3$ – CH_3]. **Accurate Mass:** $C_{12}H_{19}IO^{28}Si$ requires 334.0244; found 334.0248.

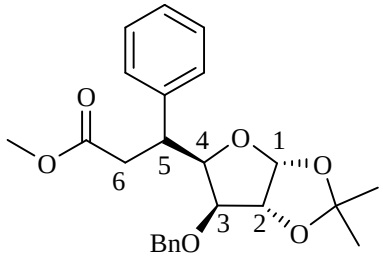
2–Iodophenyl acetate (290):[185]



A mixture of 2–iodophenol (1.00 g, 4.5 mmol) and acetic anhydride (0.8 mL, 9 mmol) in pyridine (20 mL) was stirred for 20 h at rt. The solvent was concentrated *in vacuo* and the crude product was purified by flash column chromatography (SiO_2; eluent, petrol : EtOAc 9 : 1) to afford the *title compound* (**290**, 1.08 g, 4.1 mmol, 92%) as a yellow oil. **Rf** (petrol/AcOEt 20%): 0.35. **IR** ν_{max}(film): 3063, 2930, 1850, 1766, 1464, 1366, 1183, 1043, 1017 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.72 (1H, d, *J* = 8, ArH), 7.27 (1H, app t, *J* = 8, ArH), 7.00 (1H, d, *J* = 8, ArH), 6.69 (1H, app t, *J* = 8, ArH), 2.26 (3H, s, CH_3) ppm. **^{13}C NMR** (75 MHz,

$CDCl_3$) δ 168.42, 151.08, 139.27, 129.33, 127.52, 122.93, 90.47, 21.12 ppm. **GC/MS:** 262 [M+], 220 [M – $COCH_3$]. **Accurate Mass:** $C_8H_7IO_2$ requires 261.9485; found 261.9491.

(*R*)–Methyl 3–((3a*R*,5*R*,6*R*,6a*R*)–6–(benzyloxy)–2,2–dimethyltetrahydrofuro [2,3–*d*][1,3]dioxol–5–yl)–3–phenylpropanoate (294):



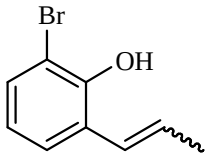
MgBrPh (0.60 mL, 0.60 mmol) was added to a mixture of CuI (85.7 mg, 0.45 mmol) in THF (4.3 mL) at –78 °C and under nitrogen. The mixture was stirred for 45 min at –78 °C. A solution of the methyl ester **260** (100 mg, 0.30 mmol) in THF (4.3 mL) was added dropwise at –78 °C. The mixture was stirred for 45 min before it was allowed to warm up to rt. The reaction mixture was left to stir a further 32 h at rt. The reaction was quenched by addition of a solution of satd. NH_4OH and satd. NH_4Cl (1 : 9, 13 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The organic extracts were combined and dried ($MgSO_4$) and the solvent concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting from 1 : 0 and progressing to 6 : 4) to afford the *title compound* (**294**, 62 mg, 0.15 mmol, 50%) as a yellow oil. **Rf** (petrol/AcOEt 40%): 0.44. **IR** ν_{max}(film): 3080, 3011, 1709, 1603, 1511, 1398, 1354, 1123 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 – 7.15 (10H, m, ArH), 5.88 (1H, d, *J* = 4, H–1), 4.44 (1H, d, *J* = 4, H–2), 4.32 (1H, d, *J* = 11, ArC<u>H</u>xHy), 4.28 (1H, dd, *J* = 11, *J* = 3, H–4), 4.02 (1H, d, *J* = 11, ArCHx<u>H</u>y), 4.62 (1H, dt, *J* = 11, *J* = 4, H–5), 3.43 (3H, s, $CO_2C\underline{H}_3$), 3.35 (1H, d, *J* = 3, H–3), 3.03 (1H, dd, *J* = 16, *J* = 4, <u>H</u>xHy–6), 2.61 (1H, dd, *J* = 16, *J* = 4, Hx<u>H</u>y–6), 1.45 (3H, s, CH_3), 1.23 (3H, s, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.53, 140.24, 137.28, 128.41, 128.40, 128.19, 127.79, 127.68, 126.99, 111.41, 105.00, 83.31, 81.85, 81.51, 71.95, 51.38, 40.79,

38.72, 26.72, 26.11 ppm. **Scan ES+:** 435 [M + Na] (100%). **Accurate Mass:** $C_{24}H_{29}O_6$ requires 413.1959; found 413.1953.

6. STUDY OF THE FORMATION OF COUMARINS THROUGH ATRC REACTIONS

6.1 SYNTHESIS OF THE ACETATES

(*E*/*Z*)–2–Bromo–6–(prop–1–enyl)phenol (312):



A mixture of 2–allyl–6–bromophenol (**123b**, 3.00 g, 14.0 mmol) and NaO^tBu (5.41 g, 56.3 mmol) in THF (20 mL) was refluxed for 24 h under nitrogen. The reaction was quenched with diluted HCl (1.0 M) until acidic pH. The layers were separated and the aqueous layer extracted with Et_2O (3 × 25 mL). The organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2; eluent petrol : AcOEt; gradient elution starting from 1 : 0 and progressing to 9 : 1) to afford the *title compound* (**312**, 2.53 g, 11.8 mmol, 84%) as a yellow oil. Two inseparable isomers were obtained in a ratio 4.4 : 1 *E*/*Z*. **Rf** (petrol/AcOEt 10%): 0.48. **IR** ν_{max}(film): 3501, 3069, 3038, 2962, 2911, 1651, 1594, 1441, 1328, 1240, 1204, 969 cm^{-1}.

E–isomer

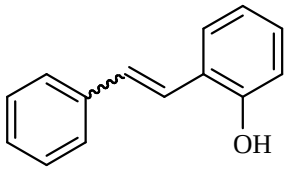
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8, ArH), 6.77 (1H, t, *J* = 8, ArH), 6.70 (1H, dd, *J* = 16, *J* = 2, ArC<u>H</u>), 6.30 (1H, dq, *J* = 16, *J* = 7, C<u>H</u>CH_3), 5.69 (1H, s, OH), 1.94 (3H, dd, *J* = 7, *J* = 2, CHC<u>H</u>$_3$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 148.72, 129.87, 128.13, 126.10, 125.12, 121.37, 129.87, 110.90, 18.85 ppm.

Z–isomer

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (1H, dd, *J* = 8, *J* = 1.5, ArH), 7.18 (1H, d, *J* = 8, ArH), 6.81 (1H, t, *J* = 8, ArH), 6.70 (1H, d, *J* = 12, ArC<u>H</u>), 6.30 (1H, dq, *J* =

12, *J* = 7, C<u>H</u>CH$_3$), 5.62 (1H, s, OH), 1.83 (3H, dd, *J* = 7, *J* = 2, CHC<u>H</u>$_3$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 149.49, 130.59, 129.34, 126.32, 124.15, 120.90, 128.13, 110.22, 14.58 ppm.

2–Styrylphenol (322):[186]



A solution of DBU (0.63 mL, 4.3 mmol), salicylaldehyde (0.43 mL, 4.1 mmol) and benzyltriphenylphosphonium chloride (1.59 g, 4.1 mmol) in CH_3CN (10 mL) was refluxed for 12 h under nitrogen. The reaction was allowed to cool and the solvent removed. The crude product was diluted in Et_2O (30 mL) and washed with H_2O (30 mL), 1.0 M HCl (30 mL) and brine (30 mL). The layers were separated and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude was purified by flash chromatography column (eluent petrol to petrol–AcOEt 20%) to afford inseparable *Z*/*E* mixture (1 : 16 ratio respectively) of the *title compound* (**322**, 540 mg, 2.8 mmol, 69%) as a white solid. **Mp:** 138 ºC (*E*–isomer lit.[187] Mp = 139 – 140 ºC). **IR** ν_{max}(film): 3526, 1584, 1497, 1454, 1331, 1087 cm^{-1}. **GC/MS:** 196 [M+]. **Accurate mass:** $C_{14}H_{12}O$ requires 196.0883; found 196.0887.

Z–isomer

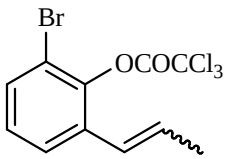
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 – 6.89 (2H, m, ArC<u>H</u>CH + ArH), 6.61 (1H, d, J = 12, ArCHC<u>H</u>) ppm.

E–isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (2H, d, *J* = 7, ArH), 7.44 (1H, d, *J* = 7, ArH), 7.41 – 7.39 (3H, m, 2 × ArH + ArC<u>H</u>CH), 7.31 (1H, tt, *J* = 7, *J* = 1, ArH), 7.17 (1H, d, *J* = 17, ArCHC<u>H</u>), 7.20 (1H, td, *J* = 7, *J* = 1, ArH), 7.01 (1H, tt, *J* = 7, *J* = 0.5, ArH), 6.85 (1H, dd, *J* = 8, *J* = 1, ArH), 5.93 (1H, s, OH) ppm. **^{13}C NMR**

(100 MHz, $CDCl_3$) δ 152.91, 137.51, 130.11, 128.63, 127.60, 127.18, 126.51, 124.63, 122.91, 121.14, 115.89 ppm.

(*E*/*Z*)–2–Bromo–6–(prop–1–enyl)phenyl 2',2',2'–trichloroacetate (311):



Followed general procedure C1 [(*E*/*Z*)–2–bromo–6–(prop–1–enyl)phenol (**312**, 1.40 g, 6.5 mmol), trichloroacetylchloride (1.0 mL, 7.8 mmol) and Et_3N (1.1 mL, 7.8 mmol) in Et_2O (60 mL)] to afford a 5 : 1 *E* and *Z* mixture of trichloroacetate (**311**, 2.18 g, 6.0 mmol, 92%) as a yellow oil.

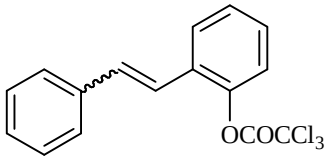
E–isomer

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (1H, d, *J* = 8, ArH), 7.50 (1H, d, *J* = 8, ArH), 7.17 (1H, t, *J* = 8, ArH), 6.48 (1H, dd, *J* = 16, *J* = 1, ArC<u>H</u>), 6.34 (1H, dq, *J* = 16, *J* = 6.5, C<u>H</u>CH_3), 1.94 (3H, dd, *J* = 6.5, *J* = 1, CHC<u>H</u>$_3$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.89, 144.07, 132.76, 131.49, 131.29, 129.69, 128.17, 125.79, 122.76, 116.02, 18.82 ppm.

Z–isomer

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (1H, dd, *J* = 8, *J* = 2, ArH), 7.34 (1H, dd, *J* = 8, *J* = 1, ArH), 7.22 (1H, t, *J* = 8, ArH), 6.39 (1H, m, ArC<u>H</u>), 6.01 (1H, dq, *J* = 11, *J* = 7, C<u>H</u>CH_3), 1.82 (3H, dd, *J* = 7, *J* = 2, CHC<u>H</u>$_3$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.77, 145.07, 132.37, 131.84, 131.32, 129.69, 127.81, 125.79, 122.45, 115.80, 14.40 ppm.

(*E*/*Z*)–2–Styrylphenyl 2',2',2'–trichloroacetate (323):

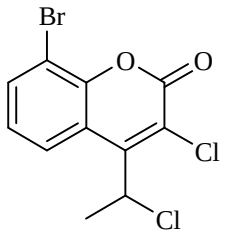


Followed general procedure C1 [2–styrylphenol (**322**, 700 mg, 3.6 mmol), trichloroacetylchloride (0.5 mL, 4.3 mmol) and Et_3N (0.6 mL, 4.3 mmol) in Et_2O (10 mL)] to afford an inseparable *cis*/*trans* mixture (1 : 5 ratio) of the *title compound* (**323**, 856 mg, 3.1 mmol, 87%) as a colourless oil. **IR** ν_{max}(film): 3028, 2980, 2934, 2590, 1941, 1751, 1601, 1586, 1498, 1454, 1330, 1251, 1091, 967, 846, 757 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.66 – 7.69 (19H, m, ArH), 7.26 (1H, d, *J* = 16, *cis* ArC<u>H</u>CH), 6.62 (1H, d, *J* = 12, *cis* ArC<u>H</u>CH), 6.43 (1H, d, *J* = 12, *cis* ArCHC<u>H</u>) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.28, 147.72, 136.74, 133.39, 132.01, 130.91, 130.48, 129.86, 129.00, 128.69, 128.78, 128.58, 128.23, 128.20, 127.56, 127.42, 126.96, 126.73, 126.70, 122.89, 121.44, 121.17, 120.35 ppm.

6.2 ATRC REACTIONS

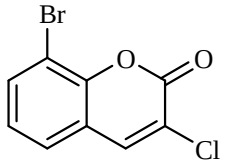
Benzannulation reaction of 2–bromo–6–(prop–1–enyl)phenyl 2',2',2'–tri chloroacetate (311): Followed general procedure E [Trichloroacetate **311** (250 mg, 0.70 mmol) and (IPr)CuCl (**156**, 15 mg, 0.04) in DCE (6 mL)]. The crude product was purified by flash column chromatography (SiO_2; eluent petrol–AcOEt gradient from 1 : 0 to 1 : 9) to afford an orange solid as an inseparable mixture of two products 8–bromo–3–chloro–4–(1–chloroethyl)–2*H*–chromen–2–one (**313**, 93 mg, 0.22 mmol, 31%) and 8–bromo–3–chloro–2*H*–chromen–2–one (**324**, 37.1 mg, 0.09 mmol, 13%) in a 1 : 0.4 ratio. **Rf** (petrol/AcOEt 20%): 0.24.

8–Bromo–3–chloro–4–(1–chloroethyl)–2*H*–chromen–2–one (313):



Mp: 102 ºC. **IR** ν_{max}(film): 1746, 1596, 1541, 1430, 1346, 1250, 1110, 1079, 1033 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.27 (1H, d, *J* = 8, ArH), 7.80 (1H, dd, *J* = 8, *J* = 1, ArH), 7.25 (1H, t, *J* = 8, ArH), 5.92 (1H, q, *J* = 7, C<u>H</u>ClCH$_3$), 2.01 (3H, d, *J* = 7, CHClC<u>H</u>$_3$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.41, 148.61, 147.64, 135.43, 125.49, 124.95, 121.44, 117.57, 111.14, 52.02, 23.07 ppm. *m/z* **EI+:** 320/322/323/324 [M+], 284/286/287 [M – Cl], 255/257/259 [M – CH_3CHCl], 205/207 [M – Br – Cl], 149 [M – CH_3CHCl – Br – Cl]. **Accurate Mass:** $C_{11}H_7{}^{79}Br^{35}Cl_2O_2$ requires 319.9001; found 319.9000.

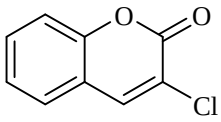
8–Bromo–3–chloro–2*H*–chromen–2–one (324):



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (1H, s, ClCC<u>H</u>), 7.89 (1H, dd, *J* = 8, *J* = 1.3, ArH), 7.51 (1H, dd, *J* = 8, *J* = 1.5, ArH), 7.30 (1H, t, *J* = 8, ArH) ppm. *m/z* **EI+:** 255/257/259 [M+], 229/232 [M – Cl], 169/167 [M – Br], 123 [M – Br – Cl – CO]. **Accurate Mass:** $C_9H_4{}^{79}Br^{35}ClO_2$ requires 257.9078; found 257.9081.

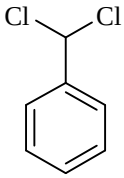
Benzannulation reaction of (*E*/*Z*)–2–styrylphenyl 2',2',2'–trichloroacetate (323): Trichloroacetate **323** (500 mg, 1.4 mmol) and (IPr)CuCl (**156**, 29 mg, 5 mol%) in diglyme (1 mL) were refluxed for 7 h. The crude product purified by flash column chromatography (eluent petrol to petrol–AcOEt 90%) to afford coumarin **312** (207 mg, 0.57 mmol, 41%) and α,α–dichlorotoluene (**326**, 62 mg, 0.72 mmol, 52%).

3–Chlorocoumarin (312):[188]



Brown solid. **Rf** (petrol/EtOAc 30%): 0.50. **Mp:** 113 ºC (lit.[189] Mp = 121 ºC). **IR** ν_{max}(film): 1732, 1610, 1447, 1348, 1277, 1249, 1161, 1142, 993, 750 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89 (1H, s, H–4), 7.57 (1H, td, *J* = 7, *J* = 1.5, ArH), 7.48 (1H, dd, *J* = 1.5, *J* = 8, ArH), 7.37 (1H, d, *J* = 8, ArH), 7.35 (1H, td, *J* = 7, *J* = 1, ArH) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.96, 152.38, 139.80, 131.61, 128.71, 125.94, 124.79, 118.77, 116.43 ppm. *m/z* **EI+:** 180/182 [M], 152/154 [M – CO]. **Accurate Mass** $C_9H_5O_2{}^{35}Cl$ requires: 179.9973; found: 179.9970.

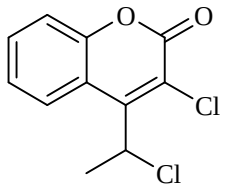
α,α–Dichlorotoluene (326):[190]



Yellow oil. **Rf** (petrol/EtOAc 30%): 0.80. **IR** ν_{max}(film): 3066, 3034, 1645, 1454, 1377, 1334, 1249, 1210 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (2H, dd, *J* = 8, *J* = 2, ArH), 7.46 – 7.40 (3H, m, 3 × ArH), 6.74 (1H, s, $CHCl_2$) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.34, 129.90, 128.74, 126.07, 71.76 ppm. *m/z* **EI+:** 160/162/164 [M], 125/127 [M – Cl], 89 [M – 2 × Cl]. **Accurate Mass** $C_7H_6{}^{35}Cl_2$ requires: 159.9841; found: 159.9837.

Benzannulation reaction of (*E*/*Z*)–2–styrylphenyl 2',2',2'–trichloroacetate (316): Trichloroacetate **316** (250 mg, 0.89 mmol) and (IPr)CuCl (**156**, 22 mg, 0.04) in diglyme (5 mL) was refluxed for 4 h. The crude product was purified by flash column chromatography (eluent petrol to petrol–AcOEt 90%) to afford 3–chloro–4–(1–chloroethyl)–2*H*–chromen–2–one (**314**, 115 mg, 0.47 mmol, 53%) as a yellow solid.

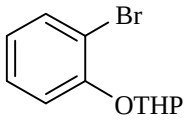
3–Chloro–4–(1–chloroethyl)–2*H*–chromen–2–one (314):



Mp: 102 ºC. **IR** ν_{max}(film): 1734, 1598, 1608, 1446, 1348, 1281, 1243, 1193, 1139, 1080, 1003, 955, 758 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.30 (1H, d, *J* = 8, ArH), 7.58 (1H, td, *J* = 8, *J* = 1, ArH), 7.40 (1H, d, *J* = 8, ArH), 7.37 (1H, dt, *J* = 8, *J* = 1, ArH), 5.93 (1H, q, *J* = 7, ClC<u>H</u>CH_3), 2.03 (1H, d, *J* = 7, ClCHC<u>H</u>$_3$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.47, 151.94, 148.07, 131.83, 126.26, 124.37, 120.37, 117.67, 116.23, 52.17, 23.13 ppm. **GC/MS:** 246/244/242 [M+], 209/207 [M – Cl], 181/179 [M – CH_3CHCl], 144 [M – CH_3CHCl – Cl]. **Accurate Mass:** $C_{11}H_8{}^{35}Cl_2O_2$ requires 241.9896; found 241.9894.

6.3 MECHANISTIC STUDIES

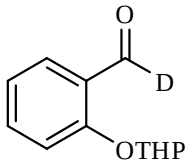
2–(2–Bromophenoxy)–tetrahydro–2*H*–pyran (337):[191]



Trifluoroacetic acid (10.0 μl, 1.8 mmol) was added dropwise to a solution of 2–bromophenol (4.2 mL, 39.8 mmol) in DHP (4.0 mL, 43.8 mmol) at 0 ºC under nitrogen. The mixture was stirred at 0 ºC for 1 h and 4 h at rt. The crude mixture was washed with brine and the layers separated. The organic layer was dried (K_2CO_3) and the crude product was distilled over K_2CO_3 under reduced pressure giving the *title compound* (**337**, 7.25 g, 28.2 mmol, 71%) as a colourless oil. **IR** ν_{max}(film): 2946, 2876, 1587, 1477, 1356, 1275, 1239, 1202, 112, 1029, 957 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (1H, d, *J* = 8, ArH), 7.32 (1H, app t, *J* = 7, ArH), 7.25 (1H, d, *J* = 8, ArH), 6.96 (1H, app t, *J* = 7, ArH), 5.62 (1H, app s, OC<u>H</u>CH_2), 4.01 (1H, td, *J* = 11, *J* = 3, OC<u>H</u>xHy), 3.70 (1H, app d, *J* = 11, OCHx<u>H</u>y), 1.29 (6H, m, CHC<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.36, 133.16, 128.27, 122.67, 116.57, 113.08, 96.61, 61.69, 30.66, 25.20, 18.28

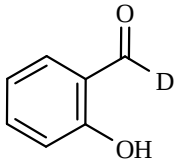
ppm. *m/z* **EI+:** 257/256 [M+], 172 [M – Br]. **Accurate Mass:** $C_{11}H_{13}{}^{79}BrO_2$ requires 256.0093; found 256.0086.

2–α–Deutero–9–tetrahydropyran–2–yloxy)benzaldehyde (338):



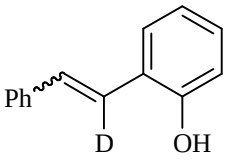
^{n}BuLi (7.09 mL of a 1.6 M solution in hexane, 11.3 mmol) was added dropwise to a solution of 2–(2–bromophenoxy)tetrahydropyrane (**337**, 2.92 g, 7.8 mmol) in Et_2O (14 mL) at 0 ºC under nitrogen. After stirring at 0 ºC for 2 h a solution of DMF–d_7 (1.00 g, 12.5 mmol) in Et_2O (2 mL) was added dropwise and the resulting mixture was stirred at rt for 3 h. The reaction was quenched with H_2O (7 mL), the layers separated and the aqueous extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the *title compound* (**338**, 2.00 g, 6.7 mmol, 86%) as a colourless oil. **IR** ν_{max}(film): 3075, 3040, 2946, 2873, 2125, 2053, 1668, 1600, 1480, 1456, 1358, 1287, 1235, 1235, 1162, 1037, 956 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 (1H, dd, *J* = 8, *J* = 2, ArH), 7.54 (1H, td, *J* = 7, *J* = 2, ArH), 7.25 (1H, d, *J* = 9, ArH), 7.54 (1H, td, *J* = 8, *J* = 1, ArH), 5.59 (1H, m, OC<u>H</u>CH_2), 6.37 (1H, td, *J* = 11, *J* = 3, OC<u>H</u>xHy), 6.37 (1H, m, OCHx<u>H</u>y), 2.01 – 1.91 (3H, m), 1.77 – 1.62 (1H, m) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.52, 135.83, 128.03, 121.52, 115.42, 96.42, 62.09, 30.09, 25.00, 18.47 ppm. **^{2}H NMR** (300 MHz, CH_2Cl_2) δ 10.53 ppm. **Scan ES+:** 207 [M+], 121 [M – THP]. **Accurate Mass:** $C_{12}H_{13}{}^{2}HO_3$ requires 207.1000; found 207.0994.

α–Deutero–2–hydroybenzaldehyde (336):[192]



Benzaldehyde (**338**, 1.90 g, 9.2 mmol), was dissolved in THF (4 mL) and 1 M aqueous HCl solution (12 mL) was added. After stirring for 16 h at rt, the layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash chromatography column (SiO_2; eluent petrol/Et_2O; gradient from 1 : 0.04 progressing to 1 : 0.064) to afford the *title compound* (**336**, 519 mg, 4.2 mmol, 46%) as a colourless oil. **IR** ν_{max}(film): 3180, 3061, 2956, 2128, 1644, 1579, 1486, 1459, 1353, 1282, 1245, 1208, 1154, 1040, 870 cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.87 (1H, s, OH), 7.37 – 7.30 (2H, m, H–6 + H–4), 6.85 – 6.78 (2H, m, H–2 + H–5) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 196.15 (t, *J* = 27, COD), 161.54, 136.84, 133.56, 120.99, 119.64, 117.45 ppm. **GC/MS:** 123 [M+], 104 [M – OH], 93 [M – COD], 76 [M – COD – OH]. **Accurate Mass:** $C_7H_5{}^2HO$ requires 123.0425; found 123.0429.

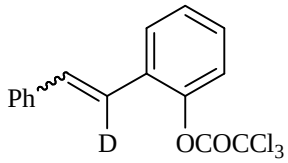
2–[(*E*/*Z*)–1–Deutero–2–phenylvinyl]phenol (334):[193]



A solution of DBU (0.62 mL, 4.2 mmol), α–deutero–2–hydroybenzaldehyde (**336**, 464 mg, 3.9 mol) and benzyltriphenylphosphonium chloride (1.48 g, 3.8 mmol) was refluxed for 12 h under nitrogen. The solvent was evaporated and the crude mixture was purified by flash chromatography column (SiO_2; eluent petrol : AcOEt, 8 : 2) to afford an inseparable *Z*/*E* mixture (1 : 3 ratio) of the *title compound* (**334**, 402 mg, 2.1 mmol, 54%) as a yellow oil. **IR** ν_{max}(film): 3366, 2928, 1646, 1486, 1454, 1282, 1207, 756 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 – 7.17 (14H, m, 14 × ArH), 7.18 – 7.16 (1H, broad s, *trans* C<u>H</u>CD), 7.00 (1H, td, *J* = 8, *J* = 1, *trans* ArH), 6.94 (1H, td, *J* = 9, *J* = 1, *cis* ArH), 6.91 (1H,

dd, *J* = 8, *J* = 1, *cis* ArH), 6.85 (1H, dd, *J* = 8, *J* = 1, *trans* ArH), 6.83 – 6.81 (1H, broad s, *cis* CHCD), 5.07 (1H, s, OH) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.94 (*trans*), 152.29 (*cis*), 137.55 (*trans*), 132.85, 129.98 (*trans*), 129.68 (*cis*), 129.08 (*cis*), 128.63 (*trans*), 128.43, 128.07 (*cis*), 127.58 (*trans*), 127.17, 126.52 (*trans*), 124.58 (*cis*), 123.69 (*cis*), 122.67 (t, *J* = 23, *trans*), 121.14 (*trans*), 120.67 (*cis*), 115.90(*trans*), 115.75 (*cis*) ppm.

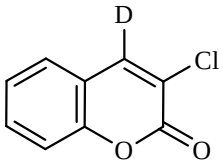
(*E*/*Z*)–1–Deutero–2–styrylphenyl 2',2',2'–trichloroacetate (330):



It was followed procedure C1 [2–[(*E*/*Z*)–1–deutero–2–phenylvinyl]phenol (**334**, 379 mg, 1.9 mmol), trichloroacetyl chloride (0.27 mL, 2.3 mmol), and triethylamine (0.31 mL, 2.3 mmol) in Et_2O (6 mL)] to afford (*E*/*Z*)–1–deutero–2–styrylphenyl 2',2',2'–trichloroacetate in a *Z*/*E* 1 : 4 ratio (**330**, 626 mg, 1.8 mmol, 96%) as a yellow oil. **IR** ν_{max}(film): 1776, 1484, 1452, 1215, 1171, 1105, 824 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.18 (20H, m, 18 × ArH + 2 × ArCH) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.28, 148.24 (*cis*), 147.72 (*trans*), 136.73 (*trans*), 136.11 (*cis*), 133.24 (*cis*), 131.88 (*trans*), 130.88, 130.35, 129.77, 129.00 (*cis*), 128.78 (*trans*), 128.69 (*cis*), 128.57 (*trans*), 128.22, 128.19, 127.53 (*cis*), 127.41 (*trans*), 126.97 (*cis*), 126.67 (*trans*), 121.43 (*trans*), 121.15 (*cis*), 120.06 (t, *J* = 24, CD, *trans*) ppm.

Benzannulation reaction of (*E*/*Z*)–1–deutero–2–styrylphenyl 2',2',2'–trichloroacetate (330): It was followed procedure E [2–[(*E*/*Z*)–1–deutero–2–phenylvinyl]phenol (**330**, 250 mg, 0.74 mmol), (IPr)CuCl (**156**, 20 mg, 0.04 mmol) and DCE (5 mL)] to afford coumarin **334** (95 mg, 0.45 mmol. 61%) as a off–white solid.

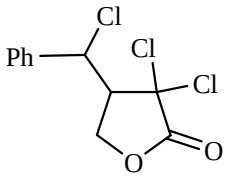
3–Chloro–2*H*–chromen–2–one–d–1 (334):



Mp: 56 ºC. **IR** ν_{max}(film): 1718, 1606, 1448, 1308, 1274, 1041, 1014, 750 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (1H, td, *J* = 7, *J* = 1, ArH), 7.48 (1H, dd, *J* =7, *J* = 1, ArH), 7.38 (1H, d, *J* = 8, ArH), 7.33 (1H, ddd, *J* = 8, *J* = 7, *J* = 1, ArH) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.29, 152.68, 139.73 (t, *J* = 25, C̲D), 131.87, 127.19, 125.03, 122.24, 118.72, 116.76 ppm. **^{2}H NMR** (61.42 MHz, CH_2Cl_2) δ 7.96 ppm. **GC/MS:** 183/181 [M+], 155/153 [M – CO], 125 [M – CO – Cl], 90 [M – OCOC(Cl)CD]. **Accurate Mass:** $C_9H_4{}^{2}HO_2{}^{35}Cl$ requires 181.0035; found 181.0028.

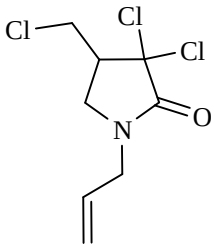
7. OTHER ATRC REACTIONS

4–Benzyl–3,3–dichloro–dihydrofuran–2(3*H*)–one (340):[194]



A solution of cinnamyl 2,2,2–trichloroacetate (**339**, 500 mg, 1.8 mmol) and (IPr)CuCl (**156**, 46 mg, 0.09 mmol) in DCE (6 mL) was heated in a microwave reactor at 110 ºC under nitrogen for 5 h. Upon cooling to ambient temperature the solvent was removed *in vacuo* and the crude product purified by flash column chromatography (SiO_2; eluent petrol : AcOEt, 9 : 1) to afford the *title compound* (**340**, 313 mg, 1.1 mmol, 63%) as a white solid. **Rf** (petrol/AcOEt 10%): 0.38. **Mp:** 67 ºC. **IR** ν_{max}(film): 1801, 1456, 1377, 1255, 1184, 1083, 1057, 1021, 967, 703 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (2H, m, ArH), 7.42 (3H, m, ArH), 5.27 (1H, d, *J* = 10, ArC<u>H</u>Cl), 4.79 (1H, dd, *J* = 10, *J* = 7, OC<u>H</u>xHy), 4.31 (1H, t, *J* = 10, OCHx<u>H</u>y), 3.64 (1H, dt, *J* = 12, *J* = 7, $CH_2C\underline{H}$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.49, 136.56, 129.64, 128.75, 127.98, 78.44, 68.76, 59.96, 57.22 ppm.

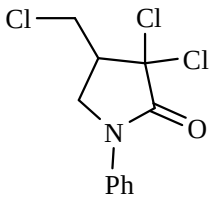
3,3–Dichloro–4–(chloromethyl)–1–allylpyrrolidin–2–one (342):[195]



A solution of *N*–allyl 2,2,2–trichloro–*N*–allylacetamide (**341**, 500 mg, 2.2 mmol) and (IPr)CuCl (**156**, 54 mg, 0.11 mmol) in DCE (6 mL) was heated in a microwave reactor at 110 ºC under nitrogen for 3 h. Upon cooling to rt the solvent was removed *in vacuo* and the crude product purified by flash column chromatography (SiO_2; eluent petrol : AcOEt, 9 : 1) to afford a the *title compound* (**342**, 399 mg, 1.8 mmol, 80%) as a colourless oil. **Rf** (petrol/AcOEt 10%): 0.41.

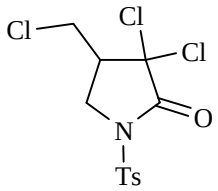
IR ν_{max}(film): 3085, 3016, 2924, 1731, 1680, 1484, 1417, 1272, 1197, 1051, 992, 955 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.73 (1H, ddt, *J* = 17, *J* = 10, *J* = 6, $NCH_2C\underline{H}CH_2$), 5.31 – 5.25 (2H, m, $NCH_2CHC\underline{H_2}$), 4.03 – 3.98 (3H, m, $NC\underline{H}xHy$ and $CCl_2CHC\underline{H_2}N$), 3.74 (1H, dd, *J* = 11, *J* = 10, $NCHx\underline{H}y$), 3.59 (1H, dd, *J* = 10, *J* = 7, $C\underline{H}xHyCl$), 3.22 (1H, dd, *J* = 10, *J* = 8, $CHx\underline{H}yCl$), 3.11 (1H, dddd, *J* = 10, *J* = 8, *J* = 7, *J* = 4, $CHCCl_2$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 165.44, 159.96, 130.22, 119.39, 83.54, 51.32, 46.09, 40.86 ppm. **GC/MS:** 241/242/243/244 [M+], 206/207/208 [M – Cl], 109/110/111/112 [M – allyl group]. **Accurate Mass:** $C_8H_{10}{}^{35}Cl_3NO$ requires 240.9822; found 240.9826.

3,3–Dichloro–4–(chloromethyl)–1–phenylpyrrolidin–2–one (344):[196]



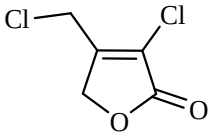
A solution of *N*–allyl 2,2,2–trichloro–*N*–phenyl acetamide (**343**, 500 mg, 1.9 mmol) and (IPr)CuCl (**156**, 46 mg, 0.09 mmol) in DCE (6 mL) was heated in a microwave reactor at 110 ºC under nitrogen for 3 h. Upon cooling to ambient temperature the solvent was removed *in vacuo* and the crude product purified by flash column chromatography (SiO_2; eluent petrol : AcOEt, 9 : 1) to afford the *title compound* (**344**, 409 mg, 1.6 mmol, 82%) as a white solid. **Rf** (petrol/AcOEt 10%): 0.24. **Mp:** 37 ºC. **IR** ν_{max}(film): 1706, 192, 1494, 1407, 1357, 1302, 1233, 815, 759 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 8, ArH), 7.35 (2H, app t, *J* = 8, ArH), 7.18 (1H, t, *J* = 8, ArH), 4.00 (2H, dd, *J* = 11, *J* = 4, $ClC\underline{H_2}CH$), 3.77 (1H, app t, *J* = 11, $NC\underline{H}xHyCH$), 3.66 (1H, app t, *J* = 10, $NC\underline{H}xHyCH$), 3.17 (1H, m, $ClCH_2C\underline{H}$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 164.40, 137.90, 129.27, 126.24, 120.27, 84.06, 51.08, 49.09, 40.99 ppm. *m/z* **EI+:** 277/279/281 [M+], 170 [M – 3 × Cl], 158 [M – 2 × Cl – CH_2Cl]. **Accurate Mass:** $C_{11}H_9{}^{35}Cl_3NO$ requires 275.9744; found 275.9751.

3,3–Dichloro–4–(chloromethyl)–1–tosylpyrrolidin–2–one (346):[197]



A solution of *N*–tosyl 2,2,2–trichloro–*N*–allylacetamide (**345**, 255 mg, 0.75 mmol) and (IPr)CuCl (**156**, 18 mg, 0.04 mmol) in DCE (6 mL) was heated in a microwave reactor at 110 ºC under nitrogen for 3 h. Upon cooling to ambient temperature the solvent was removed *in vacuo* and the crude product purified by flash column chromatography (SiO_2; eluent petrol : AcOEt, 9 : 1) to afford the *title compound* (**346**, 176 mg, 0.52 mmol, 69%) as a white solid. **Mp:** 155 ºC (lit.[198] Mp = 260 ºC). **IR** ν_{max}(film): 1756, 1595, 1371, 1247, 1173, 1133, 1189, 1089, 986 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (2H, d, *J* = 8, ArH), 7.39 (2H, d, *J* = 8, ArH), 4.26 (1H, dd, *J* = 10, *J* = 7, NCHxHy), 3.94 (1H, dd, *J* = 11, *J* = 4, ClCHxHy), 3.67 (1H, dd, *J* = 11, *J* = 10, ClCHxHy), 3.57 (1H, dd, *J* = 10, *J* = 9, NCHxHy), 3.08 (1H, dddd, *J* = 10, *J* = 9, *J* = 7, *J* = 4, H–4), 2.47 (3H, s, OCH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.04, 146.44, 133.32, 131.17, 128.29, 82.64, 50.67, 47.46, 40.17, 21.82 ppm.

3–Chloro–4–(chloromethyl) furan–2(5*H*)–one (348):[199]



A solution of 1,1,1–trichloropent–4–en–2–one (**347**, 500 mg, 2.5 mmol) and (IPr)CuCl (**156**, 60 mg, 0.12 mmol) in DCE (6 mL) was heated in a microwave reactor at 110 ºC under nitrogen for 16 h. Upon cooling to ambient temperature the solvent was removed *in vacuo* and the crude product purified by flash column chromatography (SiO_2; eluent petrol : AcOEt, 9 : 1) to afford the *title compound* (**348**, 87 mg, 0.53 mmol, 21%) as a yellow oil. **Rf** (petrol/AcOEt 10%): 0.41. **IR** ν_{max}(film): 2966, 2928, 1766, 1474, 1380, 1182, 1018 cm^{-1}. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.93 (2H, s, OCH_2), 4.40 (2H, s, $ClCH_2$) ppm. **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.41, 153.11, 121.78, 70.16, 35.48 ppm.[198]

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47- 8–Allyl coumarin **^{1}H NMR** (300 MHz, acetone–d_6) δ 9.53 (1H, s, OH), 8.25 (1H, s, 4–H), 7.37 (1H, d, *J* = 8, 5–H), 6.92 (1H, d, *J* = 8.5, 6–H), 6.77 (1H, d, *J* = 2, 8–H), 5.95 (1H, ddt, *J* = 17, *J* = 10.5, *J* = 6, $CHCH_2$), 5.01 (1H, *J* = 17, *J* = 1, CHCHxHy), 4.94 (1H, br d, *J* = 10, CHCHxHy), 3.52 (1H, d, *J* = 6, $ArCH_2$) ppm.

48- 1,1,1–Trichloro–4–(diethylamino)but–3–en–2–one **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.73 (1H, d, *J* = 12, COCH=CH), 5.58 (1H, d, *J* = 12, COCH=CH), 3.35 (2H, q, *J* = 7, CH_2CH_3), 3.28 (2H, q, *J* = 7, CH_2CH_3), 1.22 (3H, t, *J* = 7, CH_2CH_3), 1.18 (3H, t, *J* = 7, CH_2CH_3) ppm.

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67- **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.39 (2H, s, CH_2Br) ppm. **^{13}C NMR** (125.75 MHz, $CDCl_3$) δ 21.52 ppm.

68- **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.47 (1H, t, *J* = 5, 2–H), 2.86 (2H, t, *J* = 8, 4–H_2), 2.39 (2H, dt, *J* = 8, *J* = 5, 3–H_2) ppm.

69- THF was added to a flask containing IPr.HCl (**153**), CuBr and Na^{t}OBu under N_2. The mixture was stirred for 20 h at rt.

70- **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.55 (1H, d, *J* = 8.5, 9–H), 8.02 (1H, s, 5–H), 7.75 (1H, d, *J* = 9, 4–H), 7.62 (1H, d, *J* = 8, 7–H), 7.57 (1H, apt t, *J* = 8, 8–H), 7.02 (1H, s, OH), 6.56 (1H, d, *J* = 9, 3–H) ppm.

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121- The inseparable mixture contains: **1–Chloronaphthalene (92) ^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (1H, d, *J* = 8.5, ArH), 7.90 (1H, d, *J* = 8, ArH), 7.80 (1H, d, *J* = 8, ArH), 7.67 – 7.57 (3H, m, ArH) ppm.

(*Z*)–3,3–dichloro–4–methylbenzo[*b*]oxepin–2(3*H*)–one (330) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.32 (1H, d, *J* = 8, ArH), 7.38 (1H, td, *J* = 8, ArH), 7.31 (1H, td, *J* = 8, ArH), 7.29 (1H, m, ArH), 5.15 (1H, s, H–5), 2.13 (3H, s, CH_3) ppm.

3,3,5–Trichloro–4,5–dihydro–4–methylbenzo[*b*]oxepin–2(3*H*)–one (329) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.85 (1H, d, *J* = 9, H–5), 3.04 (1H, qd, *J* = 9, *J* = 7, H–4), 1.61 (3H, *J* = 7, $CHCH_3$) ppm.

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