UNIVERSITY OF SOUTHAMPTON

Radical Additions to Arenes:

Cyclisations, Rearrangements and Applications To Natural Product Synthesis

BY

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ABSTRACT

FACULTY OF SCIENCE

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The work described in this thesis concerns the intramolecular addition of an aryl radical to an arene tethered by differing linkages.

Exposure of 2-iodoaryl benzyl ethers to tributyltin hydride and AIBN resulted in the formation of an aryl-aryl bond. Attack of the aryl radical occurred in a 5-*exo*-trig manner with a subsequent fragmentation and concomitant rearomatisation. A suitably placed radical acceptor or hydrogen atom donor was found to bias the reaction pathway.

2-Iodostilbenes were subjected to tributyltin-mediated radical forming conditions with cyclisation occurring *via* a 6-*exo*/*endo*-trig pathway to give the corresponding phenanthrenes in good to excellent yield. 2-Iododihydrostilbenes gave poorer results with a mixture of dihydrophenathrene and direct reduction products observed. Mechanistic details of the reaction are also discussed.

The methodology has been applied to the synthesis of [5]helicenes by an iterative radical cyclisation approach. Tandem radical cyclisations are described providing a three step synthesis of [5]helicenes.

Application of the methodology towards the synthesis of the macrocyclic biarylheptanoid acerogenin E is detailed. The first total synthesis of toddaquinoline is also described.

Preliminary work on the use of tributyltin hydride in combination with tetrabutylammonium fluoride for the reduction of aryl halides is illustrated.

Contents

Preface

The research described in this thesis was carried out under the supervision of Dr. D. C. Harrowven at the University of Southampton between October 1999 and October 2002. No part of this thesis has previously been submitted for a degree.

Acknowledgements

My biggest thanks go to Dr. David Harrowven for giving me the opportunity to explore the wild and unpredictable world of organic chemistry in general and the area of radical chemistry in particular. Thanks also for the neverending ideas and support and for completing not insignificant quantities of proof-reading.

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Special thanks go to Stuart, Heather, Tim, Jim and Neil for proof-reading – your efforts are very much appreciated.

I also wish to thank the rest of my friends in Southampton especially Martyn, Steve, Nigel, Phil and Jim for putting up with living in the same house as me for a number of years.

Thanks to all in SUSO for seven years of playing in a fantastic orchestra and for helping to keep me (relatively!) sane.

Last but by no means least, I want to thank all my family. Thanks to Mum and Dad for supporting me in everything I do and for always being there for me. Thanks to Chris for being the best brother (and friend) that anyone could wish for. Thanks to my grandparents for great times together both past and present.

Abbreviations

ABCN, VAZO	1,1'-azobis(cyclohexanecarbonitrile)
Ac	acetyl
AIBN	azobisisobutyronitrile
app.	apparent
Ar	aryl
aq.	aqueous
Bn	benzyl
br.	broad
Bu	*n*-butyl
^{t}Bu	*tert*-butyl
18-c-6	18-crown-6
Celite	Celite 521®
c-hex, Cy	cyclohexane
CHN	combustion analysis
CI	chemical ionisation
COSY	correlation spectroscopy
d	doublet
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBP	dibenzoyl peroxide
DCE	1,2-dichloroethane
DCM	dichloromethane
DEPT	Distortionless Enhancement through Polarisation Transfer
DHP	3,4-dihydro-2*H*-pyran
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide

DMSO	dimethylsulfoxide
DPDC	diisopropylperoxydicarbonate
dppp	diphenylpropylphosphine
d.r.	diastereomeric ratio
DTBP	di-*tert*-butylperoxide
EDG	electron-donating group
EI	electron ionisation, electron impact
ES	electrospray
Et	ethyl
ether	diethyl ether
EWG	electron-withdrawing group
Expt.	experiment
FT	Fourier Transform
GC	gas chromatography
GOESY	gradient n.*O*.e. spectroscopy
h	hour(s)
HMBC	heteronuclear multiple bond connectivity
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrometry
hν	visible and ultraviolet radiation
Hz	hertz
IR	infrared
jmod	spin-modulated
LDA	lithium diisopropylamide
lit.	literature
LRMS	low resolution mass spectrometry
LTMP	lithium 1,1,6,6-tetramethylpiperamide

m	medium, multiplet
m	*meta*
M	mol dm^{-3}
Me	methyl
Mes	mesitylenesulfonyl
min	minute(s)
MP	melting point
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance spectroscopy
no.	number
n.*O*.e	nuclear Offenhauser effect
o	*ortho*
obs.	obscured
p	*para*
PCC	pyridinium chlorochromate
petrol	petroleum ether (40/60)
Ph	phenyl
PMHS	polymethylhydrosiloxane
ppm	parts per million
^{i}Pr	isopropyl
PPTS	pyridinium *p*-toluenesulfonate
pyr	pyridine
q	quartet
RSM	recovered starting material
r.t.	room temperature
r.t.p.	room temperature pressure

rxn	reaction
s	strong, singlet
sat.	saturated
SET	single-electron transfer
sext.	sextet
t	triplet
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
tol	toluene
Ts	*p*-toluenesulfonyl
TS	thermospray
UV	ultraviolet
VAZO, ABCN	1,1'-azobis(cyclohexanecarbonitrile)
v/v	volume for volume
w	weak
w.r.t.	with respect to
w/v	weight for volume
w/w	weight for weight

Chapter 1 - Intramolecular Additions of Carbon-Centred Radicals to Arenes

1 Intramolecular Additions of Carbon – Centred Radicals to Arenes

1.1 Introduction

1.1.1 Scope

This review provides a summary of work investigating the intramolecular additions of carbon – centred radicals to an aromatic ring. Work will be classified by the chain used to tether the aromatic radical acceptor and the carbon-centred radical donor. Addition of non-carbon centred radicals to aromatics and the addition of radicals to heteroaromatics are outside the scope of this review

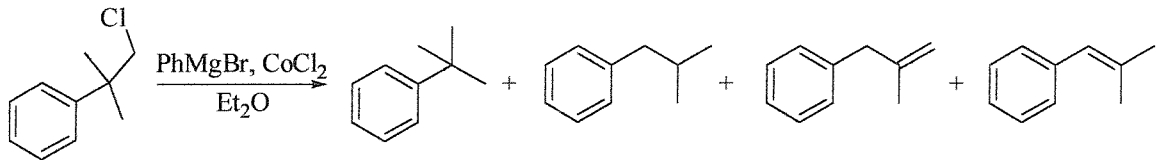
1.1.2 Background

The first report of the addition of a carbon-centred radical to an arene was made by Wieland in 1911.[1] Since then a multitude of examples have been reported. Nitrogen, oxygen, phosphorus, sulfur, silicon and tin have been utilised in a tether between a carbon-centred radical and an arene.

1.2 Intramolecular Additions of Carbon – Centred Radicals to Aromatic Rings

1.2.1 Tethering Chains Containing Carbon

To date, scant work has been carried out using a carbon tether to conjoin a carbon-centred radical to an aromatic ring. An important discovery by Urry *et al.* in 1944 pioneered this area of radical chemistry. Urry exposed an ether solution of neophyl chloride (2-methyl-2-phenylpropyl chloride) to phenylmagnesium bromide in the presence of cobalt(II) chloride. This led to homolytic cleavage of the carbon-chlorine bond to give a neophyl radical. The resulting reaction yielded a range of products (Scheme 1.1).[2]

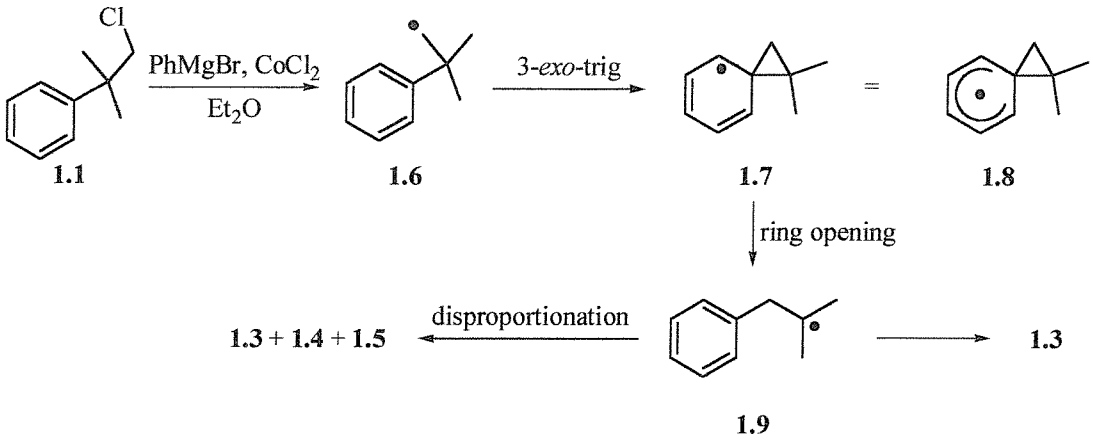


1.1 **1.2**, 27 % **1.3**, 15 % **1.4**, 9 % **1.5**, 4 %

+ dimers (41 %)

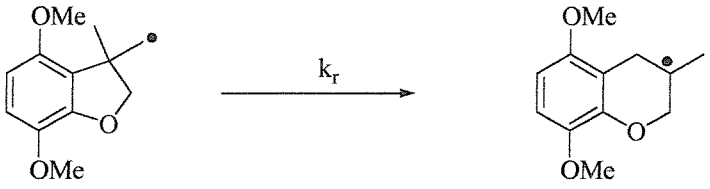
Scheme 1.1

Key to the investigation was the formation of compounds **1.3** – **1.5** that were deduced to be a result of a 'neophyl rearrangement'. Thus, the initially formed primary alkyl radical cyclised onto the adjacent arene in a 3-*exo*-trig fashion (*viz.* **1.6** → **1.7**) and subsequently ring-opened to expose a secondary alkyl radical **1.9** which was reduced or underwent disproportionation (Scheme 1.2).



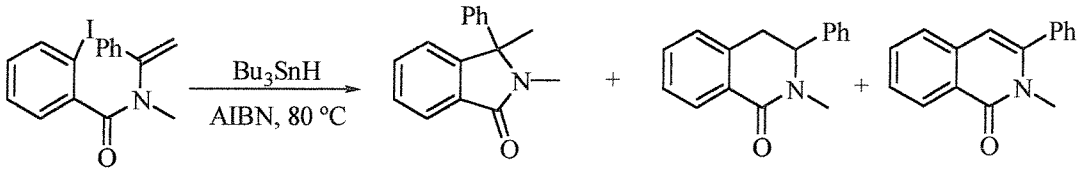
Scheme 1.2

Since its discovery, the neophyl rearrangement has received attention from a number of groups. In particular, Beckwith *et al.* have undertaken explicit kinetic studies to determine the rate of such a rearrangement.[3] Their calculations showed that the rate constant for the neophyl-type rearrangement (k_r) for **1.10** to **1.11** was 1.4×10^5 s^{-1} at 80 °C (Scheme 1.3). The study concluded that a neophyl rearrangement of this type was a relatively slow process and only became significant at low concentrations. This was opposed to the view held by Parker *et al.* in a prior publication.[4]



Scheme 1.3

The work of Beckwith was given credence by Ishibashi *et al.* in which a neophyl rearrangement was invoked to explain the formation of isoquinolinones **1.14** and **1.15**. At high tributyltin hydride concentration, a product of 5-*exo*-trig cyclisation was dominant while, at low tributyltin hydride concentration, the selectivity was reduced. The greater propensity for neophyl rearrangement explained the increasing proportion of six-membered ring products (Scheme 1.4).[5-8]

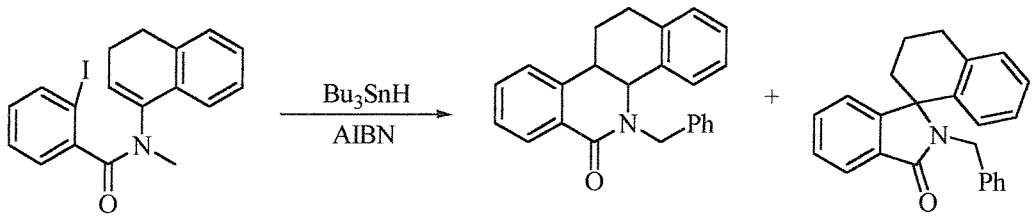


1.12 **1.13** **1.14** **1.15**

high [Bu_3SnH]:	6.9 : 1
low [Bu_3SnH]:	3.4 : 1

Scheme 1.4

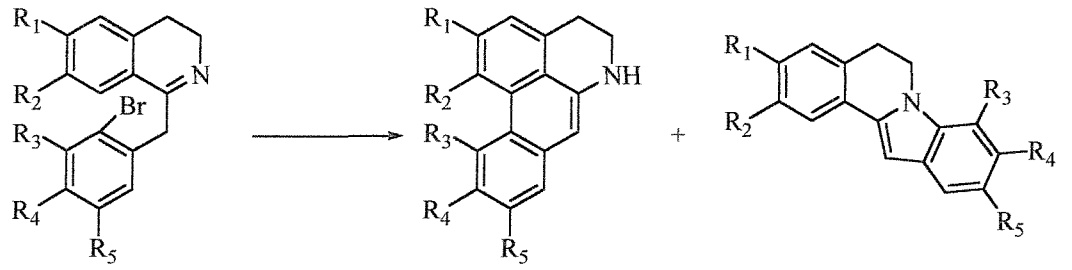
In the same study a 6-*endo*-trig cyclisation, rather than a neophyl rearrangement, was suggested to account for the formation of **1.17** from **1.16**. Stereoelectronic arguments ruled out a neophyl rearrangement (Scheme 1.5).



1.16 **1.17**, 20 % **1.18**, as a mixture

Scheme 1.5

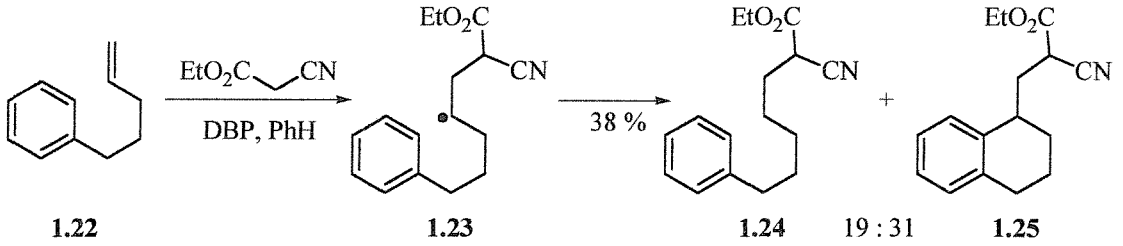
Other work in the area of radical additions to arenes tethered by a carbon chain includes a study towards the synthesis of aporphines and indoloisoquinolines. Orito *et al.* wished to determine whether an aryl radical would preferentially attack a proximal arene or an imine.[9] Thus, a range of substrates of the general structure **1.19** was synthesised and exposed to tributyltin hydride (2 equivalents) and AIBN (1 equivalent) in toluene. In most cases a mixture of two products resulted (Scheme 1.6). When R_1=R_2=R_3=R_4=OMe (**1.19a**), there was no evidence of aryl-aryl bond formation with **1.21a** formed in 68 % *via* a 5-*endo*-trig cyclisation onto nitrogen. When R_3=H, reaction was biased towards arene addition leading to **1.20** *via* a 6-*exo*/*endo*-trig cyclisation (**1.20** : **1.21** ~ 9:1). It was concluded that cyclisation of an aryl radical onto an arene proceeds efficiently unless the steric demand is too high and an alternative pathway is available. In this system, cyclisation was presumed to follow a 6-*exo*/*endo*-trig cyclisation *via* an *ortho* attack onto the arene.



1.19 **1.20** **1.21**

Scheme 1.6

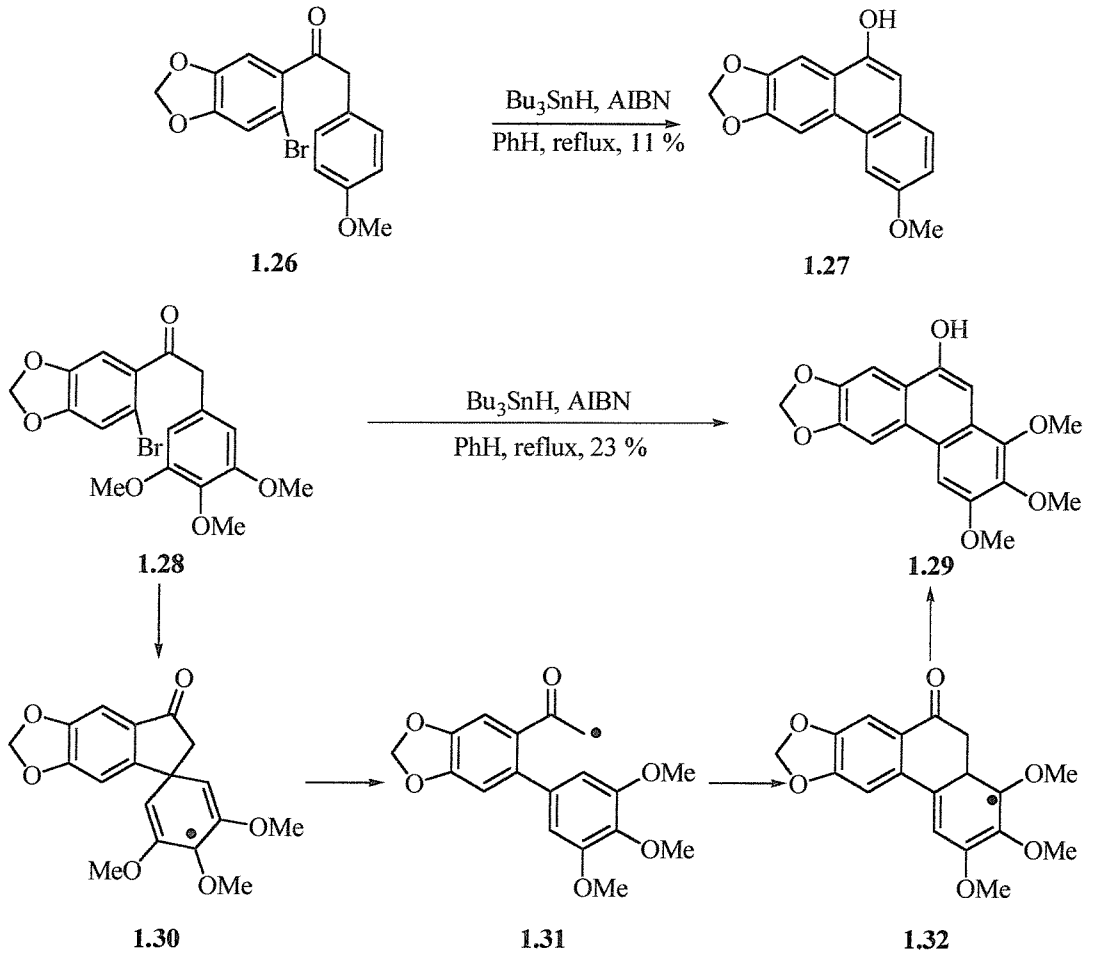
Julia *et al.* have reported a route to tetralins by addition of an alkyl radical onto an arene. Yields were moderate with tetralin products only dominating under high dilution (Scheme 1.7).[10]



1.22 **1.23** **1.24** 19 : 31 **1.25**

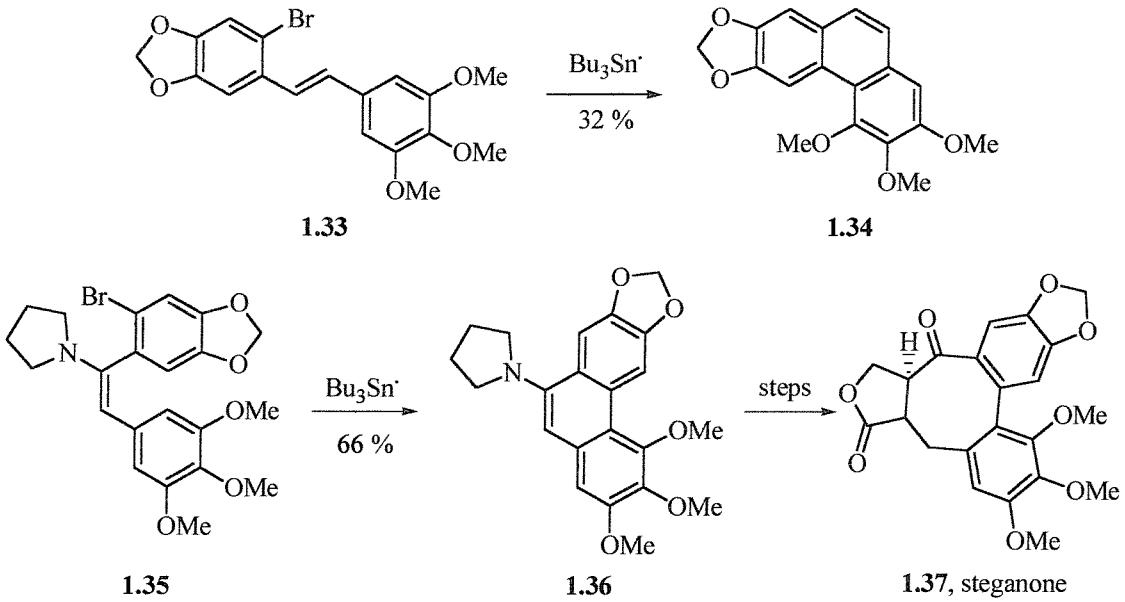
Scheme 1.7

Work by Narashimhan *et al.* targeted the medium-ring system of steganone **1.37**.[11] Early attempts to afford an aryl-aryl bond gave a phenanthrene product in low yield. Thus, treatment of aryl bromide **1.26** with tributyltin hydride and AIBN gave **1.27** in 11 %. No other products were mentioned. Increasing the electron density of the radical acceptor arene improved the yield with the treatment of **1.28** under standard radical forming conditions giving **1.29** in 23 % yield. That **1.29** was formed at all was somewhat surprising. Its formation was explained by an *ipso* attack of the aryl radical derived from **1.28** onto the arene. The resulting spirocyclic intermediate **1.30** was then presumed to fragment to give primary radical **1.31**, stabilised by an α-carbonyl group. Recyclisation onto the electron-rich arene by a 6-*endo*/*exo*-trig pathway and rearomatisation yields the observed phenanthrene **1.29** (Scheme 1.8). A neophyl-type rearrangement could also be invoked in this case but was not considered.[12]



Scheme 1.8

As a consequence of the failure of the system to access the required phenanthrene, two further substrates were investigated. *Trans*-bromostilbene **1.33** was exposed to tributyltin-mediated radical forming conditions to yield the corresponding phenanthrene **1.34** in 32 % (see Chapter 5 for our work in this area) and enamine **1.35**, when exposed to similar conditions, yielded phenanthrene **1.36** as the major product (66 %) (Scheme 1.9).[12] Formation of **1.36** completed a formal synthesis of steganone **1.37** as this is a late intermediate in Becker's total synthesis of that target.[11,13]

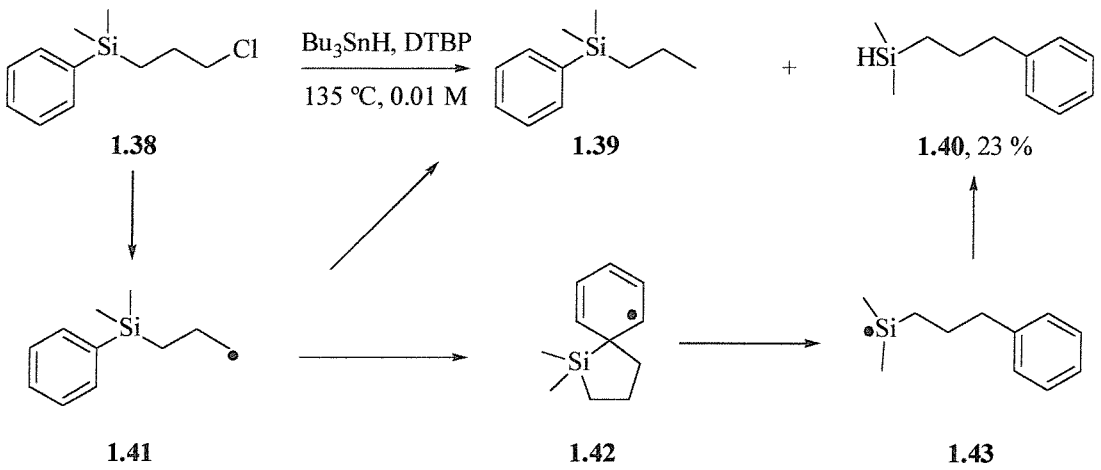


Scheme 1.9

1.2.2 Tethering Chains Containing Silicon

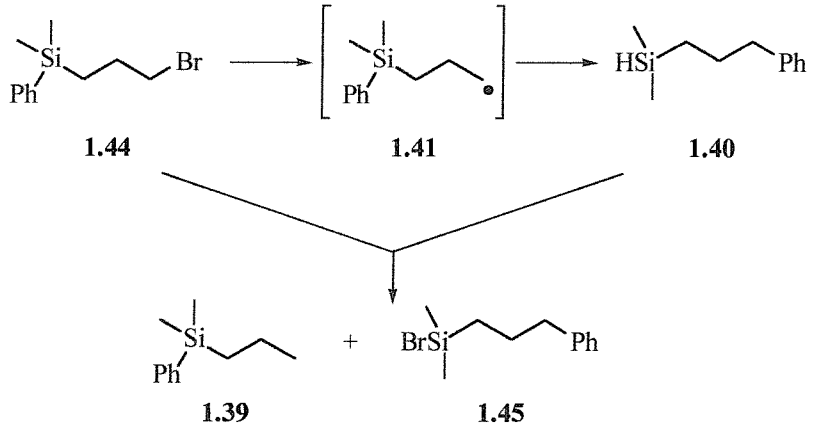
Descending Group 14 of the periodic table, a number of examples of additions of carbon-centred radicals to arenes tethered by silicon can be found. 1,3-Radical shifts involving silicon are yet to be observed and are believed to be extremely disfavoured on steric and electronic grounds.[14] However, 1,4- and 1,5-shifts are known processes.

During the 1970s, Wilt *et al.* were involved in a search of radical migrations from silicon to carbon *via ipso* attack at an arene.[14] Treatment of a benzene solution of 3-(dimethylphenylsilyl)propyl chloride **1.38**, with tributyltin hydride and di-*tert*-butylperoxide at 135 °C and under conditions of high dilution, yielded two products. One was a result of direct reduction of the carbon-chlorine bond (product **1.39**) while the other was a result of 1,4-rearrangement *via ipso* attack of a carbon-centred radical onto the proximal phenyl ring and fragmentation to expose a silicon-centred radical (Scheme 1.10).[14-16]



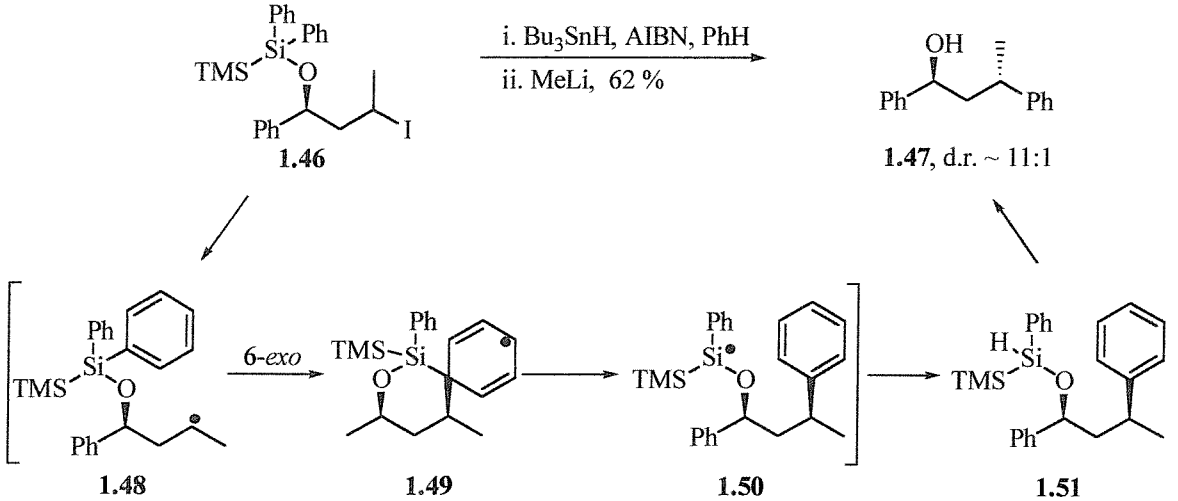
Scheme 1.10

Homologation of the alkyl chain also gave evidence of a 1,5-rearrangement with the product of rearrangement isolated in 13 % yield.[16] During the study a difference in product ratio was observed when an alkyl chloride **1.38** and alkyl bromide **1.44** were subjected to the same reaction conditions. Less rearranged product was observed when bromide **1.44** was employed (4 %). This was due to the product silane **1.40** reacting with starting material (*i.e.* reducing the carbon-bromine bond). When an alkyl chloride **1.38** was employed, the pathway was found to be insignificant hence greater quantities of the starting bromide **1.44** was consumed prior to rearrangement (Scheme 1.11).



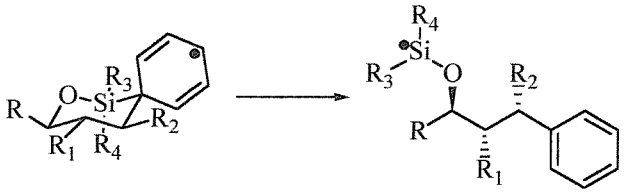
Scheme 1.11

In more recent times, silicon has found a synthetically useful role as a tether for stereoselective radical additions to aromatics with migration of the ring from silicon to carbon. Studer *et al.* have reported such reactions with good diastereoselectivities (up to 11:1).[17] The substrates were based on an iodopropyl phenylsilyl ether skeleton (*e.g.* **1.46**). Treatment with tributyltin hydride and AIBN in benzene and work up with methyllithium was shown to give good yields of the corresponding (phenylpropyl)alcohol (*e.g.* **1.47**) (Scheme 1.12).[18]



Scheme 1.12

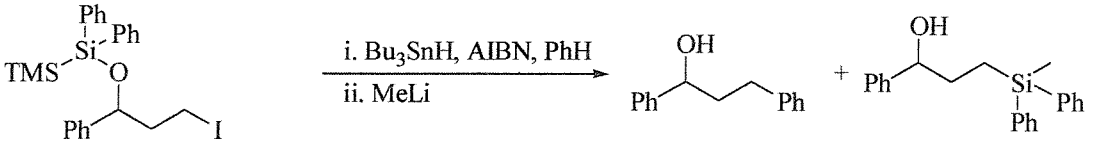
The diastereoselectivity was rationalised by reaction occurring through a six-membered chair-like transition state (Scheme 1.13).



1.51 **1.52**

Scheme 1.13

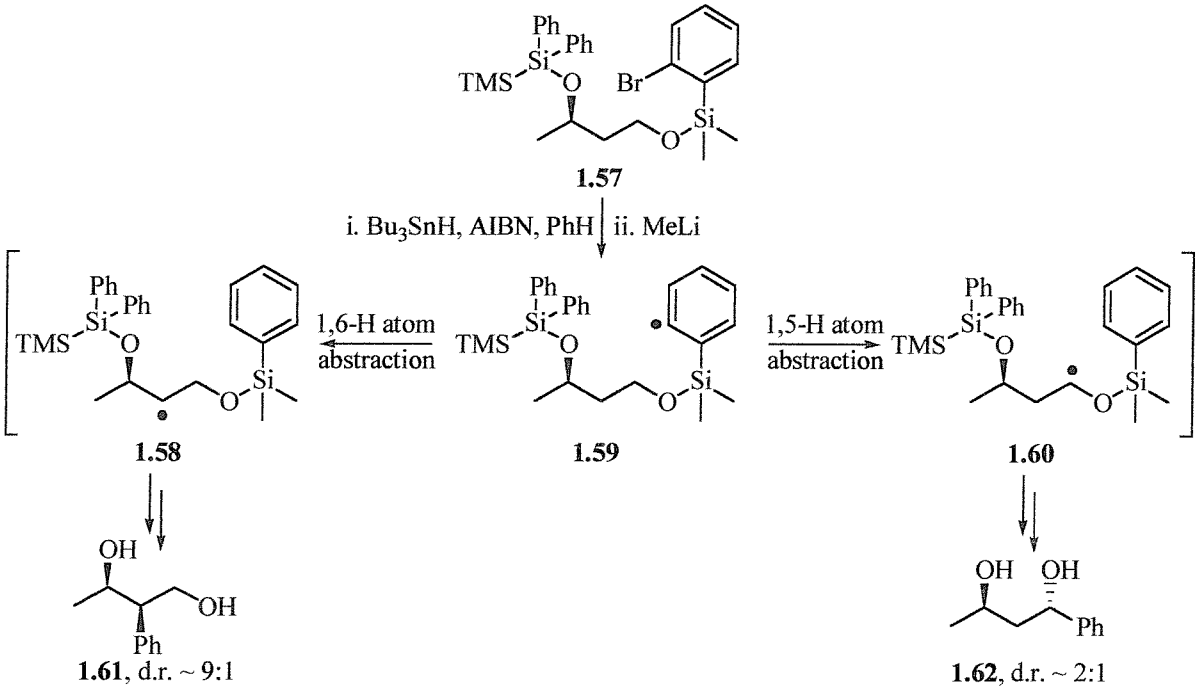
The cyclisation-fragmentation pathway was poorer when R_2=H. In this case, S_Hi reaction at silicon was observed and overall yields were lower (Scheme 1.14).[18]



1.54 **1.55**, 19 % **1.56**, 5 %

Scheme 1.14

Diastereoselectivity was lowered when a bromophenylsilyl group was introduced (*viz.* **1.57** → **1.62**). In addition a by-product **1.61**, due to 1,6-hydrogen atom abstraction, was obtained with good diastereoselectivity (Scheme 1.15).



1.57

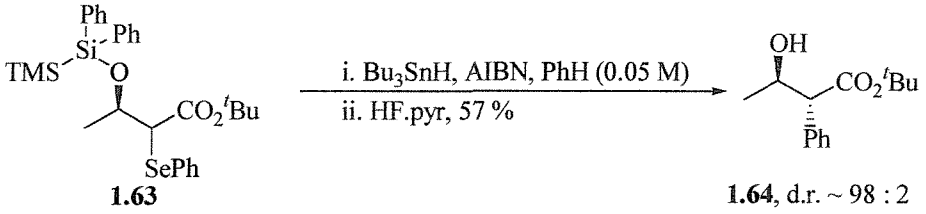
1.58 **1.59** **1.60**

1.61, d.r. ~ 9:1 **1.62**, d.r. ~ 2:1

Scheme 1.15

Selenides and aldehydes were also used as radical precursors. In the case of selenides, no products derived from radical attack on the aromatic ring were observed and the yield obtained from the aldehyde precursors was poor.[18]

Variation at the aryl groups attached to silicon proved that phenyl was the best group for attack by a carbon-centred radical. Electron-rich (*p*-methoxyphenyl) and electron-deficient (*p*-fluorophenyl) examples proceeded with high diastereoselectivity but low yield (less than 40 %). Radical attack onto a 2-thienyl moiety failed to give any product of 1,5-aryl migration. Reducing the alkyl chain length by one carbon increased the efficiency of the reaction with the product **1.64** formed from selenide **1.63** in good yield and with excellent diastereoselectivity (Scheme 1.16).

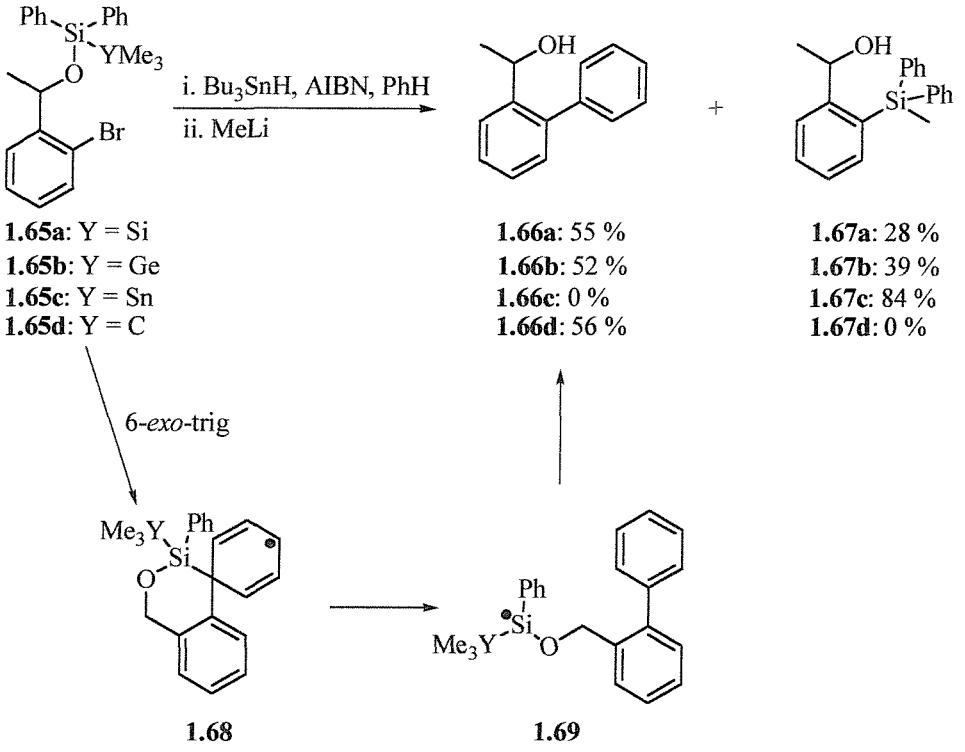


1.63 **1.64**, d.r. ~ 98 : 2

Scheme 1.16

It was the observed that these reactions could be performed using catalytic tributyltin hydride and sub-stoichiometric quantities of initiator. After attack of the initially formed carbon-centred radical onto the aromatic ring and subsequent fragmentation, the resulting silicon-centred radical was presumed to abstract bromine from starting material thus propagating a radical chain reaction. Indeed, less than half of an equivalent of tributyltin hydride was required to achieve comparable yields to those obtained with stoichiometric levels.

Extending the above methodology, Studer *et al.* have applied the method to the synthesis of biaryls.[19] Bromobenzyl diphenylsilyl ethers akin to **1.65** undergo a similar reaction with *ipso* attack at a silicon-attached phenyl group. Fragmentation results in overall migration of a phenyl group to carbon. S_Hi reactions at silicon competed with aryl migration when the silyl ether possessed trimethylsilyl or trimethylgermyl substituents and this course was the exclusive pathway when a trimethylstannyl group was used. Changing to a poor radical leaving group such as methyl, *tert*-butyl or phenyl biased reaction exclusively to biaryl formation (Scheme 1.17).



1.65a: Y = Si
1.65b: Y = Ge
1.65c: Y = Sn
1.65d: Y = C

1.66a: 55 %
1.66b: 52 %
1.66c: 0 %
1.66d: 56 %

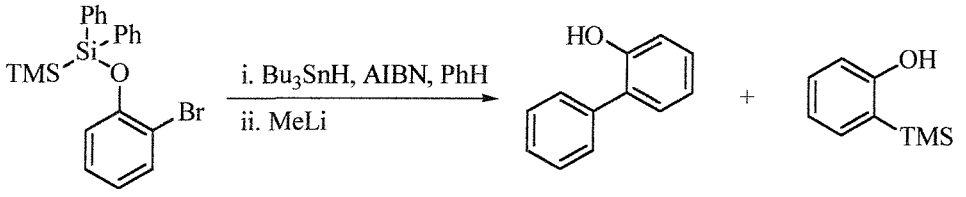
1.67a: 28 %
1.67b: 39 %
1.67c: 84 %
1.67d: 0 %

1.68 **1.69**

Scheme 1.17

As for the alkyl radical case, the replacement of the phenyl radical acceptor ring with a 2-thienyl group failed to yield the expected 2-phenylthiophene product. However, electron-rich and electron-deficient arenes tended to function well with *p*-methoxyphenyl providing a biaryl product in a 77 % yield.

Investigation of 2-bromophenyl diphenylsilyl ethers (attempting to initiate a 1,4-aryl migration) showed that the substrates would undergo this type of reaction only if a trimethylsilyl group was attached to the silicon (phenyl or methyl groups failed to react). However the yields of biaryl products were significantly lower (*ca.* 40 %) and a major by-product of the reaction, obtained in 50 % yield, was 2-trimethylsilylphenol – a consequence of S_Hi at silicon (Scheme 1.18). No products of *ortho* attack on the radical acceptor were observed. Incomplete reaction was noted when sub-stoichiometric quantities of tributyltin hydride were employed showing that bromine abstraction by silicon was not a major pathway in these systems.[19]

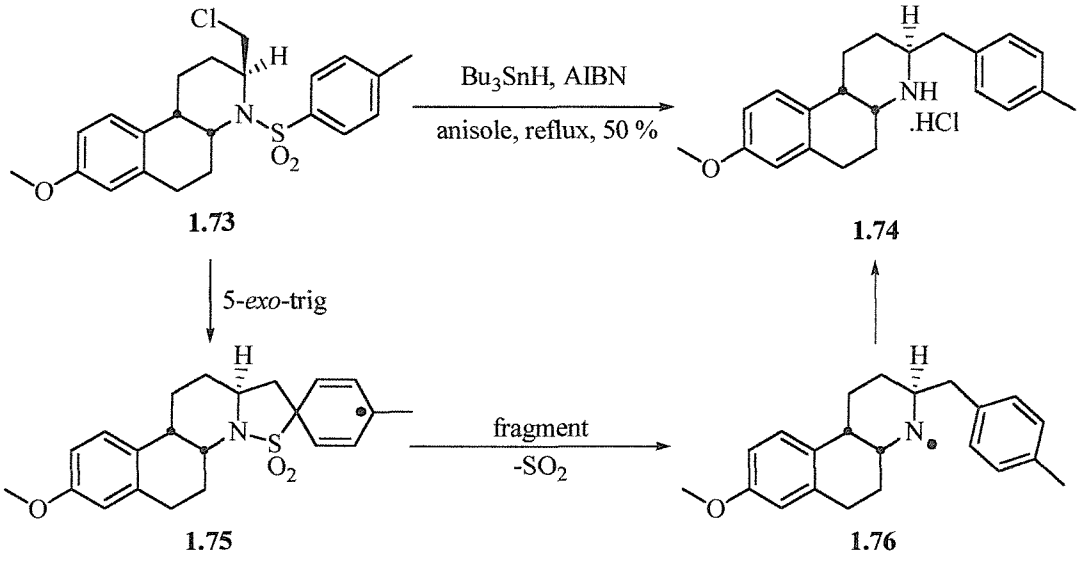


1.70 **1.71**, 38 % **1.72**, 50 %

Scheme 1.18

1.2.3 Tethering Chains Containing Sulfur

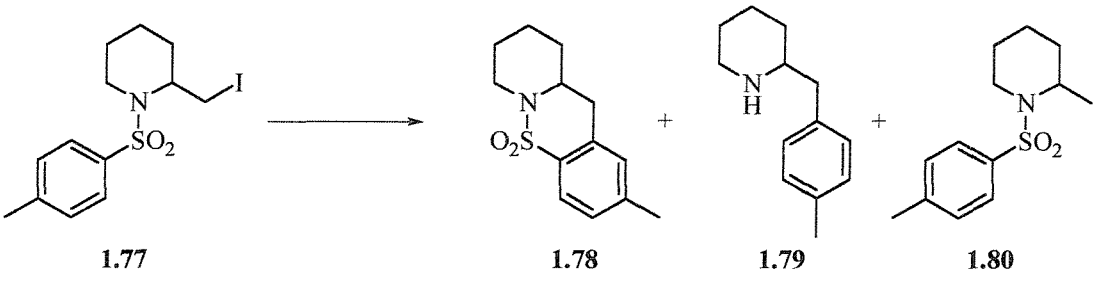
Sulfur provides another example of an atom that acts as a good radical leaving group. When employed in a high oxidation state (*i.e.* +6 oxidation state), extrusion of sulfur dioxide is frequently observed. Motherwell *et al.* have published extensively on the use of sulfonates and sulfonamides as tethers for radical cyclisation reactions though the first example was reported by Speckamp and Loven as part of a total synthesis programme.[20] They found that treatment of alkyl chloride **1.73** with tributyltin hydride and AIBN in anisole gave **1.74**.[20] Thus, an *ipso* attack of alkyl radical to the tolyl group is followed by fragmentation and expulsion of sulfur dioxide. Hydrogen atom abstraction from tributyltin hydride then gives amine **1.74**. The product was isolated as the hydrochloride salt since reaction between tributyltin hydride and tributyltin chloride in the presence of an amine generates bis(tributyltin) and hydrogen chloride (Scheme 1.19).[20]



Scheme 1.19

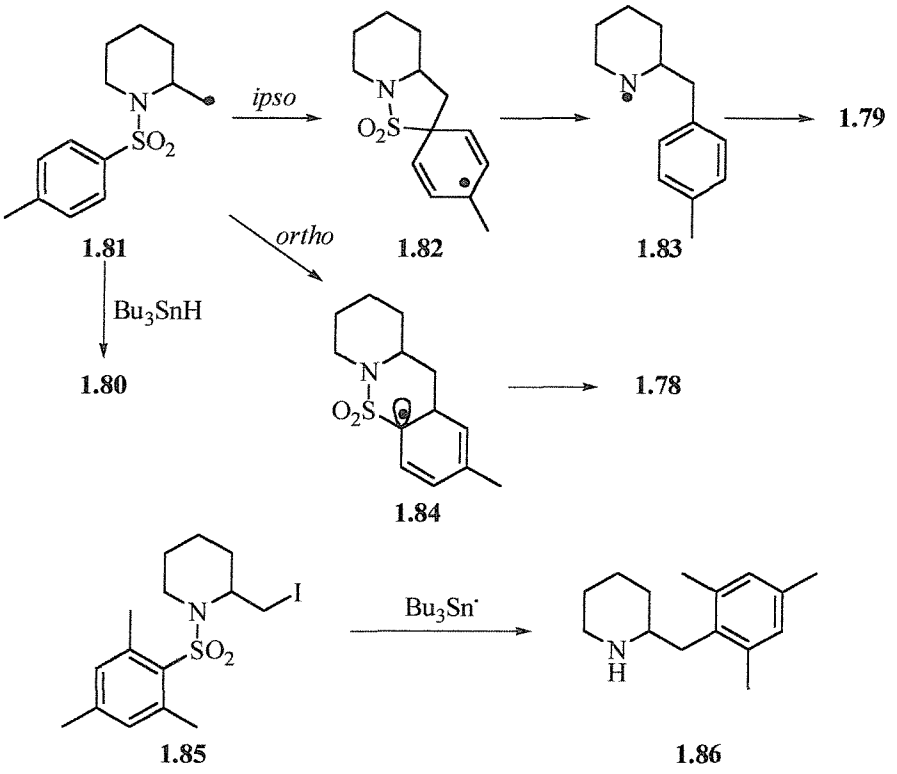
As a consequence of this study, an investigation was undertaken into the use of α-iodomethylpiperidinesulfonamides as radical cyclisation precursors. Speckamp *et al.* found that under tributyltin-mediated radical conditions, a mixture of products was formed from both *ipso* and *ortho* attack onto the adjacent arene as well as direct reduction of the carbon-to-iodine bond.[21] At reflux in benzene (*i.e.* standard radical forming conditions) a mixture of two cyclisation products was observed. At room temperature only the product derived from addition to the *ortho*-carbon was observed while at 190 °C, the product from *ipso* attack dominated (Scheme 1.20).[21] The reaction pathway was biased entirely towards *ipso* attack by inclusion of two *ortho* methyl groups on the arene (Scheme 1.20). Speckamp suggested that,

when hexabutylditin was used, the source of hydrogen atom for quenching nitrogen-centred radical **1.83** might have originated from intermediate **1.84**.[21]



1.77 **1.78** **1.79** **1.80**

Bu_3SnH, AIBN, PhH, reflux:	45 %	32 %	23 %
Bu_3SnH, AIBN, anisole, r.t.:	68 %	0 %	30 %
Bu_3SnH, AIBN, Ph_2O, 190 °C:	26 %	64 %	9 %
$(Bu_3Sn)_2$, $(^tBuO)_2$, PhH, reflux:	64 %	25 %	0 %

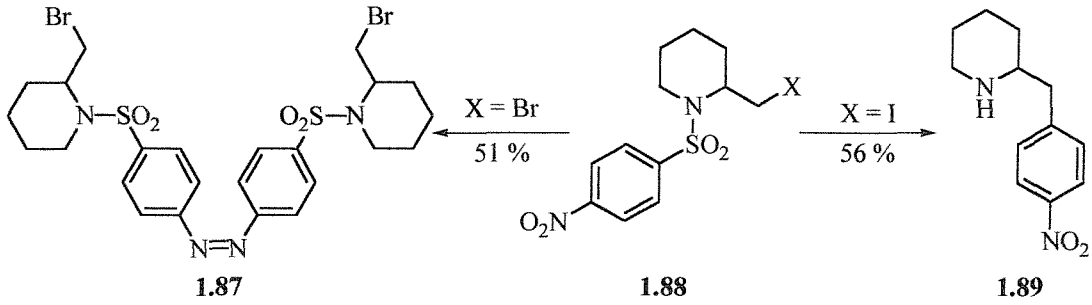


Scheme 1.20

As a footnote, it was observed that a radical initiator such as AIBN was not required in this reaction with comparable results obtained by treatment of **1.77** with tributyltin hydride (2.7 equivalents) in benzene at 40 °C.

Speckamp *et al.* extended the study further to investigate a range of aromatic sulfonamides.[22] *p*-Nitrophenylsulfonamide **1.88** led exclusively to a product derived from *ipso* attack in 56 % with no evidence of *ortho* attack.[22] This was presumed to be due to the stabilisation of the spirocyclic intermediate by the nitro group. The choice of halide was found to be critical as

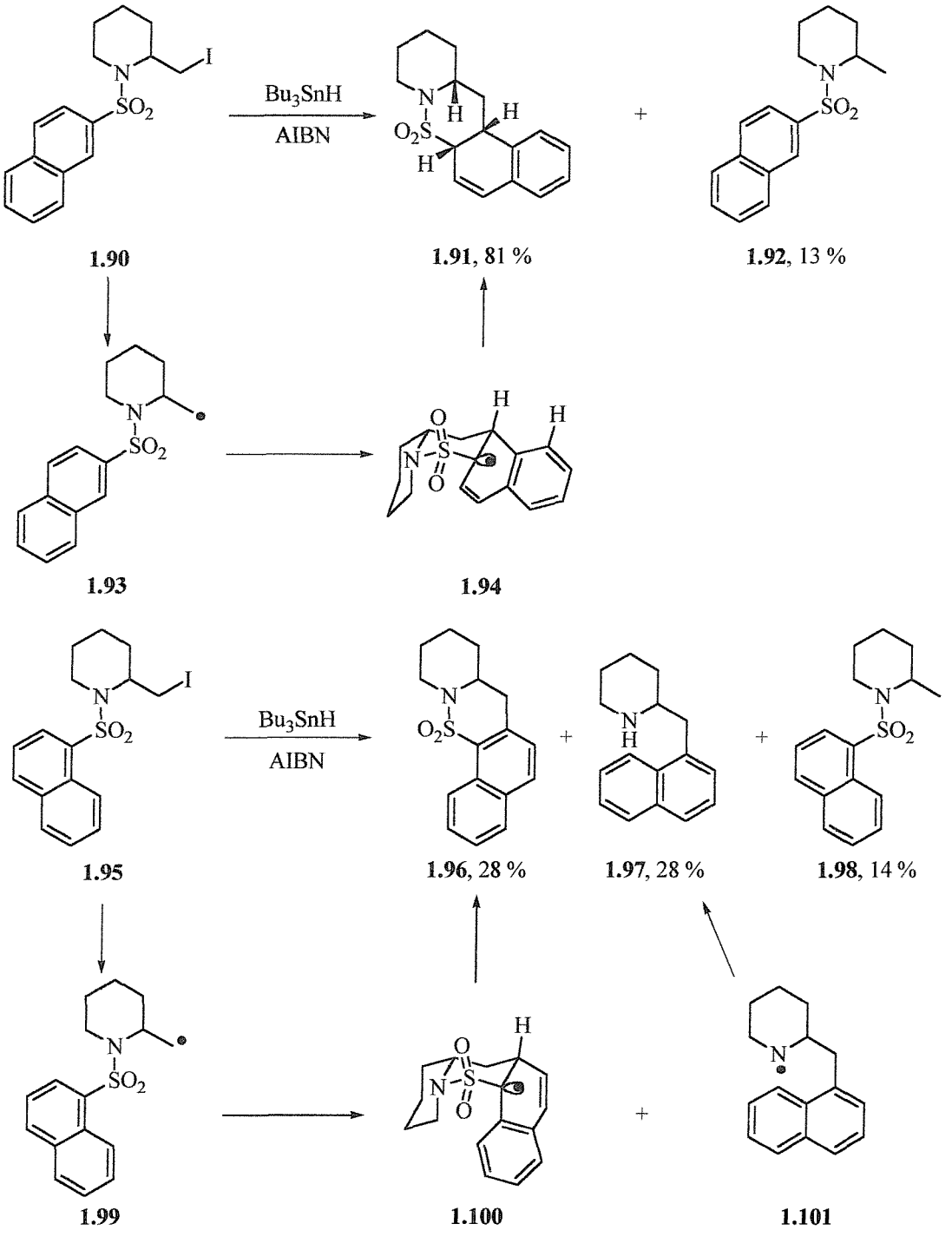
an alkyl bromide was found to be unreactive under standard conditions with a product due to reaction at the nitro group being formed (Scheme 1.21).



1.87 **1.88** **1.89**

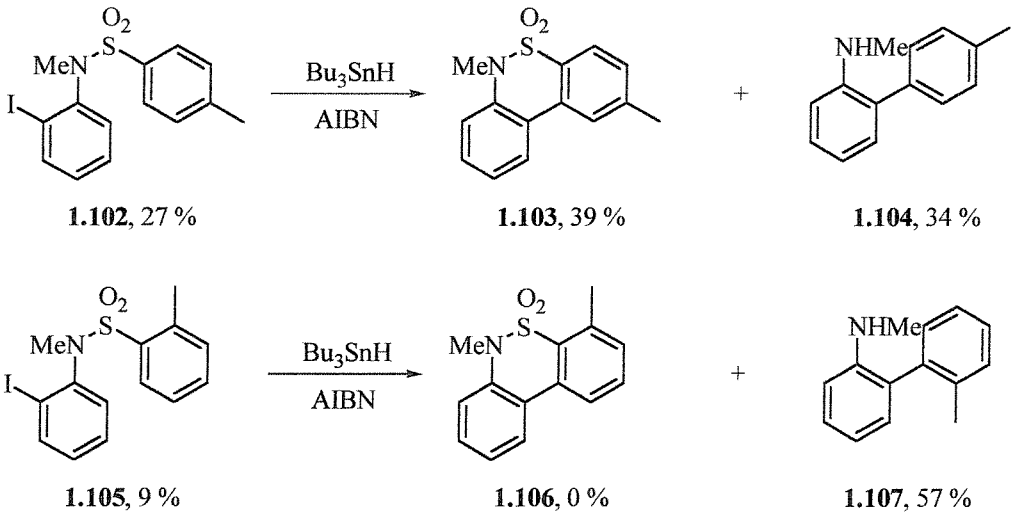
Scheme 1.21

Interestingly, different reaction pathways were followed by the naphthyl analogues, **1.90** and **1.95** respectively. Thus while **1.90** gave dihydronaphthalene **1.91**, the product of *ortho* addition, **1.95** led to a mixture of aromatic products due to both *ipso* and *ortho* attack onto the naphthalene ring system (Scheme 1.22). This was rationalised by consideration of the radical intermediates. σ-Radical **1.94** (derived from **1.90**) is stabilised by conjugation to the adjacent alkene. A 1,3-diaxial (peri) interaction then prevents abstraction of a hydrogen atom from **1.94**. As a consequence this radical intermediate abstracts a hydrogen atom from tributyltin hydride to generate dihydronaphthalene **1.91**. In the case of **1.95**, the intermediate radical **1.100** is no longer adjacent to an alkene and the hydrogen atom at the benzylic carbon is prone to abstraction. In this case rearomatisation occurs.[22]



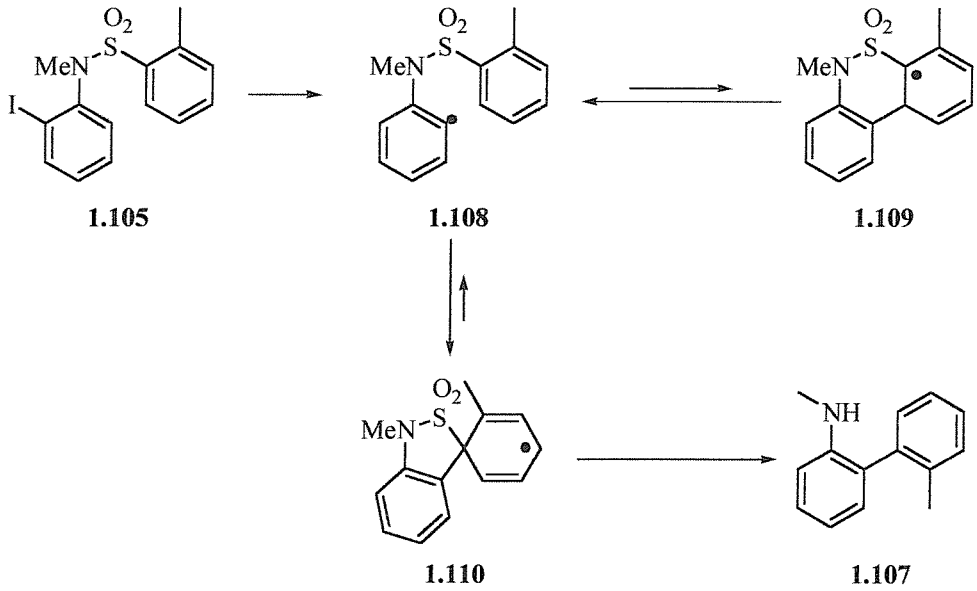
Scheme 1.22

Motherwell *et al.* have used this method to good effect in the synthesis of various biaryls.[23,24] A study into the effects of arene substituents demonstrated that inclusion of a single *ortho* methyl group biased reaction towards biaryl synthesis *via ipso* attack (Scheme 1.23).



Scheme 1.23

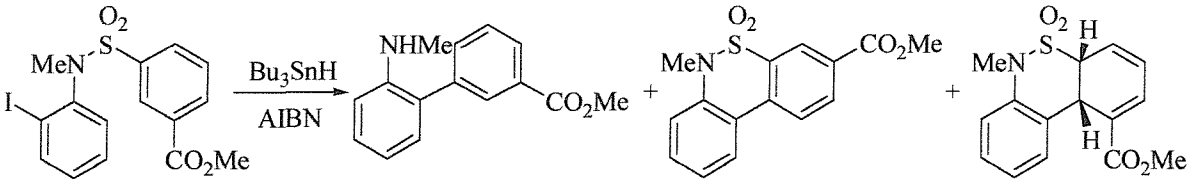
One explanation for the marked effect on selectivity was that the *ortho*-methyl has a negative steric effect after cyclisation in an *ortho* mode. Then, assuming this pathway is reversible, material is channelled through the *ipso* route leading to biaryl **1.107** (Scheme 1.24).[23] In an extreme case, a 2,4,6-trimethylphenyl group biased reaction wholly towards biaryl synthesis (64 %).



Scheme 1.24

Prior work had shown that methoxy substituents had a strong effect on the reaction profile with a *p*-methoxy group biasing reaction towards *ipso* attack due to intermediate radical stabilisation.[24] In the sulfonamide systems, it was found that an *ortho* methoxy group (favouring *ipso* attack) had a dominating effect over a *meta* methoxy group (favouring *ortho* attack). Thus, subjecting *N*-iodophenyl-2,5-dimethoxyphenylsulfonamide to standard conditions yielded 2-(2,5-dimethoxyphenyl)-*N*-methylaniline (63 %).

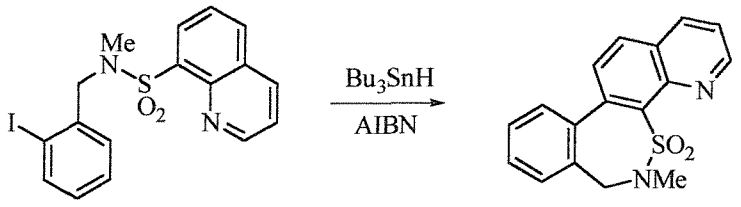
Introduction of a *meta* –carboxylate biased reaction towards *ortho* attack onto the arene (*ipso* : *ortho* ~ 1:2). Interestingly, one of the products, due to *ortho* attack at the carbon between the sulfonyl and carboxyl groups, was isolated as a dihydroarene **1.114** (Scheme 1.25).



1.111 **1.112**, 28 % **1.113**, 37 % **1.114**, 11 %

Scheme 1.25

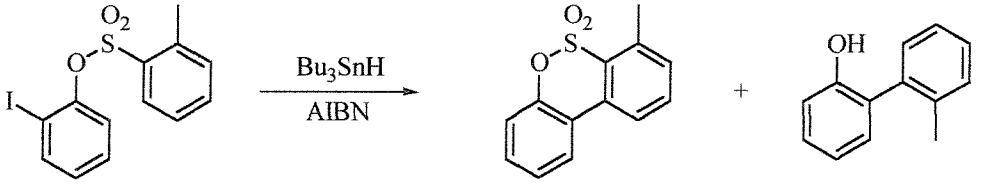
The homologues of the above substrates gave poorer results with a complex product mixture formed.[25] One example tested resulted in a product of *ortho* attack (a 7-*endo*/*exo*-trig process) being isolated in 9 % yield (Scheme 1.26). Other heteroaromatic examples also showed a preference for 7-memebered ring formation over *ipso* addition; a complete reversal of the cyclisation mode to that obtained from the series with a shorter tether. A detailed explanation was not given although stereoelectronic and conformational effect were implied.[25]



1.115 **1.116**, 9 %

Scheme 1.26

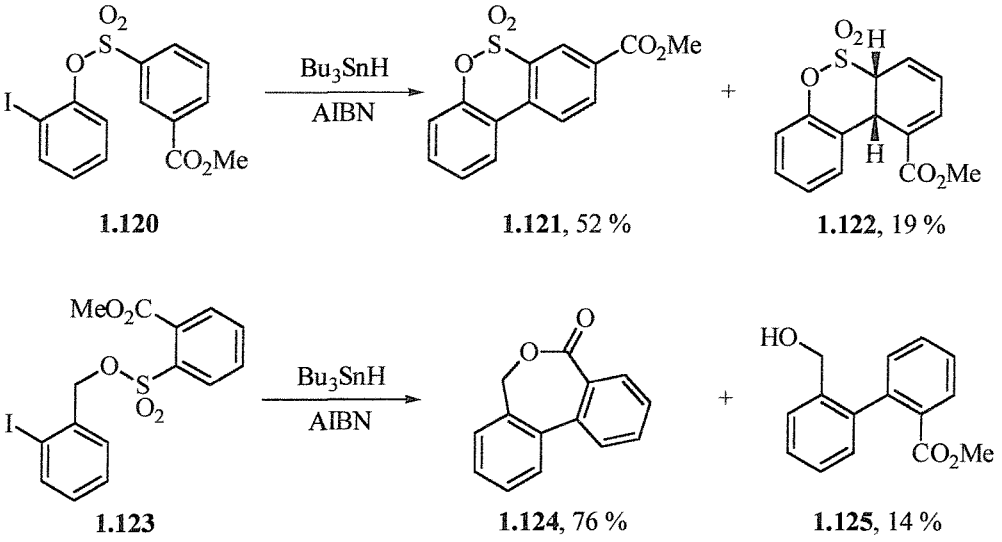
As part of the same study, sulfonates were also investigated. Replacement of a methylated nitrogen by an oxygen atom tended to reduce the reaction efficiency with a general lowering of both yield and selectivity (Scheme 1.27).[23,25]



1.117, 14 % **1.118**, 36 % **1.119**, 23 %

Scheme 1.27

An exception was observed with a *meta*–carboxyl substituent where reaction displayed good selectivity for *ortho* attack of the arene. A series of sulfonate homologues, *e.g.* **1.123**, proved more fruitful. *Ortho* attack was found to be the preferred pathway unless a powerful *ipso*-directing group was present in the radical acceptor (Scheme 1.28).[23,25]

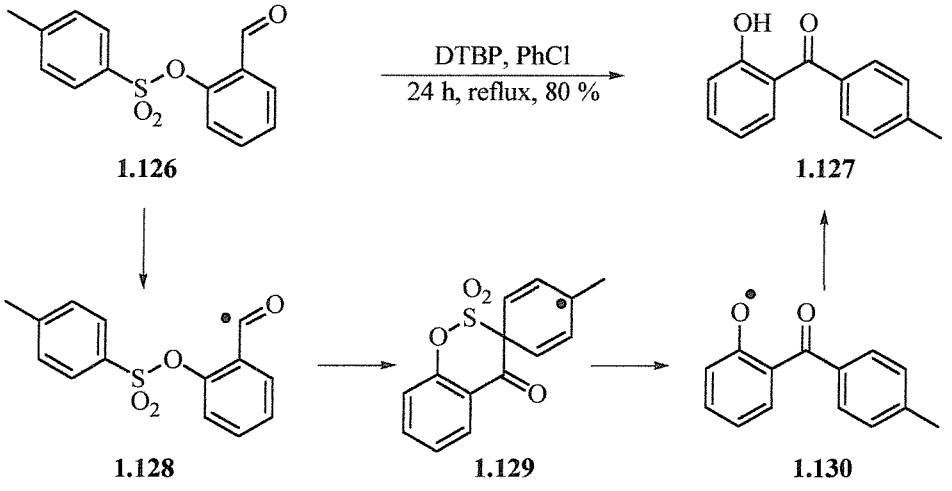


1.120 **1.121**, 52 % **1.122**, 19 %

1.123 **1.124**, 76 % **1.125**, 14 %

Scheme 1.28

More recently, Motherwell *et al.* have successfully added an acyl radical to an arene tethered by a sulfonate group to yield a diarylketone (Scheme 1.29).[26] Electron-rich and electron deficient arenes were generally tolerated although increasing steric demand at the *ortho* centres had a detrimental effect on yield. Increasing electron density on the donor ring (by addition of a methoxy group) also decreased product yields, which can be attributed to the formation of a reactive electron-rich phenol. No evidence of *ortho* attack or decarbonylation was observed.



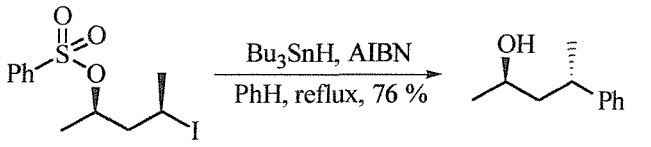
1.126 **1.127**

1.128 **1.129** **1.130**

Scheme 1.29

Togo *et al.* have also used sulfonamides in radical cyclisation reactions as a tool to prove the utility of 1,1,2,2-tetraphenyldisilane as a radical propagator. Similar results to those obtained by Motherwell using tributyltin hydride were noted.[27]

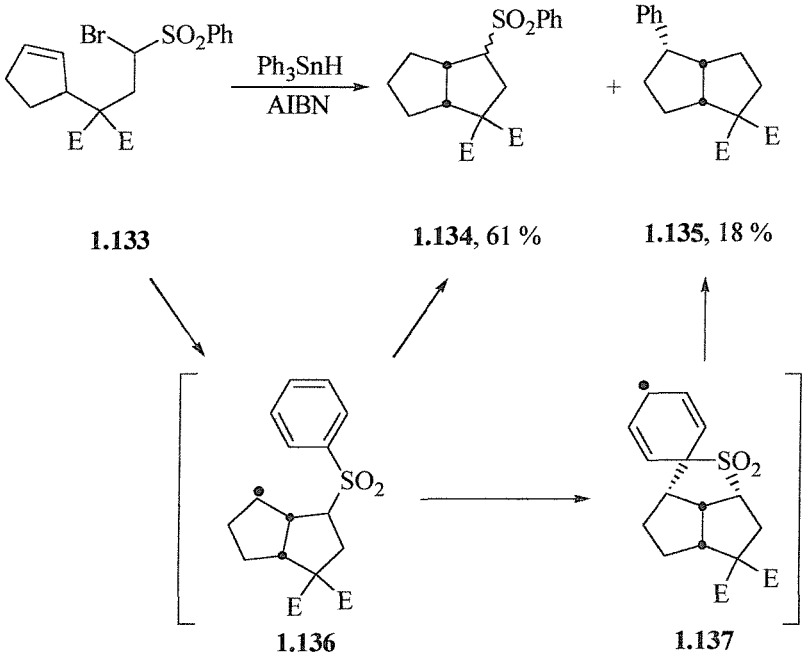
Studer and Bossart have developed a stereoselective aryl migration that closely paralleled their study with silicon tethers.[28] Thus, exposure of iodopentylsulfonates to tributyltin hydride and AIBN resulted in a diastereoselective aryl migration from sulfur to carbon with loss of sulfur dioxide (Scheme 1.30).



1.131 **1.132**, d.r. = 13:1

Scheme 1.30

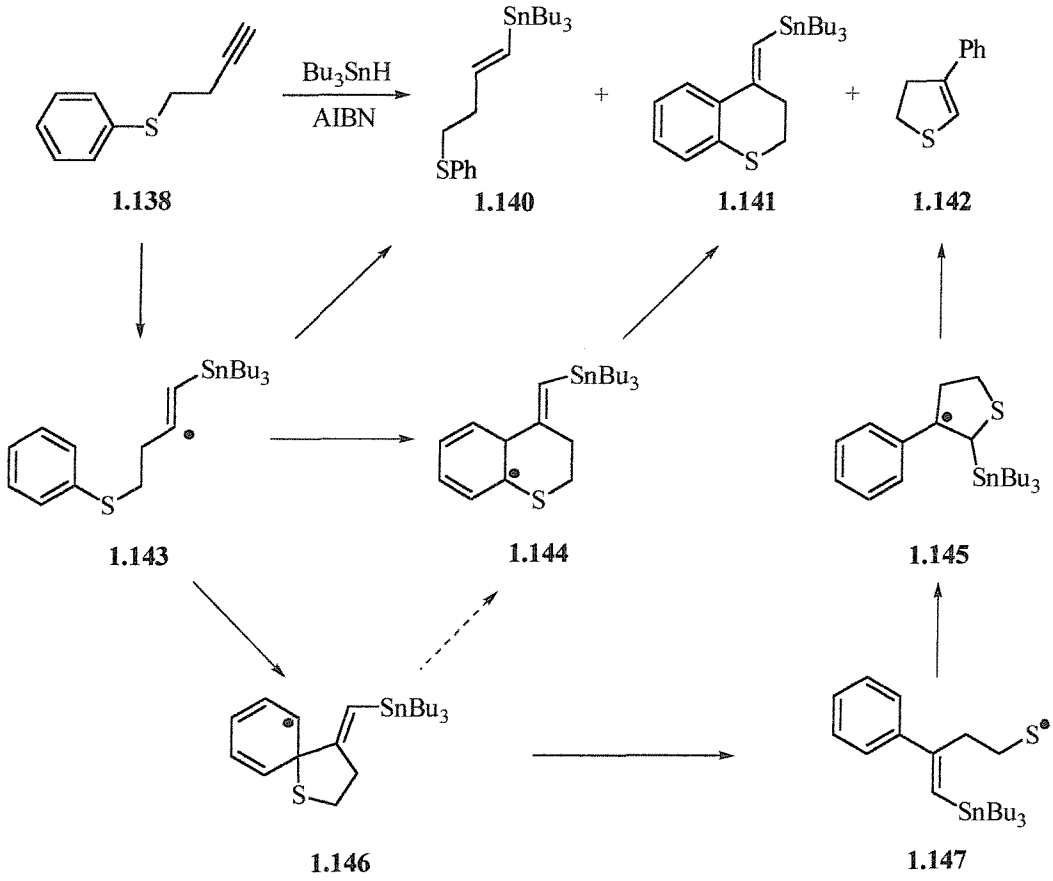
In a different study, Clive *et al.* reported the addition of a carbon-centred radical tethered by a sulfonyl linkage to an arene as part of a programme directed towards the synthesis of *cis*-fused cyclopentane skeletons (Scheme 1.31, E = CO_2Et).[29] Replacing the arylsulfonyl group by an alkylsulfonyl group prevented the radical cyclisation-fragmentation pathway.



Scheme 1.31

Though the majority of work on the addition of carbon-centred radicals to arenes tethered by sulfur employs a sulfonyl group, there is one report that utilises a sulfide linkage.[30] Addition of tributyltin radical to the alkyne **1.138** gave vinyl radical **1.143** which underwent

cyclisation onto the proximal phenyl ring. The products were rationalised by a 5-*exo*-trig or 6-*endo*/*exo*-trig cyclisation of the vinyl radical onto the adjacent arene (Scheme 1.32). The authors speculated as to whether **1.141** derived from 6-*exo*/*endo* attack, *viz.* **1.143** → **1.144**, or by a neophyl-type rearrangement of spirocycle **1.146** to **1.144**. No definitive conclusion was given (Scheme 1.32).[30]



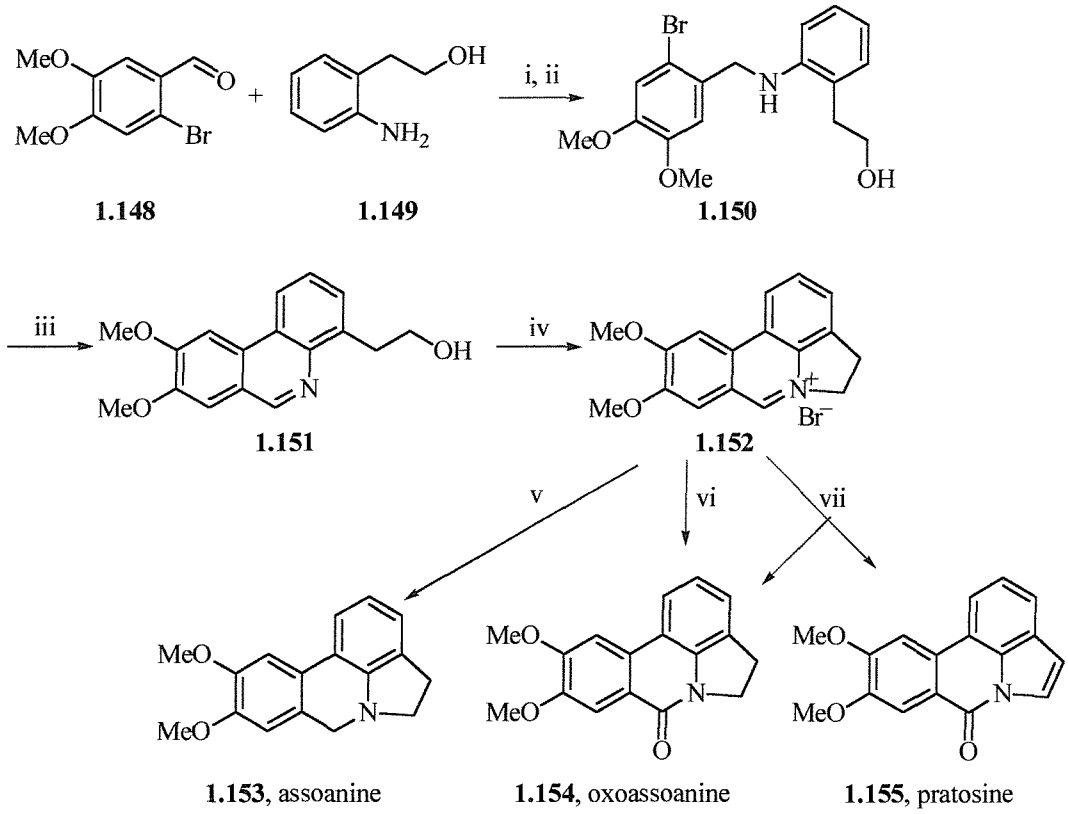
Scheme 1.32

1.2.4 Tethering Chains Containing a Nitrogen Atom

Nitrogen has proved a popular choice for linking a carbon-centred radical to an arene. The nature of the nitrogen-tether is quite diverse with linkages ranging from simple amine and amide groups through to more exotic oxaziridines.

Lobo *et al.* have demonstrated that bromobenzylanilines will undergo radical cyclisations in moderate yield and have applied their methodology in target synthesis.[31,32] Thus, union of bromoveratraldehyde **1.148** and 2-hydroxyethylaniline **1.149** and reduction of the resulting imine provided a substrate **1.150** for radical cyclisation. Treatment with tributyltin hydride and AIBN in refluxing benzene yielded the corresponding polyarene **1.151**, a result of cyclisation occurring *via* a 6-*endo*/*exo*-trig pathway. Although the yield of **1.151** was low it

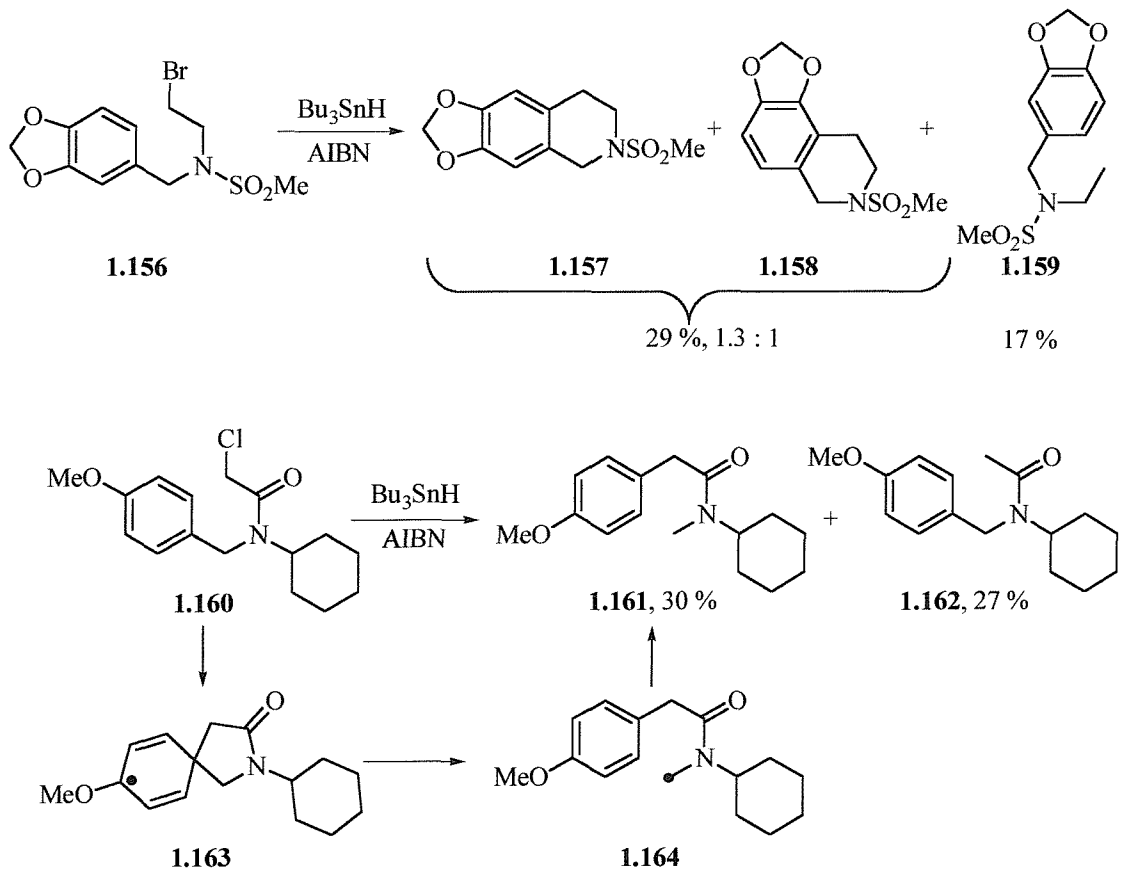
allowed four natural products to be synthesised in a very short synthetic sequence (Scheme 1.33).[32]



Reagents and Conditions: **i.** EtOH, 51 %; **ii.** $NaBH_4$, MeOH, 81 %; **iii.** Bu_3SnH, AIBN, PhH, reflux, 27 %; **iv.** PBr_3, 65 %; **v.** $NaBH_4$, MeOH, **88** %; **vi.** H_2O_2, HO^-, 63 %; **vii.** $K_3Fe(CN)_6$, HO^-, **1.154**: 59 %, **1.155**: 21 %.

Scheme 1.33

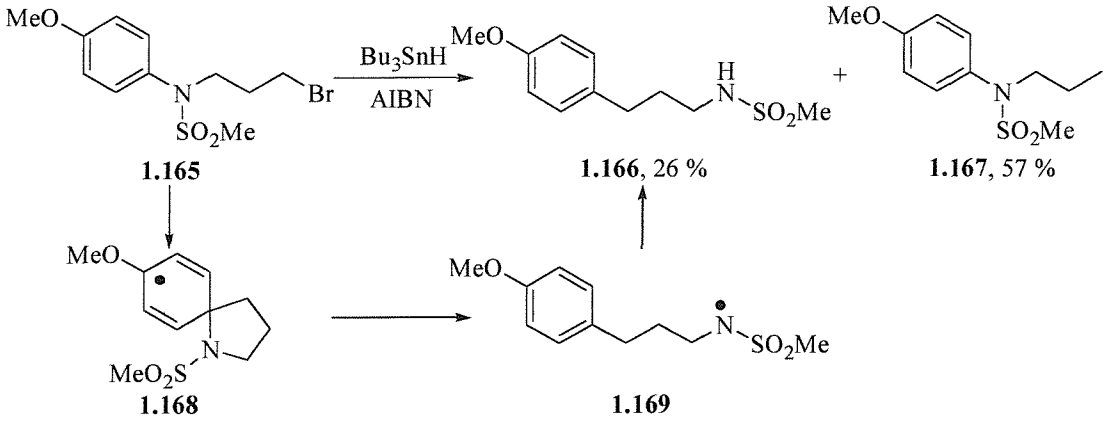
Ishibashi *et al.* have been prominent in the area of radical cyclisation chemistry for several decades. In 1990, they reported a difference in reaction pathway between sulfonamide **1.156** and amide **1.160**.[33] Thus, when bromoethyl sulfonamide **1.156** was subjected to tributyltin hydride and AIBN in refluxing toluene, products of cyclisation resulting from *ortho* attack on the arene were observed. However, when amide **1.160** was employed, a product of *ipso* attack was observed with *ortho*-attack completely disfavoured (Scheme 1.34).[33] This represents the first example of a carbon-based leaving group being ejected after an *ipso* addition reaction.



Scheme 1.34

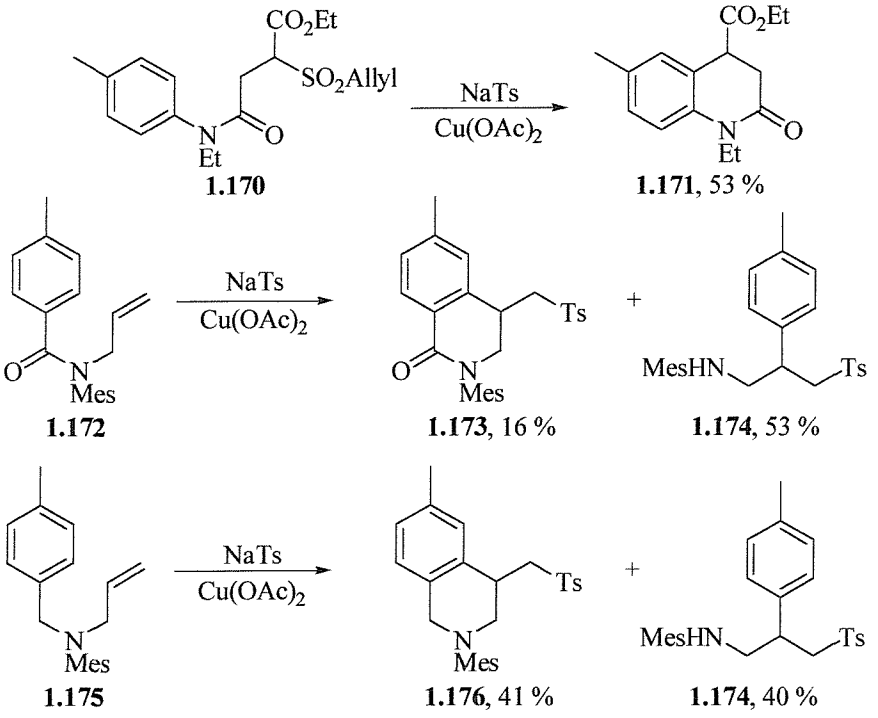
Employing a naphthalene group as the radical acceptor allowed trapping of a spirocycle akin to **1.163** in good yield (45 %).[33] That the sulfonamide and amides followed a different course was attributed to the geometry and stability of the alkyl radical formed by carbon-to-halogen homolysis.

Work by Lee *et al.* also demonstrated how a subtle change in tethering chain could indeed have a huge influence over the reaction pathway followed.[34] By moving the nitrogen atom so that it was conjugated to the arene (*e.g.* **1.165**), reaction occurred exclusively *via* an *ipso* pathway. Fragmentation of the resulting spirocycle **1.168** followed, leading to the nitrogen-centred radical **1.169**. Best results were obtained when the radical acceptor contained a *para*-carbonyl and *ortho*-methoxy group (Scheme 1.35).



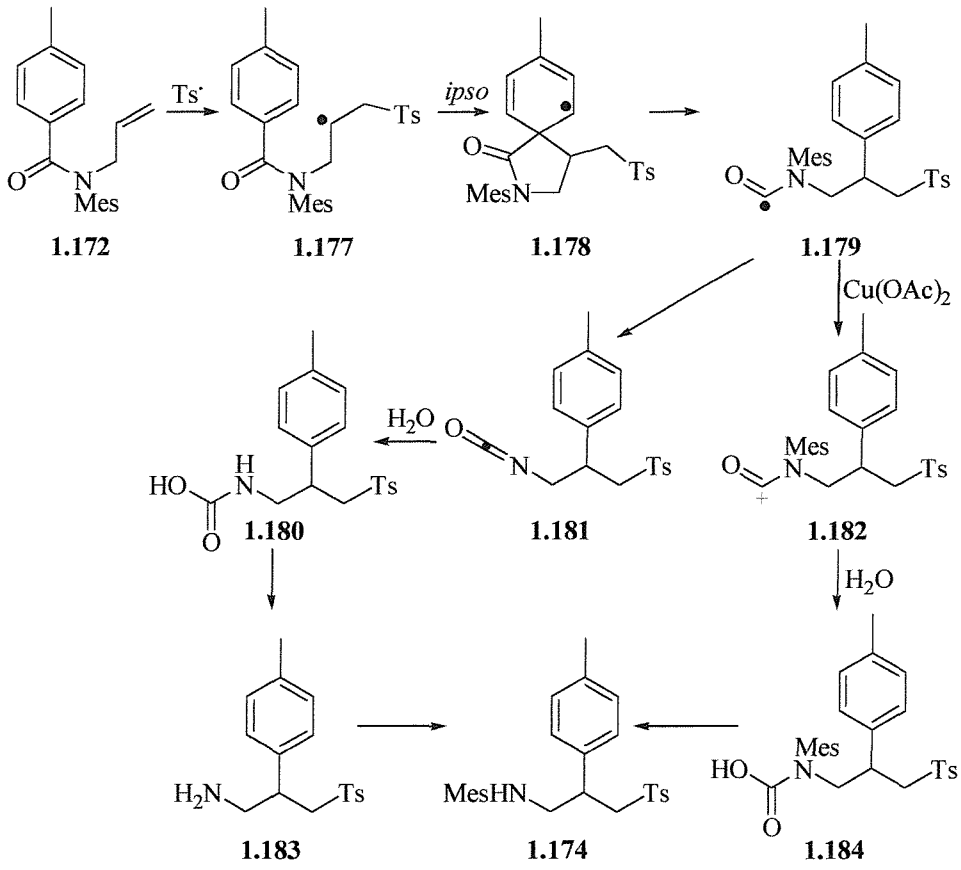
Scheme 1.35

In two publications by the group of Chuang, *N*-arylamides have been shown to preferentially undergo *ortho* attack on the arene (*viz.* **1.170** → **1.171**). However, when the orientation of the amide was reversed reaction was biased towards *ipso* attack. Removal of the carbonyl led to a 1:1 mixture of products derived from *ortho* and *ipso* attack, demonstrating the subtle influence of the tethering chain (Scheme 1.36).[35,36]



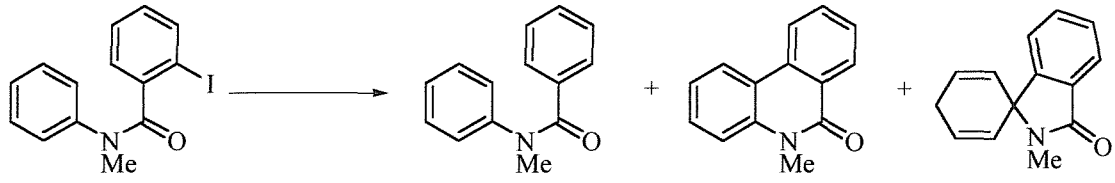
Scheme 1.36

The reversal in amide orientation undoubtedly leads to conformational change. It also effects the electronic character of the radical acceptor. It was suggested that the acyl radical intermediate **1.179** gave **1.174** by two routes; one occurring by forming an isocyanate while the other proceeds *via* oxidation of the acyl radical to an acyl cation with copper(II) (Scheme 1.37).[35]



Scheme 1.37

Several groups have examined the addition of aryl radicals to arenes tethered by a nitrogen-containing chain. Crich *et al.* and Bowman *et al.* have shown that such reactions are often inefficient processes.[37-40] Thus, subjecting **1.185** to tributyltin hydride and AIBN gave **1.187** in 12 % yield. Addition of benzeneselenol, an efficient hydrogen atom donor, improved reaction efficiency with spirocycle **1.188** being given in 43 %. It was suggested that a neophyl-type rearrangement occurred to give tricycle **1.187** (Scheme 1.38).

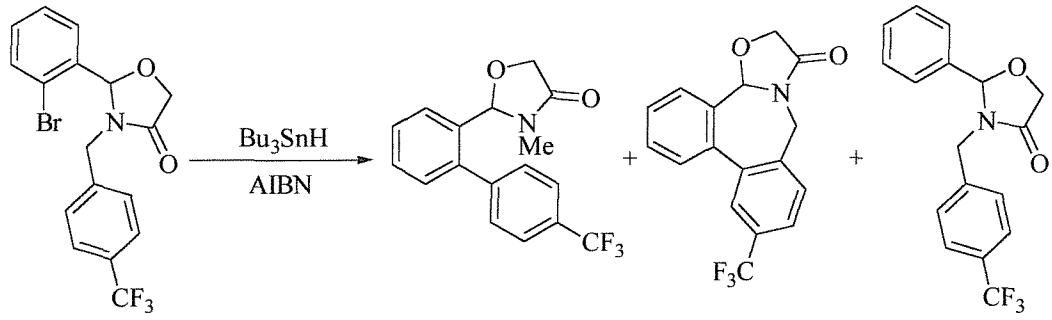


37 %	Bu_3SnH, AIBN	23 %	12 %	0 %
0 %	Bu_3SnH, PhSeH, AIBN	22 %	22 %	43 %

Scheme 1.38

Ipso attack was found to be dominant when an *N,O*-acetal was employed as part of the tethering chain.[41] Thus, treatment of aryl bromide **1.189** with tributyltin hydride and AIBN gave a mixture of two biaryl products **1.190** and **1.191** together with the product of reduction

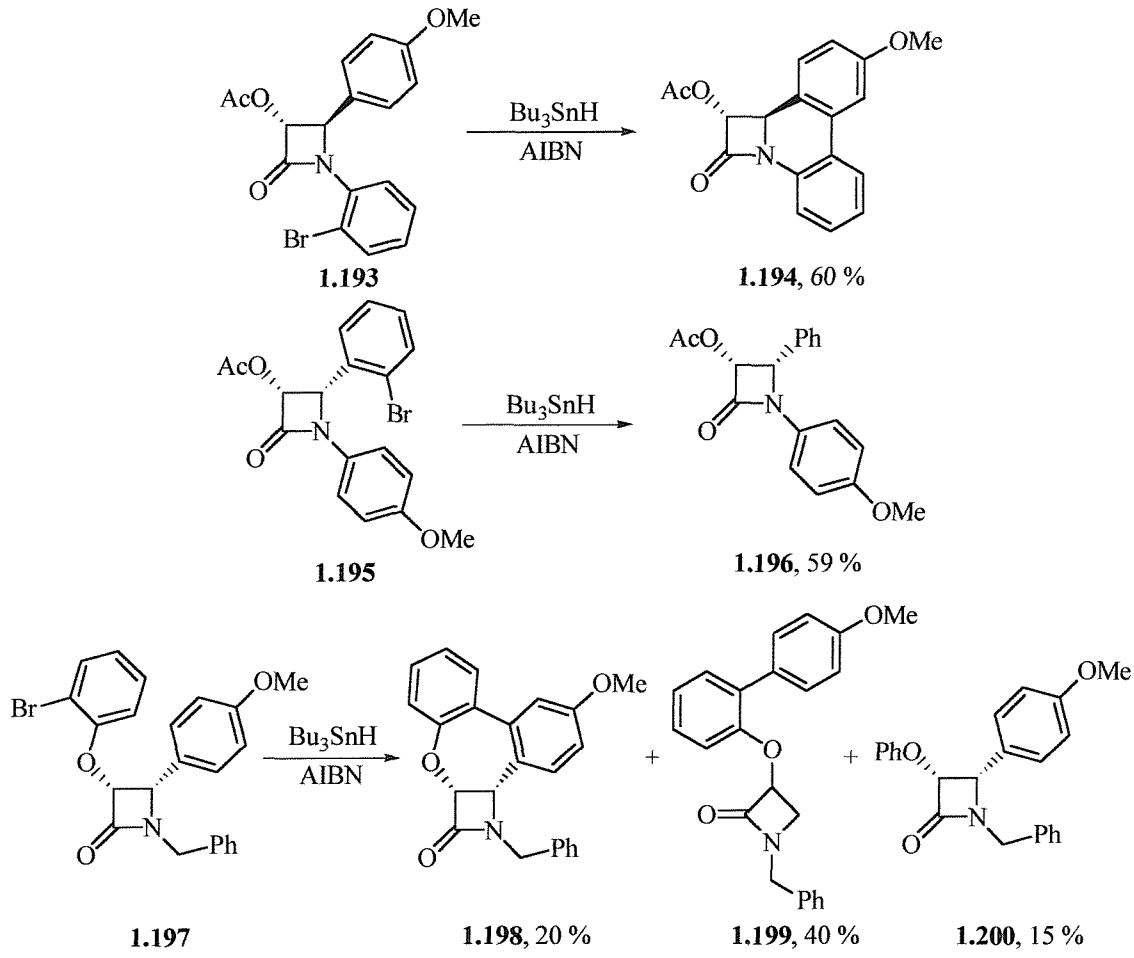
1.192 (Scheme 1.39). Notably, deuterium-labelling studies indicated that reduction of the carbon-bromine bond occurred *via* an intramolecular 1,5-hydrogen atom transfer from the benzylic carbon.



1.189 **1.190**, 46 % **1.191**, 9 % **1.192**, 28 %

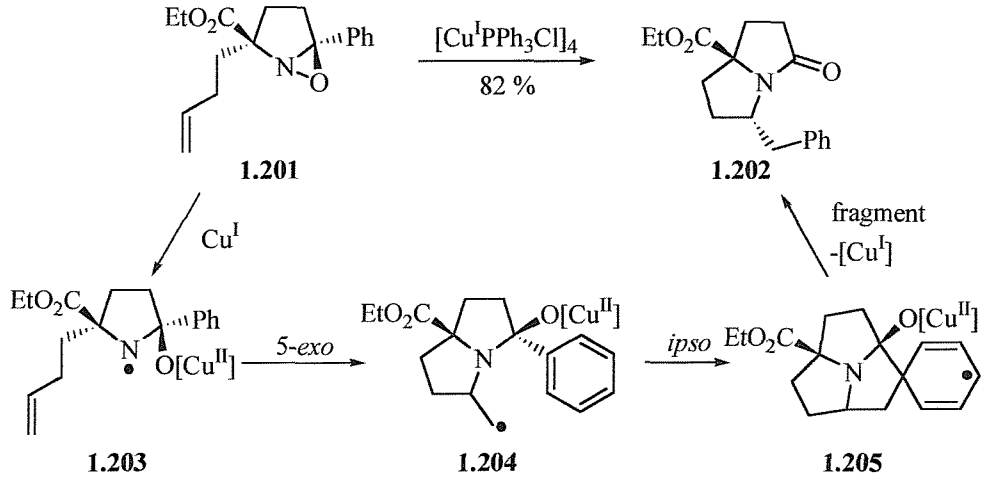
Scheme 1.39

One of the more exotic linkages to have been employed as a tether for aryl-aryl coupling is the azetidinone group.[42] The position of attachment of the radical donor and acceptor was found to have a marked effect on the course of the reaction. If the radical acceptor was located on C-4 and the donor was located on nitrogen then *ortho* attack was predominant, *viz.* **1.193** → **1.194**. By contrast, if the bromoarene was located at C-4 and the radical acceptor was located on nitrogen, simple reduction was prevalent, *viz.* **1.195** → **1.196**. Moving the bromoaryl group to C-3 resulted in a mixture of *ortho* and *ipso* attack (Scheme 1.40).[42]



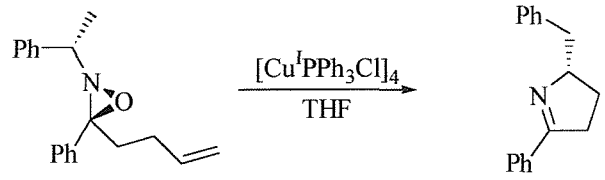
Scheme 1.40

Oxaziridines have been used to initiate a cascade of cyclisation and fragmentation reactions in which the attack of a carbon-centred radical onto an adjacent arene is implicated. For example, treatment of oxaziridine **1.201** with copper(I), iron(II) or tributyltin hydride results in a nitrogen-centred radical **1.203** which undergoes cyclisation onto a proximal alkene generating an alkyl radical **1.204**. This can then add to the adjacent arene giving **1.205**, which fragments with concomitant rearomatisation to yield bicycle **1.202** (Scheme 1.42).[43]



Scheme 1.41

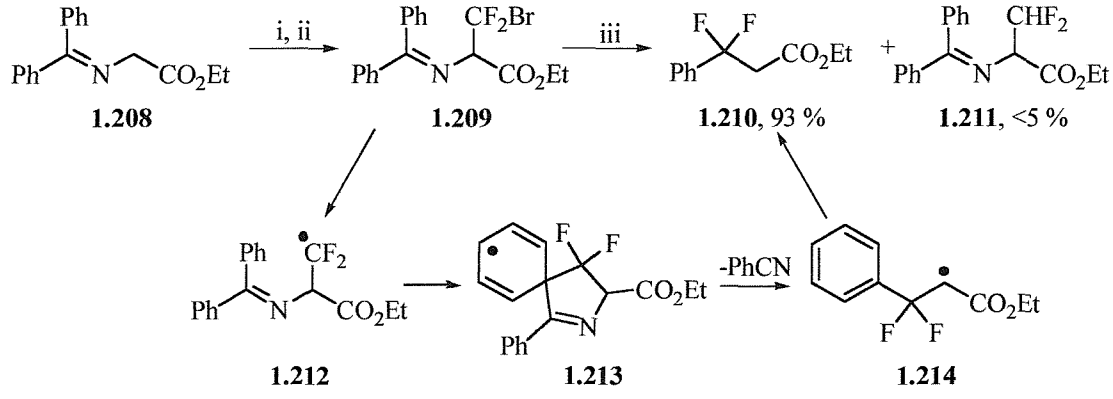
Work by the group of Aubé has also investigated open-chain examples *e.g.* **1.206** → **1.207**. Notably, excellent stereocontrol was achieved in these cyclisation reactions (Scheme 1.42).[44]



1.206 **1.207**, 66 %, ≥ 95 % e.e.

Scheme 1.42

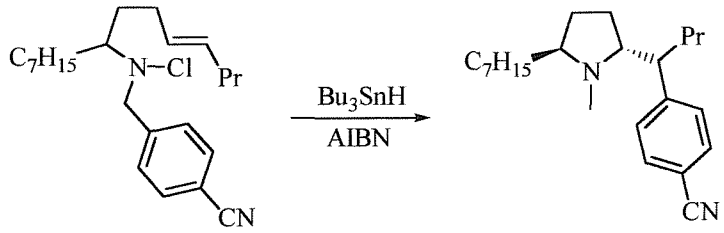
Imines provide a further tether for radical cyclisation reactions of this type. Treatment of Schiff base **1.208** with a strong hindered base and quenching with dibromodifluoromethane gave bromodifluoro derivative **1.209**. Treatment of the material with tributyltin hydride and AIBN induced a phenyl migration to give **1.210** as the major product.[45] Reaction was facilitated by the loss of cyanobenzene and required elevated reaction temperature. (Scheme 1.43).



Reagents & Conditions: **i.** LTMP, THF, -78 °C; **ii.** CF_2Br_2, 84 %; **iii.** Bu_3SnH, AIBN, benzene, 110 °C, 2½ h.

Scheme 1.43

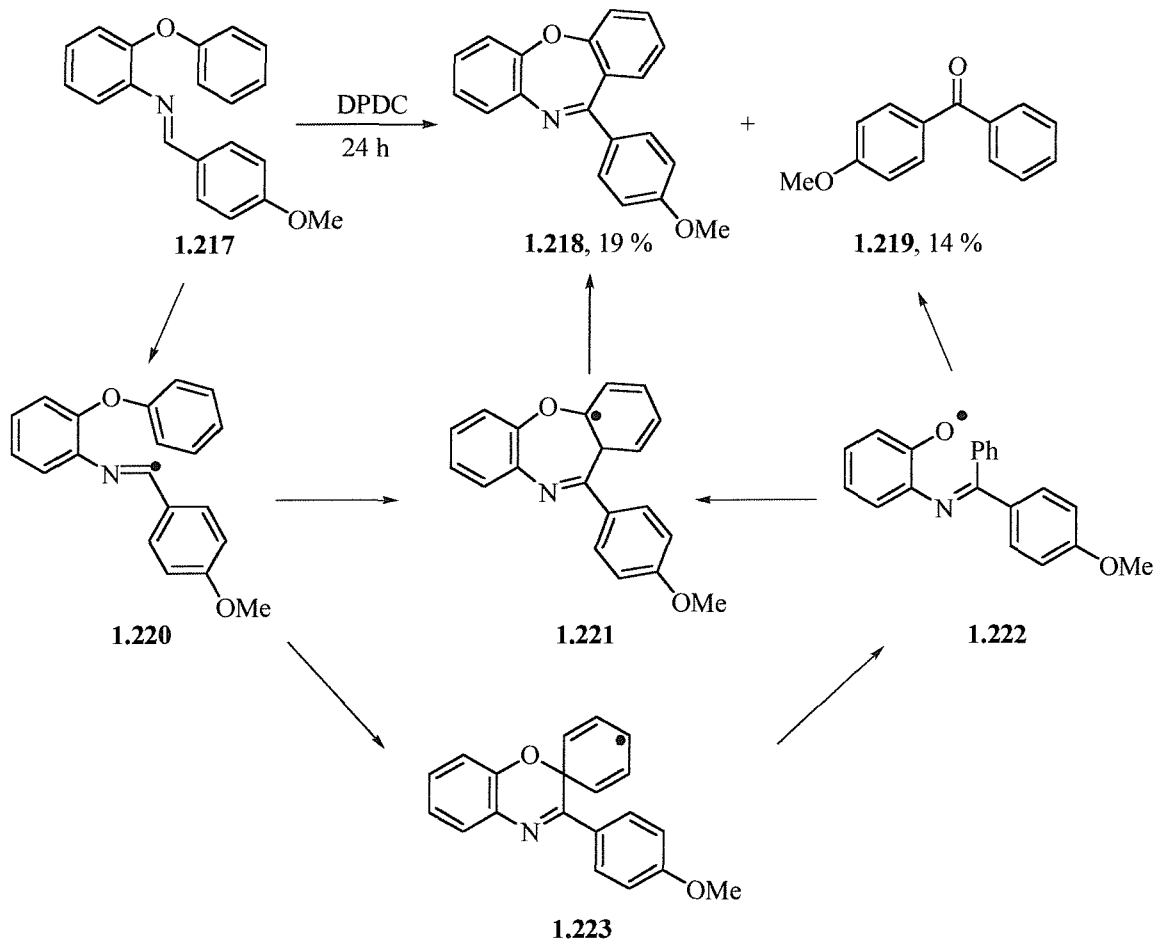
Senboku *et al.* employed an *N*-chloroamine as a precursor for radical cyclisation reaction.[9] Treatment of **1.215** with tributyltin hydride and AIBN gave a nitrogen-centred radical that cyclised in a 5-*exo*-trig fashion onto an alkene generating a carbon-centred radical. Subsequent *ipso* attack onto the adjacent *N*-benzyl group was followed by fragmentation leading to a nitrogen-stabilised methylene radical. Hydrogen atom abstraction from tributyltin hydride yielded methylamine **1.216**. Electron rich arenes were found to be poor substrates for the reaction (Scheme 1.44).[9]



1.215 **1.216**, 67 %

Scheme 1.44

Nanni *et al.* have examined related radical cyclisation reactions of *N*-arylidene-2-aryloxybenzenamines.[46,47] Although yields were generally low, they found that a mixture of products from *ipso* and *ortho* attack were formed when **1.217** was treated with DPDC. Best yields were obtained when electron rich or electron deficient radical donor arenes were employed (Scheme 1.45).[47]



1.217 **1.218**, 19 % **1.219**, 14 %

1.220 **1.221** **1.222**

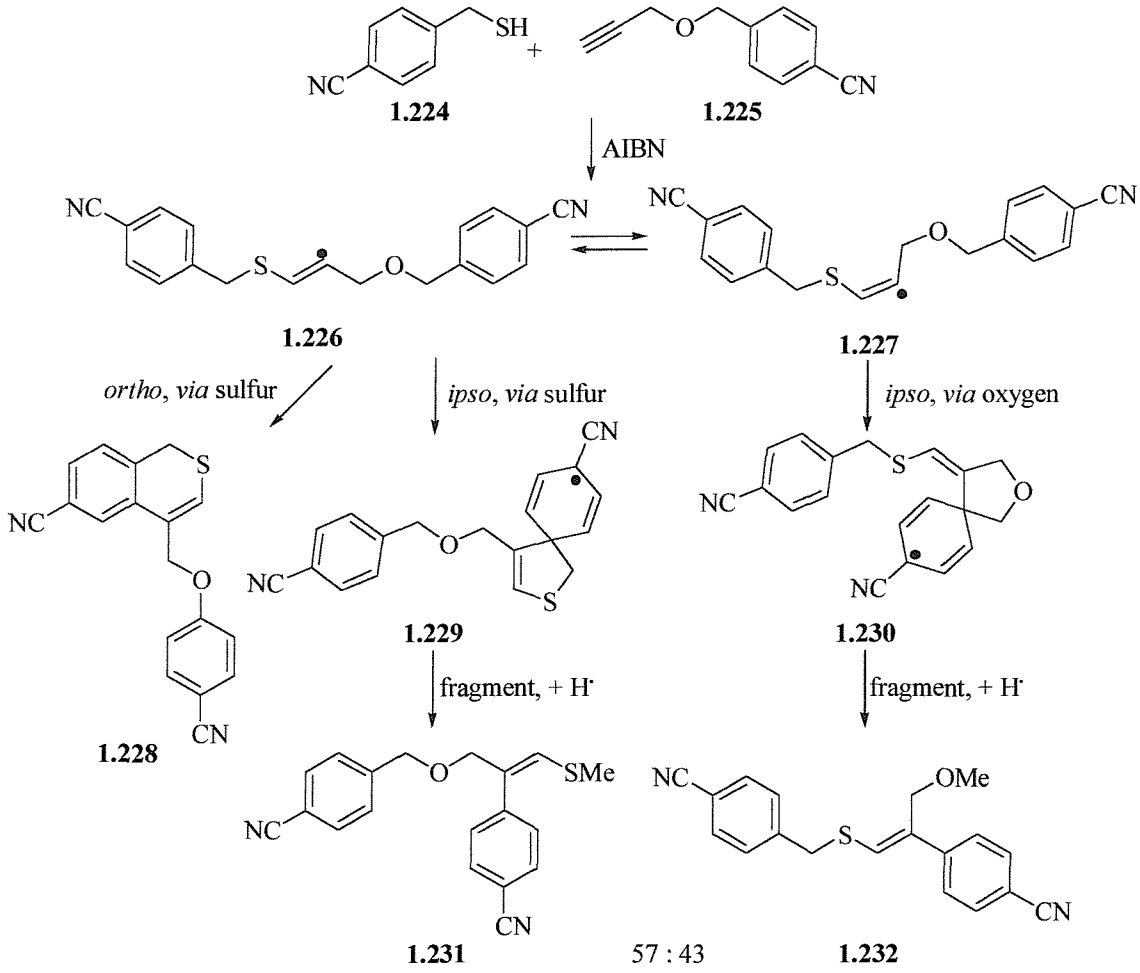
1.223

Scheme 1.45

1.2.5 Tethering Chains Containing Oxygen

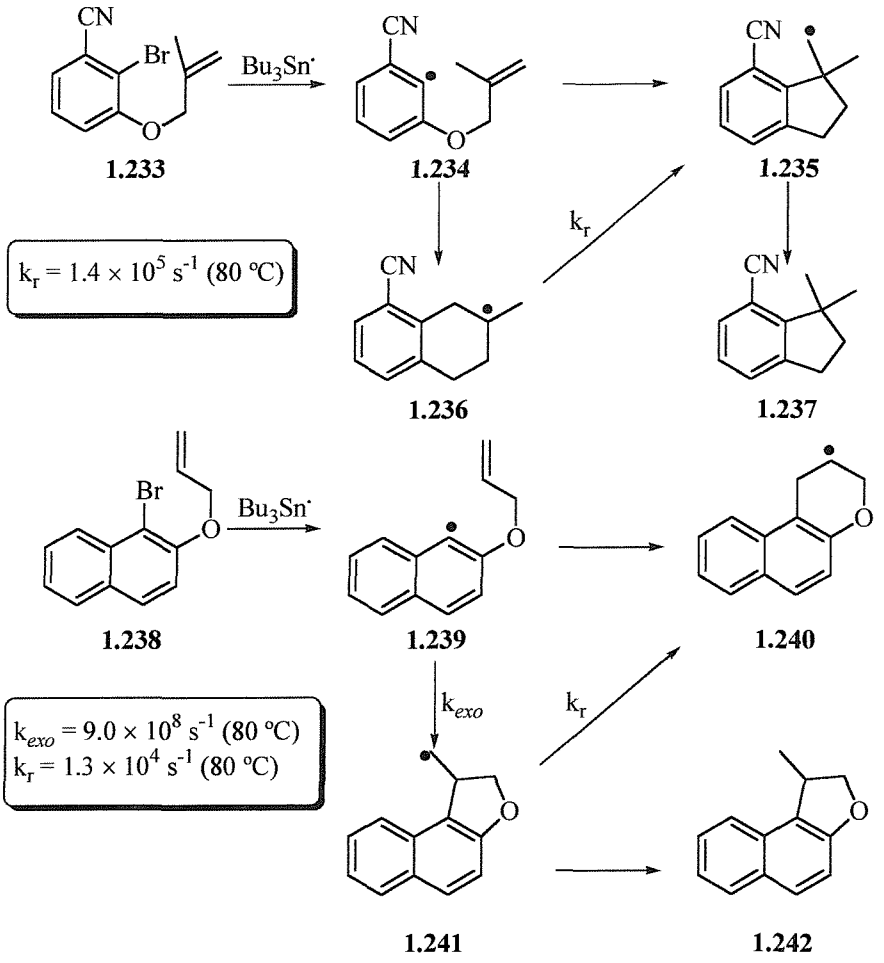
Oxygen tethers have also been widely employed. Montevecchi *et al.* detailed some examples of cyclisation using an ether linkage. Thus, addition of **1.224** to alkyne **1.225** induced an *ipso* attack of the resulting vinyl radical **1.226** onto either of the proximal arenes. Thiopyran

1.228 was also obtained as a minor product. Changing substituents on the arenes was found to alter the ratio of thiopyran to vinylmethylsulfide formed suggesting that both 5-*exo*-trig and 6-*endo*/*exo*-trig cyclisation pathways were operating (Scheme 1.46).[48]



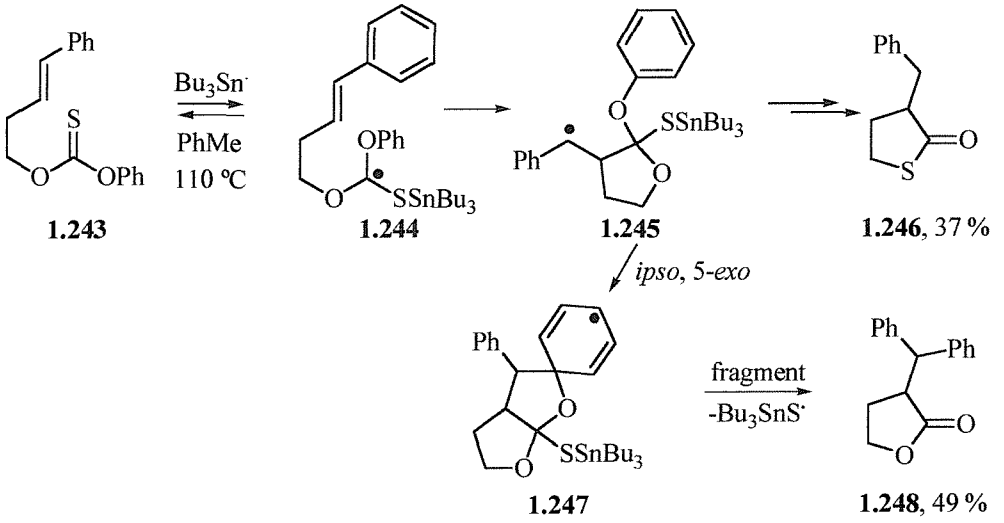
Scheme 1.46

Beckwith *et al.* during the 1980s examined the cyclisation reaction of a range of bromoaryl ethers.[3] Kinetic studies on the rate of neophyl rearrangement were undertaken (see Section 1.2.1) and it was found such rearrangements were faster with a naphthalene ring than with the equivalent arene. Introduction of an electron-withdrawing group was found to facilitate the process (Scheme 1.47).[3]



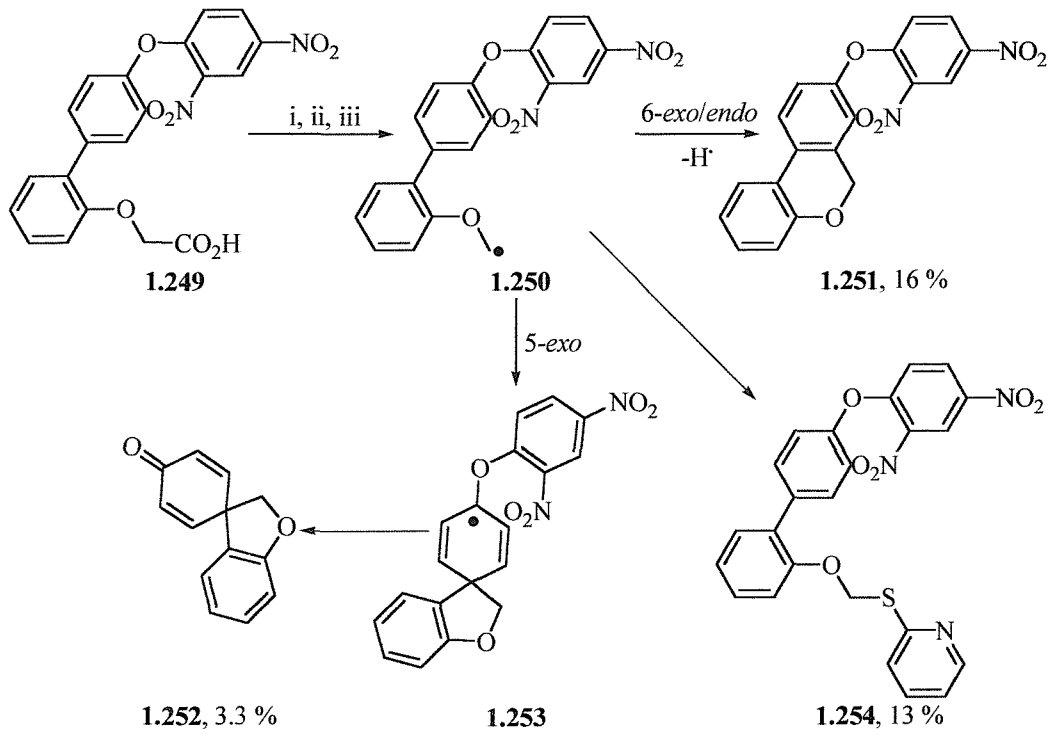
Scheme 1.47

In 1989 Bachi reported that thiocarbonate **1.243**, when exposed to tributyltin hydride, gave lactone **1.248** and thiolactone **1.246** in 49 % and 37 % yield respectively.[49,50] The formation of **1.248** was rationalised by a cascade of radical reactions ending with cyclisation onto the proximal phenyl ring **1.247**. Fragmentation and loss of tributyltinthiyl radical yielded lactone **1.248** (Scheme 1.49).



Scheme 1.49

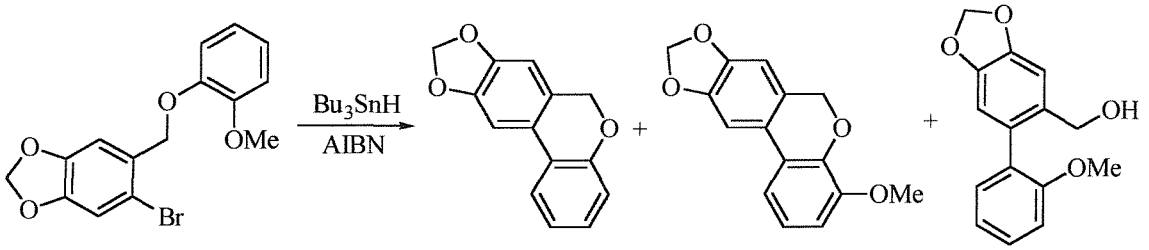
Whiting, in 1998, reported some studies relating to the biogenesis of the lignans interiorin and kadsulignans. Of particular interest was the finding that oxymethylene radical **1.250**, formed by Barton decarboxylation of **1.249**, underwent cyclisation onto an adjacent arene in a 6-*endo*/*exo*-trig manner.[51] Other products isolated included adducts such as **1.254** and traces of spirocycle **1.252** originating from an *ipso* attack of the arene (Scheme 1.49).



Reagents and Conditions: **i.** $(COCl)_2$, **ii.** sodium salt of 2-thiopyridine-*N*-oxide, **iii.** hν.

Scheme 1.49

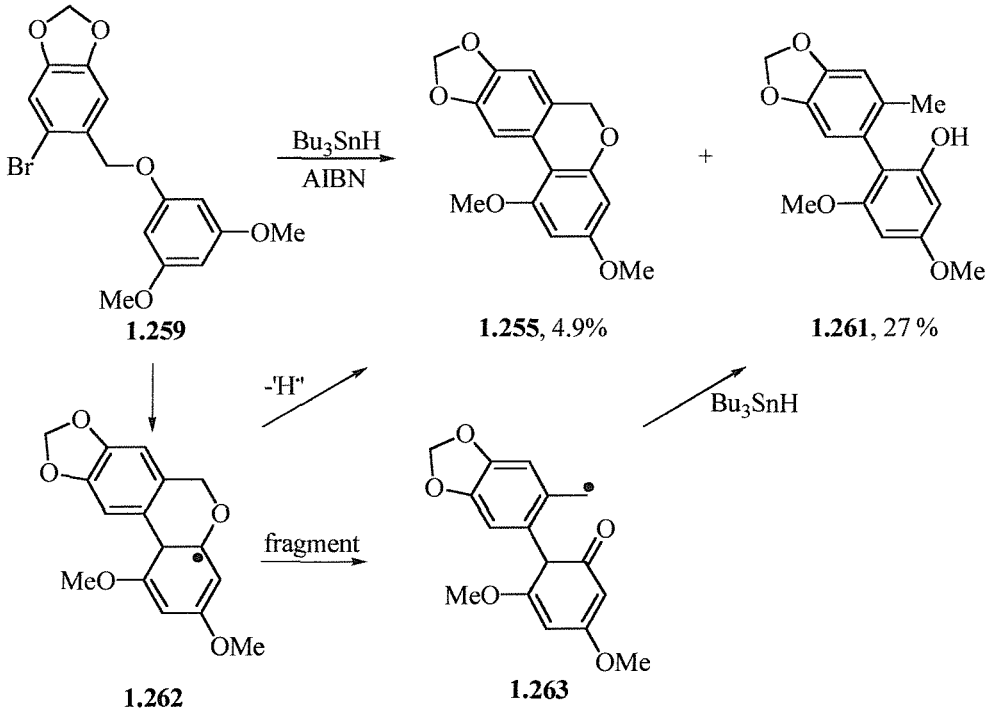
Buoyed by their successes with intramolecular radical additions of aryl radicals to arenes tethered with an amine, Lobo *et al.* reported that 2-bromobenzyl aryl ethers were also suitable substrates for radical reactions.[52] In the parent case, 2-bromobenzyl phenyl ether yielded 6*H*-benzo[*c*]chromene in 48 % under standard tin-mediated conditions. Incorporation of *ortho*/*para*- electron donating groups decreased reaction efficiency. Notably, when an *ortho*-methoxy group was introduced, *e.g.* **1.255**, products due to *ortho* addition and loss of methoxide (*e.g.* **1.256**) were isolated (Scheme 1.50).



1.255 **1.256**, 68 % **1.257**, 5.2 % **1.258**, 18 %

Scheme 1.50

When a 3,5-dimethoxyphenyl group was employed, the major product was a phenol which was rationalised by intermediate stabilisation (Scheme 1.51).[52] The methodology was subsequently applied to the synthesis of a range of natural products.[32,52]

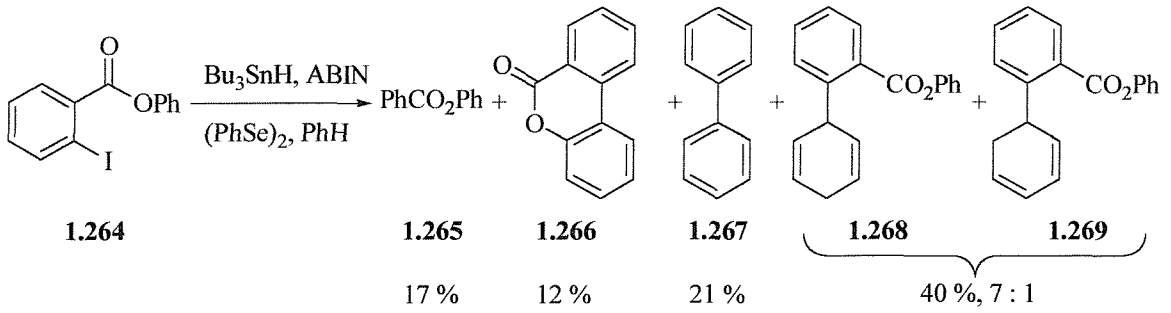


1.259 **1.255**, 4.9% **1.261**, 27 %

1.262 **1.263**

Scheme 1.51

Crich also extended his investigation of *N*-aryl arylamides to include esters. These were found to be very poor substrates due the strong preference for the ester to exist in an s-*trans* configuration. Thus, exposure of **1.264** to tributyltin hydride and AIBN in the presence of benzeneselenol gave a mixture of products including carbon-to-iodine bond reduction (**1.265**), cyclisation (**1.266** & **1.267**) and reaction with solvent (**1.268** and **1.269**) (Scheme 1.52).[37]

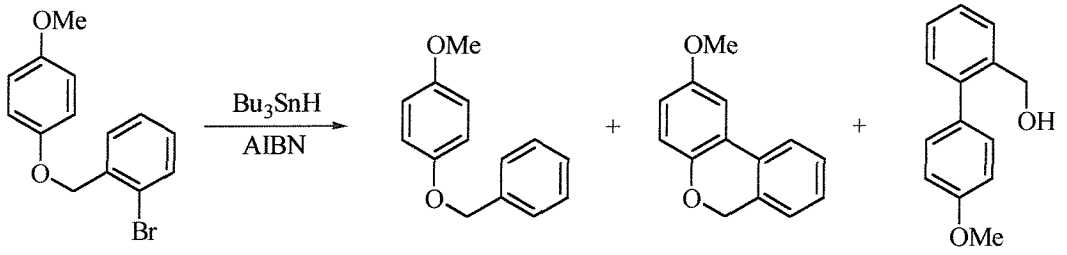


1.264 **1.265** **1.266** **1.267** **1.268** **1.269**

17 % 12 % 21 % 40 %, 7 : 1

Scheme 1.52

Bowman *et al.* also studied a range of aryl benzyl ethers with the intention of applying this method to the synthesis of 6*H*-benzo[*c*]chromenones – the core of a range of natural products.[53] After independently finding that iodoaryl benzyl esters were poor substrates, they began an investigation into the use of aryl benzyl ethers. Most cases examined employed a bromobenzyl group and resulted in a mixture of chromene and biaryl products.[53]

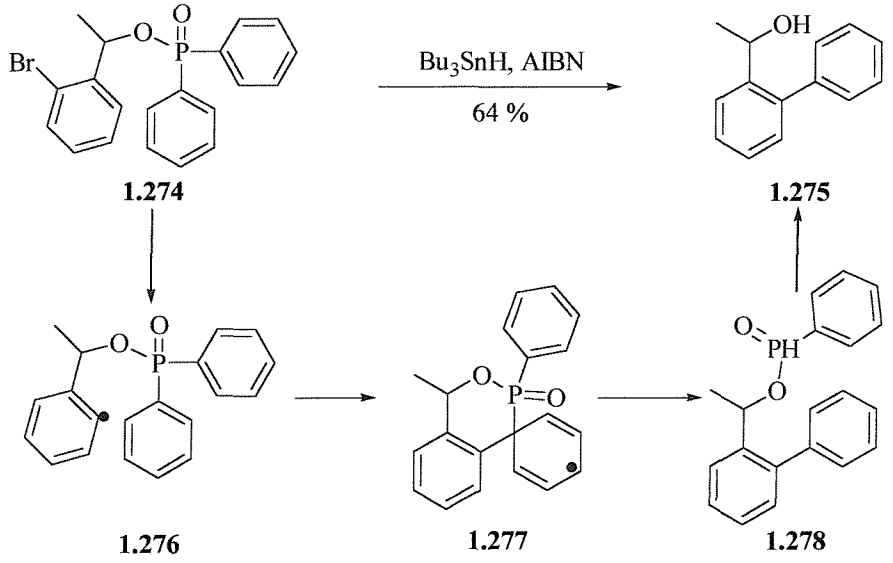


1.270 **1.271**, 14 % **1.273**, 21 % **1.273**, 24 %

Scheme 1.53

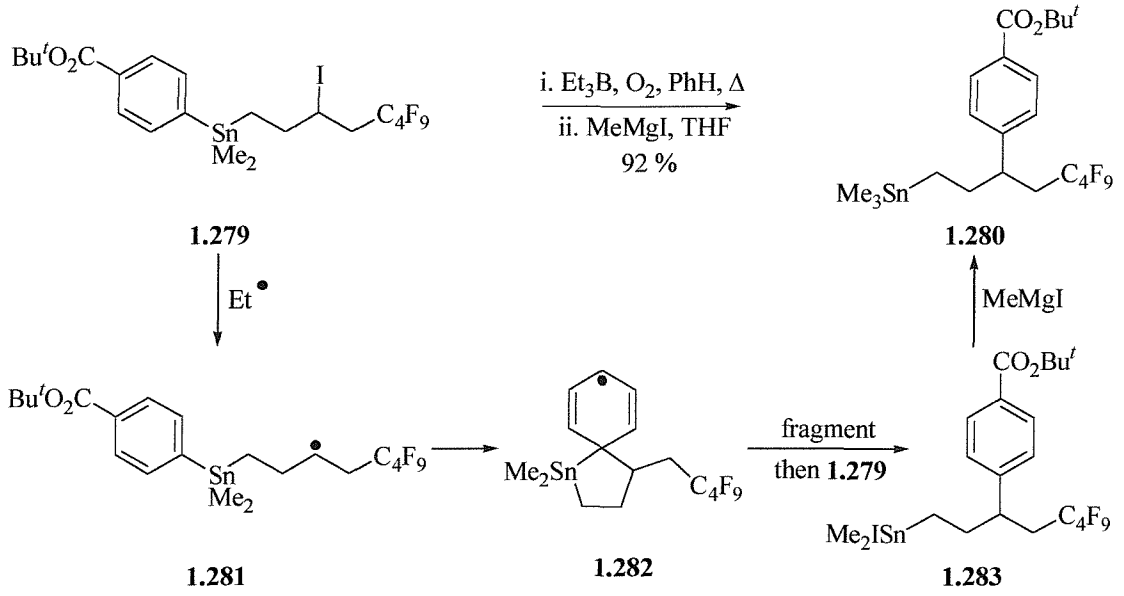
1.2.6 Miscellaneous Tethering Units

Clive *et al.* have investigated the use of phosphinates as tethers for radical reactions to induce transfer of an arene from phosphorus to carbon.[54,55] A range of phosphinates were synthesised and exposed to tributyltin hydride and AIBN in xylene. All the substrates tested underwent the desired reaction with the electron character of the aromatic attached to phosphorus having a minor influence on the course of the reaction. Reaction proceeded *via* a 6-*exo*-trig cyclisation onto the adjacent arene. Fragmentation with concomitant rearomatisation then gave a phosphorus-centred radical which was quenched by reaction with tributyltin hydride. The pathway from **1.278** to alcohol **1.275** was studied but no conclusions could be drawn (Scheme 1.54).



Scheme 1.54

To the best of our knowledge there is only one example in which a carbon-centred radical undergoes an intramolecular cyclisation onto an arene when tethered by a chain containing tin. Thus, Oshima *et al.* exposed stannane **1.279** to triethylborane in the presence of oxygen and isolated the corresponding arylalkane **1.280**. Yields were generally good with only one example proceeding in less than 50 % (a *para*-methoxyphenyl ring was attached to the tin centre in this case).[56] Reaction was presumed to occur *via* an *ipso* attack onto the arene. Fragmentation then gave a tin-centred radical that could react with alkyl iodide **1.279** to propagate the radical chain (Scheme 1.55).



Scheme 1.55

1.3 Conclusions

A wide range of substrates has been used to accomplish the cyclisation of a carbon-centred radical onto an arene and an array of tethering chains have been utilised. Reaction can proceed by attack of the radical to the *ipso* or *ortho* carbon of the radical acceptor. The nature of the tethering chain dictates which pathway is followed. Reaction yields are variable and frequently give rise to a myriad of products. Neophyl-type rearrangements of intermediates together with the mechanism of the many non-reducing radical reactions mediated by tributyltin hydride are matters of much conjecture. Notwithstanding these observations, there exists much scope for the discovery of new and synthetically useful transformations in this field.

Chapter 2 - Radical Cyclisations of 2-Haloaryl Benzyl Ethers

2 *Radical Cyclisations of 2-Haloaryl Benzyl Ethers*

2.1 Background

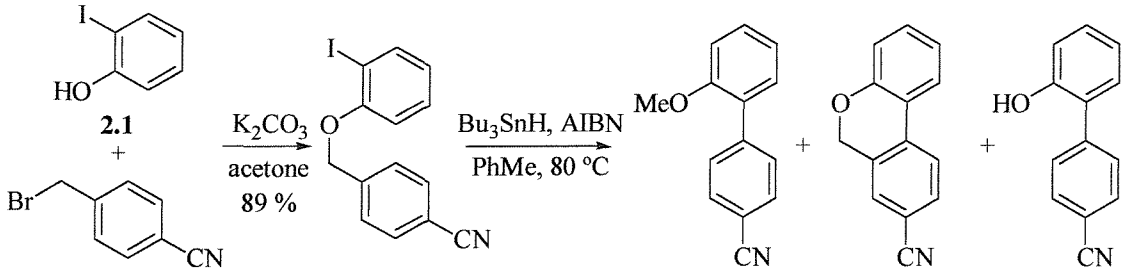
Additions of aryl radicals to arenes have received considerable attention over recent years. As described in Chapter 1, a variety of tethering chains have been employed including some incorporating an oxygen atom. When a tethering chain contains an oxygen atom cyclisation to the arene often occurs *via* a 5-*exo*-trig (*ipso*) pathway (where available).[23,53] *Ortho* attack and neophyl-type rearrangement of the spirocyclic intermediate derived from *ipso* attack are also possible.[53] The radical reactions of 2-haloaryl benzyl ethers have received only limited attention.[53] We therefore felt that there was scope for investigation of this chemistry.

2.2 Radical Cyclisations of 2-Haloaryl benzyl ethers

2.2.1 Preliminary Investigation

Our investigation began with the synthesis of an electron deficient benzyl ether. Despite some controversy over the nature of aryl radicals (there have been reports of aryl radicals having electrophilic,[57,58] nucleophilic,[59] and electron neutral character[38,60]) we believed that an electrophilic radical acceptor would provide a satisfactory test substrate for this study.

Union of 2-iodophenol **2.1** and 4-(bromomethyl)benzonitrile **2.2** provided 2-iodophenyl 4-cyanobenzyl ether **2.3** in good yield. Exposure of **2.3** to tributyltin hydride and AIBN in toluene (substrate concentration 0.03 M) at 80 °C gave three distinct products. The first was identified as aryl methyl ether **2.4**. The second was benzo[*c*]chromene **2.5** and finally the most polar compound was identified as phenol **2.6** (Scheme 2.1).



Scheme 2.1

The structure of benzo[*c*]chromene **2.5** was confirmed by GOESY NMR studies (Figure 2.2). Interestingly, this result differed from those reported in a related study by Bowman *et al.* where products akin to **2.7** had been isolated.[53] The formation of aryl methyl ether **2.4** and phenol **2.6** was equally surprising as the closest literature precedence for such a rearrangement involves fragmentation leading to a nitrogen-stabilised radical (Scheme 1.34).[33]

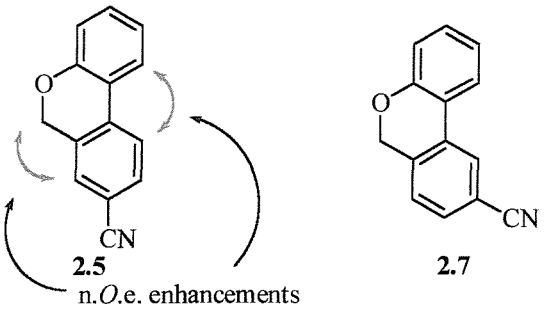
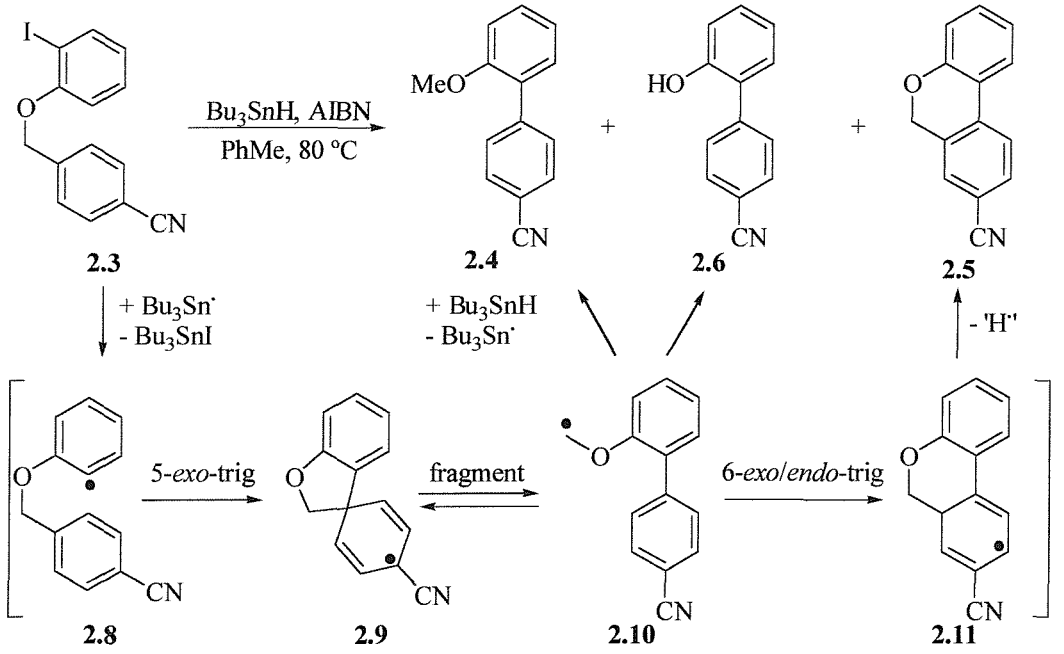


Figure 2.2

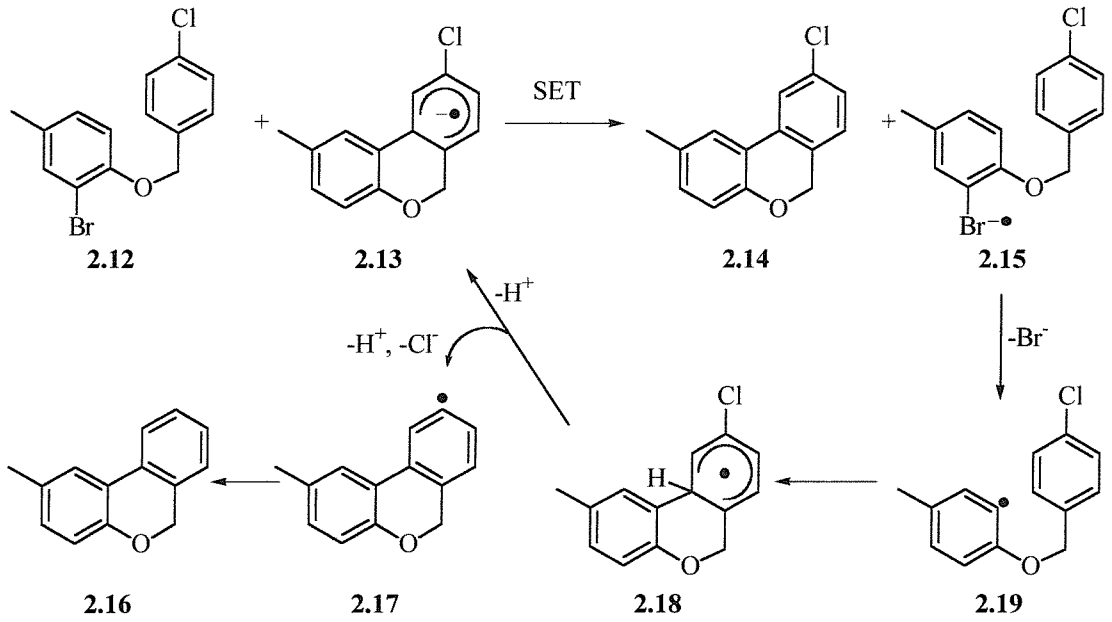
We suggest that all these products are derived from a common radical intermediate **2.10**. Exposure of iodide **2.3** to tributyltin radical first initiated a carbon-to-iodine bond homolysis. The resulting aryl radical then undergoes a 5-*exo*-trig cyclisation to the adjoining arene in an *ipso* manner. The resulting spirocyclic intermediate **2.9** then fragments regenerating the aromatic ring and producing the stabilised oxymethylene radical **2.10**. Four different pathways are now available. Firstly, hydrogen atom abstraction from tributyltin hydride accesses aryl methyl ether **2.4**. Alternatively, cyclisation to the arene may occur by one of two pathways. A 5-*exo*-trig cyclisation leads back to spirocycle **2.9** while a 6-*endo*/*exo*-trig cyclisation leads to tricycle **2.11**, a precursor to benzo[*c*]chromene **2.5**. Finally radical **2.10** can be converted to phenol **2.6** (Scheme 2.3).



Scheme 2.3

The mechanism by which **2.11** loses a hydrogen atom is unclear. There are numerous suggestions in the literature as to how this may proceed. Bowman investigated the possibility that a single-electron transfer between radical anion **2.13** and the starting material **2.12** was involved. He reasoned that with **2.12** the aryl chloride would be reduced if this mechanism

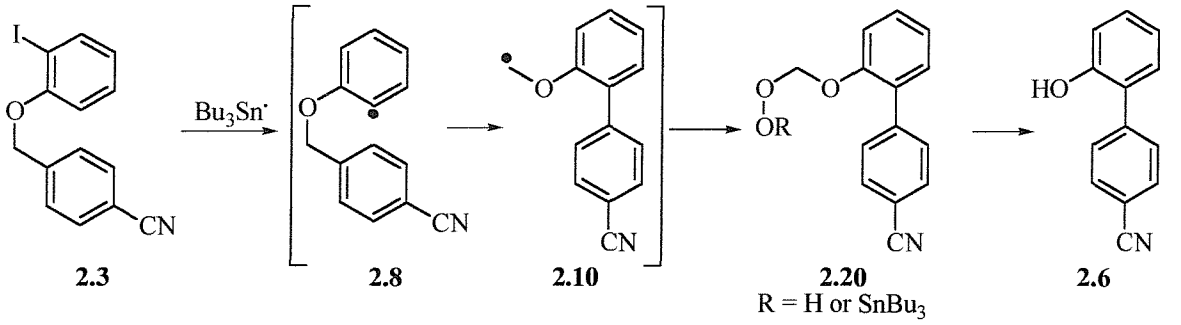
were followed. In the event the chlorine atom was retained in the major product **2.14** (Scheme 2.4).[53]



Scheme 2.4

Aromatisation by loss of hydrogen from a dihydroarene has also been suggested. Against this is the knowledge that such products can be isolated from Birch reductions and are reasonably stable. A fuller discussion of this step is presented in Chapter 5.

The origins of phenol **2.6** are also unclear. One possibility is that **2.10** is trapped with molecular oxygen and that the resultant peroxy hemiacetal collapses to reveal the phenol. Although the reaction was performed under a nitrogen atmosphere, rigorous degassing of the reaction was not undertaken. In addition, due to the low solubility of AIBN in toluene at room temperature, the initiator was added as a solid, again allowing air to enter the system. To test this hypothesis a solution of iodide **2.3** in toluene was thoroughly degassed and heated to 80 °C. A degassed solution of tributyltin hydride and a degassed toluene-solution of VAZO were then added over a period of 4 hours. After further heating, the mixture was cooled and the tributyltin residues removed by treatment with aqueous potassium fluoride. Standard work up and purification showed no evidence of phenol formation with benzo[*c*]chromene **2.5** produced as the major product (45 %) along with a small quantity of aryl methyl ether **2.4** (< 5 %) and recovered starting material (31 %). It can therefore be assumed that phenol **2.6** does indeed derive from reaction of intermediate **2.10** and oxygen and that the peroxy hemiacetal formed collapses to phenol **2.6** *in situ* or on work-up (Scheme 2.5).



2.3 **2.8** **2.10** **2.20** R = H or $SnBu_3$ **2.6**

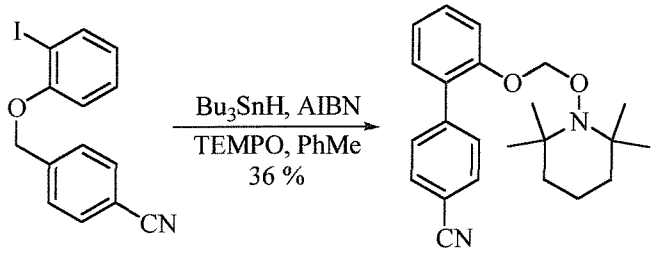
Scheme 2.5

A short investigation into the effects of temperature and concentration was undertaken, the results of which are summarised in Table 2.6. Production of benzo[*c*]chromene **2.5** was found to be much more facile at higher temperature (entry **b**). When an eight-fold increase in concentration was made (entry **c**) the yield of aryl methyl ether **2.4** increased to 30 %. Presumably with rigorous degassing of the solvent this yield could be increased yet further. Interestingly, no products derived from direct reduction of the starting material were observed.

Expt. No.	[**2.3**]/mol dm^{-3}	Temp. / °C	Yield phenol **2.6** / %	Yield benzo[*c*]chromene **2.5** / %	Yield methyl ether **2.4** / %
a.	0.03	80	43	22	< 6
b.	0.03	110	19	65	< 5
c.	0.24	80	25	30	30

Table 2.6

Further evidence for the mechanistic course outlined in Scheme 2.3 was obtained by treatment of aryl iodide **2.3** with tributyltin hydride and AIBN in the presence of TEMPO. The only product isolated from the reaction, albeit in moderate yield, was the TEMPO adduct **2.21**. From this the intermediacy of **2.10** can be inferred (Scheme 2.7).



2.3 **2.21**

Scheme 2.7

2.2.2 Exploring the Scope of the Methodology

With the mechanism of reaction sufficiently well established, an investigation into its scope and limitations was embarked on. Thus, a series of 2-iodoaryl benzyl ethers were subjected to standard tributyltin-mediated radical forming conditions (Table 2.8).

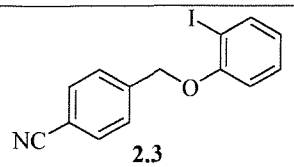
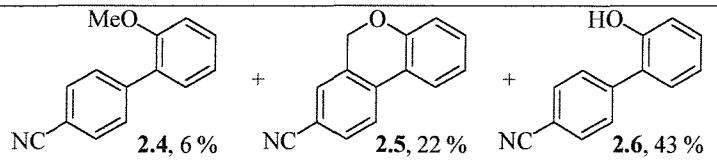
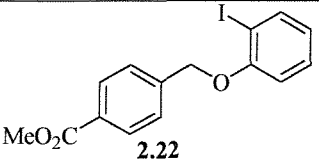
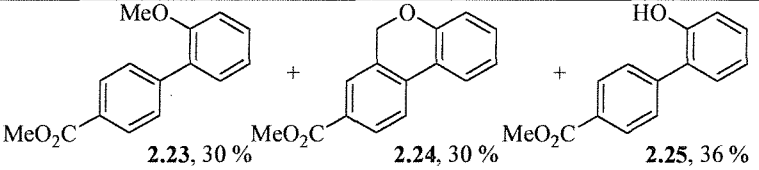
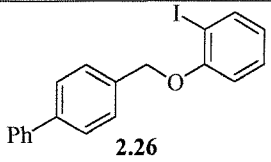
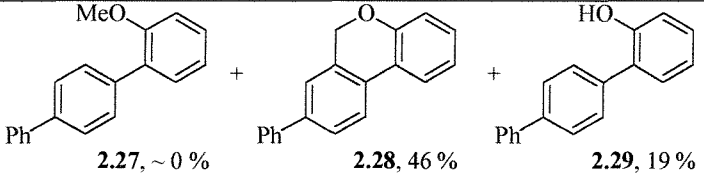
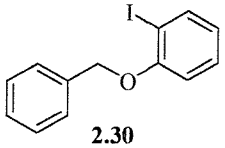
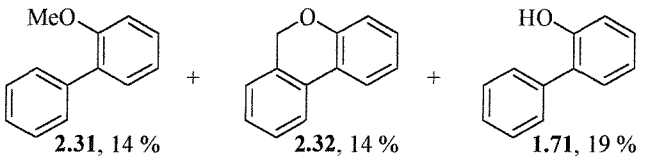
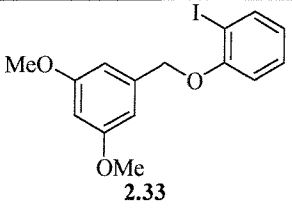
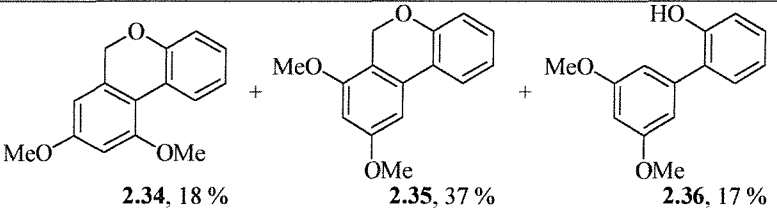
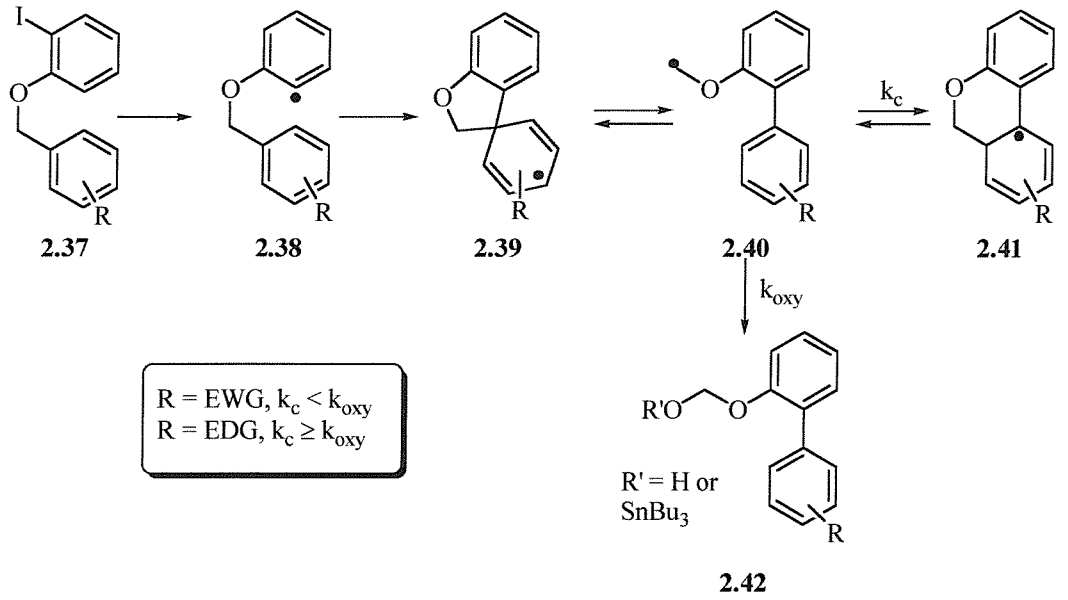
	Substrate	Products (%)
a	 **2.3**	 **2.4**, 6 % + **2.5**, 22 % + **2.6**, 43 %
b	 **2.22**	 **2.23**, 30 % + **2.24**, 30 % + **2.25**, 36 %
c	 **2.26**	 **2.27**, ~ 0 % + **2.28**, 46 % + **2.29**, 19 %
d	 **2.30**	 **2.31**, 14 % + **2.32**, 14 % + **1.71**, 19 %
e	 **2.33**	 **2.34**, 18 % + **2.35**, 37 % + **2.36**, 17 %

Table 2.8

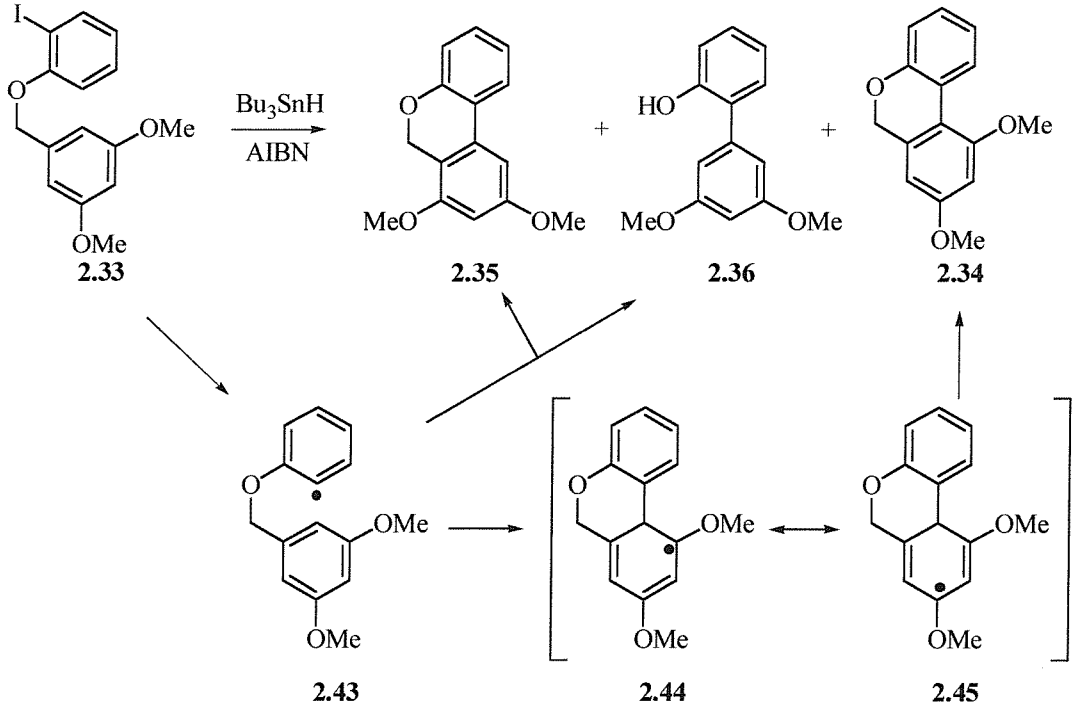
General trends observed from these results show that a phenolic product tended to dominate when an electron-deficient aryl radical acceptor was used while an electron-rich arene tended to produce benzo[*c*]chromenes as the major products. This would seem to imply that reaction of the intermediate oxymethylene radical with an adjacent arene was faster and more effective with an electron-rich aromatic system. Some qualitative information of relative rates in the reaction sequence can be obtained from this. At 80 °C, assuming that cyclisation of aryl radical **2.38** is fast and irreversible and that the subsequent fragmentation (**2.39** → **2.40**) is also relatively fast, the product mixture is determined by the rate of formation of

radical intermediate **2.41** relative to the rate of intermolecular reactions of intermediate **2.40**, such as quenching with oxygen. In the case of electron-deficient systems (R = EWG), the cyclisation is slow compared to reaction with oxygen so that the major product is a result of reaction with oxygen ($k_c < k_{oxy}$). However, under the same conditions, when the electron density of the aromatic ring is increased (R = EDG), the second cyclisation step has at least a comparable rate to oxygen quench ($k_c \geq k_{oxy}$) (Scheme 2.9).



Scheme 2.9

The formation of benzo[*c*]chromene **2.34** presumably benefits from the stabilisation of radical intermediate **2.44/2.45** by the two methoxy groups on the radical acceptor ring (Scheme 2.10). That intermediate stabilisation plays a significant role in determining product ratios has also been noted by Lobo *et al.* (Scheme 1.51).[52]

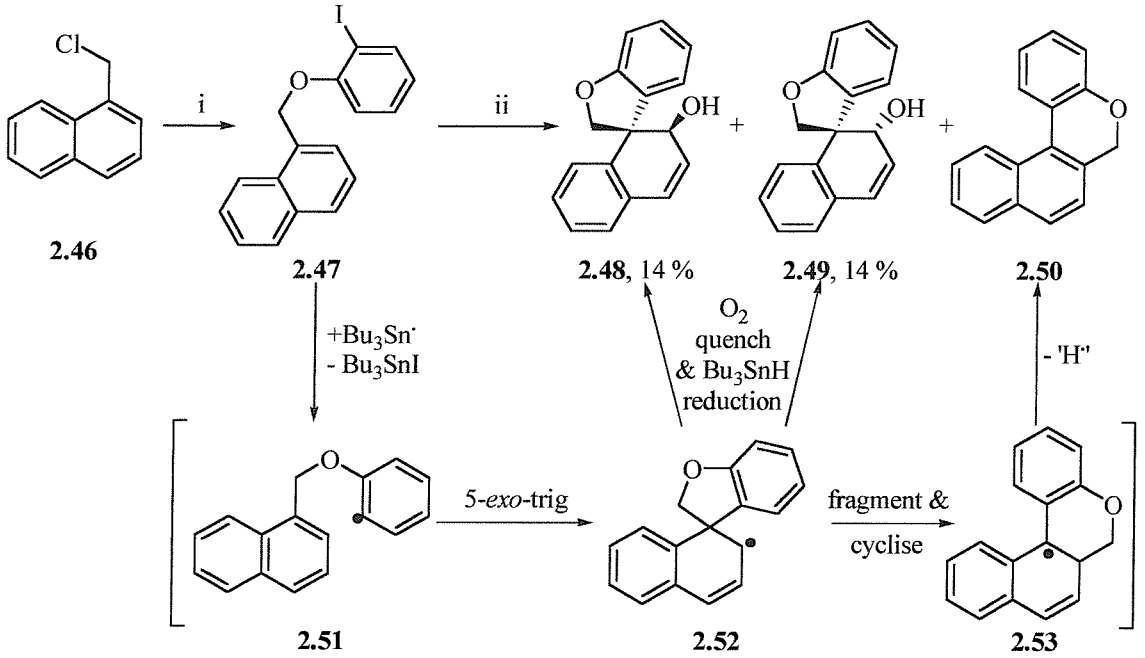


Scheme 2.10

Practically, a number of cases proved difficult to purify. Separation of tricyclic products from the corresponding aryl methyl ether was not possible in several instances. In those cases, product identification was based on ^{1}H- and ^{13}C-NMR analysis and GC-MS data (see Experimental Section).

Also, although a minor product of reaction, our methodology provides a short route to 2-hydroxy-3',5'-dimethoxy-1,1'-biphenyl **2.36**. This compound was isolated from the sapwood of *Sorbus aucuparia* and given the trivial name isoaucuparin.[61-63]

Though low yielding, cyclisation of naphthenyl ether **2.38** proved interesting from a mechanistic perspective. The majority of the mass balance was isolated as an inseparable mixture of at least three compounds containing tetracycle **2.50** (tentatively assigned on the basis of GC-MS and select ^{1}H-NMR data). Two more polar compounds were also isolated and identified as diastereomeric spirocycles **2.48** and **2.49**, providing tangible evidence in support of the spirocyclic intermediate. We presume that the smaller energy gain for rearomatisation of a naphthalene ring compared to a benzene ring extends the lifetime of the spirocyclic radical intermediate **2.52**. Thus, fragmentation is slowed and trapping with molecular oxygen competes; the resulting peroxide being reduced by tributyltin hydride under the reaction conditions (Scheme 2.11).



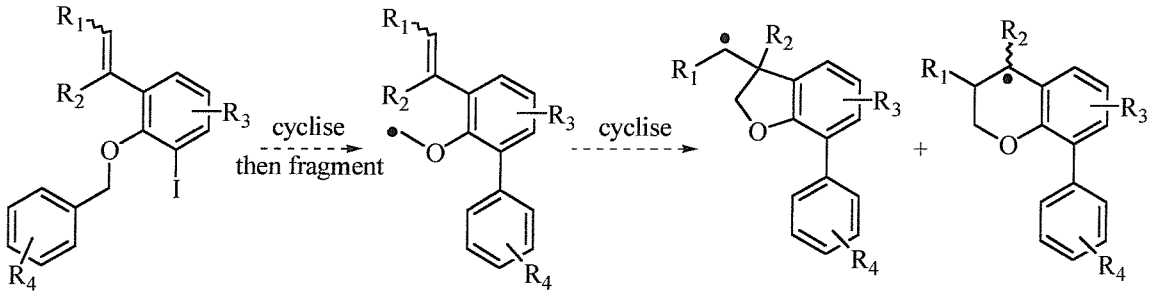
Reagents & Conditions: **i.** NaI, K_2CO_3, acetone, reflux, 12 h, 68 %; **ii.** Bu_3SnH, AIBN, PhMe, 80 °C, 24 h.

Scheme 2.11

2.3 Further Studies

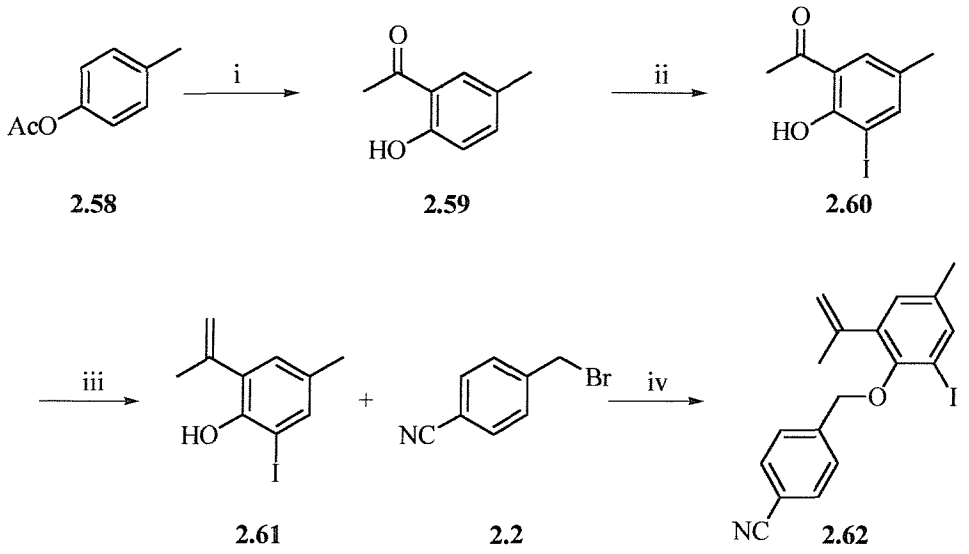
2.3.1 Benzo[*b*]furan Formation *via* an Alkene Radical Trap

Alkenes are efficient radical acceptors.[64-66] By introducing a vinyl group adjacent to the phenol, we hoped to trap the oxymethylene radical intermediate **2.55** (Scheme 2.12).



Scheme 2.12

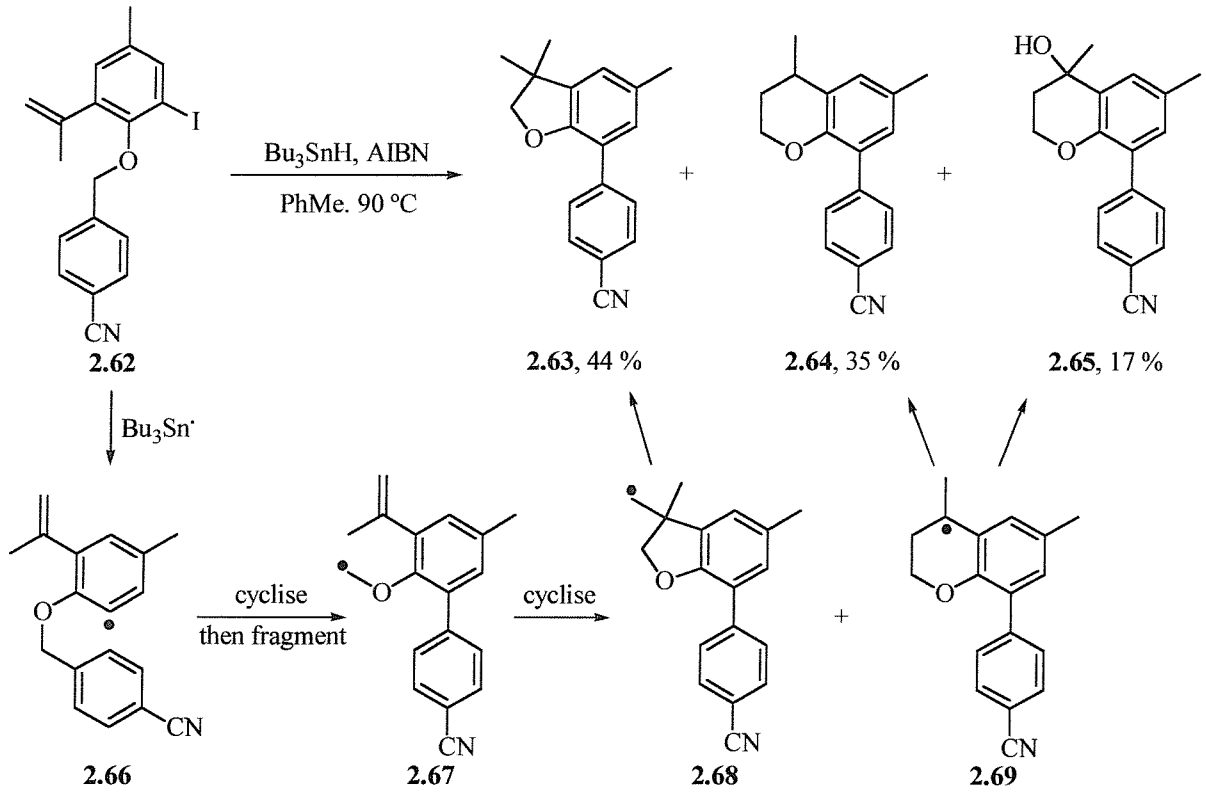
Our synthesis of styrene **2.62** began with the zirconium tetrachloride-mediated Fries rearrangement of acetate **2.58** under ultrasound irradiation.[67] Iodination and methylenation of the resulting acetophenone **2.59** gave phenol **2.61** in good yield.[68] Coupling with 4-(bromomethyl)benzonitrile **2.2** completed the synthesis (Scheme 2.13).



Reagents & Conditions: **i.** $ZrCl_4$, CH_2Cl_2, ultrasound, 24 h, 78 %; **ii.** I_2, HIO_3, EtOH, H_2O, 40 °C, 2 h, 95 %; **iii.** $CH_2{=}PPh_3$, THF, r.t., 16 h, 87 %; **iv.** 4-(bromomethyl)benzonitrile **2.2**, K_2CO_3, acetone, reflux, 20 h, 94 %.

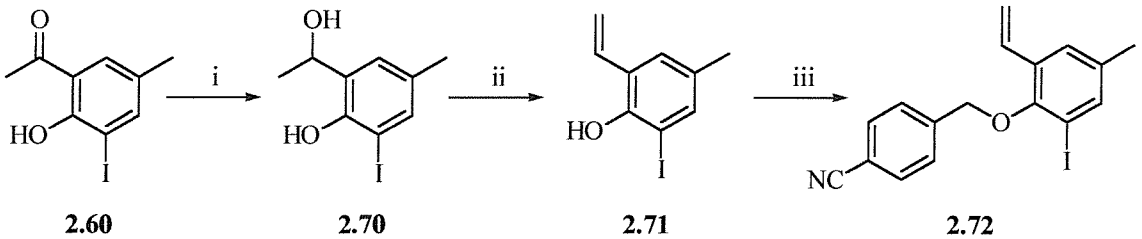
Scheme 2.13

Benzyl ether **2.62** was now subjected to standard radical forming conditions. Gratifyingly, this gave three products, **2.63**, **2.64** and **2.65**, each derived from the trapping of the intermediate oxymethylene radical **2.67** (Scheme 2.14). The observation is consistent with the proposed formation of an oxymethylene radical intermediate as this would undoubtedly react faster with a proximal alkene than an arene or oxygen. One disappointment from a synthetic viewpoint was the poor selectivity attained in the cyclisation step. Products of both 5-*exo* and 6-*endo* cyclisation were observed in an almost equimolar ratio together with a small quantity of alcohol **2.65**.



Scheme 2.14

It was hoped that changing the steric encumbrance or the electronic character of the alkene would provide regioselective addition to the alkene. A concurrent study of both possibilities was undertaken. Thus, acetophenone **2.60** was reduced to the corresponding alcohol **2.70** with sodium borohydride. Elimination of the alcohol under acidic conditions gave styrene **2.71** that was coupled with 4-(bromomethyl)benzonitrile **2.2** to yield **2.72** in 90 % (Scheme 2.15).

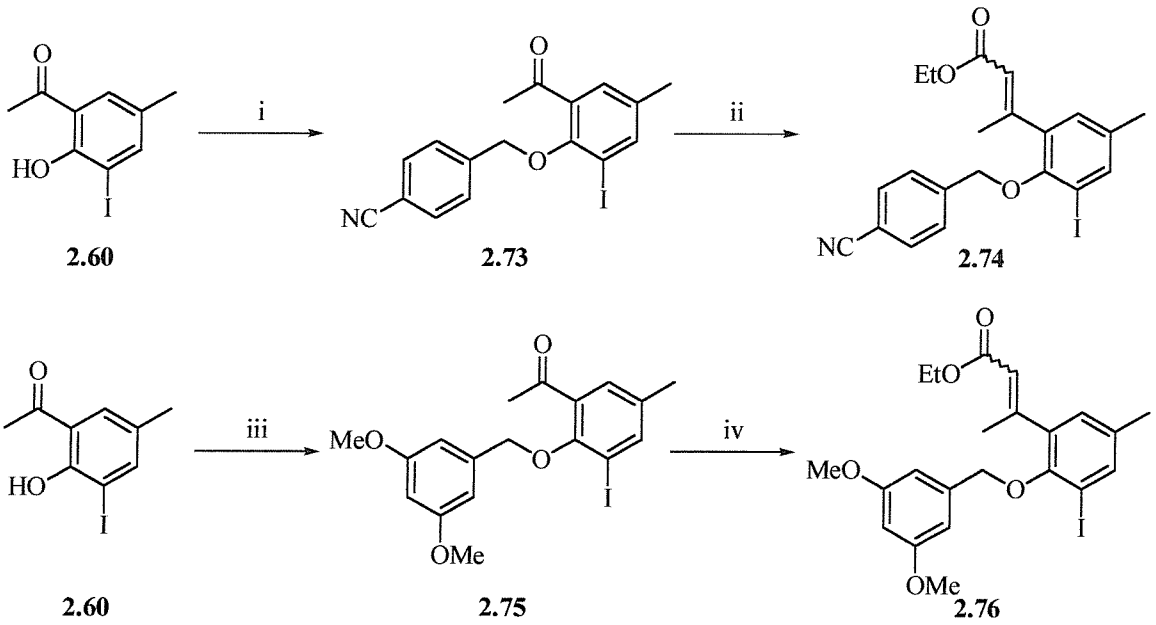


Reagents & Conditions: **i.** $NaBH_4$, MeOH, 0 °C, 30 min, 52 %; **ii.** PPTS, PhMe, reflux, 16 h, 92 %; **iii.** 4-(bromomethyl)benzonitrile **2.2**, K_2CO_3, acetone, reflux, 3 h, 90 %.

Scheme 2.15

Synthesis of an α,β-unsaturated ester provided a substrate with a polarised alkene. Thus acetophenone **2.73**, prepared by union of **2.60** and **2.2**, was subjected to a Horner-Wadsworth-Emmons reaction with ethyl dimethylphosphonoacetate yielding both (*E*)- and

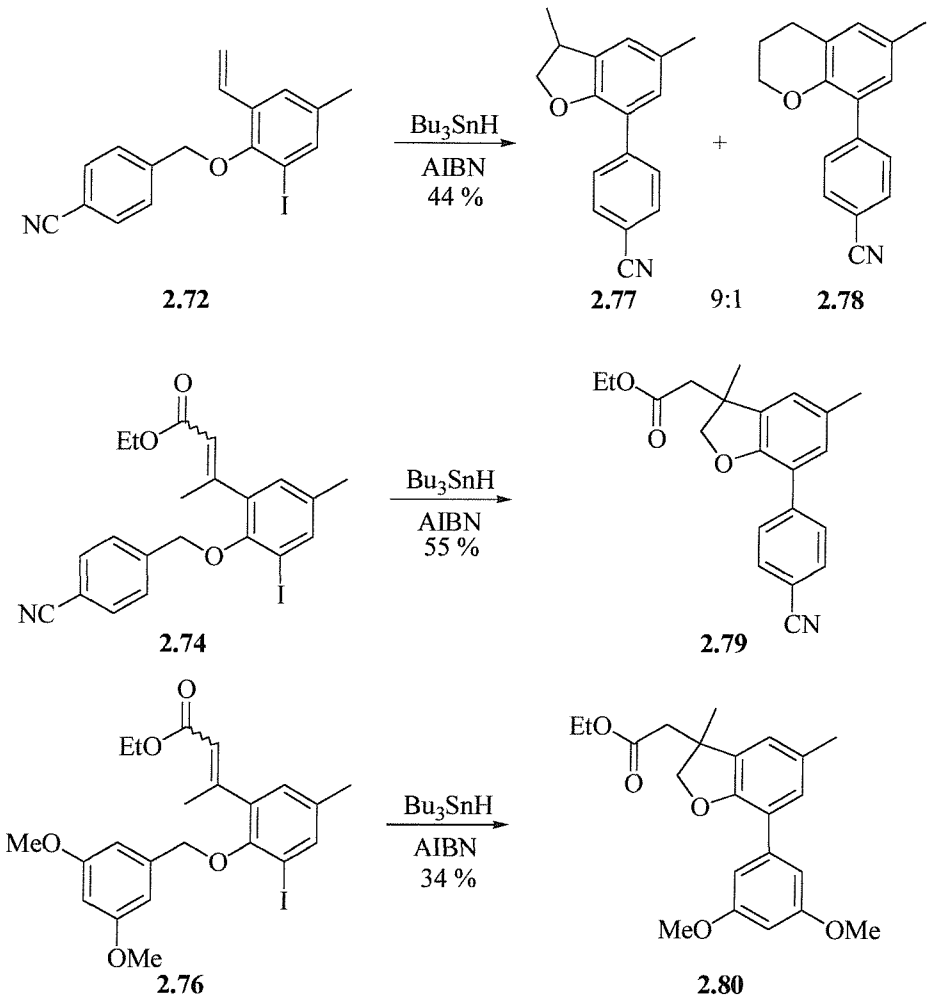
(*Z*)- isomers of ester **2.74**.[69] A second example containing a 3,5-dimethoxybenzyl moiety was synthesised by analogous chemistry (Scheme 2.16).



Reagents & Conditions: **i.** 4-(Bromomethyl)benzonitrile **2.2**, K_2CO_3, acetone, r.t., 3½ days, 83 %; **ii.** ethyl dimethylphosphonoacetate, NaH, THF; **2.73**, reflux, 2 h, 81 %, *E*:*Z* ~ 5:2; **iii.** 4-(bromomethyl)benzonitrile **2.2**, K_2CO_3, acetone, r.t., 48 h, 56 %; **iv.** ethyl dimethylphosphonoacetate, NaH, THF; **2.75**, reflux, 2 h, 80 %, *E*:*Z* ~ 2:1.

Scheme 2.16

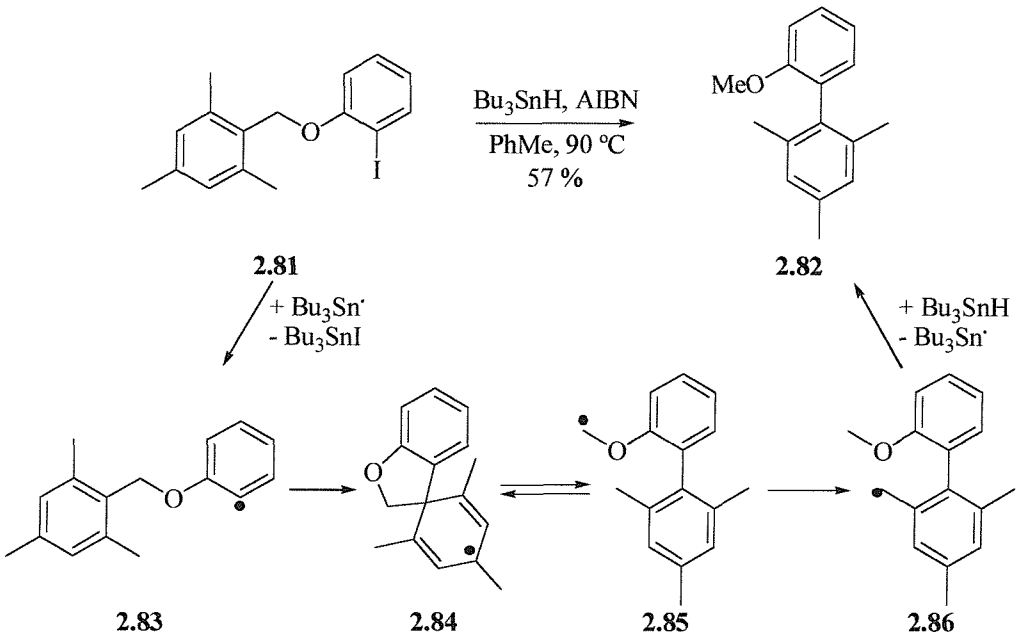
In the absence of the α-methyl group, the 5-*exo*-trig cyclisation pathway predominates. Thus, treatment of styrene **2.72** under standard radical forming conditions, gave **2.77** as the major product (40 %) with only traces of dihydrocoumarin **2.78**. The two products could not be separated by column chromatography (Scheme 2.17). Exposure of a 1.3:1 mixture of (*E*)- and (*Z*)-**2.74** to tributyltin hydride and AIBN yielded benzo[*b*]furan **2.79** in good yield. The analogous substrate **2.76** underwent the radical cyclisation-fragmentation-cyclisation sequence on treatment with tributyltin hydride and AIBN to give benzo[*b*]furan **2.80**. Mass recovery was disappointing in this case. The crude reaction mixture contained a number of by-products but our attempts to separate and characterise this were unrewarding (Scheme 2.17).



Scheme 2.17

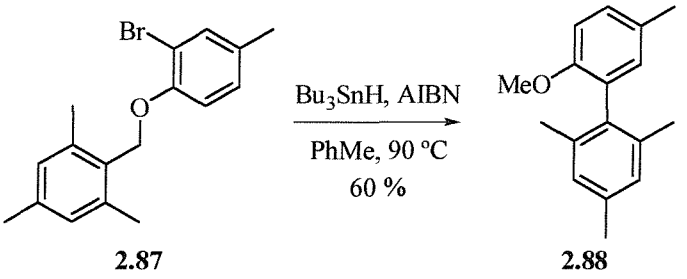
2.3.2 A Route to Hindered Biaryls

Our postulate that reaction proceeded *via* an oxymethylene radical led us to examine arene **2.81**, containing an *ortho*-methyl substituent on the acceptor arene. We reasoned that hydrogen atom abstraction by the oxymethylene radical from the methyl group (*viz.* **2.85** → **2.86**) should compete with cyclisation of the oxymethylene radical to the arene. If true, *o*-methoxy-*o*'-methylbiaryl **2.82** would be given on treatment with tributyltin hydride. Pleasingly, this proved to be the case (Scheme 2.18).



Scheme 2.18

The pathway was also seen with aryl bromide **2.87**, biaryl methyl ether **2.88** being provided in good yield (Scheme 2.19).



Scheme 2.19

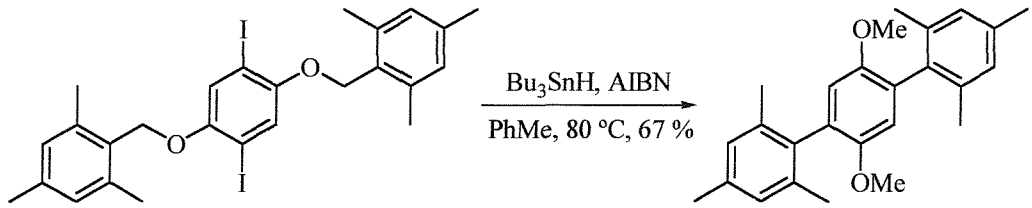
2.4 Conclusions

Radical cyclisations of 2-iodoaryl benzyl ethers have been shown to occur by 5-*exo*-trig cyclisation of the incipient aryl radical onto the adjacent arene. The spirocyclic intermediate then fragments to regenerate aromaticity. The resulting oxymethylene radical may follow a number of courses. 6-*Exo*/*endo*-trig cyclisation to the proximal arene results in benzo[*c*]chromene formation. Hydrogen-atom abstraction from tributyltin hydride or intramolecularly leads to an aryl methyl ether while quenching with molecular oxygen gives a phenol. In the presence of TEMPO, this can be trapped intermolecularly while inclusion of an alkene, appropriately situated in the substrate, leads to intramolecular trapping.

2.5 Extensions

Following on from our study, a number of extensions have been made. For example, treatment of bis-iodide **2.89** under standard tributyltin-mediated radical conditions initiated a

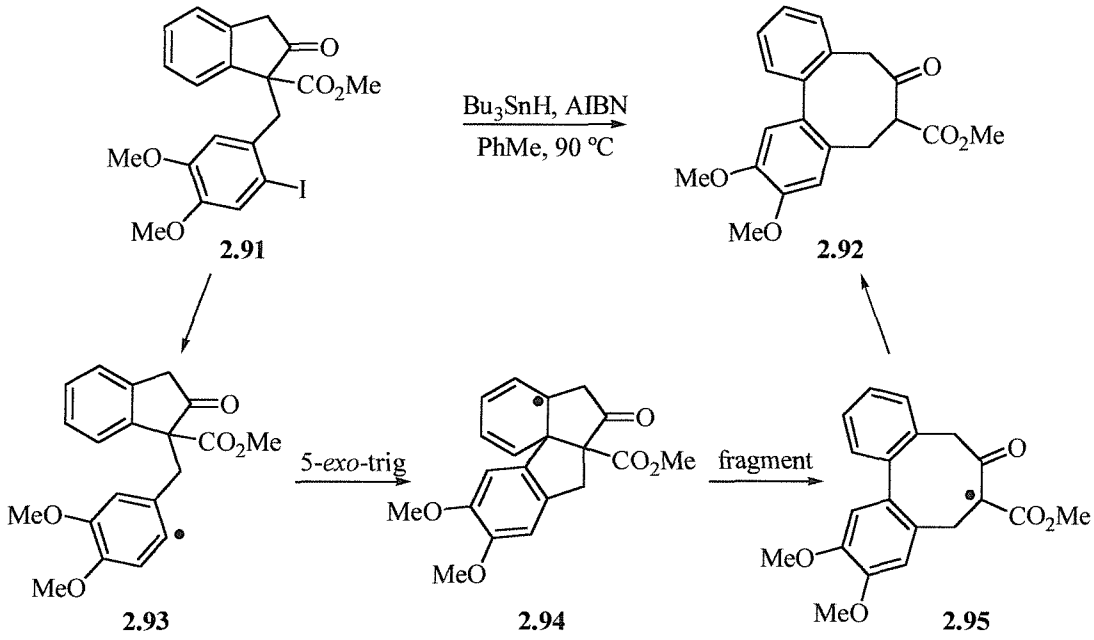
tandem cyclisation-fragmentation sequence to give triaryl **2.90** in 67 % yield (Scheme 2.20).[70]



2.89 **2.90**

Scheme 2.20

In a separate piece of work, the method has now been applied to medium ring synthesis. Treatment of 1-(iodobenzyl)-2-indanones, *e.g.* **2.91**, with tributyltin hydride and AIBN in toluene initiates a 5-*exo*-trig cyclisation with subsequent fragmentation to a dibenzocyclooctane **2.92** (Scheme 2.21).[71]



2.91 **2.92** **2.93** **2.94** **2.95**

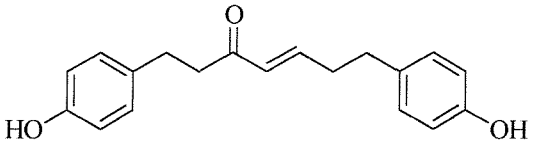
Scheme 2.21

Chapter 3 - Towards the Synthesis of Acerogenin E

3 *Towards the Synthesis of Acerogenin E*

3.1 Background

Diarylheptanoids form a unique class of natural products of which there are two distinct types. Linear diarylheptanoids (*e.g.* **3.1**) are composed of a heptyl unit with an oxygenated aromatic ring at each end of the chain.

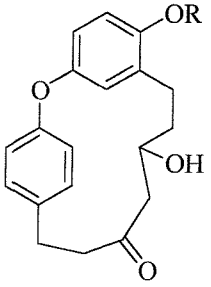


3.1

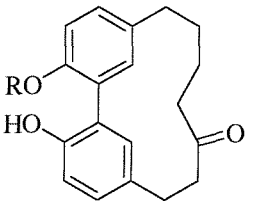
Compounds of this class have been shown to exhibit anti-inflammatory, antibacterial, antifungal and antihepatotoxic properties.[72,73] Evidence exists to show that these compounds are biogenetic precursors of the second class of diarylheptanoids that contain a macrocyclic ring.[74-76] Key features of this second class include a 13-membered macrocyclic ring with two aromatic rings conjoined *via* a *meta-meta* substitution pattern. The majority of work targeting macrocyclic products of this type employ an aryl-aryl coupling as the ring-closing step.[77-81]

3.1.1 Isolation of Acerogenin E

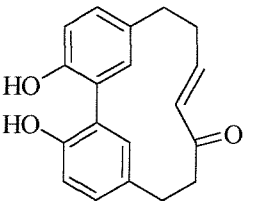
Over twenty different macrocyclic diarylheptanoids have been isolated from a variety of sources. In 1993, Nagumo *et al.* isolated two new diarylheptanoid glucosides from the phenolic extract of the stem bark of the Japanese deciduous tree *Acer nikoense* MAXIM. (Aceraceae) that they named aceroside V **3.2** and aceroside XI **3.3**.[82] Acid hydrolysis of aceroside XI **3.3** gave glucose and a genin diarylheptanoid that they named acerogenin E **3.4**.



3.2: R = β-D-glucopyranosyl



3.3: R = β-D-glucopyranosyl
3.4: R = H



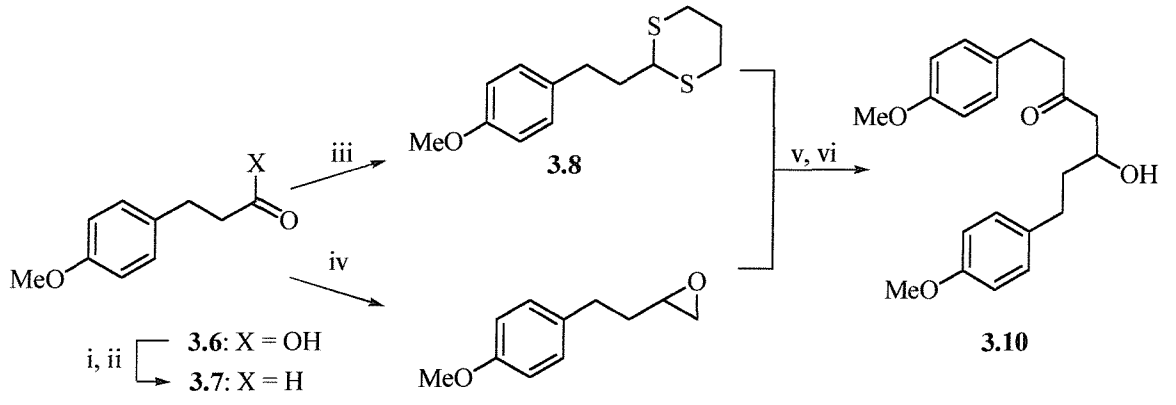
3.5: alnusone

The structure of acerogenin E **3.4** was elucidated by NMR, IR and UV methods and by comparison with alnusone **3.5**, a related diarylheptanoid containing an enone functionality. Hydrogenation of alnusone **3.5** was used to confirm the structure of acerogenin E **3.4**.[83]

Two years later, acerogenin E **3.4** was identified as a natural product in its own right by Fuchino *et al.* from extracts of the inner bark of *Betula ermanii.*[84] More recently acerogenin E **3.4** has also been isolated from *Betula platyphylla* var. *japonica,*[85] *Betula maximowicziana,*[86] and *Betula davurica.*[87] Although acerogenin E **3.4** has yet to receive attention as a target for synthesis, the closely related diarylheptanoid alnusone **3.5** has been a subject of total synthesis and its synthesis exemplifies the use of a metal-catalysed aryl-aryl coupling to form the macrocyclic skeleton.

3.1.2 Previous Syntheses of Alnusone

The first total synthesis of alnusone **3.5** was reported in 1981 by Semmelhack *et al.* and employed a nickel-catalysed coupling to form the biaryl linkage and close the macrocyclic ring.[77] The aliphatic chain was constructed in a convergent manner from the readily available 3-(4-methoxyphenyl)propionic acid **3.6** which was converted to the corresponding aldehyde **3.7** in two steps. This aldehyde was then converted into both 1,3-dithiane **3.8** and epoxide **3.9**, by treatment with the ylid of trimethylsulfonium iodide. Deprotonation of **3.8** with butyllithium and reaction with epoxide **3.9** gave diarylheptanone **3.10** after deprotection with aqueous mercury(II) salts (Scheme 3.1).[77]

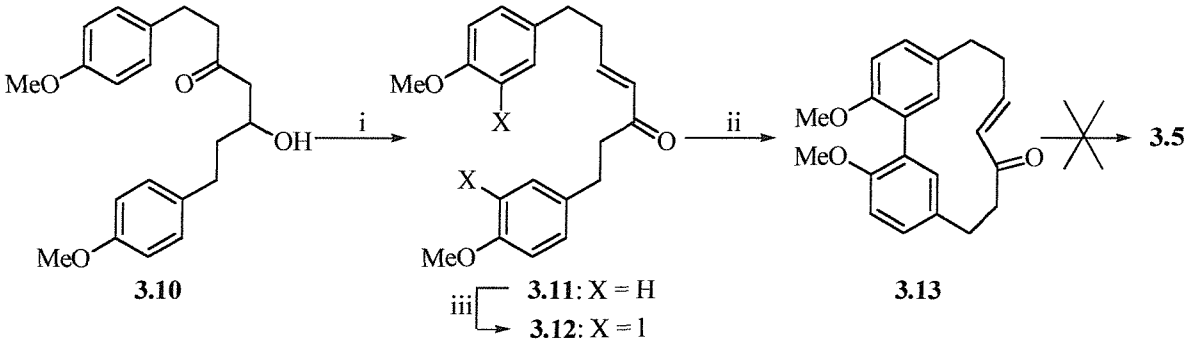


Reagents & Conditions: **i.** $LiAlH_4$, Et_2O, 5 h, 98 %; **ii.** CrO_3.pyr, CH_2Cl_2, 10 min, 83 %; **iii.** $BF_3.OEt_2$, $HSCH_2CH_2CH_2SH$, 2 h, 94 %; **iv.** NaH, DMSO, Me_3SI, THF, 2 h, 86 %; **v.** BuLi, -30 °C, THF, 1½ h; -30 °C → 0 °C; **3.9**, 12 h; **vi** HgO, $HgCl_2$, MeOH, H_2O, reflux, 18 h, 99 % (over 2 steps).

Scheme 3.1

Hydroxyketone **3.10** was converted to enone **3.11** by acetylation of the free alcohol and elimination of acetic acid in the presence of DBN. Iodination of the two aromatic rings *ortho* to the electron-donating methoxy groups was performed using silver(I) trifluoroacetate and iodine in chloroform. Macrocyclisation catalysed by nickel(0) gave alnusone dimethyl ether **3.13** in a respectable 52 % yield. However all attempts to remove the protecting groups

failed to provide alnusone **3.4** with either molecular decomposition occurring or starting material being recovered (Scheme 3.2). Changing to a methoxymethyl protecting group facilitated completion of the total synthesis of alnusone **3.5**.

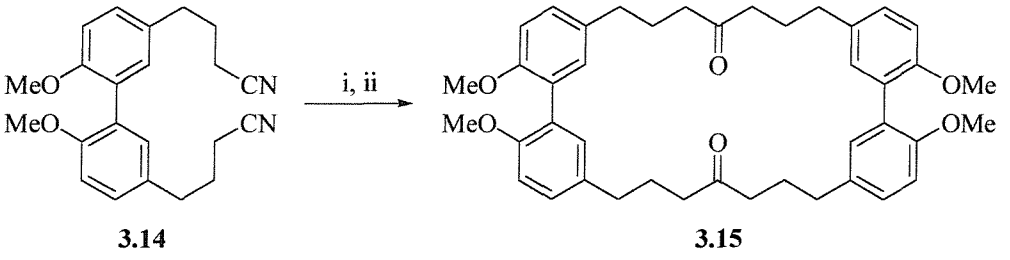


Reagents & Conditions: **i.** Ac_2O, pyr, 12 h, 99 %; DBN, $CHCl_3$, 30 min, 81 %; **ii.** $Ni(PPh_3)_4$, DMF, 50 °C, 40 h, 52 %; **iii.** $AgOCOCF_3$, I_2, $CHCl_3$, 45 min, 75 %.

Scheme 3.2

3.1.3 Other Methods Employed Towards Diarylheptanoid Synthesis

Dansou *et al.* have reported work towards this class of natural products by use of a macrocyclic Thorpe-Ziegler reaction.[88] Despite performing the reaction at high dilution, treatment of dinitrile **3.14** with sodium methylphenylamide gave only dimer **3.15** after hydrolysis with hydrochloric acid with no evidence of the required diarylheptanoidal macrocycle (Scheme 3.3).



Reagents & Conditions: **i.** $NaN(C_6H_5)Me$, THF, 28 %; **ii.** 12 M HCl, reflux, 24 h, 15 %.

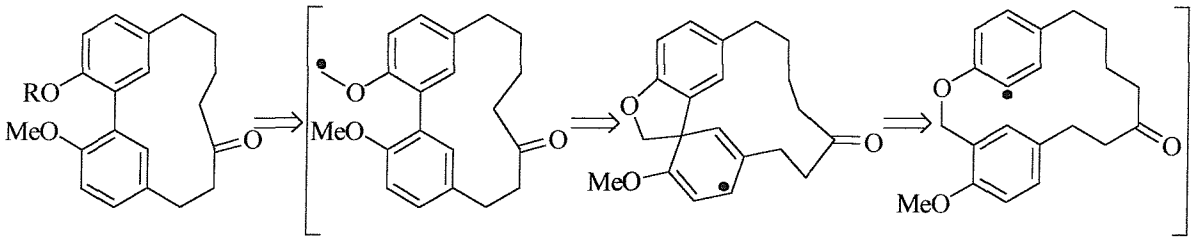
Scheme 3.3

With routes to this compound class limited to transition metal assisted macrocyclisation by aryl-aryl coupling reactions, we felt that an alternative approach would be useful in this field. Steric hindrance in formation of the macrocyclic system would seem to limit the efficiency of, or indeed prevent, cyclisation.[88] We hoped to apply our radical cyclisation and fragmentation methodology in a transannular fashion to effect the synthesis of acerogenin E **3.4**. By pre-forming a large macrocycle and subjecting this to a radical-induced ring contraction, we hoped to form the key aryl-aryl bond.[89]

3.2 Towards Acerogenin E

3.2.1 Retrosynthetic Analysis

Cyclisation of an aryl radical onto an arene tethered as a benzyl ether has been shown to occur readily (see Chapter 2). It was hoped that formation of an aryl radical akin to **3.20** under standard radical forming conditions would undergo a transannular ring contraction *via* a 5-*exo*-trig cyclisation. Fragmentation of the resulting intermediate **3.19** would then give the diarylheptanoid framework for acerogenin E **3.4** (Scheme 3.4).



3.16: R = H
3.17: R = Me

3.18 **3.19** **3.20**

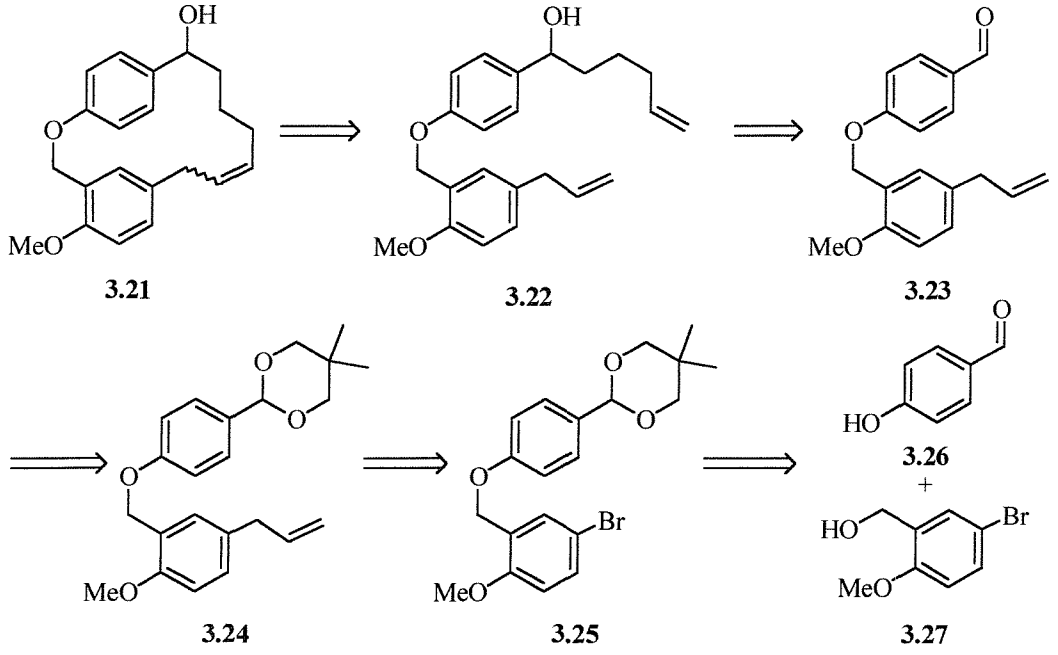
Scheme 3.4

The first synthetic challenge to address was the formation of a 16-membered macrocycle. Ring-closing metathesis and palladium-catalysed couplings have previously been used in the synthesis of medium-sized rings along with more classical methods such as etherification.[90-94] Our first task therefore was to establish a viable route to a 16-membered macrocycle. As this should have a lower steric barrier to formation than a 13-membered ring, the rate of intramolecular ring closure ought to be comparable to the rate of competing intermolecular additions.

3.3 Towards a 16-Membered Macrocycle

3.3.1 Application of Ring-Closing Metathesis

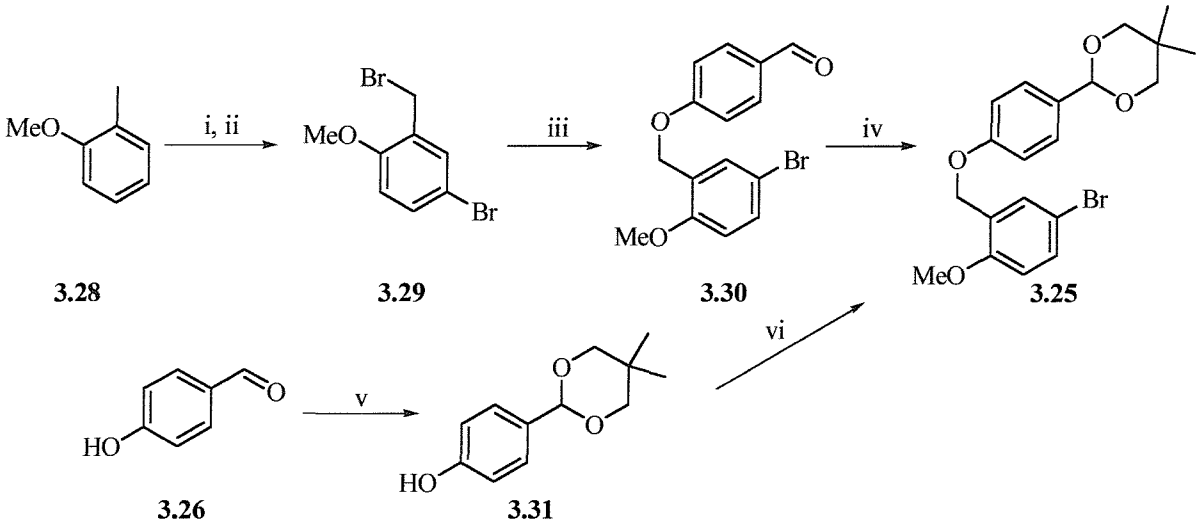
A model study was undertaken to prepare a 16-membered macrocycle. It was envisaged that a ring-closing metathesis could be used to effect the macrocyclisation reaction. The requisite diene **3.22** could in turn be formed by a Grignard reaction between aldehyde **3.23** and the organometallic derived from 5-bromo-1-pentene (Scheme 3.5).



Scheme 3.5

3.3.2 Synthesis of the Metathesis Precursor

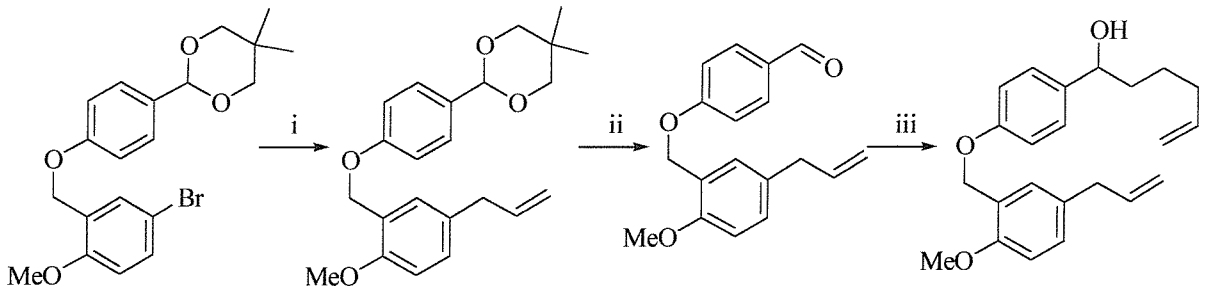
Synthesis of acetal **3.25** was accomplished by two routes. Nuclear and then benzylic bromination of 2-methylanisole **3.28** gave 4-bromo-2-(bromomethyl)anisole **3.29** in good yield.[95] Coupling of **3.29** to 4-hydroxybenzaldehyde **3.26** furnished the corresponding benzyl ether **3.30**. Subsequent treatment with neopentyl glycol and trimethylsilyl chloride, yielded **3.25**.[96] Alternatively, 4-hydroxybenzaldehyde **3.26** was protected and conjoined with commercially available 5-bromo-2-methoxybenzyl alcohol **3.27** using a Mitsunobu coupling reaction (Scheme 3.6). The yield of the second route proved superior to the first.



Reagents & Conditions: **i.** NBS, MeCN, r.t., 45 min; **ii.** NBS, CCl_4, AIBN, reflux, 2 h, 78 % (2 steps); **iii.** 4-hydroxybenzaldehyde, K_2CO_3, acetone, r.t., 16 h, 74 %; **iv.** neopentyl glycol, TMSCl, CH_2Cl_2, reflux, 18 h, 82 %; **v.** neopentyl glycol, PPTS, toluene, reflux, -H_2O, 16 h, 95 %; **vi.** 5-bromo-2-methoxybenzyl alcohol **3.27**, DIAD, PPh_3, THF, 0 °C, 2 h, 84 %.

Scheme 3.6

Exposure of **3.25** to butyllithium in the presence of copper(I) iodide at low temperature (-78 °C) provided allylarene **3.24** in good yield on quenching with allyl bromide. Removal of the acetal protecting group with aqueous acid and treatment of the resulting aldehyde with the Grignard reagent derived from 5-bromo-1-pentene, yielded alcohol **3.22** that would serve as a precursor for a macrocyclic ring-closing metathesis reaction (Scheme 3.7).

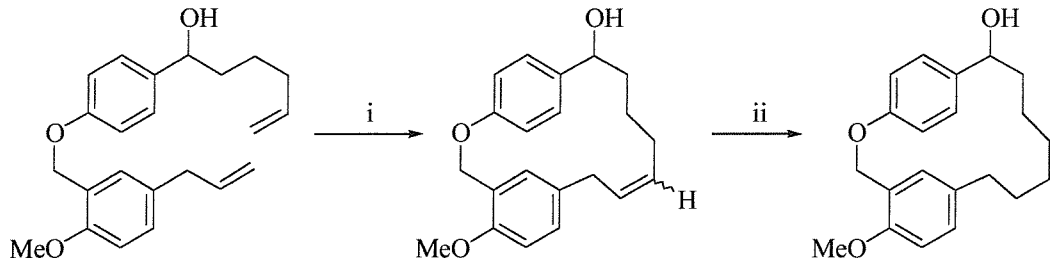


3.25 **3.24** **3.23** **3.22**

Reagents & Conditions: **i.** BuLi, CuI, -78 °C, 30 min; allylBr, -78 °C, 1 h; 0 °C, 1 h, 78 %; **ii.** PPTS, MeOH, r.t., 16 h, 90 %; **iii.** CH_2=$CHCH_2CH_2CH_2MgBr$, THF, 0 °C, 30 min, 84 %.

Scheme 3.7

We were then in a position to test macrocyclic ring-closure. To ensure the concentration of unreacted diene **3.22** was low, the substrate was added to a refluxing solution of Grubbs' catalyst in dichloromethane *via* syringe pump over 4 hours.[97] Pleasingly, macrocycle **3.21** was formed, albeit in moderate yield, with no evidence of dimerisation. The resulting alkene was formed as an inseparable mixture of *cis* and *trans* isomers. To confirm the mixture was indeed two geometric isomers, the alkene functionality was reduced with diimide to give macrocycle **3.32** as the sole product (Scheme 3.8).



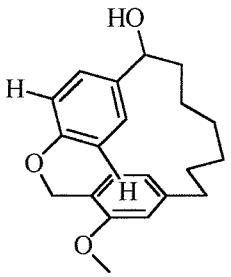
3.22 **3.21** **3.32**

Reagents & Conditions: **i.** $(PCy_3)_2Ru$=$CHPhCl_2$, CH_2Cl_2, Δ; syringe pump addition of **3.22** over 4 hours, 39 % (60 % w.r.t. RSM); **ii.** *p*$TsNHNH_2$, NaOAc, THF/H_2O, Δ, 72 h, 57 %.

Scheme 3.8

The ^{1}H-NMR spectrum of macrocycle **3.32** showed four distinct signals for the 1,4-disubstituted aromatic ring. This non-degeneracy permeated through to the ^{13}C-NMR

spectrum so that seven baseline separated aromatic C-H signals were observed. We presume that rotation of the arenes is restricted such that all carbon and hydrogen nuclei in the aromatic rings are magnetically distinct. Considering the structure of the product, a favourable edge-to-face interaction between the two aromatic rings ensures a strong anisotropic effect (Figure 3.9).[98] All remaining data were consistent with the structure proposed so that we were confident of the formation of macrocycle **3.32**. As the yield of the macrocyclisation step was moderate and the functional groups on the alkyl chain were different to those in acerogenin E **3.4** we decided to pursue an alternative pathway.



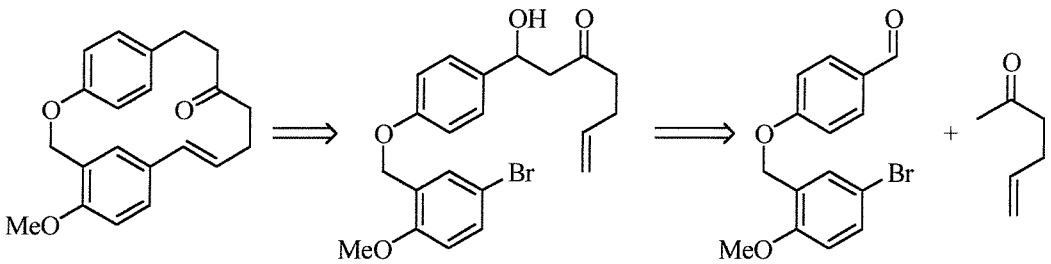
3.32

Figure 3.9

3.4 Towards the Skeleton *via* a Macrocyclic Heck Reaction

3.4.1 Retrosynthesis

Historically, palladium-catalysed ring closures have been employed for the synthesis of medium to large rings.[99] It was therefore hoped that a Heck reaction could be utilised to form the required macrocycle (Scheme 3.10). An aldol reaction between benzaldehyde **3.30** and 5-hexen-2-one **3.37** should furnish β–hydroxyketone **3.36**.



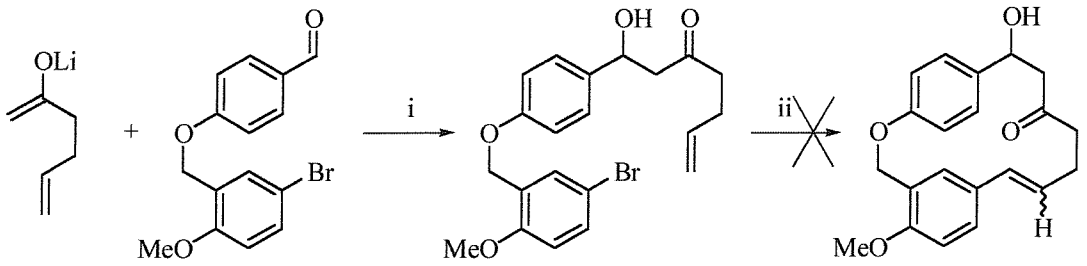
3.35 **3.36** **3.30** **3.37**

Scheme 3.10

3.4.2 Synthesis

Formation of the kinetic enolate of 5-hexen-2-one by deprotonation with LDA at low temperature, and subsequent reaction with aldehyde **3.30**, gave β-hydroxyketone **3.36** in good yield.[100] Unfortunately, exposure of **3.36** to palladium(0)-catalysed Heck conditions gave only polymeric material. We were therefore forced to assume that cyclisation of this

particular substrate was disfavoured on steric grounds. The presence of an additional hydroxyl group may have hampered macrocyclisation; a hydrogen bond between the hydroxyl and the adjacent ketone restricting rotation of the heptenyl side chain (Scheme 3.11).



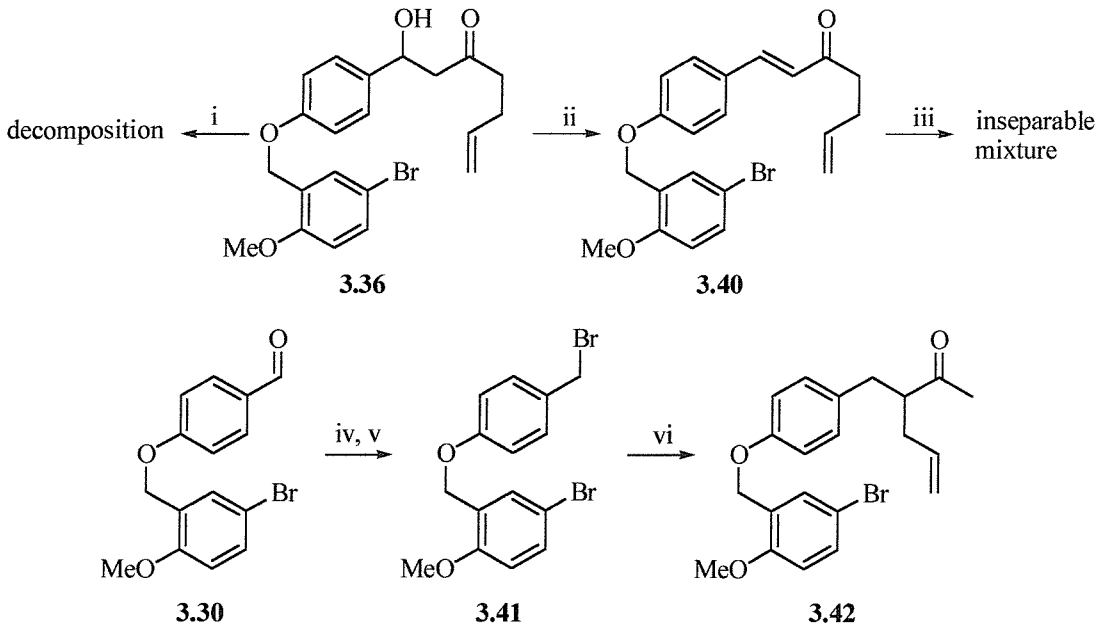
3.38 **3.30** **3.36** **3.39**

Reagents & Conditions: **i.** THF, -78 °C, 20 min, 67 %; **ii.** $Pd(OAc)_2$, P(*o*-tol)$_3$, NEt_3, DMF, 80 °C, 4 h.

Scheme 3.11

Attempts were made to remove the extraneous hydroxyl group but these proved fruitless. Elimination of the hydroxyl group gave enone **3.40** which, on treatment with triethylsilane and Wilkinson's catalyst, gave an inseparable mixture of products that were not characterisable.[101] Treatment of **3.36** with trimethylsilyl chloride, sodium iodide and acetonitrile also proved to be destructive.

An alternative approach involving exposure of benzyl bromide **3.41** (formed by sodium borohydride reduction of aldehyde **3.30** and displacement with phosphorus tribromide) to the kinetic enolate of 5-hexen-2-one was then attempted. However, at –78 °C, **3.41** proved unreactive to the enolate and only after warming to 0 °C did reaction occur. Characterisation of the product **3.42** revealed that the enolate had equilibrated to the more stable form prior to addition (Scheme 3.12). These approaches to the acerogenin E skeleton were therefore abandoned and a pathway incorporating a more classical macroetherification was investigated.



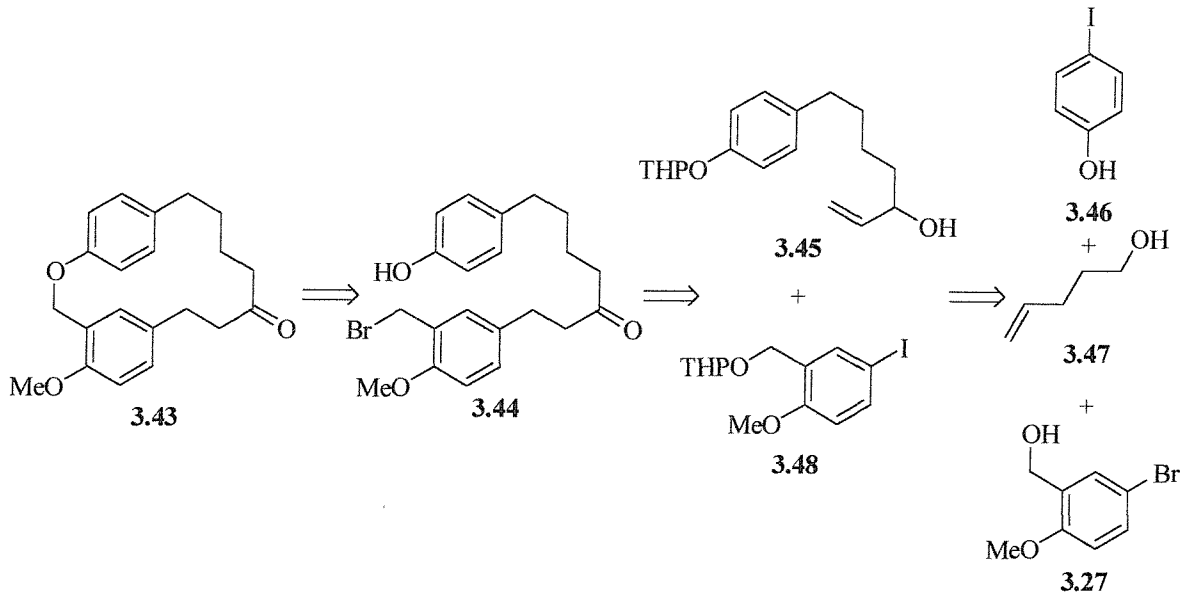
Reagents & Conditions: **i.** NaI, TMSCl, MeCN, r.t., 1 h; **ii.** *p*TsOH.H_2O, PhH, 50 °C, 12 h, 73 %; **iii.** Et_3SiH, Wilkinson's catalyst, CH_2Cl_2, r.t.; **iv.** $NaBH_4$, MeOH, 0 °C, 30 min, 89 %; **v.** PBr_3, PhH, r.t., 2 h, 100 %; **vi.** LDA, 5-hexen-2-one, -78 °C, THF, 1 min; **3.41**, -78 °C → r.t., 16 h, 27 %.

Scheme 3.12

3.5 Towards Acerogenin E *via* a Macroetherification

3.5.1 Retrosynthesis

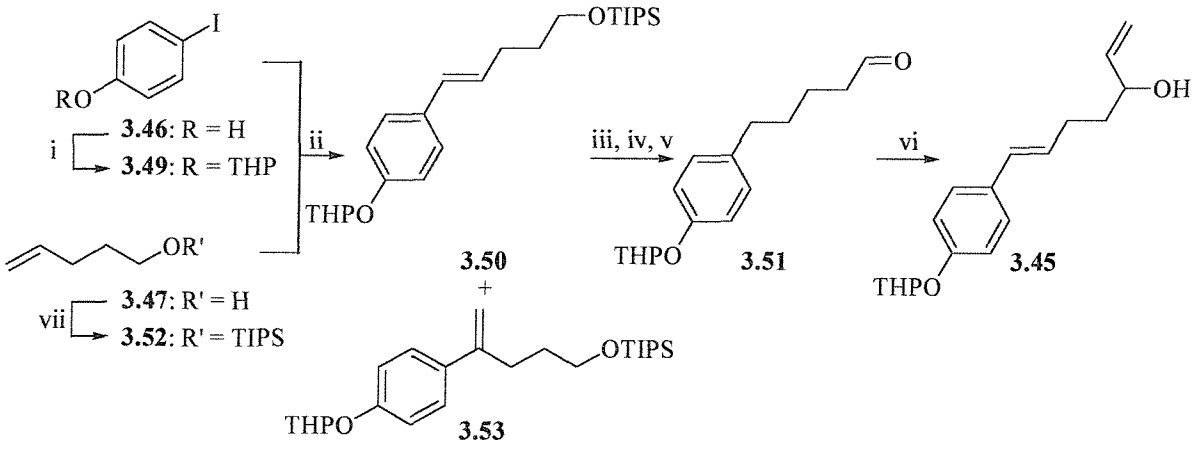
An alternative retrosynthetic analysis is outlined in Scheme 3.13. Cleavage of the benzyl ether to open the macrocyclic ring leads back to an acyclic ketone, **3.44**, that could be generated by Heck coupling of allylic alcohol **3.45** and aryl iodide **3.48**. Use of an iodide in place of a bromide should enhance reactivity, with palladium(0) more readily inserting into the carbon-halide bond. Iodide **3.48** could be formed from readily available 5-bromo-2-methoxybenzyl alcohol **3.27** while the protected phenol **3.45** could be synthesised from 4-iodophenol **3.46** and 4-penten-1-ol **3.47** (Scheme 3.13).



Scheme 3.13

3.5.2 Synthesis

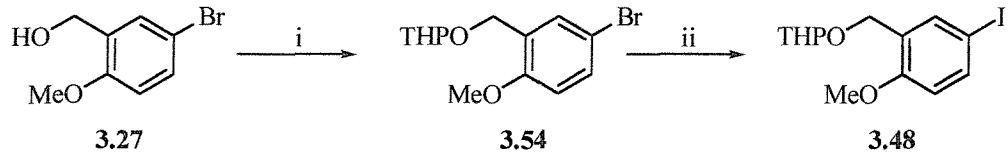
After protection of 4-iodophenol **3.46** as a THP-ether and 4-penten-1-ol **3.47** as a silyl ether, the two were unified with a Heck coupling. The product alkene was formed in good yield but the product was contaminated with *ca.* 10 % of a co-polar impurity. This was believed to be the product resulting from coupling between the arene and the internal carbon of the alkene (*i.e.* **3.53**). All attempts to separate the molecules failed and the contaminant was carried through until later in the synthesis. **3.50** was converted to allylic alcohol **3.45** as shown in Scheme 3.14.



Reagents & Conditions: **i.** DHP, PPTS, CH_2Cl_2, r.t., 16 h, 92 %; **ii.** $Pd(OAc)_2$, Bu_4NBr, K_2CO_3, DMF, 90 °C, 16 h, 80 % **3.50** : **3.53** ~ 6:1; **iii.** *p*TsNHNH$_2$, NaOAc, THF/H_2O, reflux, 16 h, 84 %; **iv.** Bu_4NF, THF, 2 h, 84 %; **v.** Dess-Martin periodinane, CH_2Cl_2, r.t., 1½ h, 76 %; **vi.** vinylMgBr, THF, 0 °C, 30 min, 57 %; **vii.** TIPSCl, imidazole, DMAP, CH_2Cl_2, r.t., 16 h, 97 %.

Scheme 3.14

Synthesis of iodide **3.48** began with protection of 5-bromo-2-methoxybenzyl alcohol **3.27** as a THP-ether. Halogen-to-metal exchange to the corresponding aryllithium and quenching with 1,2-diiodoethane gave iodide **3.48** in good yield (Scheme 3.15).

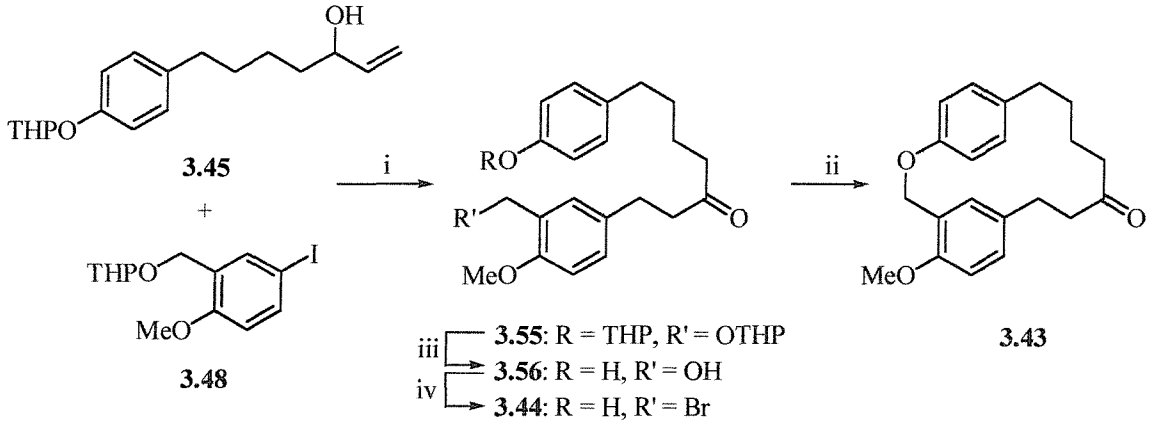


3.27 **3.54** **3.48**

Reagents & Conditions: **i.** DHP, PPTS, CH_2Cl_2, r.t., 16 h, 98 %; **ii.** BuLi, THF, -78 °C, 30 min; ICH_2CH_2I, -78 °C, 1½ h; brine, → r.t., 83 %.

Scheme 3.15

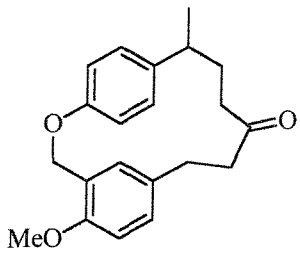
Union of **3.45** and **3.48** under phase-transfer Heck conditions using sodium hydrogen carbonate as the base yielded ketone **3.55** as the sole isolated product. The two THP protecting groups were removed simultaneously and the benzyl alcohol was converted to the corresponding bromide **3.44** by exposure to phosphorus tribromide. Gratifyingly, macroetherification under high dilution conditions (0.01 M w.r.t. substrate) gave the required macrocycle in good yield (Scheme 3.16).



Reagents & Conditions: **i.** $Pd(OAc)_2$, Bu_4NBr, $NaHCO_3$, DMF, 90 °C, 16 h, 62 %; **ii.** K_2CO_3, acetone, reflux, high dilution, 48 %; **iii.** PPTS, MeOH, r.t., 16 h, 87 %; **iv.** PBr_3, PhH, r.t., 2 h, 52 %.

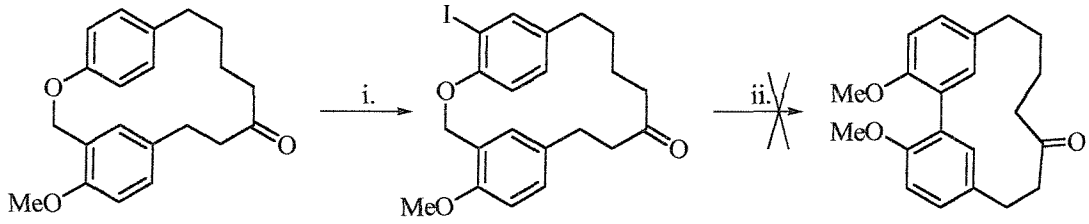
Scheme 3.16

At this juncture, the 'contaminant' present since the Heck coupling of **3.49** and **3.52** could be removed by column chromatography. The by-product isolated was tentatively assigned as **3.57** although limited material did not allow for an irrefutable assignment. Key signals were a three-proton doublet due to the *exo*-methyl group and diastereotopic proton signals at the benzylic ether centre suggesting the presence of a chiral centre in the molecule.



3.57

After formation of the macrocycle **3.43**, all that remained was a selective iodination of the less encumbered arene of the macrocycle. This was accomplished using iodine and silver(I) trifluoroacetate and gave iodide **3.58** in good yield. Treatment of **3.58** under standard tributyltin-mediated radical forming conditions gave very poor mass recovery with no evidence of the expected transannular ring contraction having occurred. Only macrocycle **3.43** (a consequence of carbon-to-iodine bond reduction) was isolated and in < 20 %. We propose that the initial 5-*exo*-trig cyclisation was slow so that other intermolecular and/or intramolecular processes became comparable in rate leading to possible formation of polymeric material (Scheme 3.17).



3.43 **3.58** **3.17**

Reagents & Conditions: **i.** I_2, $AgOCOCF_3$, CH_2Cl_2, r.t., 1 h, 60 %; **ii.** Bu_3SnH, AIBN, PhMe, 90 °C, 16 h.

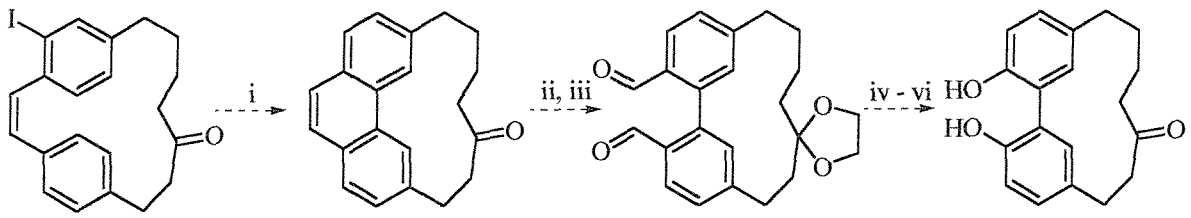
Scheme 3.17

Despite a synthetically viable route to macrocycle **3.58**, we were unable to initiate a transannular ring contraction to provide access to *O*-methyl acerogenin E **3.17**.

3.6 Conclusions and Further Work

A route to 16-membered macrocycle **3.43** had been successfully achieved with an overall yield of 7 %. Exposure of iodide **3.58** to standard tributyltin-mediated radical forming conditions did not give any evidence of the desired product arising from cyclisation and fragmentation. Only the product of carbon-to-iodine bond reduction was observed in poor yield.

A model study to determine the viability of ring-closure using an olefin metathesis strategy was realised. Further work in this area is required to complete the total synthesis of acerogenin E **3.4**. A possible alternative route to acerogenin E **3.4** involving a transannular ring-contraction of iodostilbene **3.59** is outlined in Scheme 3.18.



3.59 **3.60** **3.61** **3.4**

Reagents & Conditions: **i.** Bu_3SnH, AIBN, PhMe, 90 °C; **ii.** ethylene glycol, PPTS, $-H_2O$, PhMe; **iii.** O_3, CH_2Cl_2, -78 °C then PPh_3; **iv.** MeMgBr, THF; **v.** PCC, CH_2Cl_2; **vi.** $ArCO_3H$, K_2CO_3.

Scheme 3.18

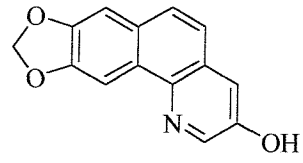
Chapter 4 - The First Total Synthesis of Toddaquinoline

4 *The First Total Synthesis of Toddaquinoline*

4.1 Background

4.1.1 Isolation

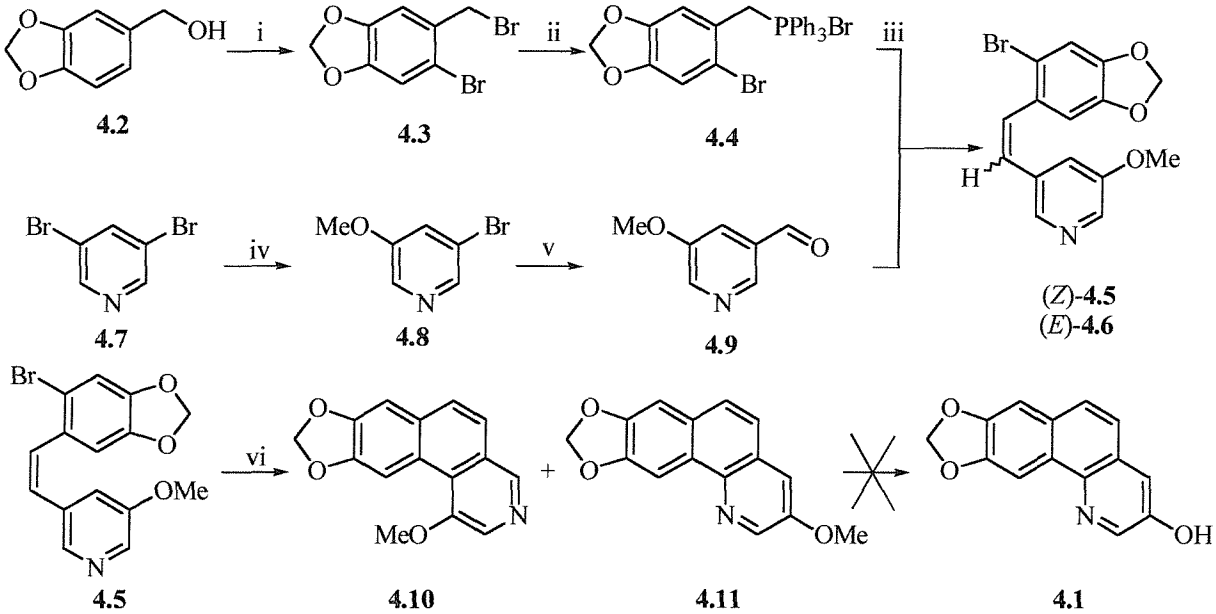
The root bark of Formasan *Toddalia asiatica* is widely used in Asian folk medicine for treatments of disorders such as stomach pain, dyspepsia and fevers.[102,103] In 1993 Chen *et al.* reported a study of the phytochemistry of *Toddalia asiatica* which had uncovered a new tetracyclic alkaloid which they named toddaquinoline **4.1**.[104] Its structure was determined by a series of NMR experiments in addition to UV, IR, MS and derivatisation information. Toddaquinoline **4.1** has subsequently been isolated from the root bark of *Zanthoxylum Simulans* and the stem bark of *Zanthoxylum nitidum*.[105-107] Biological activity of this molecule has yet to be tested.



4.1

4.1.2 Prior Synthesis

A route to toddaquinoline methyl ether **4.11** was reported in 1998 by Harrowven and Nunn.[108] The key feature was a radical cyclisation to a pyridine which at that time had little precedent. Unfortunately, attempts to effect the deprotection of the methyl ether failed (Scheme 4.1).[109]

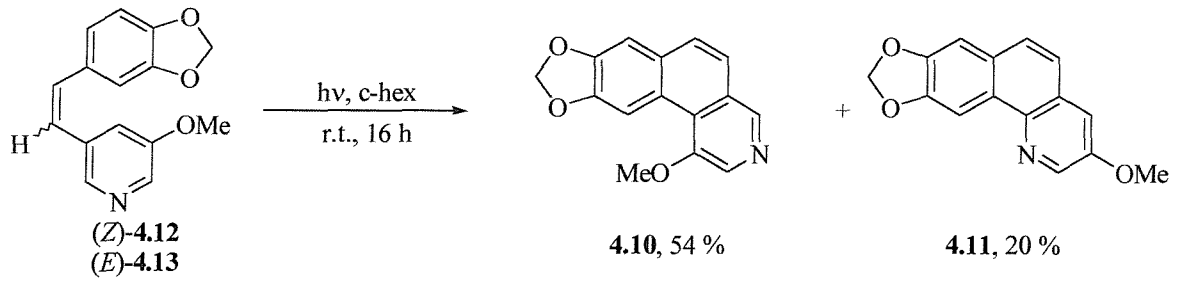


4.2 **4.3** **4.4** **4.7** **4.8** **4.9** **(*Z*)-4.5** **(*E*)-4.6** **4.5** **4.10** **4.11** **4.1**

Reagents & Conditions: **i.** Br_2, AcOH, r.t., 2 h, 49 %; **ii.** PPh_3, xylene, 80 °C, 4 h, 62 %; **iii.** NaH, THF, r.t., 2 h; 0 C, **4.9**, r.t., 2 h, 85 %, **4.5**:**4.6** ~ 2:1; **iv.** NaOMe, DMF, 65 °C, 1½ h, 71 %; **v.** BuLi, THF, -100 °C, 30 min; DMF, -100 °C → -60 °C over 30 min.; brine, -60 °C → r.t., 81 %; **vi.** Bu_3SnH, AIBN, PhMe, 80 °C, 4 h, 58 % **4.10**:**4.11** ~ 1:1.

Scheme 4.1

An alternate approach, based on a photocyclisation of an aza-stilbene, had also been examined. Irradiation of a 1:1 mixture of aza-stilbenes **4.12** and **4.13** in cyclohexane led to benzo[*f*]isoquinoline **4.10** as the major product (54 %).[110] Toddaquinoline methyl ether **4.11** was formed as a minor product in 20 % along with recovered aza-stilbenes (23 %) (Scheme 4.2).



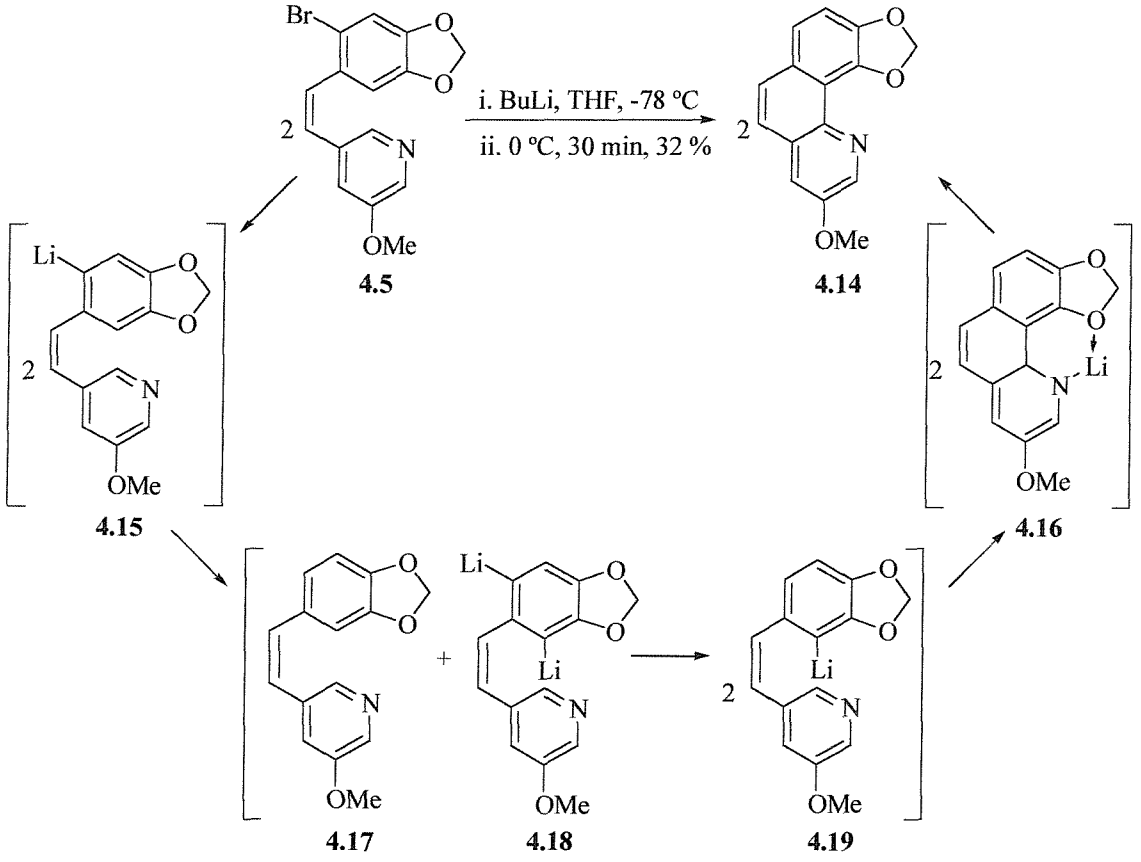
(*Z*)-**4.12**
(*E*)-**4.13**

4.10, 54 %

4.11, 20 %

Scheme 4.2

An approach based on the addition of an aryllithium intermediate to a pyridine gave a further regioisomer of toddaquinoline **4.1**. Thus, treatment of **4.5** with *n*-butyllithium at –78 °C gave benzo[*h*]quinoline **4.14** – a product of cyclisation between C-2 of the arene and C-6 of the pyridine ring. The reaction pathway was explained by halogen-to-metal exchange followed by an intermolecular deprotonation sequence to give the more stable organolithium intermediate **4.19**. This could then undergo an intramolecular cyclisation onto the pyridine moiety giving benzo[*h*]quinoline **4.14** (Scheme 4.3).[111]



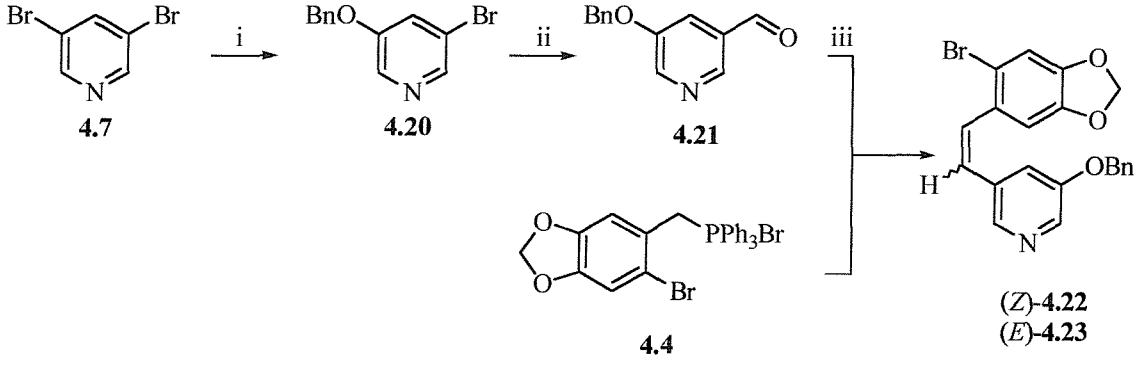
Scheme 4.3

4.2 Towards a Total Synthesis of Toddaquinoline

Although radical cyclisation onto a pyridine moiety had proved successful two problems were outstanding. Firstly, inability to remove the methyl-protecting group did not allow completion of the total synthesis. Secondly, the lack of regiocontrol in the key cyclisation step exposed a weakness in the method. We therefore decided to examine a more suitable protecting group and to investigate other methods of promoting radical formation in the hope of achieving greater selectivity in the key step.

4.2.1 The First Total Synthesis of Toddaquinoline

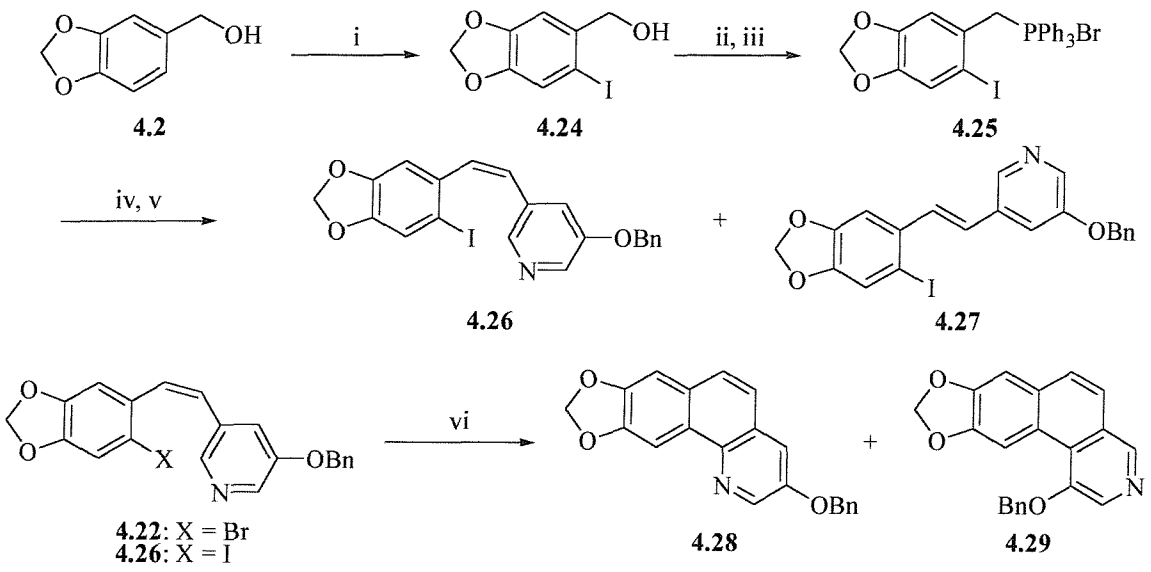
The final task to complete a total synthesis of toddaquinoline was to remove the hydroxyl protecting group. Many methods to achieve deprotection of the methyl ether functionality were examined but to no avail (BBr_3, HBr and LiCl all failed to facilitate deprotection). Employment of a different protecting group seemed a sensible option to explore. Use of a benzyl ether seemed appropriate as this would be compatible with the early stage of the synthesis. Hence, 3,5-dibromopyridine **4.7** was treated with sodium benzoxide to give **4.20** in 56 % yield. Halogen-metal exchange with butyllithium and quenching with DMF then transformed this into aldehyde **4.21**. Union with the ylid formed from **4.4** then gave the corresponding aza-stilbenes **4.22** and **4.23** in a 5:2 ratio (Scheme 4.4).



Reagents & Conditions: **i.** NaOBn, DMF, 1½ h, 65 °C, 56 %; **ii.** BuLi, THF, -100 °C, 30 min; DMF, -100 °C → -60 °C, 30 min; brine, -60 °C → r.t., 81 %; **iii.** NaH, THF, r.t., 2 h; 0 °C, **4.21**, r.t., 2 h, 81 %, **4.22**:**4.23** ~ 5:2.

Scheme 4.4

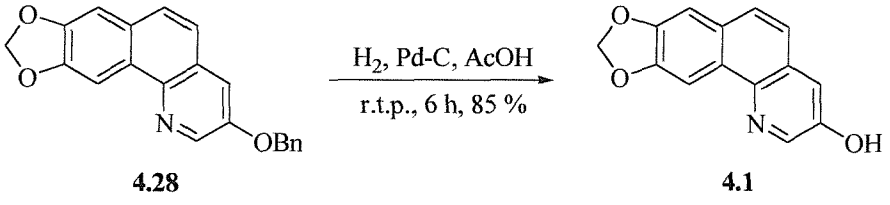
Treatment of **4.22** with tributyltin hydride and AIBN in toluene yielded toddaquinoline benzyl ether **4.28** and its regioisomer **4.29** in equal proportion but in low yield. Using aryl iodide **4.25** (formed as indicated in Scheme 4.5) under standard tributyltin-mediated radical forming conditions also gave toddaquinoline benzyl ether **4.28** and benzo[*f*]isoquinoline **4.29** as an equimolar separable mixture in an enhanced yield (71 %) (Scheme 4.5).



Reagents & Conditions: **i.** I_2, $AgOCOCF_3$, $CHCl_3$, r.t., 1½ h, 83 %;[112] **ii.** PBr_3, PhH, r.t., 2 h, 93 %; **iii.** PPh_3, toluene, reflux, 16 h, 85 %; **iv.** NaH, THF, r.t., 2 h; **v.** 0 °C, **4.21**; r.t. 16 h, 69 %, *Z*:*E* ~ 7:4; **vi.** Bu_3SnH, AIBN, PhMe, 90 °C, 46 h, 28 % + 55 % RSM (X=Br), 71 % (X=I), **4.28**:**4.29** ~ 1:1.

Scheme 4.5

Pleasingly, hydrogenolysis of the benzyl protecting group in acetic acid proceeded cleanly completing the first total synthesis of toddaquinoline **4.1** (Scheme 4.6).[111]

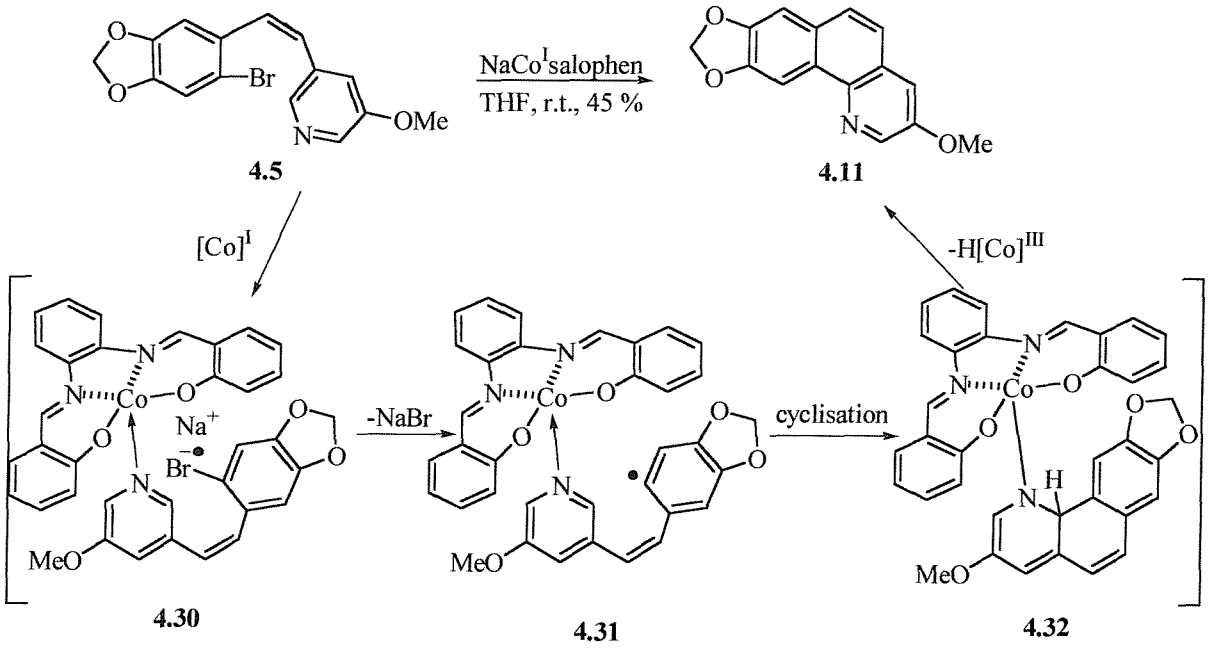


Scheme 4.6

4.2.2 Cobalt-mediated Cyclisation Towards Toddaquinoline

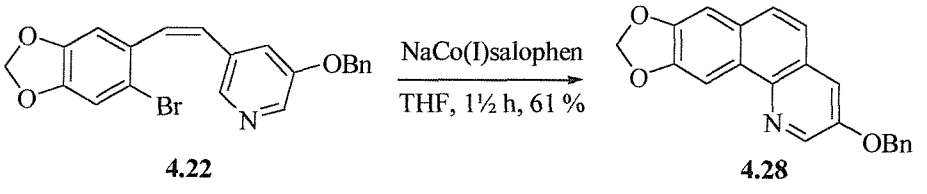
In a concurrent study, we investigated different reagents to mediate intramolecular radical cyclisation in the hope that some regioselectivity could be introduced. Our initial attempts to effect cyclisation of **4.5** by treatment with samarium(II) iodide proved unsuccessful. Pleasingly, treatment of aryl bromide **4.5** with sodium cobalt(I)salophen efficiently biased reaction towards formation of toddaquinoline methyl ether **4.11**.[113] This dichotomy between the tin and cobalt mediated radical cyclisations suggests that cobalt plays a duel role in the reaction. Initially, single-electron transfer from sodium cobalt(I)salophen to the aryl bromide produces radical anion **4.30** and cobalt(II)salophen. As cobalt(II) has Lewis acidic properties, we propose that this could interact with the Lewis basic pyridine nitrogen enhancing electrophilicity at the C-6 centre. Loss of sodium bromide from **4.30** leads to a nucleophilic aryl radical **4.31** which adds in a 6-*exo*/*endo*-trig fashion to the electrophilic C-6

centre of the pyridine exclusively. Dehydrocobaltation of intermediate **4.32** then gives toddaquinoline methyl ether **4.11** (Scheme 4.7).[114]



Scheme 4.7

Having achieved a regioselective route to toddaquinoline methyl ether **4.11**, we applied similar conditions to benzyl-protected aza-stilbene **4.22**. Thus, treatment with sodium cobalt(I)salophen gave toddaquinoline benzyl ether **4.28** as the sole product in good yield. Hence, a more efficient total synthesis of toddaquinoline **4.1** has been uncovered by use of cobalt(I) as a radical mediator (Scheme 4.8).



Scheme 4.8

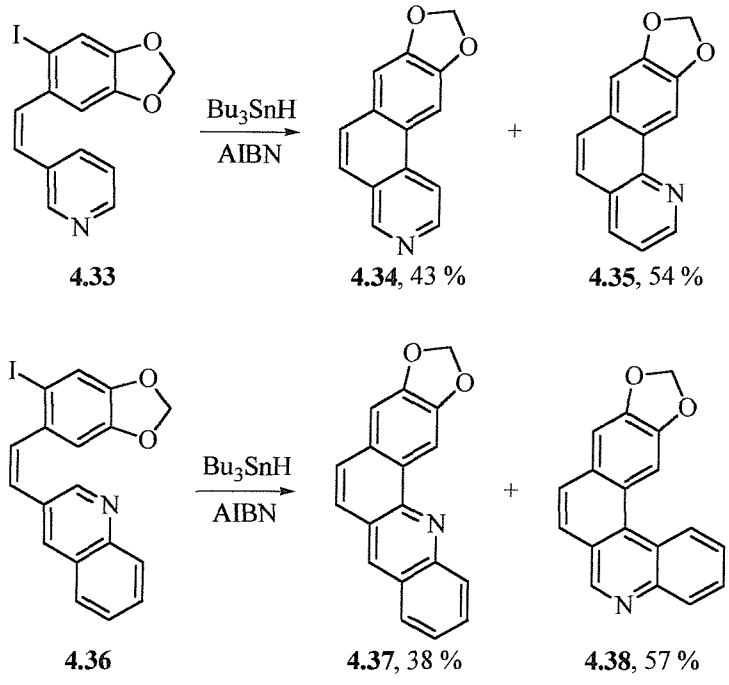
4.3 Conclusions

In conclusion, the first total synthesis of toddaquinoline **4.1**, an unusual alkaloid from the root bark of the Formosan *Toddalia asiatica*, has been completed. Radical cyclisation onto a pyridine moiety served to form the tetracyclic skeleton. Using tributyltin hydride as a mediator no regioselectivity was observed with respect to the cyclisation. Use of an aryl iodide gave higher yields than the corresponding aryl bromide. Aryl bromide **4.22**, when exposed to sodium cobalt(I)salophen, underwent radical cyclisation with complete regiocontrol in favour of addition to C-6 of the pyridine moiety. This suggests that a Lewis acid – Lewis base interaction between cobalt(II) and the Lewis basic pyridine controls the

regiochemical course of the reaction. The total synthesis was completed by a palladium-catalysed hydrogenolysis of the benzyl protecting group.

4.4 Further Work

As a consequence of this investigation, work within the research group has shown that radical additions to a range of nitrogen-containing heterocycles occur readily and efficiently. Pyridines, quinolines and isoquinolines all undergo radical cyclisation reactions under standard tributyltin-mediated radical forming conditions providing the corresponding condensed aromatics in good to excellent yield (Scheme 4.9).[115-117]



4.33 **4.34**, 43 % **4.35**, 54 %

4.36 **4.37**, 38 % **4.38**, 57 %

Scheme 4.9

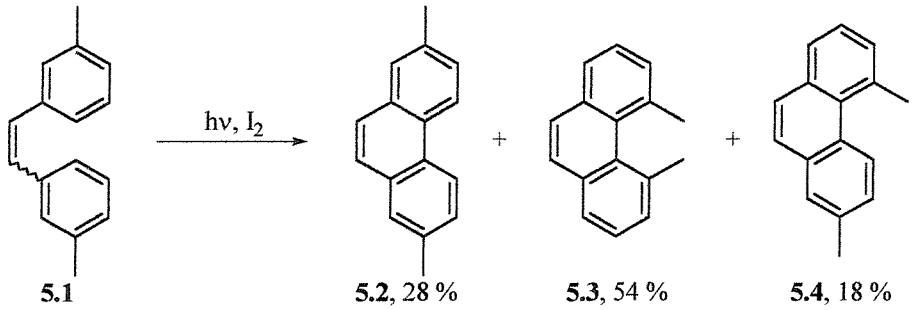
Chapter 5 - Radical Cyclisations of 2-Halostilbenes and Dihydrostilbenes

5 *Radical Cyclisations of 2-Halostilbenes and Dihydrostilbenes*

5.1 Background

5.1.1 Methods for the Synthesis of Phenanthrenes

Aryl-aryl bond formation plays an important role in modern synthetic chemistry.[118] Most commonly, organotransition metal mediated cross-coupling reactions are used to generate such systems. When phenanthrenes are the target of synthesis, oxidative photocyclisation methodologies are commonly employed as these provide a short, and often regioselective, route to phenanthrenes (Scheme 5.1).[110,119]



5.1 **5.2**, 28 % **5.3**, 54 % **5.4**, 18 %

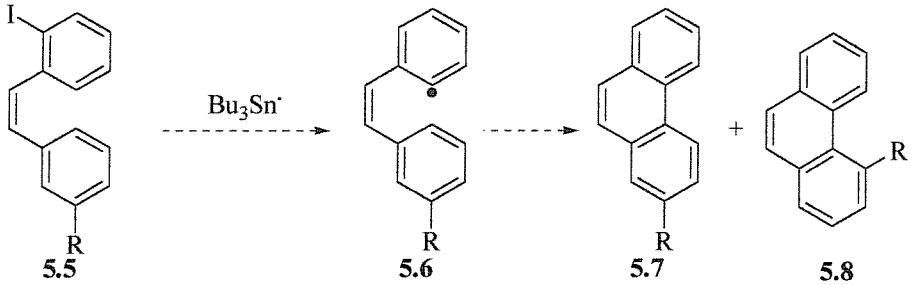
Scheme 5.1

However, in some instances regiocontrol is poor with all four possible isomers being observed in varying quantities. In such cases, and if a disfavoured regioisomer is required, an alternative method of carbon-to-carbon bond formation is required. We hoped to provide such an alternative by employing a radical cyclisation strategy.

5.2 Radical Cyclisations of 2-Halostilbenes

5.2.1 Synthesis of Phenanthrenes

The success of our radical cyclisation of a haloaza-stilbene during the total synthesis of toddaquinoline **4.1** (Chapter 4) led us to explore an extension of the methodology to 2-halostilbenes. We hoped that by subjecting such substrates to standard tributyltin-mediated radical forming conditions it might be possible to transform them into the corresponding phenanthrenes. The maximum number of phenanthrene products one would expect to attain would be two; providing a potential benefit compared to the photocyclisation methodology (Scheme 5.2).

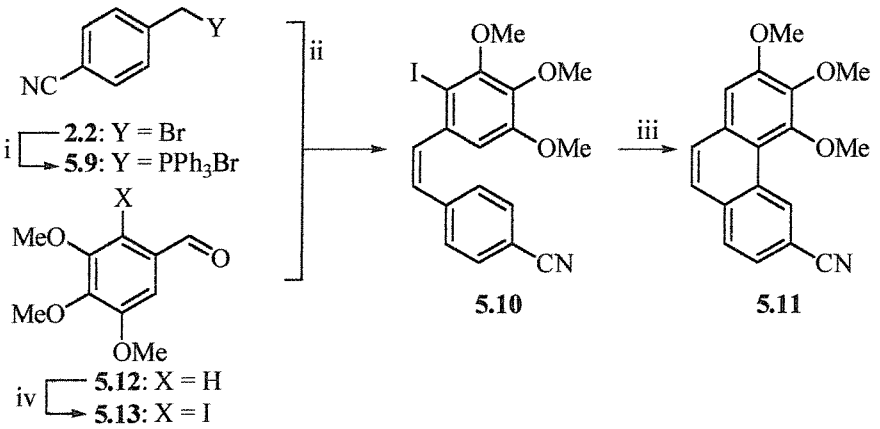


5.5 **5.6** **5.7** **5.8**

Scheme 5.2

Our first task was to synthesise the iodostilbene precursors. A *cis* geometry was required for efficient cyclisation. Alternatively, we would have to establish conditions to effect a *trans*- to *cis*- isomerisation prior to, or concomitant with, radical formation.[11,115]

As with our earlier study, our investigation began with the synthesis of an electron-deficient radical acceptor arene. Thus, 4-(bromomethyl)benzonitrile **2.2** was treated with triphenylphosphine in toluene to yield the corresponding phosphonium bromide **5.9**.[120] Deprotonation with sodium hydride and union with 2-iodo-3,4,5-trimethoxybenzaldehyde **5.13** yielded (*Z*)-iodostilbene **5.10** in 71 % yield.[121] Pleasingly, exposure of **5.10** to tributyltin hydride and AIBN in toluene gave 5,6,7-trimethoxy-3-phenanthrenecarbonitrile **5.11** in 85 % yield (Scheme 5.3).



Reagent & Conditions: **i.** PPh_3, toluene, reflux, 6 h, 96 %; **ii.** NaH, THF, r.t., 2 h; **5.13**, r.t., 2 h, 71 %; **iii.** Bu_3SnH, AIBN, PhMe, 90 °C, 85 %; **iv.** I_2, $AgOCOCF_3$, CH_2Cl_2, r.t., 1½ h, 92 %.

Scheme 5.3

To confirm the structure of **5.11**, GOESY-NMR studies were employed. n.*O*.e. enhancements between the proton signal at δ_H = 9.92 ppm (1H, br. s) and a methoxy group precluded the isomer **5.14** (the large deshielding effect of the proximal methoxy and cyano groups was consistent with this assignment) (Figure 5.4).

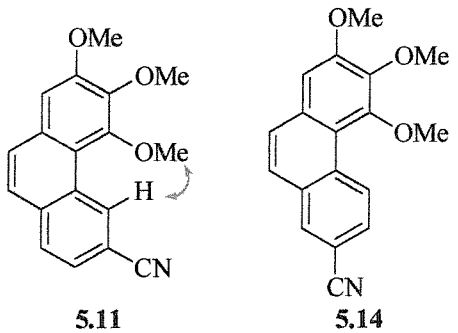
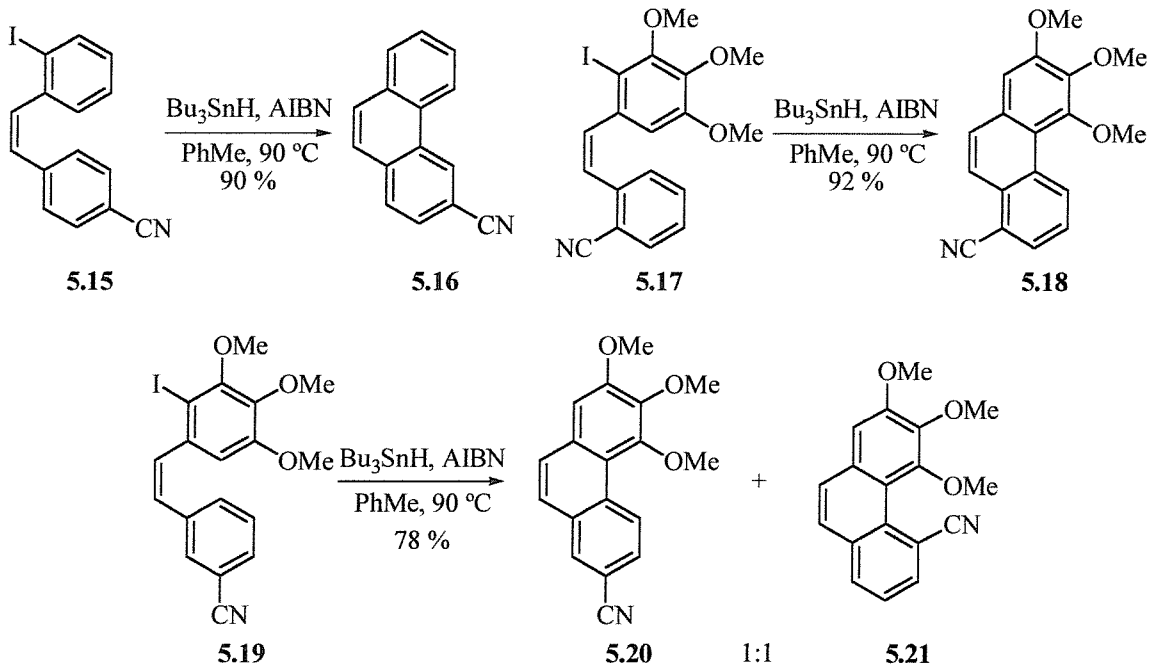


Figure 5.4

A range of substrates was then prepared using the Wittig methodology with differing steric and electronic characteristics (details in the Experimental Section). Changing the electronics of the iodinated aromatic had little effect on the reaction. Thus, 2-iodo-4'-cyanostilbene **5.15** yielded phenanthrene-3-carbonitrile **5.16** in 90 % upon treatment with tributyltin hydride and AIBN in toluene. The substitution pattern on the radical acceptor arene also had minimal effect with 2-cyano and 3-cyano substituents reacting efficiently under standard conditions (Scheme 5.5).

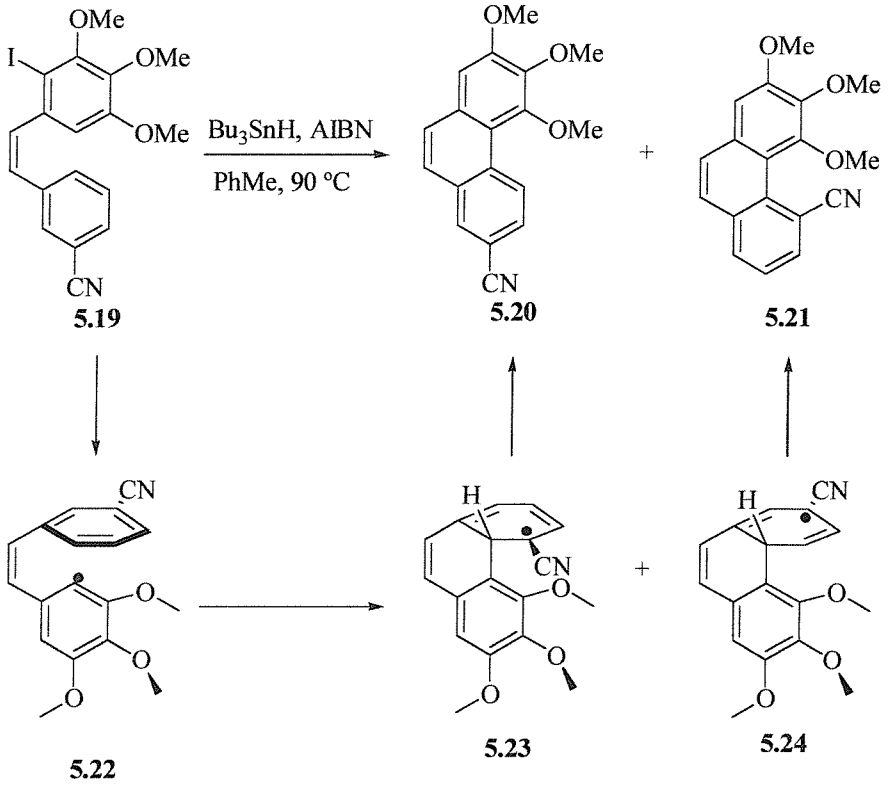


5.15 **5.16** **5.17** **5.18**

5.19 **5.20** 1:1 **5.21**

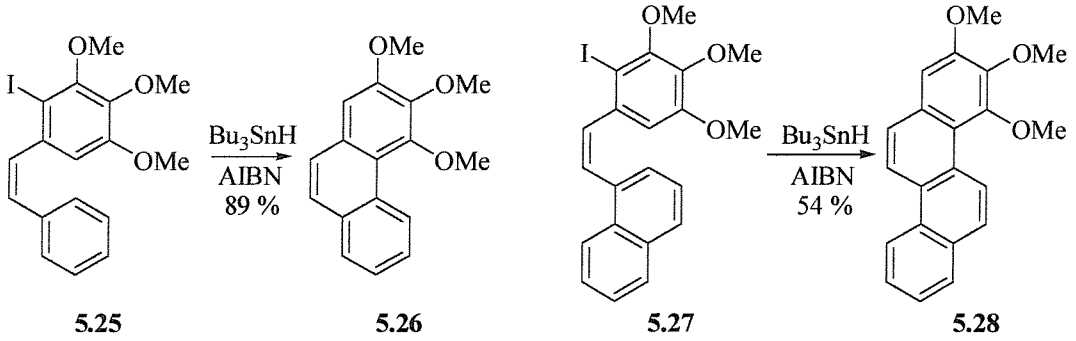
Scheme 5.5

In the case of **5.19**, two regioisomers **5.20** and **5.21** were formed in equimolar quantities. Thus, it seems that the additional steric demand for formation of **5.21** has little influence on the course of the reaction. Indeed, it can be seen that the 3-cyano group is remote from the aryl radical in the transition state. As cyclisation is irreversible, intermediates **5.23** and **5.24** are formed in equal proportion. Only when these collapse by loss of a hydrogen atom does steric repulsion between the methyl ether and cyano substituents increase. As this step too is irreversible, steric effects are minimal (Scheme 5.6).



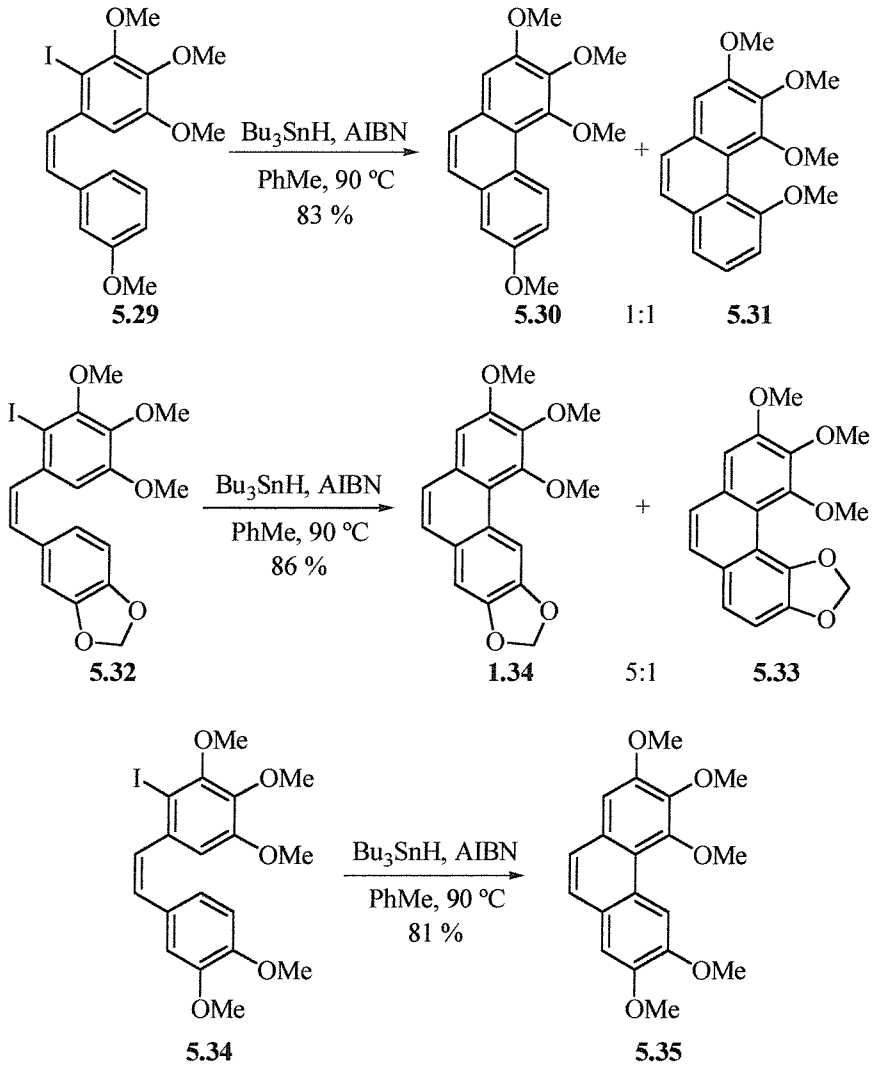
Scheme 5.6

Electron neutral arenes also showed good reactivity. Hence, 2-iodo-3,4,5-trimethoxystilbene **5.25** and naphthalene derivative **5.27** gave 2,3,4-trimethoxyphenanthrene **5.26** and 2,3,4-trimethoxychrysene **5.28** respectively in good and moderate yield (Scheme 5.7).



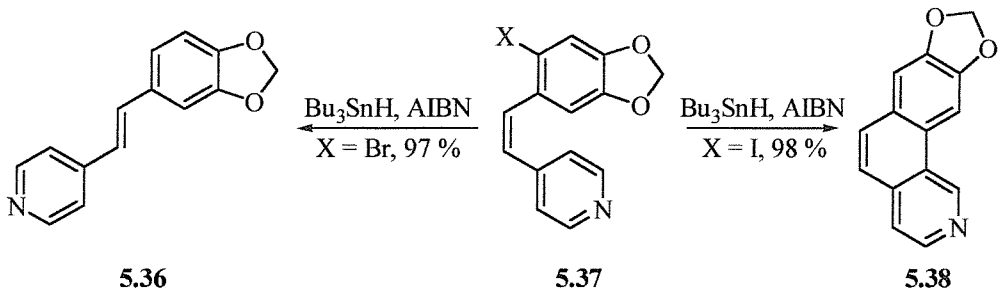
Scheme 5.7

An interesting result was obtained when a range of electron rich examples were investigated. With a 3-methoxyphenyl ring as a radical acceptor **5.29**, a separable 1:1 mixture of the regioisomers **5.30** & **5.31** was obtained. However, exposure of **5.32** to standard conditions gave a 5:1 separable mixture of **1.34** and **5.33** in favour of the less encumbered product. Similarly, when **5.34** was treated with tributyltin hydride and AIBN in toluene only **5.35** was isolated. We propose that the addition of a second electron donating substituent in the 4-position imparts an electronic bias on the system. At this time, we are unclear as to the true nature of that effect (Scheme 5.8).



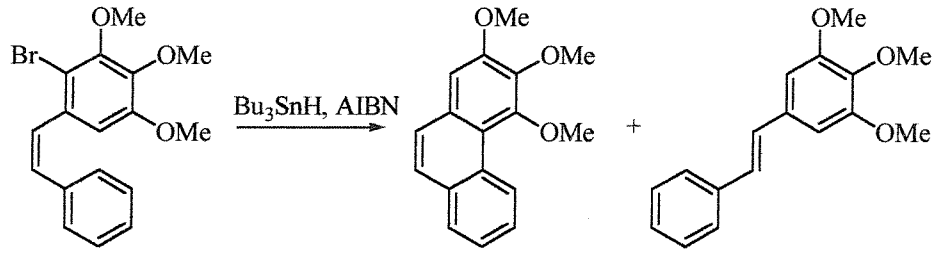
Scheme 5.8

We have shown that 2-iodostilbenes undergo efficient reaction with tributyltin hydride and AIBN. One example of an aryl bromide was tested to evaluate its effectiveness under standard conditions. Work within the research group has shown that *cis-trans* isomerisation of the alkene outpaces carbon-to-bromine homolysis in certain cases where a pyridine is the radical acceptor. For the analogous aryl iodide, by contrast, cyclisation is the primary pathway (Scheme 5.9).[115]



Scheme 5.9

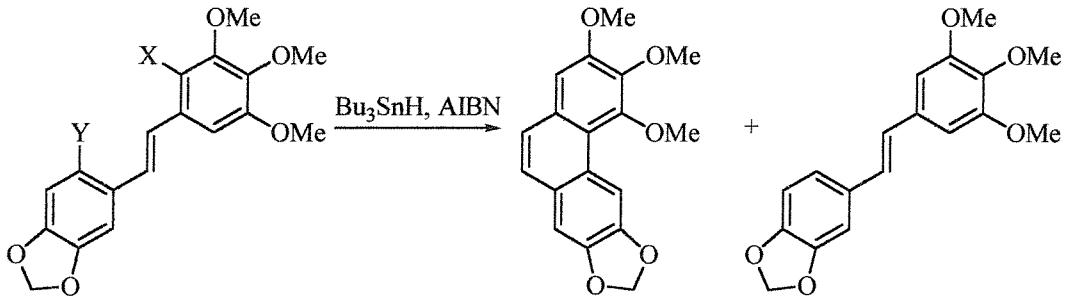
In our case, alkene isomerisation was only a very minor pathway. Subjecting 2-bromostilbene **5.39** to tributyltin-mediated radical forming conditions yielded phenanthrene **5.26** with only TLC evidence of a second compound that was assumed to be *trans*-stilbene **5.40** (there was insufficient material for isolation) (Scheme 5.10).



5.39 **5.26** **5.40**, trace

Scheme 5.10

Further information on the relative rates of these competing processes was obtained by exposure of *trans*-stilbene **5.41** to standard conditions. Narasimhan *et al.* had shown that the equivalent *trans*-bromostilbene **1.33** underwent cyclisation, albeit in low yield, using standard radical forming conditions.[11] Iodide **5.41** gave **1.34** in less than 5 % yield, the major product being reduction to **5.42**. We can therefore deduce that in this system, the rate of carbon-iodine bond homolysis is much faster than tributyltin radical induced alkene isomerisation. The rate of carbon-bromine bond homolysis is comparable with alkene isomerisation and, for a given substrate, either may be dominant. Again, electronic factors seem to play a major role (Scheme 5.11).



1.33: X = H, Y = Br
5.41: X = I, Y = H

1.34 **5.42**

X = H, Y = Br 30 %
X = I, Y = H < 5 %

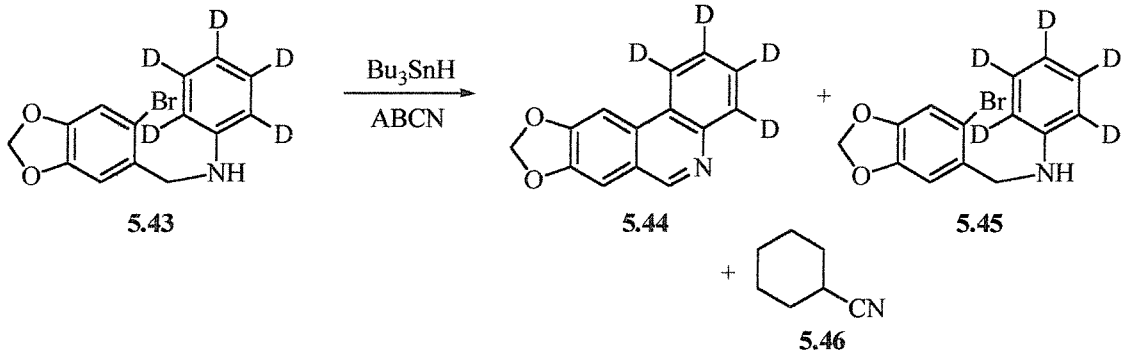
68 %

Scheme 5.11

5.2.2 Towards the Mechanism of Phenanthrene Formation

It is interesting to note that no evidence of dihydroarene products was obtained for any of the aforementioned reactions, even though they are under reducing conditions. The mechanism by which intermediates akin to **5.23** are converted to the corresponding phenanthrene is unclear. A number of proposals have been made although to date no irrefutable argument has

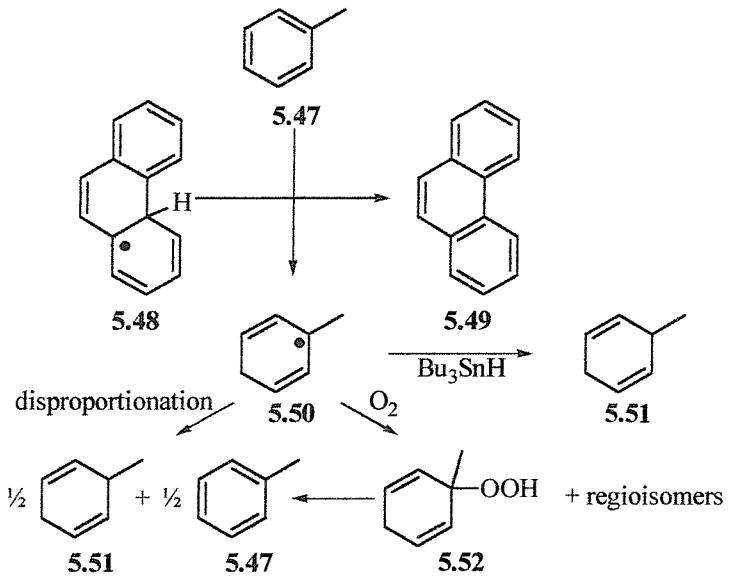
been made. Bowman hypothesised a single-electron transfer between an aryl halide and a radical anion intermediate although this was later disproved (see Chapter 2).[53] In recent years, a link has been suggested to the initiator. In many examples stoichiometric quantities of initiator are required for complete reaction suggesting it has some other role in the reaction. In 1997, Rosa *et al.* tested whether the carbon-centred radicals generated by decomposition of the initiator could abstract hydrogen from such intermediates. Thus, a deuterated substrate was subjected to tributyltin hydride and ABCN. On work up, they found only evidence of cyclohexanecarbonitrile **5.46** with no deuterium incorporation, thus ruling out this pathway (Scheme 5.12).[31] There is some evidence to suggest AIBN itself can be reduced under reaction conditions although the product of such a reduction is known to be inherently unstable so has never been isolated from a radical reaction.[122-124]



5.43 **5.44** **5.45** **5.46**

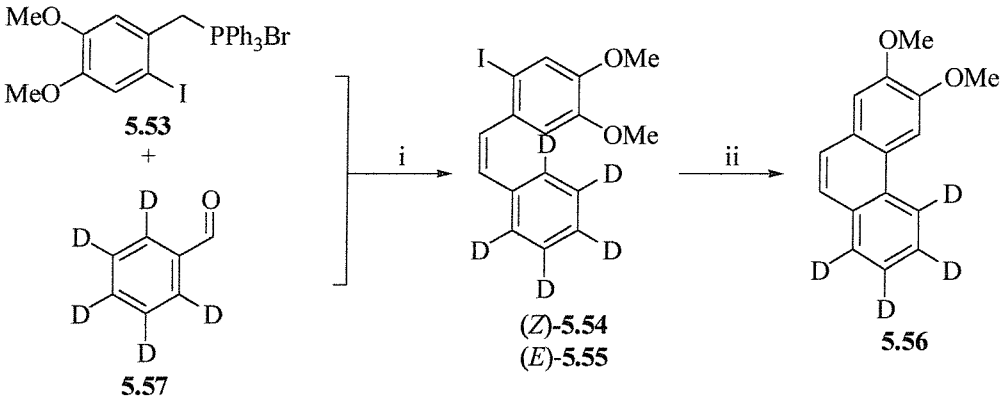
Scheme 5.12

Our proposal involves reaction between radical intermediate **5.48** and solvent (*i.e.* toluene). We hypothesised that toluene could accept a hydrogen atom from **5.48** to give phenanthrene **5.49** and toluene adduct **5.50**. This could then react with tributyltin hydride or oxygen or undergo disproportionation (Scheme 5.13).



Scheme 5.13

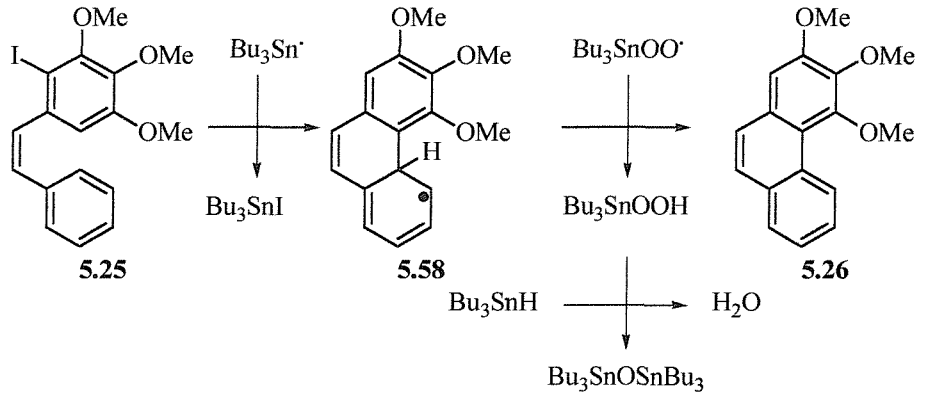
To investigate this we synthesised a deuterated iodostilbene **5.54**. This we subjected to tributyltin hydride and AIBN in refluxing benzene (substrate concentration 0.05 M). On cooling, an aliquot was removed for deuterium-NMR analysis. The results showed deuterium signals due to the product **5.56**. In addition signals in the aliphatic and unsaturated (alkenyl and/or aromatic) regions were observed. Repeating the process in tetrahydrofuran we found that again signals in the aliphatic and unsaturated regions were observed. Deuterium has therefore been transferred to some organic molecule within the reaction medium although which remains unclear (Scheme 5.14 and Appendices I-IV).



Reagents & Conditions: **i.** NaH, THF, r.t., 2 h; **5.57**, r.t., 2 h, 71 %, **5.54**:**5.55** ~ 4:3; **ii.** Bu_3SnH, AIBN, PhH, reflux, 16 h, 96 %.

Scheme 5.14

Note should be made of the quantity of tributyltin hydride used. Two equivalents of the reagent were required for complete reaction. It is probable that trace amounts of oxygen in the reaction mixture react with tributyltin radicals under the reaction conditions (generating tributyltin peroxide). This in itself could provide an alternative means of forming the aromatic products. Tributyltin peroxide radical could abstract a hydrogen atom from an intermediate akin to **5.58** leading to aromatisation with concomitant formation of tributyltin peroxide. In turn this could be reduced *in situ* by tributyltin hydride to bis(tributyltin)oxide and water. However, this would not allow for transfer of hydrogen to a hydrocarbon so if this pathway occurs it must be a minor one (it would also require three equivalents of tributyltin hydride) (Scheme 5.15). Further investigation in this area is required to fully describe the mechanism of non-reducing radical cyclisation mediated by tributyltin hydride.



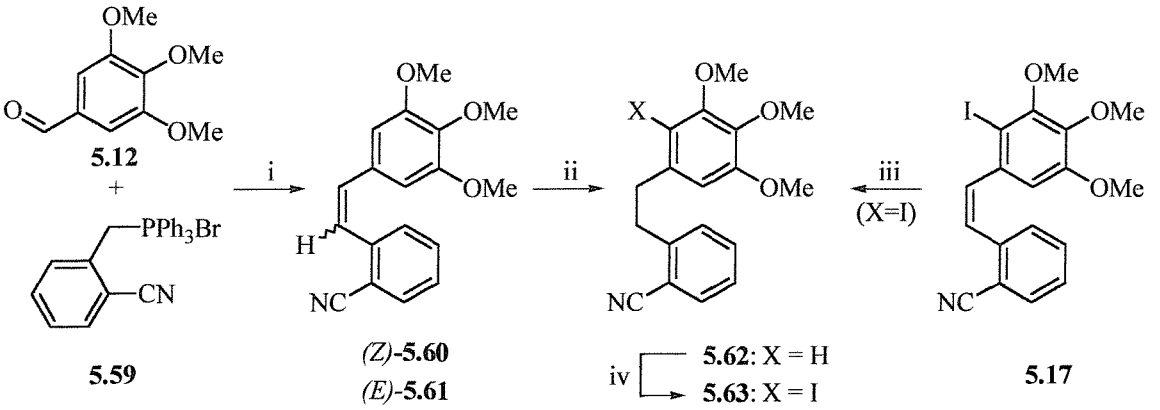
Scheme 5.15

5.3 Dihydrophenanthrenes from 2-Iododihydrostilbenes

We have demonstrated that 2-iodostilbenes are efficient precursors to phenanthrenes. Another area of investigation pursued was to evaluate the effectiveness of radical cyclisations if extra flexibility was introduced into the tether. Reduction of the alkene served to provide substrates for this.

5.3.1 Synthesis of Radical Precursors

Diimide reduction of 2-iodostilbene **5.17** gave access to 2-iododihydrostilbene **5.63** but the reaction was very slow. After 6 days with 10 equivalents of the reducing agent only 68 % yield of dihydrostilbene **5.63** was attained together with 24 % recovered starting material **5.17**. We therefore decided to implement a different strategy to allow more facile access to these compounds. Thus, Wittig reaction between the ylid of (2-cyanobenzyl)triphenylphosphonium bromide **5.59** and 3,4,5-trimethoyxbenzaldehyde **5.12** gave a separable 1:2 mixture of (*Z*)- and (*E*)-stilbenes **5.60** and **5.61** respectively. These were then reduced by palladium-catalysed hydrogenation and the 1,2-diarylethane **5.62** exposed to iodine in the presence of silver(I) trifluoroacetate to yield aryl iodide **5.63**. Despite requiring three steps, the overall efficiency was greater than a direct diimide reaction of the parent iodostilbene (>85 % over 3 steps for the formation of iodide **5.63** compared to 68 % for a diimide reduction) (Scheme 5.16).

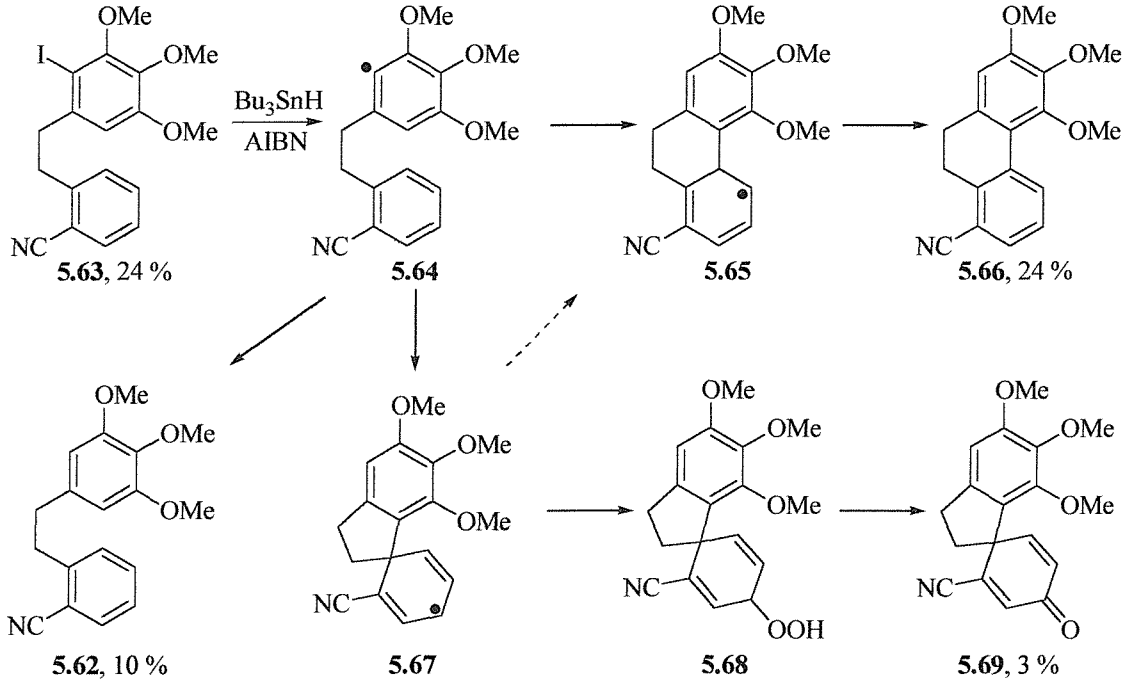


Reagents & Conditions: **i.** NaH, THF, r.t., 2 h; 0 °C, **5.12**, r.t., 16 h, 93 %, **5.60**:**5.61** ~ 1:2; **ii.** H_2, Pd-C, EtOH, CH_2Cl_2, r.t.p., 16 h, 95 %; **iii.** *p*TsNHNH$_2$, NaOAc, THF/H_2O, reflux, 6 days, 68 % (+ 24 % RSM); **iv.** I_2, $AgOCOCF_3$, CH_2Cl_2, r.t., 1 h, 99 %.

Scheme 5.16

5.3.2 Cyclisations of 2-Iododihydrostilbenes

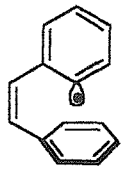
Exposure of **5.63** to tributyltin hydride and AIBN in toluene gave a mixture of compounds. These included dihydrophenanthrene **5.66** (24 % as a mixture with recovered starting material (24 %), diarylethane **5.62** (10 %) and spirocycle **5.69** (3 %) (Scheme 5.17).



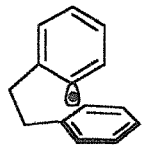
Scheme 5.17

The major pathway formally remains a 6-*exo*/*endo*-trig cyclisation with spirocycle **5.69** providing evidence of a competing 5-*exo*-trig cyclisation pathway (a 5-*exo*-trig and subsequent migration to yield intermediate **5.65** cannot be disregarded). With either mechanism in operation, the overall efficiency of reaction is much reduced in comparison with its iodostilbene counterpart. This can be rationalised by the increased flexibility in the

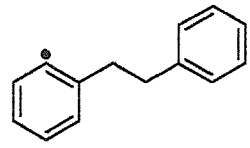
tethering chain providing a higher degree of freedom for rotation. On average, there is a smaller probability of reaction between the aryl radical and the adjacent arene. With respect to the change in cyclisation pathway, the geometry of the tether plays a critical role. In the case of a 2-iodostilbene, the tether is formed from sp^2 carbons (bond angles *ca.* 120°) so that the nascent aryl radical is aligned to react at the *ortho* carbons of the acceptor arene. However, the tetrahedral nature of the alkane tether (bond angle *ca.* 109°) changes the geometry of the intermediate so that 5-*exo*-trig cyclisation at the *ipso* carbon has a comparable rate to a 6-*exo*/*endo*-trig pathway (Figure 5.18).



5.70



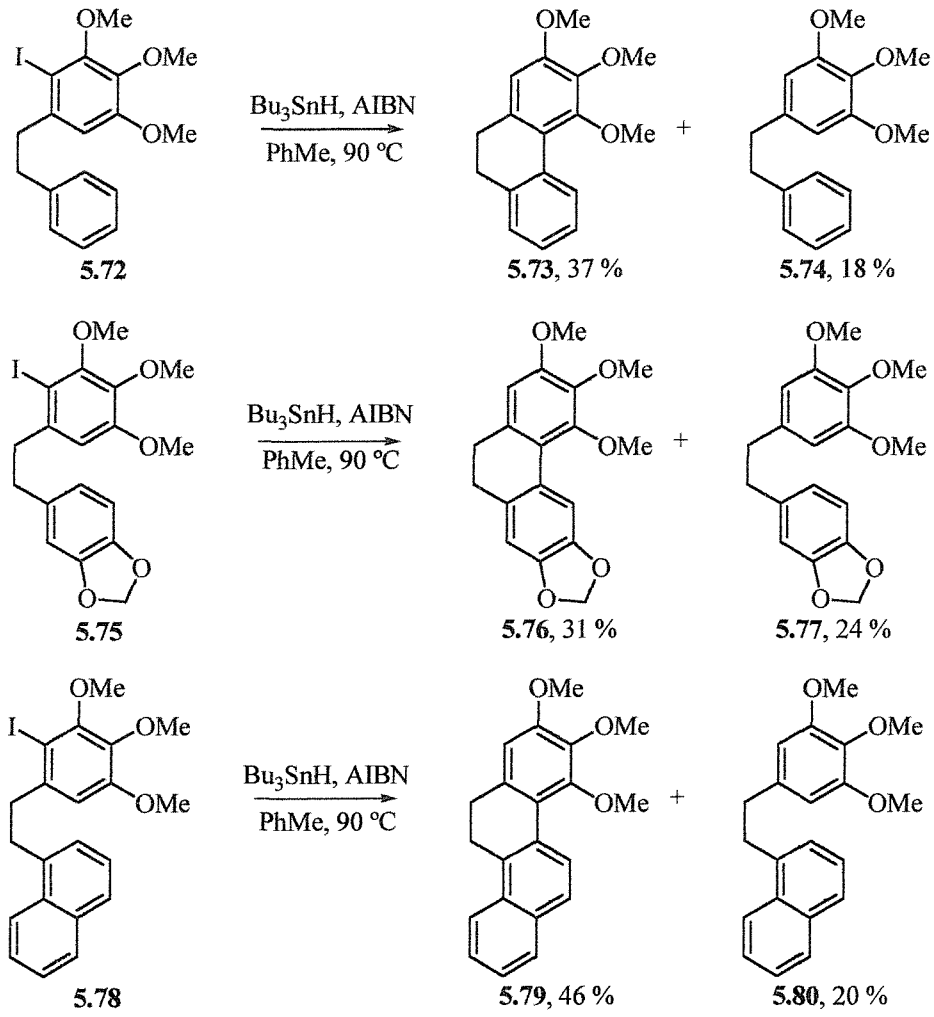
5.71



5.71

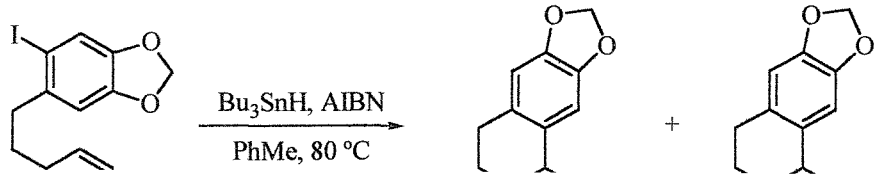
Figure 5.18

A range of substrates were synthesised and subjected to standard radical forming conditions. In each case the expected dihydrophenanthrene was formed in 30 – 50 % yield along with the product of carbon-iodine bond reduction (10 –35 %) (Scheme 5.19).



Scheme 5.19

In work within the group applying similar conditions to substrates containing a pyridine moiety as the radical acceptor, the products showed a mixture of cyclisation by direct *ortho*-attack and by *ipso* attack with subsequent rearrangement (Scheme 5.20). A GOESY NMR study of **5.79** proved the structure was that suggested.[116]



Scheme 5.20

5.4 Conclusions

We have shown that 2-halostilbenes provide excellent substrates for tributyltin hydride mediated radical cyclisation to the corresponding phenanthrene. Yields are generally good to excellent. The electronic character of the acceptor arene may play a significant role in determining the regiochemical course of reaction. Sterics have a minor effect. Regioselectivity was only observed with a 3,4-disubstituted radical acceptor arene. In each case reactions proceed to fully aromatic products although the mechanism of that is unclear. Deuterium-labelling studies have indicated that deuterium is transferred to some aliphatic and unsaturated organic molecules.

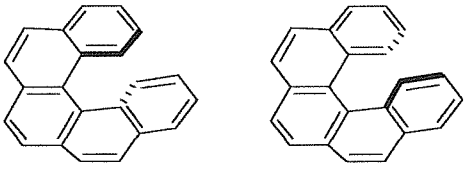
Reaction of 2-iododihydrostilbenes under standard conditions proved less efficient with dihydrophenanthrenes formed in moderate yield along with products of direct reduction. In one instance, a spirocycle was isolated resulting from 5-*exo*-trig cyclisation.

Chapter 6 - Synthesis of [5]Helicenes by a Radical Cyclisation Methodology

6 *Radical Cyclisations for the Synthesis of [5]Helicenes*

6.1 Background

Helicenes are non-planar condensed aromatic compounds. Due to steric crowding, the termini of the helicene have to overcome an energy barrier to pass each other in space resulting in chirality. The parent [5]helicene exhibits chirality although will racemise at room temperature.[125] The nomenclature used for describing the enantiomers of helicenes are denoted as M when the spiral moves upwards in a clockwise direction and P when the spiral moves downwards in a clockwise direction (Figure 6.1).



6.1 (+)-M **6.1** (-)-P

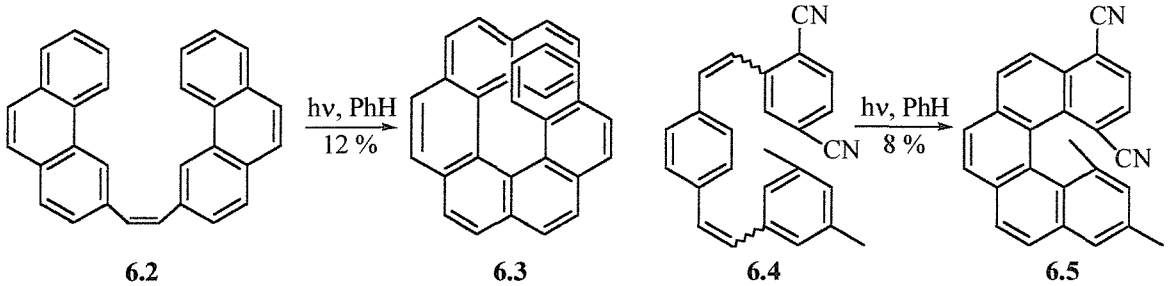
Figure 6.1

6.1.1 Uses

Although for many years helicenes were regarded as little more than an academic curiosity, recently they have found uses in as diverse areas as liquid crystals,[126] host-guest chemistry,[127-130] and asymmetric synthesis.[131-133] Enantiomerically-enriched helicenes strongly rotate the plane of polarised light with optical rotations typically in the thousands.[125] A synthetically efficient route to such compounds is therefore desirable to allow access to these fascinating structures in reasonable quantity.

6.1.2 Methods of Helicene Synthesis

Newman *et al.* reported the first helicene synthesis in 1956.[134] Since then a range of racemic and enantioselective syntheses have been reported. The most utilised method involves oxidative photocyclisation of a stilbene. Such photocyclisations have been used to generate a host of helicenes of varying size ([5]helicenes[135] up to [14]helicenes[136] have been synthesised by the methodology) and substituent complexity (Scheme 6.2).[135,137]

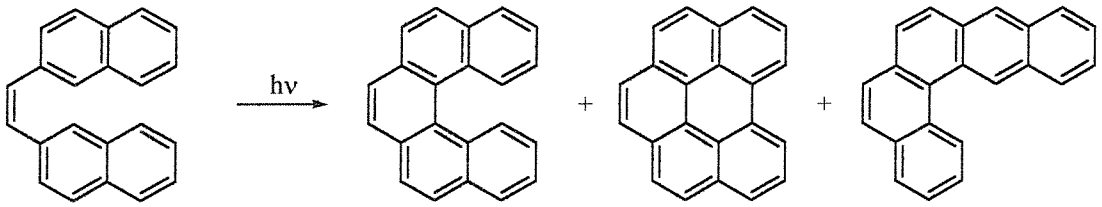


6.2 **6.3** **6.4** **6.5**

Scheme 6.2

Under standard photocyclisation conditions (*e.g.* irradiation in benzene), helicenes are formed as racemates. However, if circularly polarised light is employed enantiomerically enriched products are formed.[138,139]

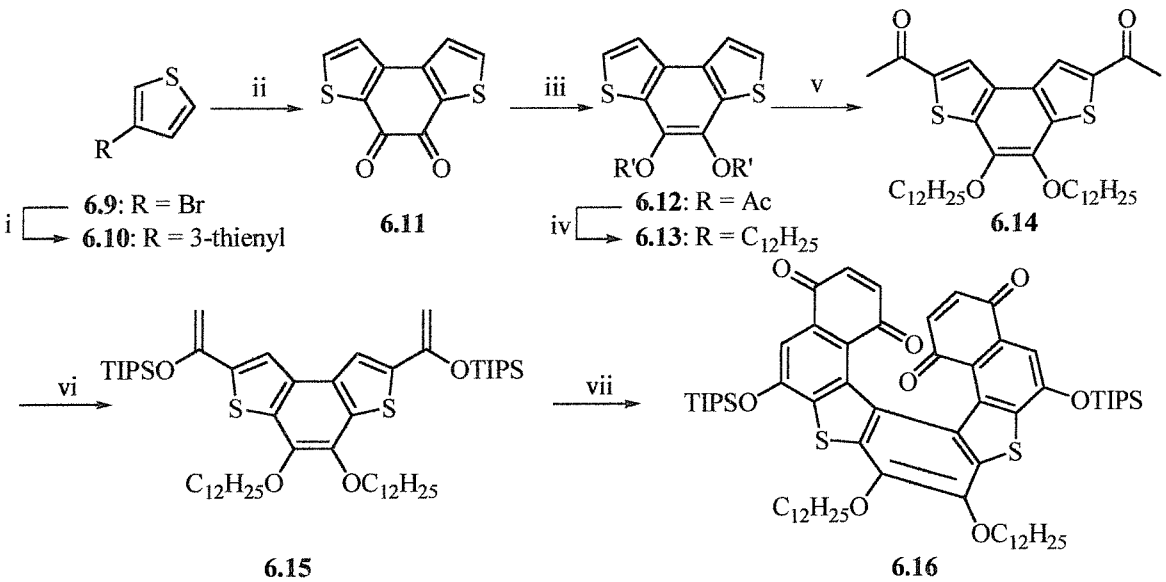
Despite its popularity, there are many problems with this method. Isolated yields are frequently variable and are generally carried out at high dilution (substrate concentration *ca.* 10^{-5} mol dm^{-3}). This is in part due to the low solubility of stilbenes in the reaction solvent and because helicenes are prone to photodimerisation. It is therefore impractical to synthesise helicenes in large quantity by this method. Yields are further compromised by a photochemical side reaction leading to the formation of a benzo[*ghi*]pyrene (Scheme 6.3).[110]



6.6 **6.1**, 25 % **6.7**, 37 % **6.8**, 38 %

Scheme 6.3

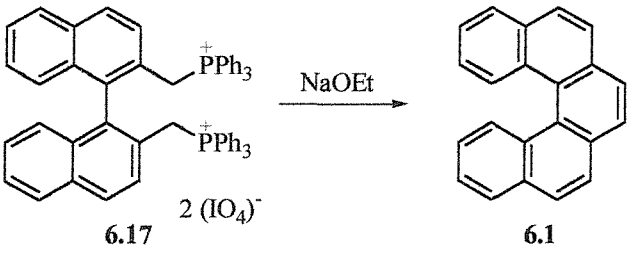
As a consequence, many groups have investigated alternative routes to helicenes. Katz *et al.* have synthesised a wide range of helicenes by a variety of methodologies. For example, in 2001 they reported the synthesis of the hetero-helicene **6.16** using a double Diels-Alder as a key step. The whole synthesis required only seven steps from 3-bromothiophene **6.9** (Scheme 6.4).[140]



Reagents & Conditions: **i.** 3-thienylMgBr, $Ni(dppp)Cl_2$; **ii.** oxalyl chloride, DCE, reflux, 68 %; **iii.** Zn, Ac_2O, CH_2Cl_2, 83 %; **iv.** Cs_2CO_3, $C_{12}H_{25}I$, MeCN, 94 %; **v.** AcCl, DCE, 83 %; **vi.** TIPSOTf, NEt_3, CH_2Cl_2, 100 %; **vii.** *p*-benzoquinone, heptanes, reflux, 95 %.

Scheme 6.4

An alternative approach by Bestmann *et al.* involved treatment of bisphosphonium salt **6.17** with sodium methoxide to provide [5]helicene **6.1** (Scheme 6.5).[141] They later described a synthesis of a chiral helicene by employing a chiral naphthyl precursor.[142]



6.17 **6.1**

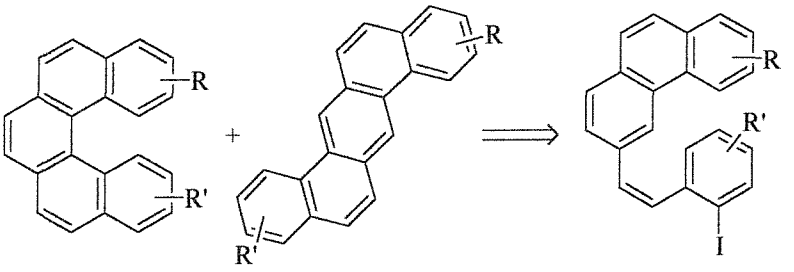
Scheme 6.5

Carbenoid insertion and McMurray reactions have also been used for the synthesis of helicenes.[143-145] We hoped to contribute an alternative route based on our radical cyclisation methodology.[146]

6.2 Helicene Synthesis by Radical Cyclisations onto Arenes

6.2.1 [5]Helicenes by an Iterative Radical Cyclisation Strategy

Our new approach to phenanthrenes by radical cyclisation of iodostilbenes has shown that radical cyclisations of this type are efficient and effective (Chapter 5). With the synthesis of [5]helicenes in mind, we were interested to see how a radical cyclisation to a phenanthrene would proceed. In particular, cyclisation of **6.20** could give a helicene product or yield the isomeric dibenzo[*a*,*h*]anthracene. Since radical reactions of this type are little influenced by steric encumbrance we hoped that the more demanding helicene would be formed (Scheme 6.6).

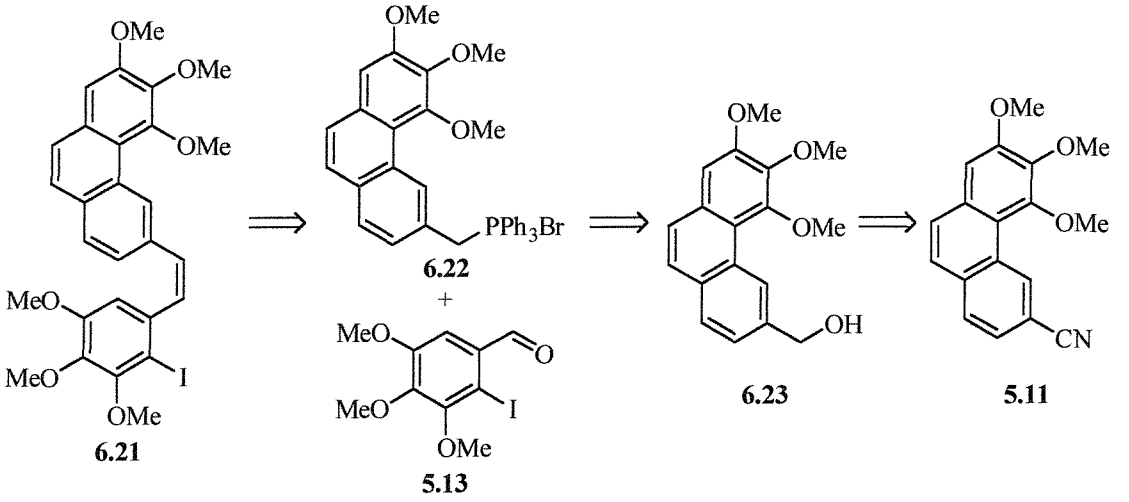


6.18 **6.19** **6.20**

Scheme 6.6

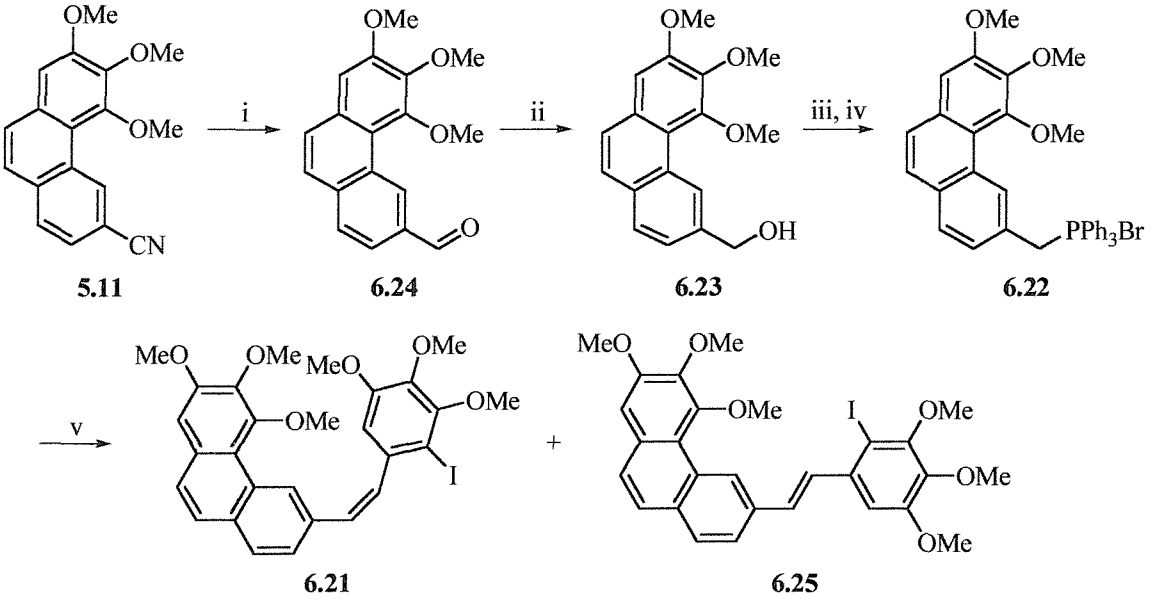
To test this hypothesis, we required access to a substrate akin to **6.20**. This could be generated from phosphonium bromide **6.22** and an iodobenzaldehyde. In turn, **6.22** could be derived from phenanthryl alcohol **6.23** which could be formed from phenanthrene-3-carbonitrile **5.11**. Wittig reactions between a phosphorane ylid and an iodobenzaldehyde were found to give good *Z*-selectivity, justifying the additional steps required to form a

(phenanthrylmethyl)phosphonium bromide compared to a phenanthrene-3-carboxaldehyde (Scheme 6.7).



Scheme 6.7

Phenanthrene-3-carbonitrile **5.11** had been synthesised as part of the methodology studies described in Chapter 5. DIBAL-H reduction of **5.11** in toluene yielded aldehyde **6.24** which was further reduced to phenanthryl alcohol **6.23** with sodium borohydride.[147] Treatment of **6.23** with phosphorus tribromide and reaction of the resulting bromide with triphenylphosphine provided phosphonium bromide **6.22** in good overall yield.[148] Deprotonation with sodium hydride and union with 2-iodo-3,4,5-trimethoxybenzaldehyde **5.13** gave a separable 5:2 mixture of iodostilbenes **6.21** and **6.25** (Scheme 6.8).

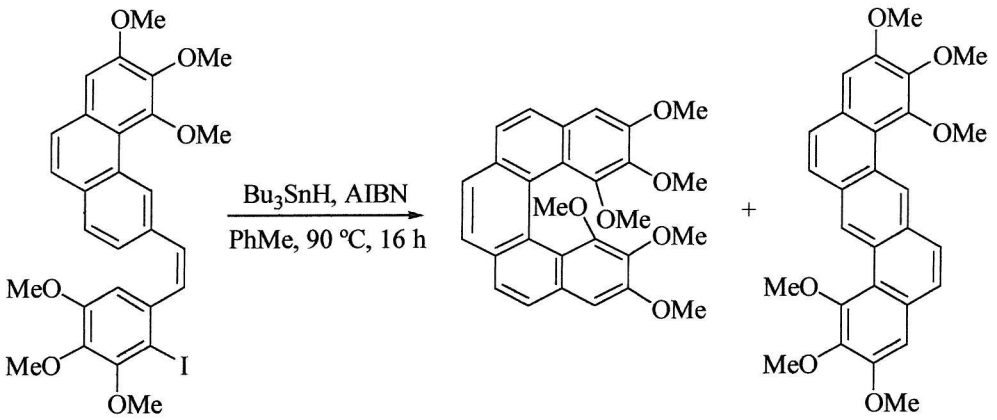


Reagents & Conditions: **i.** DIBAL-H, PhMe, 0 °C, 1 h, 81 %; **ii.** $NaBH_4$, THF, r.t., 4 h, 96 %; **iii.** PBr_3, PhH, r.t., 2 h, 85 %; **iv.** PPh_3, PhMe, reflux, 6 h, 70 %; **v.** NaH, THF, r.t., 2 h; **5.13**, r.t., 16 h, 67 % (*Z* : *E* ~ 5:2)

Scheme 6.8

Pleasingly, treatment of **6.21** under standard radical forming conditions facilitated cyclisation in good yield. To our delight, 1,2,3,12,13,14-hexamethoxy[5]helicene **6.26** was formed as

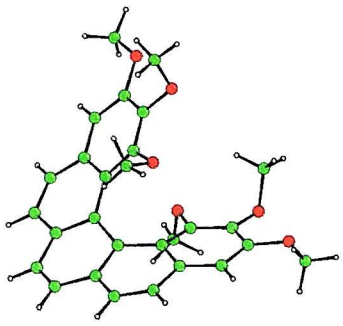
the major product in 51 % yield. 1,2,3,9,10,11-Hexamethoxydibenzo[*a*,*h*]anthracene **6.27** was also isolated in 17 % yield.[149] This result adds weight to our earlier assumption that attack of an aryl radical onto an adjacent arene is an irreversible process. Separation of the two compounds was aided by the insolubility of the linear polyarene. Thus, cooling of the reaction mixture to room temperature allowed collection of **6.27** by filtration (**6.27** was only soluble in hot toluene). The [5]helicene **6.26**, by contrast, was soluble in most common organic solvents (dichloromethane, ethyl acetate *etc.*) and was readily purified by column chromatography (Scheme 6.9).



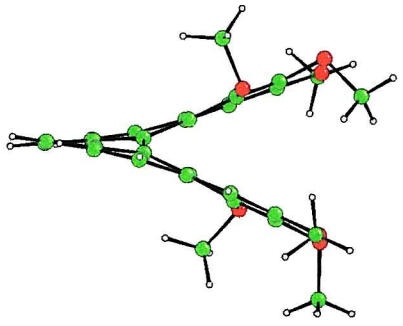
6.21 **6.26**, 51 % **6.27**, 17 %

Scheme 6.9

X-ray crystallography of [5]helicene **6.26** showed the degree of twist in the molecule. Figure 6.11 shows there is an angle of >20° between the two terminal arenes in **6.26**. Under our conditions, the helicene was formed as a racemate with the X-ray unit cell showing both M- and P-enantiomers.



6.26
Figure 6.10



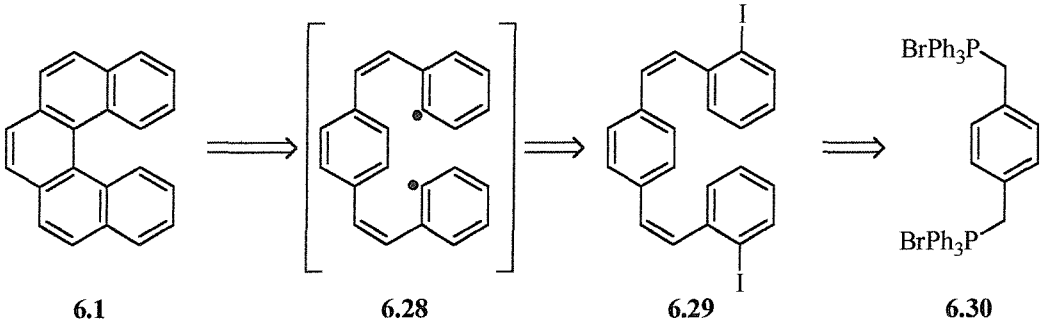
6.26
Figure 6.11

Having proved the concept of [5]helicene synthesis by an iterative radical cyclisation strategy it was clear that the synthetic route developed was too long and low yielding to be of genuine use. Since we had demonstrated that cyclisation of an iodostilbene to a phenanthrene is a

highly efficient process, and that Wittig reactions to 2-iodobenzaldehyde derivatives are *cis*-selective, we considered the possibility of performing the two cyclisation steps in the same reaction.

6.2.2 [5]Helicenes by a Tandem Radical Cyclisation Methodology

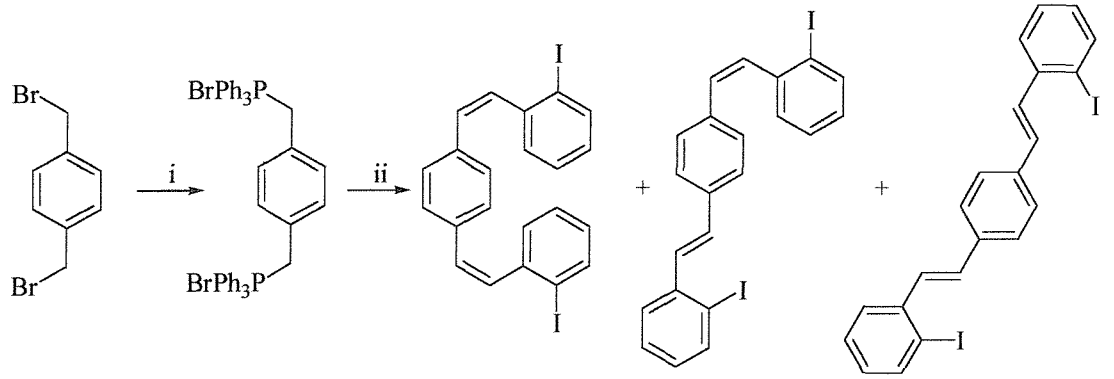
The tandem cyclisation approach leads back to a bis-iodide **6.29**. In turn, this could be formed by a double Wittig reaction with bis-phosphonium salt **6.30** (Scheme 6.12).



6.1 **6.28** **6.29** **6.30**

Scheme 6.12

Thus, exposure of α,α'-dibromo-*p*-xylene **6.31** to triphenylphosphine yielded bisphosphonium dibromide **6.30** in excellent yield. Deprotonation with sodium hydride and coupling with 2-iodobenzaldehyde **5.85** gave a 4:4:1 mixture of bis-stilbenes **6.29**, **6.32** and **6.33** in 77 % yield (Scheme 6.13).

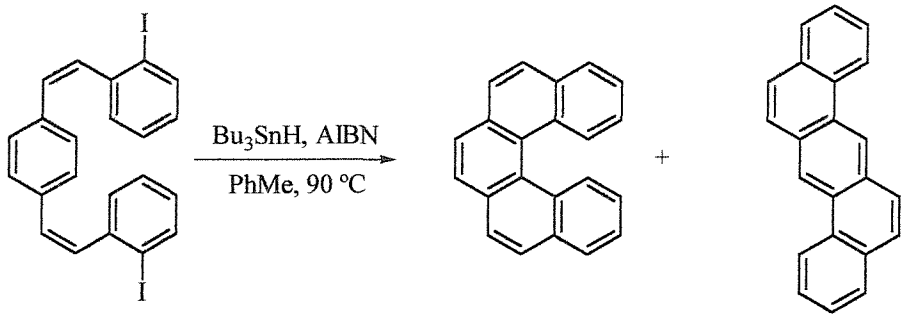


6.31 **6.30** **6.29** **6.32** **6.33**

Reagents & Conditions: **i.** PPh_3, DMF, 110 °C, 4 h, 98 %;[135] **ii.** NaH, THF, r.t., 2 h; 2-iodobenzaldehyde **5.85**, r.t., 3 h, 77 %, **6.29**:**6.32**:**6.33** ~ 4:4:1.

Scheme 6.13

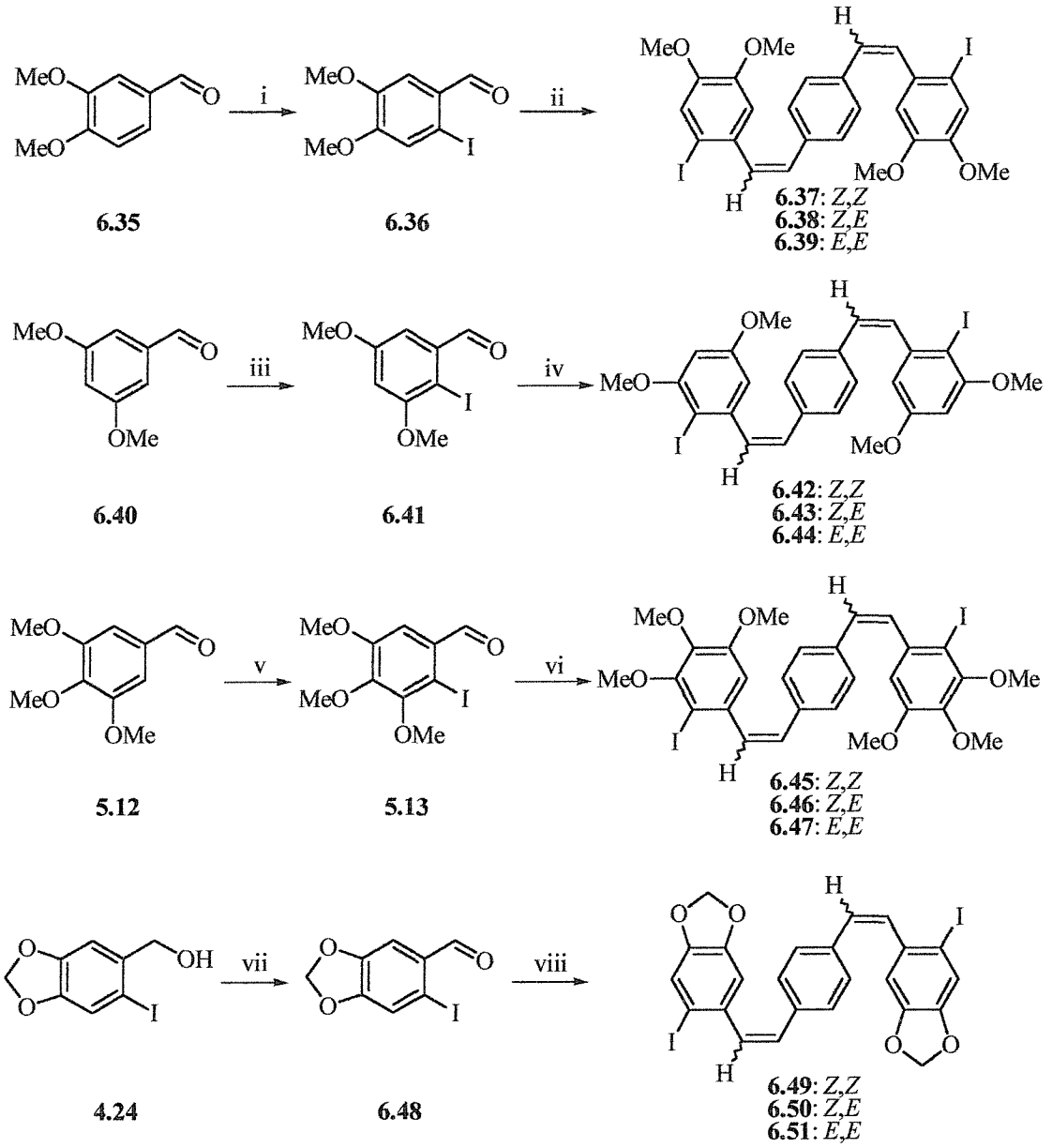
Exposure of **6.29** to tributyltin hydride and AIBN in toluene at 90 °C pleasingly gave [5]helicene **6.1** in good yield (58 %). ^1H – NMR analysis of the crude mixture provided some evidence for the formation of dibenzo[*a*,*h*]anthracene as a minor by-product (Scheme 6.14).



6.29 **6.1**, 58 % **6.34**, trace

Scheme 6.14

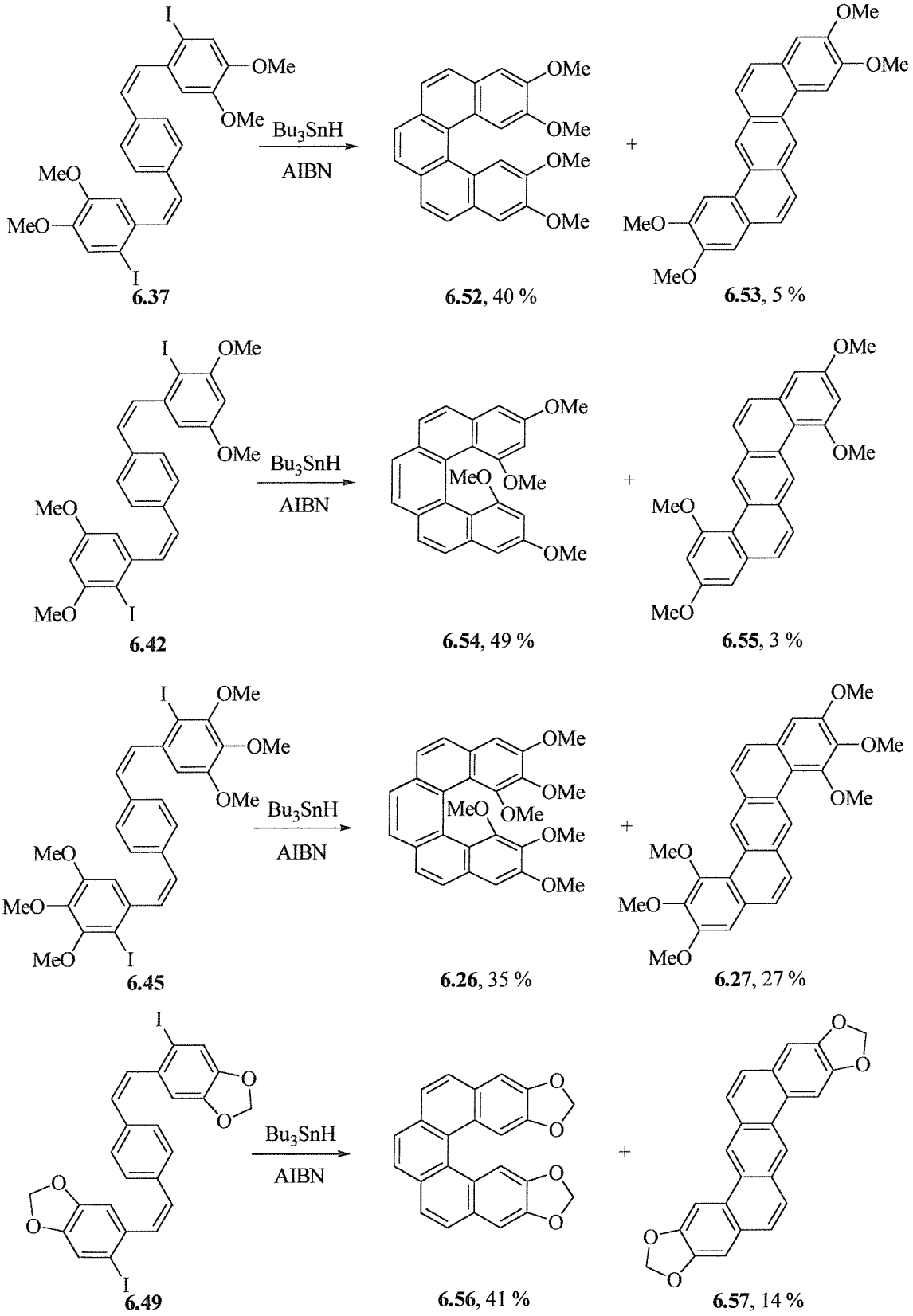
Having demonstrated that a tandem radical cyclisation of bis-*Z*,*Z*-iodostilbene **6.29** yielded [5]helicene **6.1** we decided to delineate the reaction scope. To this end a series of iodobenzaldehyde derivatives was prepared by iodination of the corresponding benzaldehyde derivatives. 3,4-Dimethoxy-, 3,5-dimethoxy- and 3,4,5-trimethoxybenzaldehydes were each converted to the corresponding iodobenzaldehydes in this manner. Piperonal failed to undergo the reaction so this substrate was prepared by oxidation of 6-iodopiperonyl alcohol with PCC. Coupling of each aldehyde with bisphosphonium salt **6.30** under standard Wittig conditions (NaH, THF, room temperature) gave the corresponding bis-stilbenes in good yield and favourable stereoselectivity (*Z*,*Z* : *Z*,*E* : *E*,*E* ~ 9 : 6 : 1) (Schemes 6.15).



Reagents & Conditions: **i.** I_2, $AgOCOCF_3$, CH_2Cl_2, r.t., 16 h, 98 %; **ii. 6.30**, NaH, THF, r.t., 2 h; add **6.36**, r.t., 16 h, 87 %; **iii.** I_2, $AgOCOCF_3$, CH_2Cl_2, r.t., 40 min, 99 %; **iv. 6.30**, NaH, THF, r.t., 2 h; add **6.41**, r.t., 16 h, 68 %; **v.** I_2, $AgOCOCF_3$, CH_2Cl_2, r.t., 1½ h, 92 %; **vi. 6.30**, NaH, THF, r.t., 2 h; add **5.13**, r.t., 72 %; **vii.** PCC, CH_2Cl_2, 12 h, 93 %; **viii. 6.30**, NaH, THF, r.t., 2 h; add **6.48**, r.t., 16 h, 91 %.

Scheme 6.15

Exposure of the bis-*Z*,*Z*-stilbenes to standard tin-mediated radical forming conditions yielded the corresponding [5]helicenes as the major products (30 – 50 %) with varying quantities of the corresponding dibenzo[*a*,*h*]anthracenes formed (4 – 43 %) (Scheme 6.16). In each case, the dibenzo[*a*,*h*]anthracene was isolated by filtration of the reaction mixture prior to work up. Characterisation of some of these linear polyarenes was difficult due to low solubility in most solvents (**6.57** was only sparingly soluble in DMSO!). Consequently only partial characterisation was possible for these compounds.



Scheme 6.16

6.3 Conclusions

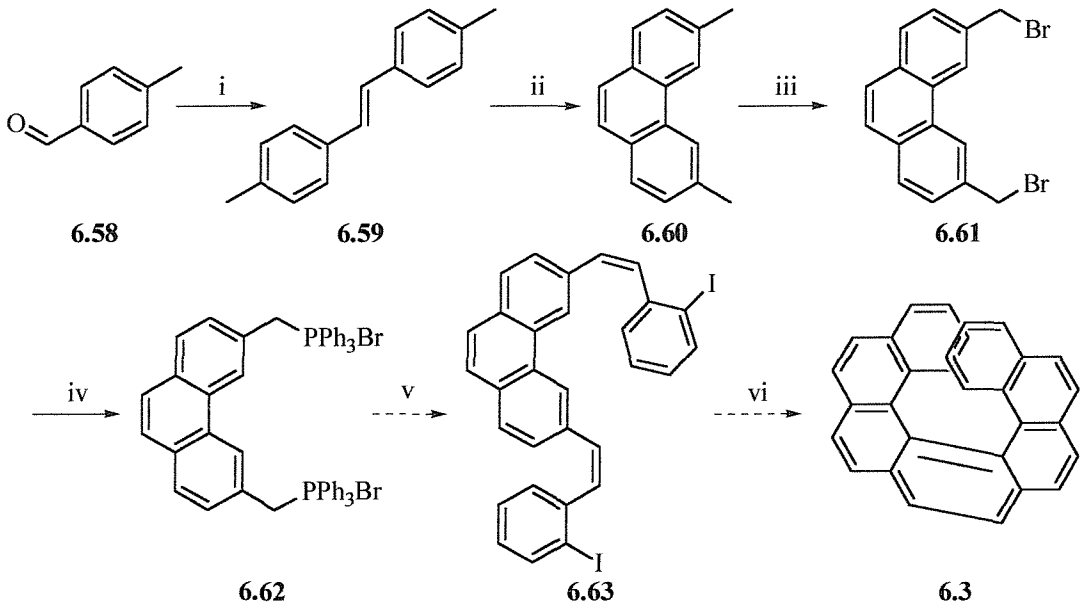
We have shown that radical cyclisations applied in an iterative sense provide access to [5]helicenes in good yield. By this methodology, 1,2,3,12,13,14-hexamethoxy[5]helicene

6.26 was formed in 51 % yield with the corresponding dibenzo[*a*,*h*]anthracene **6.27** formed as a minor by-product.[149]

Tandem cyclisation of bis-iodostilbenes synthesised from 2-iodobenzaldehydes and bisphosphonium salt **6.30** gave the corresponding [5]helicenes in moderate to good yields accompanied by varying amounts of the corresponding dibenzo[*a*,*h*]anthracenes. Steric demand imposed by the aromatic substituents appeared to have some effect on the course of reaction but pleasingly even the most hindered case examined gave the [5]helicene as the major product.[150]

6.4 Further Work

Higher helicenes should be accessible by this methodology. For example, [7]helicene **6.3** could be synthesised from **6.63** which in turn might be formed by Wittig coupling of bis-phosphonium salt **6.62** with an iodobenzaldehyde. Literature precedence for the formation of **6.62** is available (Scheme 6.19).



Reagents & Conditions: **i.** $TiCl_4$, Zn, 96 %;[151] **ii.** hν, I_2, propylene oxide, 8 h, 90 %;[152] **iii.** NBS, CCl_4, AIBN, reflux, 57 %;[153] **iv.** PPh_3, MeCN, 15 h, 82 %;[153] **v.** NaH, THF; 2-iodobenzaldehyde; **vi.** Bu_3SnH, AIBN, PhMe, 90 °C.

Scheme 6.19

Chapter 7 – The Reduction of Aryl Halides With Tributyltin Hydride-Tetrabutylammonium Fluoride

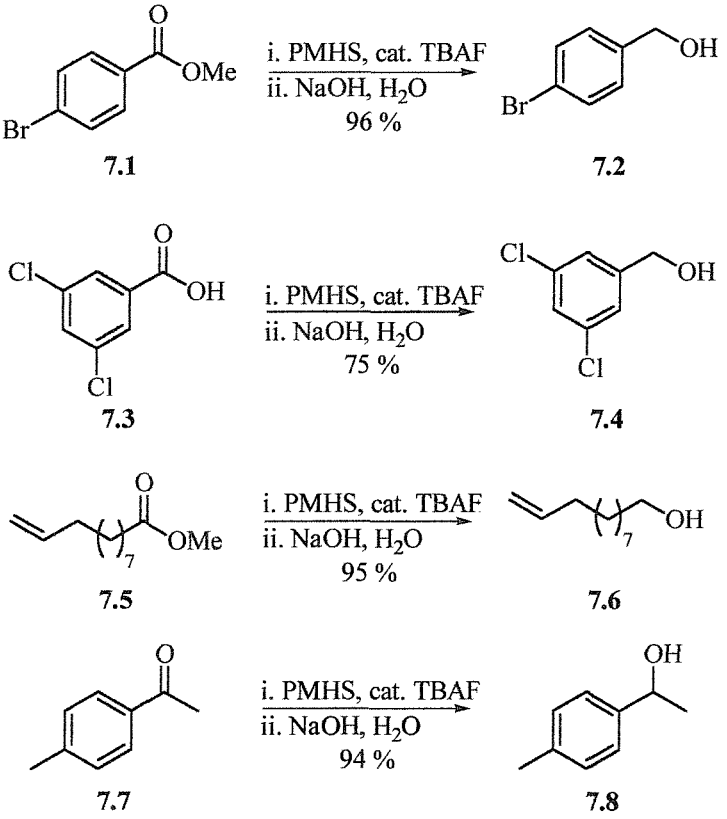
7 *The Reduction of Aryl Halides With Tributyltin Hydride-Tetrabutylammonium Fluoride*

During out investigations, we found that the combination of tributyltin hydride and tetrabutylammonium fluoride was capable of reducing aryl halides. Preliminary results of the investigation are discussed.

7.1 Background

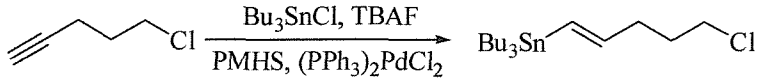
7.1.1 Reductions Involving Tetrabutylammonium Fluoride

There are few reports detailing the use of tetrabutylammonium fluoride in conjunction with a reducing agent. Lawrence *et al.* reported the use of tetrabutylammonium fluoride and polymethylhydrosiloxane for the reduction of carbonyl groups. Esters, carboxylic acids, ketones and aldehydes were shown to undergo reaction with saturated and unsaturated examples tested (Scheme 7.1).[154]



Scheme 7.1

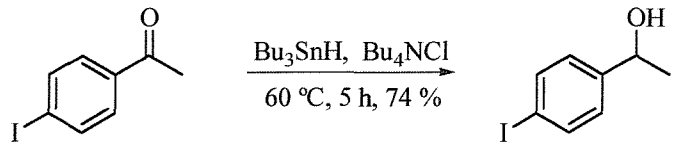
A combination of polymethylhydrosiloxane and tetrabutylammonium fluoride was reported by Maleczka *et al.* for the *in situ* reduction of tributyltin chloride for use in palladium(0)-catalysed formation of vinylstannanes (Scheme 7.2).[155] It was noted that use of this protocol with trimethyltin chloride provided a safer alternative to handling trimethyltin hydride.



7.9 **7.10**

Scheme 7.2

Shibata *et al.* have described the use of tributyltin hydride and tetrabutylammonium chloride or tetrabutylammonium fluoride for the reduction of ketones and aldehydes. A range of ketones and aldehydes were shown to undergo the reaction in good yield. In particular, it was reported that 4-iodoacetophenone was reduced to the corresponding alcohol with the aryl iodide moiety remaining intact (Scheme 7.3).[156]



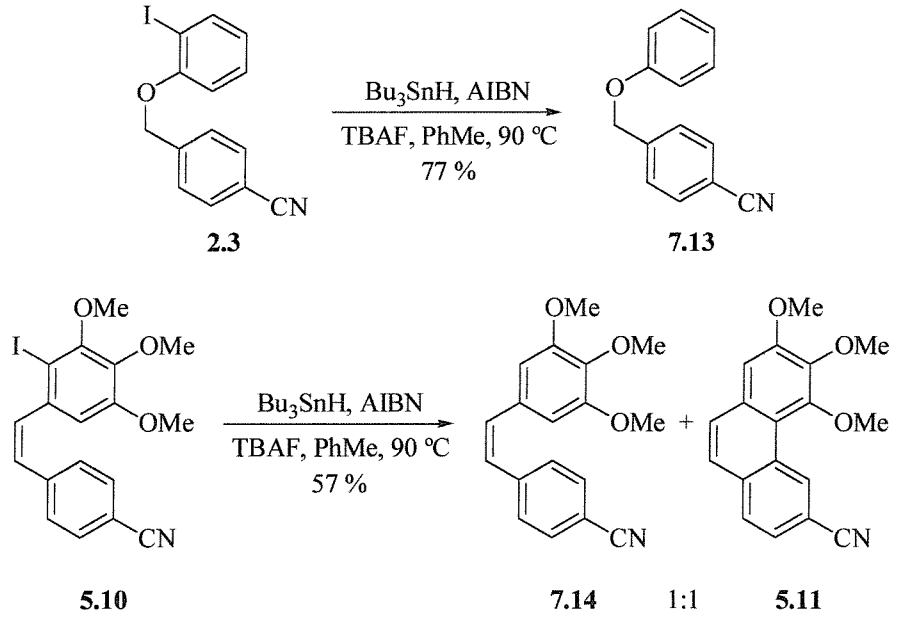
7.11 **7.12**

Scheme 7.3

7.2 Reductions of Aryl halides to Arenes

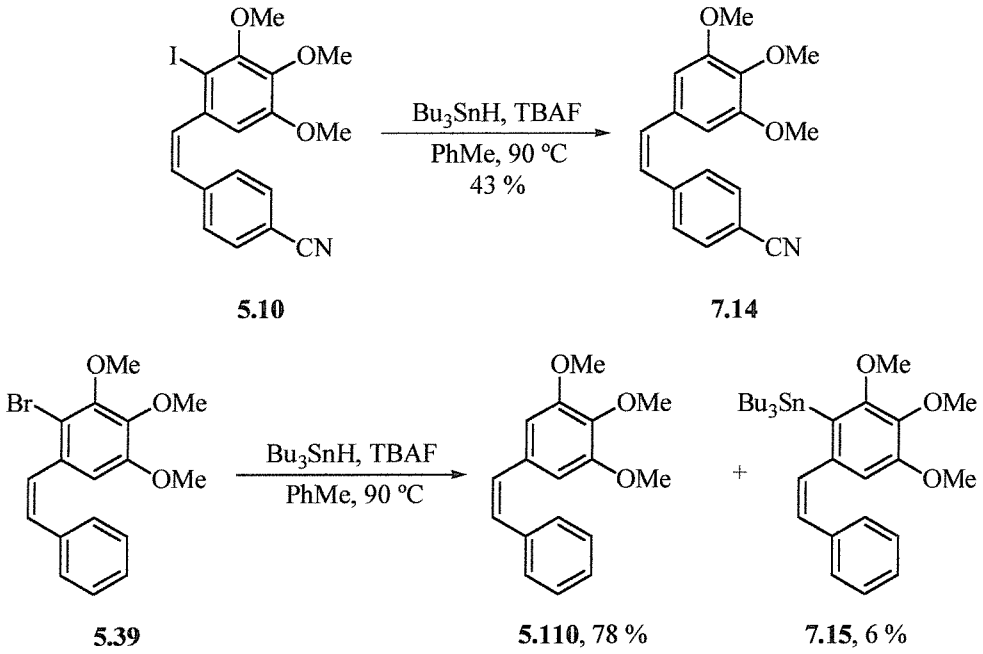
7.2.1 Preliminary Studies

During our investigations of the addition of aryl radicals to arenes, we found that tributyltin residues were difficult to remove for some systems. Our standard work-up involved vigorous stirring of the reaction mixture with aqueous potassium fluoride generating tributyltin fluoride polymer. In an attempt to improve this we investigated the possibility of converting tributyltin halide into the corresponding fluoride *in situ* by use of an organic soluble fluoride source. To this end we exposed a toluene-solution of iodide **2.3** to tributyltin hydride, AIBN and tetrabutylammonium fluoride at 90 °C. To our surprise, the product isolated was **7.13** - the result of direct reduction of the carbon-iodine bond. Equally, treatment of iodostilbene **5.10** under similar conditions gave a mixture of cyclisation and direct reduction products indicating that a second reaction pathway was occurring when tetrabutylammonium fluoride was present (Scheme 7.4).



Scheme 7.4

In the absence of AIBN, treatment of **5.10** with tributyltin hydride and tetrabutylammonium fluoride gave only **7.14** suggesting that a non-radical process was occurring. Aryl bromide **5.39** underwent a similar reduction with *Z*-stilbene **5.110** formed in 78 % yield (Scheme 7.5). To our surprise, a small quantity of stannane **7.15** was isolated. The pathway resulting in this halogen-metal exchange is unclear.

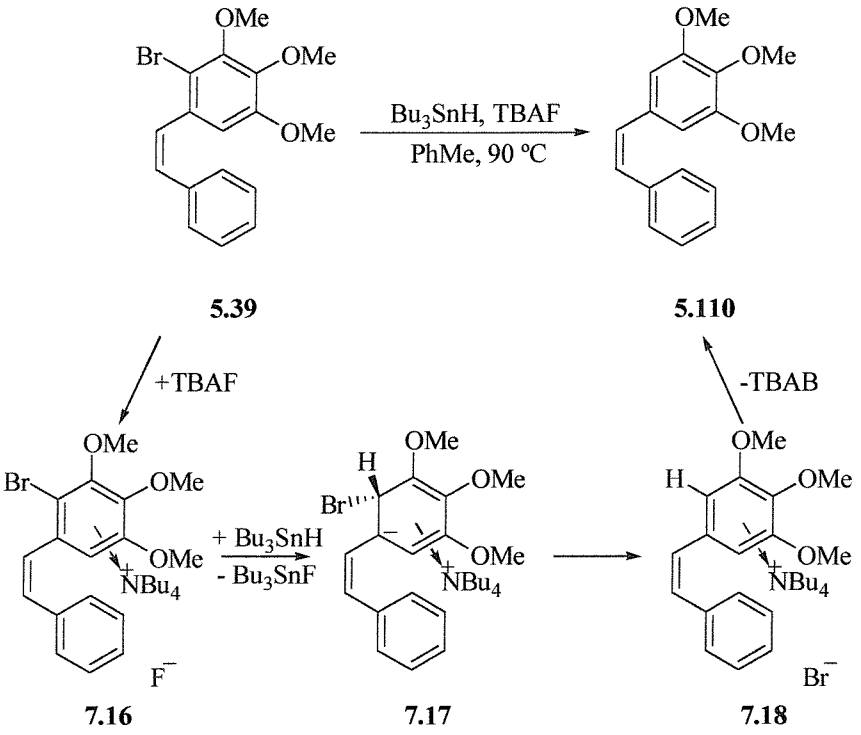


Scheme 7.5

7.2.2 Mechanistic Aspects

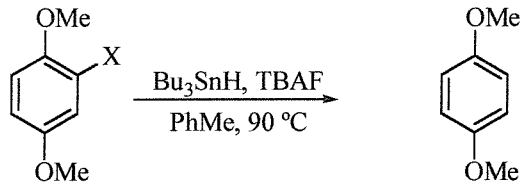
To effect the reduction of an aryl halide we hypothesised that the tetrabutylammonium cation was activating the aryl halide by a polarisation of the π-system. Subsequent hydride addition and halogen elimination could then occur to give the corresponding arene (Scheme 7.6). If

this mechanism were in operation then, within a series of compounds, reduction of an aryl fluoride should outpace reduction of the corresponding aryl chloride or aryl bromide.



Scheme 7.6

Exposure of 2-fluoro-1,4-dimethoxybenzene **7.19** and 2-chloro-1,4-dimethoyxbenzene **7.20** to tributyltin hydride and tetrabutylammonium fluoride gave no evidence of reaction while, under similar conditions, 2-bromo-1,4-dimethoxybenzene **7.21** yielded 1,4-dimethoxybenzene **7.22** in 65 % (Scheme 7.7). It can be deduced that the mechanism suggested above is not the major pathway of reaction.



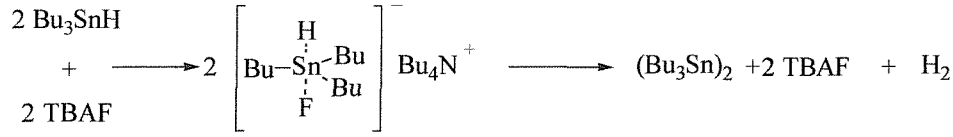
7.19: X = F X = F, 0 %
7.20: X = Cl X = Cl, 0 %
7.21: X = Br X = Br, 65 %

7.22

Scheme 7.7

An alternative mechanism may involve formation of a hypervalent tin intermediate (by interaction between tributyltin hydride and tetrabutylammonium fluoride) that could act as a powerful hydride donor. There is literature evidence to suggest that reaction between fluoride and tributyltin hydride leads to an unstable hypervalent tin intermediate which decomposes to hexabutylditin and hydrogen (Scheme 7.8).[155] Evidence for this was observed in our hands with the evolution of a gas after addition of the reagents at 50 °C. Further

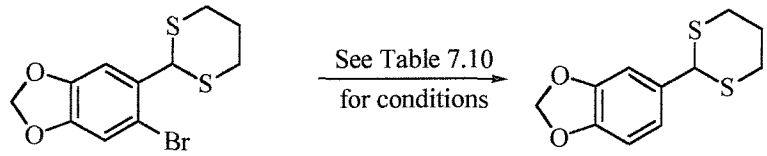
investigations are required to delineate the intermediates involved and to accurately describe the mechanism.



Scheme 7.8

7.2.3 Investigating the Scope of the Methodology

A range of conditions was investigated using aryl bromide **7.23** as a test substrate. Solvent polarity had little effect on reaction while replacing tetrabutylammonium fluoride with potassium fluoride effectively halted reaction. Addition of 18-crown-6 to aid solubility provided TLC evidence of reaction but the starting bromide **7.23** was the major constituent. Fluoride was found to be essential as the combination of tributyltin hydride and tetrabutylammonium bromide gave essentially no reaction (Scheme 7.9 and Table 7.10). The mixture of tributyltin hydride and tetrabutylammonium fluoride was found to be an effective reducing agent at room temperature with comparable yields to those reactions heated to 90 °C.



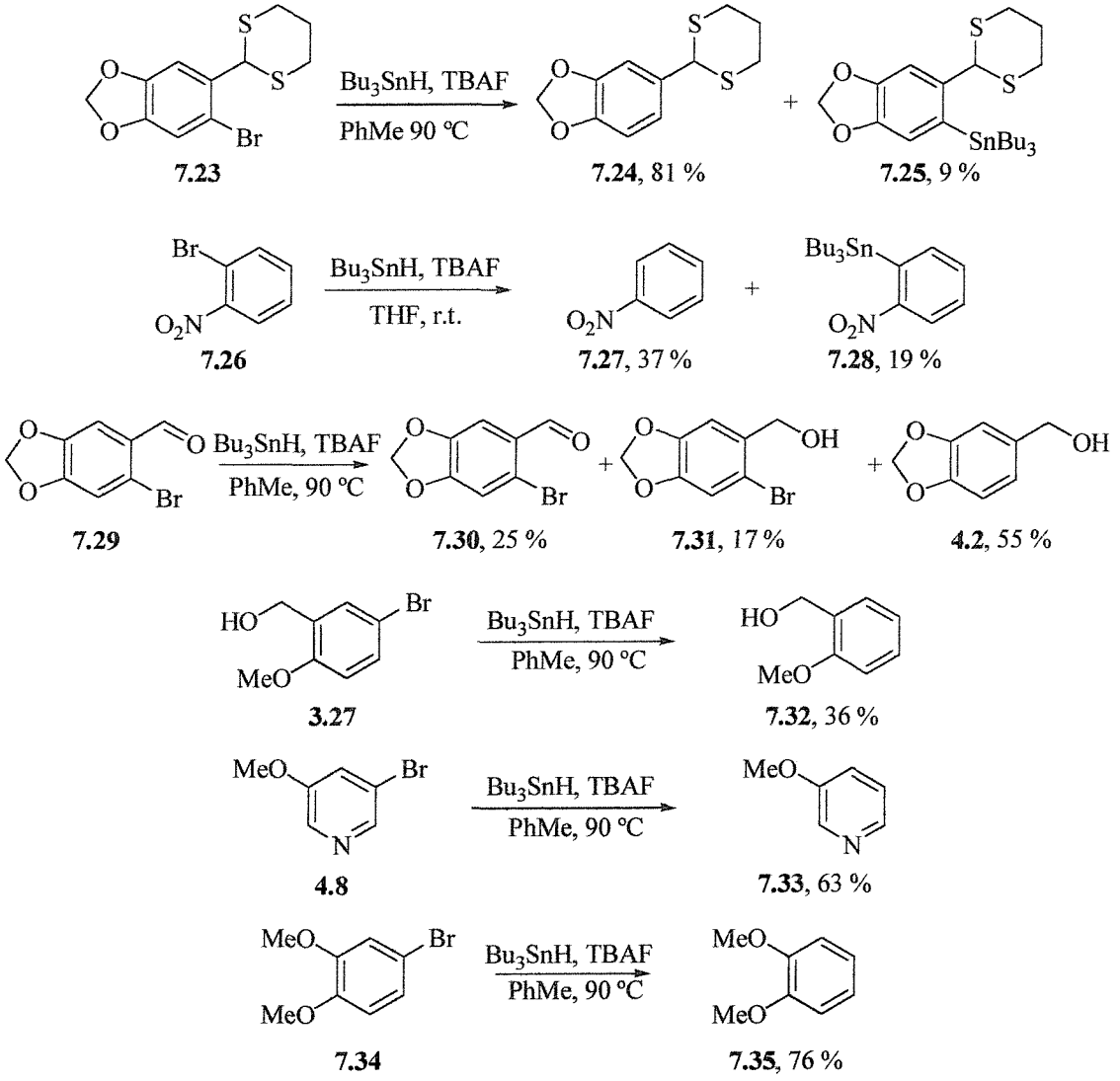
7.23 **7.24**

Scheme 7.9

	Conditions	Rxn. time	**7.24** formed?	Yield of **7.24**
a.	Bu_3SnH, TBAF, PhMe, 90 °C	24 h	✓	81 %
b.	Bu_3SnH, TBAF, PhMe, r.t.	4 days	✓	69 %
c.	Bu_3SnH, TBAB, PhMe, 90 °C	2 days	×	-
d.	Bu_3SnH, TBAF, DMF, 90 °C	20 h	✓	75 %
e.	Bu_3SnH, TBAF, THF, Δ	20 h	✓	84 %
f.	Bu_3SnH, TBAF, 1,4-dioxane, Δ	24 h	✓	79 %
g.	Bu_3SnH, KF, DMF, 70 °C	2 days	×	-
h.	Bu_3SnH, KF, 18-c-6, THF, r.t.	2 days	✓	trace

Table 7.10

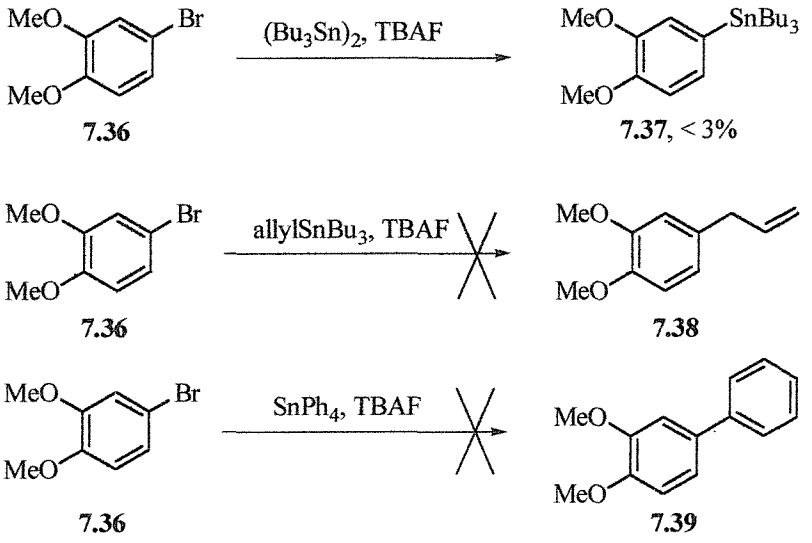
A range of aryl bromides and iodides were found to undergo reduction under standard conditions (*i.e.* tributyltin hydride and tetrabutylammonium fluoride in toluene at 90 °C). 1-Bromo-2-nitrobenzene was converted to nitrobenzene although the product was contaminated with coloured co-polar impurities, presumably due to reduction of the nitro functionality. Higher product purity was obtained when the reaction was repeated at room temperature in tetrahydrofuran. 1-Tributylstannyl-2-nitrobenzene was also isolated under these conditions. The rate of reduction of a benzaldehyde was comparable to that of reduction of an aryl bromide so that, under standard conditions, 6-bromopiperonal **7.29** yielded piperonal **7.30**, 6-bromopiperonyl alcohol **7.31** and piperonyl alcohol **4.2**.[156] Tributyltin hydride and tetrabutylammonium fluoride were also effective for the reduction of 5-bromo-3-methoxypyridine **4.8** yielding 3-methoxypyridine **7.33** in 65 %. Small quantities of the corresponding stannane were only isolable in three instances although we presume that an arylstannane was formed as a by-product in each reaction (Scheme 7.11).



Scheme 7.11

7.2.4 Extending The Methodology

Continuing our hypothesis that fluoride activates tributyltin hydride to enhance its reactivity, we investigated the possible transfer of atoms other than hydrogen from tin to carbon. Thus, exposing **7.36** to hexabutylditin and tetrabutylammonium fluoride we hoped to form stannane **7.37**. Disappointingly, despite an extended reaction time, only trace amounts of **7.37** were observed. Similarly, allyltributyltin and tetraphenyltin failed to show evidence of carbon transfer from tin to carbon (Scheme 7.12).



Scheme 7.12

In search of a more environmentally friendly alternative to tributyltin hydride we investigated the use of triethylsilane as a hydride source. Unfortunately, treatment of **7.36** with triethylsilane and tetrabutylammonium fluoride in toluene proved ineffective presumably due to the greater bond strength of the silicon-to-hydrogen bond compared to that of the tin-to-hydrogen bond. Future investigations with tris(trimethylsilyl)silane may prove more fruitful.

7.3 Conclusions

We have shown that tributyltin hydride, in the presence of tetrabutylammonium fluoride, will reduce aryl iodides and aryl bromides to the corresponding arenes. Tetrahydrofuran, toluene, 1,4-dioxane and *N,N*-dimethylformamide are suitable solvents for reaction. Organic soluble fluoride was found to be critical for reaction. Reaction readily occurred at temperatures between 25 and 100 °C. Aldehydes and ketones are also reduced cleanly by this reagent combination while many other reducible functional groups are unaffected. Most notably, esters, aryl chlorides, aryl fluorides, sulfides and pyridines were all found to be tolerated.

Chapter 8 – Experimental Section

8 Experimental

8.1 General

All reactions were performed under a positive pressure of nitrogen or argon and were magnetically stirred unless otherwise stated. Benzene, 1,4-dioxane, ether and tetrahydrofuran were distilled from sodium containing benzophenone as an internal indicator immediately prior to use. Toluene was distilled from sodium. Chloroform and dichloromethane were distilled from calcium hydride immediately prior to use. *N*,*N*-Dimethylformamide was distilled from magnesium sulfate under reduced pressure and stored over 4Å molecular sieves. All other solvents were used directly from suppliers. Cobalt(II)salophen was prepared by the method of Bäckvall *et al.*[157] Dess-Martin periodinane was prepared by the method of Dess and Martin.[158] Pyridinium *p*-toluenesulfonate was prepared by the method of Miyashita *et al.*[159] Flash column chromatography was performed using MN Kiesel 60 0.040 – 0.063 mm, 230 – 400 mesh ASTM silica gel, slurry packed and run at low pressure. Thin layer chromatography was performed on aluminium-backed sheets coated with Sil G/UV_{254} 0.25 mm silica gel 60.

Infrared spectra were recorded on a Nicolet Fourier Transform spectrometer with oils measured as thin films on sodium chloride plates and solids measured as thin films or neat using a Thunderdome adaptor. Maxima were reported as ν_{max} (in cm^{-1}) followed by relative signal intensities (s, strong; m, medium; w, weak; br., broad). UV/visible spectra were recorded on a Pye Unicam SP8-400 spectrophotometer. Maxima are reported as λ_{max} (in nm) followed by the extinction coefficient ε_{max} (in $dm^3mol^{-1}cm^{-1}$) in parentheses.

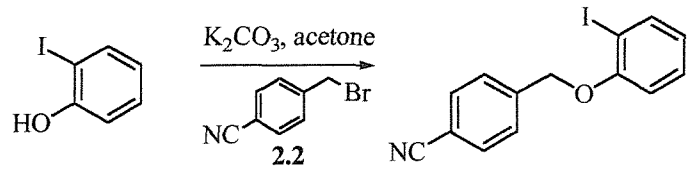
^1H – NMR spectra were recorded on a Brucker AC300 (300 MHz), AM300 (300 MHz) or DPX-400 (400 MHz) spectrometer. Chemical shifts (δ_H) are reported in parts per million relative to residual $CHCl_3$ (δ_H = 7.27 ppm) or tetramethylsilane (δ_H = 0.00). Multiplicities are reported with coupling constants (*J*) in Hertz. ^{13}C – NMR spectra were recorded on a Brucker AC300 (75 MHz) or DPX-400 (100 MHz) spectrometer. Chemical shifts (δ_C) are reported in parts per million relative to $CDCl_3$ (δ_C = 77.2 ppm) or tetramethylsilane (δ_C = 0.00 ppm). Multiplicities refer to the signals in the off-resonance spectra as determined by DEPT-135 or jmod experiments. ^2H – NMR were recorded on a Brucker DPX-400 (61 MHz) spectrometer. Chemical shifts (δ_D) are reported in parts per million relative to $CDCl_3$ (δ_D = 0.00 ppm).

Mass spectroscopic data were recorded on a variety of instruments both in-house and at the EPSRC Mass Spectrometry service at the University of Swansea. Mass spectroscopic data

are reported as values in atomic mass units with the peak intensities reported relative to the base peak (100 %).

8.2 Experimental for Chapter 2

4-(2-Iodophenoxymethyl)benzonitrile **2.3**



2.1 C_6H_5IO (220)

2.2 89 %

2.3 $C_{14}H_{10}INO$ (335)

Benzonitrile **2.3** was prepared by a modification of the method of Sheppard *et al.*[160] 2-Iodophenol **2.1** (2.29 g, 10.41 mmol), potassium carbonate (1.83 g, 13.26 mmol) and 4-(bromomethyl)benzonitrile **2.2** (2.00 g, 10.20 mmol) were stirred in acetone (20 mL) at room temperature for 16 hours. The mixture was filtered and the solvent evaporated under reduced pressure. The resulting solid was recrystallised from ethanol to yield the title compound **2.3** (3.04 g, 9.07 mmol, 89 %) as a white solid.

MP 74 – 76 °C (EtOH / petrol).

FT – IR (ν_{max}, neat) 2227 m, 1581 m, 1474 s, 1438 s, 1275 s, 1247 s, 1053 m, 1018 s, cm^{-1}.

UV (λ_{max}, MeOH) 226 (12230) nm.

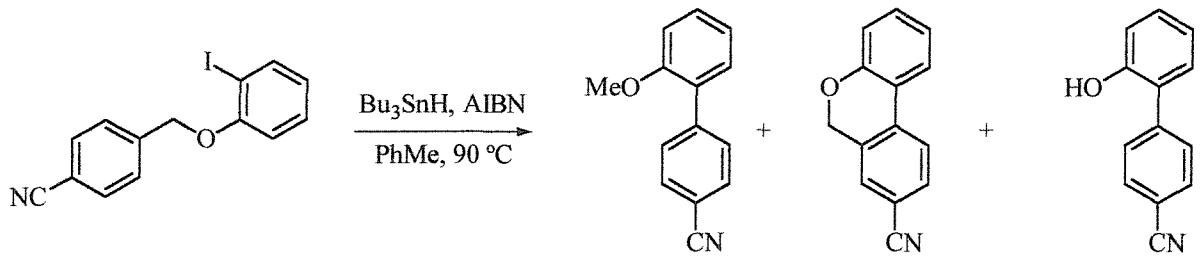
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.84 (1H, d, *J* 7.7 Hz, Ar*H*), 7.72 (2H, d, *J* 8.1 Hz, 2 × Ar*H*), 7.67 (2H, d, *J* 8.1 Hz, 2 × Ar*H*), 7.32 (1H, dd, *J* 8.4, 7.4 Hz, Ar*H*), 6.84 (1H, d, *J* 8.4 Hz, Ar*H*), 6.79 (1H, app. t, *J* 7.7 Hz, Ar*H*), 5.21 (2H, s, OCH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 156.7 (0, *C*O), 142.1 (0, *C*), 139.9 (1, *C*H), 132.6 (1, 2 × *C*H), 129.7 (1, *C*H), 127.5 (1, 2 × *C*H), 123.5 (1, *C*H), 118.9 (0, *C*N), 112.6 (1, *C*H), 111.9 (0, *C*CN), 86.8 (0, *C*I), 69.9 (2, OCH_2) ppm.

LRMS (M/z, CI) 335 (M^+, 18 %), 209 (34 %), 133 (14 %), 116 (100 %), 89 (22).

CHN $C_{14}H_{10}INO$ requires: C 50.17, H 3.01, N 4.18; Found: C 50.05, H 3.03, N 4.16.

4-(2-Methoxyphenyl)benzonitrile **2.4**, 6*H*-benzo[*c*]chromene-8-carbonitrile **2.5** & 4-(2-hydroxyphenyl)benzonitrile **2.6**



2.3
$C_{14}H_{10}INO$ (335)

2.4, 6 %
$C_{14}H_{11}NO$ (209)

2.5, 22 %
$C_{14}H_9NO$ (207)

2.6, 43 %
$C_{13}H_9NO$ (195)

4-(2-Iodophenoxymethyl)benzocarbonitrile **2.3** (800 mg, 2.39 mmol), tributyltin hydride (965 μL, 1.04 g, 3.58 mmol) and AIBN (60 mg, 0.36 mmol) were stirred in toluene (80 mL) at 90 °C for 22 hours with a further portion of AIBN (40 mg, 0.25 mmol) added after 16 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 20 mL) for 60 hours. The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Purification by column chromatography (silica gel, 10 % ether / petrol) provided a mixture of aryl methyl ether **2.4** and tricycle **2.5** (140 mg, 0.67 mmol, 28 %, **2.4**:**2.5** ~ 1:4) as an oil and then phenol **2.6** (200 mg, 1.03 mmol, 43 %) as a off-white solid.

Samples of **2.4** and **2.5** were obtained by further purification.

4-(2-Methoxyphenyl)benzonitrile **2.4**[161]

FT – IR (ν_{max}, neat) 2226 s, 1714 m, 1606 m, 1479 s, 1238 m, 1213 m, 1044 m, 1026 m cm^{-1}.

UV (λ_{max}, MeOH) 291 (2190), 260 (2860), 232 (4180) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* 8.4 Hz, 2 × Ar*H*), 7.64 (2H, d, *J* 8.4 Hz, 2 × Ar*H*), 7.40 (1H, td, *J* 7.8, 1.7 Hz, Ar*H*), 7.31 (1H, dd, *J* 7.7, 1.7 Hz, Ar*H*), 7.07 (1H, t, *J* 7.4 Hz, Ar*H*), 7.02 (1H, d, *J* 8.4 Hz, Ar*H*), 3.84 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 156.4 (0, *C*O), 143.8 (0, *C*), 131.9 (1, 2 × *C*H), 130.8 (1, *C*H), 130.4 (1, 2 × *C*H), 130.1 (1, *C*H), 128.8 (0, *C*), 121.2 (1, *C*H), 119.3 (0, *C*N), 111.5 (1, *C*H), 110.9 (0, *C*CN), 55.7 (3, OCH_3) ppm.

LRMS (M/z, CI) 227 ($[M+NH_4]^+$, 100 %), 209 (M^+, 60 %) amu.

6*H*-Benzo[*c*]chromene-8-carbonitrile **2.5**

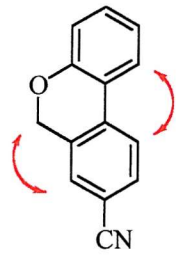
FT – IR (ν_{max}, neat) 2226 s, 1607 s, 1478 s, 1417 m, 1247 m, 1214 m, 1044 m, 1026 m cm^{-1}.

UV (λ_{max}, MeOH) 319 (6210), 276 (10900), 240 (9320) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.79 (1H, d, *J* 8.5 Hz, Ar*H*), 7.75 (1H, d, *J* 8.5 Hz, Ar*H*), 7.67 (1H, d, *J* 7.7 Hz, Ar*H*), 7.47 (1H, s, Ar*H*), 7.35 (1H, t, *J* 7.7 Hz, Ar*H*), 7.12 (1H, t, *J* 7.4 Hz, Ar*H*), 7.03 (1H, d, *J* 8.1 Hz, Ar*H*), 5.14 (2H, s, OCH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 155.3 (0, *C*O), 134.8 (0, *C*), 132.3 (1, *C*H), 132.1 (0, *C*), 131.4 (1, *C*H), 128.3 (1, *C*H), 124.0 (1, *C*H), 122.6 (1, *C*H), 122.6 (1, *C*H), 121.3 (0, *C*), 118.7 (0, *C*N), 117.8 (1, *C*H), 110.8 (0, *C*CN), 67.6 (2, OCH_2) ppm.

LRMS (M/z, CI) 225 ($[M+NH_4]^+$, 100 %), 207 (M^+, 62 %) amu.



2.5 – Enhancements from GOESY experiment

4-(2-Hydroxyphenyl)benzonitrile **2.6**[162]

MP 108 – 109 °C (ether / petrol) lit. 111.0 – 112.0 °C (DCM / petrol).[162]

FT – IR (ν_{max}, neat) 3378 br s, 2229 s, 1607 s, 1492 m, 1450 m, 1274 m cm^{-1}.

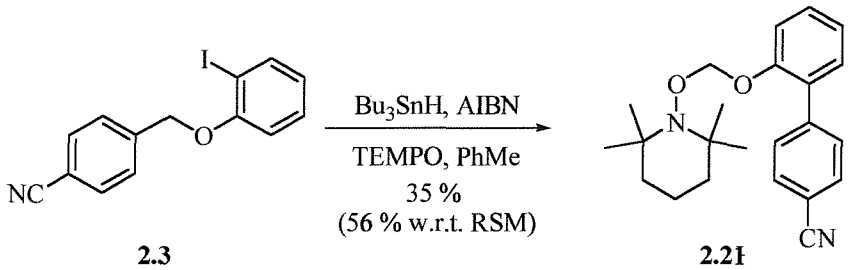
UV (λ_{max}, MeOH) 302 (6050), 265 (9560), 232 (9360) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 7.69 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 7.31 (1H, t, *J* 7.4 Hz, Ar*H*), 7.29 (1H, d, *J* 7.4 Hz, Ar*H*), 7.05 (1H, t, *J* 7.4 Hz, Ar*H*), 6.97 (1H, d, *J* 7.4 Hz, Ar*H*), 5.69 (1H, s, O*H*) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 152.9 (0, *C*O), 143.2 (0, *C*), 132.5 (1, 2 × *C*H), 130.7 (1, *C*H), 130.7 (1, *C*H), 130.2 (1, 2 × *C*H), 126.7 (0, *C*), 121.4 (1, *C*H), 119.1 (0, *C*N), 116.6 (1, *C*H), 110.7 (0, *C*CN) ppm.

LRMS (M/z, ES-) 308 ($[M-H+TFA]^-$, 100 %) amu.

2'-(2,2,6,6-Tetramethyl-1-piperidinyloxymethoxy)-1,1'-biphenyl-4-carbonitrile **2.21**



2.3
$C_{14}H_{10}INO$ (335)

2.21
$C_{23}H_{28}N_2O_2$ (364)

Iodide **2.3** (500 mg, 1.49 mmol) was dissolved in toluene (50 mL). Tributyltin hydride (600 μL 650 mg, 2.24 mmol), TEMPO (235 mg, 1.49 mmol) and AIBN (35 mg, 0.22 mmol) were added and the mixture heated at 90 °C for 24 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 20 mL) for 16 hours. The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic phases dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (silica gel, 5 – 20 % ether / petrol) yielded firstly the title compound **2.21** (190 mg, 0.52 mmol, 35 %) as a colourless oil which crystallised to a white solid on standing and then recovered starting material (190 mg, 0.57 mmol, 38 %) as an off white solid.

MP 89 – 91 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2930 s, 2227 s, 1607 s, 1485 s, 1454 s, 1397 s, 1362 s, 1219 s, 1038 s, 1012 s, 988 s cm^{-1}.

UV (λ_{max}, MeOH) 294 (13000), 266 (25000), 220 (30000) nm.

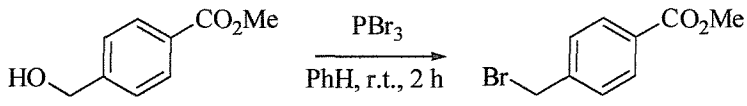
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.51 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 7.48 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 7.20 (1H, app. td, *J* 8.8, 2.2 Hz, Ar*H*), 7.11 – 7.02 (2H, m, 2 × Ar*H*), 6.88 (1H, app. t *J* 7.5 Hz, Ar*H*), 5.08 (2H, s, OCH_2), 1.40 – 1.20 (6H, br. m, 3 × CH_2), 0.96 (12H, br. s, 4 × CH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 155.0 (0, *C*O), 143.6 (0, *C*), 131.8 (1, 2 × *C*H), 130.7 (1, *C*H), 130.5 (1, 2 × *C*H), 130.1 (1, *C*H), 129.4 (0, *C*), 122.1 (1, *C*H), 119.4 (0, *C*N), 115.4 (1, *C*H), 110.5 (0, *C*CN), 96.7 (2, OCH_2O), 59.8 (0, 2 × N*C*$(CH_3)_2$), 39.6 (2, 2 × *C*H_2), 33.4 (3, 2 × *C*H_3), 20.4 (3, 2 × *C*H_3), 17.3 (2, *C*H_2) ppm.

LRMS (M/z, CI) 365 (MH^+, 61 %), 213 (10 %), 156 (10 %), 142 (100 %), 126 (35 %) amu.

HRMS (M/z, ES+) $C_{23}H_{29}N_2O_2^+$ requires: 365.2224; Found: MH^+: 365.2223.

Methyl 4-(bromomethyl)benzoate **2.98**[148]



2.97
$C_9H_{10}O_3$ (166)

2.98
$C_9H_9BrO_2$ (229)

Methyl 4-(bromomethyl)benzoate **2.98** was prepared by the method of Hawker *et al.*[148] Methyl 4-(hydroxymethyl)benzoate **2.97** (2.00 g, 12.04 mmol) was dissolved in benzene (20 mL) and cooled to 0 °C. Phosphorus tribromide (380 μL, 1.09 g, 4.01 mmol) was added dropwise over 5 minutes and the mixture allowed to stir at room temperature for 2 hours. The solvent was evaporated *in vacuo* and the residue dissolved in dichloromethane (10 mL). Water (10 mL) was added and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 % ether / petrol) yielded the title compound **2.98** (1.85 g, 8.08 mmol, 67 %) as a white solid.[148]

MP 42 – 43 °C (ether / petrol) (no literature melting point reported).

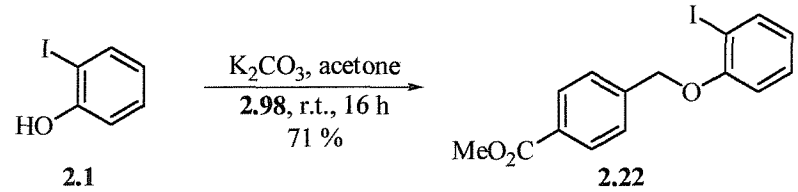
FT – IR (ν_{max}, neat) 1727 s, 1434 s, 1312 m, 1283 s, 1179 m, 1111 s, 1095 m, 1020 m cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.92 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 7.43 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 4.51 (2H, s, CH_2Br), 3.93 (3H, s, CO_2CH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 166.6 (0, *C*=O), 142.8 (0, *C*), 130.2 (1, 2 × C*H*), 129.7 (0, *C*), 129.2 (1, 2 × C*H*), 52.4 (2, CH_2Br), 32.4 (3, CO_2CH_3) ppm.

LRMS (M/z, CI) 168 ($[MH\text{-}Br+NH_4]^+$, 25 %), 151 ($[MH\text{-}Br]^+$, 75 %), 119 (100 %) amu.

Methyl 4-(2-iodophenoxymethyl)benzoate **2.22**



2.1
C_6H_5IO (220)

2.22
$C_{15}H_{13}IO_3$ (368)

Methyl 4-(2-iodophenoxymethyl)benzoate **2.22** was prepared by a modification of the method of Sheppard *et al.*[160] 2-Iodophenol **2.1** (1.17 g, 5.30 mmol), methyl 4-(bromomethyl)benzoate **2.98** (1.27 g, 5.56 mmol) and potassium carbonate (1.95 g, 14.12 mmol) were stirred in acetone (20 mL) at room temperature for 16 hours and then at reflux

for 2 hours. After cooling to room temperature, the mixture was filtered and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 % ether / petrol) provided **2.22** (1.45 g, 3.94 mmol, 71 %) as a white solid.

MP 96 – 98 °C (ether / petrol).

FT – IR (ν_{max}, neat) 1721 s, 1475 m, 1438 m, 1278 s, 1247 m, 1108 m, 1018 m cm^{-1}.

UV (λ_{max}, MeOH) 286 (5890), 226 (24290) nm.

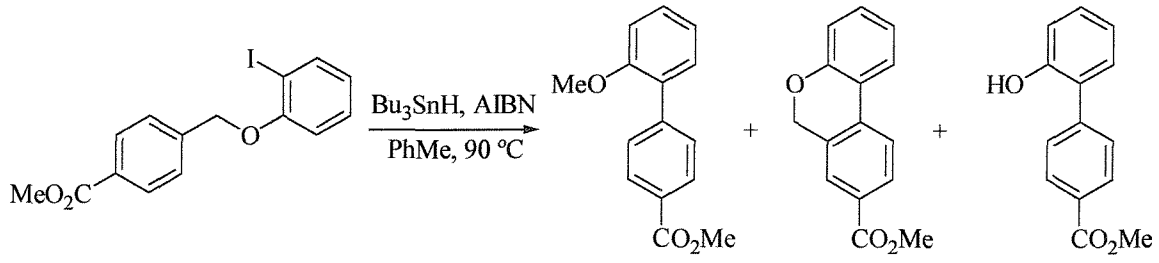
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.09 (2H, d, *J* 8.0 Hz, 2 × Ar*H*), 7.82 (1H, dd, *J* 7.7, 1.5 Hz, Ar*H*), 7.59 (2H, d, *J* 8.0 Hz, 2 × Ar*H*), 7.27 (1H, td, *J* 7.7, 1.9 Hz, Ar*H*), 6.83 (1H, dd, *J* 7.7, 1.5 Hz, Ar*H*), 6.77 (1H, td, *J* 7.7, 1.5 Hz, Ar*H*), 5.21 (2H, s, OCH_2), 3.94 (3H, s, CO_2CH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 166.9 (0, *C*=O), 157.0 (0, *C*O), 141.8 (0, *C*), 139.8 (1, *C*H), 130.0 (1, 2 × *C*H), 129.8 (0, *C*), 129.6 (1, 2 × *C*H), 126.8 (1, *C*H), 123.2 (1, *C*H), 112.7 (1, *C*H), 86.9 (0, *C*I), 70.3 (2, OCH_2), 52.3 (3, CO_2CH_3) ppm.

LRMS (M/z, CI) 368 (M^+, 6%), 260 (8 %), 242 (20 %), 166 (24 %), 149 (100 %), 121 (26 %), 90 (18 %) amu.

CHN $C_{15}H_{13}IO_3$ requires: C 48.93, H 3.56; Found: C 48.87, H 3.51.

Methyl 4-(2-methoxyphenyl)benzoate **2.23**, methyl 6*H*-benzo[*c*]chromene-8-carboxylate **2.24** & methyl 4-(2-hydroxyphenyl)benzoate **2.25**



2.22
$C_{15}H_{13}IO_3$ (368)

2.23, 31 %
$C_{15}H_{14}O_3$ (242)

2.24, 31 %
$C_{15}H_{12}O_3$ (240)

2.25, 36 %
$C_{14}H_{12}O_3$ (228)

Iodide **2.22** (800 mg, 2.17 mmol), tributyltin hydride (1.17 mL, 1.27 g, 4.35 mmol) and AIBN (50 mg, 0.31 mmol) were stirred in toluene (35 mL) at 90 °C for 24 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 10 mL) for 16 hours. The aqueous phase was extracted with ether (3 × 20 mL), and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded a mixture of **2.23** and **2.24** (320 mg, 1.33 mmol, 61 %, **2.23**:**2.24**

~ 1:1) as a yellow oil and then phenol **2.25** (180 mg, 0.79 mmol, 36 %) as a pale yellow solid.

A sample of **2.23** was prepared for analysis by methylation of **2.25** (**2.25**, K_2CO_3, MeI, acetone).

Methyl 4-(2-methoxyphenyl)benzoate **2.23**[163]

FT – IR (ν_{max}, neat) 2950 m, 1722 s, 1609 m, 1487 m, 1434 m, 1280 s, 1112 m, 1027 m cm^{-1}.

UV (λ_{max}, MeOH) 298 (9680), 270 (13400), 230 (15300) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.11 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 8.07 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 7.40 – 7.27 (2H, m, 2 × Ar*H*), 7.07 (1H, app. td, *J* 7.4, 1.1 Hz, Ar*H*), 7.02 (1H, d, *J* 8.5 Hz, Ar*H*), 3.96 (3H, s, CO_2CH_3), 3.84 (3H, s, OCH_3) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 167.3 (0, *C*=O), 156.6 (0, *C*O), 143.5 (0, *C*), 130.9 (1, *C*H), 129.9 (0, *C*), 129.7 (1, 2 × *C*H), 129.6 (1, *C*H), 129.4 (1, 2 × *C*H), 128.6 (0, *C*), 122.1 (1, *C*H), 111.5 (1, *C*H), 55.7 (3, OCH_3), 52.3 (3, CO_2CH_3) ppm.

LRMS (M/z, CI) 260 ($[M+NH_4]^+$, 62 %), 243 (MH^+, 100 %), 211 (14 %), 168 (10 %) amu.

Methyl 6*H*–benzo[*c*]chromene-8-carboxylate **2.24**

FT – IR‡ (ν_{max}, neat) 1720 s, 1607 m, 1480 m, 1434 m, 1289 s, 1238 s, 1196 s, 1112 s, 1026 m cm^{-1}.

^{1}H – NMR‡ (300 MHz, $CDCl_3$) δ_H 8.05 (1H, d, *J* 8.0 Hz, Ar*H*), 7.88 (1H, s, Ar*H*), 7.72 (1H, d, *J* 8.0 Hz, Ar*H*), 7.40 – 7.20 (2H, m, 2 × Ar*H*), 7.05 – 6.90 (2H, m, 2 × Ar*H*), 5.12 (2H, OCH_2), 3.95 (3H, s, CO_2CH_3) ppm.

^{13}C – NMR‡ (75 MHz, $CDCl_3$) δ_C 166.8 (0, *C*=O), 155.4 (0, *C*O), 134.7 (0, *C*), 131.4 (0, *C*), 130.9 (1, *C*H), 130.9 (1, *C*H), 129 .6 (0, *C*), 129.2 (1, *C*H), 128.6 (0, *C*), 124.1 (1, *C*H), 122.5 (1, *C*H), 122.1 (1, *C*H), 117.9 (1, *C*H), 68.3 (2, OCH_2), 52.4 (3, CO_2CH_3) ppm.

LRMS (M/z, CI) 258 ($[M+NH_4]^+$, 46 %), 241 (MH^+, 100 %), 181 (15 %), 152 (18 %) amu.

‡ The above data were extrapolated from a 1:1 mixture of **2.23** and **2.24**.

Methyl 4-(2-hydroxyphenyl)benzoate **2.25**[162]

MP 131 – 132 °C (DCM / petrol) lit. 133 .0 – 133.5 (DCM / petrol).[162]

FT – IR (ν_{max}, neat) 3374 br. m, 2953 m, 1694 s, 1607 m, 1450 s, 1434 s, 1275 s, 1199 m, 1100 m cm^{-1}.

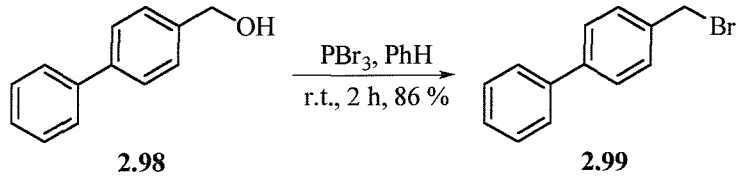
UV (λ_{max}, MeOH) 300 (9120), 268 (13300), 236 (11590), 220 (15200) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.13 (2H, d, *J* 8.1 Hz, 2 × Ar*H*), 7.61 (2H, d, *J* 8.1 Hz, 2 × Ar*H*), 7.32 - 7.27 (2H, m, 2 × Ar*H*), 7.03 (1H, td, *J* 7.4, 1.1 Hz, Ar*H*), 7.00 (1H, dd, *J* 7.4, 1.1 Hz, Ar*H*), 5.43 (1H, s, O*H*), 3.96 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 167.1 (*C*=O), 152.6 (*C*O), 142.4 (0, *C*), 130.5 (1, *C*H), 130.4 (1, 2 × *C*H), 129.9 (1, *C*H), 129.7 (0, *C*), 129.3 (1, 2 × *C*H), 127.4 (0, *C*), 121.3 (1, *C*H), 116.4 (1, *C*H), 52.4 (CO_2CH_3) ppm.

LRMS (M/z, CI) 246 ($[M+NH_4]^+$, 15 %), 229 (MH^+, 100 %), 197 (44 %), 139 (20 %), 115 (26 %), 94 (52 %) amu.

4-(Bromomethyl)-1,1'-biphenyl **2.99**



2.98
$C_{13}H_{12}O$ (184)

2.99
$C_{13}H_{11}Br$ (247)

4-(Bromomethyl)-1,1'-biphenyl **2.99** was prepared by modifications of the method of Hawker *et al.*[148] 4-Biphenylmethanol **2.98** (2.00 g, 10.86 mmol) was dissolved in benzene (30 mL) and cooled to 0 °C. Phosphorus tribromide (345 µL, 980 mg, 3.62 mmol) was added dropwise over 5 minutes. The mixture was stirred at room temperature for 2 hours. After concentration *in vacuo*, the residue was diluted with dichloromethane (20 mL) and was washed with water (20 mL). The aqueous phase was extracted with dichloromethane (2 × 20 mL) and the combined organic phases were dried ($MgSO_4$). Concentration *in vacuo* yielded the title compound **2.99** (2.31 g, 9.35 mmol, 86 %) as a pale brown solid.[164,165]

MP 76 – 77 °C (ethanol) lit. 84 – 85 °C (ethanol).[165]

FT – IR (ν_{max}, neat) 1583 m, 1406 m, 1217 m cm^{-1}.

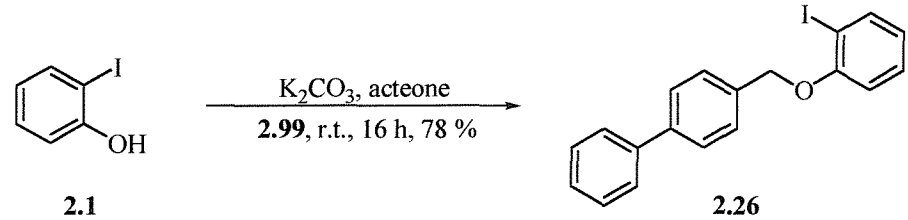
UV (λ_{max}, MeOH) 260 (19310) nm.

^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.60 – 7.52 (4H, m, 4 × Ar*H*), 7.49 – 7.25 (5H, m, 5 × Ar*H*), 4.53 (2H, s, CH_2Br) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 141.5 (0, *C*), 140.6 (0, *C*), 136.9 (0, *C*), 129.7 (1, 2 × *C*H), 129.0 (1, 2 × *C*H), 127.7 (1, 3 × *C*H), 127.3 (1, 2 × *C*H), 33.6 (2, CH_2Br) ppm.

LRMS (M/z, CI) 248 (M^+{^{81}Br}, 4 %), 246 (M^+{^{79}Br}, 4 %), 167 ([M-Br]$^+$, 100 %), 152 (10 %), 139 (6 %), 115 (7 %) amu.

4-(2-Iodophenoxymethyl)-1,1'-biphenyl **2.26**



2.1
C_6H_5IO (220)

2.26
$C_{19}H_{15}IO$ (386)

4-(2-Iodophenoxymethyl)-1,1'-biphenyl **2.26** was prepared by a modification of the method of Sheppard *et al.*[160] 2-Iodophenol **2.1** (168 g, 7.65 mmol), potassium carbonate (1.51 g, 10.94 mmol) and 4-(bromomethyl)-1,1'-biphenyl **2.99** (1.80 g, 7.29 mmol) were stirred in acetone (30 mL) at room temperature for 16 hours. The mixture was filtered and the filtrate concentrated *in vacuo*. Recrystallisation from ethanol yielded the title compound **2.26** (2.18 g, 5.65 mmol, 78 %) as a white solid.

MP 97 – 98 °C (EtOH).

FT – IR (ν_{max}, neat) 1583 m, 1487 s, 1474 s, 1276 s, 1247 s, 1050 m, 1017 m cm^{-1}.

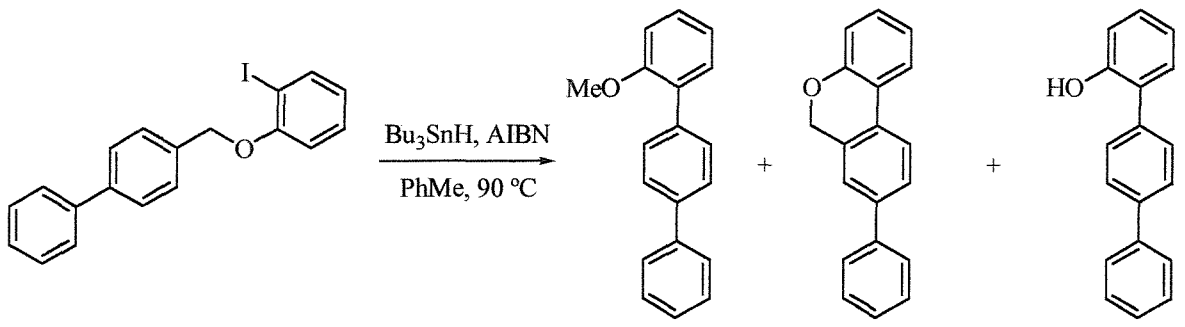
UV (λ_{max}, MeOH) 250 (22130), 234 (19040) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.83 (1H, d, *J* 7.7 Hz, Ar*H*), 7.67 – 7.58 (6H, m, 6 × Ar*H*), 7.47 (2H, app. t, *J* 7.7 Hz, Ar*H*), 7.42 – 7.38 (2H, m, 2 × Ar*H*), 6.91 (1H, d, *J* 8.1 Hz, Ar*H*), 6.76 (1H, app. t, *J* 7.7 Hz, Ar*H*), 5.22 (2H, s, OCH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 157.3 (0, *C*O), 141.0 (0, *C*), 139.8 (1, *C*H), 135.7 (0, 2 × *C*), 129.6 (1, *C*H), 129.0 (1, 2 × *C*H), 127.6 (1, 2 × *C*H), 127.5 (1, *C*H), 127.5 (1, 2 × *C*H), 127.3 (1, 2 × *C*H), 123.0 (1, *C*H), 112.9 (1, *C*H), 87.0 (0, *C*I), 70.8 (2, OCH_2) ppm.

LRMS (M/z, CI) 386 (M^+, 1 %), 167 (100 %), 152 (13 %) amu.

4-(2-Methoxyphenyl)-1,1'-biphenyl **2.27**, 8-phenyl-6*H*-benzo[*c*]chromene **2.28** & 4-(2-hydroxyphenyl)-1,1'-biphenyl **2.29**



2.26
$C_{19}H_{15}IO$ (386)

2.27, trace
$C_{19}H_{16}O$ (260)

2.28, 46 %
$C_{19}H_{14}O$ (258)

2.29, 19 %
$C_{18}H_{14}O$ (246)

Iodide **2.26** (800 mg, 2.07 mmol), tributyltin hydride (835 μL, 905 mg, 3.11 mmol) and AIBN (60 mg, 0.37 mmol) were stirred in toluene (80 mL) at 90 °C for 24 hours. On cooling, the mixture was stirred vigorously with aqueous potassium fluoride solution (10 % w/v, 30 mL) for 16 hours. The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic phases were dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (silica gel, 0 – 5 % ether / petrol) yielded firstly benzo[*c*]chromene **2.28** contaminated with traces of 4-(2-methoxyphenyl)-1,1'-biphenyl **2.27** which was further purified by recrystallisation from ether / petrol to give **2.28** (245 mg, 0.95 mmol, 46 %) as a yellow solid. Second to elute was recovered starting material **2.26** (45 mg, 0.12 mmol, 6 %) and finally phenol **2.29** (95 mg, 0.39 mmol, 19 %) as a yellow solid.

8-Phenyl-6*H*-benzo[*c*]chromene **2.28**

MP 78 – 80 °C (ether / petrol).

FT – IR (ν_{max}, neat) 1478 s, 1409 m, 1243 m, 1186 m cm^{-1}.

UV (λ_{max}, MeOH) 328 (5810), 282 (7530), 246 (6670), 232 (8600) nm.

^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.79 (2H, d, *J* 7.7 Hz, 2 × Ar*H*), 7.66 – 7.62 (3H, m, 3 × Ar*H*), 7.49 (2H, t, *J* 7.0 Hz, 2 × Ar*H*), 7.43 (1H, s, Ar*H*), 7.41 (1H, t, *J* 7.0 Hz, Ar*H*), 7.28 (1H, td, *J* 8.1, 1.1 Hz, Ar*H*), 7.10 (1H, app. t, *J* 7.4 Hz, Ar*H*), 7.04 (1H, d, *J* 8.1 Hz, Ar*H*), 5.22 (2H, s, OCH_2) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 154.9 (0, *C*O), 140.7 (0, *C*), 140.6 (0, *C*), 132.0 (0, *C*), 129.6 (1, *C*H), 129.3 (0, *C*), 129.0 (1, 2 × *C*H), 127.7 (1, *C*H), 127.3 (1, *C*H), 127.1 (1, 2 × *C*H), 123.5 (1, 2 × *C*H), 122.9 (0, *C*), 122.7 (1, *C*H), 122.4 (1, *C*H), 117.6 (1, *C*H), 68.8 (2, OCH_2) ppm.

LRMS (M/z, CI) 258 (M^+, 100 %), 226 (18 %), 181 (16 %), 152 (15 %), 129 (14 %) amu.

HRMS (M/z, EI) $C_{19}H_{14}O^+$ requires 258.1045; Found M^+: 258.1038.

4-(2-Hydroxyphenyl)-1,1'-biphenyl **2.29**[166]

MP 151 – 153 °C (ether / petrol) lit. 176 – 177 °C (MeOH).[166]

FT – IR (ν_{max}, neat) 3424 br. m, 1599 m, 1479 s cm^{-1}.

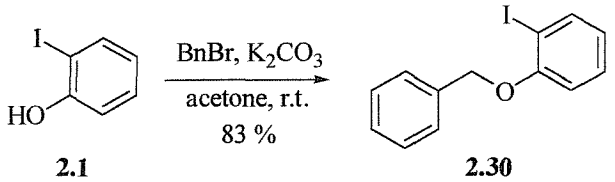
UV (λ_{max}, MeOH) 290 (11700), 263 (15700) nm.

^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.76 (2H, d, *J* 8.1 Hz, 2 × Ar*H*), 7.68 (2H, d, *J* 7.4 Hz, 2 × Ar*H*), 7.60 (2H, d, *J* 8.1 Hz, 2 × Ar*H*), 7.51 (2H, app. t, *J* 7.7 Hz, 2 × Ar*H*), 7.44 – 7.39 (1H, d, *J* 7.7 Hz, Ar*H*), 7.36 – 7.28 (2H, m , 2 × Ar*H*), 7.05 (2H, app. t, *J* 7.7 Hz, 2 × Ar*H*), 5.46 (1H, s, O*H*) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 152.8 (0, *C*O), 140.8 (0, *C*), 140.7 (0, *C*), 130.4 (1, *C*H), 129.7 (1, 2 × *C*H), 129.4 (1, *C*H), 129.1 (1, 2 × *C*H), 128.4 (0, *C*), 128.1 (1, 2 × *C*H), 127.7 (1, *C*H), 127.3 (1, 2 × *C*H), 126.9 (0, *C*), 121.1 (1, *C*H), 116.0 (1, *C*H) ppm.

LRMS (M/z, CI) 246 (M^+, 100 %), 215 (18 %), 189 (12 %), 165 (8 %), 139 (7 %), 115 (9 %) amu.

Benzyl 2-iodophenyl ether **2.30**



2.1
C_6H_5IO (220)

2.30
$C_{13}H_{11}IO$ (310)

Benzyl 2-iodophenyl ether **2.30** was prepared by a modification of the method of Sheppard *et al.*[160] 2-Iodophenol **2.1** (800 mg, 3.64 mmol), benzyl bromide (520 µL, 750 mg, 4.36 mmol), and potassium carbonate (1.66 g, 12.01 mmol) were stirred in acetone (20 mL) for 16 hours at room temperature. Filtration, concentration *in vacuo* and purification by column chromatography (silica gel, 5 % ether / petrol) provided the title compound **2.30** (930 mg, 3.00 mmol, 83 %) as a colourless oil.[167]

FT – IR (ν_{max}, neat) 1582 m, 1470 s, 1438 s, 1274 s, 1246 s, 1050 m, 1017 s cm^{-1}.

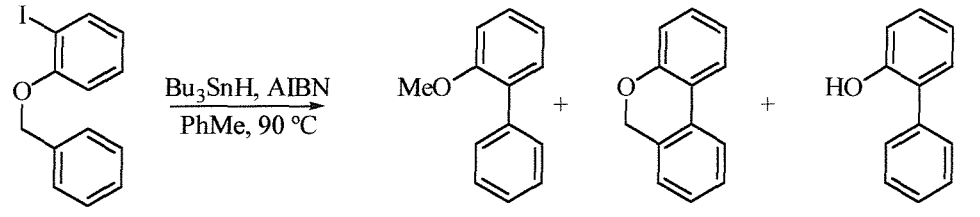
UV (λ_{max}, MeOH) 266 (1160), 242 (1400), 220 (2440) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.82 (1H, dd, *J* 7.7, 1.9 Hz, Ar*H*), 7.52 (2H, d, *J* 7.6 Hz, 2 × Ar*H*), 7.41 (2H, dd, *J* 7.7, 7.6 Hz, 2 × Ar*H*), 7.40 – 7.24 (2H, m, 2 × Ar*H*), 6.88 (1H, dd, *J* 8.1, 1.1 Hz, Ar*H*), 6.73 (1H, td, *J* 8.1, 1.1 Hz, Ar*H*), 5.18 (2H, s, OCH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 157.3 (0, *C*O), 139.7 (1, *C*H), 136.7 (0, *C*), 129.6 (1, *C*H), 128.7 (1, 2 × *C*H), 128.0 (1, *C*H), 127.1 (1, 2 × *C*H), 123.0 (1, *C*H), 112.9 (1, *C*H), 87.5 (0, *C*I), 71.0 (2, OCH_2) ppm.

LRMS (M/z, CI) 310 (M^+, 10 %), 184 (10 %), 108 (14 %), 91 (100 %), 65 (14 %) amu.

2-Methoxy-1,1'-biphenyl **2.31**, 6*H*-benzo[*c*]chromene **2.32** and 2-hydroxy-1,1'-biphenyl **1.71**



2.30 $C_{13}H_{11}IO$ (310)

2.31, 14 % $C_{13}H_{12}O$ (184)

2.32, 14 % $C_{13}H_{10}O$ (182)

1.71, 19 % $C_{12}H_{10}O$ (170)

Benzyl 2-iodophenyl ether **2.30** (800 mg, 2.58 mmol), tributyltin hydride (950 μL, 1.00 g, 3.43 mmol), and AIBN (55 mg, 0.34 mmol) were stirred in toluene (85 mL) at 90 °C for 24 hours with a further portion of tributyltin hydride (200 μL, 215 mg, 0.74 mmol) and AIBN (10 mg, 0.06 mmol) added after 16 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 20 mL) for 16 hours. The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 2 % ether / petrol) yielded **2.31** and **2.32** (130 mg, 0.71 mmol, 28 %, **2.31**:**2.32** ~ 1:1) as a colourless oil and then **1.71** (85 mg, 0.50 mmol, 19 %) as a colourless oil.

Select data are reported from the mixture of **2.31** and **2.32**.

2-Methoxy-1,1'-biphenyl **2.31**[168]

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 3.85 (3H, s, OCH_3) plus aromatic signals obscured by **2.32**.

LRMS (M/z, CI) 202 ($[M+NH_4]^+$, 96 %), 184 (M^+, 100 %), 169 ($[M-CH_3]^+$, 18 %), 141 (16 %), 115 (16 %) amu.

6*H*-Benzo[*c*]chromene **2.32**[169]

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 5.17 (2H, s, OCH_2) plus aromatic signals obscured by **2.31**.

LRMS (M/z, CI) 182 (MH^+, 100 %), 152 (22 %) amu.

2-Hydroxy-1,1'-biphenyl **1.71**[19,170]

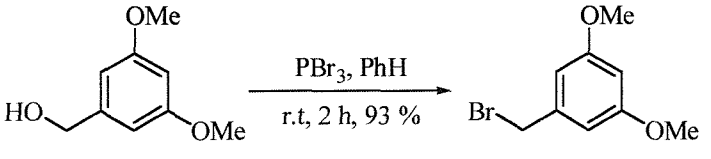
FT – IR (ν_{max}, neat) 3434 br. m, 2955 s, 2922 s, 2853 m, 1478 m, 1457 m ,1434 m, 1270 m cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.51 (4H, m, 4 × Ar*H*), 7.44 – 7.42 (1H, m, Ar*H*), 7.29 (1H, td, *J* 7.4, 1.5 Hz, Ar*H*), 7.28 (1H, d, *J* 7.4 Hz, Ar*H*), 7.02 (1H, t, *J* 7.4 Hz, Ar*H*), 7.01 (1H, d, *J* 7.4 Hz, Ar*H*), 5.35 (1H, s, O*H*) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 156.2 (0, *C*O), 137.3 (0, *C*), 130.4 (1, 2 × *C*H), 129.4 (1, 3 × *C*H), 129.2 (1, *C*H), 128.3 (0, *C*), 128.0 (1, *C*H), 121.0 (1, *C*H), 116.0 (1, *C*H) ppm.

LRMS (M/z, CI) 170 (M^+, 100 %), 141 (26 %), 115 (32 %) amu.

3,5-Dimethoxybenzyl bromide **2.101**



2.100
$C_9H_{12}O_3$ (168)

2.101
$C_9H_{11}BrO_2$ (231)

3,5-Dimethoxybenzyl bromide **2.101** was prepared by a modification of the method of Hawker *et al.*[148] 3,5-Dimethoxybenzyl alcohol **2.100** (2.90 g, 17.26 mmol) was dissolved in benzene (20 mL) and cooled to 0 °C. Phosphorus tribromide (550 µL, 1.56 g, 5.76 mmol) was added dropwise over 5 minutes and the mixture allowed to stir at room temperature for 2 hours. The solvent was evaporated *in vacuo* and the residue diluted with dichloromethane (10 mL) and washed with water (10 mL). The aqueous phase was extracted with dichloromethane (2 × 20 mL), the combined organic phases dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield the title compound **2.101** (3.70 g, 16.01 mmol, 93 %) as a white solid.[171]

MP 66 - 68 °C (ether / petrol) lit. 69 – 70 °C (DCM / hexane).[171]

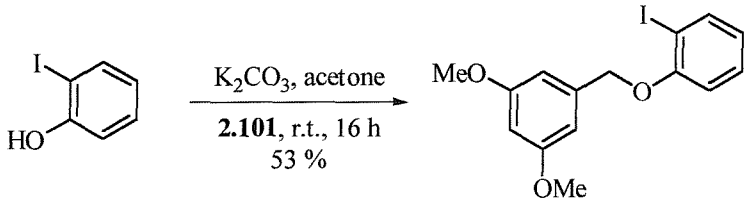
FT – IR (ν_{max}, neat) 1596 s, 1462 m, 1428 m, 1324 m, 1205 s, 1154 s, 1062 m cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 6.56 (2H, d, *J* 2.2 Hz, 2 × Ar*H*), 6.41 (1H, t, *J* 2.2 Hz, Ar*H*), 4.44 (2H, s, CH_2Br), 3.81 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 161.0 (0, 2 × *C*O), 139.9 (0, *C*), 107.1 (1, 2 × *C*H), 100.7 (1, *C*H), 55.6 (3, 2 × OCH_3), 33.8 (2, CH_2Br) ppm.

LRMS (M/z, Cl) 153 ($[M-Br+2H]^+$, 100 %) amu.

1-(2-Iodophenoxymethyl)-3,5-dimethoxybenzene **2.33**



2.1
C_6H_5IO (220)

2.33
$C_{15}H_{15}IO_3$ (370)

1-(2-Iodophenoxymethyl)-3,5-dimethoxybenzene **2.33** was prepared by a modification of the method of Sheppard *et al.*[160] 2-Iodophenol **2.1** (3.54 g, 16.10 mmol), 3,5-dimethoxybenzyl bromide **2.101** (3.70 g, 16.03 mmol) and potassium carbonate (2.88 g, 20.84 mmol) were stirred in acetone (40 mL) at room temperature for 16 hours. Filtration, concentration *in vacuo* and purification by column chromatography (silica gel, 5 % ether / petrol) provided **2.33** (3.14 g, 8.49 mmol, 53 %) as a white solid after recrystallisation from ethanol. 3,5-Dimethoxybenzyl bromide **2.101** (500 mg, 2.16 mmol, 17 %) was also recovered.

MP 54 – 56 °C (ether / petrol).

FT – IR (ν_{max}, neat) 1598 s, 1470 s, 1428 s, 1372 m, 1246 m, 1204 s, 1153 s, 1050 s, 1017 s cm^{-1}.

UV (λ_{max}, MeOH) 280 (3170) nm.

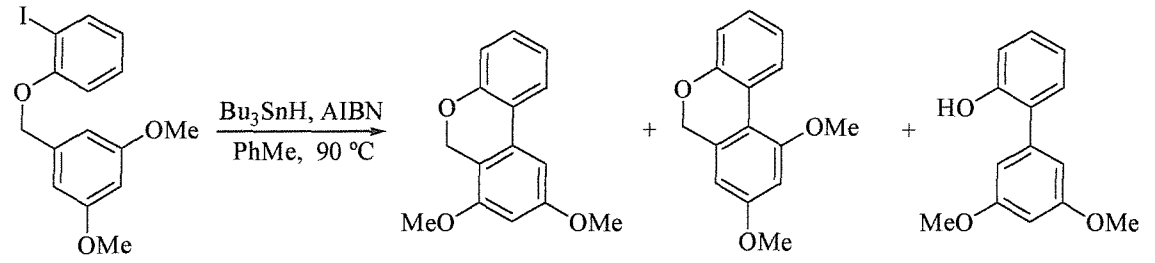
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.82 (1H, dd, *J* 7.5, 1.3 Hz, Ar*H*), 7.30 (1H, td, *J* 7.5, 1.3 Hz, ArH), 6.87 (1H, d, *J* 7.5 Hz, Ar*H*), 6.76 (1H, td, *J* 7.5 1.3 Hz, Ar*H*), 6.72 (2H, d, *J* 2.2 Hz, 2 × Ar*H*), 6.44 (1H, t, *J* 2.2 Hz, Ar*H*), 5.12 (2H, s, OCH_2), 3.83 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 161.1 (0, 2 × *C*O), 157.2 (0, *C*), 139.7 (1, *C*H), 139.1 (0, *C*), 129.6 (1, *C*H), 123.0 (1, *C*H), 112.9 (1, *C*H), 104.8 (1, 2 × *C*H), 100.0 (1, *C*H), 87.0 (0, *C*I), 70.7 (2, CH_2O), 55.6 (3, 2 × OCH_3) ppm.

LRMS (M/z, CI) 371 (MH^+, 8 %), 245 (48 %), 153 (100 %) amu.

CHN $C_{15}H_{15}IO_3$ requires: C 48.67, H 4.08; Found: C 48.64, H 4.03.

8,10-Dimethoxy-6*H*-benzo[*c*]chromene **2.34**, 7,9-dimethoxy-6*H*-benzo[*c*]chromene **2.35**, 2-hydroxy-3',5'-dimethoxy-1,1'-biphenyl (Isoaucuparin) **2.36**



2.33
$C_{15}H_{15}IO_3$ (370)

2.35, 37 %
$C_{15}H_{14}O_3$ (242)

2.34, 18 %
$C_{15}H_{14}O_3$ (242)

2.36, 17 %
$C_{14}H_{14}O_3$ (230)

Iodide **2.33** (750 mg, 2.03 mmol), tributyltin hydride (820 μL, 885 mg, 3.04 mmol) and AIBN (50 mg, 0.30 mmol) were stirred in toluene at 90 °C for 40 hours with an additional portion of tributyltin hydride (200 μL, 216 mg, 0.74 mmol) and AIBN (10 mg, 0.06 mmol) added after 24 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 20 mL). The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 % ether / petrol) provided firstly tricyclic **2.35** (170 mg, 0.70 mmol, 35 %) as a pale yellow oil, then a mixture of **2.34** & **2.35** (100 mg, 0.41 mmol, 20 %, **2.34**:**2.35** ~ 8:1) as a yellow oil and finally phenol **2.36** (80 mg, 0.35 mmol, 17 %) as a yellow oil.

8,10-Dimethoxy-6*H*-benzo[*c*]chromene **2.34**

FT – IR (ν_{max}, neat) 2963 m, 2928 m, 2833 m, 1609 s, 1461 s, 1420 m, 1336 s, 1232 s, 1157 s, 1027 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 298 (8600), 264 (8800) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 8.37 (1H, d, *J* 8.0 Hz, Ar*H*), 7.23 (1H, td, *J* 7.7, 1.5 Hz, Ar*H*), 7.10 (1H, td, *J* 8.0, 1.5 Hz, Ar*H*), 7.07 (1H, dd, *J* 8.0, 1.5 Hz, Ar*H*), 6.58 (1H, d, *J* 2.1 Hz, Ar*H*), 6.40 (1H, d, *J* 2.0 Hz, Ar*H*), 5.03 (2H, s, OCH_2), 3.97 (3H, s, OCH_3), 3.90 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 160.4 (0, *C*O), 158.3 (0, *C*O), 154.8 (0, *C*O), 135.9 (0, *C*), 128.2 (1, *C*H), 128.0 (1, *C*H), 122.7 (0, *C*), 122.2 (1, *C*H), 117.1 (1, *C*H), 112.5 (0, *C*), 102.0 (1, *C*H), 99.2 (1, *C*H), 69.5 (2, OCH_2), 55.9 (3, OCH_3), 55.8 (3, OCH_3) ppm.

LRMS (M/z, CI) 242 (M^+, 100 %), 227 (16 %), 211 (10 %), 168 (13 %), 155 (18 %), 128 (20 %) amu.

HRMS (M/z, EI) $C_{15}H_{14}O_3^+$ requires: 242.0943; Found M^+: 242.0942.

7,9-Dimethoxy-6*H*-benzo[*c*]chromene **2.35**

FT – IR (ν_{max}, neat) 1608 s, 1571 m, 1456 m, 1420 s, 1340 m, 1276 m, 1229 m, 1206 s, 1153 s, 1096 m, 1031 s cm^{-1}.

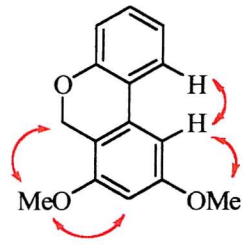
UV (λ_{max}, MeOH) 300 (9960) 266 (11000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.68 (1H, d, *J* 7.4 Hz, Ar*H*), 7.23 (1H, td, *J* 7.5, 1.5 Hz, Ar*H*), 7.07 (1H, t, *J* 7.4 Hz, Ar*H*), 7.04 (1H, d, *J* 7.5 Hz, Ar*H*), 6.86 (1H, d, *J* 1.8 Hz, ArH), 6.43 (1H, d, *J* 1.8 Hz, Ar*H*), 5.17 (2H, s, OCH_2), 3.92 (3H, s, OCH_3), 3.85 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 160.8 (0, *C*O), 156.2 (0, *C*O), 155.1 (0, *C*O), 131.8 (0, *C*), 129.7 (1, *C*H), 123.7 (1, *C*H), 122.9 (0, *C*), 121.9 (1, *C*H), 117.5 (0, *C*), 112.9 (1, *C*H), 98.5 (1, *C*H), 97.8 (1, *C*H), 63.2 (2, OCH_2), 55.6 (3, 2 × OCH_3) ppm.

LRMS (M/z, CI) 243 (MH^+, 100 %), 227 (7 %), 168 (8 %), 139 (11 %) amu.

HRMS (M/z, EI) $C_{15}H_{14}O_3^+$ requires 242.0943; Found M^+: 242.0936.



2.35 – Enhancements from GOESY experiment

2-Hydroxy-3',5'-dimethoxy-1,1'-biphenyl (isoaucuparin) **2.36**[61]

FT – IR (ν_{max}, neat) 3441 br. m, 2956 m, 1594 s, 1462 m, 1417 m, 1204 s, 1155 s, 1064 m cm^{-1}.

UV (λ_{max}, MeOH) 290 (6900), 258 (10000) nm.

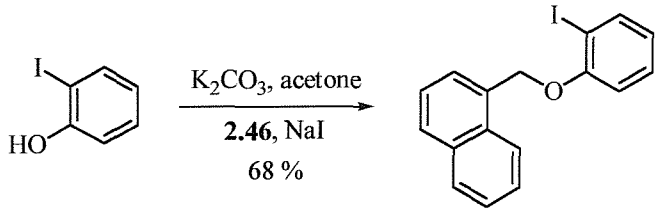
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.28 (1H, t, *J* 7.4 Hz, Ar*H*), 7.26 (1H, d, *J* 7.4 Hz, Ar*H*), 7.00 (1H, d, *J* 7.4 Hz, Ar*H*), 6.99 (1H, t, *J* 7.4 Hz, Ar*H*), 6.06 (2H, d, *J*

1.8 Hz, 2 × Ar*H*), 6.51 (1H, t, *J* 1.8 Hz, Ar*H*), 5.48 (1H, s, O*H*), 3.84 (6H, s, 2 × OCH_3).[‡‡,61]

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 161.7 (0, 2 × *C*O), 152.7 (0, *C*O), 139.1 (0, *C*), 130.0 (1, *C*H), 129.5 (1, *C*H), 128.1 (0, *C*), 120.8 (1, *C*H), 116.0 (1, *C*H), 107.0 (1, 2 × *C*H), 100.1 (1, *C*H), 55.6 (3, 2 × O*C*H_3) ppm.

LRMS (M/z, CI) 231 (MH^+, 100 %), 115 (12 %) amu.

1-(2-Iodophenoxymethyl)naphthalene **2.47**



2.1
C_6H_5IO (220)

2.47
$C_{17}H_{13}IO$ (360)

2-Iodophenol **2.1** (2.57 g, 1.66 mmol), potassium carbonate (2.35 g, 16.98 mmol), 1-(chloromethyl)naphthalene **2.46** (2.00 g, 11.32 mmol), and sodium iodide (1.75 g, 11.66 mmol) were stirred at room temperature for 5 hours, at reflux for 3 hours, at room temperature for 16 hours and at reflux for 4 hours. After cooling to room temperature, the mixture was filtered and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 0 – 1 % ether / petrol) yielded the title compound **2.47** (2.76 g, 7.67 mmol, 68 %) as an off – white solid.

MP 47 – 50 °C (petrol).

FT – IR (ν_{max}, neat) 1580 m, 1511 m, 1470 s, 1438 s, 1277 s, 1234 s, 1063 m, 1017 s, 1000 m cm^{-1}.

UV (λ_{max}, MeOH) 280 (13600), 220 (40240) nm.

^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 8.11 (1H, d, *J* 8.4 Hz, Ar*H*), 7.94 – 7.82 (3H, m, 3 × Ar*H*), 7.75 (1H, d, *J* 7.0 Hz, Ar*H*), 7.62 – 7.48 (3H, m, 3 × Ar*H*), 7.32 (1H, td, *J* 7.4, 1.5 Hz, Ar*H*), 7.03 (1H, d, *J* 8.1 Hz, Ar*H*), 6.77 (1H, app. t, *J* 7.7 Hz, Ar*H*), 5.61 (2H, s, O*C*H_2) ppm.

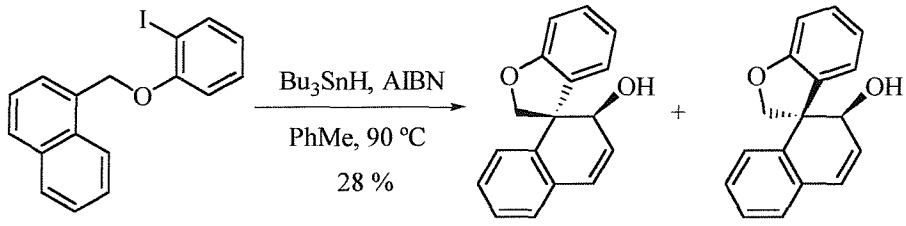
^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 157.4 (0, *C*O), 139.8 (1, *C*H), 133.8 (0, C), 131.9 (0, *C*), 131.2 (0, *C*), 129.6 (1, *C*H), 129.0 (1, *C*H), 128.9 (1, *C*H), 126.5 (1, *C*H),

‡‡ The ^{1}H – NMR data was similar to that in the isolation paper although the data reported was obtained using d_6-acetone as solvent.

126.1 (1, *C*H), 126.1 (1, *C*H), 125.6 (1, *C*H), 123.8 (1, *C*H), 123.1 (1, *C*H), 112.8 (1, *C*H), 87.0 (0, *C*I), 69.6 (2, O*C*H_2) ppm.

LRMS (M/z, CI) 360 (M^+, 5%), 219 (3 %), 141 (100 %), 115 (34 %) amu.

rel-(3*R*,2'*S*)-2'-Hydroxyspiro((2,3-dihydrobenzofuran)-3,1'-(1',2'-dihydronaphthalene)) **2.48** & *rel*-(3*S*,2'*S*)-2'-hydroxyspiro((2,3-dihydrobenzofuran)-3,1'-(1',2'-dihydronaphthalene)) **2.49**



2.47 $C_{17}H_{13}IO$ (360) — **2.48** $C_{17}H_{14}O_2$ (250) 1:1 **2.49** $C_{17}H_{14}O_2$ (250)

Iodide **2.47** (800 mg, 2.22 mmol), tributyltin hydride (900 μL, 970 mg, 3.33 mmol) and AIBN (50 mg, 0.30 mmol) were stirred in toluene (50 mL) at 90 °C for 24 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 20 mL) for 16 hours. The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic phases dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (silica gel, 5 – 10 % ether / petrol) yielded recovered starting material **2.47** (200 mg, 0.56 mmol, 25 %) as a white solid, an inseparable mixture of compounds (80 mg) as a colourless oil and then spirocycle **2.48** (75 mg, 0.30 mmol, 14 %) and **2.49** (80 mg, 0.32 mmol, 14 %) both as colourless oils.

rel-(3*R*,2'*S*)-2'-Hydroxyspiro((2,3-dihydrobenzofuran)-3,1'-(1',2'-dihydronaphthalene)) **2.48**

FT – IR (ν_{max}, neat) 3439 br. m, 1666 m, 1594 m, 1498 s, 1461 s, 1232 s, 1116 m, 1074 m, 1019 m cm^{-1}.

UV (λ_{max}, MeOH) 270 (11700) nm.

^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.28 – 7.10 (5H, m, 5 × Ar*H*), 6.97 – 6.89 (3H, m, 3 × Ar*H*), 6.53 (1H, dd, *J* 9.9, 2.2 Hz, C*H*=CH), 6.03 (1H, dd, *J* 9.5, 2.2 Hz, CH=C*H*), 5.25 (1H, d, *J* 9.2 Hz, OC*H*H), 4.89 – 4.70 (1H, m, C*H*OH), 4.32 (1H, d, *J* 9.2 Hz, OCH*H*), 1.81 (1H, d, *J* 4.8 Hz, O*H*) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 161.8 (0, *C*O), 139.7 (0, *C*), 132.5 (0, *C*), 130.5 (1, *C*H), 129.8 (1, *C*H), 129.7 (0, *C*), 128.8 (1, *C*H), 128.6 (1, *C*H), 127.9 (1, *C*H),

127.1 (1, *C*H), 126.9 (1, *C*H), 124.6 (1, *C*H), 121.1 (1, *C*H), 110.3 (1, *C*H), 77.9 (2, O*C*H$_2$), 73.6 (1, *C*HOH), 56.9 (0, *C*) ppm.

LRMS (M/z, CI) 250 (M^+, 22 %), 232 (24 %), 221 (100 %), 202 (41 %), 189 (19 %), 165 (16 %), 152 (12 %), 128 (10 %) amu.

HRMS (M/z, EI) $C_{17}H_{14}O_2^+$ requires 250.0994. Found M^+: 250.0993.

rel-(3*S*,2'*S*)-2'-Hydroxyspiro((2,3-dihydrobenzofuran)-3,1'-(1',2'-dihydronaphthalene)) **2.49**

FT – IR (ν_{max}, neat) 3416 br. m, 1592 m, 1479 s, 1459 m, 1234 m, 1214 m, 1053 m, 985 m cm^{-1}.

UV (λ_{max}, MeOH) 266 (13400) nm.

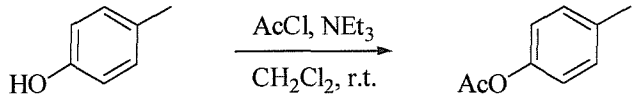
^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.39 (1H, dd, *J* 7.4, 1.5 Hz, Ar*H*), 7.32 – 7.16 (4H, m, 4 × Ar*H*), 7.12 (1H, d, *J* 7.0 Hz, Ar*H*), 6.98 (1H, td, *J* 7.4, 0.7 Hz, Ar*H*), 6.93 (1H, d, *J* 7.7 Hz, Ar*H*), 6.70 (1H, d, *J* 9.6 Hz, C*H*=CH), 6.20 (1H, dd, *J* 9.5, 5.1 Hz, CH=C*H*), 4.68 (1H, d, *J* 9.2 Hz, OC*H*H), 4.26 (1H, app. t, *J* 5.1 Hz, C*H*OH), 4.21 (1H, d, *J* 8.8 Hz, OCH*H*), 1.74 (1H, d, *J* 6.6 Hz, O*H*) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 161.1 (0, *C*O), 137.9 (0, *C*), 132.1 (0, *C*), 131.0 (1, *C*H), 129.6 (1, *C*H), 129.1 (1, *C*H), 128.3 (0, *C*), 127.9 (1, *C*H), 127.7 (1, *C*H), 127.5 (1, *C*H), 127.2 (1, *C*H), 127.0 (1, *C*H), 121.0 (1, *C*H), 110.4 (1, *C*H), 80.5 (2, O*C*H$_2$), 69.3 (1, *C*HOH), 55.9 (0, *C*) ppm.

LRMS (M/z, CI) 250 (M^+, 20 %), 232 (21 %), 221 (100 %), 202 (38 %), 189 (18 %), 165 (17 %), 152 (10 %), 128 (11 %) amu.

HRMS (M/z, EI) $C_{17}H_{14}O_2^+$ requires: 250.0994; Found M^+: 250.0998.

4-Methylphenyl acetate **2.58**



2.102 C_7H_8O (108) — **2.58** $C_9H_{10}O_2$ (150)

To a cooled solution (0 °C) of *p*-cresol **2.102** (20.05 g, 0.19 mol) and triethylamine (31.0 mL, 22.46 g, 0.22 mol) in dichloromethane (200 mL) was added acetyl chloride (14.5 mL, 15.97 g, 0.20 mol) over 20 minutes. The mixture was stirred at room temperature for 4 hours and then poured into ice-water (*ca.* 200 mL). The organic phase was washed with potassium carbonate (sat. aq., 80 mL) and brine (40 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound **2.58** (27.78 g, 0.19 mol, > 99 %) as a pale brown oil.[172]

FT – IR (ν_{max}, neat) 3033 w, 2922 w, 2861 w, 1761 s, 1507 m, 1369 m, 1218 s, 1195 s, 1018 m cm^{-1}.

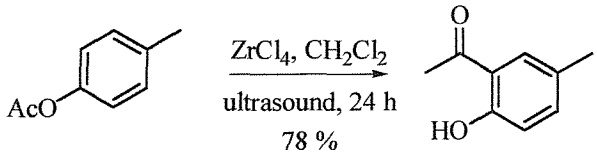
UV (λ_{max}, CH_2Cl_2) 256 (870) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.19 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 6.98 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 2.36 (3H, s, CH_3), 2.30 (3H, s, CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 170.1 (0, *C*=O), 148.9 (0, *C*O), 135.9 (0, *C*), 130.4 (1, 2 × *C*H), 121.7 (1, 2 × *C*H), 21.5 (3, CH_3), 21.3 (3, CH_3) ppm.

LRMS (M/z, EI) 150 (M^+, 8 %), 108 ($[MH-Ac]^+$, 100 %), 77 (21 %) amu.

1-(2-Hydroxy-5-methylphenyl)-1-ethanone **2.59**



2.58
$C_9H_{10}O_2$ (150)

2.59
$C_9H_{10}O_2$ (150)

1-(2-Hydroxy-5-methylphenyl)-1-ethanone **2.59** was prepared using the method of Harrowven *et al.*[67] Thus, a mixture of acetate **2.58** (25.00 g, 0.17 mol) and zirconium tetrachloride (77.68 g, 0.33 mol) in dichloromethane (350 mL) was subjected to ultrasound for 24 hours. After cooling to room temperature, the suspension was poured into ice-water (400 mL) and the aqueous phase extracted with dichloromethane (4 × 100 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. The resulting brown solid was recrystallised from petrol to yield the title compound **2.59** (19.54 g, 0.13 mol, 78 %) as a yellow solid.[173]

MP 40 –41 °C (petrol) lit. 45 – 48 °C (no solvent stated).[173]

FT – IR (ν_{max}, neat) 3263 br w, 3038 w, 2925 w, 2855 w, 1643 s, 1618 m, 1489 s, 1369 m, 1294 s, 1217 s, 1199 s cm^{-1}.

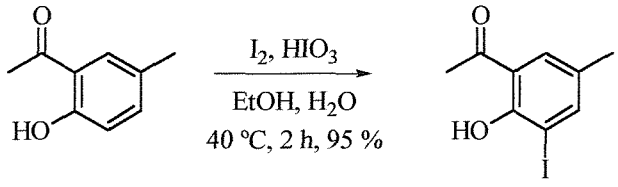
UV (λ_{max}, CH_2Cl_2) 330 (4300), 246 (11000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 12.11 (1H, s, O*H*), 7.51 (1H, d, *J* 2.2 Hz, Ar*H*), 7.29 (1H, dd, *J* 8.4, 2.2 Hz, Ar*H*), 6.89 (1H, d, *J* 8.4 Hz, Ar*H*), 2.62 (3H, s, CH_3), 2.32 (3H, s, CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 204.8 (0, *C*=O), 160.7 (0, *C*O), 137.9 (1, *C*H), 130.9 (1, *C*H), 128.4 (0, *C*), 119.8 (0, *C*), 118.6 (1, *C*H), 27.0 (3, *C*H_3), 20.9 (3, *C*H_3) ppm.

LRMS (M/z, EI) 150 (M^+, 48 %), 135 ($[M\text{-}CH_3]^+$, 100 %), 107 (21 %), 84 (29 %), 77 (38 %) amu.

1-(2-Hydroxy-3-iodo-5-methylphenyl)-1-ethanone **2.60**[68]



2.59 $C_9H_{10}O_2$ (150) **2.60** $C_9H_9IO_2$ (276)

1-(2-Hydroxy-3-iodo-5-methylphenyl)-1-ethanone **2.60** was prepared by a modification of the method of Dawane *et al.*[68] To a solution of phenol **2.59** (5.00 g, 33.33 mmol) in ethanol (100 mL) and water (80 mL) was added iodine (9.31 g, 36.67 mmol) and iodic acid (6.45 g, 36.67 mmol). The mixture was stirred at 40 °C for 2 hours before allowing to cool to room temperature. Dichloromethane (100 mL) was added and the organic phase washed with water (100 mL), sodium hydrogen carbonate (sat. aq., 50 mL) and sodium thiosulfate (sat. aq., 70 mL) then dried ($MgSO_4$). Concentration *in vacuo* yielded the title compound **2.60** (8.74 g, 31.67 mmol, 95 %) as a pale yellow solid.[68]

MP 95 – 96 °C (petrol) lit. 90 °C (ethanol).[68]

FT – IR (ν_{max}, neat) 3059 w, 2940 w, 2905 w, 1642 s, 1438 m, 1370 m, 1315 m, 973 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 340 (5300), 259 (7800) nm.

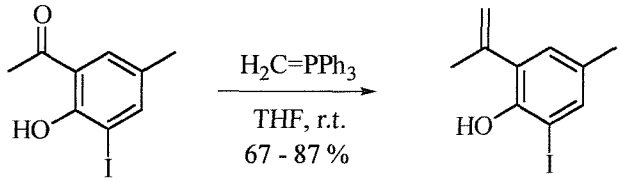
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 13.00 (1H, s, O*H*), 7.84 (1H, d, *J* 2.0 Hz, Ar*H*), 7.54 – 7.50 (1H, m, Ar*H*), 2.64 (3H, s, CH_3), 2.30 (3H, d, *J* 0.6 Hz, CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 204.4 (0, *C*=O), 159.4 (0, *C*O), 146.9 (1, *C*H), 131.4 (1, *C*H), 130.4 (0, *C*), 119.6 (0, *C*), 86.7 (0, *C*I), 26.8 (3, *C*H_3), 20.5 (3, *C*H_3) ppm.

LRMS (M/z, EI) 276 (M^+, 60 %), 261 ($[M\text{-}CH_3]^+$, 72 %), 127 (25 %), 106 (26 %), 86 (42 %), 84 (67 %), 49 (100 %) amu.

CHN $C_9H_9IO_2$ requires: C 39.16, H 3.29; Found: C 39.13, H 3.22.

2-Iodo-6-isopropenyl-4-methylphenol **2.61**



2.60
$C_9H_9IO_2$ (276)

2.61
$C_{10}H_{11}IO$ (274)

Method 1

To a cooled (0 °C) suspension of methyltriphenylphosphonium bromide (19.42 g, 54.35 mmol) in tetrahydrofuran (100 mL) was added *n*-butyllithium (1.1 M in hexanes, 43.5 mL, 47.83 mmol) over 5 minutes. The mixture was stirred at room temperature for 1 hour before cooling to 0 °C. Ketone **2.60** (6.00 g, 21.74 mmol) was added as a solution in tetrahydrofuran (30 mL) and the mixture stirred at room temperature for 36 hours. Ammonium chloride solution (sat. aq, 80 mL) was added and the mixture extracted with ether (3 × 40 mL). The combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica gel, 1 % ether / petrol) to yield the title compound **2.61** (3.98 g, 14.53 mmol, 67 %) as a pale yellow oil.

Method 2

To a suspension of methyltriphenylphosphonium bromide (2.74 g, 7.68 mmol) in tetrahydrofuran (20 mL) was added potassium *tert*-butoxide (1.72 g, 15.36 mmol) and the mixture was stirred at room temperature for 10 minutes. Ketone **2.60** (1.63 g, 5.91 mmol) was added as a solution in tetrahydrofuran (10 mL) and the mixture stirred for a further 2½ hours before the addition of ammonium chloride (sat. aq., 20 mL). The mixture was extracted with ether (3 × 20 mL) and the combined organic phases were dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (silica gel, 5 % ether / petrol) yielded the title compound **2.61** (1.41 g, 5.15 mmol, 87 %) as a pale yellow oil.

FT – IR (ν_{max}, neat) 3488 br. s, 3082 w, 2969 w, 2916 w, 1635 w, 1459 s, 1322 m, 1234 m, 1167 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 286 (3600) nm.

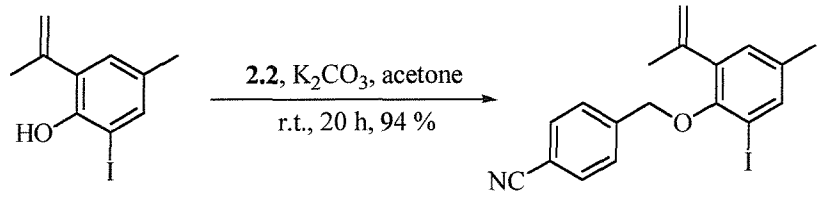
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.44 – 7.43 (1H, m, Ar*H*), 6.94 – 6.93 (1H, m, Ar*H*), 5.75 (1H, s, O*H*), 5.31 (1H, dq, *J* 1.8, 1.5 Hz, =C*H*H), 5.13 (1H, dq, *J* 1.8, 1.0 Hz, =CH*H*), 2.24 (3H, app. t, *J* 0.6 Hz, CH_3), 2.11 (3H, dd, *J* 1.5, 1.0 Hz, CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 149.4 (0, *C*O), 143.3 (0, *C*), 138.3 (1, *C*H), 131.9 (0, *C*), 129.9 (1, *C*H), 129.8 (0, *C*), 116.5 (2, =*C*H_2), 85.2 (0, *C*I), 24.1 (3, *C*H_3), 20.4 (3, *C*H_3) ppm.

LRMS (M/z, CI) 274 (M^+, 98 %), 148 ($[MH\text{-}I]^+$, 100 %), 133 (28 %), 105 (32 %), 91 (26 %) amu.

HRMS (M/z, EI) $C_{10}H_{11}IO^+$ requires 273.9855; Found M^+: 273.9853.

4-(2-Iodo-6-isopropenyl-4-methylphenoxymethyl)benzonitrile **2.62**



2.61
$C_{10}H_{11}IO$ (274)

2.62
$C_{18}H_{16}INO$ (389)

Phenol **2.61** (2.00 g, 7.30 mmol), 4-(bromomethyl)benzonitrile **2.2** (1.57 g, 8.03 mmol) and potassium carbonate (1.51 g, 10.95 mmol) were stirred in acetone (30 mL) at room temperature for 16 hours. The resulting solid was removed by filtration and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 2 – 4 % ether / petrol) yielded the title compound **2.62** (2.66 g, 6.84 mmol, 94 %) as a white solid.

MP 61 – 62 °C (petrol).

FT – IR (ν_{max}, neat) 3085 w, 2963 w, 2911 w, 2228 s, 1611 w, 1443 s, 1371 s, 1230 s, 1092 m, 1016 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 267 (4600) nm.

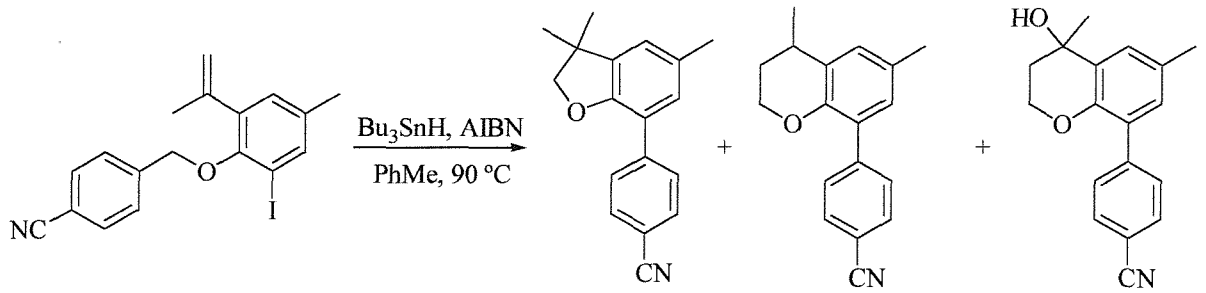
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* 8.0 Hz, 2 × Ar*H*), 7.64 (2H, d, *J* 8.0 Hz, 2 × Ar*H*), 7.56 – 7.55 (1H, m, Ar*H*), 7.02 – 7.01 (1H, m, Ar*H*), 5.18 (1H, app. t, *J* 1.5 Hz, =C*H*H), 5.15 – 5.14 (1H, m, =CH*H*), 4.88 (2H, s, OCH_2), 2.30 (3H, s, ArCH_3), 2.10 (3H, s, CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 152.9 (0, *C*O), 143.8 (0, *C*), 142.8 (0,*C*), 139.1 (1, *C*H), 138.1 (0, *C*), 136.7 (0, *C*), 132.6 (1, 2 × *C*H), 131.4 (1, *C*H), 128.8 (1, 2 × *C*H), 119.0 (0, *C*N), 116.7 (2, =*C*H_2), 112.2 (0, *C*CN), 93.0 (0, *C*I), 74.0 (2, O*C*H_2), 23.6 (3, *C*H_3), 20.7 (3, *C*H_3) ppm.

LRMS (M/z, CI) 279 (68 %), 261 ($[M\text{-}I\text{-}H]^+$, 100 %), 246 (16 %), 147 (78 %), 117 (40 %) amu.

CHN $C_{18}H_{16}INO$ requires: C 55.54, H 4.14, N 3.60; Found: C 55.40, H 4.16, N 3.49.

4-(3,3,5-Trimethyl-2,3-dihydrobenzo[*b*]furan-7-yl)benzonitrile **2.63**, 4-(4,6-dimethyl-2,3-dihydro-2*H*-8-chromenyl)benzonitrile **2.64** and 4-(4-hydroxy-4,6-dimethyl-2,3-dihydro-2*H*-8-chromenyl)benzonitrile **2.65**



2.62 $C_{18}H_{16}INO$ (389)

2.63, 44 % $C_{18}H_{17}NO$ (263)

2.64, 35 % $C_{18}H_{17}NO$ (263)

2.65, 17 % $C_{18}H_{17}NO_2$ (279)

Iodide **2.62** (500 mg, 1.29 mmol), tributyltin hydride (420 μL, 450 mg, 1.55 mmol) and AIBN (20 mg, 0.13 mmol) were stirred in toluene at 90 °C for 20 hours with additional portions of tributyltin hydride (200 μL, 215 mg, 0.74 mmol) and AIBN (10 mg, 0.06 mmol) added after 4 and 8 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 20 mL) for 16 hours. The organic phase was diluted with ether (20 mL), washed with water (2 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5- 10 % ether / petrol) yielded firstly benzo[*b*]furan **2.63** (60 mg, 0.23 mmol, 18 %) as a colourless oil, then a mixture of **2.63** and **2.64** (175 mg, 0.67 mmol, 52 %, **2.63** : **2.64** ~ 1:1) then **2.64** (30 mg, 0.11 mmol, 9 %) as a colourless oil and finally alcohol **2.65** (60mg, 0.22 mmol, 17 %) as a pale yellow oil.

4-(3,3,5-Trimethyl-2,3-dihydrobenzo[*b*]furan-7-yl)benzonitrile **2.63**

FT – IR (ν_{max}, neat) 2960 m, 2924 m, 2863 w, 2225 s, 1607 s, 1459 s, 1395 m, 1193 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 318 (7800), 266 (16000), 241 (12000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.84 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 7.69 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 7.12 – 7.11 (1H, m, Ar*H*), 6.97 (1H, d, *J* 1.7 Hz, Ar*H*), 4.30 (2H, s, OCH_2), 2.38 (3H, s, ArCH_3), 1.39 (6H, s, 2 × CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 154.9 (0, *C*O), 142.5 (0, *C*), 138.5 (0, *C*), 132.5 (1, 2 × *C*H), 131.3 (0, *C*), 129.4 (1, 2 × *C*H), 128.2 (1, *C*H), 124.0 (1, *C*H), 121.4 (0,

C), 119.6 (0, *C*N), 110.6 (0, *C*CN), 85.1 (2, O*C*H_2), 42.3 (0, *C*), 27.9 (3, 2 × *C*H_3), 21.3 (3, Ar*C*H_3) ppm.

LRMS (M/z, EI) 263 (M^+, 90 %), 248 ([M-CH_3]$^+$, 100 %), 206 (90 %), 190 (68 %), 124 (30 %) amu.

HRMS (M/z, EI) $C_{18}H_{17}NO^+$ requires: 263.1310; Found M^+: 263.1312.

4-(4,6-Dimethyl-2,3-dihydro-2*H*-8-chromenyl)benzonitrile **2.64**

FT – IR (ν_{max}, neat) 2962 m, 2918 m, 2874 w, 2225 s, 1606 s, 1476 s, 1459 s, 1251 m, 1223 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 322 (1200), 266 (2800) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.63 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.04 (1H, d, *J* 2.2 Hz, Ar*H*), 6.94 (1H, d, *J* 2.2 Hz, Ar*H*), 4.20 – 4.15 (2H, m, OCH_2), 2.90 (1H, app. sext., *J* 6.3 Hz, C*H*CH_3), 2.26 (3H, s, ArCH_3), 2.12 (1H, dddd, *J* 13.3, 7.6. 6.0, 4.3, CH*H*), 1.74 (1H, dtd, *J* 13.6, 5.8, 3.8 Hz, C*H*H), 1.33 (3H, d, *J* 6.3 Hz, CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 149.4 (0, *C*O), 144.2 (0, *C*), 131.7 (1, 2 × *C*H), 130.3 (1, 2 × *C*H), 129.9 (1, *C*H), 129.5 (0, *C*), 129.1 (1, *C*H), 128.6 (0, *C*), 119.7 (0, *C*N), 116.1 (0, *C*), 110.6 (0, *C*CN), 64.3 (2, OCH_2), 30.5 (2, *C*H_2), 29.2 (1, *C*HCH_3), 23.0 (3, *C*H_3) 21.2 (3, Ar*C*H_3) ppm.

LRMS (M/z, CI) 281 ([M+NH_4]$^+$, 100 %), 263 (M^+, 30 %), 248 (10 %) amu.

HRMS $C_{18}H_{17}NO^+$ requires: 263.1310; Found M^+: 263.1314.

4-(4-Hydroxy-4,6-dimethyl-2,3-dihydro-2*H*-8-chromenyl)benzonitrile **2.65**

FT – IR (ν_{max}, neat) 3442 br. s, 2958 m, 2924 m, 2226 s, 1605 s, 1476 s, 1449 m, 1253 m, 1223 m, 1054 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 307 (6400), 263 (11000), 235 (12000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.58 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 7.52 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 7.29 (1H, d, *J* 2.3 Hz, Ar*H*), 6.93 (1H, d, *J* 2.3 Hz, Ar*H*), 4.21 – 4.09 (2H, m, OCH_2), 2.26 (3H, s, ArCH_3), 2.03 – 2.00 (2H, m), 1.96 (1H, s, O*H*), 1.59 (3H, s, CH_3) ppm.

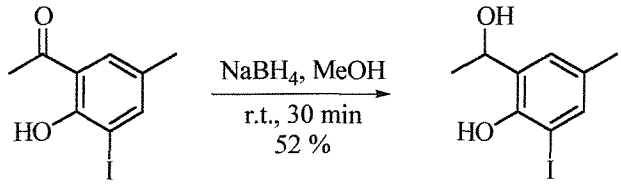
^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 148.8 (0, *C*O), 143.6 (0, *C*), 131.9 (1, 2 × *C*H), 131.1 (1, *C*H), 130.4 (1, 2 × *C*H), 130.2 (0, *C*), 129.3 (0, *C*), 128.3 (0, *C*), 127.6 (1,

*C*H), 119.3 (0, *C*N), 110.6 (0, *C*CN), 80.6 (0, *C*OH(CH_3), 60.6 (2, OCH_2), 38.2 (2, *C*H_2), 30.2 (3, *C*H_3), 21.0 (3, Ar*C*H_3) ppm.

LRMS (M/z, CI) 261 ([M-H_2O]$^+$, 98 %), 246 ([M-CH_3-H_2O]$^+$, 100 %), 216 (16 %), 203 (26 %), 190 (28 %) amu.

HRMS $C_{18}H_{17}NO_2^+$ requires: 279.1259; Found M^+: 279.1260.

2-(1-Hydroxyethyl)-6-iodo-4-methylphenol **2.70**



2.60 $C_9H_9IO_2$ (276) **2.70** $C_9H_{11}IO_2$ (278)

To a solution of ketone **2.60** (1.00 g, 3.58 mmol) in methanol (30 mL) was added sodium borohydride (165 mg, 4.30 mmol) over 5 minutes and the mixture stirred at room temperature for 30 minutes. The solvent was removed under reduced pressure and the resulting solid diluted with dichloromethane (50 mL). After sequential washing with a solution of ammonium chloride (sat. aq., 30 mL) and brine (20 mL), the organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 40 % ether / petrol) yielded the title phenol **2.70** (520 mg, 1.87 mmol, 52 %) as a pale yellow solid.

MP 113 – 116 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3258 br. m, 2958 w, 2839 w, 1458 m, 1364 m, 1229 m, 1038 m cm^{-1}.

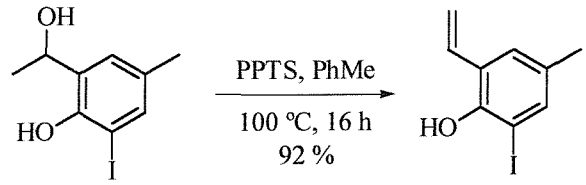
UV (λ_{max}, MeCN) 298 (24000), 263 (24000), 242 (60000) nm.

^{1}H – NMR (400 MHz, d_4-MeOH) δ_H 7.40 – 7.39 (1H, m, Ar*H*), 6.95 – 6.94 (1H, m, Ar*H*), 4.98 (1H, q, *J* 6.5 Hz, C*H*OH), 4.83 (2H, br s, 2 × O*H*), 2.20 (3H, s, ArCH_3), 1.42 (3H, d, *J* 6.5 Hz, CH(OH)CH_3) ppm.

^{13}C – NMR (100 MHz, d_4-MeOH) δ_C 153.5 (0, *C*O), 139.2 (1, *C*H), 133.0 (0, *C*), 132.6 (0, *C*), 128.6 (1, *C*H), 86.7 (0, *C*I), 70.3 (1, *C*HOH), 24.6 (3, *C*H_3), 20.5 (3, *C*H_3) ppm.

LRMS (M/z, CI) 260 ([M-H_2O]$^+$, 14 %), 134 ([M-OH-I]$^+$, 50 %), 44 (100 %) amu.

2-Iodo-4-methyl-6-vinylphenol **2.71**



2.70
$C_9H_{11}IO_2$ (278)

2.71
C_9H_9IO (260)

A solution of alcohol **2.70** (500 mg, 1.80 mmol) and pyridinium *p*-toluenesulfonate (90 mg, 0.36 mmol) in toluene (50 mL) was heated at 100 °C for 16 hours. After cooling to room temperature, the mixture was diluted with ether (30 mL), washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 % ether / petrol) yielded the title phenol **2.71** (430 mg, 1.65 mmol, 92 %) as a pale yellow oil.

FT – IR (ν_{max}, neat) 3486 br. m, 3090 w, 3026 w, 2921 w, 1624 w, 1565 w, 1458 s, 1322 m, 1270 m, 1236 m, 1184 m, 1096 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 259 (20000) nm

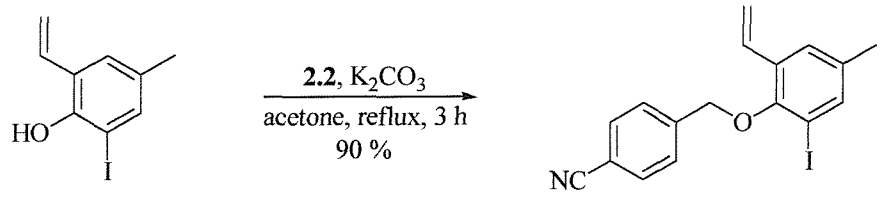
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.40 (1H, d, *J* 1.4 Hz, Ar*H*), 7.23 – 7.19 (1H, m, Ar*H*), 6.97 (1H, dd, *J* 17.6, 11.0 Hz, C*H*=CH_2), 5.75 (1H, dd, *J* 17.6, 1.4 Hz, =C*H*H), 5.30 (1H, dd, *J* 11.0, 1.4 Hz, =CH*H*), 5.30 (1H, s, O*H*), 2.26 (3H, s, CH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 149.8 (0, *C*O), 137.7 (1, *C*H), 131.9 (1, *C*H), 131.8 (0, *C*), 128.2 (1, *C*H), 124.8 (0, *C*), 116.0 (2, =CH_2), 87.0 (0, *C*I), 20.3 (3, CH_3) ppm.

LRMS (M/z, Cl) 260 (M^+, 100 %), 134 ($[MH-I]^+$, 40 %), 133 ($[M-I]^+$, 38 %), 105 (3 %), 77 (58 %) amu.

HRMS (M/z, EI) $C_9H_9IO^+$ requires: 259.9698; Found M^+: 259.9697.

4-(2-Iodo-4-methyl-6-vinylphenoxymethyl)benzonitrile **2.72**



2.71
C_9H_9IO (260)

2.72
$C_{17}H_{14}INO$ (375)

Phenol **2.71** (395 mg, 1.52 mmol), 4-(bromomethyl)benzonitrile **2.2** (285 mg, 1.45 mmol) and potassium carbonate (315 mg, 2.28 mmol) were heated in acetone (30 mL) at reflux for 3 hours. After cooling to room temperature, the resulting solid was removed by filtration and the filtrate concentrated *in vacuo*. Recrystallisation from ethanol yielded the title styrene **2.72** (160 mg, 0.43 mmol, 29 %) as a white solid. Purification of the mother liquor by column chromatography (silica gel, 5 % ether / petrol) yielded a further portion of **2.72** (330 mg, 0.88 mmol, 61 %).

MP 90 – 92 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2923 w, 2853w, 2228 s, 1612 w, 1447 m, 1371 m, 1267 m, 1223 s, 1015 s cm^{-1}.

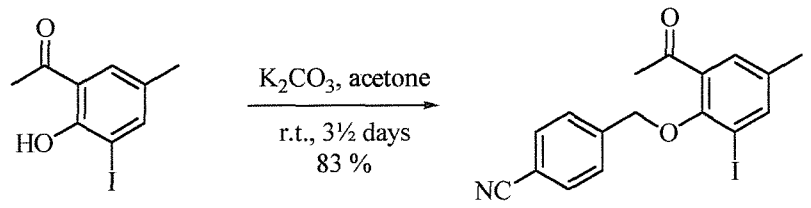
UV (λ_{max}, CH_2Cl_2) 286 (5100), 254 (22000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.73 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 7.68 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 7.57 (1H, d, *J* 1.4 Hz, Ar*H*), 7.31 – 7.30 (1H, m, Ar*H*), 6.91 (1H, dd, *J* 17.6, 11.0 Hz, C*H*=CH_2), 5.76 (1H, dd, *J* 17.6, 1.2 Hz, =C*H*H), 5.30 (1H, dd, *J* 11.0, 1.2 Hz, =CH*H*), 4.90 (2H, s, OCH_2), 2.32 (3H, s, CH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.1 (0, *C*O), 142.3 (0, *C*), 139.4 (1, *C*H), 136.6 (0, *C*), 132.5 (1, 2 × *C*H), 131.9 (0, *C*), 131.4 (1, *C*H), 128.3 (1, 2 × *C*H), 127.8 (1, *C*H), 119.0 (0, *C*N), 116.8 (2, =CH_2), 111.9 (0, *C*CN), 92.4 (0, *C*I), 74.1 (2, OCH_2), 20.1 (3, CH_3) ppm.

LRMS (M/z, CI) 248 ([M-I]$^+$, 40 %), 247 (60 %), 154 (38 %) amu.

4-(2-Acetyl-6-iodo-4-methylphenoxymethyl)benzonitrile **2.73**



2.60
$C_9H_9IO_2$ (276)

2.73
$C_{17}H_{14}INO_2$ (391)

Phenol **2.60** (2.76 g, 10.00 mmol), 4-(bromomethyl)benzonitrile **2.2** (1.87 g, 9.52 mmol) and potassium carbonate (2.07 g, 15.00 mmol) were stirred in acetone at room temperature for 3½ days. The mixture was filtered and the filtrate concentrated *in vacuo*. Recrystallisation from ethanol yielded the title acetophenone **2.73** (3.11 g, 7.95 mmol, 83 %) as a pale yellow solid.

MP 92 – 95 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3059 w, 2927 w, 2228 m, 1684 s, 1591 m, 1446 m, 1374 m, 1279 m, 1255 m, 1233 m, 1174 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 292 (2500), 251 (6900) nm.

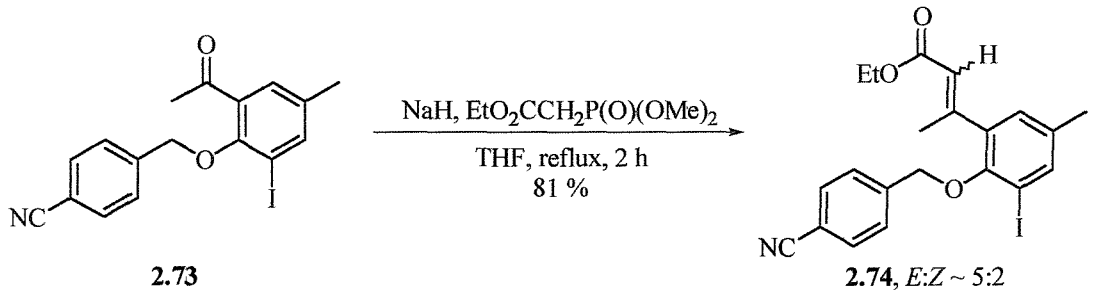
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.80 – 7.78 (1H, m, Ar*H*), 7.71 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 7.67 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 7.38 – 7.37 (1H, m, Ar*H*), 4.97 (2H, s, OCH_2), 2.55 (3H, s, CH_3), 2.35 (3H, s, CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 200.1 (0, *C*=O), 154.2 (0, *C*O), 143.8 (1, *C*H), 142.0 (0, *C*), 137.1 (0, *C*), 134.8 (0, *C*), 132.8 (1, 2 × *C*H), 130.9 (1, *C*H), 128.8 (1, 2 × *C*H), 119.1 (0, *C*N), 112.5 (0, *C*CN), 93.8 (0, *C*I), 76.1 (2, OCH_2), 30.7 (3, CH_3), 20.7 (3, ArCH_3) ppm.

LRMS (M/z, Cl) 283 (10 %), 266 (26 %), 151 (24 %), 135 (42 %), 108 (40 %), 44 (100 %) amu.

HRMS (M/z, ES+) $C_{34}H_{28}I_2N_2O_4Na^+$ requires: 805.0031; Found $[2M+Na]^+$: 805.0049

Ethyl (*E*)-3-(2-(4-cyanobenzyloxy)-3-iodo-5-methylphenyl)-2-butenoate & ethyl (*Z*)-3-(2-(4-cyanobenzyloxy)-3-iodo-5-methylphenyl)-2-butenoate **2.74**



2.73
$C_{17}H_{14}INO_2$ (391)

2.74, *E*:*Z* ~ 5:2
$C_{21}H_{20}INO_3$ (461)

Ester **2.74** was prepared by a modification of the method of Fuganti *et al.*[69] To sodium hydride (60 % in mineral oil, 75 mg, 1.84 mmol) in tetrahydrofuran (20 mL) was added ethyl dimethylphosphonoacetate (255 μL, 300 mg, 1.53 mmol) and the mixture stirred for 5 minutes. A solution of ketone **2.73** (500 mg, 1.28 mmol) in tetrahydrofuran (5 mL) was added and the mixture heated at reflux for 2 hours. After cooling to room temperature, water (20 mL) was added and the mixture extracted with ether (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica gel, 10 % ether / petrol) to yield firstly *E*-**2.74** (100 mg, 0.17 mmol, 17 %) as a colourless oil then a mixture of *E* and *Z* isomers (325 mg, 0.70 mmol, 55 %, *E*:*Z* ~ 1.3:1) and finally *Z*-**2.74** (55 mg, 0.12 mmol, 9 %) as a colourless oil.

Ethyl (*E*)-3-(2-(4-cyanobenzyloxy)-3-iodo-5-methylphenyl)-2-butenoate *E*-**2.74**

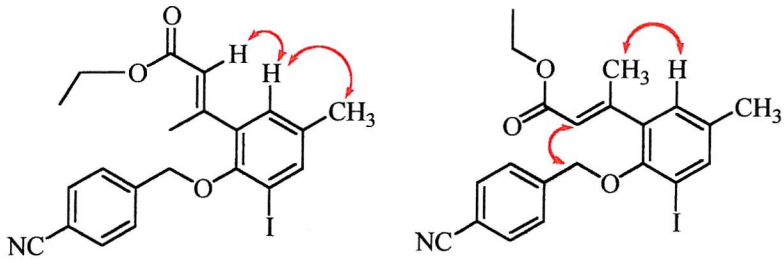
FT – IR (ν_{max}, neat) 2977 w, 2923 w, 2866 w, 2226 m, 1713 s, 1635 m, 1445 s, 1371 m, 1339 m, 1192 s, 1150 s, 1041 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 257 (13000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 7.63 – 7.62 (1H, m, Ar*H*), 7.57 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 6.98 (1H, d, *J* 1.4 Hz, Ar*H*), 5.94 (1H, q, *J* 1.4 Hz, C=C*H*), 4.83 (2H, s, OCH_2), 4.21 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 2.47 (3H, d, *J* 1.4 Hz, $CH=CCH_3$), 2.31 (3H, s, $ArCH_3$), 1.31 (3H, t, *J* 7.0 Hz. OCH_2CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 166.6 (0, *C*=O), 154.9 (0, *C*O & *C*), 142.1 (0, *C*), 140.3 (1, *C*H), 138.3 (0, *C*), 136.9 (0, *C*), 132.7 (1, 2 × *C*H), 130.7 (1, *C*H), 129.0 (1, 2 × *C*H), 120.7 (1, *C*H), 119.1 (0, *C*N), 112.4 (0, *C*CN), 93.1 (0, *C*I), 74.7 (2, OCH_2CH_3), 60.5 (2, OCH_2), 20.6 (3, CH_3), 20.2 (3, CH_3), 14.7 (3, OCH_2CH_3) ppm.

HRMS (M/z, ES+) $C_{42}H_{40}I_2N_2O_6Na^+$ requires: 945.0868; Found $[2M+Na]^+$: 945.0868.



E-**2.74** – Enhancements from GOESY experiment

Ethyl (*Z*)-3-(2-(4-cyanobenzyloxy)-3-iodo-5-methylphenyl)-2-butenoate *Z*-**2.74**

FT – IR (ν_{max}, neat) 2977 w, 2928 w, 2874 w, 2230 m, 1717 s, 1649 m, 1446 s, 1372 m, 1264 m, 1226 m, 1196 s, 1142 m, 1045 m, 1014 m cm^{-1}.

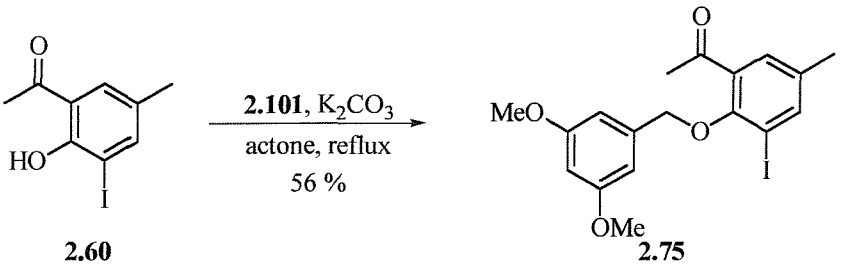
UV (λ_{max}, CH_2Cl_2) 277 (11000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* 8.0 Hz, 2 × Ar*H*), 7.59 – 7.55 (3H, m, 3 × Ar*H*), 6.84 – 6.83 (1H, m, Ar*H*), 5.94 (1H, q, *J* 1.6 Hz, C=C*H*), 4.91 – 4.85 (2H, br. s, OCH_2), 4.02 (2H, q, *J* 7.1 Hz, OCH_2CH$_3$), 2.29 (3H, s, ArCH_3), 2.15 (3H, d, *J* 1.6 Hz, CH=CCH_3), 1.12 (3H, t, *J* 7.0 Hz, OCH$_2$CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 165.7 (0, *C*=O), 153.2 (0, *C*O), 151.7 (0, *C*), 142.6 (0, *C*), 138.4 (1, *C*H), 136.3 (0, *C*), 135.9 (0, *C*), 132.4 (1, 2 × *C*H), 129.6 (1, *C*H), 128.4 (1, 2 × C*H*), 119.7 (1, *C*H), 119.0 (0, *C*N), 111.8 (0, *C*CN), 92.1 (0, *C*I), 74.1 (2, OCH$_2$CH$_3$), 60.2 (2, OCH$_2$), 26.3 (3, *C*H$_3$), 20.5 (3, *C*H$_3$), 14.2 (3, OCH$_2$CH$_3$) ppm.

HRMS (M/z, ES+) $C_{42}H_{40}I_2N_2O_6Na^+$ requires: 945.0868; Found $[2M+Na]^+$: 945.0871.

1-(2-(3,5-Dimethoxybenzyloxy)-3-iodo-5-methylphenyl)ethanone **2.75**



2.60
$C_9H_9IO_2$ (276)

2.75
$C_{18}H_{19}IO_4$ (426)

Phenol **2.60** (2.76 g, 10.00 mmol), 3,5-dimethoxybenzyl bromide **2.102** (2.20 g, 9.52 mmol) and potassium carbonate (2.07 g, 14.98 mmol) were heated at reflux in acetone (40 mL) for 8 hours and then stirred at room temperature for 48 hours. The solid was removed by filtration and the filtrate concentrated *in vacuo*. The resulting oil was diluted with ether (60 mL), washed with potassium carbonate (sat. aq., 2 × 20 mL) and brine (20 mL), dried (K_2CO_3) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 % ether / petrol) yielded firstly recovered phenol **2.60** (950 mg, 3.44 mmol, 34 %) and then the title compound **2.75** (2.26 g, 5.31 mmol, 56 %) as a pale yellow oil.

FT – IR (ν_{max}, neat) 3005 w, 2930 m, 2831 w, 1684 m, 1597 s, 1458 m, 1442 m, 1371 m, 1204 m, 1154 s, 1068 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 304 (1900), 264 (5000) nm.

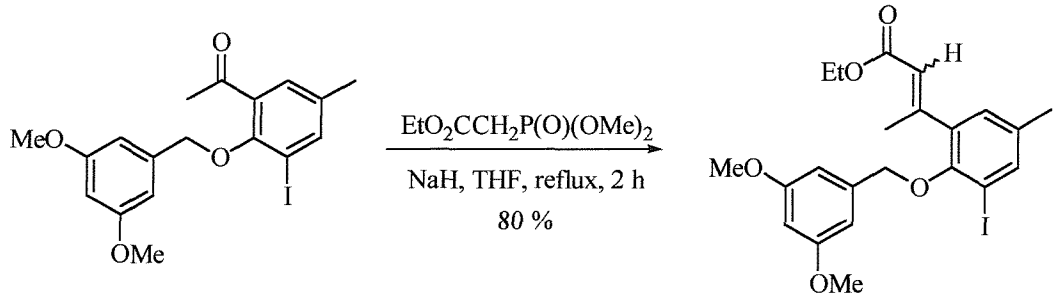
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.80 - 7.79 (1H, m, Ar*H*), 7.36 – 7.35 (1H, m, Ar*H*), 6.70 (2H, d, *J* 2.0 Hz, 2 × Ar*H*), 6.46 (1H, t, *J* 2.0 Hz, Ar*H*), 4.82 (2H, s, OCH_2), 3.82 (6H, s, 2 × OCH_3), 2.57 (3H, s, CH_3), 2.33 (3H, s, CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 200.7 (0, *C*=O), 161.3 (0, 2 × *C*O), 154.8 (0, *C*O), 143.8 (1, *C*H), 138.7 (0, *C*), 136.7 (0, *C*), 135.1 (0, *C*), 130.8 (1, *C*H), 106.6 (1, 2 × *C*H), 100.8 (1, *C*H), 93.7 (0, *C*I), 77.8 (2, O*C*H$_2$), 55.8 (3, 2 × O*C*H$_3$), 30.9 (3, *C*H$_3$), 20.6 (3, *C*H$_3$) ppm.

LRMS (M/z, EI) 426 (M^+, 12 %), 299 ($[M-I]^+$, 9 %), 151 (100 %) amu.

HRMS (M/z, EI) $C_{18}H_{19}IO_4^+$ requires: 426.0328; Found M^+: 426.0331.

Ethyl (*E*)-3-(2-(3,5-dimethoxybenzyloxy)-3-iodo-5-methylphenyl)-2-butenoate & ethyl (*Z*)-3-(2-(3,5-dimethoxybenzyloxy)-3-iodo-5-methylphenyl)-2-butenoate **2.76**



2.75
$C_{18}H_{19}IO_4$ (426)

2.76, *E* : *Z* ~ 2:1
$C_{22}H_{25}IO_5$ (496)

Ester **2.76** was prepared by modifications of the method of Fuganti *et al.*[69] Ethyl dimethylphosphonoacetate (700 μL, 830 mg, 4.23 mmol) was added over 2 minutes to a suspension of sodium hydride (60 % in mineral oil, 205 mg, 5.08 mmol) in tetrahydrofuran (30 mL). After stirring for a further 5 minutes, ketone **2.75** (1.50 g, 3.52 mmol) was added as a solution in tetrahydrofuran (5 mL) and the mixture heated at reflux for 2 hours. After cooling to room temperature, water (20 mL) was added and the mixture extracted with ether (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 – 20 % ether / petrol) yielded firstly *E*-**2.76** (490 mg, 0.98 mmol, 28 %) then a mixture of *E* and *Z* isomers (695 mg, 1.40 mmol, 40 %, *E* : *Z* ~ 2:1) and finally a mixture of Z-**2.76** and recovered **2.75** (380 mg, 0.82 mmol, 23 %, **2.75**:**2.76** ~ 1:1)

Ethyl (*E*)-3-(2-(3,5-dimethoxybenzyloxy)-3-iodo-5-methylphenyl)-2-butenoate *E*-**2.76**

FT – IR (ν_{max}, neat) 2931 m, 2839 w, 1713 s, 1598 s, 1429 m, 1369 m, 1192 s, 1152 s, 1069 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 268 (34000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.62 (1H, d, *J* 1.6 Hz, Ar*H*), 6.97 (1H, d, *J* 1.6 Hz, Ar*H*), 6.63 (2H, d, *J* 2.3 Hz, 2 × Ar*H*), 6.43 (1H, t, *J* 2.3 Hz, Ar*H*), 5.97 (1H, q, *J* 1.3 Hz, COC*H*=C), 4.72 (2H, s, OCH_2), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH$_3$), 3.81 (6H, s, 2 × OCH_3), 2.52 (3H, d, *J* 1.3 Hz, CH=CCH_3), 2.30 (3H, s, ArCH_3), 1.31 (3H, t, *J* 7.1 Hz, OCH$_2$CH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 166.5 (0, *C*=O), 160.9 (0, 2 × *C*O), 155.3 (0, *C*O), 153.1 (0, *C*), 139.9 (1, *C*H), 138.7 (0, *C*), 138.2 (0, *C*), 136.2 (0, *C*), 130.4 (1, *C*H), 120.2 (1, *C*H), 106.5 (1, 2 × *C*H), 100.6 (1, *C*H), 93.2 (0, *C*I), 75.8 (2, OCH$_2$),

60.1 (2, OCH_2), 55.5 (3, 2 × OCH_3), 20.4 (3, CH_3), 20.0 (3, CH_3), 14.4 (3, CH_2CH_3) ppm.

LRMS (M/z, EI) 496 (M^+, 8 %), 481 ($[M-CH_3]^+$, 10 %), 435 (24 %), 369 (12 %), 151 (100 %), 91 (8 %) amu.

HRMS (M/z, ES+) $C_{22}H_{25}IO_5Na^+$ requires: 519.0639; Found $[M+Na]^+$: 519.0637.

Ethyl (*Z*)-3-(2-(3,5-dimethoxybenzyloxy)-3-iodo-5-methylphenyl)-2-butenoate *Z*-**2.76**

FT – IR (ν_{max}, neat) 2945 m, 2828 w, 1717 s, 1598 s, 1444 s, 1430 s, 1372 s, 1205 s, 1155 s, 1069 m cm^{-1}.

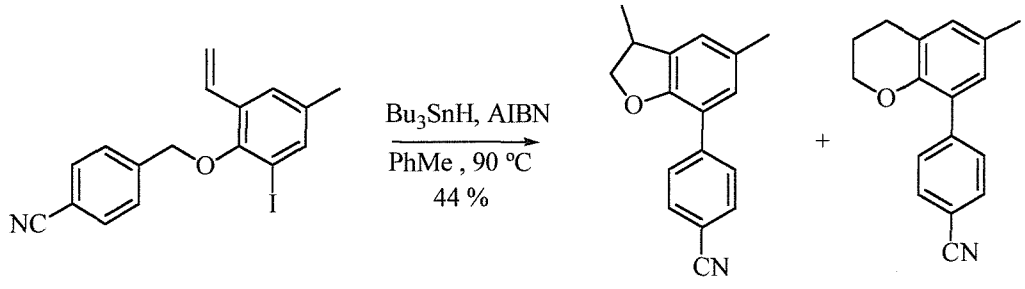
UV (λ_{max}, CH_2Cl_2) 261 (4000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.59 (1H, d, *J* 2.2 Hz, Ar*H*), 6.84 (1H, d, *J* 2.2 Hz, Ar*H*), 6.65 (2H, d, *J* 2.6 Hz, 2 × Ar*H*), 6.44 (1H, t, *J* 2.6 Hz, Ar*H*), 5.97 (1H, q, *J* 1.5 Hz, C=C*H*), 4.83 – 4.75 (2H, br. s, OCH_2), 4.03 (2H, q, *J* 7.4 Hz, OCH_2CH_3), 3.83 (6H, s, 2 × OCH_3), 2.29 (3H, s, $ArCH_3$), 2.19 (3H, d, *J* 1.5 Hz, $CH=CCH_3$), 1.11 (3H, t, *J* 7.4 Hz, OCH_2CH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 165.8 (0, *C*=O), 160.9 (0, 2 × *C*O), 156.0 (0, *C*O), 153.8 (0, *C*), 143.5 (1, *C*H), 139.3 (1, *C*H), 138.4 (0, *C*), 136.5 (0, *C*), 135.9 (0, *C*), 129.7 (1, *C*H), 106.1 (1, 2 × *C*H), 100.2 (1, *C*H), 92.1 (0, *C*I), 75.3 (2, OCH_2), 60.0 (2, OCH_2), 55.5 (3, 2 × OCH_3), 26.3 (3, CH_3), 20.4 (3, CH_3), 14.2 (3, OCH_2CH_3) ppm.

LRMS (M/z, ES+) 519 ($[M+Na]^+$, 40 %), 497 (MH^+, 100 %) amu.

4-(3,5-Dimethyl-2,3-dihydrobenzo[*b*]furan-7-yl)benzonitrile **2.77** and 4-(6-methyl-2,3-dihydro-2*H*-8-chromenyl)benzonitrile **2.78**



2.72 $C_{17}H_{14}INO$ (375)

2.77 $C_{17}H_{15}NO$ (249) 9:1 **2.78** $C_{17}H_{15}NO$ (249)

Iodide **2.72** (430 mg, 1.15 mmol), tributyltin hydride (370 μL, 400 mg, 1.38 mmol) and AIBN (20 mg, 0.12 mmol) were stirred in toluene (25 mL) at 90 °C for 16 hours with

additional portions of tributyltin hydride (150 μL, 160 mg, 0.56 mmol) and AIBN (10 mg, 0.06 mmol) added after 6 and 9 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 20 mL) for 4 hours. The organic phase was diluted with ether (20 mL), washed with water (2 × 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 % ether / petrol) yielded the title compounds **2.77** and **2.78** (125 mg, 0.50 mmol, 44 %, **2.77**:**2.78** ~ 9:1) as a pale yellow oil.

4-(3,5-Dimethyl-2,3-dihydrobenzo[*b*]furan-7-yl)benzonitrile **2.77**

FT – IR (ν_{max}, neat) 2961 m, 2923 m, 2225 s, 1606 s, 1475 s, 1395 m, 1203 s cm^{-1}

UV (λ_{max}, CH_2Cl_2) 321 (7500), 266 (16000), 241 (15000) nm.

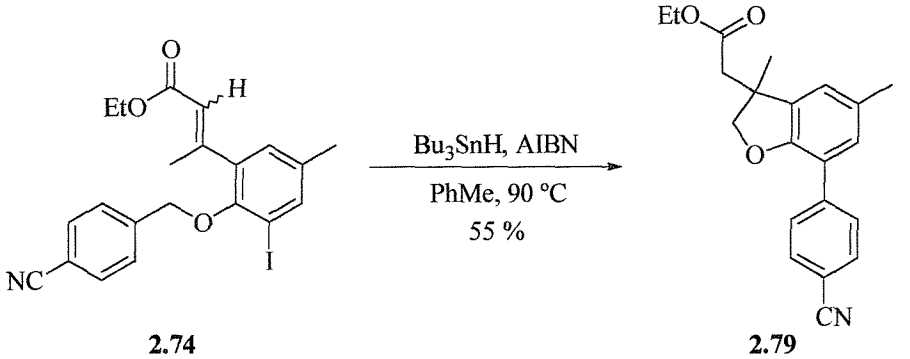
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.87 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.73 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.15 – 7.14 (1H, m, Ar*H*), 7.07 (1H, s, Ar*H*), 4.79 (1H, app. t, *J* 8.8 Hz, OC*H*H), 4.18 (1H, dd, *J* 8.6, 7.5 Hz, OCH*H*), 3.61 (1H, app. sext., *J* 7.5 Hz, ArC*H*CH_3), 2.36 (3H, s, ArCH_3), 1.36 (3H, d, *J* 7.0 Hz, ArCHCH_3) ppm plus signals attributed to **2.78**.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 155.3 (0, *C*O), 142.3 (0, *C*), 134.0 (0, *C*), 132.2 (1, 2 × *C*H), 130.8 (0, *C*), 128.9 (1, 2 × *C*H), 127.9 (1, *C*H), 125.2 (1, *C*H), 119.3 (0, *C*N), 115.6 (0, *C*), 110.4 (0, *C*CN), 78.9 (2, OCH_2), 36.6 (1, ArC*H*CH_3), 21.0 (3, ArCH_3), 19.4 (3, ArCHCH_3) ppm plus signals attributed to **2.78**.

LRMS (M/z, CI) 267 ($[M+NH_4]^+$, 100 %), 249 (M^+, 55 %), 234 (10 %) amu.

HRMS (M/z, EI) $C_{17}H_{15}NO^+$ requires: 249.1124; Found M^+: 249.1150

Ethyl 2-(7-(4-cyanophenyl)-3,5-dimethyl-2,3-dihydrobenzo[*b*]furan-3-yl)acetate **2.79**



2.74
$C_{21}H_{20}INO_3$ (461)

2.79
$C_{21}H_{21}NO_3$ (335)

Ester **2.74** (325 mg, 0.70 mmol, *E* : *Z* ~ 1.3:1), tributyltin hydride (230 μL, 245 mg, 0.85 mmol) and AIBN (12 mg, 0.07 mmol) were heated in toluene (15 mL) at 90 °C for 4 hours

with additional tributyltin hydride (100 μL, 110 mg, 0.37 mmol) and AIBN (10 mg, 0.06 mmol) added after 3 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 15 mL) for 16 hours. The organic phase was diluted with ether (10 mL), washed with water (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 % ether / petrol) yielded the title compound **2.79** (130 mg, 0.39 mmol, 55 %) as a pale yellow oil.

FT – IR (ν_{max}, neat) 2962 m, 2922 m, 2225 m, 1731 s, 1607 m, 1474 m, 1456 m, 1199 s, 1112 m, 981 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 319 (7300), 265 (16000), 242 (11000) nm.

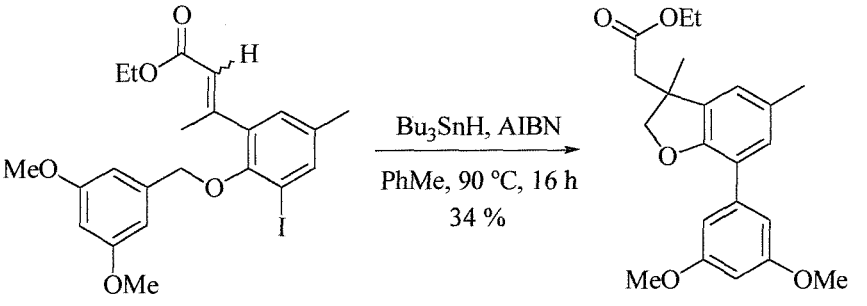
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.83 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.69 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.15 – 7.12 (1H, m, Ar*H*), 6.98 – 6.96 (1H, m, Ar*H*), 4.70 (1H, d, *J* 9.0 Hz, OC*H*H), 4.37 (1H, d, *J* 9.0 Hz, OCH*H*), 4.14 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 2.72 (1H, d, *J* 15.0 Hz, C(=O)C*H*H), 2.67 (1H, d, *J* 15.0 Hz, C(=O)CH*H*), 2.37 (3H, s, $ArCH_3$), 1.47 (3H, s, CH_3), 1.24 (3H, t, *J* 7.0 Hz, OCH_2CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 171.4 (0, *C*=O), 154.9 (0, *C*O), 142.3 (0, *C*), 136.2 (0, *C*), 132.5 (1, 2 × *C*H), 131.3 (0, *C*), 129.2 (1, 2 × *C*H), 128.8 (1, *C*H), 124.4 (1, *C*H), 121.6 (0, *C*), 119.5 (0, *C*N), 110.8 (0, *C*CN), 83.1 (2, OCH_2), 61.0 (2, OCH_2CH_3), 44.8 (2, $C(=O)CH_2$), 44.2 (0, $ArCCH_3$), 25.6 (3, CH_3), 21.3 (3, $ArCH_3$), 14.6 (3, OCH_2CH_3) ppm.

LRMS (M/z, EI) 335 (M^+, 38 %), 248 (100 %), 206 (46 %), 190 (25 %) amu.

HRMS (M/z, EI) $C_{21}H_{21}NO_3^+$ requires 335.1521. Found M^+: 335.1529.

Ethyl 2-(7-(3,5-dimethoxyphenyl)-3,5-dimethyl-2,3-dihydrobenzo[*b*]furan-3-yl)acetate **2.80**



2.76
$C_{22}H_{25}IO_5$ (496)

2.80
$C_{22}H_{26}O_5$ (370)

Iodide **2.76** (700 mg, 1.41 mmol), tributyltin hydride (460 μL, 495 mg, 1.70 mmol) and AIBN (25 mg, 0.14 mmol) were stirred in toluene (30 mL) at 90 °C for 20 hours with additional portions of tributyltin hydride (200 μL, 215 mg, 0.74 mmol) and AIBN (15 mg, 0.09 mmol) added after 8 and 16 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 20 mL) for 16 hours. The organic phase was diluted with ether (20 mL) and washed with water (2 × 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 – 10 % ether / petrol) yielded the title compound **2.80** (175 mg, 0.47 mmol, 34 %) as a colourless oil.

FT – IR (ν_{max}, neat) 2862 m, 2930 m, 2841 w, 1732 s, 1592 s, 1456 m, 1203 s, 1154 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 296 (7100), 250 (11000) nm.

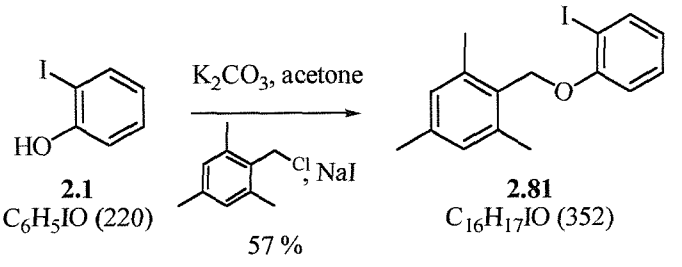
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.13 – 7.12 (1H, m, Ar*H*), 6.91 – 6.90 (1H, m, Ar*H*), 6.87 (2H, d, *J* 2.3 Hz, 2 × Ar*H*), 6.45 (1H, t, *J* 2.3 Hz, Ar*H*), 4.68 (1H, d, *J* 9.3 Hz, OC*H*H), 4.35 (1H, d, *J* 9.3 Hz, OCH*H*), 4.16 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 3.84 (6H, s, 2 × OCH_3), 2.72 (1H, d, *J* 15.1 Hz, C(=O)C*H*H), 2.67 (1H, d, *J* 15.1 Hz, C(=O)CH*H*), 2.35 (3H, d, *J* 0.5 Hz, $ArCH_3$), 1.46 (3H, s, CH_3), 1.25 (3H, t, *J* 7.0 Hz, OCH_2CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 171.6 (0, *C*=O), 161.1 (0, 2 × *C*O), 154.6 (0, *C*O), 139.5 (0, *C*), 135.8 (0, *C*), 130.8 (0, *C*), 129.1 (1, *C*H), 123.7 (0, *C*), 123.0 (1, *C*H), 107.1 (1, 2 × *C*H), 99.7 (1, *C*H), 82.9 (2, OCH_2), 60.9 (2, OCH_2), 55.8 (3, 2 × OCH_3), 44.8 (2, C(=O)CH_2), 44.3 (0, Ar*C*CH_3), 25.4 (3, CH_3), 21.3 (3, $ArCH_3$), 14.6 (3, OCH_2CH_3) ppm.

LRMS (M/z, EI) 370 (M^+, 4 %), 283 (8 %), 207 (34 %), 154 (16 %), 44 (100 %) amu.

HRMS $C_{22}H_{26}O_5Na^+$ requires: 393.1672; Found $[M+Na]^+$: 393.1668.

1-(2-Iodophenoxymethyl)-2,4,6-trimethylbenzene **2.81**



1-(2-Iodophenoxymethyl)-2,4,6-trimethylbenzene **2.81** was prepared by a modification of the method of Sheppard *et al.*[160] 2-Iodophenol **2.1** (2.74 g, 12.45 mmol), potassium carbonate (2.79 g, 20.16 mmol), sodium iodide (1.87 g, 12.45 mmol) and 2,4,6-trimethylbenzyl chloride (2.00 g, 11.86 mmol) were stirred in acetone (30 mL) at room temperature for 22 hours. The mixture was filtered and the solvent removed under reduced pressure. Purification by column chromatography (silica gel, petrol) yielded the title compound **2.81** (2.37 g, 6.73 mmol, 57 %) as a white solid.

MP 56 – 58 °C (petrol)

FT – IR (ν_{max}, neat) 1614 s, 1581 s, 1568 s, 1470 s, 1438 s, 1372 m, 1273 s, 1240 s, 1120 m, 1046 m, 1017 s, 992 s cm^{-1}.

UV (λ_{max}, MeOH) 274 (2930), 223 (20920) nm.

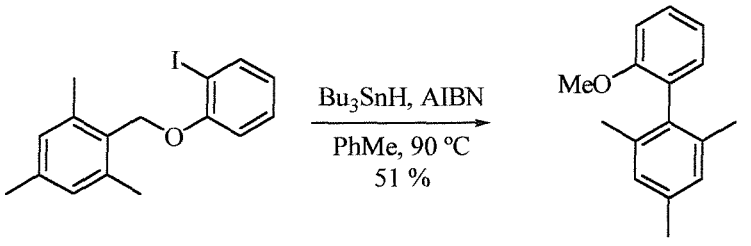
^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.86 (1H, d, *J* 7.7 Hz, Ar*H*), 7.40 (1H, app. t, *J* 8.1 Hz, Ar*H*), 7.07 (1H, d, *J* 8.1 Hz, Ar*H*), 6.99 (2H, s, 2 × Ar*H*), 6.81 (1H, app. t, *J* 7.7 Hz, Ar*H*), 5.12 (2H, s, OCH_2), 2.48 (6H, s, 2 × CH_3), 2.39 (3H, s, CH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 158.1 (0, *C*O), 139.8 (0, *C*), 139.8 (1, *C*H), 138.4 (0, *C*), 138.4 (0, 2 × *C*), 129.7 (1, *C*H), 129.3 (1, 2 × *C*H), 123.0 (1, *C*H), 113.0 (1, *C*H), 87.3 (0, *C*I), 66.3 (2, OCH_2), 21.4 (3, CH_3), 20.0 (3, 2 × CH_3) ppm.

LRMS (M/z, CI) 352 (M^+, 1 %), 219 (4 %), 191 (4 %), 133 (100 %), 117 (21 %), 91 (19 %) amu.

CHN $C_{16}H_{17}IO$ requires: C 54.56, H 4.86; Found: C 54.53, H 4.82.

2'-Methoxy-2,4,6-trimethyl-1,1'-biphenyl **2.82**



2.81
$C_{16}H_{17}IO$ (352)

2.82
$C_{16}H_{18}O$ (226)

Iodide **2.81** (800 mg, 2.27 mmol) was dissolved in toluene (70 mL). Tributyltin hydride (915 μL, 990 mg, 3.41 mmol) and AIBN (60 mg, 0.37 mmol) were added and the mixture stirred at 90 °C for 16 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 20 mL) for 16 hours. The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic phases were dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (silica gel, petrol) provided the title compound **2.82** (260 mg, 1.15 mmol, 51 %) as an off white solid.[174,175]

MP 47 – 49 °C (petrol) lit. 55 – 56 °C.[175]

FT – IR (ν_{max}, neat) 1599 m, 1500 m, 1478 s, 1464 s, 1434 s, 1255 s, 1235 s, 1118 m, 1052 m, 1028 m, 1004 m cm^{-1}.

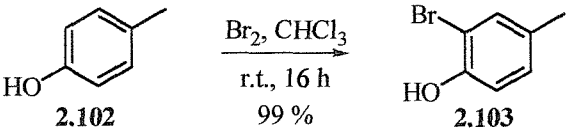
UV (λ_{max}, MeOH) 274 (2825) nm.

^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.40 – 7.35 (1H, m, Ar*H*), 7.10 – 7.00 (3H, m, 3 × Ar*H*), 7.00 (2H, s, 2 × Ar*H*), 3.79 (3H, OCH_3), 2.39 (3H, s, CH_3), 2.05 (6H, s, 2 × CH_3) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 156.9 (0, *C*O), 136.7 (0, *C*), 136.7 (0, 2 × *C*), 135.5 (0, *C*), 131.1 (1, *C*H), 129.6 (0, *C*), 128.4 (1, *C*H), 128.1 (1, 2 × *C*H), 120.8 (1, *C*H), 110.9 (1, *C*H), 55.6 (3, OCH_3), 21.4 (3, CH_3), 20.6 (3, 2 × CH_3) ppm.

LRMS (M/z, CI) 226 (M^+, 100 %), 211 ($[M-CH_3]^+$, 57 %), 195 ($[M-OCH_3]^+$, 48 %), 178 (20 %), 165 (29 %), 152 (20 %) amu.

2-Bromo-4-methylphenol **2.103**



2.102 C_7H_8O (108) — **2.103** C_7H_7BrO (187)

p-Cresol **2.102** (10.10 g, 93.52 mmol) was dissolved in chloroform (40 mL) and cooled to 0 °C. Bromine (5.0 mL, 15.60 g, 97.58 mmol) was added dropwise as a solution in chloroform (20 mL) and the solution was stirred at room temperature for 16 hours. The solvent was removed under reduced pressure then purified by column chromatography (silica gel, $CHCl_3$) to give **2.103** (17.35 g, 92.78 mmol, 99 %) as a pale yellow oil.[176]

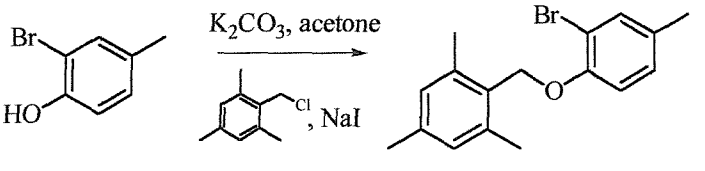
FT – IR (ν_{max}, neat) 3503 br. m, 1507 m, 1496 s, 1282 m, 1252 m, 1210 m, 1180 m, 1040 m cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.30 (1H, d, *J* 1.8 Hz, Ar*H*), 7.02 (1H, dd, *J* 8.1, 2.2 Hz, Ar*H*), 6.91 (1H, d, *J* 8.1 Hz, Ar*H*), 5.33 (1H, br. s, O*H*), 2.30 (3H, s, CH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 150.1 (0, *C*O), 132.3 (1, *C*H), 131.6 (0, *C*), 129.9 (1, *C*H), 115.9 (1, *C*H), 110.0 (0, *C*Br), 20.4 (3, *C*H_3) ppm.

LRMS (M/z, CI) 188 (M{^{81}Br}$^+$, 68%), 186 (M{^{79}Br}$^+$, 74 %), 107 ([M-Br]$^+$, 100 %) amu.

1-(2-Bromo-4-methylphenoxymethyl)-2,4,6-trimethylbenzene **2.87**



2.103 C_7H_7BrO (187) — 63 % — **2.87** $C_{17}H_{19}BrO$ (319)

2-Bromo-4-methylphenol **2.103** (1.16 g, 6.23 mmol), potassium carbonate (1.07 g, 7.71 mmol), 2,4,6-trimethylbenzyl chloride (1.00 g, 5.93 mmol), and sodium iodide (935 mg, 6.23 mmol) were stirred in acetone at room temperature for 16 hours. Filtration, concentration of the filtrate *in vacuo* and purification by column chromatography (silica gel, petrol) provided the title compound **2.87** (1.19 g, 3.73 mmol, 63 %) as a white solid.

MP 96 – 99 °C (ether / petrol)

FT – IR (ν_{max}, neat) 1606 m, 1494 s, 1277 m, 1244 s, 1046 s cm^{-1}.

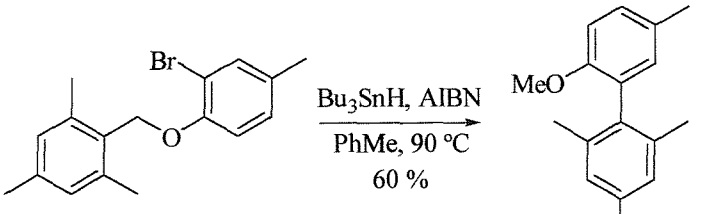
UV (λ_{max}, MeOH) 278 (3190) nm.

^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.39 (1H, d, *J* 1.8 Hz, Ar*H*), 7.05 (1H, dd, *J* 7.7, 1.8 Hz, Ar*H*), 6.94 (1H, d, *J* 7.7 Hz, Ar*H*), 6.90 (2H, s, 2 × Ar*H*), 5.05 (2H, s, OCH_2), 2.40 (6H, s, 2 × CH_3), 2.28 (6H, s, 2 × CH_3) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 153.7 (0, *C*O), 138.3 (0, 3 × *C*), 134.0 (1, *C*H), 132.1 (0, *C*), 129.8 (0, *C*), 129.2 (1, 2 × *C*H), 129.0 (1, *C*H), 114.6 (1, *C*H), 112.8 (0, *C*), 68.6 (2, OCH_2), 21.2 (3, CH_3), 20.4 (3, CH_3), 19.8 (3, 2 × CH_3) ppm.

LRMS (M/z, CI) 320 ($M^+\{^{81}Br\}$, 0.5 %), 318 ($M^+\{^{79}Br\}$, 0.5 %), 189 (4 %), 187 (4 %), 133 (100 %), 117 (21 %), 91 (20 %), 78 (12 %) amu.

2'-Methoxy-2,4,5',6-tetramethyl-1,1'-biphenyl **2.88**



2.87
$C_{17}H_{19}BrO$ (319)

2.88
$C_{17}H_{20}O$ (240)

Bromide **2.87** (400 mg, 1.25 mmol), tributyltin hydride (500 μL, 545 mg, 1.88 mmol) and AIBN (35 mg, 0.20 mmol) were stirred in toluene (40 mL) at 90 °C for 16 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride solution (10 % w/v, 20 mL) for 16 hours. The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic phases were dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (silica gel, 0 – 0.5 % ether / petrol) yielded the title compound **2.88** (170 mg, 0.75 mmol, 60 %) as a colourless oil.

FT – IR (ν_{max}, neat) 2918 m, 1504 s, 1480 m, 1462 m, 1262 m, 1235 s, 1042 m cm^{-1}.

UV (λ_{max}, MeOH) 281 (7290) nm.

^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.23 (1H, d, *J* 8.1 Hz, Ar*H*), 7.05 (2H, s, 2 × Ar*H*), 6.97 (1H, d, *J* 8.1 Hz, Ar*H*), 6.96 (1H, s, Ar*H*), 3.81 (3H, s, OCH_3), 2.44 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.11 (6H, s, 2 × CH_3) ppm.

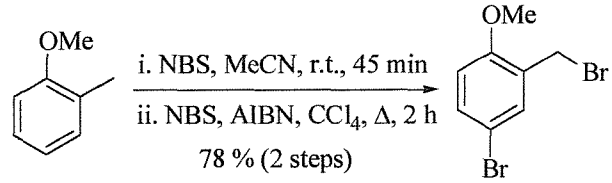
^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 154.9 (0, *C*O), 136.7 (0, 3 × *C*), 135.6 (0, *C*), 131.8 (1, *C*H), 129.9 (0, *C*), 129.5 (0, *C*), 128.8 (1, *C*H), 128.2 (1, 2 × *C*H), 111.0 (1, *C*H), 55.8 (3, OCH_3), 21.4 (3, CH_3), 20.8 (3, CH_3), 20.7 (3, 2 × CH_3) ppm.

LRMS (M/z, CI) 240 (M^+, 100 %), 225 ($[M-CH_3]^+$, 38 %), 209 ($[M-OCH_3]^+$, 42 %), 195 (18 %), 165 (19 %), 152 (11 %) amu.

HRMS (M/z, EI) $C_{17}H_{20}O^+$ requires: 240.1514; Found M^+: 240.1507.

8.3 Experimental for Chapter 3

4-Bromo-2-(bromomethyl)anisole **3.29**



3.28 $C_8H_{10}O$ (122)

3.29 $C_8H_8Br_2O$ (280)

2-Methylanisole **3.28** (20.3 mL, 20.00 g, 0.16 mol) was dissolved in acetonitrile (650 mL) and *N*-bromosuccinimide (30.6 g, 0.17 mol) added. The mixture was stirred at room temperature for 45 minutes then concentrated *in vacuo*. The resulting solid was diluted with carbon tetrachloride (200 mL), filtered and the filtrate further diluted with carbon tetrachloride (400 mL). *N*-Bromosuccinimide (30.6 g, 0.17 mol) was added and the mixture stirred at reflux for 2 hours with AIBN (500 mg, 0.61 mmol) added portionwise over 1½ hours. After cooling to room temperature, the mixture was filtered and the filtrate concentrated *in vacuo*. Recrystallisation from petrol yielded the title compound **3.29** (34.92 g, 0.12 mol, 78 %) as off-white needles.

MP 47 – 49 °C (petrol).

FT – IR (ν_{max}, neat) 1488 s, 1462 m, 1299 m, 1276 m, 1256 s, 1216 m, 1179 m, 1027 m, 808 m cm^{-1}.

UV (λ_{max}, MeOH) 295 (3730), 238 (14900) nm.

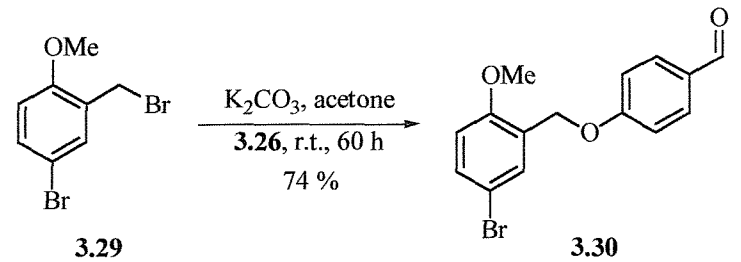
^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.48 (1H, d, *J* 2.6 Hz, Ar*H*), 7.38 (1H, dd, *J* 8.8, 2.6 Hz, Ar*H*), 6.72 (1H, d, *J* 8.8 Hz, Ar*H*), 4.49 (2H, s, CH_2Br), 3.88 (3H, s, OCH_3) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 156.7 (0, *C*O), 133.6 (1, *C*H), 132.9 (1, *C*H), 128.3 (0, *C*), 112.8 (1, *C*H), 112.7 (0, *C*Br), 56.0 (3, OCH_3), 27.8 (2, CH_2Br) ppm.

LRMS (M/z, CI) 282 ($M^+\{^{81}Br, ^{81}Br\}$, 9 %), 280 ($M^+\{^{79}Br, ^{81}Br\}$, 18 %), 278 ($M^+\{^{79}Br, ^{79}Br\}$, 8 %), 201 ($[M-Br\{^{81}Br\}]^+$, 100 %), 199 ($[M-Br\{^{79}Br\}]^+$, 92 %), 171 (25 %), 90 (23 %) amu.

CHN $C_8H_8Br_2O$ requires: C 34.32, H 2.88; Found: C 34.13, H 2.87.

4-(5-Bromo-2-methoxybenzyloxy)benzaldehyde **3.30**



3.29
$C_8H_8Br_2O$ (280)

3.30
$C_{15}H_{13}BrO_3$ (321)

4-Hydroxybenzaldehyde **3.26** (8.40 g, 68.50 mmol), 4-bromo-2-(bromomethyl)anisole **3.29** (17.50 g, 62.50 mmol) and potassium carbonate (12.96 g, 93.80 mmol) were stirred in acetone (200 mL) at room temperature for 60 hours. The mixture was filtered and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded the title compound **3.30** (16.30 g, 50.78 mmol, 74 %) as a white solid.

MP 83 – 85 °C (ether / petrol).

FT – IR (ν_{max}, neat) 1693 s, 1600 s, 1578 m, 1509 m, 1488 m, 1254 s, 1159 s, 1110 m cm^{-1}.

UV (λ_{max}, MeOH) 363 (480), 347 (710), 264 (12680), 227 (8830), 224 (9050) nm.

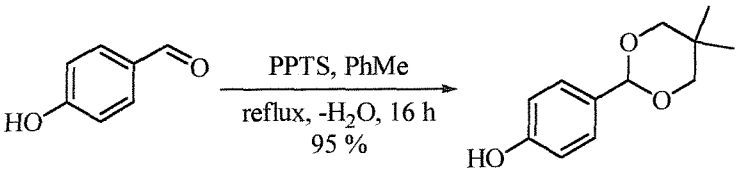
^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 9.91 (1H, s, C*H*O), 7.86 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.57 (1H, d, *J* 2.6 Hz, Ar*H*), 7.42 (1H, dd, *J* 8.8, 2.6 Hz, Ar*H*), 7.11 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 6.80 (1H, d, *J* 8.8 Hz, Ar*H*), 5.15 (2H, s, OCH_2), 3.87 (3H, s, OCH_3) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 190.8 (1, *C*HO), 163.7 (0, *C*O), 155.7 (0, *C*O), 132.0 (1, 2 × *C*H), 131.8 (1, *C*H), 131.0 (1, *C*H), 130.2 (0, *C*), 126.6 (0, *C*), 115.1 (1, 2 × *C*H), 113.0 (0, *C*Br), 112.0 (1, *C*H), 64.6 (2, OCH_2), 55.9 (3, OCH_3) ppm.

LRMS (M/z, CI) 323 ($MH^+\{^{81}Br\}$, 7 %), 321 ($MH^+\{^{79}Br\}$, 7 %), 201 (100 %), 199 (95 %), 171 (22 %), 120 (8 %), 90 (33 %), 77 (24 %) amu.

CHN $C_{15}H_{13}BrO_3$ requires: C 56.10, H 4.08; Found: C 56.06, H 4.06.

2-(4-hydroxyphenyl)-5,5-dimethyl-1,3-dioxane **3.31**



3.26
$C_7H_6O_2$ (122)

3.31
$C_{12}H_{16}O_3$ (208)

4-Hydroxybenzaldehyde **3.26** (12.23 g, 0.10 mol), neopentyl glycol (20.83 g, 0.20 mol) and pyridinium *p*-toluenesulfonate (1.26 g, 5.00 mmol) were stirred at reflux in toluene (300 mL) under a soxhlet containing 4Å molecular sieves for 16 hours. After cooling to room temperature, the mixture was washed with sodium hydrogen carbonate (sat. aq., 3 × 80 mL), brine (40 mL) and the organic phase was dried ($MgSO_4$). Concentration *in vacuo* provided the title phenol **3.31** (19.70 g, 0.095 mol, 95 %) as an off-white solid.

MP 133 – 134 °C (ether / petrol) lit. 135 – 136 °C (benzene).[177]

FT – IR (ν_{max}, neat) 3362 br. s, 2955 m, 2851 m, 1614 m, 1599 m, 1520 s, 1470 m, 1454 m, 1392 s, 1216 s, 1086 s, 1036 m, 1014 m cm^{-1}.

UV (λ_{max}, MeOH) 272 (2000), 223 (8700) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.34 (2H, d, *J* 8.7 Hz, 2 × Ar*H*), 6.70 (2H, d, *J* 8.7 Hz, 2 × Ar*H*), 6.07 (1H, br. s, O*H*), 5.35 (1H, s, OC*H*O), 3.77 (2H, d, *J* 11.2 Hz, 2 × OC*H*H), 3.64 (2H, d, *J* 11.2 Hz, 2 × OCH*H*), 1.31 (3H, s, CH_3), 0.80 (3H, s, CH_3) ppm.

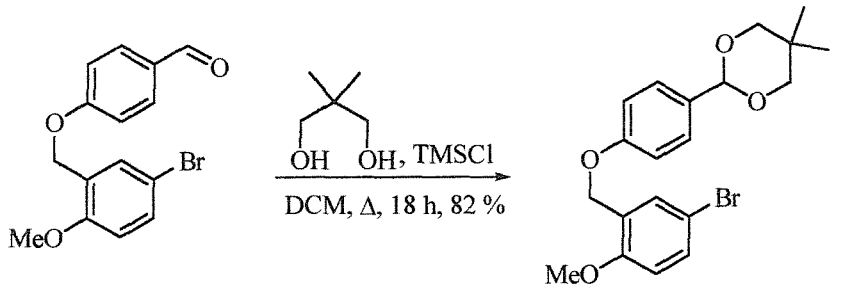
^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 156.5 (0, *C*O), 130.8 (0, *C*), 127.8 (1, 2 × *C*H), 115.4 (1, 2 × *C*H), 102.0 (1, O*C*HO), 77.8 (2, 2 × OCH_2), 30.3 (0, *C*(CH_3)$_2$), 23.2 (3, *C*H_3), 22.0 (3, *C*H_3) ppm.

LRMS (M/z, CI) 209 (MH^+, 100 %), 121 (10 %) amu.

CHN $C_{12}H_{16}O_3$ requires: C 69.21, H 7.74; Found: C 69.28, H 7.73.

2-(4-(5-Bromo-2-methoxybenzyloxy)phenyl)-5,5-dimethyl-1,3-dioxane **3.25**

Method 1

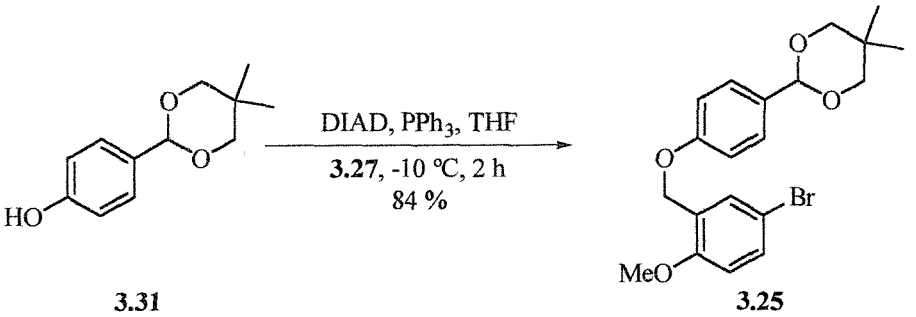


3.30
$C_{15}H_{13}BrO_3$ (321)

3.25
$C_{20}H_{23}BrO_4$ (407)

3.25 was synthesised by modifications to the method of Chan *et al.*[96] To a solution of neopentyl glycol (3.57 g, 34.27 mmol) in dichloromethane (80 mL) was added firstly aldehyde **3.30** (5.00 g, 15.58 mmol) and then chlorotrimethylsilane (8.70 mL, 7.45 g, 68.54 mmol). The mixture was stirred at reflux for 18 hours. After cooling to room temperature, a solution of sodium hydrogen carbonate (5 % w/v, 80 mL) was added and the aqueous phase extracted with ether (2 × 80 mL). The combined organic phases were washed with brine (80 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded firstly the title acetal **3.25** (5.17 g, 12.70 mmol, 82 %) as a white solid and then a mixture of title acetal **3.25** and recovered starting material **3.30** (1.10 g).

Method 2



3.31
$C_{12}H_{16}O_3$ (208)

3.25
$C_{20}H_{23}BrO_4$ (407)

Bromide **3.25** was prepared using the method of Gao *et al.*[178] Thus, phenol **3.31** (2.00 g, 9.62 mmol), 5-bromo-2-methoxybenzyl alcohol **3.27** (1.90 g, 8.75 mmol) and triphenylphosphine (2.52 g, 9.62 mmol) were dissolved in tetrahydrofuran (30 mL) and cooled to –10 ° C. Diisopropyl azodicarboxylate (1.9 mL, 1.95 g, 9.62 mmol) was added dropwise over 2 minutes and the mixture allowed to stir at *ca.* –10 °C for 2 hours. Concentration *in vacuo* and

purification by column chromatography (silica gel, 20 % ether / petrol) yielded the title compound **3.25** (3.00 g, 7.37 mmol, 84 %) as a white solid.

MP 121 – 122 °C (ether / petrol).

FT – IR (ν_{max}, neat) 1614 m, 1516 s, 1489 s, 1385 m, 1248 s, 1100 s, 1033 m cm^{-1}.

UV (λ_{max}, MeOH) 278 (1400), 226 (8400) nm.

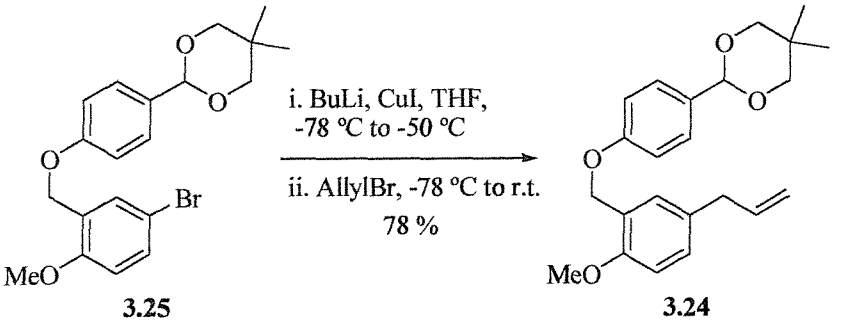
^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.58 (1H, d, *J* 2.5 Hz, Ar*H*), 7.45 (2H, d, *J* 7.9 Hz, 2 × Ar*H*), 7.38 (1H, dd, *J* 8.7, 2.5 Hz, Ar*H*), 6.98 (2H, d, *J* 7.9 Hz, 2 × Ar*H*), 6.77 (1H, d, *J* 8.7 Hz, Ar*H*), 5.36 (1H, s, OC*H*O), 5.07 (2H, s, OCH_2), 3.85 (3H, s, OCH_3), 3.76 (2H, d, *J* 11.2 Hz, 2 × OC*H*H), 3.64 (2H, d, *J* 11.2 Hz, 2 × OCH*H*), 1.31 (3H, s, CH_3), 0.81 (3H, s, CH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 159.2 (0, *C*O), 155.8 (0, *C*O), 131.5 (0, *C*), 131.4 (1, *C*H), 130.9 (1, *C*H), 127.8 (0, *C*), 127.6 (1, 2 × *C*H), 114.7 (1, 2 × *C*H), 113.1 (0, *C*Br), 112.0 (1, *C*H), 101.8 (1, O*C*HO), 77.8 (2, 2 × OCH_2C), 64.5 (2, OCH_2Ar), 55.8 (3, OCH_3), 30.4 (0, *C*(CH_3)$_2$), 23.2 (3, C(*C*H_3)(CH_3)), 22.1 (3, C(CH_3)(*C*H_3)) ppm.

LRMS (M/z, CI) 409 (MH$^+${^{81}Br}, 90 %), 407 (MH$^+${^{79}Br}, 98 %), 329 (38 %), 209 (100 %), 121 (40 %), 107 (34 %) amu.

CHN $C_{20}H_{23}BrO_4$ requires: C 58.98, H 5.69; Found: C 58.83, H 5.71.

2-(4-(5-Allyl-2-methoxybenzyloxy)phenyl)-5,5-dimethyl-1,3-dioxane **3.24**



3.25
$C_{20}H_{23}BrO_4$ (407)

3.24
$C_{23}H_{28}O_4$ (368)

To a suspension of copper(I) iodide (235 mg, 1.23 mmol) in tetrahydrofuran (30 mL) was added bromide **3.25** (940 mg, 2.31 mmol) and the mixture cooled to –78 °C. *n*-Butyllithium (1.88 M in hexanes, 1.44 mL, 2.70 mmol) was added dropwise over 5 minutes. The mixture was allowed to warm to –50 °C over 30 minutes before re-cooling to –78 °C. Allyl bromide (415 μL, 595 mg, 4.91 mmol) was added dropwise over 5 minutes and the mixture allowed to stir for 1½ hours while warming to room temperature. Brine (20 mL) was added and the

aqueous phase extracted with ether (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. Purification by column chromatography (20 % ether / petrol) yielded the title compound **3.24** (660 mg, 1.79 mmol, 78 %) as a white solid.

MP 59 – 60 °C (petrol).

FT – IR (ν_{max}, neat) 2953 m, 1614 m, 1515 s, 1386 m, 1248 s, 1172 m, 1101 s, 1034 s cm^{-1}.

UV (λ_{max}, MeOH) 276 (3800), 224 (23000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.47 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 7.30 (1H, d, *J* 2.0 Hz, Ar*H*), 7.11 (1H, dd, *J* 7.8, 2.0 Hz, Ar*H*), 6.97 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 6.71 (1H, d, *J* 7.8 Hz, Ar*H*), 5.96 (1H, ddt, *J* 16.9, 10.3, 6.8 Hz, C*H*=CH_2), 5.38 (1H, s, OC*H*O), 5.13 – 4.95 (4H, m, OCH_2 & =CH_2), 3.82 (3H, s, OCH_3), 3.76 (2H, d, *J* 10.5 Hz, 2 × OC*H*HC), 3.68 (2H, d, *J* 10.5 Hz, 2 × OCH*H*C), 3.31 (2H, d, *J* 6.3 Hz, CH_2CH=CH_2), 1.29 (3H, s, CH_3), 0.78 (3H, s, CH_3) ppm.

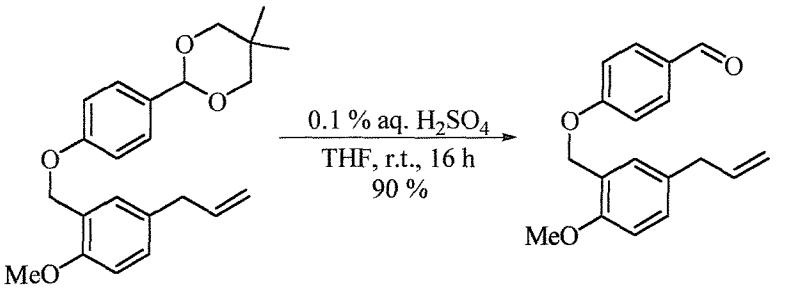
^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 159.9 (0, *C*O), 155.7 (0, *C*O), 138.2 (1, *C*H), 132.5 (0, *C*), 131.5 (0, *C*), 129.3 (1, *C*H), 129.2 (1, *C*H), 127.8 (1, 2 × *C*H), 125.7 (0, *C*), 115.9 (2, =CH_2), 115.1 (1, 2 × *C*H), 110.8 (1, *C*H), 102.2 (1, O*C*HO), 78.1 (1, 2 × O*C*HH), 65.5 (2, OCH_2Ar), 56.0 (3, OCH_3), 39.8 (2, CH_2CH=CH_2), 30.6 (0, *C*$(CH_3)_2$), 23.5 (3, CH_3), 22.3 (3, CH_3) ppm.

LRMS (M/z, CI) 369 (MH^+, 20 %), 209 (100 %), 162 (66 %), 147 (28 %), 107 (24 %) amu.

HRMS (M/z, ES+) $C_{46}H_{56}O_8Na^+$ requires: 759.3867; Found $[2M+Na]^+$: 759.3878.

CHN $C_{23}H_{28}O_4$ requires: C 74.97, H 7.66; Found: C 74.75, H 7.76.

4-(5-Allyl-2-methoxybenzyloxy)phenylbenzaldehyde **3.23**



3.24
$C_{23}H_{28}O_4$ (368)

3.23
$C_{18}H_{18}O_3$ (282)

Acetal **3.24** (600 mg, 1.63 mmol) was dissolved in tetrahydrofuran (30 mL) to which was added sulfuric acid (0.1 % v/v, 30 mL). The mixture was stirred at room temperature for 16 hours and then extracted with ether (5 × 20 mL). The combined organic phases were washed with brine (20 mL), dried (K_2CO_3) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded the title compound **3.23** (415 mg, 1.47 mmol, 90 %) as a colourless oil.

FT - IR (ν_{max}, neat) 2932 w, 1694 s, 1600 s, 1577 m, 1506 s, 1463 m, 1312 m, 1256 s, 1159 s, 1032 m cm^{-1}.

UV (λ_{max}, MeOH) 282 (39000), 221 (40000) nm.

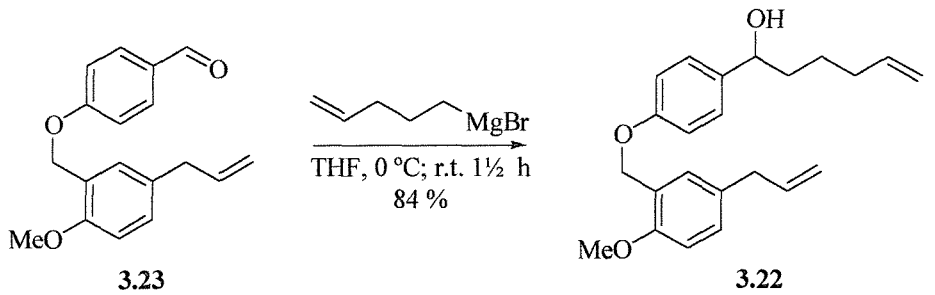
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 9.89 (1H, s, C*H*O), 7.86 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.20 (1H, d, *J* 2.2 Hz, Ar*H*), 7.15 (1H, dd, *J* 8.5, 2.2 Hz, Ar*H*), 7.08 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 6.83 (1H, d, *J* 8.5 Hz, Ar*H*), 5.96 (1H, ddt, *J* 11.0, 9.2, 6.6 Hz, C*H*=CH_2), 5.17 (2H, s, OCH_2), 5.07 – 4.99 (2H, m, =CH_2), 3.82 (3H, s, OCH_3), 3.46 (2H, d, *J* 6.6 Hz, CH_2CH=CH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 191.1 (1, *C*HO), 164.2 (0, *C*O), 155.5 (0, *C*O), 137.8 (1, *C*H), 132.3 (0, *C*), 132.1 (1, 2 × *C*H), 130.1 (0, *C*), 129.5 (1, *C*H), 129.3 (1, *C*H), 124.2 (0, *C*), 115.8 (2, =CH_2), 115.3 (1, 2 × *C*H), 110.6 (1, *C*H), 65.6 (2, OCH_2), 55.7 (3, OCH_3), 39.5 (2, CH_2CH=CH_2) ppm.

LRMS (M/z, CI) 283 (MH^+, 66 %), 178 (16 %), 162 (100 %), 147 (4 %0, 123 (80 %), 91 (27 %) amu.

HRMS (M/z, EI) $C_{18}H_{18}O_3^+$ requires: 282.1256; Found M^+: 282.1261.

1-(4-(5-Allyl-2-methoxybenzyloxy)phenyl)-5-hexen-1-ol **3.22**



3.23
$C_{18}H_{18}O_3$ (282)

3.22
$C_{23}H_{28}O_3$ (352)

To a stirred suspension of magnesium powder (70 mg, 2.77 mmol) in ether (10 mL) was added 5-bromo-1-pentene (250 µL, 317 mg, 2.13 mmol) and a crystal of iodine. The mixture was stirred at room temperature for 30 minutes before heating briefly to reflux. After 1 hour, the solution was added *via* cannula to a cooled (0 °C) solution of aldehyde **3.23** (400 mg, 1.42 mmol) in tetrahydrofuran (30 mL). After stirring at room temperature for 1½ hours, a solution of ammonium chloride (sat. aq., 20 mL) was added and the mixture was extracted with ether (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 30 % ether / petrol) yielded the title compound 3.**22** (420 mg, 1.19 mmol, 84 %) as a colourless oil.

FT – IR (ν_{max}, neat) 3404 br. m, 2933 m, 1610 m, 1509 s, 1461 m, 1246 s, 1173 m, 1035 m cm^{-1}.

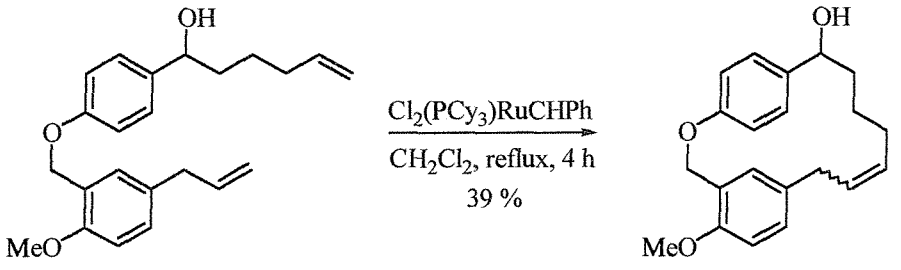
UV (λ_{max}, MeOH) 274 (7000), 221 (33000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.30 – 7.20 (3H, m, 3 × Ar*H*), 7.13 (1H, dd, *J* 8.5, 2.0 Hz, Ar*H*), 6.99 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 6.83 (1H, d, *J* 8.5 Hz, Ar*H*), 5.91 (1H, ddt, *J* 13.6, 10.3, 6.6 Hz, C*H*=CH_2), 5.81 (1H, ddt, *J* 13.6, 10.3, 6.6 Hz, C*H*=CH_2), 5.13 – 4.93 (4H, m, 2 × =CH_2), 5.09 (2H, s, OCH_2), 4.64 (1H, td, *J* 7.0, 3.3 Hz, ArC*H*OH), 3.85 (3H, s, OCH_3), 3.35 (2H, d, *J* 6.6 Hz, ArCH_2CH=CH_2), 2.10 – 2.00 (2H, m, CH(OH)CH_2), 1.80 – 1.60 (3H, m, CH_2 & O*H*), 1.30 – 1.18 (2H, m, CH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 158.7 (0, *C*O), 155.5 (0, *C*O), 138.8 (1, *C*H=CH), 137.1 (0, *C*), 132.2 (0, *C*), 129.2 (1, *C*H), 129.0 (1, *C*H), 128.8 (1, *C*H), 127.3 (1, 2 × *C*H), 125.3 (0, *C*), 115.7 (2, =CH_2), 115.0 (1, 2 × *C*H), 114.8 (2, =CH_2), 110.5 (1, *C*H), 74.3 (1, Ar*C*HOH), 65.3 (2, OCH_2), 55.7 (3, OCH_3), 39.6 (2, CH_2), 38.5 (2, CH_2), 29.4 (2, CH_2), 25.3 (2, CH_2) ppm.

LRMS (M/z, CI) 335 ($[M-OH]^+$, 6 %), 175 (50 %), 162 (100 %), 147 (38 %), 133 (22 %), 91 (20 %) amu.

5-Methoxy-2-oxatricyclo[14.2.2.1^{4,8}]henicosa-1(18),4,6,8(21),10,16,19-heptaen-15-ol **3.21**



3.22
$C_{23}H_{28}O_3$ (352)

3.21
$C_{21}H_{24}O_3$ (324)

To a refluxing solution of benzylidene-bis(tricyclohexylphosphine)dichlororuthenium (20 mg, 0.02 mmol) in dichloromethane (100 mL) was added diene **3.22** (140 mg, 0.40 mmol) as a solution in dichloromethane (20 mL) *via* syringe pump over 4 hours. The mixture was stirred for a further 30 minutes at reflux before cooling to room temperature. Concentration *in vacuo* and purification by column chromatography (silica gel, 20 % ether / petrol) gave firstly recover starting material **3.22** (50 mg, 0.14 mmol, 36 %), and then macrocycle **3.21** (50 mg, 0.15 mmol, 39 %, mixture of geometric isomers ~ 3:7) as a colourless oil.

FT – IR (ν_{max}, neat) 3416 br. m, 2932 m, 1607 m, 1504 s, 1456 m, 1250 s, 1209 m, 1036 m, 970 m, 909 m cm^{-1}.

UV (λ_{max}, MeOH) 273 (7800), 224 (24000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H major isomer 7.31 (1H, dd, *J* 8.2, 2.0 Hz, Ar*H*), 6.87 – 6.72 (4H, m, 4 × Ar*H*), 6.63 (1H, d, *J* 8.2 Hz, Ar*H*), 6.38 (1H, d, *J* 2.0 Hz, Ar*H*), 5.18 (2H, s, OCH_2), 5.04 – 4.95 (1H, m, C*H*=CH), 4.80 – 4.70 (1H, m, CH=C*H*), 4.46 (1H, dd, *J* 9.4, 3.0 Hz, C*H*OH), 3.77 (3H, s, OCH_3), 2.88 – 2.75 (2H, m, CH=CHCH_2Ar), 1.75 – 1.00 (7H, m, 3 × CH_2 & O*H*) ppm.

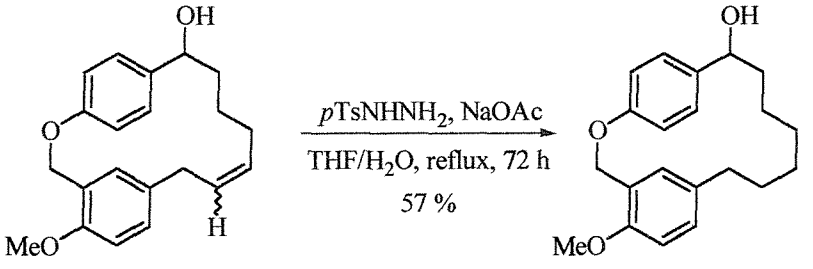
^{13}C – NMR (75 MHz, $CDCl_3$) δ_C major isomer 157.3 (0, *C*O), 155.9 (0, *C*O), 137.8 (0, *C*), 132.2 (0, *C*), 130.8 (1, *C*H), 130.2 (1, *C*H), 129.7 (1, *C*H), 128.9 (1, *C*H), 128.1 (1, *C*H), 126.0 (1, *C*H), 124.7 (0, *C*), 119.7 (1, *C*H), 117.7 (1, *C*H), 110.1 (1, *C*H), 74.2 (1, ArCHOH), 67.4 (2, OCH_2), 55.7 (3, OCH_3), 38.4 (2, CH_2), 38.1 (2, CH_2), 32.7 (2, CH_2), 23.4 (2, CH_2); minor isomer 157.8 (0, *C*O), 155.9 (0, *C*O), 137.9 (0, *C*), 132.2 (0, *C*), 130.6 (1, CH), 130.4 (1, *C*H), 129.7 (1,*C*H), 128.5 (1, *C*H), 128.3 (1, *C*H), 126.1 (1, *C*H), 124.1 (0, *C*), 120.8 (1, *C*H), 118.8 (1, *C*H), 110.7 (1, *C*H), 74.8 (1, Ar*C*HOH), 68.5 (2, OCH_2),

55.7 (3, OCH_3), 38.2 (2, CH_2), 32.7 (2, CH_2), 26.2 (2, CH_2), 25.1 (2, CH_2) ppm.

LRMS (M/z, CI) 325 (MH^+, 12 %), 307 ($[MH-H_2O]^+$, 100 %), 224 (40 %), 207 (20 %) amu.

HRMS (M/z, ES+) $C_{42}H_{48}O_6Na^+$ requires: 671.3343; Found $[2M+Na]^+$: 671.3355.

5-Methoxy-2-oxatricyclo[14.2.2.1^{4,8}]henicosa-1(18),4,6,8(21),16,19-hexaen-15-ol **3.32**



3.21
$C_{21}H_{24}O_3$ (324)

3.32
$C_{21}H_{26}O_3$ (326)

To a solution of alcohol **3.21** (40 mg, 0.12 mmol) in tetrahydrofuran (20 mL) and water (20 mL) was added sodium acetate (60 mg, 0.74 mmol) and *p*-toluenesulfonyl hydrazide (140 mg, 0.74 mmol). The mixture was heated at reflux for 72 hours with additional sodium acetate (60 mg, 0.74 mmol) and *p*-toluenesulfonyl hydrazide (140 mg, 0.74 mmol) added after 36 hours. After cooling to room temperature, the mixture was stirred with potassium carbonate solution (sat. aq., 20 mL) for 4 hours then extracted with dichloromethane (2 × 40 mL). The combined organic phases were dried ($MgSO_4$), concentration *in vacuo* and purified by column chromatography (silica gel, 25 % ether / petrol) to yield the title compound **3.32** (23 mg, 0.08 mmol, 57 %) as a white solid.

MP 105 – 106 °C (ether).

FT – IR (ν_{max}, neat) 3390 br. m, 2927 s, 2853 m, 1617 m, 1503 s, 1461 m, 1249 s, 1210 m, 1036 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 267 (9200) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.40 (1H, dd, *J* 8.4, 2.3 Hz, Ar*H*), 6.95 – 6.87 (3H, m, 3 × Ar*H*), 6.78 (1H, d, *J* 8.4 Hz, Ar*H*), 6.71 (1H, dd, *J* 8.2, 2.6 Hz, Ar*H*), 6.56 (1H, d, *J* 2.1 Hz, Ar*H*), 5.33 (2H, s, OCH_2), 4.57 (1H, dd, *J* 12.5, 4.7 Hz, ArC*H*OH), 3.88 (3H, s, OCH_3), 2.41 – 2.25 (2H, m), 1.89 – 1.78 (2H, m), 1.63 (1H, d, *J* 2.1 Hz, O*H*), 1.55 – 1.45 (1H, m), 1.30 – 1.20 (5H, m), 0.88 – 0.75 (2H, m) ppm.

^{1}H – NMR (400 MHz, C_6D_6) δ_H 7.45 (1H, dd, *J* 8.5, 2.0 Hz, Ar*H*), 7.03 (1H, dd, *J* 8.6, 2.5 Hz, Ar*H*), 6.94 (1H, dd, *J* 8.3, 2.2 Hz, Ar*H*), 6.85 (1H, d, *J* 2.2 Hz, Ar*H*), 6.82 (1H, dd, *J* 8.3, 2.8 Hz, Ar*H*), 6.71 (1H, dd, *J* 8.3, 2.2 Hz, Ar*H*), 6.59 (1H, d, *J* 8.3 Hz, Ar*H*), 5.58 (1H, d, *J* 15.1 Hz, OC*H*H), 5.52 (1H, d, *J* 15.1, Hz, OCH*H*), 4.38 (1H, dd, *J* 8.8, 2.5 Hz, C*H*OH), 3.48 (3H, s, OCH_3), 2.50 – 2.35 (2H, m), 1.82 (1H, dddd, *J* 13.3, 8.0, 6.0, 3.8 Hz), 1.57 (1H, ddt, *J* 13.0, 8.8, 6.0 Hz), 1.50 – 1.38 (1H, m), 1.40 – 1.28 (4H, m), 0.98 – 0.88 (2H, m), 0.78 – 0.69 (2H, m) ppm.

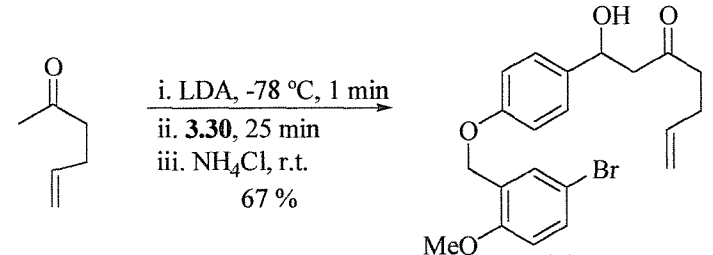
^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 157.4 (0, *C*O), 155.6 (0, *C*O), 137.3 (0, *C*), 138.9 (0, *C*), 130.1 (1, *C*H), 128.4 (1, *C*H), 128.4 (1, *C*H), 126.5 (1, *C*H), 124.4 (0, *C*), 119.0 (1, *C*H), 116.9 (1, *C*H), 110.4 (1, *C*H), 75.0 (1, Ar*C*HOH), 66.4 (2, OCH_2), 55.9 (3, OCH_3), 38.3 (2, CH_2), 34.1 (2, CH_2), 30.8 (2, CH_2), 29.0 (2, CH_2), 26.8 (2, CH_2), 22.7 (2, CH_2) ppm.

^{13}C – NMR (100 MHz, C_6D_6) δ_C 157.9 (0, *C*O), 156.0 (0, *C*O), 137.7 (0, *C*), 134.0 (0, *C*), 130.3 (1, 2 × *C*H), 128.5 (1, *C*H), 127.0 (1, *C*H), 125.1 (0, *C*), 118.8 (1, *C*H), 116.7 (1, *C*H), 110.7 (1, *C*H), 74.7 (1, OCH), 65.0 (2, OCH_2), 55.3 (3, OCH_3), 38.8 (2, CH_2), 34.5 (2, CH_2), 31.3 (2, CH_2), 29.6 (2, CH_2), 21.2 (2, CH_2), 23.0 (2, CH_2) ppm.

LRMS (M/z, CI) 326 (M^+, 15 %), 309 ($[M\text{-}OH]^+$, 100 %), 154 (25 %), 94 (32 %) amu.

HRMS (M/z, ES+) $C_{42}H_{52}O_6Na^+$ requires: 675.3656; Found $[2M+Na]^+$: 675.3667.

1-(4-(5-Bromo-2-methoxybenzyloxy)phenyl)-1-hydroxy-6-hepten-3-one **3.36**



3.37
$C_6H_{10}O$ (98)

3.36
$C_{21}H_{23}BrO_4$ (419)

Alcohol **3.36** was prepared using the method of Narasaka *et al.*[100] Diisopropylamine (290 μL, 210 mg, 2.07 mmol) was dissolved in tetrahydrofuran (20 mL) and cooled to –78 °C. *n*-Butyllithium (1.21 M in hexanes, 1.64 mL, 1.98 mmol) was added and the mixture allowed to warm to 0 °C. After cooling to –78 °C, 5-hexen-2-one **3.37** (209 μL, 177 mg, 1.80 mmol) was added as a solution in tetrahydrofuran (1 mL) and the mixture stirred at –78 °C for 1

minute. Aldehyde **3.30** (500 mg, 1.56 mmol) was added as a solution in tetrahydrofuran (1 mL) and the solution stirred for a further 20 minutes. A solution of ammonium chloride (sat. aq., 10 mL) was added and the mixture allowed to warm to room temperature. The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic phases were washed with brine (20 mL) and dried (Na_2SO_4). Concentration *in vacuo* and purification by column chromatography (silica gel, 30 % ether / petrol) yielded the title alcohol **3.36** (435 mg, 1.04 mmol, 67 %) as a white solid.

MP 45 – 47 °C (petrol).

FT – IR (ν_{max}, neat) 3443 br. m, 1712 s, 1611 m, 1511 s, 1488 s, 1462 m, 1380 m, 1302 m, 1249 s, 1172 m, 1031 m cm^{-1}.

UV (λ_{max}, MeOH) 279 (4190), 226 (21230) nm.

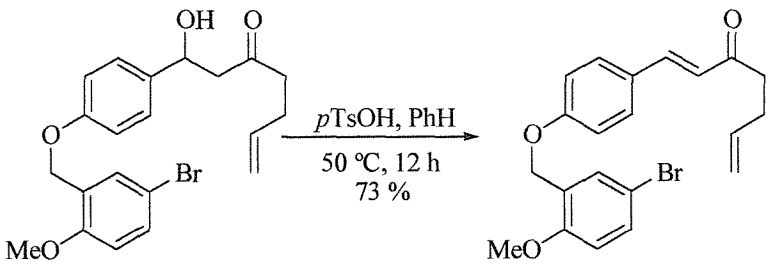
^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.59 (1H, d, *J* 1.8 Hz, Ar*H*), 7.39 (1H, dd, *J* 8.4, 1.8 Hz, Ar*H*), 7.29 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 6.97 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 6.79 (1H, d, *J* 8.4 Hz, Ar*H*), 5.80 (1H, ddt, *J* 16.7, 10.1, 6.3 Hz, C*H*=CH_2), 5.12 (1H, dt, *J* 8.9, 3.3 Hz, ArC*H*OH), 5.06 (2H, s, OCH_2Ar), 5.08 – 4.97 (2H, m, =CH_2), 3.80 (3H, s, OCH_3), 3.23 (1H, d, *J* 3.1 Hz, O*H*), 2.88 (1H, dd, *J* 17.6, 8.8 Hz, C*H*HCO), 2.78 (1H, dd, *J* 17.6, 3.3 Hz, CH*H*CO), 2.56 (2H, t, *J* 7.0 Hz, CH_2C=O), 2.37 (2H, td, *J* 7.3, 6.8 Hz, CH_2CH=CH_2) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 210.7 (0, C=O), 158.3 (0, *C*O), 155.8 (0, *C*O), 136.9 (1, *C*H=CH_2), 135.8 (0, *C*), 131.5 (1, *C*H), 131.0 (1, *C*H), 127.6 (0, *C*), 127.1 (1, 2 × *C*H), 115.6 (2, =CH_2), 115.0 (1, 2 × *C*H), 113.1 (0, *C*Br), 112.1 (1, *C*H), 69.7 (1, ArCHOH), 64.5 (2, OCH_2), 55.8 (3, OCH_3), 51.3 (2, CH_2), 42.8 (2, CH_2), 27.6 (2, CH_2) ppm.

LRMS (M/z, CI) 323 (8 %), 321 (8%), 201 (100 %), 199 (96 %), 171 (24 %), 120 (8 %), 90 (32 %), 77 (24 %) amu.

CHN $C_{21}H_{23}BrO_4$ requires: C 60.15, H 5.53; Found: C 60.10, H 5.40.

(1*E*)-1-(4-(5-Bromo-2-methoxybenzyloxy)phenyl)-1,6-heptadien-3-one **3.40**



3.36
$C_{21}H_{23}BrO_4$ (419)

3.40
$C_{21}H_{21}BrO_3$ (401)

Enone **3.40** was prepared by a modification of the method of Zhang *et al.*[179] Hence, alcohol **3.36** (1.07 g, 2.55 mmol) was dissolved in benzene (25 mL). *p*-Toluenesulfonic acid monohydrate (24 mg, 0.13 mmol) was added and the mixture stirred at 50 °C for 16 hours. Concentration *in vacuo* and purification by column chromatography (silica gel, 20 % ether / petrol) yielded the title compound **3.40** (750 mg, 1.87 mmol, 73 %) as an off-white solid.

MP 70 – 73 °C (ether).

FT – IR (ν_{max}, neat) 1686 m, 1657 m, 1599 m, 1573 m, 1509 s, 1488 s, 1460 m, 1422 m, 1379 m, 1248 s, 1170 s, 1032 s, 904 m cm^{-1}.

UV (λ_{max}, MeOH) 308 (32880) nm.

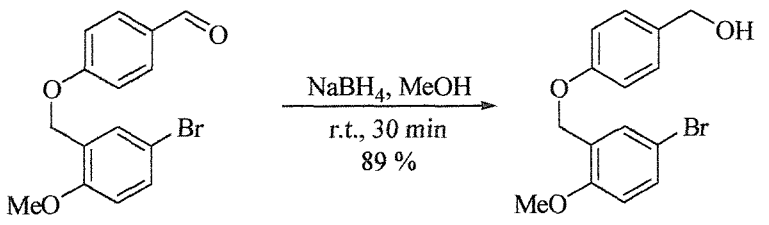
^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.65 – 7.51 (4H, m, 3 × Ar*H* & C*H*=CHC=O), 7.43 (1H, dd, *J* 8.8, 2.6 Hz, Ar*H*), 7.01 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 6.81 (1H, d, *J* 8.5 Hz, Ar*H*), 6.65 (1H, d, *J* 16.2 Hz, CH=C*H*C=O), 5.89 (1H, ddt, *J* 16.9, 10.3, 6.6 Hz, C*H*=CH_2), 5.10 – 4.90 (4H, m, OCH_2 & CH=CH_2), 3.84 (3H, s, OCH_3), 2.77 (2H, t, *J* 7.4 Hz, CH_2), 2.40 (2H, td, *J* 7.4, 6.6, CH_2) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 199.7 (0, *C*=O), 160.7 (0, *C*O), 155.8 (0, *C*O), 142.5 (1, *C*H), 137.5 (1, *C*H), 131.8 (1, *C*H), 131.1 (1, *C*H), 130.2 (1, 2 × *C*H), 127.6 (0, *C*), 127.2 (0, *C*), 124.3 (1, *C*H), 115.4 (1, 2 × *C*H) 115.4 (2, =CH_2), 113.2 (0, *C*Br), 112.1 (1, *C*H), 64.6 (2, OCH_2), 55.8 (3, OCH_3), 40.0 (2, CH_2), 28.5 (2, CH_2) ppm.

LRMS (M/z, CI) 403 (MH^+{^{81}Br}, 5 %), 401 (MH^+{^{79}Br}, 4 %), 207 (31 %), 201 (100 %), 199 (85 %), 171 (27 %), 169 (24 %), 120 (7 %), 90 (30 %), 77 (15 %).

CHN $C_{21}H_{21}BrO_3$ requires: C 62.85, H 5.10; Found: C 62.70, H 5.10.

(4-(5-Bromo-2-methoxybenzyloxy)phenyl)methanol **3.62**



3.30
$C_{15}H_{13}BrO_3$ (321)

3.62
$C_{15}H_{15}BrO_3$ (323)

Aldehyde **3.30** (1.50 g, 4.67 mmol) was suspended in methanol (100 mL) and the mixture cooled to 0 °C. Sodium borohydride (215 mg, 5.61 mmol) was added portionwise over 5 minutes and the mixture allowed to stir at room temperature for a further 30 minutes. Upon concentration *in vacuo* the residue was diluted with dichloromethane (30 mL) and washed with water (20 mL). The organic phase was further washed with brine (20 mL), dried ($MgSO_4$) and the solvent evaporated under reduced pressure to yield the title compound **3.62** (1.34 g, 4.15 mmol, 89 %) as a white solid.

MP 97 – 98 °C (ether / petrol).

FT - IR (ν_{max}, neat) 3320 br. m, 1613 m, 1514 s, 1488 s, 1378 m, 1304 m, 1248 s, 1027 m cm^{-1}.

UV (λ_{max}, MeOH) 280 (5600) nm.

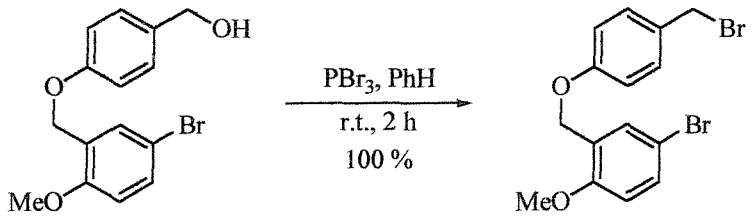
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.59 (1H, d, *J* 2.2 Hz, Ar*H*), 7.37 (1H, dd, *J* 8.8, 2.2 Hz, Ar*H*), 7.25 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 6.98 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 6.73 (1H, d, *J* 8.8 Hz, Ar*H*), 5.02 (2H, s, OCH_2Ar), 4.62 (2H, d, *J* 5.9 Hz, CH_2OH), 3.85 (3H, s, OCH_3), 1.61 (1H, t, *J* 5.9 Hz, O*H*) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 158.4 (0, *C*O), 155.8 (0, *C*O), 133.6 (0, *C*), 131.5 (1, *C*H), 131.0 (1, *C*H), 128.9 (1, 2 × *C*H), 127.8 (0, *C*), 115.0 (1, 2 × *C*H), 113.1 (0, *C*Br), 112.0 (1, *C*H), 65.2 (2, *C*H_2OH), 64.5 (2, OCH_2), 55.8 (3, OCH_3) ppm.

LRMS (M/z, EI) 324 ($M^+\{^{81}Br\}$, 1 %), 322 ($M^+\{^{79}Br\}$, 1 %), 207 (100 %), 201 (29 %), 199 (30 %), 77 (40 %), 51 (36 %), 36 (40 %) amu.

CHN $C_{15}H_{15}BrO_3$ requires: C 55.75, H 4.68; Found: C 55.60, H 4.66.

4-(5-Bromo-2-methoxybenzyloxy)benzyl bromide **3.41**



3.62
$C_{15}H_{15}BrO_3$ (323)

3.41
$C_{15}H_{14}Br_2O_2$ (386)

Bromide **3.41** was prepared using a modification of the method of Hawker *et al.*[148] Alcohol **3.62** (1.20 g, 3.72 mmol) was dissolved in benzene (20 mL) and cooled to 0 °C. Phosphorus tribromide (120 μL, 335 mg, 1.24 mmol) was added dropwise over 5 minutes and the mixture allowed to stir at room temperature for 2 hours. The mixture was concentrated *in vacuo* and the residue was diluted with dichloromethane (20 mL). The solution was washed with water (10 mL) and the aqueous phase extracted with dichloromethane (2 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to yield the title compound **3.41** (1.44 g, 3.72 mmol, 100 %) as a white solid.

MP 71 – 72 °C (ether / petrol).

FT - IR (ν_{max}, neat) 1608 m, 1511 s, 1489 s, 1460 m, 1249 s, 1172 m, 1032 m cm^{-1}.

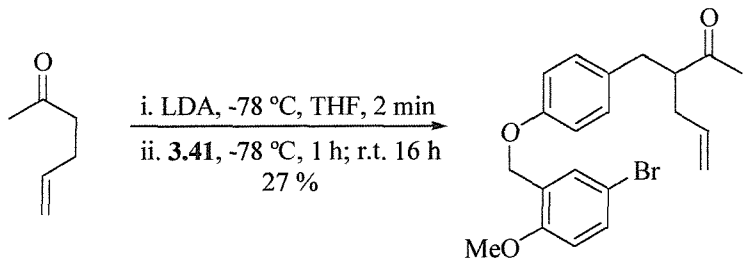
UV (λ_{max}, MeOH) 276 (5400), 224 (27000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.58 (1H, d, *J* 2.6 Hz, Ar*H*), 7.39 (1H, dd, *J* 8.5, 2.6 Hz, Ar*H*), 7.30 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 6.96 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 6.72 (1H, d, *J* 8.5 Hz, Ar*H*), 5.06 (2H, s, OCH_2), 4.52 (2H, s, CH_2Br), 3.86 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 159.2 (0, *C*O), 156.0 (0, *C*O), 131.5 (1, *C*H), 131.0 (1, *C*H), 130.5 (1, 2 × *C*H), 130.2 (0, *C*), 127.7 (0, *C*), 115.1 (1, 2 × *C*H), 112.5 (0, *C*Br), 111.9 (1, *C*H), 64.4 (2, OCH_2), 55.7 (3, OCH_3), 34.0 (2, CH_2Br) ppm.

LRMS (M/z, CI) 246 (70 %), 224 (90 %), 218 (97 %), 216 (100 %) amu.

3-(4-(5-Bromo-2-methoxybenzyloxy)benzyl)-5-hexen-2-one **3.42**



3.37
$C_6H_{10}O$ (98)

3.42
$C_{21}H_{23}BrO_3$ (403)

To a solution of diisopropylamine (340 µL, 245 mg, 2.41 mmol) in tetrahydrofuran (40 mL), cooled to –78 °C, was added *n*-butyllithium (2.18 M in hexanes, 1.05 mL, 2.30 mmol) over 5 minutes. The solution was allowed to warm to 0 °C before cooling to –78 °C. 5-Hexen-2-one **3.37** (242 µL, 205 mg, 2.09 mmol) was added as a solution in tetrahydrofuran (2 mL) and the solution stirred at –78 °C for 2 minutes. Bromide **3.41** (700 mg, 1.81 mmol) was added as a solution in tetrahydrofuran (5 mL) over 5 minutes. After stirring at –78 °C for 1 hour and at room temperature for 16 hours, ammonium chloride (sat. aq., 20 mL) was added. The aqueous phase was extracted with ether (2 × 30 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and solvent evaporated *in vacuo*. Purification by column chromatography (silica gel, 15 % ether / petrol) yielded the title compound **3.42** (200 mg, 0.50 mmol, 27 %) as a colourless oil.

FT – IR (ν_{max}, neat) 2937 m, 1712 s, 1611 s, 1544 s, 1488 s, 1462 s, 1300 s, 1246 s, 1173 s, 1031 s cm^{-1}.

UV (λ_{max}, MeOH) 280 (7800), 226 (40000) nm.

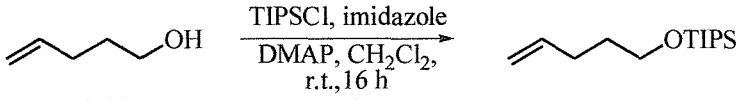
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.58 (1H, d, *J* 2.6 Hz, Ar*H*), 7.38 (1H, dd, *J* 8.5, 2.6 Hz, Ar*H*), 7.07 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 6.90 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 6.75 (1H, d, *J* 8.5 Hz, Ar*H*), 5.72 (1H, ddt, *J* 16.2, 10.3, 7.0 Hz, C*H*=CH_2), 5.09 – 5.02 (4H, m, OCH_2 & =CH_2), 3.82 (3H, s, OCH_3), 2.94 – 2.60 (3H, m), 2.40 – 2.20 (2H, m), 2.00 (3H, s, CH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 211.8 (0, *C*=O), 157.2 (0, *C*O), 155.7 (0, *C*O), 135.2 (1, *C*H), 131.7 (0, *C*), 131.3 (1, *C*H), 130.9 (1, *C*H), 129.9 (1, 2 × *C*H), 127.7 (0, *C*), 117.2 (2, CH=CH_2), 114.8 (1, 2 × *C*H), 112.9 (0, *C*), 111.9 (1, *C*H=CH_2), 64.3 (2, OCH_2), 55.6 (3, OCH_3), 54.4 (1, *C*HCO), 36.8 (2, CH_2), 35.9 (2, CH_2), 30.7 (3, COCH_3) ppm.

LRMS (M/z, CI) 422 ($[M+NH_4]^+\{^{81}Br\}$, 54 %), 420 ($[M+NH_4]^+\{^{79}Br\}$, 55 %), 404 ($M^+\{^{81}Br\}$, 10 %), 402 ($M^+\{^{79}Br\}$, 10 %), 306 (56 %), 305 (54 %), 222 (47 %), 199 (100 %), 163 (38 %), 121 (70 %) amu.

HRMS $C_{21}H_{23}{}^{79}BrO_3Na^+$ requires: 425.0723; Found $[M+Na]^+$: 425.0719.

Triisopropyl(4-pentenyloxy)silane **3.52**



3.47 $C_5H_{10}O$ (86) **3.52** $C_{14}H_{30}OSi$ (242)

Silyl ether **3.52** was prepared by the method of Delgado *et al.*[97] To solution of 4-penten-1-ol **3.47** (10.0 mL, 8.34 g, 0.10 mol) in dichloromethane (200 mL) was added imidazole (16.50 g, 0.24 mol) then triisopropylsilyl chloride (22.8 mL, 20.54 g, 0.11 mol) and finally 4-dimethylaminopyridine (250 mg, 2.00 mmol). The mixture was stirred at room temperature for 16 hours. Ammonium chloride (sat. aq., 50 mL) was added and the organic phase separated, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 1 - 2 % ethyl acetate / hexane) yielded the title compound **3.52** (22.67 g, 0.09 mol, 97 %) as a colourless oil.

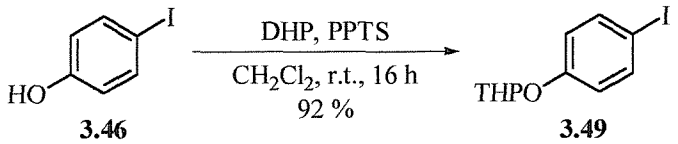
FT – IR (ν_{max}, neat) 2942 m, 2865 m, 1453 m, 1106 s, 1072 s cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 5.85 (1H, ddt, *J* 16.9, 9.9, 6.6 Hz, C*H*=CH_2), 5.04 (1H, ddd, *J* 16.9, 3.3, 1.5 Hz, =C*H*H), 4.96 (1H, ddd, *J* 9.9, 3.3, 2.2 Hz, =CH*H*), 3.70 (2H, t, *J* 6.6 Hz, OCH_2), 2.18 – 2.11 (2H, m, CH_2), 1.70 – 1.60 (2H, m, CH_2), 1.08 – 1.06 (21H, m, 3 × C*H*(CH_3)$_2$) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 138.8 (1, *C*H=CH_2), 114.6 (2, =*C*H_2), 62.9 (2, O*C*H_2), 32.3 (2, *C*H_2), 30.2 (2, *C*H_2), 18.2 (3, 6 × *C*H_3), 12.1 (1, 3 × *C*H(CH_3)$_2$) ppm.

LRMS (M/z, CI) 243 (MH^+, 78 %), 199 (44 %), 174 (42 %), 157 ($^iPr_3Si^+$, 100 %), 129 (38 %), 75 (28 %) amu.

2-(4-Iodophenoxy)tetrahydro-2*H*-pyran **3.49**



3.46 C_6H_5IO (220) **3.49** $C_{11}H_{13}IO_2$ (304)

4-Iodophenol **3.46** (20.0 g, 0.09 mol), 3,4-dihydro-2*H*-pyran (12.5 mL, 11.52 g, 0.14 mol) and pyridinium *p*-toluenesulfonate (1.13 g, 4.50 mmol) were dissolved in dichloromethane

(120 mL) and stirred at room temperature for 3 days. The mixture was washed with potassium carbonate (sat. aq., 2 × 40 mL) and the organic phase was dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (silica gel, 5 % ethyl acetate / hexane) yielded the title compound **3.49** (25.44 g, 0.08 mol, 92 %) as a white solid.

MP 76 – 78 °C (hexane).

FT – IR (ν_{max}, neat) 2939 m, 2862 m, 1483 s, 1234 s, 1200 m, 1174 m, 1120 s, 1036 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 267 (1600) nm.

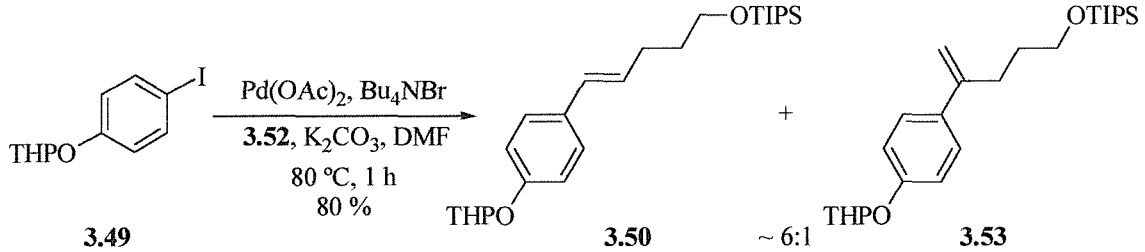
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.55 (2H, d, *J* 8.8 Hz, 2 ×Ar*H*), 6.84 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 5.39 (1H, t, *J* 2.9 Hz, OC*H*O), 3.89 (1H, ddd *J* 11.4, 9.6, 3.3 Hz, OC*H*H), 3.62 (1H, ddt, *J* 11.4, 3.3, 1.1 Hz, OCH*H*), 2.10 – 1.85 (3H, m), 1.80 – 1.53 (3H, m) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 157.1 (0, *C*O), 138.3 (1, 2 × *C*H), 119.0 (1, 2 × *C*H), 96.4 (1, O*C*HO), 84.1 (0, *C*I), 62.1 (2, O*C*H_2), 30.4 (2, *C*H_2), 25.3 (2, *C*H_2), 18.8 (2, *C*H_2) ppm.

LRMS (M/z, TS+) 322 ($[M+NH_4]^+$, 60 %), 312 (100 %) amu.

CHN $C_{11}H_{13}IO_2$ requires: C 43.44, H 4.31; Found: C 43.37, H 4.27.

(*E*)-5-(4-Tetrahydro-2*H*-pyran-2-yloxy)phenyl)pent-5-enyl triisopropylsilyl ether **3.50**



3.49 $C_{11}H_{13}IO_2$ (304)

3.50 $C_{25}H_{42}O_3Si$ (418) ~ 6:1 **3.53** $C_{25}H_{42}O_3Si$ (419)

Iodide **3.49** (16.15 g, 53.13 mmol), alkene **3.52** (13.50 g, 55.79 mmol), tetra-*n*-butylammonium bromide (18.88 g, 58.58 mmol), potassium carbonate (29.37 g, 0.21 mol) and palladium(II) acetate (600 mg, 2.66 mmol) were stirred in *N,N*-dimethylformamide (180 mL) at 80 °C for 16 hours. After cooling to room temperature, water (100 mL) and ether (150 mL) were added. The aqueous phase was extracted with ether (100 mL) and the combined organic phases were washed with water (4 × 50 mL) and dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (silica gel, 0.5 % ether / petrol) yielded the title compound **3.50** as a mixture with arylalkene **3.53** (17.69 g, 42.32 mmol, 80 %, **3.50**:**3.53** ~ 6:1) as a colourless oil.

FT – IR (ν_{max}, neat) 2943 m, 2866 m, 1509 s, 1238 s, 1202 m, 1110 s, 1038 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 287 (4100), 251 (29000) nm.

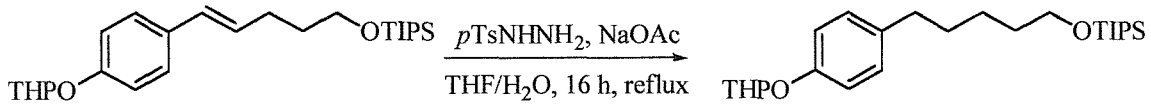
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.25 (2H, d, *J* 8.7 Hz, 2 × Ar*H*), 6.98 (2H, d, *J* 8.7 Hz, 2 × Ar*H*), 6.35 (1H, d, *J* 15.9 Hz, ArC*H*=CH), 6.11 (1H, dt, *J* 15.9, 7.0 Hz, ArCH=C*H*), 5.41 (1H, t, *J* 3.2 Hz, OC*H*O), 3.92 (1H, app. tt, *J* 8.9, 3.0 Hz, OCHOC*H*H), 3.73 (2H, t, *J* 6.2 Hz, SiOCH_2), 3.67 – 3.55 (1H, m, OCHOCH*H*), 2.32 – 2.25 (2H, m, CH_2), 1.87 – 1.82 (2H, m, CH_2), 1.78 – 1.60 (6H, m, 3 × CH_2), 1.20 – 1.05 (21H, m, 6 × CH_3 & 3 × SiC*H*) ppm plus additional signals attributed to **3.53**.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 156.3 (0, *C*O), 131.8 (0, *C*), 129.6 (1, *C*H=CH), 128.9 (1, CH=*C*H), 127.1 (1, 2 × *C*H), 127.1 (1, 2 × *C*H), 96.7 (1, O*C*HO), 63.1 (2, OCH_2), 62.3 (2, OCH_2), 33.1 (2, *C*H_2), 30.7 (2, *C*H_2), 29.6 (2, *C*H_2), 25.6 (2, *C*H_2), 19.2 (2, *C*H_2), 18.4 (3, 6 × *C*H_3), 12.4 (1, 3 × Si*C*H(CH_3)$_2$) ppm plus additional signals attributed to **3.53**.

LRMS (M/z, CI) 335 ([MH-THP]$^+$, 30 %), 207 (57 %), 160 (74 %), 131 (72 %), 75 (75 %), 41 (100 %) amu.

HRMS (M/z, ES+) $C_{50}H_{84}O_6Si_2Na^+$ requires 859.5699; Found [2M+Na]$^+$: 859.5708.

5-(4-Tetrahydro-2*H*-pyran-2-yloxy)phenyl)pentyl triisopropylsilyl ether **3.63**



3.50
$C_{25}H_{42}O_3Si$ (419)

3.63
$C_{25}H_{44}O_3Si$ (421)

Alkene **3.50** (17.22 g, 41.20 mmol) was dissolved in tetrahydrofuran (150 mL). Water (150 mL), sodium acetate (10.14 g, 0.12 mol) and *p*-toluenesulfonyl hydrazide (23.02 g, 0.12 mol) were added and the solution heated at reflux for 16 hours. After cooling to room temperature, a solution of potassium carbonate (sat. aq., 80 mL) was added and the mixture stirred for 15 minutes. The mixture was extracted with ether (3 × 80 mL) and the combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica gel, 2 % ether / petrol) to yield the title compound **3.63** (14.55 g, 34.56 mmol, 84 %) as a colourless oil.

FT – IR (ν_{max}, neat) 2941 s, 2865 s, 1510 s, 1462 m, 1235 s, 1202 m, 1109 s, 1041 m, 1019 m, 971 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 294 (800), 250 (2500) nm.

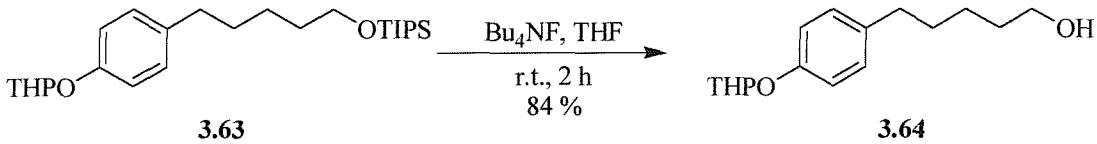
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.09 (2H, d, *J* 8.4 Hz, 2 × Ar*H*), 6.96 (2H, d, *J* 8.4 Hz, 2 × Ar*H*), 5.38 (1H, t, *J* 3.2 Hz, OC*H*O), 4.00 – 3.90 (1H, m, OC*H*H), 3.68 (2H, t, *J* 6.5 Hz, SiOCH_2), 3.65 – 3.58 (1H, m, OCH*H*), 2.56 (2H, t, *J* 7.4 Hz, CH_2), 1.90 – 1.82 (2H, m, CH_2), 1.72 – 1.55 (10H, m, 5 × CH_2), 1.17 – 1.04 (21H, m, 6 × CH_3 & 3 × C*H*) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 155.4 (0, *C*O), 136.2 (0, *C*), 129.4 (1, 2 × *C*H), 116.6 (1, 2 × *C*H), 96.9 (1, O*C*HO), 63.7 (2, OCH_2), 62.3 (2, OCH_2), 35.5 (2, *C*H_2), 33.4 (2, *C*H_2), 31.8 (2, *C*H_2), 30.5 (2, *C*H_2), 25.8 (2, *C*H_2), 25.6 (2, *C*H_2), 19.3 (2, *C*H_2), 18.4 (3, 6 × *C*H_3), 12.4 (1, 3 × Si*C*H(CH_3)$_2$) ppm.

LRMS (M/z, CI) 337 ([MH-THP]$^+$, 30 %), 293 (86 %), 237 (37 %), 163 (50 %), 107 (100 %), 75 (34 %) amu.

HRMS (M/z, ES+) $C_{25}H_{44}O_3SiNa^+$ requires: 443.2952; Found [M+Na]$^+$: 443.2953.

5-(4-(Tetrahydro-2*H*-pyran-2-yloxy)phenyl)-1-pentanol **3.64**



3.63
$C_{25}H_{44}O_3Si$ (421)

3.64
$C_{16}H_{24}O_3$ (264)

Alcohol **3.64** was prepared by modifications of the method of Delgado *et al.*[97] Silyl ether **3.63** (14.09 g, 33.55 mmol) was dissolved in tetrahydrofuran (80 mL). Tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 50.3 mL, 50.32 mmol) was added and the mixture stirred at room temperature for 2 hours. Concentration *in vacuo* and purification by column chromatography (silica gel, 20 – 50 % ether / petrol) yielded the title compound **3.64** (7.43 g, 28.14 mmol, 84 %) as a colourless oil.

FT – IR (ν_{max}, neat) 3407 br. w, 2934 m, 2862 m, 1510 s, 1235 s, 1202 m, 1109 m, 1037 s cm^{-1}.

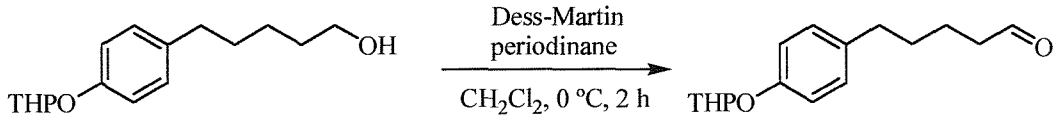
UV (λ_{max}, CH_2Cl_2) 272 (650) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.11 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 6.98 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 5.39 (1H, t, *J* 3.3 Hz, OC*H*O), 3.93 (1H, td, *J* 10.1, 2.9 Hz, OC*H*H), 3.68 – 3.55 (3H, m, OCH*H* & CH_2OH), 2.57 (2H, t, *J* 7.4 Hz, CH_2), 2.10 – 1.95 (1H, m), 1.88 – 1.82 (2H, m), 1.73 – 1.55 (7H, m), 1.47 – 1.28 (3H, m) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 155.3 (0, *C*O), 135.8 (0, *C*), 129.3 (1, 2 × *C*H), 116.5 (1, 2 × *C*H), 96.7 (1, O*C*HO), 63.1 (2, OCH_2), 62.2 (2, OCH_2), 35.2 (2, *C*H_2), 32.8 (2, *C*H_2), 31.6 (2, *C*H_2), 30.6 (2, *C*H_2), 25.5 (2, *C*H_2), 25.4 (2, *C*H_2), 19.0 (2, *C*H_2) ppm.

HRMS (M/z, ES+) $C_{32}H_{48}O_6Na^+$ requires: 551.3343; Found $[2M+Na]^+$: 551.3345.

5-(4-(Tetrahydro-2*H*-pyran-2-yloxy)phenyl)pentanal **3.51**



3.64
$C_{16}H_{24}O_3$ (264)

3.51
$C_{16}H_{22}O_3$ (262)

To a solution of alcohol **3.64** (7.02 g, 26.59 mmol) in dichloromethane (100 mL) at 0 °C was added Dess-Martin periodinane (11.84 g, 27.92 mmol). The mixture was stirred for 30 minutes before sodium hydrogen carbonate (12.00 g, 14.28 mmol) was added. After a further 40 minutes the reaction mixture was filtered through Celite, concentrated *in vacuo* and purified by column chromatography (silica gel, 20 % ether / petrol) to yield the title compound **3.51** (5.28 g, 20.15 mmol, 76 %) as a colourless oil.

FT – IR (ν_{max}, neat) 2941 m, 1724 s, 1510 s, 1233 s, 1202 m, 1109 m, 1037 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 315 (900), 262 (2500) nm.

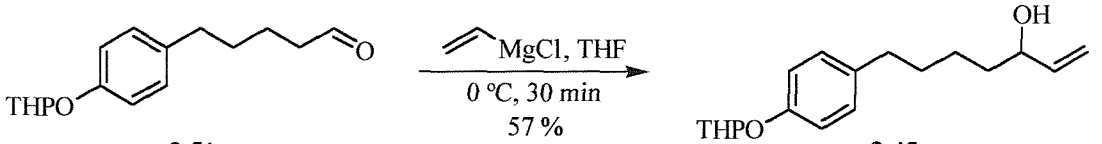
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 9.61 (1H, t, *J* 1.8 Hz, C*H*O), 6.88 (2H, d, *J* 8.6 Hz, 2 × Ar*H*), 6.61 (2H, d, *J* 8.6 Hz, 2 × Ar*H*), 4.82 (1H, dd, *J* 5.0, 2.8 Hz, OC*H*O), 3.91 – 3.86 (1H, m, OC*H*H), 3.77 – 3.71 (1H, m, OCH*H*), 3.42 – 3.36 (2H, m), 2.42 (2H, t, *J* 7.3 Hz, CH_2), 2.30 (2H, td, *J* 7.3, 1.7 Hz, CH_2), 1.73 – 1.68 (4H, m, 2 × CH_2), 1.51 – 1.46 (4H, m, 2 × CH_2) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 203.0 (1, *C*HO), 155.7 (0, *C*O), 135.4 (0, *C*), 129.6 (1, 2 × *C*H), 116.9 (1, 2 × *C*H), 97.0 (1, O*C*HO), 62.5 (2, O*C*H_2), 44.2 (2, *C*H_2), 35.2 (2, *C*H_2), 31.4 (2, *C*H_2), 31.0 (2, *C*H_2), 25.7 (2, *C*H_2), 22.0 (2, *C*H_2), 19.3 (2, *C*H_2) ppm.

LRMS (M/z, CI) 196 ($[M-THP+NH_4]^+$, 100 %), 178 ($[MH-THP]^+$, 65 %) amu.

HRMS (M/z, EI) $C_{16}H_{22}O_3^+$ requires: 262.1569; Found M^+: 262.1567.

7-(4-(Tetrahydro-2*H*-pyran-2-yloxy)phenyl)-1-hepten-3-ol **3.45**



3.51
$C_{16}H_{22}O_3$ (262)

3.45
$C_{18}H_{26}O_3$ (290)

To a cooled (0 °C) solution of aldehyde **3.51** (5.02 g, 19.16 mmol) in tetrahydrofuran (60 mL) was added vinylmagnesium chloride (1.78 M in THF, 11.8 mL, 21.08 mmol). After 30 minutes, a solution of ammonium chloride (sat. aq., 20 mL) was added and the mixture extracted with ether (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica gel, 20 % ether / petrol) to yield the title allylic alcohol **3.45** (3.18 g, 11.00 mmol, 57 %) as a colourless oil.

FT – IR (ν_{max}, neat) 3350 br. w, 2937 w, 2859 w, 1509 s, 1234 s, 1202 m, 1037 m, 971 s cm^{-1}.

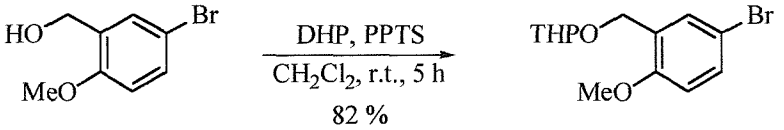
UV (λ_{max}, CH_2Cl_2) 267 (14000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.12 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 7.01 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 5.91 (1H, ddd, *J* 16.3, 10.3, 6.3 Hz, C*H*=CH_2), 5.42 (1H, t, *J* 3.2 Hz, OC*H*O), 5.25 (1H, br. d, *J* 16.3 Hz, =C*H*H), 5.14 (1H, br. d, *J* 10.3 Hz, =CH*H*), 4.14 (1H, dd, *J* 10.4, 6.0 Hz, OC*H*H), 3.98 (1H, app. td, *J* 10.4, 3.0 Hz, OCH*H*), 3.67 – 3.63 (1H, m, C*H*OH), 2.61 (2H, t, *J* 7.8 Hz, CH_2), 2.12 – 2.00 (1H, m), 1.92 – 1.87 (2H, m), 1.80 – 1.30 (10H, m) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 155.6 (0, *C*O), 141.7 (1, *C*H=CH_2), 136.1 (0, *C*), 129.6 (1, 2 × *C*H), 116.8 (1, 2 × *C*H), 115.0 (2, =CH_2), 97.0 (1, *O*CHO), 73.8 (1, *C*HOH), 62.5 (2, O*C*H_2), 37.3 (2, *C*H_2), 35.4 (2, *C*H_2), 32.0 (2, *C*H_2), 30.9 (2, *C*H_2), 25.7 (2, *C*H_2), 25.4 (2, *C*H_2), 19.3 (2, *C*H_2) ppm.

HRMS (M/z, ES+) $C_{36}H_{52}O_6Na^+$ requires 603.3656; Found $[2M+Na]^+$: 603.3660.

2-(5-Bromo-2-methoxybenzyloxy)tetrahydro-2*H*-pyran **3.54**



3.27
$C_8H_9BrO_2$ (217)

3.54
$C_{13}H_{17}BrO_3$ (301)

5-Bromo-2-methoxybenzyl alcohol **3.27** (10.00 g, 46.07 mmol), 3,4-dihydro-2*H*-pyran (6.3 mL, 5.81 g, 69.10 mmol) and pyridinium *p*-toluenesulfonate (580 mg, 2.30 mmol) were

stirred in dichloromethane (80 mL) at room temperature for 16 hours. The mixture was washed with sodium hydrogen carbonate (sat. aq., 30 mL) and the organic phase dried ($MgSO_4$). Concentration *in vacuo* and purification by column chromatography (silica gel, 10 % ether / petrol) yielded the title compound **3.54** (13.56 g, 45.05 mmol, 98 %) as a colourless oil.

FT – IR (ν_{max}, neat) 2941 w, 1489 m, 1244 m, 1118 m, 1062 m, 1034 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 274 (2400) nm.

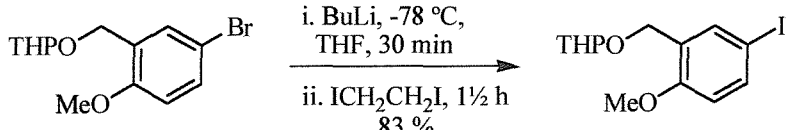
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.58 (1H, d, *J* 2.5 Hz, Ar*H*), 7.38 (1H, dd, *J* 8.5, 2.5 Hz, Ar*H*), 6.76 (1H, d, *J* 8.5 Hz, Ar*H*), 4.80 (1H, d, *J* 13.5 Hz, OC*H*HAr), 4.79 (1H, t, *J* 3.5 Hz, OC*H*O), 4.55 (1H, d, *J* 13.5 Hz, OCH*H*Ar), 3.98 - 3.89 (1H, ddd, *J* 11.3, 8.8, 3.0 Hz, OC*H*HCH$_2$), 3.78 (3H, s, OCH_3), 3.56 (1H, ddd, *J* 11.3, 5.8, 1.2 Hz, OCH*H*CH$_2$), 2.00 - 1.55 (6H, m, 3 × CH_2) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 156.3 (0, *C*O), 131.4 (1, *C*H), 131.2 (1, *C*H), 129.8 (0, *C*), 113.3 (0, *C*Br), 112.2 (1, *C*H), 98.7 (1, OC*H*O), 63.7 (2, OCH$_2$), 62.4 (2, OCH$_2$), 56.0 (3, OCH$_3$), 30.9 (2, *C*H$_2$), 25.9 (2, *C*H$_2$), 19.7 (2, *C*H$_2$) ppm.

LRMS (M/z, CI) 302 (M^+{^{81}Br}, 20 %), 300 (M^+{^{79}Br}, 20 %), 201 (40 %), 199 (37 %), 102 (57 %), 85 (100 %) amu.

HRMS (M/z, EI) $C_{13}H_{17}O_3{}^{79}Br^+$ requires: 300.0361; Found M^+: 300.0357.

2-(5-Iodo-2-methoxybenzyloxy)tetrahydro-2*H*-pyran **3.48**



3.54
$C_{13}H_{17}BrO_3$ (301)

3.48
$C_{13}H_{17}IO_3$ (348)

Bromide **3.54** (3.01 g, 10.00 mmol) was dissolved in tetrahydrofuran (60 mL) and cooled to –78 °C. *n*-Butyllithium (1.80 M in hexanes, 6.7 mL, 12.00 mmol) was added dropwise over 5 minutes and the mixture stirred for a further 30 minutes at –78 °C. 1,2-Diiodoethane (3.95 g, 14.00 mmol) was added as solution in tetrahydrofuran (10 mL) over 5 minutes and the mixture stirred for a further 1½ hours. Brine (30 mL) was added and the mixture allowed to warm to room temperature. The aqueous phase was extracted with ether (3 × 30 mL) and the combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica gel, 10 % ether / petrol) to yield a dark orange oil. This was diluted with ether (30 mL), washed with sodium thiosulfate (sat. aq., 30 mL), dried ($MgSO_4$) and

concentrated *in vacuo* to yield the title compound **3.48** (2.90 g, 8.33 mmol, 83 %) as a pale yellow oil.

FT – IR (ν_{max}, neat) 2941 m, 1487 m, 1244 s, 1118 m, 1061 m, 1033 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 274 (2400) nm.

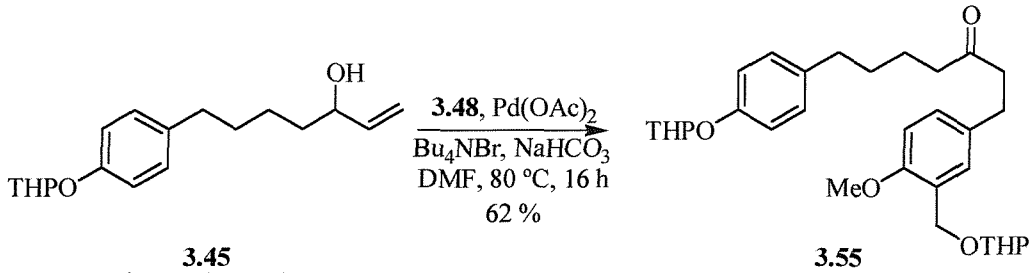
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.62 (1H, d, *J* 2.2 Hz, Ar*H*), 7.45 (1H, dd, *J* 8.5, 2.2 Hz, Ar*H*), 6.54 (1H, d, *J* 8.5 Hz, Ar*H*), 4.66 (1H, d, *J* 13.0 Hz, OC*H*HAr), 4.65 (1H, t, *J* 3.4 Hz, OC*HO*), 4.47 (1H, d, *J* 13.0 Hz, OCH*H*Ar), 3.84 (1H, ddd, 11.3, 8.8, 3.2 Hz, OC*H*HCH$_2$), 3.72 (3H, s, OCH_3), 3.50 – 3.44 (1H, m, OCH*H*CH$_2$), 1.88 – 1.43 (6H, m, 3 × CH_2) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 156.9 (0, *C*O), 137.1 (1, *C*H), 137.0 (1, *C*H), 129.8 (0, *C*), 112.5 (1, *C*H), 98.4 (1, O*C*HO), 83.0 (0, *C*I), 63.4 (2, O*C*H$_2$), 62.2 (2, O*C*H$_2$), 55.6 (3, O*C*H$_3$), 30.7 (2, *C*H$_2$), 25.6 (2, *C*H$_2$), 19.5 (2, *C*H$_2$) ppm.

LRMS (M/z, CI) 348 (M^+, 10 %), 247 ([M-OTHP]$^+$, 30 %), 137 (24 %), 121 (66 %), 85 (100 %) amu.

HRMS (M/z, EI) $C_{13}H_{17}IO_3^+$ requires 348.0222; Found M^+: 348.0222.

1-(4-Methoxy-3-(tetrahydro-2*H*-pyran-2-yloxymethyl)phenyl)-7-(4-(tetrahydro-2*H*-pyran-2-yloxy)phenyl)-3-heptanone **3.55**



3.45
$C_{18}H_{26}O_3$ (290)

3.55
$C_{31}H_{42}O_6$ (510)

Ketone **3.55** was prepared by a modification of the method of Dyker.[180] Alcohol **3.45** (1.50 g, 5.17 mmol), aryl iodide **3.48** (2.16 g, 6.20 mmol), sodium hydrogen carbonate (1.09 g, 12.93 mmol), tetra-*n*-butylammonium bromide (1.75 g, 5.43 mmol) and palladium(II) acetate (58 mg, 0.26 mmol) were stirred in *N*,*N*-dimethylformamide (25 mL) at 80 °C for 16 hours and then at room temperature for a further 24 hours. The mixture was poured into water (40 mL) and extracted with ether (2 × 40 mL). The combined organic phases were washed with water (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded the title compound **3.55** (1.63 g, 3.19 mmol, 62 %) as a pale yellow oil.

FT – IR (ν_{max}, neat) 2947 w, 2925 w, 1713 m, 1509 m, 1248 m, 1075 m, 1035 s, cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 269 (4200) nm.

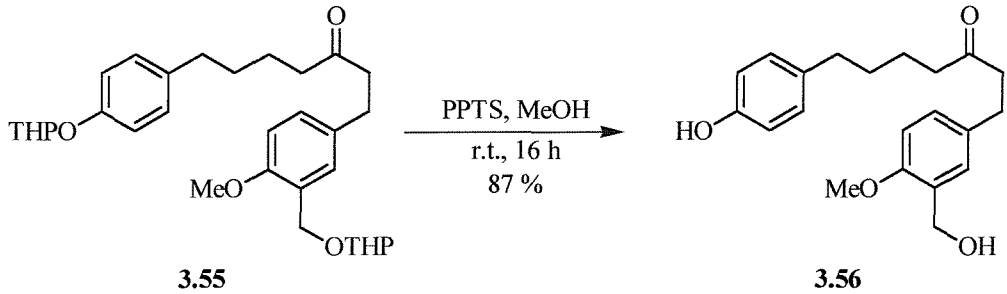
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.22 (1H, d, *J* 2.2 Hz, Ar*H*), 7.08 – 7.03 (3H, m, 3 × Ar*H*), 6.96 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 6.77 (1H, d, *J* 8.1 Hz, Ar*H*), 5.38 (1H, t, *J* 3.3 Hz ArOC*H*O), 4.78 (1H, d, *J* 12.5 Hz, OC*H*HAr), 4.74 (1H, t, *J* 3.3 Hz, OC*H*O), 4.54 (1H, d, *J* 12.5 Hz, OCH*H*Ar), 3.99 – 3.87 (2H, m, 2 × OC*H*H), 3.80 (3H, s, OCH_3), 3.65 – 3.52 (2H, m, 2 × OCH*H*), 2.83 (2H, dt, *J* 7.7, 6.6 Hz), 2.71 – 2.60 (2H, m), 2.54 (1H, t, *J* 7.4 Hz), 2.40 (1H, t, *J* 7.0 Hz), 1.80 – 1.72 (2H, m), 1.70 – 1.48 (16H, m) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 210 (0, *C*=O), 155.5 (0, *C*O), 155.2 (0, *C*O), 135.3 (0, *C*), 132.8 (0, *C*), 129.2 (1, 2 × *C*H), 128.8 (1, *C*H), 128.1 (1, *C*H), 127.8 (0, *C*), 116.4 (1, 2 × *C*H), 110.3 (1, *C*H), 98.2 (1, OCHO), 96.5 (1, OCHO), 64.0 (2, OCH_2), 62.1 (2, OCH_2), 62.0 (2, OCH_2), 55.5 (3, OCH_3), 44.6 (2, CH_2), 42.9 (2, CH_2), 34.9 (2, CH_2), 31.2 (2, CH_2), 30.6 (2, CH_2), 30.4 (2, CH_2), 29.0 (2, CH_2), 25.5 (2, CH_2), 25.2 (2, CH_2), 23.4 (2, CH_2), 19.5 (2, CH_2), 18.9 (2, CH_2) ppm.

LRMS (M/z, ES+) 533 ($[M+Na]^+$, 30 %), 449 ($M-THP+Na]^+$, 100 %), 325 (30 %), 209 (40 %) amu.

HRMS (M/z, ES+) $C_{31}H_{42}O_6Na^+$ requires: 533.2874; Found $[M+Na]^+$: 533.2868.

1-(3-Hydroxymethyl-4-methoxyphenyl)-7-(4-hydroxyphenyl)-3-heptanone **3.56**



3.55
$C_{31}H_{42}O_6$ (511)

3.56
$C_{21}H_{26}O_4$ (342)

Diacetal **3.55** (1.53 g, 3.00 mmol) was dissolved in methanol (40 mL). Pyridinium *p*-toluenesulfonate (75 mg, 0.30 mmol) was added and the mixture was stirred at room temperature for 16 hours and then concentrated *in vacuo*. The residue was diluted with dichloromethane (30 mL), washed with sodium hydrogen carbonate (sat. aq., 20 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica gel, 50 – 80

% ether / petrol) to yield the title compound **3.56** (895 mg, 2.62 mmol, 87 %) as a white solid.

MP 69 – 70 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3403 br. m, 2937 m, 1707 m, 1610 m, 1515 s, 1503 s, 1250 s, 1037 s cm^{-1}.

UV (λ_{max}, MeCN) 307 (1700), 273 (7500), 220 (21000) nm.

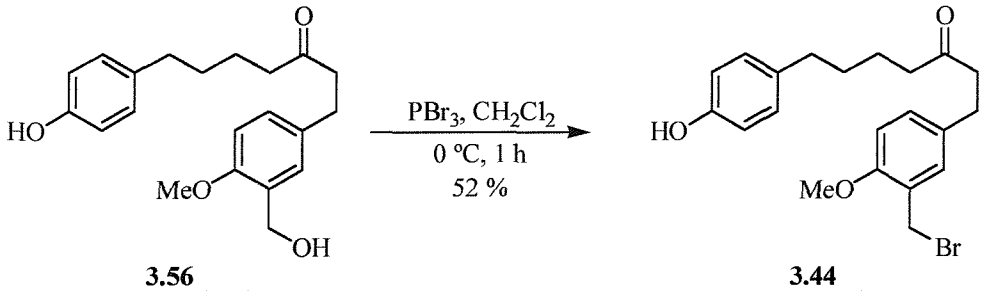
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.10 – 7.04 (2H, m, 2 × Ar*H*), 6.99 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 6.79 (1H, d, *J* 8.5 Hz, Ar*H*), 6.73 (2H, d, *J* 8.5 Hz, 2 ×Ar*H*), 5.88 (1H, s, ArO*H*), 4.67 (2H d, *J* 6.5 Hz, CH_2OH), 3.84 (3H, s, OCH_3), 2.81 (2H, t, *J* 7.5 Hz, CH_2), 2.64 (2H, t, *J* 7.5 Hz, CH_2), 2.58 (1H, t, *J* 6.5 Hz, CH$_2$O*H*), 2.52 (2H, t, *J* 7.0 Hz, CH_2), 2.37 (2H, t, *J* 7.0 Hz, CH_2), 1.63 – 1.48 (4H, m, 2 × CH_2) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 211.2 (0, *C*=O), 156.2 (0, *C*O), 154.4 (0, *C*O), 134.3 (0, 2 × *C*), 133.6 (0, *C*), 129.8 (1, 2 × *C*H), 129.2 (1, *C*H), 129.1 (1, *C*H), 115.6 (1, 2 × *C*H), 110.7 (1, *C*H), 62.5 (2, *C*H$_2$OH), 55.8 (3, O*C*H$_3$), 44.7 (2, *C*H$_2$), 43.3 (2, *C*H$_2$), 35.1 (2, *C*H$_2$), 31.4 (2, *C*H$_2$), 29.3 (2, *C*H$_2$), 23.7 (2, *C*H$_2$) ppm.

LRMS (M/z, ES-) 455 ([M+TFA-H]$^-$, 100 %), 249 (14 %) amu.

CHN $C_{21}H_{26}O_4$ requires: C 73.66, H 7.65; Found C 73.27, H 7.67.

1-(3-Bromomethyl-4-methoxyphenyl)-7-(4-hydroxyphenyl)-3-heptanone **3.44**



3.56
$C_{21}H_{26}O_4$ (342)

3.44
$C_{21}H_{25}BrO_3$ (405)

Alcohol **3.56** (865 mg, 2.53 mmol) was dissolved in dichloromethane (80 mL) and cooled to 0 °C. Phosphorus tribromide (165 µL, 480 mg, 1.77 mmol) was added and the mixture stirred for 2 hours at 0 °C. Water (20 mL) was added then the organic phase was washed with sodium hydrogen carbonate (sat. aq., 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 50 % ether / petrol) yielded the title compound **3.44** (530 mg, 1.31 mmol, 52 %) as a colourless oil.

FT – IR (ν_{max}, neat) 3371 br. m, 2932 m, 1705 m, 1614 m, 1514 s, 1504 s, 1259 s, 1234 m, 1030 m cm^{-1}.

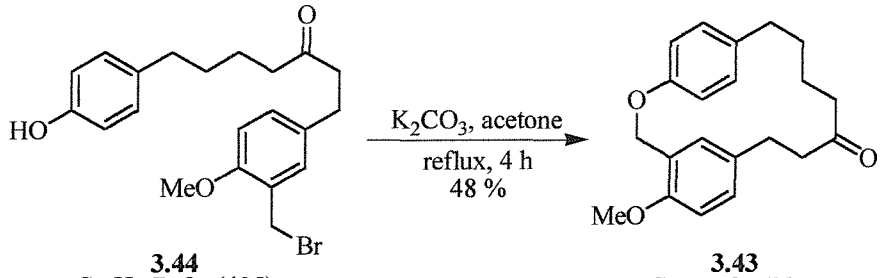
UV (λ_{max}, CH_2Cl_2) 273 (25000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.14 (1H, d, *J* 2.2 Hz, Ar*H*), 7.10 (1H, dd, *J* 8.4, 2.2 Hz, Ar*H*), 7.01 (2H, d, *J* 8.4 Hz, 2 × Ar*H*), 6.78 (1H, d, *J* 8.4 Hz, Ar*H*), 6.74 (2H, d, *J* 8.4 Hz, 2 × Ar*H*), 4.54 (2H, s, CH_2Br), 4.08 (1H, br s, ArO*H*), 3.87 (3H, s, OCH_3), 2.82 (2H, t, *J* 7.2 Hz, CH_2), 2.69 (2H, t, *J* 7.2 Hz, CH_2), 2.53 (2H, t, *J* 7.2 Hz, CH_2), 2.40 (2H, t, *J* 7.0 Hz, CH_2), 4.58 – 4.54 (4H, m, 2 × CH_2) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 211.0 (0, *C*=O), 156.3 (0, *C*O), 154.2 (0, *C*O), 134.7 (0, *C*), 133.6 (0, *C*), 131.2 (1, *C*H), 130.4 (1, *C*H), 129.8 (1, 2 × *C*H), 126.5 (0, *C*), 115.6 (1, 2 × *C*H), 111.5 (1, *C*H), 56.3 (3, OCH_3), 44.7 (2, CH_2), 43.4 (2, CH_2), 35.2 (2, CH_2), 31.5 (2, CH_2), 29.5 (2, CH_2), 29.5 (2, CH_2), 23.7 (2, CH_2) ppm.

LRMS (M/z, ES-) 519 ([M+TFA-H{^{81}Br}]$^-$, 100 %), 517 ([M+TFA-H{^{79}Br}]$^-$, 100 %), 380 (20 %), 378 (20 %) amu.

5-Methoxy-2-oxatricyclo[14.2.2.1^{4,8}]henicosa-1(18),4(21),5,7,16,19-hexaen-11-one **3.43**



3.44
$C_{21}H_{25}BrO_3$ (405)

3.43
$C_{21}H_{24}O_3$ (324)

To a refluxing mixture of potassium carbonate (355 mg, 2.56 mmol) in acetone (80 mL) was added phenol **3.44** (520 mg, 1.28 mmol) as a solution in acetone (20 mL) over 30 minutes. The mixture was stirred at reflux for a further 16 hours then cooled to room temperature, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 – 20 % ether / petrol) yielded the title compound **3.43** (200 mg, 0.62 mmol, 48 %) as a white solid.

MP 99 –102 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2928 m, 1710 m, 1503 s, 1252 s, 1207 m, 1035 m cm^{-1}.

UV (λ_{max}, MeOH) 320 (100), 279 (2900), 224 (11000) nm.

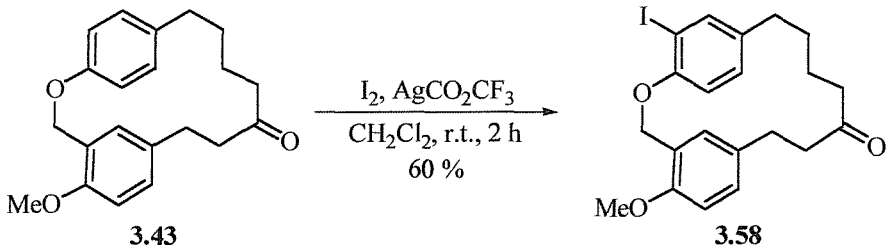
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.00 – 6.95 (3H, m, 3 × Ar*H*), 6.76 (1H, d, *J* 8.3 Hz, Ar*H*), 6.70 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 6.49 (1H, d, *J* 2.3 Hz, Ar*H*), 5.24 (2H, s, OCH_2), 3.86 (3H, s, OCH_3), 2.63 (2H, t, *J* 6.8 Hz, CH_2), 2.55 (2H, t, *J* 5.8 Hz, CH_2), 2.23 (2H, t, *J* 7.0 Hz, CH_2), 1.68 (2H, t, *J* 7.5 Hz, CH_2), 1.55 (2H, tt, *J* 6.5, 6.5 Hz, CH_2), 1.42 (2H, tt, *J* 7.3, 6.5 Hz, CH_2) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 210.8 (0, *C*=O), 156.1 (0, *C*O), 156.1 (0, *C*O), 135.3 (0, *C*), 132.4 (0, *C*), 130.2 (1, 2 × *C*H), 129.3 (1,*C*H), 129.0 (1, *C*H), 124.7 (0, *C*), 119.0 (1, 2 × *C*H), 110.7 (1, *C*H), 67.3 (2, OCH_2), 55.9 (3, OCH_3), 44.4 (2, CH_2), 42.6 (2, CH_2), 35.3 (2, CH_2), 30.0 (2, CH_2), 28.7 (2, CH_2), 21.8 (2, CH_2) ppm.

LRMS (M/z, CI) 324 (M^+, 100 %), 307 (6 %), 191 (10 %), 147 (20 %), 134 (40 %), 104 (40 %) amu.

18-Iodo-5-methoxy-2-oxatricyclo[14.2.2.1^{4,8}]henicosa-1(18),4(21),5,7,16,19-hexaen-11-one

3.58



3.43
$C_{21}H_{24}O_3$ (324)

3.58
$C_{21}H_{23}IO_3$ (450)

Silver(I) trifluoroacetate (102 mg, 0.46 mmol) was added to a solution of macrocycle **3.43** (125 mg, 0.39 mmol) in dichloromethane (50 mL). Iodine (98 mg, 0.39 mmol) was added as a solution in dichloromethane (50 mL) over 30 minutes then the mixture was stirred at room temperature for 2 hours. The resulting precipitate was removed by filtration through Celite and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded the title compound **3.58** (105 mg, 0.23 mmol, 60 %) as an off white solid.

MP 110 – 112 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2926 m, 1701 s, 1504 s, 1438 s, 1255 s, 1216 m, 1036 m cm^{-1}.

UV (λ_{max}, MeOH) 279 (5400), 227 (18000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.56 (1H, d, *J* 2.0 Hz, Ar*H*), 7.00 (1H, dd, *J* 8.2, 2.2 Hz, Ar*H*), 6.90 (1H, dd, *J* 8.4, 2.0 Hz, Ar*H*), 6.75 (1H, d, *J* 8.4 Hz, Ar*H*), 6.54 (1H, d, *J* 8.2 Hz, Ar*H*), 6.42 (1H, d, *J* 2.2 Hz, Ar*H*), 5.37 (1H, d, *J* 13.4 Hz,

OC*H*H), 5.29 (1H, d, *J* 13.4 Hz, OCH*H*), 3.88 (3H, s, OCH_3), 2.73 (1H, app. q, *J* 7.4 Hz), 2.61 – 2.54 (2H, m), 2.45 (1H, ddd, *J* 12.5, 8.1, 3.7 Hz), 2.27 (2H, t, *J* 7.0 Hz, CH_2), 2.01 – 1.92 (1H, m), 1.65 – 1.32 (5H, m) ppm.

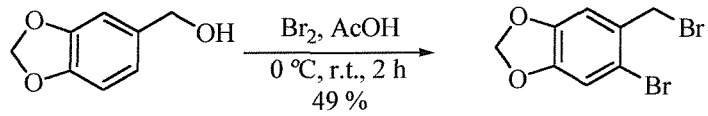
^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 210.7 (0, *C*=O), 156.4 (0, *C*O), 155.0 (0, *C*O), 139.8 (1, *C*H), 137.7 (0, *C*), 132.5 (0, *C*), 130.2 (1, *C*H), 129.8 (1, *C*H), 129.4 (1, *C*H), 124.0 (0, *C*), 118.9 (1, *C*H), 110.7 (1, *C*H), 90.0 (0, *C*I), 68.0 (2, O*C*H_2), 55.9 (3, O*C*H_3), 44.1 (2, *C*H_2), 42.9 (2, *C*H_2), 34.7 (2, *C*H_2), 29.8 (2, *C*H_2), 28.9 (2, *C*H_2), 21.9 (2, *C*H_2) ppm.

LRMS (M/z, CI) 324 ([MH-I]$^+$, 42 %), 224 (24 %), 207 (24 %), 154 (53 %), 44 (100 %) amu.

HRMS (M/z, ES+) $C_{42}H_{46}I_2O_6Na^+$ requires: 923.1276; Found [2M+Na]$^+$: 923.1267.

8.4 Experimental for Chapter 4

6-Bromo-5-(bromomethyl)-1,3-benzodioxole **4.3**[181]



4.2
$C_8H_8O_3$ (152)

4.3
$C_8H_6Br_2O_2$ (294)

6-Bromo-5-(bromomethyl)-1,3-benzodioxole **4.3** was prepared by the method of Padwa *et al.*[181] Piperonyl alcohol **4.2** (10.00 g, 65.72 mmol) was dissolved in acetic acid (20 mL) and cooled to 0 °C. Bromine (4.0 mL, 12.41 g, 77.65 mmol) was added dropwise as a solution in acetic acid (12 mL) over 15 minutes and the reaction was stirred at room temperature for 2 hours. Collection of the resulting solid by filtration, washing with water (2 × 30 mL) and recrystallisation from hot ethanol provided the title compound **4.3** (9.39 g, 31.9 mmol, 49 %) as a white solid.[181,182]

MP 83 – 86 °C (ethanol) lit. 89 – 91 °C (hexanes).[181]

FT – IR (ν_{max}, neat) 1501 s, 1483 s, 1409 m, 1388 m, 1250 s, 1212 m, 1124 m, 1036 m cm^{-1}.

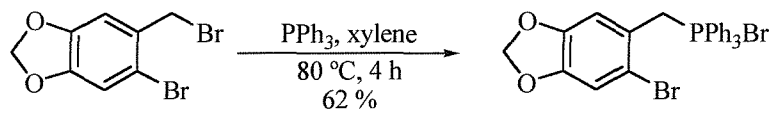
UV (λ_{max}, MeOH) 298 (4640), 260 (5440) nm.

^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.00 (1H, s, Ar*H*), 6.91 (1H, s, Ar*H*), 6.00 (2H, s, OCH_2O), 4.53 (2H, s, CH_2Br) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 148.9 (0, *C*O), 147.8 (0, *C*O), 130.1 (0, *C*), 115.8 (0, *C*Br), 113.3 (1, *C*H), 110.7 (1, *C*H), 102.3 (2, OCH_2O), 34.3 (2, *C*H_2Br) ppm.

LRMS (M/z, CI) 216 ([M+2H-Br{^{81}Br}]$^+$, 41 %), 214 ([M+2H-Br{^{79}Br}]$^+$, 42 %), 136 ([M+2H-2Br]$^+$, 100 %) amu.

((6-Bromo-1,3-benzodioxol-5-yl)methyl)triphenylphosphonium bromide **4.4**



4.3
$C_8H_6Br_2O_2$ (294)

4.4
$C_{26}H_{21}Br_2O_2P$ (556)

6-Bromo-5-(bromomethyl)-1,3-benzodioxole **4.3** (8.00 g, 27.2 mmol) and triphenylphosphine (9.50 g, 36.22 mmol) were dissolved in xylene (50 mL). After heating at 80 °C for 4 hours, the resulting precipitate was collected by filtration, washed with cold xylene (2 × 20 mL), cold petrol (3 × 20 mL) and dried *in vacuo* to provide the title compound **4.4** (9.40 g, 16.91 mmol, 62 %) as a white solid.[182]

MP > 250 °C (EtOH) lit. 278 – 280 °C (ether / MeOH).[182]

FT – IR (ν_{max}, neat) 1503 m, 1476 s, 1437 s, 1243 m, 1111 s, 1032 m cm^{-1}.

UV (λ_{max}, MeOH) 302 (3890), 271 (5000) nm.

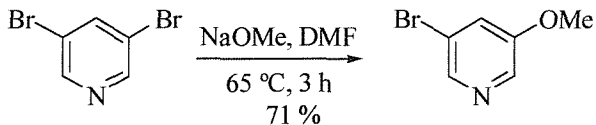
^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 7.90 – 7.55 (15H, m, 15 × Ar*H*), 7.02 (1H, d, *J* 2.0 Hz, Ar*H*), 6.80 (1H, s, Ar*H*), 5.95 (2H, s, OCH_2O), 5.52 (2H, d, *J* 12.9 Hz, CH_2P) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 149.1 (0, *C*O), 148.1 (0, *C*O), 135.4 (1, 3 × *C*H), 134.5 (1, d, *J* 10.0 Hz, 6 × *C*H), 130.4 (1, d, *J* 12.5 Hz, 6 × *C*H), 120.1 (0, d, *J* 8.8 Hz, *C*), 118.3 (0, *C*Br), 117.5 (0, d, *J* 85.6 Hz, 3 × *C*), 112.7 (1, *C*H), 112.3 (1, *C*H), 102.4 (2, OCH_2O), 31.2 (2, d, *J* 48.3 Hz, CH_2P) ppm.

LRMS (M/z, ES+) 477 ([M-Br{^{81}Br}]$^+$, 100 %), 475 ([M-Br{^{79}Br}]$^+$, 90 %) amu.

CHN $C_{26}H_{21}Br_2O_2P$ requires: C 56.14, H 3.81; Found: C 55.96, H 3.77.

5-Bromo-3-methoxypyridine **4.8**[183]



4.7
$C_5H_3Br_2N$ (237)

4.8
C_6H_6BrNO (188)

5-Bromo-3-methoxypyridine **4.8** was prepared by the method of Comins and Killpack.[183] Sodium (970 mg, 42.2 g atom) was added portionwise to methanol at 0 °C. After complete

dissolution of the metal the solvent was evaporated *in vacuo* and the resulting white solid dissolved in *N,N*-dimethylformamide (20 mL). 3,5-Dibromopyridine **4.7** (5.00 g, 21.11 mmol) was added and the mixture stirred at 65 °C for 3 hours. After cooling to room temperature, water (30 mL) was added and the mixture extracted with ether (5 × 30 mL). Concentration *in vacuo* and purification by column chromatography (silica gel, 25 % ether / petrol) provided the title compound **4.8** (2.82 g, 15.00 mmol, 71 %) as a white solid.[183]

MP 33 – 35 °C (petrol) lit. 34 – 35 °C (hexanes).[183]

FT – IR (ν_{max}, neat) 1576 s, 1556 s, 1457s, 1416 s, 1313 s, 1265 s, 1222 m, 1094 m, 1029 s, 1008 s cm^{-1}.

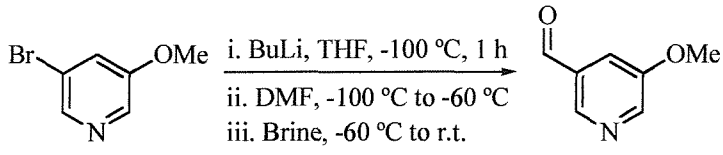
UV (λ_{max}, MeOH) 292 (2880) nm.

^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 8.28 (1H, d, *J* 2.0 Hz, Ar*H*), 8.23 (1H, d, *J* 2.0 Hz, Ar*H*), 7.37 (1H, t, *J* 2.0 Hz, Ar*H*), 3.83 (3H, s, OCH_3) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 156.2 (0, *C*O), 143.0 (1, *C*H), 136.3 (1, *C*H), 123.4 (1, *C*H), 120.5 (0, *C*Br), 56.0 (3, O*C*H_3) ppm.

LRMS (M/z, ES+) 231 ([MH+MeCN{^{81}Br}]$^+$, 100 %), 229 ([MH+MeCN{^{79}Br}]$^+$, 96 %), 190 (MH{^{81}Br}$^+$, 85 %), 188 (MH{^{79}Br}$^+$, 82 %) amu.

5-Methoxy-3-pyridinecarboxaldehyde **4.9**[183]



4.8 C_6H_6BrNO (188)

4.9 $C_7H_7NO_2$ (137)

Aldehyde **4.9** was prepared by the method of Comins and Killpack.[183] 5-Bromo-3-methoxypyridine **4.8** (980 mg, 5.21 mmol) was dissolved in tetrahydrofuran (30 mL) and cooled to –100 °C. *n*-Butyllithium (1.77 M in hexanes, 3.6 mL, 6.38 mmol) was added dropwise over 15 minutes while maintaining the internal temperature below –95 °C. The reaction was stirred at –100 °C for 1 hour before the addition of *N,N*-dimethylformamide (1.2 mL, 1.10 g, 15.00 mmol). The mixture was allowed to warm to –60 °C over 30 minutes when brine (20 mL) was added. After warming to room temperature, the mixture was extracted with ether (3 × 30 mL) and the combined organic phases were dried (K_2CO_3). Concentration *in vacuo* and purification by column chromatography (silica gel, 40 % ether / petrol) provided the title aldehyde **4.9** (580 mg, 4.23 mmol, 81 %) as a pale yellow oil.[183]

FT – IR (ν_{max}, neat) 1691 s, 1587 s, 1471 s, 1427 m, 1388 m, 1321 s, 1289 s, 1253 m, 1014 m cm^{-1}.

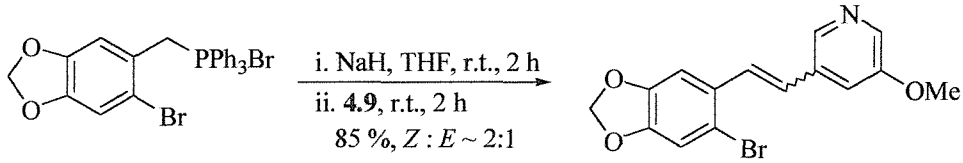
UV (λ_{max}, MeOH) 312 (380), 286 (1320) nm.

^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 10.10 (1H, s, C*H*O), 8.62 (1H, d, *J* 1.2 Hz, Ar*H*), 8.55 (1H, d, *J* 2.0 Hz, Ar*H*), 7.58 (1H, dd, *J* 2.0, 1.2 Hz, Ar*H*), 3.92 (3H, s OCH_3) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 190.8 (1, C*H*O), 156.3 (0, *C*O), 145.3 (1, *C*H), 145.0 (1, *C*H), 132.2 (0, *C*), 116.4 (1, *C*H), 56.0 (3, OCH_3) ppm.

LRMS (M/z, ES+) 351 (20 %), 310 ($[2M+H_2O+NH_4]^+$, 60 %), 207 (30 %), 166 (100 %) amu.

(*Z*)-3-(2-(6-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl)-5-methoxypyridine **4.5** and (*E*)-3-(2-(6-bromo-1,3-benzodioxol-5-yl)-1-ethenyl)-5-methoxypyridine **4.6**



4.4 $C_{26}H_{21}Br_2O_2P$ (556)

(*Z*)-**4.5**
(*E*)-**4.6** $C_{15}H_{12}BrNO_3$ (334)

Sodium hydride (60 % in mineral oil, 132 mg, 3.30 mmol), pre-washed with tetrahydrofuran (10 mL), was suspended in tetrahydrofuran (30 mL) and cooled to 0 °C. ((6-Bromo-1,3-benzodioxol-5-yl)methyl)triphenylphosphonium bromide **4.4** (1.67 g, 3.00 mmol) was added in one portion and the mixture allowed to stir at room temperature for 2 hours. After cooling to 0 °C, 5-methoxy-3-pyridinecarboxaldehyde **4.9** (340 mg, 2.48 mmol) was added as a solution in tetrahydrofuran (10 mL) and the mixture stirred at room temperature for a further 2 hours. The mixture was filtered through Celite and the organic filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 40 % ether / petrol) provided firstly the *Z*-isomer **4.5** (420 mg, 1.26 mmol, 51 %) as a pale yellow solid, then a mixture of *Z* & *E* isomers (75 mg, 0.22 mmol, 9 %) and finally the *E*-isomer **4.6** (210 mg, 0.63 mmol, 25 %) as an off-white solid.

(*Z*)-3-(2-(6-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl)-5-methoxypyridine **4.5**

MP 106 - 109 °C (ether / petrol).

FT – IR (ν_{max}, neat) 1583 m, 1501 m, 1476 s, 1283 m, 1229 m, 1037 s cm^{-1}.

UV (λ_{max}, MeOH) 336 (6350), 302 (8680) nm.

^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 8.12 (1H, d, *J* 1.9 Hz, Ar*H*), 8.05 (1H, d, *J* 1.2 Hz, Ar*H*), 7.06 (1H, s, Ar*H*), 6.98 (1H, app. t, *J* 1.6 Hz, Ar*H*), 6.67 (1H, d, *J* 11.8 Hz, C*H*=CH), 6.59 (1H, s, Ar*H*), 6.54 (1H, d, *J* 11.8 Hz, CH=C*H*), 5.93 (2H, OCH_2O), 3.72 (3H, s, OCH_3) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 155.3 (0, *C*O), 148.2 (0, *C*O), 147.4 (0, *C*O), 142.8 (1, *C*H), 136.3 (1, *C*H), 132.8 (0, *C*), 132.1 (1, *C*H), 130.3 (0, *C*), 127.2 (1, *C*H=CH), 120.0 (1, CH=*C*H), 114.9 (0, *C*Br), 112.9 (1, *C*H), 110.1 (1, *C*H), 102.0 (2, O*C*H_2O), 55.5 (3, O*C*H_3) ppm.

LRMS (M/z, ES+) 336 ($MH^+\{^{81}Br\}$, 100 %), 334 ($MH^+\{^{79}Br\}$, 95 %) amu.

HRMS (M/z, EI) $C_{15}H_{12}{}^{79}BrNO_3{}^+$ requires: 333.0001; Found M^+: 332.9995.

(*E*)-3-(2-(6-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl)-5-methoxypyridine **4.6**

MP 112 – 114 °C (ether / petrol).

FT – IR (ν_{max}, neat) 1582 m, 1503 m, 1475 s, 1411 m, 1245 m, 1170 m, 1037 s cm^{-1}.

UV (λ_{max}, MeOH) 342 (13550), 304 (9920), 258 (9730) nm.

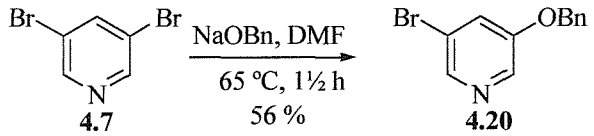
^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 8.33 (1H, d, *J* 1.9 Hz, Ar*H*), 8.22 (1H, d, *J* 2.6 Hz, Ar*H*), 7.43 (1H, d, *J* 16.2 Hz, C*H*=CH), 7.31 (1H, app. t, *J* 2.2 Hz, Ar*H*), 7.12 (1H, s, Ar*H*), 7.03 (1H, s, Ar*H*), 6.84 (1H, d, *J* 16.2 Hz, CH=C*H*), 6.00 (2H, s, OCH_2O), 3.90 (3H, s, OCH_3) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 156.0 (0, *C*O), 148.6 (0, *C*O), 148.0 (0, *C*O), 141.4 (1, *C*H), 136.8 (1, *C*H), 129.9 (0, *C*), 129.7 (1, *C*H), 125.9 (1, C*H*=CH), 122.9 (0, *C*), 117.0 (1, CH=C*H*), 115.8 (0, *C*Br), 113.0 (1, *C*H), 106.0 (1, *C*H), 102.1 (2, O*C*H_2O), 55.8 (3, O*C*H_3) ppm.

LRMS (M/z, ES+) 336 ($MH^+\{^{81}Br\}$, 100 %), 334 ($MH^+\{^{79}Br\}$, 95 %) amu.

HRMS (M/z, EI) $C_{15}H_{12}{}^{79}BrNO_3{}^+$ requires: 333.0001; Found M^+: 333.0001.

3-(Benzyloxy)-5-bromopyridine **4.20**



4.7 $C_5H_3Br_2N$ (237)

4.20 $C_{12}H_{10}BrNO$ (264)

Sodium (160 mg, 6.96 g atom) was added portionwise to benzyl alcohol (10 mL). After complete dissolution, excess alcohol was removed by distillation under reduced pressure. The resulting pale brown solid was dissolved in *N,N*-dimethylformamide (20 mL) to which was added 3,5-dibromopyridine **4.7** (1.00 g, 4.22 mmol). The mixture was stirred at 65 °C for 1½ hours. After cooling to room temperature, water (20 mL) was added and the mixture extracted with ether (3 × 20 mL). The combined organic phases were washed with water (15 mL) and brine (15 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded benzaldehyde (80 mg, 0.75 mmol) and then the title compound **4.20** (625 mg, 2.37 mmol, 56 %) as a white solid.[184]

MP 64 – 65 °C (ether / petrol).

FT – IR (ν_{max}, neat) 1574 s, 1553 m, 1446 m, 1429 s, 1380 m, 1310 s, 1262 s, 1220 m, 1184 m, 1008 s cm^{-1}.

UV (λ_{max}, MeOH) 290 (5120) nm.

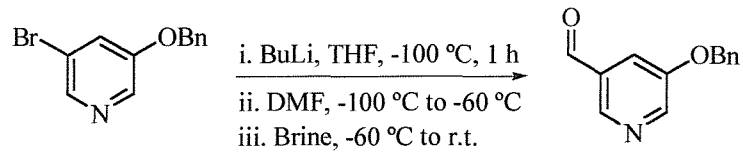
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.34 – 8.30 (2H, m, 2 × Ar*H*), 7.46 – 7.33 (6H, m, Ar*H* & C_6H_5), 5.10 (2H, s, OCH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 155.4 (0, *C*O), 143.3 (1, *C*H), 136.8 (1, *C*H), 135.6 (0, *C*), 129.0 (1, 2 × *C*H), 128.7 (1, *C*H), 127.7 (1, 2 × *C*H), 124.6 (1, *C*H), 120.6 (0, *C*Br), 70.8 (2, O*C*H$_2$) ppm.

LRMS (M/z, ES+) 307 ([MH+MeCN{^{81}Br}]$^+$, 42 %), 305 ([MH+MeCN{^{79}Br}]$^+$, 40 %), 266 (MH$^+${^{81}Br}, 27 %), 264 (MH$^+${^{79}Br}, 28 %), 140 (38 %), 138 (43 %) amu.

CHN $C_{12}H_{10}BrNO$ requires: C 56.57, H 3.82, N 5.30; Found: C 56.49, H 3.80, N 5.23.

5-(Benzyloxy)nicotinaldehyde **4.21**



4.20 $C_{12}H_{10}BrNO$ (264)

69 %

4.21 $C_{13}H_{11}NO_2$ (213)

3-(Benzyloxy)-5-bromopyridine **4.20** (1.09 g, 4.11 mmol) was dissolved in tetrahydrofuran (50 mL) and cooled to –100 °C. *n*-Butyllithium (1.37 M in hexanes, 3.6 mL, 4.93 mmol) was added dropwise over 10 minutes and the mixture stirred at -100 °C for 1 hour. *N,N*-Dimethylformamide (1.2 mL, 1.16 g, 15.92 mmol) was added dropwise over 5 minutes, the mixture was allowed to warm to –60 °C over 30 minutes then quenched with brine (25 mL) and extracted with ether (3 × 20 mL). The combined organic phases were dried (K_2CO_3), concentrated *in vacuo* and purified by column chromatography (silica gel, 30 % ether / petrol) to yield the title aldehyde **4.21** (600 mg, 2.82 mmol, 69 %) as a white solid.

MP 62 – 64 °C (ether / petrol).

FT – IR (ν_{max}, neat) 1698 s, 1584 m, 1454 m, 1380 m, 1318 s, 1280 s, 1249 m, 1172 m cm^{-1}.

UV (λ_{max}, MeOH) 310 (910), 286 (4260), 220 (19470) nm.

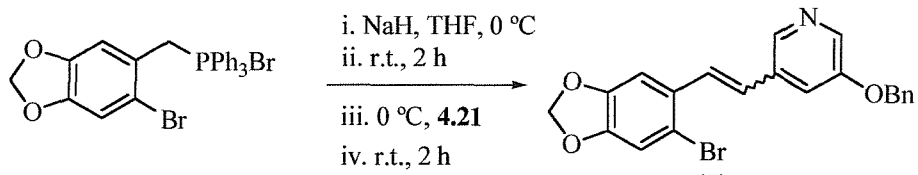
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 10.08 (1H, s, C*H*O), 8.68 (1H, d, *J* 1.5 Hz, Ar*H*), 8.63 (1H, d, *J* 2.9 Hz, Ar*H*), 7.69 (1H, dd, *J* 2.9, 1.5 Hz, Ar*H*), 7.46 – 7.35 (5H, m, C_6H_5), 5.17 (2H, s, OCH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 190.8 (1, *C*HO), 155.5 (0, *C*O), 145.6 (1, *C*H), 145.4 (1, *C*H), 135.5 (0, *C*), 132.2 (0, *C*), 129.0 (1, 2 × *C*H), 128.7 (1, *C*H), 127.8 (1, 2 × *C*H), 117.8 (1, *C*H), 70.7 (OCH_2) ppm.

LRMS (M/z, ES+) 255 ($[MH+MeCN]^+$, 55 %), 214 (MH^+, 43 %), 186 ($[MH-CO]^+$, 60 %), 140 (46 %) amu.

CHN $C_{13}H_{11}NO_2$ requires: C 73.22, H 5.20, N 6.57; Found: C 73.18, H 5.20, N 6.52.

(*Z*)-3-(Benzyloxy)-5-(2-(6-bromo-1,3-benzodioxol-5-yl)-1-ethenyl)pyridine **4.22** and (*E*)-3-(benzyloxy)-5-(2-(6-bromo-1,3-benzodioxol-5-yl)-1-ethenyl)pyridine **4.23**



4.4
$C_{26}H_{21}Br_2O_2P$ (556)

(*Z*)-**4.22**
(*E*)-**4.23**
$C_{21}H_{16}BrNO_3$ (410)

Sodium hydride (60 % in mineral oil, 180 mg, 4.50 mmol), pre-washed with petrol (10 mL), was suspended in tetrahydrofuran (30 mL) and cooled to 0 °C. ((6-Bromo-1,3-benzodioxol-5-yl)methyl)triphenylphosphonium bromide **4.4** (1.79 g, 3.22 mmol) was added and the mixture allowed to stir at room temperature for 2 hours. Upon cooling to 0 °C, 5-(benzyloxy)nicotinaldehyde **4.21** (527 mg, 2.47 mmol) was added as a solution in tetrahydrofuran (5 mL). The mixture was allowed to warm to room temperature and stirred for a further 2 hours. The mixture was filtered through Celite and the organic filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 40 % ether / petrol) firstly gave **4.22** (420 mg, 1.02 mmol, 41 %) as a colourless oil then a mixture of isomers (90 mg, 0.22 mg, 9 %) and finally **4.23** (260 mg, 0.63 mmol, 26 %) as a pale yellow solid.

(*Z*)-3-(Benzyloxy)-5-(2-(6-bromo-1,3-benzodioxol-5-yl)-1-ethenyl)pyridine **4.22**

FT – IR (ν_{max}, neat) 3031 m, 1574 m, 1500 m, 1475 s, 1432 m, 1271 m, 1230 s, 1037 m cm^{-1}.

UV (λ_{max}, MeOH) 296 (8920), 282 (8920), 228 (20300) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.20 (1H, d, *J* 2.9 Hz, Ar*H*), 8.05 (1H, d, *J* 1.8 Hz, Ar*H*), 7.44 – 7.33 (5H, m, C_6H_5), 7.06 (1H, s, Ar*H*), 7.04 (1H, t, *J* 2.2 Hz, Ar*H*), 6.67 (1H, d, *J* 12.1 Hz, C*H*=CH), 6.58 (1H, s, Ar*H*), 6.54 (1H, d, *J* 12.1 Hz, CH=C*H*), 5.92 (2H, s, OCH_2O), 4.96 (2H, s, OCH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 154.6 (0, *C*O), 148.3 (0, *C*O), 147.4 (0, *C*O), 143.0 (1, *C*H), 137.2 (1, *C*H), 136.2 (0, *C*), 132.8 (1, *C*H), 132.1 (0, *C*), 130.2 (0, *C*), 128.9 (1, 2 × *C*H), 128.4 (1, *C*H), 127.6 (1, 2 × *C*H), 127.1 (1, *C*H=CH), 121.3 (1, *C*H), 114.9 (0, *C*Br), 113.0 (1, CH=*C*H), 110.1 (1, *C*H), 102.0 (2, OCH_2O), 70.5 (2, OCH_2) ppm.

LRMS (M/z, ES+) 412 ($MH^+\{^{81}Br\}$, 100 %), 410 ($MH^+\{^{79}Br\}$, 98 %) amu.

HRMS (M/z, EI) $C_{21}H_{16}{}^{79}BrNO_3{}^+$ requires: 409.0314; Found M^+: 409.0317.

(*E*)-3-(Benzyloxy)-5-(2-(6-bromo-1,3-benzodioxol-5-yl)-1-ethenyl)pyridine **4.23**

MP 146 – 147 °C (ether / petrol).

FT – IR (ν_{max}, neat) 1580 m, 1502 m, 1474 s, 1410 m, 1292 m, 1244 m, 1173 m, 1037 s cm^{-1}.

UV (λ_{max}, MeOH) 334 (15500), 297 (11100), 253 (12000), 226 (21100) nm.

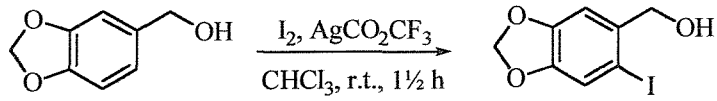
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.35 (1H, d, *J* 1.5 Hz, Ar*H*), 8.28 (1H, d, *J* 2.9 Hz, Ar*H*), 7.55 – 7.30 (7H, m, Ar*H*, C*H*=CH & C_6H_5), 7.17 (1H, s, Ar*H*), 7.09 (1H, s, Ar*H*), 6.83 (1H, d, *J* 16.2 Hz, CH=C*H*), 6.02 (2H, s, OCH_2O), 5.17 (2H, s, OCH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 155.2 (0, *C*O), 148.6 (0, *C*O), 148.1 (0, *C*O), 141.8 (1, *C*H), 137.1 (1, *C*H), 136.2 (0, *C*), 133.7 (0, *C*), 130.0 (0, *C*), 129.8 (1, *C*H), 128.9 (1, 2 × *C*H), 128.5 (1, *C*H), 127.8 (1, 2 × *C*H), 125.8 (1, CH=*C*H), 118.1 (1, *C*H), 115.9 (0, *C*Br), 113.1 (1, CH=*C*H), 106.0, (1, *C*H) 102.1 (2, OCH_2O), 70.7 (2, OCH_2) ppm.

LRMS (M/z, ES+) 412 (MH{^{81}Br}$^+$, 100 %), 410 (MH{^{79}Br}$^+$, 98 %) amu.

CHN $C_{21}H_{16}BrNO_3$ requires: C 61.48, H 3.93, N 3.41; Found: C 61.27, H 3.96, N 3.35.

(6-Iodo-1,3-benzodioxol-5-yl)methanol **4.24**[112]



4.2 $C_8H_8O_3$ (152) **4.24** $C_8H_7IO_3$ (278)

(6-Iodo-1,3-benzodioxol-5-yl)methanol **4.24** was prepared by the method of Cossy *et al.*[112] Thus, silver(I) trifluoroacetate (4.79 g, 21.69 mmol) was added to a solution of piperonyl alcohol **4.2** (3.00 g, 19.72 mmol) in chloroform (150 mL). Iodine (5.26 g, 20.71 mmol) was added in one portion and the mixture stirred at room temperature for 1½ hours. The resulting silver iodide was removed by filtration through Celite and the filtrate washed with sodium hydrogen carbonate (sat. aq., 50 mL) then sodium thiosulfate (sat. aq., 30 mL) and dried ($MgSO_4$). Concentrated *in vacuo* yielded the title compound **4.24** (4.53 g, 16.29 mmol, 83 %) as an orange solid.[112]

MP 103 – 104 °C (EtOH) lit. 108 – 109 °C ($CHCl_3$).[112]

FT – IR (ν_{max}, neat) 3261 br. s, 2898 w, 1502 m, 1478 s, 1447 m, 1242 s, 1097 m, 1033 s cm^{-1}.

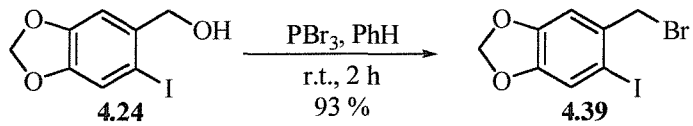
UV (λ_{max}, CH_2Cl_2) 285 (4700), 236 (8600) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.23 (1H, s, Ar*H*), 6.99 (1H, s, Ar*H*), 5.98 (2H, s, OCH_2O), 4.58 (2H, d, *J* 5.9 Hz, CH_2OH), 2.05 (1H, t, *J* 5.9 Hz, O*H*) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 149.0 (0, *C*O), 148.3 (0, *C*O), 136.7 (0, *C*), 118.9 (1, *C*H), 109.5 (1, *C*H), 102.1 (2, OCH_2O), 85.8 (0, *C*I), 69.7 (2, CH_2OH) ppm.

LRMS (M/z, CI) 278 (M^+, 53 %), 261 ($[M\text{-}OH]^+$, 98 %), 168 (13 %), 151 ($[M\text{-}I]^+$, 74 %), 135 ($[MH\text{-}I\text{-}OH]^+$, 100 %) amu.

5-(Bromomethyl)-6-iodo-1,3-benzodioxole **4.39**



4.24 $C_8H_7IO_3$ (278)

4.39 $C_8H_6BrIO_2$ (341)

To a cooled solution (0 °C) of (6-Iodo-1,3-benzodioxol-5-yl)methanol **4.24** (1.85 g, 6.65 mmol) in benzene (30 mL) was added phosphorus tribromide (230 μL, 630 mg, 2.32 mmol) and the mixture stirred at room temperature for 2 hours. The solvent was removed under reduced pressure and the residue diluted with dichloromethane (30 mL), washed with water (20 mL) then sodium hydrogen carbonate (sat. aq., 20 mL) and dried ($MgSO_4$). Concentration *in vacuo* yielded the title bromide **4.39** (2.11 g, 6.19 mmol, 93 %) as an off-white solid.[112,117]

MP 83 – 84 °C (petrol) lit. 72 - 73 °C (ethanol).[117]

FT – IR (ν_{max}, neat) 3097 w, 3036 w, 2976 w, 2885 m, 1609 m, 1500 s, 1481 s, 1383 m, 1344 m, 1251 s, 1236 s, 1210 m, 1123 m, 1041 s cm^{-1}.

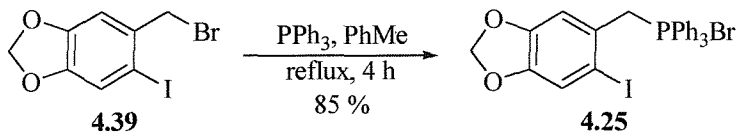
UV (λ_{max}, CH_2Cl_2) 264 (42000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.25 (1H, s, Ar*H*), 6.97 (1H, s, Ar*H*), 6.00 (2H, s, OCH_2O), 4.56 (2H, s, CH_2Br) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 149.1 (0, 2 × *C*O), 133.8 (0, *C*), 119.5 (1, *C*H), 110.5 (1, *C*H), 102.4 (2, OCH_2O), 89.2 (0, *C*I), 39.9 (2, CH_2Br) ppm.

LRMS (M/z, Cl) 261 ($[M-Br]^+$, 15 %), 136 ($[M+2H-Br-I]^+$, 100 %), 135 ($[MH-Br-I]^+$, 52 %), 78 (18 %) amu.

(6-Iodo-1,3-benzodioxol-5-ylmethyl)triphenylphosphonium bromide **4.25**



4.39 $C_8H_6BrIO_2$ (341)

4.25 $C_{26}H_{21}BrIO_2P$ (603)

A solution of 5-(bromomethyl)-6-iodo-1,3-benzodioxole **4.39** (1.56 g, 4.57 mmol) and triphenylphosphine (1.26 g, 4.80 mmol) in toluene (30 mL) was heated at reflux for 16 hours. After cooling to room temperature, the resulting white solid was collected by filtration and washed with petrol (2 × 10 mL) to yield the title compound **4.25** (2.34 g, 3.88 mmol, 85 %) as a white solid.[117]

MP 269 – 271 °C dec. (EtOH) lit. 268 – 272 °C (EtOH).[117]

FT – IR (ν_{max}, neat) 3054 w, 2898 w, 2851 m, 1503 m, 1480 s, 1438 s, 1233 s, 1112 s, 1033 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 296 (3600), 265 (4500).

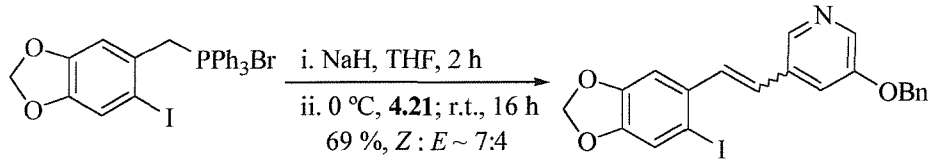
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.82 – 7.76 (3H, m, 3 × Ar*H*), 7.70 – 7.61 (12H, m, 12 × Ar*H*), 7.04 (1H, d, *J* 0.7 Hz, Ar*H*), 6.97 (1H, d, *J* 2.4 Hz, Ar*H*), 5.93 (2H, s, OCH_2O), 5.52 (2H, d, *J* 13.6 Hz, CH_2P) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 149.4 (0, d, *J* 3.6 Hz, *C*O), 149.3 (0, d, *J* 3.7 Hz, *C*O), 135.7 (1, d, *J* 2.4 Hz, 3 × *C*H), 134.9 (1, d, *J* 9.9 Hz, 6 × *C*H), 130.7 (1, d, *J* 12.6 Hz, 6 × *C*H), 123.9 (0, d, *J* 9.1 Hz, *C*), 119.0 (1, d, *J* 2.7 Hz, *C*H), 117.7 (0, d, *J* 85.5 Hz, 3 × *C*), 112.0 (1, d, *J* 4.1 Hz, *C*H), 102.6 (2, OCH_2O), 93.8 (0, d, *J* 8.1 Hz, *C*I), 36.2 (2, d, *J* 48.0 Hz, CH_2P) ppm.

^{31}P – NMR (121 MHz, $CDCl_3$) δ_P 22.7 ppm.

LRMS (M/z, ES+) 523 ($[M-Br]^+$, 100 %) amu.

(*Z*)-3-(Benzyloxy)-5-(2-(6-iodo-1,3-benzodioxol-5-yl)-1-ethenyl)pyridine **4.26** and (*E*)-3-(benzyloxy)-5-(2-(6-iodo-1,3-benzodioxol-5-yl)-1-ethenyl)pyridine **4.27**



4.25 — $C_{26}H_{21}BrIO_2P$ (603)

(*Z*)-**4.26**, (*E*)-**4.27** — $C_{21}H_{16}INO_3$ (457)

To a suspension of sodium hydride (60 % in mineral oil, 180 mg, 4.56 mmol, pre-washed with tetrahydrofuran (10 mL)) in tetrahydrofuran (50 mL) was added phosphonium bromide **4.25** (2.29 g, 3.80 mmol) and the mixture stirred at room temperature for 2 hours. After cooling to 0 °C, aldehyde **4.21** (735 mg, 3.45 mmol) was added as a solution in tetrahydrofuran (10 mL) and the mixture stirred at room temperature for 16 hours. The resulting orange mixture was filtered through Celite and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 40 – 60 % ether / petrol) yielded firstly **4.26** (700 mg, 1.53 mmol, 44 %) as a pale yellow oil and then **4.27** (400 mg, 0.88 mmol, 25 %) as a pale yellow solid.

(*Z*)-3-(Benzyloxy)-5-(2-(6-iodo-1,3-benzodioxol-5-yl)-1-ethenyl)pyridine **4.26**

FT – IR (ν_{max}, neat) 3032 w, 2953 w, 2918 m, 1578 m, 1474 s, 1432 m, 1282 m, 1227 s, 1037 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 290 (10000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.19 (1H, d, *J* 2.8 Hz, Ar*H*), 8.02 (1H, d, *J* 1.6 Hz, Ar*H*), 7.45 – 7.33 (5H, m, C_6H_5), 7.31 (1H, s, Ar*H*), 6.99 (1H, dd, *J* 2.8, 1.6 Hz, Ar*H*), 6.59 (1H, s, Ar*H*), 6.57 (1H, d, *J* 12.0 Hz, C*H*=CH), 6.49 (1H, d, *J* 12.0 Hz, CH=C*H*), 5.93 (2H, s, OCH_2O), 4.95 (2H, s, OCH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 154.6 (0, *C*O), 148.5 (0, *C*O), 148.2 (0, *C*O), 143.1 (1, *C*H), 142.5 (0, *C*), 137.3 (1, *C*H), 136.1 (1, *C*H), 134.3 (0, *C*), 132.7 (0, *C*), 128.9 (1, 2 × *C*H), 128.4 (1, *C*H), 127.6 (1, 2 × *C*H), 126.9 (1, *C*H), 121.2 (1, *C*H), 118.6 (1, *C*H), 109.9 (1, *C*H), 101.9 (2, OCH_2O), 88.1 (0, *C*I), 70.4 (2, OCH_2) ppm.

LRMS (M/z, ES+) 523 (35 %), 499 ($[MH+MeCN]^+$, 20 %), 458 (MH^+, 100 %) amu.

HRMS (M/z, ES+) $C_{21}H_{17}INO_3^+$ requires: 458.0248; Found MH^+: 458.0248.

(*E*)-3-(Benzyloxy)-5-(2-(6-iodo-1,3-benzodioxol-5-yl)-1-ethenyl)pyridine **4.29**

MP 139 – 141 °C (ethanol).

FT – IR (ν_{max}, neat) 3028 w, 2883 w, 1578 m, 1498 m, 1474 s, 1295 m, 1229 m, 1173 m, 1037 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 333 (20000), 238 (19000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.33 (1H, d, *J* 1.8 Hz, Ar*H*), 8.29 (1H, d, *J* 2.9 Hz, Ar*H*) , 7.50 – 7.38 (6H, m, Ar*H* & C_6H_5), 7.36 (1H, s, Ar*H*), 7.28 (1H, d, *J* 16.0 Hz, C*H*=CH), 7.13 (1H, s, Ar*H*), 6.77 (1H, d, *J* 16.0 Hz, CH=C*H*), 6.01 (2H, s, OCH_2O), 5.17 (2H, s, OCH_2) ppm.

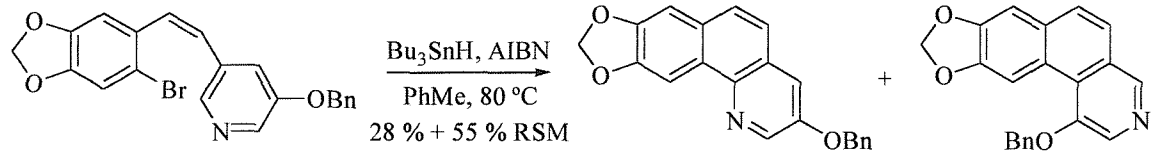
^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 155.1 (0, *C*O), 149.1 (0, *C*O), 148.7 (0, *C*O), 141.7 (1, *C*H), 137.5 (1, *C*H), 136.2 (0, *C*), 134.7 (1, *C*H), 133.5 (0, *C*), 133.2 (0, *C*), 129.0 (1, 2 × *C*H), 128.5 (1, *C*H), 127.8 (1, 2 × *C*H), 126.1 (1, *C*H), 118.9 (1, *C*H), 118.1 (1, *C*H), 106.0 (1, *C*H), 102.1 (2, OCH_2O), 89.7 (0, *C*I), 70.6 (2, OCH_2) ppm.

LRMS (M/z, ES+) 523 (100 %), 499 ($[MH+MeCN]^+$, 25 %), 458 (MH^+, 80 %) amu.

CHN $C_{21}H_{16}INO_3$ requires: C 55.16, H 3.53, N 3.06; Found: C 54.91, H 3.48, N 3.04.

3-(Benzyloxy)[1,3]dioxolo[4',5':4,5]benzo[*h*]quinoline (toddaquinoline benzyl ether) **4.28** and 1-(benzyloxy)[1,3]dioxolo[4',5':4,5]benzo[*f*]isoquinoline **4.29**

Method 1



4.22 $C_{21}H_{16}BrNO_3$ (410)

4.28 $C_{21}H_{15}NO_3$ (329) ~1:1 **4.29** $C_{21}H_{15}NO_3$ (329)

Bromide **4.22** (400 mg, 0.98 mmol) was dissolved in toluene (30 mL). Tributyltin hydride (395 µL, 426 mg, 1.46 mmol) and AIBN (36 mg, 0.22 mmol) were added and the mixture stirred at 90 °C for 46 hours with further portions of tributyltin hydride (140 µL, 151 mg, 0.52 mmol) and AIBN (10 mg) added after 20 and 30 hours. After cooling to room temperature, the mixture was stirred with a solution of aqueous potassium fluoride (10 % w/v, 20 mL) for 5 hours. The aqueous phase was extracted with ether (3 × 20 mL) and the combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by column

chromatography (silica gel, 30 % ether / petrol) to yield benzo[*h*]quinoline **4.28** (50 mg, 0.15 mmol, 16 %) as a white solid then recovered starting material **4.22** (220 mg, 0.54 mmol, 55 %) as a colourless oil, and finally benzo[*f*]isoquinoline **4.29** (40 mg, 0.12 mmol, 12 %) as a white solid.

3-(Benzyloxy)[1,3]dioxolo[4',5':4,5]benzo[*h*]quinoline **4.28**

MP 129 – 131 °C (ether / petrol).

FT – IR (ν_{max}, neat) 1603 m, 1462 s, 1379 m, 1254 s, 1171 s, 1038 m cm^{-1}.

UV (λ_{max}, MeOH) 360 (1320), 340 (2630), 292 (27640), 241 (47380) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 8.77 (1H, d, *J* 3.0 Hz, Ar*H*), 8.56 (1H, s, Ar*H*), 7.65 (1H, d, *J* 8.8 Hz, Ar*H*), 7.52 – 7.38 (7H, m, 7 × Ar*H*), 7.20 (1H, s, Ar*H*), 6.11 (2H, s, OCH_2O), 5.23 (2H, s, OCH_2) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 152.9 (0, *C*O), 148.6 (0, *C*O), 148.3 (0, *C*O), 141.5 (1, *C*H), 140.8 (0, *C*), 136.4 (0, *C*), 129.1 (0, *C*), 129.0 (1, 2 × *C*H), 128.5 (0, *C*), 128.5 (1, *C*H), 127.9 (1, *C*H), 127.8 (1, 2 × *C*H), 126.3 (0, *C*), 123.5 (1, *C*H), 115.9 (1, *C*H), 105.1 (1, *C*H), 102.1 (1, *C*H), 101.5 (2, O*C*H_2O), 70.7 (2, O*C*H_2) ppm.

LRMS (M/z, ES+) 330 (MH^+, 100 %) amu.

HRMS (M/z, EI) $C_{21}H_{15}NO_3^+$ requires: 329.1052; Found M^+: 329.1055.

CHN $C_{21}H_{15}NO_3$ requires: C 76.58, H 4.59, N 4.25; Found: C 76.35, H 4.66, N 4.21.

1-(Benzyloxy)[1,3]dioxolo[4',5':4,5]benzo[*f*]isoquinoline **4.29**

MP 160 – 163 °C (ether / petrol).

FT – IR (ν_{max}, neat) 1468 s, 1281 m, 1240 m, 1208 m, 1070 m, 1037 m, 932 m cm^{-1}.

UV (λ_{max}, MeOH) 280 (17000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 9.09 (1H, s, Ar*H*), 8.86 (1H, s, Ar*H*), 8.38 (1H, s, Ar*H*), 7.73 (1H, d, *J* 8.4 Hz, Ar*H*), 7.68 (1H, d, *J* 8.4 Hz, Ar*H*), 7.61 – 7.55 (2H, m, 2 × Ar*H*), 7.50 – 7.37 (3H, m, 3 × Ar*H*), 7.25 (1H, s, Ar*H*), 6.10 (2H, s, OCH_2O), 5.45 (2H, s, OCH_2) ppm.

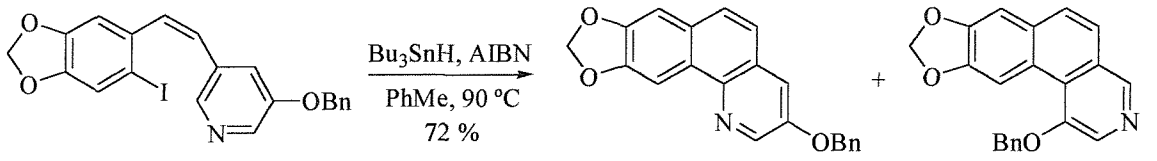
^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 152.2 (0, *C*O), 148.3 (0, *C*O), 148.2 (0, *C*O), 145.4 (1, *C*H), 136.3 (0, *C*), 131.4 (0, *C*), 129.1 (1, *C*H), 129.0 (1, 3 × *C*H), 128.6 (1,

*C*H), 128.3 (0, *C*), 127.9 (1, 2 × *C*H), 125.5 (0, *C*), 124.5 (0, *C*), 123.3 (1, *C*H), 107.6 (1, *C*H), 105.8 (1, *C*H), 101.7 (2, OCH_2O), 71.8 (2, OCH_2) ppm.

LRMS (M/z, ES+) 330 (MH^+, 83 %), 168 (30 %), 138 (100 %) amu.

CHN $C_{21}H_{15}NO_3$ requires: C 76.58, H 4.59, N 4.25; Found: C 76.98, H 4.56, N 4.19.

Method 2



4.26 $C_{21}H_{16}INO_3$ (457)

4.28 $C_{21}H_{15}NO_3$ (329)

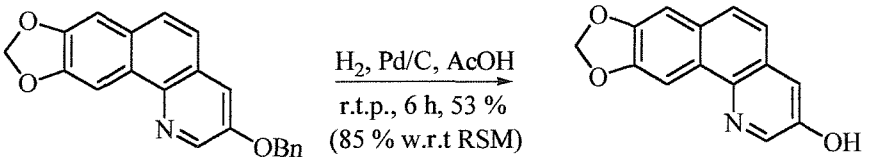
~1:1

4.29 $C_{21}H_{15}NO_3$ (329)

Iodide **4.26** (350mg, 0.77 mmol), tributyltin hydride (250μL, 270mg, 0.92 mmol) and AIBN (15 mg, 0.08 mmol) were heated in toluene (40 mL) at 90 °C for 18 hours with additional tributyltin hydride (100 μL, 110 mg, 0.37 mmol) and AIBN (15 mg, 0.08 mmol) added after 4 and 7 hours. After cooling to room temperature, the mixture was vigorously stirred with a solution of potassium fluoride (10 % w/v, 20 mL) for 16 hours. The mixture was diluted with ether (30 mL) and the organic phase washed with water (2 × 20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 40 – 100 % ether / petrol) yielded firstly benzo[*h*]quinoline **4.28** (95 mg, 0.29 mmol, 38 %) as a white solid and then benzo[*f*]isoquinoline **4.29** (85 mg, 0.26 mmol, 34 %) as a white solid.

The data were identical to that obtained previously.

[1,3]Dioxolo[4',5':4,5]benzo[*h*]quinolin-3-ol (toddaquinoline) **4.1**



4.28 $C_{21}H_{15}NO_3$ (329)

4.1 $C_{14}H_9NO_3$ (239)

Benzyl ether **4.28** (52 mg, 0.16 mmol) was dissolved in acetic acid (5 mL). 5 % Palladium on carbon (65 mg, 0.03 g atom Pd) was added and the mixture stirred under an atmosphere of hydrogen for 6 hours with an additional portion of catalyst (10 mg, 0.005 g atom Pd) added after 4 hours. Water (1 mL) and ether (5 mL) were added and the mixture neutralised to pH 7 with sodium hydrogen carbonate. The organic phases were washed with sodium hydrogen carbonate (sat. aq., 2 × 5 mL) and dried ($MgSO_4$). Concentration *in vacuo* and purification

by column chromatography (silica gel, 1 % MeOH / $CHCl_3$) yielded recovered starting material **4.28** (20 mg, 0.06 mmol, 38 %) and toddaquinoline **4.1** (20 mg, 0.08 mmol, 53 %) as a white solid.[104]

MP 229 – 231 °C ($CHCl_3$ / MeOH) lit. 235 – 237 °C (MeOH / ether).[104]

FT – IR (ν_{max}, neat) 3416 br. m, 2916 m, 1463 m, 1256 m, 1113 m, 1054 s, 1028 s, 1008 m cm^{-1}.

UV (λ_{max}, MeOH) 288 (1070), 236 (2550) nm

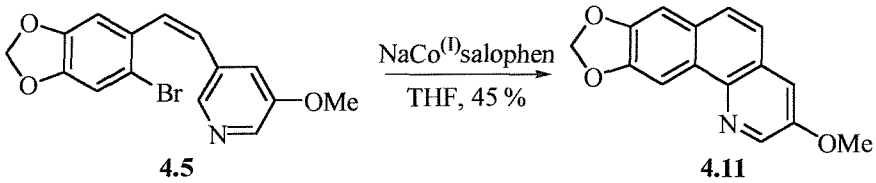
^{1}H – NMR (300 MHz, $CDCl_3$ + d_6-DMSO) δ_H 9.42 (1H, s, O*H*), 8.55 (1H, d, *J* 2.9 Hz, Ar*H*), 8.38 (1H, s, Ar*H*), 7.50 (1H, d, *J* 8.8 Hz, Ar*H*), 7.38 (1H, d, *J* 2.9 Hz, Ar*H*), 7.35 (1H, d, *J* 8.8 Hz, Ar*H*), 7.08 (1H, s, Ar*H*), 5.99 (2H, s, OCH_2O) ppm.†

^{13}C – NMR (75 MHz, $CDCl_3$+ d_6-DMSO) δ_C 151.4 (0, *C*O), 148.2 (0, *C*O), 147.7 (0, *C*O), 140.7 (1, *C*H), 139.7 (0, *C*), 128.4 (0, *C*), 128.3 (0, *C*), 127.3 (1, *C*H), 126.7 (0, *C*), 123.2 (1, *C*H), 117.8 (1, *C*H), 104.9 (1, *C*H), 101.6 (1, *C*H), 101.2 (2, OCH_2O) ppm.

LRMS (M/z, ES+) 240 (MH^+, 100 %) amu.

HRMS (M/z, EI) $C_{14}H_9NO_3^+$ requires: 239.0852; Found M^+: 239.0584.

3-(Methoxy)[1,3]dioxolo[4',5':4,5]benzo[*h*]quinoline (toddaquinoline methyl ether) **4.11**



4.5
$C_{15}H_{12}BrNO_3$ (334)

4.11
$C_{15}H_{11}NO_3$ (253)

Sodium (100 mg, 4.35 g atom) was added portionwise to mercury (10 g, 49.50 g atom). Tetrahydrofuran (30 mL) and cobalt(II)salophen (380 mg, 1.56 mmol) were added and the reaction mixture stirred at room temperature under an argon atmosphere for 3 hours. The resulting green solution was transferred to a second flask *via* cannula and this cooled to –78 °C. Bromide **4.5** (130 mg, 0.39 mmol) was added as a solution in tetrahydrofuran (5 mL) and the solution stirred at this temperature for 2 hours before the solution was stirred at 0 °C for 1 hour and then at room temperature for 16 hours. The mixture was filtered through a pad of silica (silica gel, ether) and concentrated *in vacuo*. Purification by column chromatography

† d_6-DMSO was added to facilitate solubilisation. The isolation paper used only $CDCl_3$. A dilute sample was analysed in $CDCl_3$ confirming the ^{1}H-NMR was in agreement with the isolation paper.

(silica gel, 40 % ether / petrol) provided the title compound **4.11** (40 mg, 0.16 mmol, 45 %) as an off – white solid.[104]

MP 151 – 153 °C (ether / petrol) lit. 145 – 148 °C (MeOH / $CHCl_3$).[104]

FT – IR (ν_{max}, neat) 1604 m, 1498 s, 1406 m, 1382 m, 1255 s, 1169 s, 1036 s cm^{-1}.

UV (λ_{max}, MeOH) 341 (6070), 296 (4430), 233 (5440) nm.

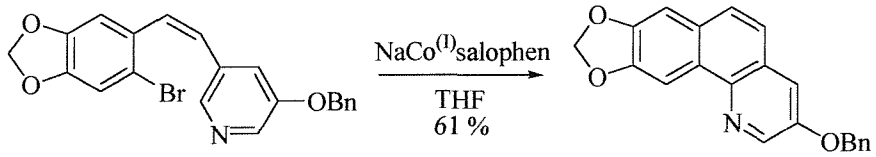
^{1}H - NMR (300 MHz, $CDCl_3$) δ_H 8.70 (1H, d, *J* 2.0 Hz, Ar*H*), 8.55 (1H, s, Ar*H*), 7.68 (1H, d, *J* 8.8 Hz, Ar*H*), 7.55 (1H, d, *J* 8.8 Hz, Ar*H*), 7.50 (1H, d, *J* 2.0 Hz, Ar*H*), 7.21 (1H, s, Ar*H*), 6.10 (2H, s, OCH_2O), 3.99 (3H, s, OCH_3) ppm.

^{13}C- NMR (75 MHz, $CDCl_3$) δ_C 154.6 (0, *C*O), 148.6 (0, *C*O), 148.2 (0, *C*O), 141.2 (1, *C*H), 140.3 (0, *C*), 129.0 (0, *C*), 127.9 (1, *C*H), 127.0 (0, *C*), 123.4 (0, *C*), 123.4 (1, *C*H), 114.3 (1, *C*H), 105.0 (1, *C*H), 102.0 (1, *C*H), 101.5 (2, OCH_2O), 55.8 (3, OCH_3) ppm.

LRMS (M/z, ES+) 254 (MH^+, 100 %) amu.

HRMS (M/z, ES+) $C_{15}H_{12}NO_3^+$ requires: 254.0817; Found MH^+: 254.0817.

3-(Benzyloxy)[1,3]dioxolo[4',5':4,5]benzo[*h*]quinoline (toddaquinoline benzyl ether) **4.28**



4.22
$C_{21}H_{16}BrNO_3$ (410)

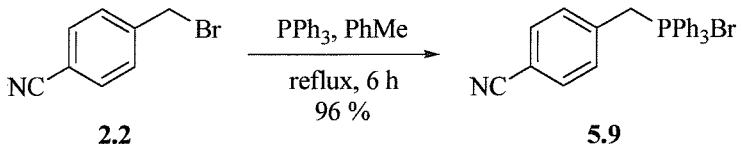
4.28
$C_{21}H_{15}NO_3$ (329)

Sodium (60 mg, 2.64 g atom) was added portionwise to mercury (6 g, 29.70 g atom). The resulting amalgam was covered with tetrahydrofuran (30 mL). Cobalt(II)salophen (180 mg, 0.75 mmol) was added and the mixture stirred at room temperature for 2 hours. The resulting green solution was transferred to a second flask *via* cannula and cooled to –78 °C. Bromide **4.22** (62 mg, 0.15 mmol) was added as a solution in tetrahydrofuran (5 mL) and the mixture was stirred at this temperature for 2 hours, at 0 °C for 1 hour and then at room temperature for 1 hour. The mixture was left to stand in air for 16 hours. Filtration through Celite, concentration *in vacuo* and purification by column chromatography (silica gel, 20 % ether / petrol) yielded benzoquinoline **4.28** (30 mg, 0.09 mmol, 61 %) as a pale yellow solid.

The data were identical to that reported previously.

8.5 Experimental for Chapter 5

(4-Cyanobenzyl)triphenylphosphonium bromide **5.9**[120]



2.2
C_8H_6BrN (196)

5.9
$C_{26}H_{21}BrNP$ (458)

(4-Cyanobenzyl)triphenylphosphonium bromide **5.9** was prepared by the method of Rafizadeh *et al.*[120] 4-(Bromomethyl)benzonitrile **2.2** (2.00 g, 10.20 mmol) and triphenylphosphine (2.68 g, 10.20 mmol) were dissolved in toluene (30 mL) and the mixture heated at reflux for 6 hours. The resulting solid was collected by filtration to yield the title compound **5.9** (4.50 g, 9.83 mmol, 96 %) as a white solid.[120]

MP >260 °C (toluene) lit. 315 – 316 °C ($CHCl_3$ / toluene).[120]

FT – IR (ν_{max}, neat) 3046 m, 1557 m, 1119 m, 1103 m, 858 m, 831 m cm^{-1}.

UV (λ_{max}, MeCN) 270 (63000) nm.

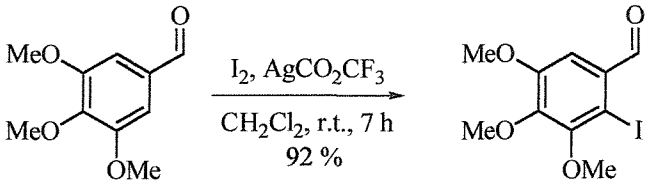
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.84 – 7.70 (9H, m, 9 × Ar*H*), 7.63 – 7.54 (6H, m, 6 × Ar*H*), 7.43 (2H, dd, *J* 8.3, 2.6 Hz, 2 × Ar*H*), 7.31 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 5.92 (2H, d, *J* 15.8 Hz, CH_2P) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 135.2 (1, 3 × *C*H), 134.6 (1, d, *J* 10.0 Hz, 6 × *C*H), 133.8 (0, d, *J* 8.9 Hz, *C*), 132.8 (1, d, *J* 5.2 Hz, 2 × *C*H), 132.1 (1, 2 × *C*H), 130.3 (1, d, *J* 12.6 Hz, 6 × *C*H) , 118.4 (0, *C*N), 117.5 (0, d, *J* 85.9 Hz, 3 × *C*), 112.0 (0, *C*CN), 30.1 (2, d, *J* 46.3 Hz, *C*H_2P) ppm.

^{31}P – NMR (121 MHz, $CDCl_3$) δ_P 24.9 ppm.

LRMS (M/z, ES+) 378 ($[M-Br]^+$, 100 %), 153 (38 %) amu.

2-Iodo-3,4,5-trimethoxybenzaldehyde **5.13**[121]



5.12
$C_{10}H_{12}O_4$ (196)

5.13
$C_{10}H_{11}IO_4$ (322)

2-Iodo-3,4,5-trimethoxybenzaldehyde **5.13** was prepared by the method of Bradley *et al.*[121] To a solution of 3,4,5-trimethoxybenzaldehyde **5.12** (6.00 g, 30.58 mmol) in dichloromethane (70 mL) was added silver(I) trifluoroacetate (7.09 g, 32.11 mmol). A solution of iodine (7.77 g, 30.60 mmol) in dichloromethane (280 mL) was added over 50 minutes and the mixture stirred at room temperature for 7 hours. The resulting solid was removed by filtration through Celite and the filtrate concentrated *in vacuo* to yield the title compound **5.13** (9.09 g, 28.23 mmol, 92 %) as a pale brown solid.[121]

MP 55 – 57 °C (ether / petrol) lit. 66 – 66.5 °C (no solvent stated).[185]

FT – IR (ν_{max}, neat) 2940 m, 1686 s, 1574 m, 1477 m, 1378 s, 1324 s, 1197 m, 1161 m, 1104 s, 1002 m cm^{-1}.

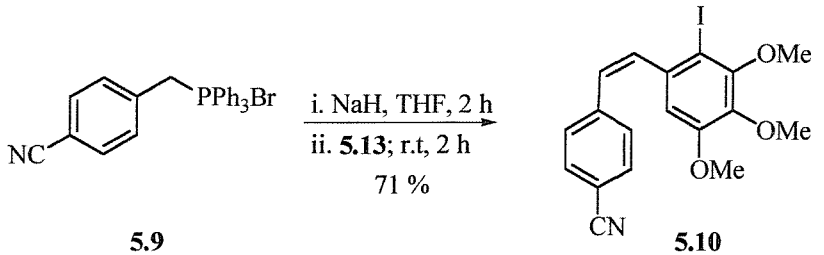
UV (λ_{max}, CH_2Cl_2) 318 (6900) 283 (19000), 253 (32000), 230 (42000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 10.05 (1H, s, C*H*O), 7.35 (1H, s, Ar*H*), 3.98 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.91 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 195.6 (1, *C*HO), 154.2 (0, *C*O), 153.2 (0, *C*O), 148.0 (0, *C*O), 130.7 (0, *C*), 108.8 (1, *C*H), 91.8 (0, *C*I), 61.3 (3, O*C*H_3), 61.2 (3, O*C*H_3), 56.4 (3, O*C*H_3) ppm.

LRMS (M/z, CI) 323 (MH^+, 84 %), 197 ($[M-I+2H]^+$, 100 %), 181 (10 %) amu.

4-((Z)-2-(2-Iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)benzonitrile **5.10**



5.9
$C_{26}H_{21}BrNP$ (458)

5.10
$C_{18}H_{16}INO_3$ (421)

To a pre-washed (tetrahydrofuran, 10 mL) suspension of sodium hydride (60 % in mineral oil, 215 mg, 5.40 mmol) in tetrahydrofuran (30 mL) was added phosphonium bromide **5.9** (2.06 g, 4.50 mmol) at 0 °C. The mixture was stirred at room temperature for 2 hours before the deep yellow mixture was cooled to 0 °C. 2-Iodo-3,4,5-trimethoxybenzaldehyde **5.13** (1.32 g, 4.09 mmol) was added as a solution in tetrahydrofuran (20 mL) and the mixture stirred at room temperature for a further 2 hours. The mixture was filtered through Celite and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded the title compound **5.10** (1.23 g, 2.92 mmol, 71 %) as a white solid.

MP 86 – 87 °C (ethanol).

FT – IR (ν_{max}, neat) 2931 w, 2227 m, 1604 w, 1479 s, 1409 m, 1381 m, 1323 s, 1103 s, 1005 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 324 (10000), 270 (39000) nm.

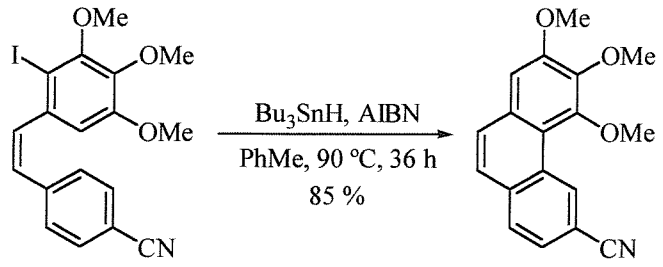
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.49 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 7.24 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 6.68 (1H, d, *J* 11.8 Hz, C*H*=CH), 6.58 (1H, d, *J* 11.8 Hz, CH=C*H*), 6.44 (1H, s, Ar*H*), 3.92 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.52 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 154.1 (0, 2 × *C*O), 154.0 (0, *C*O), 141.6 (0, *C*), 137.2 (1, *C*H=CH), 136.3 (0, *C*), 132.4 (1, 2 × *C*H), 130.0 (1, 2 × *C*H), 129.1 (1, CH=*C*H), 119.2 (0, *C*N), 111.0 (0, *C*CN), 109.8 (1, *C*H), 87.3 (0, *C*I), 61.5 (3, O*C*H_3), 61.2 (3, O*C*H_3), 56.4 (3, O*C*H_3) ppm.

LRMS (M/z, Cl) 439 ($[M+NH_4]^+$, 6 %), 421 (M^+, 14 %), 311 (12 %), 296 ($[M-I+2H]^+$, 100 %), 220 (12 %), 164 (26 %) amu.

CHN $C_{18}H_{16}INO_3$ requires: C 51.32, H 3.83, N 3.33; Found: 51.23, H 3.78, N 3.26.

5,6,7-Trimethoxy-3-phenanthrenecarbonitrile **5.11**



5.10
$C_{18}H_{16}INO_3$ (421)

5.11
$C_{18}H_{15}NO_3$ (293)

Iodide **5.10** (500 mg, 1.19 mmol), tributyltin hydride (385 μL, 415 mg, 1.43 mmol) and AIBN (40 mg, 0.24 mmol) were dissolved in toluene (40 mL) and heated at 90 °C for 36 hours. Additional portions of tributyltin hydride (200 μL, 215 mg, 0.74 mmol) and AIBN (10 mg, 0.06 mmol) were added after 16 and 24 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 30 mL) for 16 hours. The organic phase was diluted with ether (20 mL), washed with water (3 × 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 – 20 % ether / petrol) yielded the title compound **5.11** (295 mg, 1.01 mmol, 85 %) as a white solid.

MP 128 – 129 °C (ethanol).

FT – IR (ν_{max}, neat) 2929 w, 1501 m, 1466 m, 1420 m, 1347 m, 1273 s, 1131 m, 1078 s, 1059 m, 1009 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 319 (11000), 262 (49000) nm.

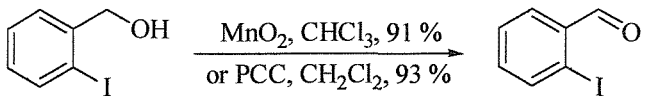
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 9.92 (1H, br. s, Ar*H*), 7.88 (1H, d, *J* 8.3 Hz, Ar*H*), 7.75 (1H, d, *J* 8.8 Hz, Ar*H*), 7.69 (1H, dd, *J* 8.3, 1.5 Hz, Ar*H*), 7.65 (1H, d, *J* 8.8 Hz, Ar*H*), 7.12 (1H, s, Ar*H*), 4.07 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 4.04 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 153.9 (0, *C*O), 152.9 (0, *C*O), 143.9 (0, *C*O), 134.4 (0, *C*), 132.8 (1, *C*H), 130.7 (0, *C*), 130.2 (1, *C*H), 129.9 (0, *C*), 129.6 (1, *C*H), 127.3 (1, *C*H), 126.7 (1, *C*H), 120.6 (0, *C*), 118.4 (0, *C*N), 110.0 (0, *C*CN), 105.8 (1, *C*H), 61.7 (3, O*C*H$_3$), 60.8 (3, O*C*H$_3$), 56.4 (3, O*C*H$_3$) ppm.

LRMS (M/z, CI) 311 ($[M+NH_4]^+$, 50 %), 294 (MH^+, 100 %), 278 (17 %), 250 (12 %), 164 (39 %) amu.

CHN $C_{18}H_{15}NO_3$ requires: C 73.71, H 5.15, N 4.78; Found: C 73.38, H 5.13, N 4.77.

2-Iodobenzaldehyde **5.85**[186]



5.84
C_7H_7IO (234)

5.85
C_7H_5IO (232)

Method 1: **5.85** was prepared by the method of Olivera *et al.*[186] Thus, manganese(IV) oxide (22.30 g, 0.26 mol) was added to a solution of 2-iodobenzyl alcohol **5.84** (3.00 g, 12.82 mmol) in chloroform (60 mL) in three portions over 5 minutes. After stirring for 24 hours, the mixture was filtered through Celite and the filtrate concentrated *in vacuo* to yield the title compound **5.85** (2.72 g, 11.72 mmol, 91 %) as a pale yellow solid.

Method 2: To a solution of 2-iodobenzyl alcohol **5.84** (3.00 g, 12.82 mmol) in dichloromethane (40 mL) was added pyridinium chlorochromate (3.32 g, 15.38 mmol) and the mixture stirred at room temperature for 8 hours. The mixture was filtered through Celite and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded the title compound **5.85** (2.77 g, 11.94 mmol, 93 %) as a pale yellow solid.[186]

MP 24 – 25 °C (ether / petrol) lit. 37 – 38 °C (hexanes).[186]

FT – IR (ν_{max}, neat) 2836 w, 2737 w, 1696 s, 1580 m, 1427 m, 1261 m, 1199 m, 1015 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 302 (2700), 246 (8400) nm.

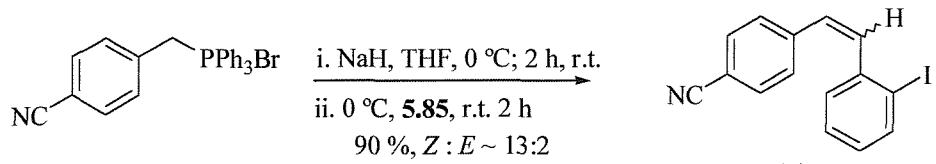
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 10.07 (1H, s, C*H*O), 7.96 (1H, d, *J* 7.9 Hz, Ar*H*), 7.88 (1H, dd, *J* 7.7, 1.7 Hz, Ar*H*), 7.47 (1H, t, *J* 7.4 Hz, Ar*H*), 7.29 (1H, td, *J* 7.9, 1.7 Hz, Ar*H*) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 196.1 (1, C*H*O), 141.1 (1, *C*H), 135.9 (1, *C*H), 135.6 (0, *C*), 130.7 (1, *C*H), 129.1 (1, *C*H), 101.1 (0, *C*I) ppm.

LRMS (M/z, CI) 232 (M^+, 100 %), 203 (10 %), 105 (56 %), 77 (44 %), 50 (70 %) amu.

4-(2-(*Z*)-(2-Iodophenyl)ethenyl)benzonitrile **5.15** &

4-(2-(*E*)-(2-iodophenyl)ethenyl)benzonitrile **5.86**



5.9

$C_{26}H_{21}BrNP$ (458)

(*Z*)-**5.15**
(*E*)-**5.86**
$C_{15}H_{10}IN$ (331)

To pre-washed (tetrahydrofuran, 10 mL) sodium hydride (60 % in mineral oil, 315 mg, 7.86 mmol) in tetrahydrofuran (30 mL) at 0 °C was added phosphonium bromide **5.9** (3.00 g, 6.55 mmol) and the mixture stirred at room temperature for 2 hours. On cooling to 0 °C, 2-iodobenzaldehyde **5.85** (1.38 g, 5.95 mmol) was added as a solution in tetrahydrofuran (10 mL) and the mixture stirred at room temperature for a further 2 hours. The mixture was filtered through Celite and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 3 – 5 % ether / petrol) yielded the title compound **5.15** (910 mg, 2.75 mg, 46 %) as a white solid and then a mixture of isomers (860 mg, 2.60 mmol, 44 %, *Z* : *E* ~ 5:2) as a white solid.

4-(2-(*Z*)-(2-Iodophenyl)ethenyl)benzonitrile **5.15**

MP 85 – 87 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3049 w, 3010 w, 2226 s, 1604 m, 1503 m, 1462 m, 1431 m, 1014 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 283 1(17000) nm.

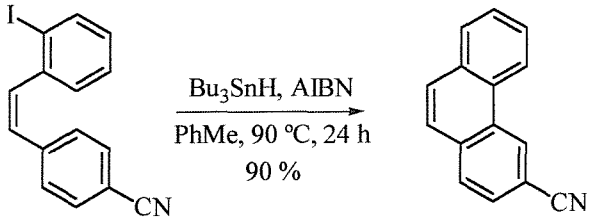
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.91 (1H, dd, *J* 8.0, 1.2 Hz, Ar*H*), 7.46 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 7.20 – 7.16 (3H, m, 3 × Ar*H*), 7.05 (1H, dd, *J* 7.6, 1.5 Hz, Ar*H*), 6.98 (1H, app. td, *J* 7.6, 1.8 Hz, Ar*H*), 6.70 (1H, d, *J* 12.0 Hz, C*H*=CH), 6.63 (1H, d, *J* 12.0 Hz, CH=C*H*) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 141.4 (0, *C*), 141.2 (0, *C*), 139.8 (1, *C*H), 137.2 (1, *C*H), 132.4 (1, 2 × *C*H), 130.3 (1, *C*H), 130.0 (1, 2 × *C*H), 129.8 (1, *C*H), 129.7 (1, *C*H), 128.6 (1, *C*H), 119.2 (0, *C*N), 111.1 (0, *C*CN), 99.6 (0, *C*I) ppm.

LRMS (M/z, CI) 331 (M^+, 90 %), 203 (100 %), 176 (32 %) amu.

HRMS (M/z, EI) $C_{15}H_{10}IN^+$ requires: 330.9858; Found M^+: 330.9876.

2-Phenanthrenecarbonitrile **5.16**



5.15
$C_{15}H_{10}IN$ (331)

5.16
$C_{15}H_9N$ (203)

Iodide **5.15** (500 mg, 1.51 mmol), tributyltin hydride (490 μL, 525 mg, 1.81 mmol) and AIBN (50 mg, 0.30 mmol) were heated in toluene at 90 °C for 24 hours with additional portions of tributyltin hydride (250 μL, 270 mg, 0.93 mmol) and AIBN (15 mg, 0.09 mmol) added after 6 and 8 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 25 mL) for 16 hours. The organic phase was diluted with ether (30 mL) and washed with water (2 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 % ether / petrol) yielded the title compound **5.16** (275 mg, 1.35 mmol, 90 %) as a white solid.[187]

MP 95 – 96 °C (ether / petrol) lit. 102 °C (ethanol).[187]

FT – IR (ν_{max}, neat) 3054 w, 2952 w, 2225 s, 1618 m, 1509 m, 1454 m, 1399 m, 1247 m cm^{-1}.

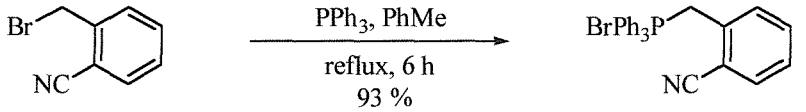
UV (λ_{max}, CH_2Cl_2) 307 (12000), 249 (42000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.96 (1H, s, Ar*H*), 8.59 (1H, d, *J* 8.8 Hz, Ar*H*), 7.96 – 7.85 (3H, m, 3 × Ar*H*), 7.77 – 7.68 (4H, m, 4 × Ar*H*) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 134.4 (0, *C*), 132.3 (0, *C*), 130.5 (1, *C*H), 130.1 (0, *C*), 129.6 (1, *C*H), 129.4 (0, *C*), 129.0 (1, *C*H), 128.3 (1, *C*H), 128.1 (1, *C*H), 128.0 (1, *C*H), 127.9 (1, *C*H), 126.2 (1, *C*H), 122.7 (1, *C*H), 119.7 (0, *C*N), 109.9 (0, *C*CN) ppm.

LRMS (M/z, CI) 203 (M^+, 100 %), 176 (10 %), 150 (8 %) amu.

(2-Cyanobenzyl)triphenylphosphonium bromide **5.59**



5.87
C_8H_6BrN (196)

5.59
$C_{26}H_{21}BrNP$ (458)

(2-Cyanobenzyl)triphenylphosphonium bromide **5.59** was prepared by modifications of the method of Rafizadeh *et al.*[120] 2-(Bromomethyl)benzonitrile **5.87** (4.00 g, 20.40 mmol) and triphenylphosphine (5.35 g, 20.40 mmol) were heated in toluene (50 mL) at reflux for 6 hours. The resulting solid was collected by filtration, washed with toluene (*ca.* 15 mL) and dried *in vacuo* to yield the title compound **5.59** (8.67 g, 18.93 mmol, 93 %) as a white solid.[188]

MP >260 °C (toluene) (no literature melting point).[188]

FT – IR (ν_{max}, neat) 3154 w, 2216 m, 1649 m, 1439 s, 1109 m, 995 m cm^{-1}.

UV (λ_{max}, MeCN) 265 (5700) nm.

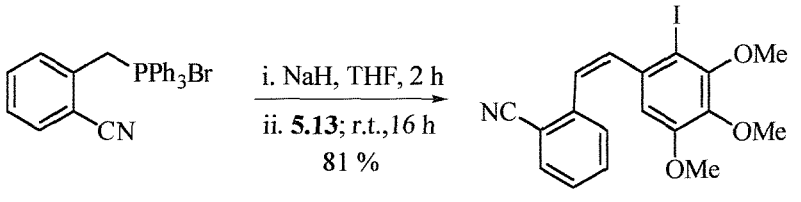
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.85 – 7.58 (16H, m, 3 × C_6H_5 & Ar*H*), 7.49 (1H, app. tdd, *J* 7.2, 2.0, 1.2 Hz, Ar*H*), 7.45 – 7.35 (2H, m, 2 × Ar*H*), 5.79 (2H, d, *J* 14.6 Hz, CH_2P) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 135.6 (1, 3 × *C*H), 134.6 (1, d, *J* 10.1 Hz, 6 × *C*H), 134.0 (1, *C*H), 133.1 (1, d, *J* 5.1 Hz, *C*H), 132.8 (1, *C*H), 131.8 (0, d, *J* 8.9 Hz, *C*), 130.5 (1, d, *J* 12.6 Hz, 6 × *C*H), 129.3 (1, *C*H), 116.9 (0, d, *J* 86.2 Hz, 3 × *C*), 116.9 (0, *C*N), 114.8 (0, *C*CN), 30.0 (2, d, *J* 48.3 Hz, CH_2P) ppm.

^{31}P – NMR (121 MHz, $CDCl_3$) δ_P 24.7 ppm.

LRMS (M/z, ES+) 378 ($[M-Br]^+$, 100 %), 153 (38 %) amu.

2-((*Z*)-2-(2-Iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)benzonitrile **5.17**



5.59
$C_{26}H_{21}BrNP$ (458)

5.17
$C_{18}H_{16}INO_3$ (421)

To a suspension of pre-washed (tetrahydrofuran, 10 mL) sodium hydride (60 % in mineral oil, 480 mg, 12.00 mmol) in tetrahydrofuran (40 mL) at 0 °C was added phosphonium

bromide **5.59** (4.58 g, 10.00 mmol) and the mixture stirred at room temperature for 2 hours. After cooling to 0 °C, aldehyde **5.13** (2.93 g, 9.09 mmol) was added as a solution in tetrahydrofuran (20 mL) and the mixture stirred at room temperature for 3 hours. The mixture was filtered through Celite and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 –25 % ether / petrol) yielded the title compound **5.17** (3.09 g, 7.34 mmol, 81 %) as a white solid.

MP 94 – 96 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2986 m, 2935 w, 2223 m, 1553 m, 1473 s, 1382 s, 1321 s, 1244 m, 1202 m, 1157 m, 1103 s, 1004 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 299 (15000) nm.

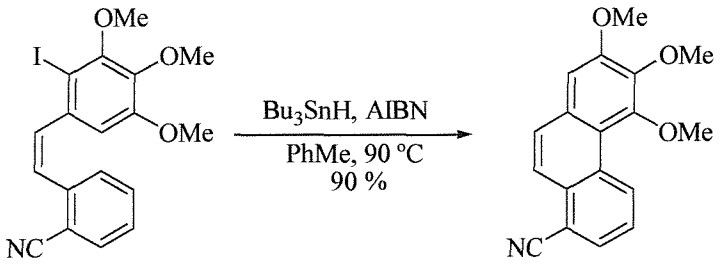
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.64 (1H, dd, *J* 7.5, 1.5 Hz, Ar*H*), 7.32 (1H, td, *J* 7.8, 1.5 Hz, Ar*H*), 7.27 (1H, td, *J* 7.5, 1.4 Hz, Ar*H*), 7.15 (1H, br. d, *J* 7.8 Hz, Ar*H*), 6.84 (1H, d, *J* 11.8 Hz, C*H*=CH), 6.79 (1H, d, *J* 11.8 Hz, CH=C*H*), 6.35 (1H, s, Ar*H*), 3.90 (3H, s, O*CH*$_3$), 3.86 (3H, s, O*CH*$_3$), 3.45 (3H, s, O*CH*$_3$) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 153.9 (0, 2 × *C*O), 142.1 (0, *C*O), 140.7 (0, *C*), 138.3 (1, *C*H), 136.0 (0, *C*), 133.2 (1, *C*H), 132.5 (1, *C*H), 130.2 (1, *C*H), 127.9 (1, *C*H), 126.9 (1, *C*H), 118.1 (0, *C*N), 112.8 (0, *C*CN), 110.0 (1, *C*H), 87.6 (0, *C*I), 61.5 (3, O*C*H$_3$), 61.3 (3, O*C*H$_3$), 56.2 (3, O*C*H$_3$) ppm.

LRMS (M/z, CI) 439 ($[M+NH_4]^+$, 10 %), 421 (M^+, 14 %), 296 ($[M-I+2H]^+$, 100 %), 235 (10 %), 220 (8 %), 164 (26 %) amu.

CHN $C_{18}H_{16}INO_3$ requires: C 51.32, H 3.83, N 3.33; Found: C 51.18, H 3.74, N 3.26.

5,6,7-Trimethoxy-1-phenanthrenecarbonitrile **5.18**



5.17
$C_{18}H_{16}INO_3$ (421)

5.18
$C_{18}H_{15}NO_3$ (293)

Iodide **5.17** (800 mg, 1.90 mmol), tributyltin hydride (670 μL, 720 mg, 2.47 mmol) and AIBN (40 mg, 0.25 mmol) were heated in toluene (60 mL) at 90 °C for 8 hours with additional tributyltin hydride (300 μL, 325 mg, 1.12 mmol) and AIBN (20 mg, 0.12 mmol) added after 4 and 6 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 40 mL) for 16 hours. The organic phase was diluted with ether (20 mL) and washed with water (3 × 20 mL). Drying ($MgSO_4$), concentration *in vacuo* and purification by column chromatography (silica gel, 10 – 20 % ether / petrol) yielded the title compound **5.18** (500 mg, 1.71 mmol, 90 %) as a white solid.

MP 116 – 117 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3024 m, 2225 m, 1605 m, 1472 s, 1353 s, 1276 s, 1152 m, 1110 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 282 (140000), 253 (410000) nm.

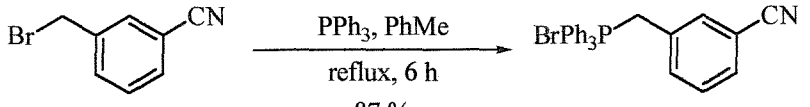
H – NMR (400 MHz, $CDCl_3$) δ_H 9.80 (1H, app. dt, *J* 8.8, 0.7 Hz Ar*H*), 8.09 (1H, dd, *J* 9.0, 0.7 Hz, Ar*H*), 7.91 (1H, dd, *J* 7.3, 1.0 Hz, Ar*H*), 7.81 (1H, d, *J* 9.0 Hz, Ar*H*), 7.64 (1H, dd, *J* 8.8, 7.3 Hz, Ar*H*), 7.15 (1H, s, Ar*H*), 4.04 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 4.03 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.8 (0, *C*O), 152.9 (0, *C*O), 144.0 (0, *C*O), 132.3 (0, *C*), 132.2 (1, *C*H), 131.6 (1, *C*H), 130.6 (0, *C*), 130.5 (0, *C*), 130.1 (1, *C*H), 126.2 (1, *C*H), 123.5 (1, *C*H), 118.9 (0, *C*), 118.8 (0, *C*), 110.6 (0, *C*CN), 105.9 (1, *C*H), 61.7 (3, O*C*H_3), 60.8 (3, O*C*H_3), 56.4 (3, O*C*H_3) ppm.

LRMS (M/z, CI) 311 ($[M+NH_4]^+$, 18 %), 294 (M^+, 100 %), 278 (20 %), 250 (12 %), 164 (30 %) amu.

CHN $C_{18}H_{15}NO_3$ requires: C 73.71, H 5.15, N 4.78; Found: C 73.46, H 5.19, N 4.78.

(3-Cyanobenzyl)triphenylphosphonium bromide **5.89**[120]



5.88
C_8H_6BrN (196)

5.89
$C_{26}H_{21}BrNP$ (458)

(3-Cyanobenzyl)triphenylphosphonium bromide **5.89** was prepared by the method of Rafizadeh *et al.*[120] 3-(Bromomethyl)benzonitrile **5.88** (4.00 g, 20.40 mmol) and triphenylphosphine (5.35 g, 20.40 mmol) were heated at reflux in toluene (50 mL) for 6 hours. The resulting solid was collected by filtration, washed with toluene (*ca.* 15 mL) and dried *in vacuo* to yield the title compound **5.89** (8.11 g, 17.71 mmol, 87 %) as an off - white solid.

MP > 260 °C (toluene) lit. 313 – 314 °C ($CHCl_3$/toluene).[120]

FT – IR (ν_{max}, neat) 2887 w, 2166 m, 1573 m, 1539 m, 1440 m, 1359 m, 1114 s, 1100 s, 1052 m cm^{-1}.

UV (λ_{max}, MeCN) 265 (6300) nm.

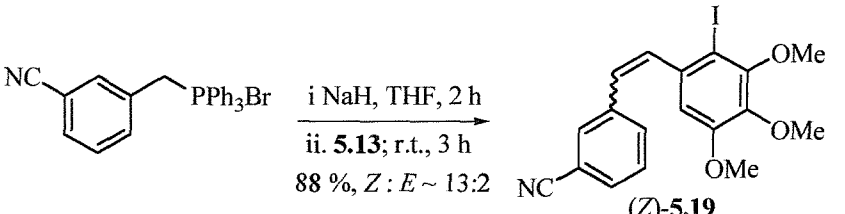
^{1}H – NMR (300 MHz, d_6-DMSO) δ_H 7.87 – 7.55 (16H, m, 3 × C_6H_5 & Ar*H*), 7.40 (1H, br. d, *J* 7.4 Hz, Ar*H*), 7.29 – 7.16 (2H, m, 2 × Ar*H*), 5.87 (2H, d, *J* 15.1 Hz, CH_2P) ppm.

^{13}C – NMR (75 MHz, d_6-DMSO) δ_C 135.5 (1, *C*H), 135.4 (1, *C*H), 135.2 (1, d, *J* 2.8 Hz, 3 × *C*H), 134.2 (0, *C*), 134.0 (1, d, *J* 11.3 Hz, 6 × *C*H), 132.2 (1, d, *J* 4.0 Hz, *C*H), 130.3 (1, d, *J* 12.5 Hz, 6 × *C*H), 129.9 (1, d, *J* 8.5 Hz, *C*H), 118.0 (0, *C*N), 117.4 (0, d, *J* 85.9 Hz, 3 × *C*), 111.7 (0, d, *J* 3.4 Hz, *C*CN), 27.6 (2, d, *J* 47.2 Hz, *C*H_2P) ppm.

^{31}P – NMR (121 MHz, d_6-DMSO) δ_P 25.3 ppm.

LRMS (M/z, ES+) 378 ([M-Br]$^+$, 100 %), 153 (65 %) amu.

3-((*Z*)-2-(2-Iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)benzonitrile **5.19** & 3-((*E*)-2-(2-iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)benzonitrile **5.90**



5.89
$C_{26}H_{21}BrNP$ (458)

(*Z*)-**5.19**
(*E*)-**5.90**
$C_{18}H_{16}INO_3$ (421)

Sodium hydride (60 % in mineral oil, 480 mg, 12.00 mmol) was washed with tetrahydrofuran (10 mL) then suspended in tetrahydrofuran (40 mL) and cooled to 0 °C. Phosphonium bromide **5.89** (4.58 g, 10.00 mmol) was added and the mixture stirred at room temperature for 2 hours. The resulting yellow mixture was cooled to 0 °C and aldehyde **5.13** (2.93 g, 9.09 mmol) was added as a solution in tetrahydrofuran (20 mL). After stirring at room temperature for 3 hours, the mixture was filtered through Celite and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 – 20 % ether / petrol) yielded firstly **5.19** (2.59 g, 6.15 mmol, 68 %) as a white solid, then a mixture of isomers (780 mg, 1.85 mmol, 20 %, *E*:*Z* ~ 7:5).

3-((*Z*)-2-(2-Iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)benzonitrile **5.19**

MP 94 – 96 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2956 w, 2222 m, 1545 m, 1480 s, 1427 m, 1381 s, 1323 s, 1244 m, 1168 m, 1104 s, 1008 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 280 (17000), 257 (32000), 227 (45000) nm.

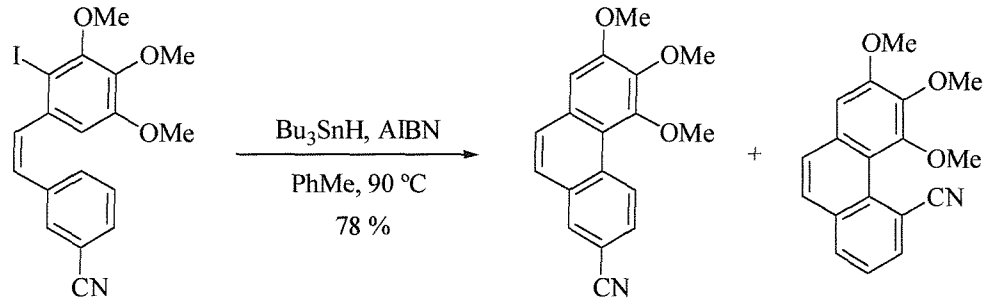
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.52 – 7.44 (2H, m, 2 × Ar*H*), 7.38 – 7.28 (2H, m, 2 × Ar*H*), 6.65 (1H, d, *J* 11.9 Hz, C*H*=CH), 6.56 (1H, d, *J* 11.9 Hz, CH=C*H*), 6.44 (1H, s, Ar*H*), 3.93 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.51 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 154.1 (0, 2 × *C*O), 154.0 (0, *C*O), 138.2 (0, *C*), 136.6 (1, *C*H), 136.2 (0, *C*), 133.6 (1, *C*H), 132.9 (1, *C*H), 131.0 (1, *C*H), 129.4 (1, *C*H), 128.6 (1, *C*H), 119.0 (0, *C*N), 112.9 (0, *C*CN), 109.8 (1, *C*H), 87.5 (0, *C*I), 61.5 (3, OCH_3), 61.3 (3, OCH_3), 56.4 (3, OCH_3) ppm.

LRMS (M/z, CI) 439 ($[M+NH_4]^+$, 24 %), 421 (M^+, 8 %), 313 ($[MH-I+NH_4]^+$, 48 %), 296 ($[M-I+2H]^+$, 100 %), 263 (14 %), 220 (12 %), 164 (30 %) amu.

CHN $C_{18}H_{16}INO_3$ requires: C 51.32, H 3.83, N 3.33; Found: C 51.30, H 3.79, N 3.26.

5,6,7-Trimethoxy-2-phenanthrenecarbonitrile **5.20** & 5,6,7-trimethoxy-4-phenanthrenecarbonitrile **5.21**



5.19 $C_{18}H_{16}INO_3$ (421)

5.20 $C_{18}H_{15}NO_3$ (293) 1:1 **5.21** $C_{18}H_{15}NO_3$ (293)

Iodide **5.19** (800 mg, 1.90 mmol), tributyltin hydride (670 μL, 720 mg, 2.47 mmol) and AIBN (40 mg, 0.25 mmol) were heated in toluene (60 mL) at 90 °C for 24 hours with additional portions of tributyltin hydride (300 μL, 325 mg, 1.12 mmol) and AIBN (20 mg, 0.12 mmol) added after 16 and 20 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 40 mL) for 16 hours. The organic phase was diluted with ether (20 mL) and washed with water (3 × 20 mL). Drying ($MgSO_4$), concentration *in vacuo* and purification by column chromatography (silica gel, 20 % ether / petrol) yielded firstly phenanthrene **5.20** (130 mg, 0.44 mmol, 23 %), then a mixture of **5.20** and **5.21** (150 mg, 0.51 mmol, 27 %, **5.20**:**5.21** ~ 1:1) and finally phenanthrene **5.21** (155 mg, 0.53 mmol, 28 %) all as white solids.

5,6,7-Trimethoxy-2-phenanthrenecarbonitrile **5.20**

MP 138 – 140 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3024 w, 2227 m, 1597 m, 1475 m, 1353 m, 1280 m, 1198 m, 1132 m, 1003 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 354 (1700), 323 (11000), 302 (34000), 271 (110000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 9.62 (1H, d, *J* 8.9 Hz, Ar*H*), 8.18 (1H, d, *J* 1.7 Hz, Ar*H*), 7.79 (1H, dd, *J* 8.9, 2.0 Hz, Ar*H*), 7.71 (1H, d, *J* 8.9 Hz, Ar*H*), 7.65 (1H, d, *J* 8.9 Hz, Ar*H*), 7.14 (1H, s, Ar*H*), 4.05 (3H, s, OCH_3), 4.05 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 154.0 (0, *C*O), 152.3 (0, *C*O), 143.7 (0, *C*O), 133.6 (1, CH), 132.9 (0, *C*), 131.6 (0, *C*), 131.6 (0, *C*), 128.8 (1, *C*H), 128.4 (1, *C*H),

128.2 (1, *C*H), 126.6 (1, *C*H), 119.8(0, *C*), 118.6 (0, *C*N), 109.0 (0, *C*CN), 105.8 (1, *C*H), 61.7 (3, O*C*H$_3$), 60.9 (3, O*C*H$_3$), 56.4 (3, O*C*H$_3$) ppm.

LRMS (M/z, CI) 311 ([M+NH$_4$]$^+$, 56 %), 294 (MH$^+$, 100 %), 278 (18 %), 235 (14 %), 164 (48 %).

5,6,7-Trimethoxy-4-phenanthrenecarbonitrile **5.21**

MP 122 – 124 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2906 m, 1604 m, 1470 m, 1435 m, 1351 m, 1280 m, 1144 m, 1112 m, 1105 m, 1005 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 280 (48000), 253 (70000) nm.

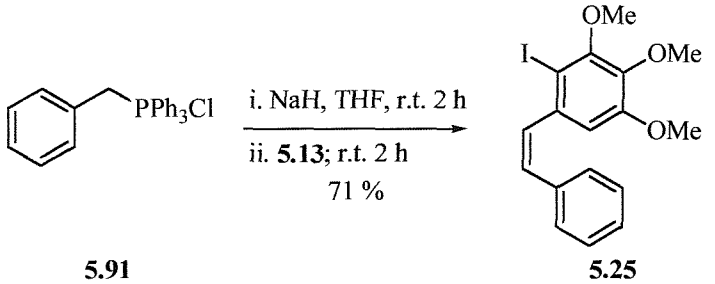
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 8.00 (1H, dd, *J* 8.0, 1.3 Hz, Ar*H*), 7.97 (1H, dd, *J* 7.5, 1.5 Hz, Ar*H*), 7.63 (1H, d, *J* 8.8 Hz, Ar*H*), 7.59 (1H, d, *J* 8.8 Hz, Ar*H*), 7.56 (1H, t, *J* 7.8 Hz, Ar*H*), 7.06 (1H, s, Ar*H*), 4.16 (3H, s, OC*H*$_3$), 4.04 (3H, s, OC*H*$_3$), 3.76 (3H, s, OC*H*$_3$) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 154.3 (0, 2 × *C*O), 148.3 (0, *C*O), 138.5 (0, *C*), 134.5 (1, *C*H), 132.8 (0, *C*), 132.7 (1, *C*H), 131.2 (0, *C*), 128.4 (0, *C*), 128.0 (1, *C*H), 126.5 (1, *C*H), 125.4 (1, *C*H), 120.3 (0, *C*N), 111.6 (0, *C*CN), 104.1 (1, *C*H), 62.5 (3, O*C*H$_3$), 61.3 (3, O*C*H$_3$), 56.5 (3, O*C*H$_3$) ppm.

LRMS (M/z, CI) 311 ([M+NH$_4$]$^+$, 72 %), 294 (MH$^+$, 100 %), 278 (14 %), 250 (22 %), 235 (10 %), 207 (10 %), 164 (34 %).

CHN $C_{18}H_{15}NO_3$ requires: C 73.71, H 5.15, N 4.75; Found: C 73.61, H 5.21, N 4.79.

2-Iodo-3,4,5-trimethoxy-1-((*Z*)-2-phenyl-1-ethenyl)benzene **5.25**



5.91
$C_{25}H_{22}ClP$ (389)

5.25
$C_{17}H_{17}IO_3$ (396)

To a cooled (0 °C) suspension of sodium hydride (60 % in mineral oil, 180 mg, 4.48 mmol), pre-washed with tetrahydrofuran (10 mL), in tetrahydrofuran (20 mL) was added benzyltriphenylphosphonium chloride **5.91** (1.45 g, 3.73 mmol). The mixture was stirred at

room temperature for 2 hours before cooling to 0 °C. Aldehyde **5.13** (1.00 g, 3.11 mmol) was added as a solution in tetrahydrofuran (10 mL) and the mixture stirred at room temperature for a further 2 hours. The solid was removed by filtration through Celite and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 – 10 % ether / petrol) yielded the title compound **5.25** (875 mg, 2.21 mmol, 71 %) as a white solid.

MP 101 – 103 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2936 w, 1547 m, 1477 s, 1380 s, 1320 s, 1249 m, 1207 m, 1155 m, 1104 s, 1039 m, 1008 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) , 286 (26000), 250 (83000) nm.

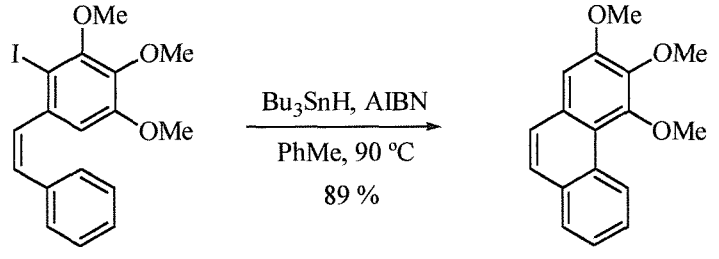
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.22 – 7.16 (5H, m, C_6H_5), 6.62 (1H, d, *J* 12.2 Hz, C*H*=CH), 6.57 (1H, s, Ar*H*), 6.52 (1H, d, *J* 12.2 Hz, CH=C*H*), 3.92 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.47 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.4 (0, 2 × *C*O), 141.3 (0, *C*O), 136.9 (0, *C*), 136.5 (0, *C*), 133.8 (1, *C*H), 130.8 (1, *C*H), 129.2 (1, 2 × *C*H), 128.3 (1, 2 × *C*H), 127.4 (1, *C*H), 109.9 (1, *C*H), 87.4 (0, *C*I), 61.2 (3, O*C*H$_3$), 61.0 (3, O*C*H$_3$), 55.9 (3, O*C*H$_3$) ppm.

LRMS (M/z, CI) 397 (MH^+, 14 %), 271 ($[M-I+2H]^+$, 100 %), 238 (18 %), 210 (10 %), 139 (27 %) amu.

CHN $C_{17}H_{17}IO_3$ requires: C 51.53, H 4.32; Found: C 51.46, H 4.28.

2,3,4-Trimethoxyphenanthrene **5.26**



5.25
$C_{17}H_{17}IO_3$ (396)

5.26
$C_{17}H_{16}O_3$ (268)

Iodide **5.25** (500 mg, 1.26 mmol), tributyltin hydride (410 µL, 440 mg, 1.51 mmol) and AIBN (25 mg, 0.15 mmol) were heated in toluene (40 mL) at 90 °C for 6 hours with further portions of tributyltin hydride (200 µL, 215 mg, 0.74 mmol) and AIBN (10 mg, 0.06 mmol) added after 2 and 4 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 30 mL) for 16 hours. The organic phase was

diluted with ether (20 mL) and washed with water (3 × 20 mL). Drying ($MgSO_4$), concentration *in vacuo* and purification by column chromatography (silica gel, 10 % ether / petrol) yielded the title compound **5.26** (300 mg, 1.12 mmol, 89 %) as a white solid.[189]

MP 84 – 85 °C (ether / petrol) lit. 92 – 93 °C (no solvent stated).[182]

FT – IR (ν_{max}, neat) 2938 m, 1598 m, 1500 m, 1470 s, 1350 m, 1274 s, 1130 s, 1084 s, 1005 m cm^{-1}.

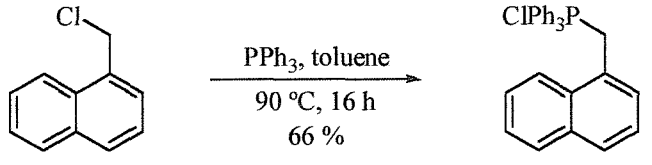
UV (λ_{max}, CH_2Cl_2) 254 (150000), 304 (16000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 9.42 (1H, dd, *J* 8.8, 0.5 Hz, Ar*H*), 7.76 (1H, dd, *J* 7.8, 1.3 Hz, Ar*H*), 7.58 (1H, d, *J* 9.0 Hz, Ar*H*), 7.56 – 7.52 (1H, m, Ar*H*), 7.51 (1H, d, *J* 9.0 Hz, Ar*H*), 7.46 (1H, ddd, *J* 8.0, 7.4, 1.3 Hz, Ar*H*), 7.02 (1H, s, Ar*H*), 3.97 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 3.94 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 152.9 (0, 3 × *C*O), 132.3 (0, *C*), 130.6 (0, *C*), 130.3 (0, *C*), 128.8 (1, *C*H), 127.6 (1, *C*H), 127.2 (1, 2 × *C*H), 126.9 (1, *C*H), 125.9 (1, *C*H), 119.4 (0, *C*), 105.6 (1, *C*H), 61.7 (3, OCH_3), 60.7 (3, OCH_3), 56.3 (3, OCH_3) ppm.

LRMS (M/z, CI) 269 (MH^+, 100 %), 253 (14 %), 210 (10 %), 139 (20 %) amu.

1-(Naphthylmethyl)triphenylphosphonium chloride **5.92**



2.46
$C_{11}H_9Cl$ (177)

5.92
$C_{29}H_{24}ClP$ (439)

1-(Chloromethyl)naphthalene **2.46** (5.00 g, 28.30 mmol) and triphenylphosphine (7.42 g, 28.30 mmol) were heated in toluene (30 mL) at 90 °C for 30 hours. The resulting white solid was collected by filtration and washed with petrol (2 × 20 mL) to yield the title compound **5.92** (8.23 g, 18.75 mmol, 66 %) as a white solid.[190,191]

MP > 295 °C (toluene) lit. 308 – 310 °C (no solvent stated).[191]

FT – IR (ν_{max}, neat) 3059 w, 3007 w, 2870 w, 1588 w, 1438 s, 1111 s, 997 cm^{-1}.

UV (λ_{max}, MeCN) 272 (15000) nm.

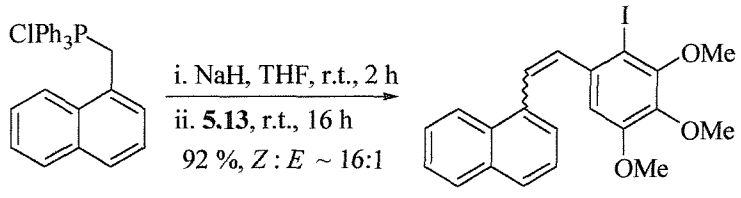
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.65 – 7.49 (12H, m, 12 × Ar*H*), 7.45 – 7.38 (6H, m, 6 × Ar*H*), 7.24 (1H, d, 8.8 Hz, Ar*H*), 7.16 (1H, t, *J* 7.7 Hz, Ar*H*), 7.11 (1H, t, *J* 7.7 Hz, Ar*H*), 6.90 (1H, t, *J* 8.1 Hz, Ar*H*), 5.69 (2H, d, *J* 14.3 Hz, CH_2P) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 134.8 (1, d, *J* 2.8 Hz, 3 × *C*H), 134.1 (1, d, *J* 9.6 Hz, 6 × *C*H), 133.3 (0, d, *J* 2.8 Hz, *C*), 132.2 (0, d, *J* 4.5 Hz, *C*), 130.5 (1, d, *J* 6.8 Hz, *C*H), 130.0 (1, d, *J* 12.4 Hz, 6 × *C*H), 129.1 (1, d, *J* 4.0 Hz, *C*H), 128.5 (1, *C*H), 126.2 (1, *C*H), 125.6 (1, *C*H), 125.3 (1, d, *J* 4.0 Hz, *C*H), 123.2 (0, d, *J* 9.6 Hz, *C*), 123.0 (1, d, *J* 2.3 Hz, *C*H), 117.6 (0, d, *J* 85.3 Hz, 3 × *C*), 27.1 (2, d, *J* 47.5 Hz, CH_2P) ppm.

^{31}P – NMR (121 MHz, $CDCl_3$) δ_P 23.0 ppm.

LRMS (M/z, ES+) 403 ($[M\text{-}Cl]^+$, 100 %) amu.

1-(2-(*Z*)-(2-Iodo-3,4,5-trimethoxyphenyl)ethenyl)naphthalene **5.27** & 1-(2-(*E*)-(2-iodo-3,4,5-trimethoxyphenyl)ethenyl)naphthalene **5.93**



5.92
$C_{29}H_{24}ClP$ (439)

(*Z*)-**5.27**
(*E*)-**5.93**
$C_{21}H_{19}IO_3$ (446)

To a cooled (0 °C) suspension of sodium hydride (60 % in mineral oil, 165 mg, 4.10 mmol) in tetrahydrofuran (20 mL) was added phosphonium chloride **5.92** (1.50 g, 3.42 mmol). The mixture was stirred at room temperature for 3 hours before cooling to 0 °C. 2-Iodo-3,4,5-trimethoxybenzaldehyde **5.13** (1.00 g, 3.11 mmol) was added as a solution in tetrahydrofuran (10 mL) and the mixture stirred for a further 16 hours at room temperature. Filtration through Celite, concentration *in vacuo* and purification by column chromatography (silica gel, 5 – 10 % ether / petrol) yielded firstly the *Z*-isomer **5.27** as a pale yellow oil (985 mg, 2.21 mmol, 71 %) and then a mixture of *Z* and *E* isomers (290 mg, 0.65 mmol, 21 %, *Z*:*E* ~ 3:1). The mixture was further purified to obtain a sample of **5.93** for analysis.

1-(2-(*Z*)-(2-Iodo-3,4,5-trimethoxyphenyl)ethenyl)naphthalene **5.27**

FT – IR (ν_{max}, neat) 2988 w, 2926 m, 2836 w, 1555 m, 1477 s, 1381 s, 1320 s, 1102 s, 1006 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 319 (20000), 264 (88000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 8.11 – 8.06 (1H, m, Ar*H*), 7.90 – 7.85 (1H, m, Ar*H*), 7.78 (1H, d, *J* 8.0 Hz, Ar*H*), 7.56 – 7.50 (2H, m, 2 × Ar*H*), 7.38 (1H, app. t, *J* 7.3 Hz, Ar*H*), 7.31 (1H, d, *J* 7.0 Hz, Ar*H*), 7.19 (1H, d, *J* 11.8 Hz, C*H*=CH), 6.95 (1H, d, *J* 11.8 Hz, CH=C*H*), 6.26 (1H, s, Ar*H*), 3.92 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.00 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 153.3 (0, *C*O), 153.2 (0, *C*O), 141.5 (0, *C*O), 136.4 (1, *C*H), 136.2 (0, *C*), 134.8 (0, *C*), 133.9 (0, *C*), 132.0 (0, *C*), 129.6 (1, *C*H), 128.8 (1, *C*H), 127.9 (1, *C*H), 127.1 (1, *C*H), 126.5 (1, *C*H), 126.3 (1, *C*H), 125.9 (1, *C*H), 125.2 (1, *C*H), 110.2 (1, *C*H), 88.3 (0, *C*I), 61.3 (3, O*C*H_3), 61.2 (3, O*C*H_3), 55.7 (3, O*C*H_3) ppm.

LRMS (M/z, CI) 446 (M^+, 28 %), 320 (80 %), 318 (100 %), 288 (42 %), 189 (80 %) amu.

HRMS (M/z, ES+) $C_{42}H_{38}O_6I_2Na^+$ requires 915.0650. Found: $[2M+Na]^+$ 915.0622.

1-(2-(*E*)-(2-Iodo-3,4,5-trimethoxyphenyl)ethenyl)naphthalene **5.93**

FT – IR (ν_{max}, neat) 3055 w, 2932 m, 2852 m, 1551 m, 1476 s, 1423 m, 1383 s, 1331 s, 1162 m, 1103 s, 1005 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 328 (15000), 232 (16000) nm.

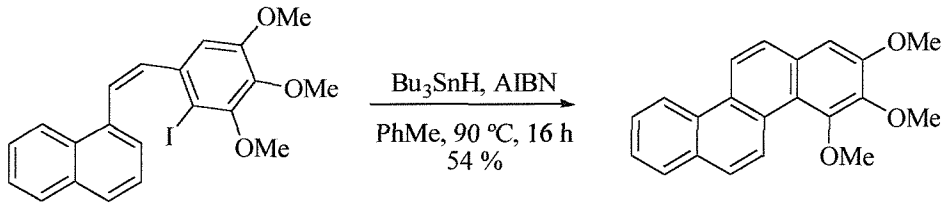
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 8.24 – 8.20 (1H, m, Ar*H*), 7.92 – 7.79 (3H, m, 3 × Ar*H*), 7.65 (1H, d, *J* 15.7 Hz, C*H*=CH), 7.58 – 7.50 (3H, m, 3 × Ar*H*), 7.41 (1H, d, *J* 15.7 Hz, CH=C*H*), 7.15 (1H, s, Ar*H*), 3.99 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.94 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 154.4 (0, *C*O), 153.7 (0, *C*O), 142.5 (0, *C*O), 136.8 (0, *C*), 136.1 (1, *C*H), 135.5 (0, *C*), 134.2 (0, *C*), 131.6 (0, *C*), 129.1 (1, *C*H), 128.8 (1, *C*H), 127.9 (1, *C*H), 126.8 (1, *C*H), 126.6 (1, *C*H), 126.5 (1, *C*H), 124.7 (1, *C*H), 124.1 (1, *C*H), 106.5 (1, *C*H), 89.3 (0, *C*I), 61.5 (3, O*C*H_3), 61.2 (3, O*C*H_3), 56.7 (3, O*C*H_3) ppm.

LRMS (M/z, CI) 447 (MH^+, 8 %), 321 ($[M+2H-I]^+$, 100 %) amu.

HRMS (M/z, ES+), $C_{21}H_{19}O_3Na^+$ requires: 469.0271; Found $[M+Na]^+$: 469.0265.

2,3,4-Trimethoxychrysene **5.28**



5.27
$C_{21}H_{19}IO_3$ (446)

5.28
$C_{21}H_{18}O_3$ (318)

Iodide **5.27** (940 mg, 2.11 mmol), tributyltin hydride (680 μL, 735 mg, 2.53 mmol) and AIBN (70 mg, 0.42 mmol) were heated in toluene (65 mL) at 90 °C for 7 hours with additional tributyltin hydride (350 μl, 380 mg, 1.30 mmol) and AIBN (30 mg, 0.18 mmol) added after 3 and 5 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 30 mL) for 16 hours. The mixture was diluted with ether (30 mL) and the organic phase were washed with water (2 × 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 – 10 % ether / petrol) yielded firstly recovered starting material **5.27** (90 mg, 0.20 mmol, 10 %) and then the title compound **5.28** (360 mg, 1.13 mmol, 54 %) as a pale yellow solid.

MP 172 – 173 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2935 w, 2841 w, 1611 m, 1487 m, 1467 s, 1420 m, 1354 m, 1270 m, 1144 m, 1113 s, 1073 m, 1016 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 334 (12000), 316 (25000), 274 (160000) nm.

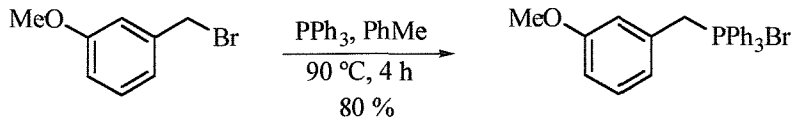
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 9.63 (1H, d, *J* 9.6 Hz, Ar*H*), 8.77 (1H, d, *J* 8.5 Hz, Ar*H*), 8.68 (1H, d, *J* 8.8 Hz, Ar*H*), 8.01 – 7.97 (2H, m, 2 × Ar*H*), 7.88 (1H, d, *J* 9.2 Hz, Ar*H*), 7.73 – 7.60 (2H, m, 2 × Ar*H*), 7.19 (1H, s, Ar*H*), 4.10 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 4.05 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 152.7 (0, 2 × *C*O), 152.5 (0, *C*O), 143.4 (0, *C*), 131.7 (0, *C*), 130.6 (0, 2 × *C*), 128.3 (1, *C*H), 127.9 (0, *C*), 127.1 (1, *C*H), 127.0 (1, *C*H), 126.4 (1, *C*H), 126.2 (1, *C*H), 125.3 (1, *C*H), 123.2 (1, *C*H), 121.4 (1, *C*H), 120.2 (0, *C*), 104.8 (1, *C*H), 61.6 (3, O*C*H$_3$), 60.9 (3, O*C*H$_3$), 56.1 (3, O*C*H$_3$) ppm.

LRMS (M/z, CI) 319 (MH^+, 68 %), 318 (M^+, 66 %), 189 (100 %).

CHN $C_{21}H_{18}O_3$ requires: C 79.22, H 5.70; Found: C 79.04, H 5.71.

(3-Methoxybenzyl)triphenylphosphonium bromide **5.95**



5.94
C_8H_9BrO (201)

5.95
$C_{26}H_{24}BrOP$ (463)

3-Methoxybenzyl bromide **5.94** (2.8 mL, 4.02 g, 20.00 mmol) and triphenylphosphine (5.25 g, 20.00 mmol) were heated in toluene (50 mL) at reflux for 4 hours. The resulting white solid was collected by filtration, washed sequentially with toluene (15 mL) and petrol (20 mL) and dried *in vacuo* to yield the title compound **5.95** (7.40 g, 15.98 mmol, 80 %) as a white solid.[192]

MP 234 – 235 °C (toluene) lit. 246 - 248 °C (no solvent stated).[192]

FT – IR (ν_{max}, neat) 2906 m, 1591 m, 1490 m, 1329 m, 1253 m, 1172 m, 1108 m cm^{-1}.

UV (λ_{max}, MeCN) 265 (13000) nm.

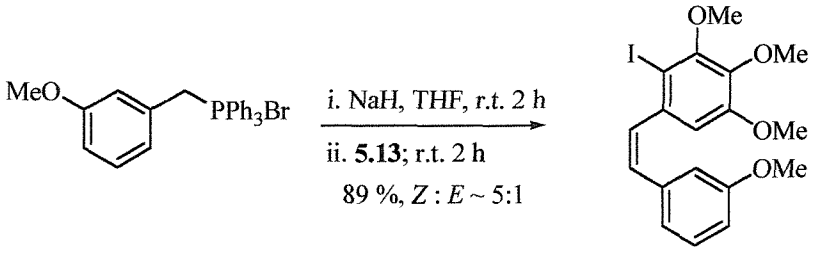
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.80 – 7.56 (15H, m, 3 × C_6H_5), 7.00 (1H, app. t, *J* 8.0 Hz, Ar*H*), 6.75 – 6.71 (2H, m, 2 × Ar*H*), 6.62 (1H, br. d, *J* 8.0 Hz, Ar*H*), 5.28 (2H, d, *J* 14.3 Hz, CH_2P), 3.50 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 159.4 (0, d, *J* 3.4 Hz, *C*O), 135.0 (1, d, *J* 3.4 Hz, 3 × *C*H), 134.4 (1, d, *J* 10.2 Hz, 6 × *C*H), 130.1 (1, d, *J* 12.4 Hz, 6 × *C*H), 129.6 (1, d, *J* 3.4 Hz, *C*H), 128.4 (0, d, *J* 8.5 Hz, *C*), 123.5 (1, d, *J* 5.6 Hz, *C*H), 117.7 (0, d, *J* 85.9 Hz, 3 × *C*), 116.1 (1, d, *J* 5.1 Hz, *C*H), 115.2 (1, d, *J* 4.0 Hz, *C*H), 55.4 (3, OCH_3), 30.8 (2, d, *J* 47.5 Hz, CH_2P) ppm.

^{31}P – NMR (121 MHz, $CDCl_3$) δ_P 23.8 ppm.

LRMS (M/z, ES+) 383 ($[M-Br]^+$, 100 %), 153 (25 %) amu.

2-Iodo-3,4,5-trimethoxy-1-(2-(*Z*)-(3-methoxyphenyl)ethenyl)benzene **5.29** & 2-iodo-3,4,5-trimethoxy-1-(2-(*E*)-(3-methoxyphenyl)ethenyl)benzene **5.96**



5.95

$C_{26}H_{24}BrOP$ (463)

(*Z*)-**5.29**
(*E*)-**5.96**

$C_{18}H_{19}IO_4$ (426)

Sodium hydride (60 % in mineral oil, 360 mg, 8.94 mmol), pre-washed with tetrahydrofuran (10 mL), was suspended in tetrahydrofuran (30 mL) and cooled to 0 °C. Phosphonium bromide **5.95** (3.45 g, 7.45 mmol) was added and the mixture stirred at room temperature for 2 hours. The resulting yellow mixture was cooled to 0 °C and aldehyde **5.13** (2.00 g, 6.21 mmol) was added as a solution in tetrahydrofuran (10 mL). After stirring at room temperature for a further 2 hours, the mixture was filtered through Celite and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 % ether / petrol) yielded firstly **5.29** (1.11 g, 2.61 mmol, 42 %) as a pale yellow solid then a mixture of isomers (1.01 g, 2.37 mmol, 38 %, **5.29**:**5.96** ~ 5:1) as a yellow oil and finally **5.96** (225 mg, 0.53 mmol, 9 %) as a pale yellow oil.

2-Iodo-3,4,5-trimethoxy-1-(2-(*Z*)-(3-methoxyphenyl)ethenyl)benzene **5.29**

MP 41 – 43 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2939 m, 1590 m, 1558 m, 1477 m, 1418 m, 1382 m, 1323 s, 1104 s, 1049 m, 1005 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 282 (28000), 250 (72000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.13 (1H, t, *J* 7.7 Hz, Ar*H*), 6.80 – 6.66 (3H, m, 3 × Ar*H*), 6.59 (1H, d, *J* 11.9 Hz, C*H*=CH), 6.59 (1H, s, Ar*H*), 6.52 (1H, d, *J* 11.9 Hz, CH=C*H*), 3.91 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.52 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 159.8 (0, *C*O), 153.8 (0, *C*O), 153.7 (0, *C*O), 141.6 (0, *C*O), 138.1 (0, *C*), 137.3 (0, *C*), 134.3 (1, *C*H), 131.0 (1, *C*H), 129.6 (1, *C*H), 122.1 (1, *C*H), 114.4 (1, *C*H), 113.8 (1, *C*H), 110.2 (1, *C*H), 87.6 (0, *C*I), 61.5 (3, O*C*H_3), 61.2 (3, O*C*H_3), 56.3 (3, O*C*H_3), 55.4 (3, O*C*H_3) ppm.

LRMS (M/z, CI) 427 (MH^+, 2 %), 301 ($[M-I+2H]^+$, 100 %), 268 (10 %), 225 (8 %), 169 (8 %) amu.

HRMS (M/z, ES+) $C_{18}H_{19}IO_4K^+$ requires: 464.9960; Found $[M+K]^+$: 464.9980.

2-Iodo-3,4,5-trimethoxy-1-(2-(*E*)-(3-methoxyphenyl)ethenyl)benzene **5.96**

FT – IR (ν_{max}, neat) 2925 m, 1594 m, 1577 m, 1477 s, 1383 m ,1269 m, 1103 s, 1051 m, 1004 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 285 (26000), 250 (72000) nm.

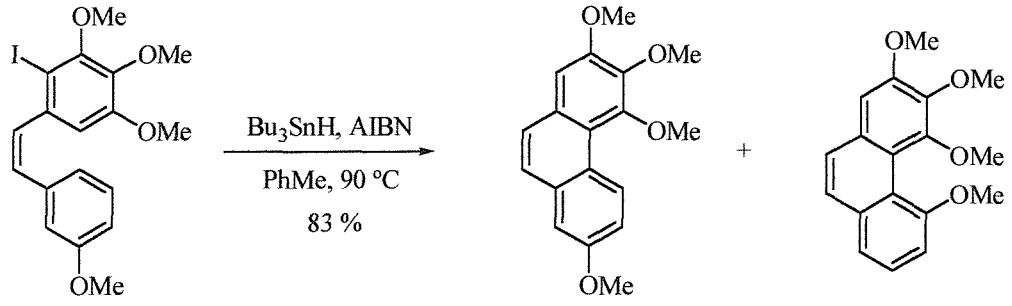
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.38 (1H, d, *J* 15.9 Hz, C*H*=CH), 7.31 (1H, t, *J* 7.9 Hz, Ar*H*), 7.16 (1H, br. d, 7.9 Hz, Ar*H*), 7.09 (1H, app. t, *J* 2.2 Hz, Ar*H*), 7.02 (1H, s, Ar*H*), 6.87 (1H, dd, *J* 7.9, 2.2 Hz, Ar*H*), 6.84 (1H, d, *J* 15.9 Hz, CH=C*H*), 3.95 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.87 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 160.1 (0, *C*O), 154.0 (0, *C*O), 153.3 (0, *C*O), 142.0 (0, *C*O), 138.5 (0, *C*), 136.2 (0, *C*), 133.2 (1, *C*H), 130.9 (1, *C*H), 129.9 (1, *C*H), 119.6 (1, *C*H), 113.6 (1, *C*H), 112.3 (1, *C*H), 105.7 (1, *C*H), 89.1 (0, *C*I), 61.2 (3, O*C*H_3), 60.9 (3, O*C*H_3), 56.3 (3, O*C*H_3), 55.4 (3, O*C*H_3) ppm.

LRMS (M/z, CI) 427 (MH^+, 10 %), 301 ($[M-I+2H]^+$, 100 %), 285 (16 %), 268 (10 %).

HRMS (M/z, ES+) $C_{36}H_{38}I_2O_8Na^+$ requires: 875.0548; Found $[2M+Na]^+$: 875.0541.

2,3,4,7-Tetramethoxyphenanthrene **5.30** & 2,3,4,5-tetramethoxyphenanthrene **5.31**



5.29 $C_{18}H_{19}IO_4$ (426)

5.30 $C_{18}H_{18}O_4$ (298) 1:1 **5.31** $C_{18}H_{18}O_4$ (298)

Iodide **5.29** (800 mg, 1.88 mmol), tributyltin hydride (610 μL, 655 mg, 2.25 mmol) and AIBN (35 mg, 0.20 mmol) were heated in toluene (65 mL) at 90 °C for 6 hours with further portions of tributyltin hydride (300 μL, 325 mg, 1.12 mmol) and AIBN (15 mg, 0.09 mmol) added after 2 and 4 hours. After cooling to room temperature, the mixture was stirred with a

solution of potassium fluoride (10 % w/v, 30 mL) for 3 days. The organic phase was diluted with ether (20 mL) and washed with water (3 × 20 mL). Drying ($MgSO_4$), concentration *in vacuo* and purification by column chromatography (silica gel, 15 – 20 % ether / petrol) yielded firstly phenanthrene **5.30** (205 mg, 0.69 mmol, 37 %) as a white solid then a mixture of **5.30** & **5.31** (50 mg, 0.17 mmol, 9 %, **5.30**:**5.31** ~ 1:1) and finally phenanthrene **5.31** (205 mg, 0.69 mmol, 37 %) as a colourless oil.

2,3,4,7-Tetramethoxyphenanthrene **5.30**[193-195]

MP 154 – 155 °C (ether / petrol) lit. 150 – 151 °C (no solvent stated).[194,195]

FT – IR (ν_{max}, neat) 2969 m, 2922 m, 1619 m, 1455 m, 1287 m, 1224 s, 1147 m, 1125 s, 1001 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 284 (34000), 257 (120000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 9.33 (1H, d, *J* 9.3 Hz, Ar*H*), 7.50 (2H, s, 2 × Ar*H*), 7.20 – 7.14 (2H, m, 2 × Ar*H*), 6.99 (1H, s, Ar*H*), 3.95 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.87 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 157.6 (0, 2 × *C*O), 152.2 (0, 2 × *C*O), 133.8 (0, *C*), 129.5 (0, *C*), 128.8 (1, *C*H), 127.5 (1, *C*H), 127.1 (1, *C*H), 124.6 (0, *C*), 119.6 (0, *C*), 117.2 (1, *C*H), 109.1 (1, *C*H), 105.7 (1, *C*H), 61.7 (3, OCH_3), 60.6 (3, OCH_3), 56.3 (3, OCH_3), 55.7 (3, OCH_3) ppm.

LRMS (M/z, CI) 299 (MH^+, 100 %), 283 (10 %), 240 (12 %), 169 (14 %) amu.

2,3,4,5-Tetramethoxyphenanthrene **5.31**[193]

FT – IR (ν_{max}, neat) 3001 m, 2922 m, 2830 m, 1605 m, 1469 s, 1424 m, 1345 m, 1278 s, 1229 m, 1083 s, 1003 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 284 (84000), 254 (270000) nm.

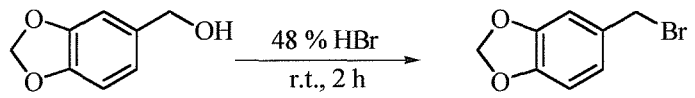
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.51 (1H, d, *J* 8.5 Hz, Ar*H*), 7.48 (1H, d, *J* 8.5 Hz, Ar*H*), 7.46 (1H, t, *J* 7.8 Hz, Ar*H*), 7.39 (1H, dd, *J* 7.8, 1.3 Hz, Ar*H*), 7.05 (1H, dd, *J* 7.8, 1.3 Hz, Ar*H*), 7.00 (1H, s, Ar*H*), 4.00 (6H, s, 2 × OCH_3), 4.00 (3H, s, OCH_3), 3.73 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 157.9 (0, *C*O), 153.0 (0, 2 × *C*O), 152.8 (0, *C*O), 134.1 (0, *C*), 130.8 (0, *C*), 127.0 (1, *C*H), 126.6 (1, *C*H), 126.5 (1, *C*H), 120.1 (1,

*C*H), 119.6 (0, *C*), 117.3 (0, *C*), 108.3 (1, *C*H), 103.8 (1, *C*H), 61.7 (3, OCH_3), 61.2 (3, OCH_3), 56.4 (3, OCH_3), 56.4 (3, OCH_3) ppm.

LRMS (M/z, CI) 299 (MH^+, 100 %), 267 (8 %), 240 (6 %), 169 (8 %) amu.

(1,3-Benzodioxol-5-yl)methyl bromide **5.97**[109]



4.2 $C_8H_8O_3$ (152) — **5.97** $C_8H_7BrO_2$ (215)

(1,3-Benzodioxol-5-yl)methyl bromide **5.97** was prepared by the method of Beard *et al.*[109] Piperonyl alcohol **4.2** (5.0 g, 32.86 mmol) was added portionwise to hydrobromic acid (48 %, 10 mL). After standing at room temperature for 2 hours the mixture was diluted with dichloromethane (20 mL) and the aqueous phase extracted with dichloromethane (2 × 20 mL). The combined organic phases were washed with water (2 × 20 mL), sodium hydrogen carbonate (sat. aq., 3 × 20 mL) and brine (20 mL) then dried ($MgSO_4$). Concentration *in vacuo* provided the title compound **5.97** (6.35 g, 29.5 mmol, 90 %) as a white solid.[109]

MP 44 – 46 °C (petrol) lit. 46 – 48 °C (light petrol).[109]

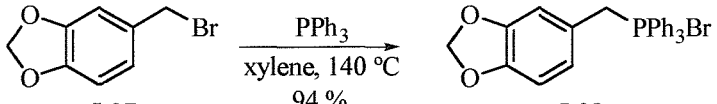
FT – IR (ν_{max}, neat) 1501 s, 1488 s, 1444 s, 1360 m, 1257 s, 1096 m, 1037 s cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 6.90 (1H, s, Ar*H*), 6.87 (1H, d, *J* 7.8 Hz, Ar*H*), 6.76 (1H, d, *J* 7.8 Hz, Ar*H*), 5.98 (2H, s, OCH_2O), 4.47 (2H, s, CH_2Br) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 148.1 (0, *C*O), 148.0 (0, *C*O), 131.7 (0, *C*), 122.9 (1, *C*H), 109.6 (1, *C*H), 108.5 (1, *C*H), 101.5 (2, OCH_2O), 34.4 (2, CH_2Br) ppm.

LRMS (M/z, CI) 216 ($M^+\{^{81}Br\}$, 6 %), 214 ($M^+\{^{79}Br\}$, 6 %), 135 ($[M\text{-}Br]^+$, 100 %), 105 (5 %), 77 (18 %), 51 (12 %) amu.

(1,3-Benzodioxol-5-ylmethyl)triphenylphosphonium bromide **5.98**



5.97 $C_8H_7BrO_2$ (215) — **5.98** $C_{26}H_{22}BrO_2P$ (477)

(1,3-Benzodioxol-5-yl)methyl bromide **5.97** (5.70 g, 26.51 mmol) and triphenylphosphine (8.33 g, 31.81 mmol) were dissolved in xylene (60 mL) and the mixture stirred at reflux for 3 hours. After cooling, the resulting white solid was collected by filtration and washed with

cold xylene (2 × 20 mL) and petrol (3 × 20 mL) to yield the title compound **5.98** (11.92 g, 24.99 mmol, 94 %) as a white solid.[196]

MP 227 – 229 °C (xylene) lit. 236.5 – 238.5 °C (toluene).[196]

FT – IR (ν_{max}, nujol mull) 1586 w, 1502 w, 1488 m, 1250 m, 1110 m, 1037 m cm^{-1}.

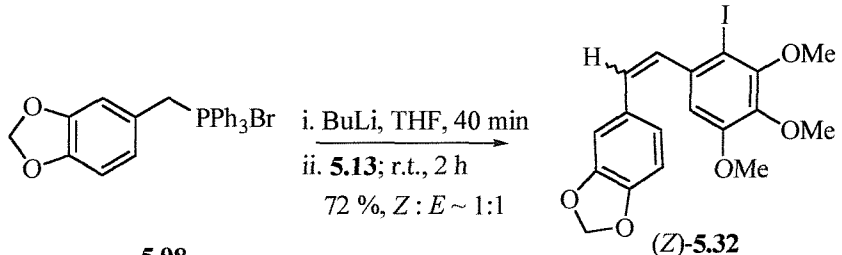
UV (λ_{max}, MeOH) 286 (6360), 272 (7160), 224 (38560) nm.

^{1}H – NMR (300 MHz, $CDCl_3$ + d_6-DMSO) δ_H 7.79 (3H, t, *J* 7.5 Hz, 3 × Ar*H*), 7.65 – 7.35 (15H, m, 15 × Ar*H*), 5.88 (2H, s, OCH_2O), 4.83 (2H, d, *J* 12.5 Hz, CH_2P) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$ + d_6-DMSO) δ_C 147.9 (0, 2 × *C*O), 135.2 (1, 3 × *C*H), 134.5 (1, d, *J* 9.7 Hz, 6 × *C*H), 130.3 (1, d, *J* 12.5 Hz, 6 × *C*H), 125.6 (1, d, *J* 6.3 Hz, *C*H), 120.2 (0, d, *J* 9.1 Hz, *C*), 117.9 (0, d, *J* 85.4 Hz, 3 × *C*), 111.5 (1, *C*H), 108.7 (1, *C*H), 101.4 (2, OCH_2O), 30.7 (2, d, *J* 46.7 Hz, CH_2P) ppm.

LRMS (M/z, ES+) 397 ($[M-Br]^+$, 100 %) amu.

5-((*Z*)-2-(2-Iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)-1,3-benzodioxole **5.32** & 5-((*E*)-2-(2-iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)-1,3-benzodioxole **5.99**



5.98
$C_{26}H_{22}BrO_2P$ (477)

(*Z*)-**5.32**
(*E*)-**5.99**
$C_{18}H_{17}IO_5$ (440)

Phosphonium bromide **5.98** (2.22 g, 4.66 mmol) was suspended in tetrahydrofuran (30 mL) and cooled to –78 °C. *n*-Butyllithium (2.26 M in hexanes, 1.9 mL, 4.27 mmol) was added over 5 minutes and the mixture allowed to warm to room temperature (40 minutes). After cooling to –78 °C, aldehyde **5.13** (1.25 g, 3.88 mmol) was added as a solution in tetrahydrofuran (10 mL) and the mixture allowed to stir at room temperature for 2 hours. The mixture was filtered through Celite and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 – 20 % ether / petrol) firstly gave **5.32** (350 mg, 0.80 mmol, 21 %) as a white solid, then a mixture of isomers (570 mg, 1.30 mmol, 33 %, **5.32**:**5.99** ~ 1:1) and finally **5.99** (300 mg, 0.68 mmol, 18 %) as a white solid.

5-((*Z*)-2-(2-Iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)-1,3-benzodioxole **5.32**

MP 76 – 78 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2944 w, 1549 m, 1487 m, 1479 s, 1380 m, 1244 m, 1104 s, 1038 s, 1007 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2), 282 (18000), 253 (29000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 6.69 (2H, app. s, 2 × Ar*H*), 6.64 – 6.61 (2H, m, 2 × Ar*H*), 6.50 (1H, d, *J* 11.9 Hz, C*H*=CH), 6.39 (1H, d, *J* 11.9 Hz, CH=C*H*), 5.91 (2H, s, OCH_2O), 3.92 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.60 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 153.9 (0, 2 × *C*O), 153.7 (0, *C*O), 147.8 (0, *C*O), 147.2 (0, *C*O), 137.4 (0, *C*), 132.8 (1, *C*H), 130.8 (0, *C*), 130.5 (1, *C*H), 123.8 (1, *C*H), 110.0 (1, *C*H), 109.3 (1, *C*H), 108.5 (1, *C*H), 101.3 (2, O*C*H_2O), 87.7 (0, *C*I), 61.5 (3, O*C*H_3), 61.2 (3, O*C*H_3), 56.4 (3, O*C*H_3) ppm.

LRMS (M/z, Cl) 440 (M^+, 4 %), 315 ($[M-I+2H]^+$, 100 %), 299 (20 %), 282 (20 %), 254 (8 %), 183 (11 %) amu.

CHN $C_{18}H_{17}IO_5$ requires: C 49.11, H 3.89; Found: C 49.09, H 3.85.

5-((*E*)-2-(2-Iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)-1,3-benzodioxole **5.99**

MP 105 – 107 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2901 w, 1558 m, 1503 m, 1489 s, 1478 m, 1393 m, 1254 s, 1197 m, 1102 m, 1040 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 331 (32000), 288 (27000), 246 (48000) nm.

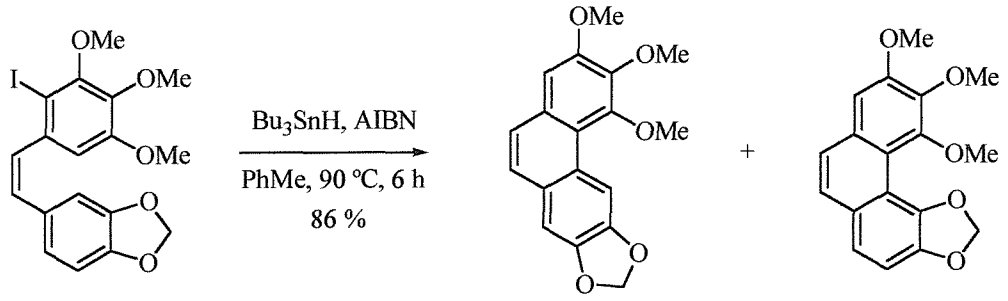
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.19 (1H, d, *J* 15.8 Hz, C*H*=CH), 7.11 (1H, d, *J* 1.8 Hz, Ar*H*), 6.97 (1H, s, Ar*H*), 6.96 (1H, dd, *J* 8.0, 1.8 Hz, Ar*H*), 6.81 (1H, d, *J* 8.0 Hz, Ar*H*), 6.78 (1H, d, *J* 15.8 Hz, CH=C*H*), 6.00 (2H, s, OCH_2O), 3.94 (3H, s, OCH_3), 3.90 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 154.3 (0, *C*O), 153.6 (0, *C*O), 148.7 (0, *C*O), 148.0 (0, *C*O), 142.1 (0, *C*O), 136.7 (0, *C*), 131.9 (0, *C*), 131.5 (1, *C*H=CH), 131.0 (1, CH=*C*H), 122.2 (1, *C*H), 108.9 (1, *C*H), 106.2 (1, *C*H), 105.8 (1, *C*H), 101.6 (2, O*C*H_2O), 89.2 (0, *C*I), 61.5 (3, O*C*H_3), 61.1 (3, O*C*H_3), 56.6 (3, O*C*H_3) ppm.

LRMS (M/z, CI) 441 (MH^+, 4 %), 315 ($[M-I+2H]^+$, 100 %), 299 (20 %), 239 (4 %), 181 (4 %) amu.

CHN $C_{18}H_{17}IO_5$ requires: C 49.11, H 3.89; Found: C 49.06, H 3.84.

1,2,3-Trimethoxyphenanthro[2,3-*d*][1,3]dioxole **1.34** & 9,10,11-trimethoxyphenanthro[3,4-*d*][1,3]dioxole **5.33**



5.32 $C_{18}H_{17}IO_5$ (440) — **1.34** $C_{18}H_{16}O_5$ (312) — 5:1 — **5.33** $C_{18}H_{16}O_5$ (312)

Iodide **5.32** (245 mg, 0.56 mmol), tributyltin hydride (180 μL, 195 mg, 0.67 mmol) and AIBN (16 mg, 0.10 mmol) were heated in toluene (20 mL) at 90 °C for 8 hours with additional portions of tributyltin hydride (90 μL, 97 mg, 0.33 mmol) and AIBN (10 mg, 0.06 mmol) added after 4 and 6 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 30 mL) for 16 hours. The organic phase was diluted with ether (20 mL) and washed with water (3 × 20 mL). Concentration *in vacuo* and purification by column chromatography (silica gel, 10 – 20 % ether / petrol) yielded dioxole **1.34** (125 mg, 0.40 mmol, 72 %) as a white solid and then dioxole **5.33** (25 mg, 0.08 mmol, 14 %) as a pale yellow solid.

1,2,3-Trimethoxyphenanthro[2,3-*d*][1,3]dioxole **1.34**[11]

MP 126 – 127 °C (ether / petrol) lit. 132 °C (pentane / ether).[182]

FT – IR (ν_{max}, neat) 2906 w, 1604 m, 1515 m, 1470 s, 1291 m, 1239 s, 1103 m, 1045 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 354 (2400), 279 (37000), 254 (110000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 9.00 (1H, s, Ar*H*), 7.55 (1H, d, *J* 8.5 Hz, Ar*H*), 7.51 (1H, d, *J* 8.5 Hz, Ar*H*), 7.20 (1H, s, Ar*H*), 7.07 (1H, s, Ar*H*), 6.10 (2H, s, OCH_2O), 4.03 (3H, s, OCH_3), 4.02 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 151.9 (0, *C*O), 151.8 (0, *C*O), 147.9 (0, *C*O), 146.3 (0, *C*O), 142.5 (0, *C*O), 129.5 (0, *C*), 128.3 (0, *C*), 126.6 (1, *C*H), 125.6 (0, *C*), 124.9 (1, *C*H), 119.1 (0, *C*), 105.5 (1, *C*H), 105.1 (1, *C*H), 104.9 (1, *C*H), 101.1 (2, O*C*H_2O), 61.3 (3, O*C*H_3), 60.3 (3, O*C*H_3), 55.9 (3, O*C*H_3) ppm.

LRMS (M/z, CI) 313 (MH^+, 100 %), 297 (10 %), 254 (10 %), 183 (14 %) amu.

9,10,11-Trimethoxyphenanthro[3,4-*d*][1,3]dioxole **5.33**

FT – IR (ν_{max}, neat) 2925 m, 1598 m, 1505 m, 1466 s, 1425 s, 1350 m, 1285 s, 1273 s, 1107 s, 1050 m cm^{-1}.

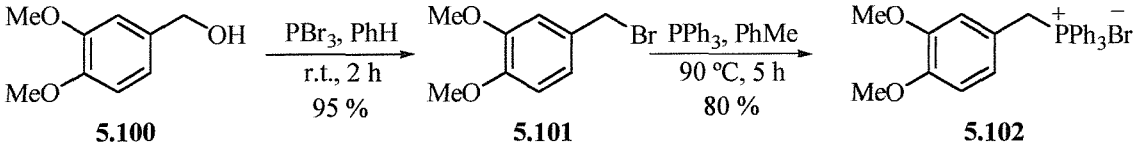
UV (λ_{max}, CH_2Cl_2) 308 (11000), 255 (76000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.52 (1H, d, *J* 8.8 Hz, Ar*H*), 7.40 (1H, d, *J* 8.0 Hz, Ar*H*), 7.36 (1H, d, *J* 8.8 Hz, Ar*H*), 7.20 (1H, d, *J* 8.0 Hz, Ar*H*), 6.92 (1H, s, Ar*H*), 6.17 (2H, s, OCH_2O), 4.02 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 3.93 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 153.6 (0, *C*O), 146.5 (0, *C*O), 143.0 (0, *C*O), 131.3 (0, 2 × *C*), 129.2 (0, 2 × *C*), 127.8 (1, *C*H), 124.7 (1, *C*H), 123.1 (1, *C*H), 116.6 (0, *C*), 115.0 (0, *C*), 109.1 (1, *C*H), 105.0 (1, *C*H), 100.7 (2, OCH_2O), 61.8 (3, OCH_3), 61.7 (3, OCH_3), 56.3 (3, OCH_3) ppm.

LRMS (M/z, CI) 313 (MH^+, 100 %), 297 (12 %), 254 (10 %), 183 (10 %).

(3,4-Dimethoxybenzyl)triphenylphosphonium bromide **5.102**



5.100 $C_9H_{12}O_3$ (168)

5.101 $C_9H_{11}BrO_2$ (231)

5.102 $C_{27}H_{26}BrO_2P$ (493)

To a cooled solution (0 °C) of 3,4-dimethoxybenzyl alcohol **5.100** (1.68 g, 10.00 mmol) in benzene (30mL) was added phosphorus tribromide (330 μL, 950 mg, 3.50 mmol) and the mixture stirred at room temperature for a further 2 hours. The solvent was removed under reduced pressure and the residue diluted with dichloromethane (50 mL) then washed with water (2 × 20 mL). Further washing with sodium hydrogen carbonate (sat. aq., 2 × 20 mL) and brine (10 mL) then drying ($MgSO_4$) and concentration *in vacuo* yielded 3,4-dimethoxybenzyl bromide **5.101** (2.24 g, 9.70 mmol, 97 %) as a pale yellow oil. Bromide **5.101** (2.00 g, 8.66 mmol) and triphenylphosphine (2.38 g, 9.09 mmol) were dissolved in toluene (30 mL) and heated at 90 °C for 5 hours. After cooling to room temperature, the resulting white solid was collected by filtration and washed with petrol (2 × 10 mL) to yield the title compound **5.102** (3.40 g, 6.90 mmol, 80 %) as a white solid.

3,4-Dimethoxybenzyl bromide **5.101**[197]

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 6.95 (1H, dd, *J* 8.2, 2.1 Hz, Ar*H*), 6.91 (1H, d, *J* 2.1 Hz, Ar*H*), 6.81 (1H, d, *J* 8.2 Hz, Ar*H*), 4.51 (2H, s, CH_2Br), 3.90 (3H, s, OCH_3), 3.88 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 149.5 (0, *C*O), 149.3 (0, *C*O), 130.5 (0, *C*), 121.8 (1, *C*H), 112.4 (1, *C*H), 111.3 (1, *C*H), 56.3 (3, O*C*H$_3$), 56.3 (3, O*C*H$_3$), 34.8 (2, *C*H$_2$Br) ppm.

(3,4-Dimethoxybenzyl)triphenylphosphonium bromide **5.102**

MP 255 – 256 °C (EtOH).

FT – IR (ν_{max}, neat) 3056 w, 3008 w, 2960 w, 2827 m, 1584 m, 1517 s, 1438 m, 1265 s, 1111 m, 1029 m cm^{-1}.

UV (λ_{max}, MeCN) 267 (25000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.70 – 7.55 (15H, m, 15 × Ar*H*), 6.77 (1H, app. t, *J* 2.0 Hz, Ar*H*), 6.60 (1H, dt, *J* 8.2, 2.0 Hz, Ar*H*), 6.54 (1H, d, *J* 8.2 Hz, Ar*H*), 5.22 (2H, d, *J* 13.9 Hz, CH_2P), 3.74 (3H, s, OCH_3), 3.46 (3H, s, OCH_3) ppm.

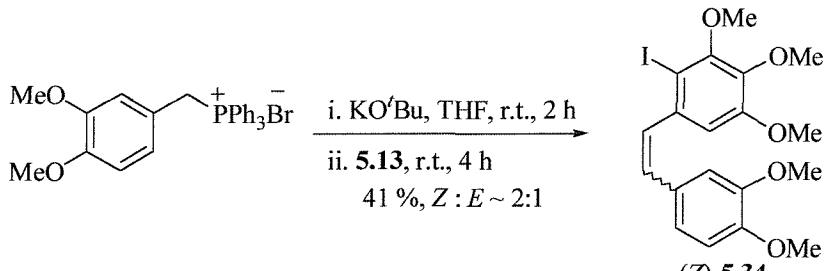
^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 148.9 (0, *C*O), 148.8 (0, *C*O), 135.0 (1, 3 × *C*H), 134.6 (1, d, *J* 9.9 Hz, 6 × *C*H), 130.2 (1, d, *J* 12.5 Hz, 6 × *C*H), 123.9 (1, d, *J* 6.4 Hz, *C*H), 119.1 (0, d, *J* 8.8 Hz, *C*), 118.0 (0, d, *J* 85.6, 3 × *C*), 115.0 (1, d, *J* 4.6 Hz, *C*H), 111.0 (1, *C*H), 56.2 (3, O*C*H$_3$), 55.9 (3, O*C*H$_3$), 30.3 (2, d, *J* 46.6 Hz, *C*H$_2$P) ppm.

^{31}P – NMR (121 MHz, $CDCl_3$) δ_P 23.1 ppm.

LRMS (M/z, ES+) 413 ([M+Br]$^+$, 100 %) amu.

1-((*Z*)-2-(3,4-Dimethoxyphenyl)-1-ethenyl)-2-iodo-3,4,5-trimethoxybenzene **5.34** &

1-((*E*)-2-(3,4-dimethoxyphenyl)-1-ethenyl)-2-iodo-3,4,5-trimethoxybenzene **5.103**



5.102

$C_{27}H_{26}BrO_2P$ (493)

(*Z*)-**5.34**

(*E*)-**5.103**

$C_{19}H_{21}IO_5$ (456)

To a suspension of (3,4-dimethoxybenzyl)triphenylphosphonium bromide **5.102** (1.35 g, 2.73 mmol) in tetrahydrofuran (30 mL) was added potassium *tert*-butoxide (335 mg, 3.00 mmol) and the mixture stirred at room temperature for 2 hours before cooling to 0 °C. 2-Iodo-3,4,5-trimethoxybenzaldehhyde **5.13** (800 mg, 2.48 mmol) was added as a solution in tetrahydrofuran (10 mL) and the mixture stirred at room temperature for 4 hours. Ether (50 mL) and water (30 mL) were added and the aqueous phase was extracted with ether (3 × 20 mL). The combined organic phases were washed with brine (20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded firstly **5.34** (240 mg, 0.53 mmol 21 %) as a colourless oil and then a mixture of isomers (230 mg, 0.50 mmol, 20 %, **5.34**:**5.103** ~ 2:5).

1-((*Z*)-2-(3,4-Dimethoxyphenyl)-1-ethenyl)-2-iodo-3,4,5-trimethoxybenzene **5.34**

FT – IR (ν_{max}, neat) 3006 w 2927 m, 2930 w, 1514 s, 1477 s, 1418 m, 1379 s, 1322 s, 1238 s, 1141 m, 1102 s, 1027 m, 1005 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 266 (36000) nm.

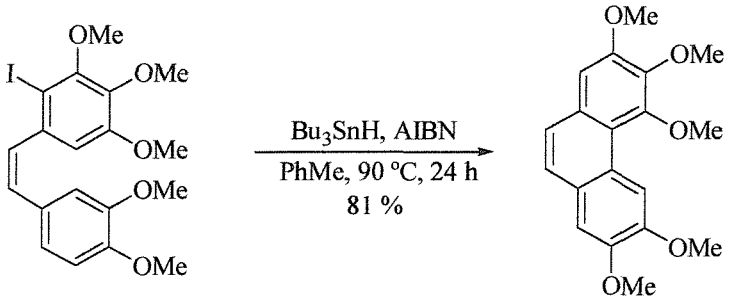
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 6.78 (1H, dd, *J* 8.2, 1.6 Hz, Ar*H*), 6.72 (1H, d, *J* 8.2 Hz, Ar*H*), 6.65 (1H, s, Ar*H*), 6.63 (1H, d, *J* 1.6 Hz, Ar*H*), 6.53 (1H, d, *J* 12.0 Hz, C*H*=CH), 6.42 (1H, d, *J* 12.0 Hz, CH=C*H*), 3.90 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 3.59 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.7 (0, *C*O), 153.5 (0, *C*O), 148.4 (0, *C*O), 148.4 (0, *C*O), 141.1 (0, *C*O), 137.8 (0, *C*), 132.1 (1, *C*H), 130.4 (1, *C*H), 129.1 (0, *C*), 122.4 (1, *C*H), 111.8 (1, *C*H), 110.8 (1, *C*H), 109.7 (1, *C*H), 87.3 (0, *C*I), 61.2 (3, O*C*H_3), 61.0 (3, O*C*H_3), 56.2 (3, O*C*H_3), 56.0 (3, O*C*H_3), 55.5 (3, O*C*H_3) ppm.

LRMS (M/z, CI) 329 ([M-I]$^+$, 100 %), 315 (32 %), 181 (45 %) amu.

HRMS $C_{19}H_{21}IO_5Na^+$ requires: 479.0326; Found $[M+Na]^+$: 479.0326.

2,3,4,6,7-Pentamethoxyphenanthrene **5.35**



5.34
$C_{19}H_{21}IO_5$ (456)

5.35
$C_{19}H_{20}O_5$(328)

Iodide **5.34** (240 mg, 0.53 mmol), tributyltin hydride (170 μL, 185 mg, 0.63 mmol) and AIBN (15 mg, 0.10 mmol) were stirred in toluene (15 mL) at 90 °C for 30 hours with additional portions of tributyltin hydride (100 μL, 110 mg, 0.37 mmol) and AIBN (15 mg, 0.10 mmol) added after 8 and 16 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 10 mL) for 5 hours. The mixture was diluted with ether (10 mL) and the organic phase were washed with water (2 × 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 50 % ether / petrol) yielded the title compound **5.35** (140 mg, 0.43 mmol, 81 %) as a white solid.[194,198]

MP 119 – 122 °C (ether / petrol) lit. 131 – 132 °C (no solvent reported).[198]

FT – IR (ν_{max}, neat) 3002 m, 2937 s, 2836 m, 1587 m, 1504 s, 1464 s, 1422 m, 1269 s, 1125 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 253 (41000) nm.

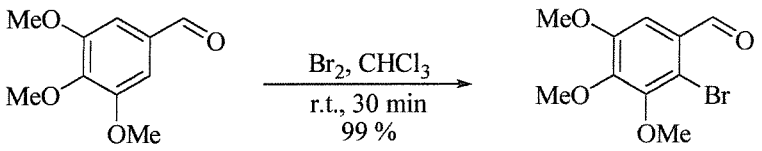
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 9.20 (1H, s, Ar*H*), 7.61 (1H, d, *J* 7.8 Hz, Ar*H*), 7.55 (1H, d, *J* 7.8 Hz, Ar*H*), 7.22 (1H, s, Ar*H*), 7.11 (1H, s, Ar*H*), 4.13 (3H, s, OCH_3), 4.09 (3H, s, OCH_3), 4.07 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 4.02 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 151.9 (0, *C*O), 151.7 (0, *C*O), 148.9 (0, *C*O), 148.2 (0, *C*O), 142.7 (0, *C*O), 130.9 (0, *C*), 129.6 (0, *C*), 127.2 (0, *C*), 126.3 (1, *C*H), 124.9 (1, *C*H), 118.7 (0, *C*), 108.2 (1, *C*H), 107.7 (1, *C*H), 105.3 (1, *C*H), 61.5 (3, OCH_3), 60.7 (3, OCH_3), 56.1 (3, OCH_3), 56.0 (3, OCH_3), 55.9 (3, OCH_3) ppm.

LRMS (M/z, CI) 329 (MH^+, 100 %), 313 (14 %), 270 (11 %), 199 (10 %) amu.

CHN $C_{19}H_{20}O_5$ requires: C 69.50, H 6.14; Found: C 69.28, H 6.12.

2-Bromo-3,4,5-trimethoxybenzaldehyde **5.104**[199]



5.12
$C_{10}H_{12}O_4$ (196)

5.104
$C_{10}H_{11}BrO_4$ (275)

2-Bromo-3,4,5-trimethoxybenzaldehyde **5.104** was prepared by the method of Brown *et al.*[199] 3,4,5-Trimethoxybenzaldehyde **5.12** (3.00 g, 15.29 mmol) was dissolved in chloroform (30 mL) and bromine (785 μL, 2.44 g, 15.29 mmol) was added over 5 minutes. The mixture was stirred for a further 25 minutes before the solvent was removed *in vacuo*. The resulting solid was dissolved in dichloromethane (30 mL), washed with sodium hydrogen carbonate (sat. aq., 20 mL) and sodium thiosulfate (sat. aq., 20 mL) then dried ($MgSO_4$). Concentrated *in vacuo* yielded the title compound **5.104** (4.16 g, 15.13 mmol, 99 %) as a white solid.[199]

MP 59 – 60 °C (ether / petrol) lit. 69.5 – 71 °C (petrol).[199]

FT – IR (ν_{max}, neat) 2940 m, 2860 w, 1690 s, 1577 m,1479 m, 1384 m,1328 s, 1199 m, 1108 s, 1003 m cm^{-1}.

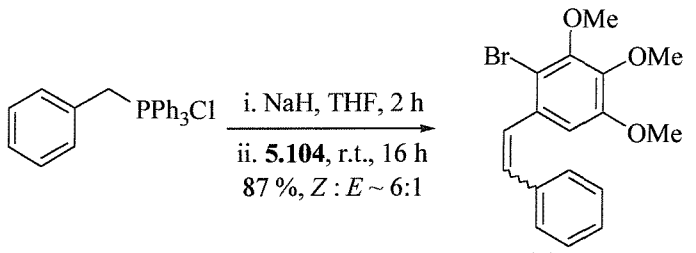
UV 319 (4200), 274 (9900) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 10.30 (1H, s, C*H*O), 7.31 (1H, s, Ar*H*), 3.98 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.91 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 191.4 (1, *C*HO), 153.5 (0, *C*O), 151.2 (0, *C*O), 149.1 (0, *C*O), 129.3 (0, *C*), 116.0 (0, *C*Br), 107.9 (1, *C*H), 61.7 (3, O*C*H_3), 61.6 (3, O*C*H_3), 56.7 (3, O*C*H_3) ppm.

LRMS (M/z, CI) 276 ($M^+\{^{81}Br\}$, 100 %), 274 ($M^+\{^{79}Br\}$, 98 %), 261 (14 %), 259 (14 %), 196 (24 %) amu.

2-Bromo-3,4,5-trimethoxy-1-((*Z*)-2-phenyl-1-ethenyl)benzene **5.39** & 2-bromo-3,4,5-trimethoxy-1-((*E*)-2-phenyl-1-ethenyl)benzene **5.105**



5.91
$C_{25}H_{22}ClP$ (389)

(*Z*)-**5.39**
(*E*)-**5.105**
$C_{17}H_{17}BrO_3$ (349)

To a suspension of pre-washed (tetrahydrofuran, 10 mL) sodium hydride (60 % in mineral oil, 630 mg, 15.71 mmol) in tetrahydrofuran (50 mL) was added benzyltriphenylphosphonium chloride **5.91** (5.09 g, 13.09 mmol) and the mixture stirred at room temperature for 2 hours before cooling to 0 °C. Aldehyde **5.104** (3.00 g, 10.91 mmol) was added and the mixture stirred at room temperature for a further 16 hours. Filtration through Florosil (eluent: ether), concentration *in vacuo* and purification of the residue by column chromatography (silica gel, 5 % ether / petrol) yielded firstly **5.39** (2.44 g, 6.99 mmol, 64 %) as a white solid then a mixture of isomers (775 mg, 2.22 mmol, 20 %, **5.39**:**5.105** ~ 1:1) and finally **5.105** (100 mg, 0.29 mmol, 3 %) as a white solid.

2-Bromo-3,4,5-trimethoxy-1-((*Z*)-2-phenyl-1-ethenyl)benzene **5.39**

MP 87 – 88 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2931 m, 2827 w, 1555 m, 1480 s, 1389 s, 1327 m, 1195 m, 1106 s, 1009 m cm^{-1}.

UV 277 (9400) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.22 – 7.18 (5H, m, 5 × Ar*H*), 6.78 (1H, d, *J* 11.9 Hz, C*H*=CH), 6.61 (1H, d, *J* 11.9 Hz, CH=C*H*), 6.54 (1H, s, Ar*H*), 3.93 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.45 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 152.6 (0, *C*O), 151.4 (0, *C*O), 143.8 (0, *C*O), 137.0 (0, *C*), 133.3 (0, *C*), 131.5 (1, *C*H), 129.8 (1, *C*H), 129.8 (1, 2 × *C*H), 129.4 (1, 2 × *C*H), 127.7 (1, *C*H), 110.8 (0, *C*Br), 110.0 (1, *C*H), 61.6 (3, OCH_3), 61.4 (3, OCH_3), 56.1 (3, OCH_3)

LRMS (M/z, CI) 350 ($M^+\{^{81}Br\}$, 62 %), 348 ($M^+\{^{79}Br\}$, 60 %), 268 (100 %), 254 (40 %), 238 (65 %), 210 (32 %), 139 (70 %) amu.

CHN $C_{17}H_{17}BrO_3$ requires: C 58.47, H 4.91; Found: C 58.62, H 4.95.

2-Bromo-3,4,5-trimethoxy-1-((*E*)-2-phenyl-1-ethenyl)benzene **5.105**

MP 51 – 53 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3002 m, 2936 m, 2827 m, 1557 m, 1480 s, 1427 s, 1392 s, 1237 m, 1107 s, 1009 s cm^{-1}.

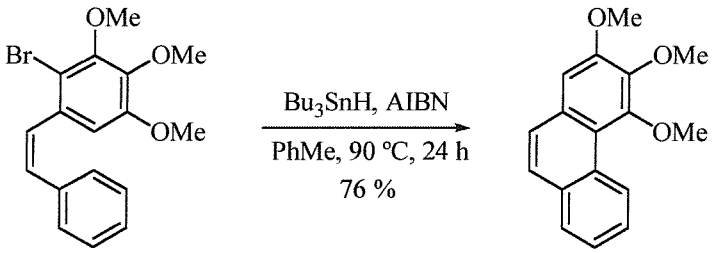
UV 299 (16000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.56 (2H, dd, *J* 7.0, 1.5 Hz, 2 × Ar*H*), 7.48 (1H, d, *J* 16.2 Hz, C*H*=CH), 7.39 (2H, app. t, *J* 7.2 Hz, 2 × ArH), 7.33 – 7.28 (1H, m, Ar*H*), 7.02 (1H, s, Ar*H*), 6.96 (1H, d, *J* 16.2 Hz, CH=C*H*), 3.95 (3H, s, OCH_3), 3.93 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 152.9 (0, *C*O), 151.1 (0, *C*O), 143.0 (0, *C*O), 137.1 (0, *C*), 133.0 (0, *C*), 130.9 (1, *C*H), 128.9 (1, 2 × *C*H), 128.2 (1, *C*H), 127.8 (1, *C*H), 126.9 (1, 2 × *C*H), 111.2 (0, *C*Br), 105.3 (1, *C*H), 61.4 (3, OCH_3), 61.1 (3, OCH_3), 56.4 (3, OCH_3) ppm.

LRMS (M/z, Cl) 351 ($MH^+\{^{81}Br\}$, 40 %), 349 ($MH^+\{^{79}Br\}$, 40 %), 270 ($[MH\text{-}Br]^+$, 100 %), 238 (44 %), 140 (26 %) amu.

2,3,4-Trimethoxyphenanthrene **5.26**



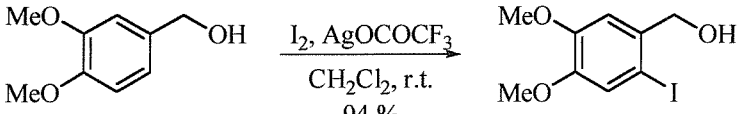
5.39 $C_{17}H_{17}BrO_3$ (349)

5.26 $C_{17}H_{16}O_3$ (268)

Bromide **5.39** (700 mg, 2.01 mmol), tributyltin hydride (650 μL, 705mg, 2.41 mmol) and AIBN (65 mg, 0.40 mmol) were heated in toluene (60 mL) at 90 °C for 24 hours with additional portions of tributyltin hydride (310 μL, 335 mg, 1.15 mmol) and AIBN (15 mg, 0.09 mmol) added after 4 and 6 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 40 mL) for 48 hours. The organic phase was washed with water (2 × 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 % ether / petrol) yielded the title compound **5.26** (410 mg, 1.53 mmol, 76 %) as a white solid.

The data were consistent with that reported previously.

2-Iodo-4,5-dimethoxybenzyl alcohol **5.107**



5.106
$C_9H_{12}O_3$ (168)

5.107
$C_9H_{11}IO_3$ (294)

To a solution of 3,4-dimethoxybenzyl alcohol **5.106** (5.00 g, 29.73 mmol) in dichloromethane (20 mL) was added silver(I) trifluoroacetate (7.22 g, 32.70 mmol). A solution of iodine (7.92 g, 31.21 mmol) in dichloromethane (200 mL) was added over 40 minutes. The mixture was stirred for a further 30 minutes before the resulting solid was removed by filtration. The filtrate was washed with sodium hydrogen carbonate (sat. aq., 50 mL) and sodium thiosulfate (sat. aq., 50 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound **5.107** (8.20 g, 27.89 mmol, 94 %) as a pale cream solid.[200]

MP 94 – 96 °C (EtOH) lit. 103 – 104 °C (DCM / petrol).[200]

FT – IR (ν_{max}, neat) 3483 br. m, 2928 w, 2841 w, 1600 w, 1501 s, 1380 m, 1257 s, 1155 s, 1025 m cm^{-1}.

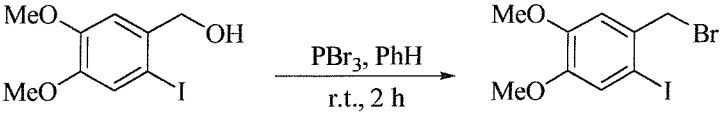
UV (λ_{max}, CH_2Cl_2) 277 (3500) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.22 (1H, s, Ar*H*), 7.01 (1H, s, Ar*H*), 4.61 (2H, s, OCH_2), 3.88 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 2.01 (1H, br. s, O*H*) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 149.6 (0, *C*O), 149.0 (0, *C*O), 136.4 (0, *C*), 121.5 (1, *C*H), 111.7 (1, *C*H), 85.5 (0, *C*I), 69.3 (2, OCH_2), 56.4 (3, OCH_3), 56.1 (3, OCH_3)

LRMS (M/z, CI) 294 (M^+, 30 %), 277 ($[M\text{-}OH]^+$, 47 %), 167 ($[M\text{-}I]^+$, 90 %), 151 (100 %) amu.

2-Iodo-4,5-dimethoxybenzyl bromide **5.108**



5.107
$C_9H_{11}IO_3$ (294)

5.108
$C_9H_{10}BrIO_2$ (357)

2-Iodo-4,5-dimethoxybenzyl alcohol **5.107** (4.20 g, 14.29 mmol) was dissolved in benzene and cooled to 0 °C. Phosphorus tribromide (480 μL, 1.35 g, 5.00 mmol) was added and the mixture stirred at room temperature for 1½ hours. The mixture was concentrated *in vacuo*

and the residue diluted with dichloromethane (50 mL) then washed with water (2 × 30 mL), sodium hydrogen carbonate (sat. aq, 2 × 20 mL) and brine (20 mL) then dried ($MgSO_4$). Concentration *in vacuo* yielded the title compound **5.108** (4.59 g, 12.86 mmol, 90 %) as an off-white solid.[186]

MP 87 – 89 °C (ether / petrol) lit. 89 – 90 °C (ether).[186]

FT – IR (ν_{max}, neat) 3002 w, 2959 w, 2837 w, 1593 m, 1507 m, 1342 m, 1243 m, 1167 m cm^{-1}.

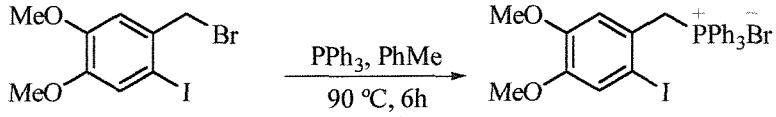
UV (λ_{max}, CH_2Cl_2) 294 (5400), 255 (12000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.23 (1H, s, Ar*H*), 6.97 (1H, s, Ar*H*), 4.59 (2H, s, CH_2Br), 3.89 (3H, s, OCH_3), 3.87 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 150.1 (0, 2 × *C*O), 132.9 (0, *C*), 122.3 (1, *C*H), 113.2 (1, *C*H), 89.0 (0, *C*I), 56.6 (3, O*C*H$_3$), 56.5 (3, O*C*H$_3$), 39.9 (2, *C*H$_2$Br) ppm.

LRMS (M/z, CI) 390 (6 %), 278 ([MH-Br]$^+$, 44 %), 263 (8 %), 152 (100 %), 137 (28 %) amu.

(2-Iodo-4,5-dimethoxybenzyl)triphenylphosphonium bromide **5.53**



5.108 $C_9H_{10}BrIO_2$ (357)

5.53 $C_{27}H_{25}BrIO_2P$ (619)

2-Iodo-4,5-dimethoxybenzyl bromide **5.108** (4.20 g, 11.76 mmol) and triphenylphosphine (3.15 g, 12.00 mmol) were heated in toluene (40 mL) at 80 °C for 16 hours. The resulting solid was collected by filtration and washed with petrol (2 × 10 mL) to yield the title compound **5.53** (6.27 g, 10.13 mmol, 58 %) as an off-white solid.

MP 166 – 168 °C (EtOH).

FT – IR (ν_{max}, neat) 3053 w, 3003 w, 2930 w, 2828 m, 1505 s, 1438 s, 1374 m, 1258 s, 1217 m, 1110 m cm^{-1}.

UV (λ_{max}, MeCN) 270 (43000), 214 (45000) nm.

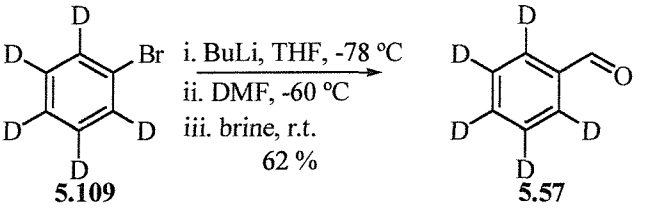
^{1}H – NMR (300 MHz, $CDCl_3$ + d_6-DMSO) δ_H 7.75 – 7.72 (3H, m, 3 × Ar*H*) , 7.58 – 7.55 (12H, m, 12 × Ar*H*), 6.96 (1H, s, Ar*H*), 6.95 (1H, s, Ar*H*), 5.29 (2H, d, *J* 13.7 Hz, CH_2P), 3.74 (3H, s, OCH_3), 3.43 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$ + d_6-DMSO) δ_C 149.4 (0, 2 × *C*O), 135.1 (1, 3 × *C*H), 134.3 (1, d, *J* 9.7 Hz, 6 × *C*H), 130.1 (1, d, *J* 12.5 Hz, 6 × *C*H), 122.1 (0, d, *J* 9.1 Hz, *C*), 120.9 (1, *C*H), 117.1 (0, d, *J* 85.3 Hz, 3 × *C*), 114.7 (1, *C*H), 92.6 (0, d, *J* 7.9 Hz, *C*I), 56.1 (3, O*C*H$_3$), 56.0 (3, O*C*H$_3$), 35.1 (2, d, *J* 47.9 Hz, *C*H$_2$P) ppm.

^{31}P – NMR (121 MHz, $CDCl_3$ + d_6-DMSO) δ_P 27.3 ppm.

LRMS (M/z, ES+) 539 ([M-Br]$^+$, 100 %) amu.

<u>d_5-Benzaldehyde **5.57**</u>



5.109 C_6D_5Br (162)

5.57 C_7HD_5O (111)

d_5-Bromobenzene **5.109** (2.0 mL, 2.98 g, 18.40 mmol) was dissolved in tetrahydrofuran (30 mL) and the solution cooled to –78 °C. *n*-Butyllithium (0.87 M in hexanes, 23.3 mL, 20.24 mmol) was added over 10 minutes and the mixture stirred at –78 °C for a further 25 minutes. *N,N*-Dimethylformamide (2.9 mL, 2.69 g, 36.80 mmol) was added over 5 minutes and the mixture allowed to warm to –60 °C over 30 minutes. Brine (20 mL) was added and the mixture allowed to warm to room temperature. The aqueous phase was extracted with ether (3 × 30 mL) and the combined organic phases were dried (K_2CO_3) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 % ether / petrol) yielded d_5-benzaldehyde **5.57** (1.26 g, 11.35 mmol, 62 %) as a pale yellow oil.[201]

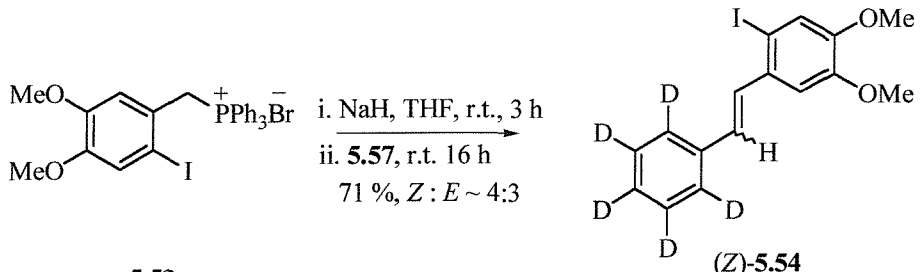
FT – IR (ν_{max}, neat) 2824 w, 2754 w, 1698 s, 1564 m, 1324 m, 1146 m cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 10.03 (1H, s, C*H*O) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 192.8 (1, *C*HO), 136.7 (0, *C*), 134.4 (0, 1:1:1 t, *J* 24.5 Hz, *C*D), 129.8 (0, 1:1:1 t, *J* 24.5 Hz, 2 × *C*D), 128.9 (0, 1:1:1 t, *J* 25.0 Hz, 2 × *C*D) ppm.

LRMS (M/z, CI) 111 (M$^+$, 40 %), 110 (85 %), 96 (25 %), 83 (25 %), 80 (37 %), 46 (100 %) amu.

1-Iodo-4,5-dimethoxy-2-((*Z*)-2-phenylethenyl)benzene-d_5 **5.54** & 1-iodo-4,5-dimethoxy-2-((*E*)-2-phenylethenyl)benzene-d_5 **5.55**



5.53
$C_{27}H_{25}BrIO_2P$ (619)

(*Z*)-**5.54**
(*E*)-**5.55**
$C_{16}H_{10}D_5IO_2$ (371)

To sodium hydride (60 % in mineral oil, 285 mg, 7.04 mmol) in tetrahydrofuran (30 mL) at 0 °C was added (2-iodo-4,5-dimethoxybenzyl)triphenylphosphonium bromide **5.53** (4.00 g, 6.46 mmol) and the mixture stirred at room temperature for 3 hours. After cooling to 0 °C, d_5-benzaldehyde **5.57** (650 mg, 5.87 mmol) was added as a solution in tetrahydrofuran (10 mL). The mixture was stirred for a further 3 hours at room temperature and then filtered through Celite. The filtrate was concentrated *in vacuo* and purified by column chromatography (silica gel, 5 – 10 % ether / petrol) to yield firstly **5.54** (895 mg, 2.41 mmol, 41 %) as an off-white solid and then **5.55** (645 mg, 1.74 mmol, 30 %) as a white solid.

1-Iodo-4,5-dimethoxy-2-((*Z*)-2-phenylethenyl)benzene-d_5 **5.54**

MP 70 – 72 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2997 w, 2950 w, 2903 w, 2841 w, 1588 m, 1499 s, 1462 m, 1258 s, 1207 s, 1161 s, 1027 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 282 (14000), 225 (26000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.32 (1H, s, Ar*H*), 6.71 (1H, s, Ar*H*), 6.66 (1H, d, *J* 12.0 Hz, C*H*=CH), 6.52 (1H, d, *J* 12.0 Hz, CH=C*H*), 3.92 (3H, s, OCH_3), 3.51 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 149.2 (0, *C*O), 149.2 (0, *C*O), 136.8 (0, *C*), 134.0 (0, *C*), 133.8 (1, *C*H=CH), 130.8 (1, CH=*C*H), 129.0 (0, 1:1:1 t, *J* 24.0 Hz, 2 × *C*D), 128.1 (0, 1:1:1 t, *J* 23.9 Hz, 2 × *C*D), 127.1 (0, 1:1:1 t, *J* 23.8 Hz, *C*D), 121.5 (1, *C*H), 113.5 (1, *C*H), 88.5 (0, *C*I), 56.5 (3, O*C*H$_3$), 56.0 (3, O*C*H$_3$) ppm.

^{2}H – NMR (61 MHz, C_6H_6) δ_D -0.07 (2D, s, 2 × Ar*D*), -0.30 (3D, s, 3 × Ar*D*) ppm.

LRMS (M/z, CI) 371 (M^+, 90 %), 245 ($[MH\text{-}I]^+$, 100 %), 239 (24 %), 213 (35 %), 199 (12 %), 170 (26 %), 156 (44 %) amu.

CHN $C_{16}H_{10}D_5IO_2$ requires: C 51.77, H 4.13; Found: C 51.61, H 4.06.

1-Iodo-4,5-dimethoxy-2-((*E*)-2-phenylethenyl)benzene-d_5 **5.55**

MP 99 – 101 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2941 w, 2832 w, 1588 m, 1501 s, 1436 m, 1259 s, 1204 s, 1167 m, 1026 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 331 (19000), 299 (21000), 226 (20000) nm.

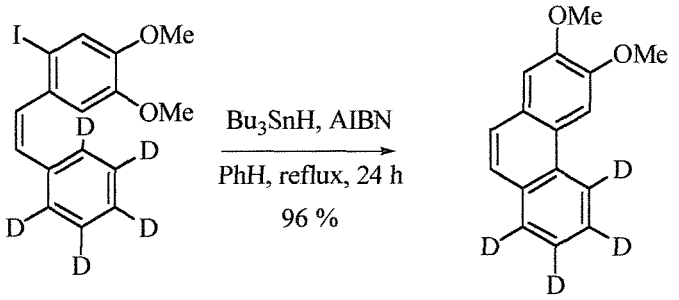
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.33 (1H, s, Ar*H*), 7.29 (1H, d, *J* 16.1 Hz, C*H*=CH), 7.18 (1H, s, Ar*H*), 6.91 (1H, d, *J* 16.1 Hz, CH=C*H*), 3.99 (3H, s, OCH_3), 3.93 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 150.0 (0, *C*O), 149.8 (0, *C*O), 137.3 (0, *C*), 133.3 (0, *C*), 132.7 (1, *C*H), 130.2 (1, *C*H), 128.6 (0, 1:1:1 t, *J* 24.0 Hz, 2 × *C*D), 127.7 (0, 1:1:1 t, *J* 24.5 Hz, *C*D), 126.6 (0, 1:1:1 t, *J* 23.5 Hz, 2 × *C*D), 122.1 (1, *C*H), 109.0 (1, *C*H), 89.7 (0, *C*I), 56.6 (3, OCH_3), 56.4 (3, OCH_3) ppm.

LRMS (M/z, CI) 371 (M^+, 50 %), 246 ($[M+2H\text{-}I]^+$, 100 %), 245 (97 %), 170 (24 %), 156 (34 %) amu.

CHN $C_{16}H_{10}D_5IO_2$ requires: C 51.77, H 4.13; Found: C 51.71, H 4.06.

2,3-Dimethoxy-d_5,d_6,d_7,d_8-phenanthrene **5.56**



5.54
$C_{16}H_{11}D_4IO_2$ (370)

5.56
$C_{16}H_{10}D_4O_2$ (242)

Iodide **5.54** (200 mg, 0.54 mmol), tributyltin hydride (175 μL, 190 mg, 0.65 mmol) and AIBN (18 mg, 0.11 mmol) were heated at reflux in benzene (10 mL) for 24 hours with additional portions of tributyltin hydride (100 μL, 108 mg, 0.37 mmol) and AIBN (15 mg, 0.09 mmol) added after 8 and 16 hours. After cooling to room temperature, 2 mL of the reaction mixture were removed for analysis. The remainder was stirred with a solution of potassium fluoride (10 % w/v, 10 mL) for 16 hours. The mixture was diluted with ether (30

mL) and the organic phase was washed with water (2 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 % ether / petrol) yielded the title compound **5.56** (100 mg, 0.41 mmol, *ca.* 96 % based on material purified) as a white solid.

MP 131 – 132 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2963 w, 2932 w, 2837 w, 1613 m, 1515 m, 1462 m, 1267 m, 1218 s, 1163 s, 1143 m, 1019 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 273 (3500), 252 (6500) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 8.02 (1H, s, Ar*H*), 7.67 (2H, app. s, 2 × Ar*H*), 7.26 (1H, s, Ar*H*), 4.13 (3H, s, OCH_3), 4.06 (3H, s, OCH_3) ppm.

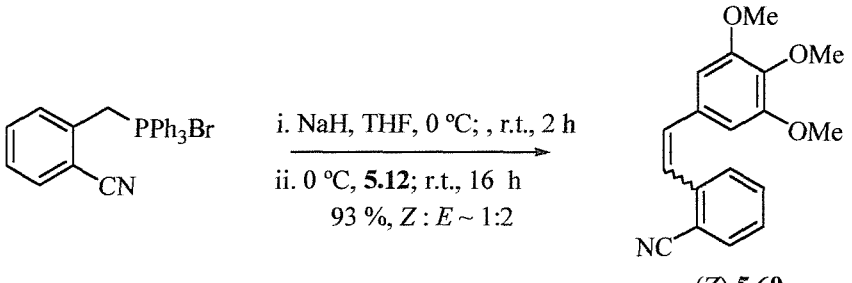
^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 149.8 (0, *C*O), 149.7 (0, *C*O), 131.7 (0, *C*), 130.1 (0, *C*), 128.7 (0, 1:1:1 t, *J* 23.3 Hz, *C*D), 127.6 (0, *C*), 126.3 (1, *C*H), 125.9 (0, 1:1:1 t, *J* 23.8 Hz, *C*D), 125.7 (1, *C*H), 125.5 (0, 1:1:1 t, *J* 26.7 Hz, *C*D), 125.2 (0, *C*), 122.1 (0, 1:1:1 t, *J* 22.8 Hz, *C*D), 108.8 (1, *C*H), 103.7 (1, *C*H), 56.4 (3, OCH_3), 56.3 (3, OCH_3) ppm.

^{2}H – NMR (61 MHz, C_6H_6) δ_D 1.22 (1D, s, Ar*D*), 0.55 (1D, s, Ar*D*), 0.24 (2D, br. s, 2 × Ar*D*) ppm.

LRMS (M/z, CI) 242 (M^+, 100 %), 199 (14 %), 169 (12 %), 156 (33 %), 121 (11 %) amu.

CHN $C_{16}H_{10}D_4O_2$ requires: C 79.31, H 5.92; Found: C 79.29, H 5.92.

2-(2-(*Z*)-(3,4,5-Trimethoxyphenyl)ethenyl)benzonitrile **5.60** & 2-(2-(*E*)-(3,4,5-trimethoxyphenyl)ethenyl)benzonitrile **5.61**



5.59
$C_{26}H_{21}BrNP$ (458)

(*Z*)-**5.60**
(*E*)-**5.61**
$C_{18}H_{17}NO_3$ (295)

To a cooled (0 °C) suspension of sodium hydride (60 % in mineral oil, 275 mg, 6.85 mmol) in tetrahydrofuran (20 mL) was added phosphonium bromide **5.59** (2.62 g, 5.71 mmol) and the mixture stirred at room temperature for 2 hours. After cooling to 0 °C, 3,4,5-

trimethoxybenzaldehyde **5.12** (1.00 g, 5.19 mmol) was added as a solution in tetrahydrofuran (10 mL) and the mixture was stirred at room temperature for a further 16 hours. Filtration through Celite, concentration *in vacuo* and purification by column chromatography (silica gel, 20 – 50 % ether / petrol) firstly gave **5.60** (185 mg, 0.63 mmol, 12 %) as a white solid then a mixture of isomers (625 mg, 2.12 mmol, 41 %, **5.60**:**5.61** ~ 1:1) and finally **5.61** (620 mg, 2.10 mmol, 40 %) as a white solid.

2-(2-(*Z*)-(3,4,5-Trimethoxyphenyl)ethenyl)benzonitrile **5.60**

MP 86 – 88 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3002 m, 2931 m, 2828 m, 2226 m, 1580 s, 1506 s, 1463 s, 1420 m, 1328 s, 1239 s, 1128 s, 1006 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 302 (14000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.67 (1H, app. d, *J* 7.4 Hz, Ar*H*), 7.44 – 7.30 (2H, m, 2 × Ar*H*), 7.34 – 7.30 (1H, m, Ar*H*), 6.78 (1H, d, *J* 11.4 Hz, C*H*=CH), 6.73 (1H, d, *J* 11.4 Hz, CH=C*H*), 6.35 (2H, s, 2 × Ar*H*), 3.83 (3H, s, OCH_3), 3.63 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.1 (0, 2 × *C*O), 141.6 (0, *C*O), 137.9 (0, *C*), 134.4 (1, *C*H), 133.1 (1, *C*H), 132.3 (1, *C*H), 131.4 (0, *C*), 130.1 (1, *C*H), 127.7 (1, CH), 125.7 (1, *C*H), 118.0 (0, *C*N), 111.5 (0, *C*CN), 106.2 (1, 2 × *C*H), 61.1 (3, O*C*H$_3$), 56.0 (3, 2 × O*C*H$_3$) ppm.

LRMS (M/z, CI) 296 (MH^+, 72 %), 295 (M^+, 100 %), 280 (50 %), 166 (29 %) amu.

CHN $C_{18}H_{17}NO_3$ requires: C 73.20, H 5.80, N 4.74; Found: C 72.70, H 5.77, N 4.70.

2-(2-(*E*)-(3,4,5-Trimethoxyphenyl)ethenyl)benzonitrile **5.61**

MP 125 – 128 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2996 w, 2936 m, 2822 m, 2217 m, 1581 m, 1506 s, 1455 m, 1419 m, 1343 m, 1242 m, 1127 s, 1006 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 330 (26000), 246 (20000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.79 (1H, app. d, *J* 7.7 Hz, Ar*H*), 7.66 (1H, d, *J* 7.7 Hz, Ar*H*), 7.58 (1H, app. t, *J* 7.7 Hz, Ar*H*), 7.37 – 7.30 (2H, m, Ar*H* & C*H*=CH),

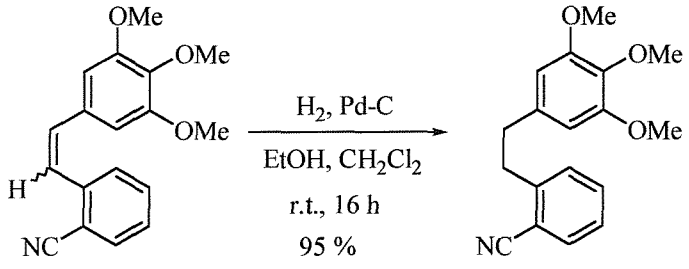
7.19 (1H, d, *J* 16.1 Hz, CH=C*H*), 6.80 (2H, s, 2 × Ar*H*), 3.93 (6H, s, 2 × OCH_3), 3.89 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.6 (0, 2 × *C*O), 140.6 (0, *C*O), 139.0 (0, *C*), 133.6 (1, *C*H), 133.4 (1, *C*H), 133.0 (1, *C*H), 132.0 (0, *C*), 127.7 (1, *C*H), 125.4 (1, *C*H), 123.6 (1, *C*H), 118.2 (0, *C*N), 111.2 (0, *C*CN), 104.3 (1, 2 × *C*H), 61.2 (3, *OCH*$_3$), 56.3 (3, 2 × *OCH*$_3$) ppm.

LRMS (M/z, CI) 296 (MH^+, 76 %), 295 (M^+, 100 %), 280 (52 %), 207 (41 %), 166 (34 %) amu.

CHN $C_{18}H_{17}NO_3$ requires: C 73.20, H 5.80, N 4.74; Found: C 73.19, H 5.85, N 4.73.

2-(3,4,5-Trimethoxyphenethyl)benzonitrile **5.62**



5.60 & 5.61
$C_{18}H_{17}NO_3$ (295)

5.62
$C_{18}H_{19}NO_3$ (297)

A mixture of **5.60** & **5.61** (600 mg, 2.03 mmol, *Z*:*E* ~ 1:1) was dissolved in ethanol (20 mL) and dichloromethane (20 mL). Palladium on carbon (5 % w/w, 215 mg, 0.10 g atom Pd) was added and the mixture stirred under an atmosphere of hydrogen for 16 hours. Filtration through Celite and concentrated *in vacuo* yielded the title compound **5.62** (570 mg, 1.92 mmol, 95 %) as a white solid.

MP 80 – 82 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2941 m, 2841 w, 2217 m, 1590 m, 1508 m, 1458 m, 1421 m, 1238 m, 1127 s, 1011 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 266 (8200) nm.

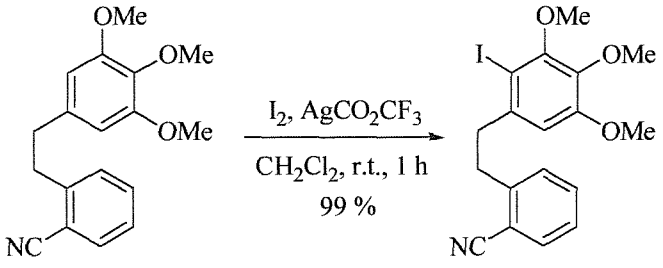
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.64 (1H, dd, *J* 7.7, 1.1 Hz, Ar*H*), 7.50 (1H, td, *J* 7.7, 1.1 Hz, Ar*H*), 7.31 (1H, td, *J* 7.7, 1.1 Hz, Ar*H*), 7.25 (1H, app. d, *J* 7.7 Hz, Ar*H*), 6.39 (2H, s, 2 × Ar*H*), 3.83 (3H, s, OCH_3), 3.82 (6H, s, 2 × OCH_3), 3.13 (2H, dd, *J* 9.9, 7.0 Hz, CH_2), 2.91 (2H, dd, *J* 9.9, 7.0 Hz, CH_2) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 153.6 (0, 2 × *C*O), 145.8 (0, *C*O), 136.6 (0, 2 × *C*), 133.2 (1, *C*H), 133.1 (1, *C*H), 130.2 (1, *C*H), 127.1 (1, *C*H), 118.5 (0, *C*N), 112.8 (0, *C*CN), 105.9 (1, 2 × *C*H), 61.3 (3, O*C*H$_3$), 56.5 (3, 2 × O*C*H$_3$), 37.9 (2, *C*H$_2$), 37.2 (2, *C*H$_2$) ppm.

LRMS (M/z, CI) 298 (MH^+, 36 %), 181 (100 %), 116 (48 %).

CHN $C_{18}H_{19}NO_3$ requires: C 72.71, H 6.44, N 4.71; Found: C 72.62, H 6.44, N 4.67.

2-(2-Iodo-3,4,5-trimethoxyphenethyl)benzonitrile **5.63**



5.62
$C_{18}H_{19}NO_3$ (297)

5.63
$C_{18}H_{18}INO_3$ (423)

To a solution of arene **5.62** (510 mg, 1.72 mmol) in dichloromethane (40 mL) was added silver(I) trifluoroacetate (415 mg, 1.89 mmol). Iodine (440 mg, 1.73 mmol) was then added as a solution in dichloromethane (80 mL) over 20 minutes. The mixture was stirred at room temperature for 1 hour before removal of the resulting silver iodide by filtration through Celite. The filtrate was washed with sodium thiosulfate (sat. aq., 30 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to yield **5.63** (735 mg, 1.71 mmol, 99 %) as a pale yellow oil.

FT – IR (ν_{max}, neat) 2936 m, 2841 w, 2217 m, 1559 m, 1480 s, 1387 s, 1329 m, 1199 m, 1164 m, 1105 s, 1006 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 273 (5200), 226 (22000) nm.

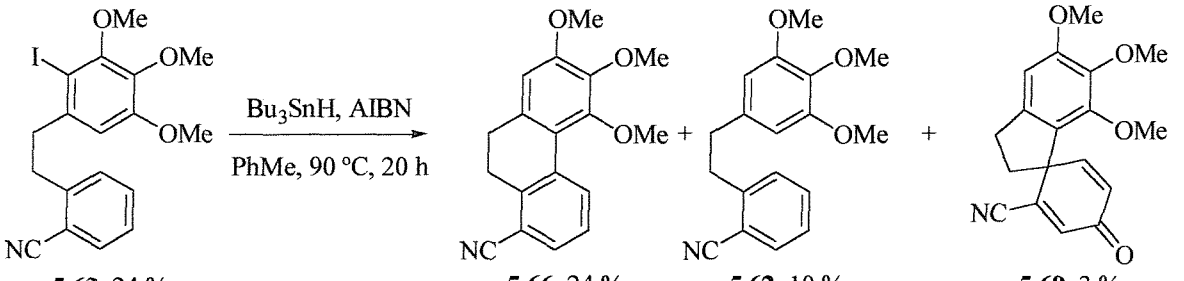
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.55 (1H, dd, *J* 7.8, 0.5 Hz, Ar*H*), 7.44 (1H, td, *J* 7.5, 0.8 Hz, Ar*H*), 7.30 – 7.22 (2H, m, 2 × Ar*H*), 6.51 (1H, s, Ar*H*), 3.81 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 3.71 (3H, s, OC*H*$_3$), 3.06 – 2.98 (4H, m, 2 × C*H*$_2$) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 154.0 (0, *C*O), 153.6 (0, *C*O), 145.5 (0, *C*O), 141.1 (0, *C*), 139.1 (0, *C*), 133.2 (1, 2 × *C*H), 130.3 (1, *C*H), 127.2 (1, *C*H), 118.5 (0, *C*N), 112.9 (0, *C*CN), 109.5 (1, *C*H), 88.3 (0, *C*I), 61.4 (3, O*C*H$_3$), 61.2 (3, O*C*H$_3$), 56.5 (3, O*C*H$_3$), 42.6 (2, *C*H$_2$), 35.6 (2, *C*H$_2$) ppm.

LRMS (M/z, CI) 441 ($[M+NH_4]^+$, 16 %), 423 (M^+, 32 %), 298 ($[M-I+2H]^+$, 85 %), 297 ($[M-I+H]^+$, 100 %), 181 (90 %), 116 (32 %) amu.

HRMS (M/z, ES+) $C_{18}H_{18}INONa^+$ requires 446.0228; Found $[M+Na]^+$: 446.0223.

5,6,7-Trimethoxy-9,10-dihydro-1-phenanthrenecarbonitrile **5.66**, 2-(2-(3,4,5-trimethoxyphenyl)ethyl)benzonitrile **5.62** and 5',6',7'-trimethoxy-4-oxo-2',3'-dihydrospiro(cyclohexa-2,5-diene-1,1'-indene)-2-carbonitrile **5.69**



5.63, 24 %
$C_{18}H_{18}INO_3$ (423)

5.66, 24 %
$C_{18}H_{17}NO_3$ (295)

5.62, 10 %
$C_{18}H_{19}NO_3$ (297)

5.69, 3 %
$C_{18}H_{17}NO_4$ (311)

Iodide **5.63** (690 mg, 1.63 mmol), tributyltin hydride (530 μL, 570 mg, 1.96 mmol) and AIBN (25 mg, 0.16 mmol) were stirred in toluene (50 mL) at 90 °C for 24 hours with additional portions of tributyltin hydride (250 μL, 270 mg, 0.93 mmol) and AIBN (10 mg, 0.06 mmol) added after 4, 8, and 20 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 30 mL) for 16 hours. The mixture was diluted with ether (20 mL) and the organic phase was washed with water (2 × 30 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 % ether / petrol) yielded dihydrophenanthrene **5.66** as a 1:1 mixture with starting material **5.63** (285 mg, 0.80 mmol, 24 % **5.66** + 24 % **5.63**) then alkane **5.62** (50 mg, 0.17 mmol, 10 %) as a colourless oil, and finally spirocycle **5.69** (15 mg, 0.05 mmol, 3 %) as a yellow oil.

5,6,7-Trimethoxy-9,10-dihydro-1-phenanthrenecarbonitrile **5.66** (Select data only)

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 8.50 (1H, d, *J* 7.9 Hz, Ar*H*), 7.62 – 7.48 (1H, m, Ar*H*), 7.35 – 7.28 (1H, m, Ar*H*), 6.63 (1H, s, Ar*H*), 3.92 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.09 – 3.02 (2H, m, CH_2), 2.81 – 2.77 (2H, m, CH_2) ppm.

LRMS (M/z, CI) 313 ($[M+NH_4]^+$, 82 %), 295 (M^+, 100 %), 280 (16 %), 166 (30 %).

5',6',7'-trimethoxy-4-oxo-2',3'-dihydrospiro(cyclohexa-2,5-diene-1,1'-indene)-2-carbonitrile **5.69**

FT – IR (ν_{max}, neat) 2937 m, 2846 m, 1663 s, 1588 m, 1483 m, 1465 m, 1338 m, 1122 s, 1044 m cm^{-1}.

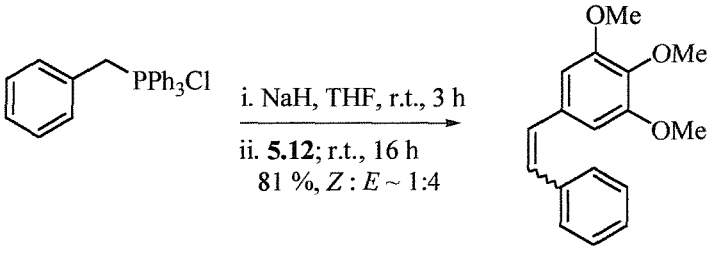
UV (λ_{max}, CH_2Cl_2) 282 (2500), 240 (9300) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 6.92 (1H, d, *J* 10.2 Hz, C*H*=CH), 6.81 (1H, d, *J* 1.7 Hz, C*H*=CH), 6.63 (1H, s, Ar*H*), 6.33 (1H, dd, *J* 10.2, 1.7 Hz, CH=C*H*), 3.88 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.25 (1H, ddd, *J* 8.9, 4.7, 0.7 Hz, C*H*H), 3.15 (1H, app. dt, *J* 8.9, 7.7 Hz, CH*H*), 2.59 (1H, ddd, *J* 13.4, 8.9, 7.7 Hz, C*H*H), 2.36 (1H, ddd, *J* 13.4, 8.9, 4.7 Hz, CH*H*) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 183.4 (0, *C*=O), 155.4 (0, 2 × CO), 152.9 (1, *C*H), 150.2 (0, *C*O), 140.7 (0, *C*), 136.8 (1, *C*H), 135.8 (0, *C*), 125.8 (1, *C*H), 123.3 (0, *C*), 115.8 (0, *C*N), 103.6 (1, *C*H), 60.6 (3, OCH_3), 60.4 (3, OCH_3), 55.9 (3, OCH_3), 53.6 (0, *C*), 38.4 (2, CH_2), 32.3 (2, CH_2) ppm.

LRMS (M/z, CI) 329 ($[M+NH_4]^+$, 10 %), 312 (MH^+, 100 %) amu.

1-(2-(*Z*)-Phenylethenyl)-3,4,5-trimethoxybenzene **5.110** & 1-(2-(*E*)-phenylethenyl)-3,4,5-trimethoxybenzene **5.111**



5.91
$C_{25}H_{22}ClP$ (389)

(*Z*)-**5.110**
(*E*)-**5.111**
$C_{17}H_{18}O_3$ (270)

To a suspension of benzyltriphenylphosphonium chloride **5.91** (4.27 g, 11.00 mmol) in tetrahydrofuran (40 mL) was added sodium hydride (60 % in mineral oil, 530 mg, 13.20 mmol) and the mixture stirred at room temperature for 2 hours. The orange mixture was cooled to 0 °C and 3,4,5-trimethoxybenzaldehyde **5.12** (1.96 g, 10.00 mmol) was added as a solution in tetrahydrofuran (20 mL). After stirring for a further 16 hours at room temperature, the mixture was filtered through Celite and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 % ether / petrol) yielded firstly **5.110** (225 mg, 0.83 mmol, 8 %) as a colourless oil, then a mixture of isomers (840 mg, 3.11 mmol, 31 %, *Z*:*E* ~ 1:3) and finally **5.111** (1.13 g, 4.19 mmol, 42 %) as a white solid.[202,203]

1-(2-(Z)-phenylethenyl)-3,4,5-trimethoxybenzene **5.110**[202]

FT – IR (ν_{max}, neat) 3007 w, 2935 m, 2832 w, 1580 s, 1506 s, 1452 m, 1420 m, 1238 m, 1127 s, 1007 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 289 (15000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.30 – 7.22 (5H, m, C_6H_5), 6.61 (1H, d, *J* 12.2 Hz, C*H*=CH), 6.50 (1H, d, *J* 12.2 Hz, CH=C*H*), 6.47 (2H, s, 2 × Ar*H*), 3.84 (3H, s, OCH_3), 3.66 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.0 (0, 3 × *C*O), 137.6 (0, *C*), 132.6 (0, *C*), 132.3 (1, *C*H), 130.1 (1, *C*H), 129.1 (1, 2 × *C*H), 128.4 (1, 2 × *C*H), 127.3 (1, *C*H), 106.2 (1, 2 × *C*H), 61.1 (3, OCH_3), 56.0 (3, 2 × OCH_3) ppm.

LRMS (M/z, CI) 271 (MH^+, 100 %), 255 (20 %), 195 (8 %), 141 (12 %) amu.

1-(2-(*E*)-Phenylethenyl)-3,4,5-trimethoxybenzene **5.111**[203]

MP 100 – 101 °C (ether / petrol) lit. 109 – 110 °C (benzene).[203]

FT – IR (ν_{max}, neat) 3002 w, 2931 m, 2832 w, 1582 s, 1507 s, 1453 m, 1418 m, 1345 m, 1241 m, 1127 s, 1006 m cm^{-1}.

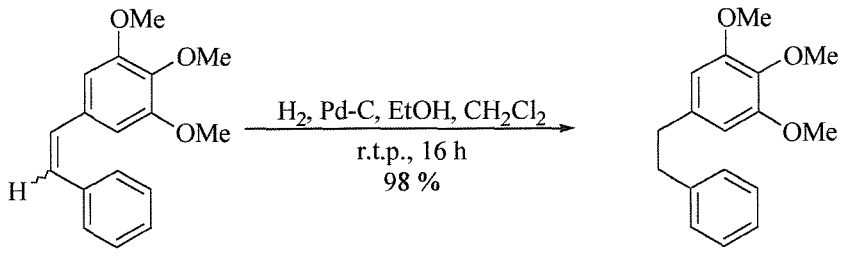
UV (λ_{max}, CH_2Cl_2) 315 (27000), 234 (19000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.52 (2H, d, *J* 7.5 Hz, 2 × Ar*H*), 7.40 – 7.35 (2H, m, 2 × Ar*H*), 7.27 – 7.26 (1H, m, Ar*H*), 7.06 (1H, d, *J* 16.2 Hz, C*H*=CH), 7.01 (1H, d, *J* 16.2 Hz, CH=C*H*), 6.76 (2H, s, 2 × Ar*H*), 3.93 (6H, s, 2 × OCH_3), 3.89 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.8 (0, 3 × *C*O), 137.6 (0, *C*), 133.5 (0, *C*), 129.1 (1, 2 × *C*H), 129.1 (1, *C*H), 128.6 (1, *C*H), 128.0 (1, *C*H), 126.9 (1, 2 × *C*H), 104.0 (1, 2 × *C*H), 61.4 (3, OCH_3), 56.6 (3, 2 × OCH_3) ppm.

LRMS (M/z, CI) 271 (MH^+, 100 %), 255 (22 %), 195 (10 %), 165 (8 %), 141 (14 %) amu.

3,4,5-Trimethoxy-1-phenethylbenzene **5.74**



5.110 & **5.111**
$C_{17}H_{18}O_3$ (270)

5.74
$C_{17}H_{20}O_3$ (272)

A mixture of **5.110** and **5.111** (1.61 g, 5.96 mmol) was dissolved in dichloromethane (30 mL) and ethanol (30 mL). Palladium on carbon (5 % w/w, 380 mg, 0.18 g atom Pd) was added and the mixture stirred under hydrogen for 16 hours. Filtration through Celite and concentration *in vacuo* yielded the title compound **5.74** (1.59 g, 5.85 mmol, 98 %) as a pale yellow oil.[204]

FT – IR (ν_{max}, neat) 3001 w, 2937 m, 2835 w, 1589 s, 1507 s, 1455 s, 1421 m, 1327 m, 1238 s, 1126 s, 1011 m cm^{-1}.

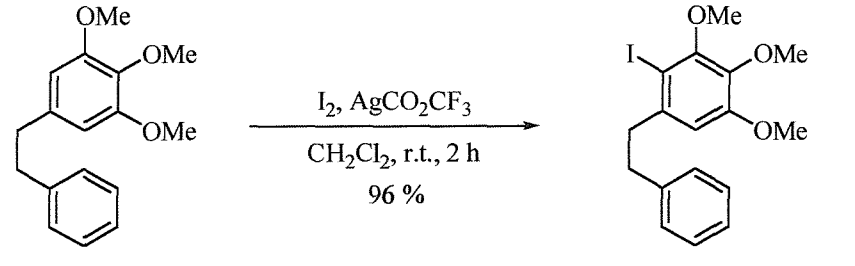
UV (λ_{max}, CH_2Cl_2) 263 (9100) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.33 – 7.19 (5H, m, C_6H_5), 6.38 (2H, s, 2 × Ar*H*), 3.85 (3H, s, OCH_3), 3.83 (6H, s, 2 × OCH_3), 2.95 – 2.86 (4H, m, 2 × CH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.5 (0, 2 × *C*O), 142.0 (0, *C*O), 137.9 (0, 2 × *C*), 128.9 (1, 2 × *C*H), 128.8 (1, 2 × *C*H), 126.4 (1, *C*H), 105.8 (1, 2 × *C*H), 61.3 (3, OCH_3), 56.5 (3, 2 × OCH_3), 38.7 (2, CH_2), 28.4 (2, CH_2) ppm.

LRMS (M/z, CI) 273 (MH^+, 18 %), 181 (30 %), 91 (100 %) amu.

2-Iodo-3,4,5-trimethoxy-1-phenethylbenzene **5.72**



5.74
$C_{17}H_{20}O_3$ (272)

5.72
$C_{17}H_{19}IO_3$ (398)

Silver(I) trifluoroacetate (895 mg, 4.04 mmol) was added to a solution of arene **5.74** (1.00 g, 3.67 mmol) in dichloromethane (20 mL). Iodine (940 mg, 3.70 mmol) was added as a solution in dichloromethane (90 mL) over 30 minutes. The mixture was stirred at room

temperature for 1 hour before the mixture was filtered through Celite. The filtrate was concentrated *in vacuo* and purified by column chromatography (silica gel, 20 % ether / petrol) to yield the title compound **5.72** (1.40 g, 3.52 mmol, 96 %) as a pale yellow oil.

FT – IR (ν_{max}, neat) 2932 m, 2849 w, 1568 m, 1479 s, 1453 s, 1426 m, 1387 s, 1322 m, 1198 m, 1164 m, 1103 s, 1007 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 357 (300), 267 (8500) nm.

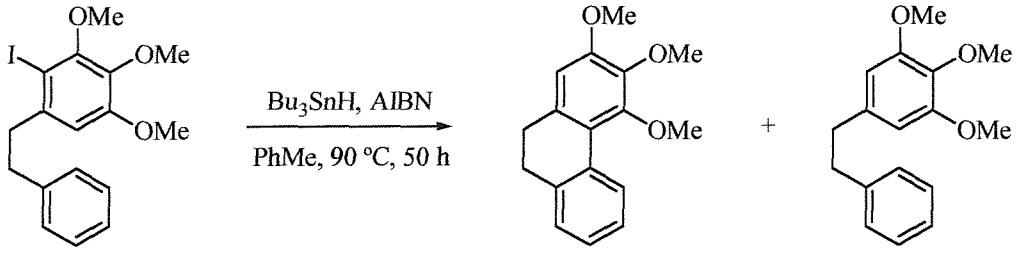
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.34 – 7.22 (5H, m, C_6H_5), 6.53 (1H, s, Ar*H*), 3.90 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.06 – 3.00 (2H, m, CH_2), 2.91 – 2.85 (2H, m, CH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.8 (0, *C*O), 153.5 (0, *C*O), 141.7 (0, *C*O), 140.8 (0, *C*), 140.2 (0, *C*), 129.0 (1, 2 × *C*H), 128.8 (1, 2 × *C*H), 126.2 (1, *C*H), 109.4 (1, *C*H), 88.3 (0, *C*I), 61.4 (3, OCH_3), 61.2 (3, OCH_3), 56.5 (3, OCH_3), 43.7 (2, CH_2), 37.0 (2, CH_2) ppm.

LRMS (M/z, CI) 399 (MH^+, 20 %), 398 (M^+, 20 %), 307 (50 %), 273 ($[M\text{-}I+2H]^+$, 100 %), 181 (54 %), 91 (46 %) amu.

HRMS (M/z, EI) $C_{17}H_{19}IO_3^+$ requires: 398.0379; Found: M^+: 398.0382.

2,3,4-Trimethoxy-9,10-dihydrophenanthrene **5.73** & 3,4,5-trimethoxy-1-phenethylbenzene **5.74**



5.72
$C_{17}H_{19}IO_3$ (398)

5.73, 37 %
$C_{17}H_{18}O_3$ (270)

5.74, 28 %
$C_{17}H_{20}O_3$ (272)

Iodide **5.72** (500 mg, 1.26 mmol), tributyltin hydride (405 μL, 440 mg, 1.51 mmol) and AIBN (40 mg, 0.25 mmol) were heated in toluene (40 mL) at 90 °C for 50 hours with additional portions of tributyltin hydride (400 μL, 435 mg, 1.49 mmol) and AIBN (20 mg, 0.13 mmol) added after 30 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 30 mL) for 16 hours. The mixture was diluted with ether (30 mL) and the organic phase was washed with water (2 × 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica

gel, 5 – 20 % ether / petrol) yielded firstly dihydrophenanthrene **5.73** (125 mg, 0.46 mmol, 37 %) as a white solid and then **5.74** (95 mg, 0.35 mmol, 28 %) as a colourless oil.

2,3,4-Trimethoxy-9,10-dihydrophenanthrene **5.73**

MP 71 – 72 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2934 m, 2830 m, 1595 m, 1487 s, 1449 s, 1402 s, 1349 m, 1330 m, 1312 m, 1144 s, 1117 s, 1084 s, 1009 m cm^{-1}.

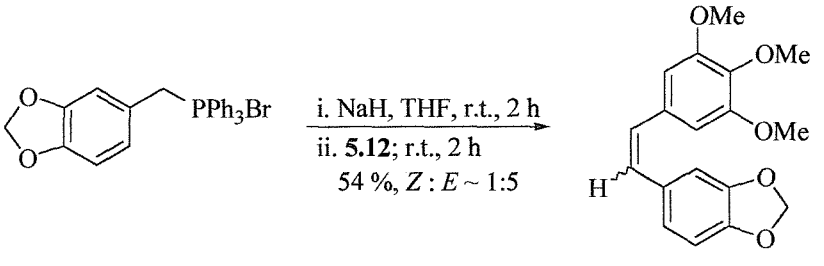
UV (λ_{max}, CH_2Cl_2) 276 (16000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.30 (1H, d, *J* 8.0 Hz, Ar*H*), 7.31 – 7.16 (3H, m, 3 × Ar*H*), 6.62 (1H, s, Ar*H*), 3.94 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 2.83 – 2.70 (4H, m, 2 × CH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 152.4 (0, 2 × *C*O), 141.6 (0, *C*O), 137.7 (0, 2 × *C*), 135.2 (0, *C*), 132.8 (0, *C*), 128.1 (1, *C*H), 127.7 (1, *C*H), 126.8 (1, *C*H), 126.6 (1, *C*H), 107.4 (1, *C*H), 61.3 (3, OCH_3), 60.8 (3, OCH_3), 56.1 (3, OCH_3), 30.5 (2, CH_2), 30.0 (2, CH_2) ppm.

LRMS (M/z, CI) 271 (MH^+, 100 %), 141 (14 %) amu.

5-((*Z*)-2-(3,4,5-Trimethoxyphenyl)ethenyl)-1,3-benzodioxole **5.112** & 5-((*E*)-2-(3,4,5-trimethoxyphenyl)ethenyl)-1,3-benzodioxole **5.113**



5.98
$C_{26}H_{22}BrO_2P$ (477)

(*Z*)-5.112
(*E*)-5.113
$C_{18}H_{18}O_5$ (314)

Phosphonium bromide **5.98** (6.00 g, 12.58 mmol) was added to a suspension of sodium hydride (60 % in mineral oil, 605 mg, 15.09 mmol) in tetrahydrofuran (50 mL) and the mixture was stirred at room temperature for 2 hours then cooled to 0 °C. 3,4,5-trimethoxybenzaldehyde **5.12** (2.24 g, 11.44 mmol) was added as a solution in tetrahydrofuran (20 mL) and the mixture stirred at room temperature for 20 hours. Filtration through Celite, concentration *in vacuo* and purification by column chromatography (silica gel, 10 –25 % ether / petrol) firstly yielded **5.112** (100 mg, 0.32 mmol, 3 %) as a pale yellow

solid, then a mixture of isomers (1.13 g, 3.60 mmol, 31 %, **5.112**:**5.113** ~ 1: 4) as a white solid and finally **5.113** (730 mg, 2.32 mmol, 20 %) as a white solid.[182]

5-((*Z*)-2-(3,4,5-Trimethoxyphenyl)ethenyl)-1,3-benzodioxole **5.112**[182]

MP 120 – 121 °C (ether / petrol) (no literature value).

FT – IR (ν_{max}, neat) 2997 w, 2935 m, 2841 w, 1579 m, 1504 s, 1438 s, 1447 s, 1328 m, 1239 s, 1038 m, 1007 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 291 (7400) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 6.82 – 6.80 (2H, m, 2 × Ar*H*), 6.73 (1H, d, *J* 7.4 Hz, Ar*H*), 6.52 (2H, s, 2 × Ar*H*), 6.48 (1H, d, *J* 12.1 Hz, C*H*=CH), 6.42 (1H, d, *J* 12.1 Hz, CH=C*H*), 5.93 (2H, s, OCH_2O), 3.86 (3H, s, OCH_3), 3.73 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.1 (0, 2 × *C*O), 147.5 (0, *C*O), 146.8 (0, *C*O), 137.3 (0, *C*O), 132.7 (0, *C*), 131.3 (0, *C*), 129.7 (1, *C*H), 129.3 (1, *C*H), 123.1 (1, *C*H), 109.2 (1, *C*H), 108.3 (1, *C*H), 106.1 (1, 2 × *C*H), 101.1 (2, OCH_2O), 61.1 (3, OCH_3), 56.1 (3, 2 × OCH_3) ppm.

LRMS (M/z, CI) 315 (MH^+, 100 %) amu.

5-((*E*)-2-(3,4,5-Trimethoxyphenyl)ethenyl)-1,3-benzodioxole **5.113**[182]

MP 182 – 183 °C (ethanol) (no literature value).

FT – IR (ν_{max}, neat) 2997 w, 2941 m, 2835 w, 1580 m, 1505 s, 1489 s, 1446 m, 1333 m, 1251 s, 1240 s, 1126 s, 1038 m cm^{-1}.

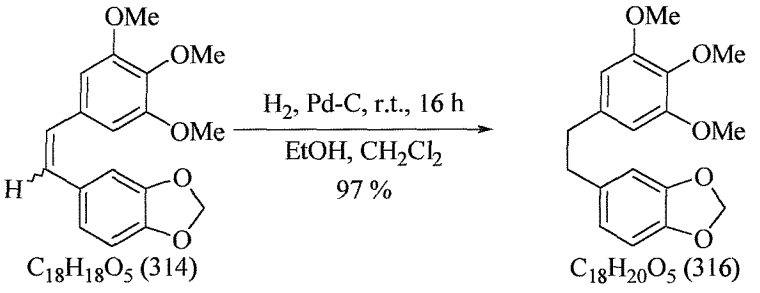
UV (λ_{max}, CH_2Cl_2) 332 (28000), 300 (19000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.06 (1H, d, *J* 1.9 Hz, Ar*H*), 6.95 (1H, d, *J* 16.2 Hz, C*H*=CH), 6.95 (1H, dd, *J* 8.1, 1.9 Hz, Ar*H*), 6.87 (1H, d, *J* 16.2 Hz, C*H*=CH), 6.81 (1H, d, *J* 8.1 Hz, Ar*H*), 6.72 (2H, s, 2 × Ar*H*), 5.99 (2H, s, OCH_2O), 3.93 (6H, s, 2 × OCH_3), 3.88 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.5 (0, 2 × *C*O), 148.3 (0, *C*O), 147.5 (0, *C*O), 137.8 (0, *C*O), 133.3 (0, *C*), 131.9 (0, *C*), 128.0 (1, *C*H), 127.1 (1, *C*H), 121.6 (1, *C*H), 108.6 (1, *C*H), 105.6 (1, *C*H), 103.4 (1, 2 × *C*H), 101.3 (2, OCH_2O), 61.1 (3, OCH_3), 56.3 (3, 2 × OCH_3) ppm.

LRMS (M/z, CI) 315 (MH^+, 100 %), 299 (30 %), 155 (10 %) amu.

5-(3,4,5-Trimethoxyphenethyl)-1,3-benzodioxole **5.77**



$C_{18}H_{18}O_5$ (314)
5.112 & 5.113

$C_{18}H_{20}O_5$ (316)
5.77

To a solution of **5.112 & 5.113** (1.00 g, 3.18 mmol, *Z*:*E* ~ 1:4) in ethanol (20 mL) and dichloromethane (20 mL) was added palladium on carbon (5 % w/w, 135 mg, 0.06 g atom Pd). The mixture was stirred under an atmosphere of hydrogen for 16 hours then filtered through Celite and concentrated *in vacuo* to yield the title alkane **5.77** (970 mg, 3.07 mmol, 97 %) as an off-white solid.[205]

MP 79 – 81 °C (ethanol) (no literature value).

FT – IR (ν_{max}, neat) 2945 m, 2841 w, 1589 m, 1504 s, 1489 s, 1456 m, 1420 m, 1240 s, 1127 s, 1038 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 282 (9200) nm.

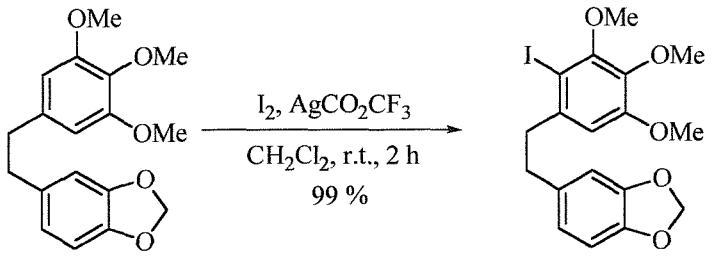
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 6.74 (1H, d, *J* 7.8 Hz, Ar*H*), 6.70 (1H, d, *J* 1.5 Hz, Ar*H*), 6.63 (1H, dd, *J* 7.8, 1.5 Hz, Ar*H*), 6.38 (2H, s, 2 × Ar*H*), 5.93 (2H, s, OCH_2O), 3.84 (9H, s, 3 × OCH_3), 2.83 (4H, s, 2 × CH_2) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 153.5 (0, 2 × *C*O), 148.0 (0, *C*O), 146.1 (0, *C*O), 137.8 (0, *C*O & *C*), 135.1 (0, *C*), 121.6 (1, *C*H), 109.4 (1, *C*H), 108.5 (1, *C*H), 105.8 (1, 2 × *C*H), 101.2 (2, OCH_2O), 61.3 (3, OCH_3), 56.5 (3, 2 × OCH_3), 39.0 (2, CH_2), 38.1 (2, CH_2) ppm.

LRMS (M/z, CI) 317 (MH^+, 28 %), 181 (58 %), 135 (100 %) amu.

CHN $C_{18}H_{20}O_5$ requires: C 68.34, H 6.37; Found: 68.21, H 6.40.

5-(2-Iodo-3,4,5-trimethoxyphenethyl)-1,3-benzodioxole **5.75**



5.77
$C_{18}H_{20}O_5$ (316)

5.75
$C_{18}H_{19}IO_5$ (442)

To a solution of arene **5.77** (800 mg, 2.53 mmol) in dichloromethane (20 mL) was added silver(I) trifluoroacetate (615 mg, 2.78 mmol). Iodine (650 mg, 2.55 mmol) was added dropwise over 30 minutes as a solution in dichloromethane (100 mL). The mixture was stirred for 1 hour before filtration through Celite. The filtrate was concentrated *in vacuo* to *ca.* 30 mL then washed with sodium hydrogen carbonate (sat. aq., 20 mL) and sodium thiosulfate (sat. aq., 20 mL) then dried ($MgSO_4$). Concentration *in vacuo* yielded the title compound **5.75** (1.11 g, 2.51 mmol, 99 %) as a pale orange solid.

MP 94 – 95 °C (ethanol).

FT – IR (ν_{max}, neat) 3001 w, 2932 m, 1564 m, 1481 s, 1448 m, 1387 m, 1326 m, 1102 s, 1039 s, 1006 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 282 (7100), 229 (19000) nm.

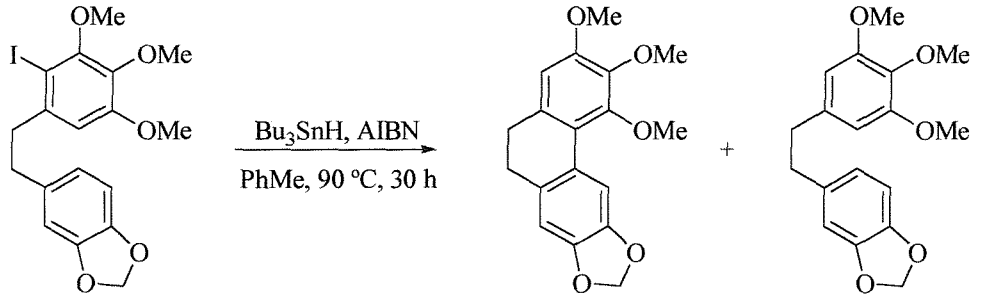
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 6.77 (1H, d, *J* 1.5 Hz, Ar*H*), 6.75 (1H, d, *J* 7.7 Hz, Ar*H*), 6.69 (1H, dd, *J* 7.7, 1.5 Hz, Ar*H*), 6.57 (1H, s, Ar*H*), 5.94 (2H, s, OCH_2O), 3.90 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.01 – 2.95 (2H, m, CH_2), 2.83 – 2.76 (2H, m, CH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.6 (0, *C*O), 153.2 (0, *C*O), 147.7 (0, *C*O), 145.9 (0, *C*O), 140.5 (0, *C*O), 139.9 (0, *C*), 135.3 (0, *C*), 121.4 (1, *C*H), 109.2 (1, *C*H), 109.0 (1, *C*H), 108.3 (1, *C*H), 101.0 (2, OCH_2O), 88.1 (0, *C*I), 61.2 (3, OCH_3), 60.9 (3, OCH_3), 56.3 (3, OCH_3), 43.8 (2, CH_2), 36.5 (2, CH_2) ppm.

LRMS (M/z, CI) 315 ($[M-I]^+$, 40 %), 178 (30 %), 135 (100 %) amu.

CHN $C_{18}H_{19}IO_5$ requires: C 48.89, H 4.33; Found: C 48.74, H 4.27.

1,2,3-Trimethoxy-5,6-dihydrophenanthro[2,3-*d*][1,3]dioxole **5.76** & 5-(2-(3,4,5-Trimethoxyphenyl)ethyl)-1,3-benzodioxole **5.77**



$C_{18}H_{19}IO_5$ (442)
5.75

$C_{18}H_{18}O_5$ (314)
5.76, 31 %

$C_{18}H_{20}O_5$ (316)
5.77, 24 %

Iodide **5.75** (500 mg, 1.13 mmol), tributyltin hydride (365 μL, 395 mg, 1.36 mmol) and AIBN (20 mg, 0.11 mmol) were heated in toluene (35 mL) for 30 hours with additional portions of tributyltin hydride (200 μL, 215 mg, 0.74 mmol) and AIBN (20 mg, 0.11 mmol) added after 8 and 18 hours. After cooling to room temperature, a solution of potassium fluoride (10 % w/v, 20 mL) was added and the mixture stirred for 16 hours. The mixture was diluted with ether (20 mL) and the organic phase washed with water (2 × 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded firstly dihydrophenanthrene **5.76** (110 mg, 0.35 mmol, 31 %) as a white solid and then arene **5.77** (85 mg, 0.27 mmol, 24 %) as an off-white solid.

1,2,3-Trimethoxy-5,6-dihydrophenanthro[2,3-*d*][1,3]dioxole **5.76**[206]

MP 112 – 113 °C (ether / petrol) lit. 127 – 129 °C (acetone).[206]

FT – IR (ν_{max}, neat) 2988 w, 2941 m, 2890 w, 2826 w, 1601 m, 1484 s, 1463 s, 1424 m, 1408 m, 1243 m, 1137 m, 1103 m, 1039 s cm^{-1}.

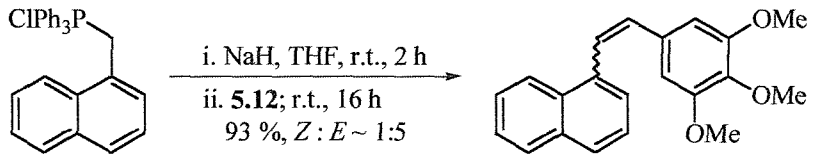
UV (λ_{max}, CH_2Cl_2) 311 (12000), 281 (12000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.87 (1H, s, Ar*H*), 6.72 (1H, s, Ar*H*), 6.59 (1H, s, Ar*H*), 5.96 (2H, s, OCH_2O), 3.92 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 2.71 – 2.65 (4H, m, 2 × CH_2) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 152.1 (0, *C*O), 152.0 (0, *C*O), 146.6 (0, *C*O), 146.0 (0, *C*O), 141.9 (0, *C*O), 134.7 (0, *C*), 132.2 (0, *C*), 126.5 (0, *C*), 121.8 (0, *C*), 108.5 (1, *C*H), 108.4 (1, *C*H), 106.5 (1, *C*H), 101.2 (2, OCH_2O), 61.5 (3, OCH_3), 61.0 (3, OCH_3), 56.4 (3, OCH_3), 31.0 (2, CH_2), 30.3 (2, CH_2) ppm.

LRMS (M/z, CI) 315 (MH^+, 100 %), 269 (8 %), 213 (7 %), 185 (10 %) amu.

1-((*Z*)-2-(3,4,5-Trimethoxyphenyl)ethenyl)naphthalene **5.114** & 1-((*E*)-2-(3,4,5-trimethoxyphenyl)ethenyl)naphthalene **5.115**



5.92
$C_{29}H_{24}ClP$ (439)

(*Z*)-**5.114**
(*E*)-**5.115**
$C_{21}H_{20}O_3$ (320)

Phosphonium chloride **5.92** (3.69 g, 8.41 mmol) was added to a cooled (0 °C) suspension of sodium hydride (60 % in mineral oil, 405 mg, 10.09 mmol) in tetrahydrofuran (30 mL). The mixture was stirred at room temperature for 3 hours before cooling to 0 °C. A solution of 3,4,5-trimethoxybenzaldehyde **5.12** (1.50 g, 7.65 mmol) in tetrahydrofuran (10 mL) was added and the mixture was stirred at room temperature for 16 hours. Filtration through Celite, concentration *in vacuo* and purification by column chromatography (silica gel, 20 % ether / petrol) yielded firstly a mixture of **5.114** and **5.115** (1.69 g, 5.28 mmol, 69 %, *Z*:*E* ~ 1:3) as a white solid and then **5.115** (590 mg, 1.84 mmol, 24 %) as a white solid.

A sample of **5.114** was obtained as a colourless oil by further purification of the mixture.

1-((*Z*)-2-(3,4,5-trimethoxyphenyl)ethenyl)naphthalene **5.114**

FT – IR (ν_{max}, neat) 3055 w, 3006 w, 2922 w, 2825 w, 1578 m, 1237 m, 1127 s, 1004 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 316 6300), 262 (12000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.09 – 8.05 (1H, m, Ar*H*), 7.89 – 7.85 (1H, m, Ar*H*), 7.81 – 7.77 (1H, m, Ar*H*), 7.53 – 7.41 (4H, m, 4 × Ar*H*), 7.04 (1H, d, *J* 12.2 Hz, C*H*=CH), 6.75 (1H, d, *J* 12.2 Hz, CH=C*H*), 6.29 (2H, s, 2 × Ar*H*), 3.76 (3H, s, OCH_3), 3.40 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.0 (0, 3 × *C*O), 136.1 (0, *C*), 132.4 (0, *C*), 132.3 (1, *C*H), 132.2 (0, *C*), 131.9 (0, *C*), 128.8 (1, *C*H), 128.3 (1, *C*H), 127.9 (1, *C*H), 126.6 (1, *C*H), 126.6 (1, *C*H), 126.3 (1, *C*H), 125.8 (1, *C*H), 124.2 (1,CH), 106.7 (1, 2 × *C*H), 61.2 (3, OCH_3), 56.0 (3, 2 × OCH_3) ppm.

HRMS (M/z, ES+) $C_{42}H_{40}O_6Na^+$ requires: 663.2717; Found $[2M+Na]^+$: 663.2713.

1-((*E*)-2-(3,4,5-trimethoxyphenyl)ethenyl)naphthalene **5.115**

MP 109 – 111 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3049 w, 3002 w, 2941 m, 2827 w, 1580, s, 1506 s, 1456 m, 1412 m, 1332 m, 1240 m, 1127 s, 1006 m cm^{-1}.

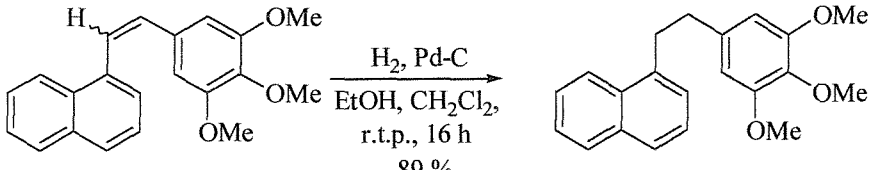
UV (λ_{max}, CH_2Cl_2) 329 (150000), 230 (290000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 8.23 (1H, d, *J* 8.3 Hz, Ar*H*), 7.89 (1H, dd, *J* 7.5, 1.8 Hz, Ar*H*), 7.83 – 7.72 (3H, m, 2 × Ar*H* & C*H*=CH), 7.59 – 7.48 (3H, m, 3 × Ar*H*), 7.09 (1H, d, *J* 16.1 Hz, CH=C*H*), 6.85 (2H, s, 2 × Ar*H*), 3.97 (6H, s, 2 × OCH_3), 3.92 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 153 .9 (0, 3 × *C*O), 135.4 (0, *C*), 134.2 (0, *C*), 132.2 (0, *C*), 131.8 (1, *C*H), 129.4 (1, *C*H), 129.1 (0, *C*), 129.1 (1, *C*H), 128.5 (1, *C*H), 126.5 (1, *C*H), 126.3 (1, *C*H), 126.1 (1, *C*H), 125.8 (1, *C*H), 124.1 (1, *C*H), 104.3 (1, 2 × *C*H), 61.4 (3, O*C*H_3), 56.6 (3, 2 × O*C*H_3) ppm.

LRMS (M/z, CI) 321 (MH^+, 100 %), 305 (18 %), 245 (8 %), 215 (8 %), 202 (14 %), 153 (12 %) amu.

1-(3,4,5-Trimethoxyphenethyl)naphthalene **5.80**



5.114 & 5.115
$C_{21}H_{20}O_3$ (320)

5.80
$C_{21}H_{22}O_3$ (322)

A mixture of **5.114 & 5.115** (1.50 g, 4.69 mmol) was dissolved in ethanol (30 mL) and dichloromethane (20 mL). Palladium on carbon (5 % w/w, 300 mg, 0.14 g atom Pd) was added and the mixture stirred under an atmosphere of hydrogen for 16 hours. Filtration through Celite and concentration *in vacuo* yielded the title compound **5.80** (1.35 g, 4.19 mmol, 89 %) as an off-white solid.

MP 85 – 87 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2945 m, 2827 m, 1589 m, 1507 m, 1457 m, 1419 m, 1238 s, 1126 s, 1006 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 319 (8800), 280 (13000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 8.12 (1H, d, *J* 8.3 Hz, Ar*H*), 7.93 (1H, dd, *J* 7.5, 1.5 Hz, Ar*H*), 7.79 (1H, d, *J* 8.0 Hz, Ar*H*), 7.62 – 7.52 (2H, m, 2 × Ar*H*), 7.45 (1H, app. t, *J* 8.0 Hz, Ar*H*), 7.36 (1H, d, *J* 7.0 Hz, Ar*H*), 6.45 (2H, s, 2 × Ar*H*),

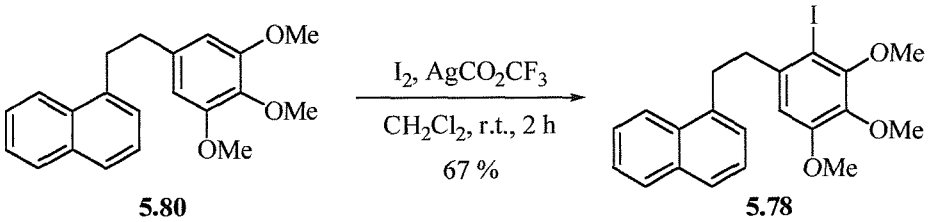
3.90 (3H, s, OCH_3), 3.87 (6H, s, 2 × OCH_3), 3.45 (2H, dd, *J* 10.0, 7.8 Hz, CH_2), 3.05 (2H, dd, *J* 10.4, 7.8 Hz, CH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.5 (0, 3 × *C*O), 138.1 (0, 2 × *C*), 134.3 (0, *C*), 132.2 (0, *C*), 129.3 (1, *C*H), 127.2 (1, *C*H), 126.6 (1, *C*H), 126.3 (1, *C*H), 126.0 (1, *C*H), 125.9 (1, *C*H), 124.0 (1, *C*H), 105.9 (1, 2 × *C*H), 61.3 (3, OCH_3), 56.5 (3, 2 × OCH_3), 37.9 (2, CH_2), 35.4 (2, CH_2) ppm.

LRMS (M/z, CI) 323 (MH^+, 100 %), 181 (74 %), 141 (64 %), 115 (20 %) amu.

CHN $C_{21}H_{22}O_3$ requires: C 78.23, H 6.88; Found: C 78.18, H 6.91.

1-(2-Iodo-3,4,5-trimethoxyphenethyl)naphthalene **5.78**



5.80
$C_{21}H_{22}O_3$ (322)

5.78
$C_{21}H_{21}IO_3$ (448)

1-(3,4,5-Trimethoxyphenethyl)naphthalene **5.80** (1.00 g, 3.11 mmol) was dissolved in dichloromethane (20 mL). Silver(I) trifluoroacetate (755 mg, 3.42 mmol) was added in one portion and then a solution of iodine (795 mg, 3.13 mmol) in dichloromethane (90 mL) was added over 30 minutes. After stirring for 1 hour the mixture was filtered through Celite and the filtrate concentrated to *ca.* 30 mL under reduced pressure. Washing sequentially with sodium hydrogen carbonate (sat. aq., 20 mL) and sodium thiosulfate (sat. aq., 20 mL) then drying ($MgSO_4$), concentration *in vacuo* and purification by column chromatography (silica gel, 10 - 20 % ether / petrol) yielded the title compound **5.78** (930 mg, 2.08 mmol, 67 %) as a white solid.

MP 69 – 71 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3056 w, 2931 m, 2851 w, 1559 m, 1479 s, 1425 m, 1386 s, 1324 m, 1198 m, 1103 s, 1006 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 278 (25000) nm.

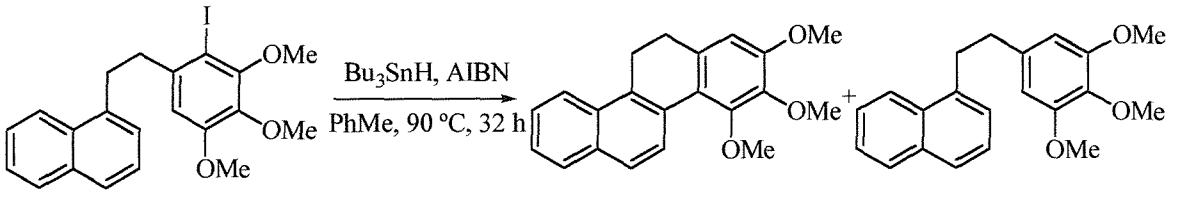
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.17 (1H, dd, *J* 7.4, 1.5 Hz, Ar*H*), 7.88 (1H, dd, *J* 7.4, 2.2 Hz, Ar*H*), 7.76 (1H, d, *J* 8.1 Hz, Ar*H*), 7.57 – 7.47 (2H, m, 2 × Ar*H*), 7.43 (1H, t, *J* 8.1 Hz, Ar*H*), 7.36 (1H, dd, *J* 7.0, 1.5 Hz, Ar*H*), 6.44 (1H, s, Ar*H*), 3.92 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.36 (2H, dd, *J* 10.3, 6.6 Hz, CH_2), 3.17 (2H, dd, *J* 10.3, 6.6 Hz, CH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.5 (0, *C*O), 152.8 (0, *C*O), 140.6 (0, *C*O), 140.2 (0, *C*), 137.6 (0, *C*), 134.0 (0, *C*), 132.1 (0, *C*), 128.9 (1, *C*H), 127.0 (1, *C*H), 126.5 (1, *C*H), 126.0 (1, *C*H), 125.7 (1, *C*H), 125.6 (1, *C*H), 124.0 (1, *C*H), 109.3 (1, *C*H), 88.0 (0, *C*I), 61.2 (3, O*C*H$_3$), 61.0 (3. O*C*H$_3$), 56.2 (3, O*C*H$_3$), 42.6 (2, *C*H$_2$), 33.6 (2, *C*H$_2$) ppm.

LRMS (M/z, CI) 321 ([M-I]$^+$, 88 %), 202 (55 %), 141 (100 %) amu.

CHN $C_{21}H_{21}IO_3$ requires: C 56.26, H 4.72; Found: 56.20, H 4.73.

8,9,10-Trimethoxy-5,6-dihydrochrysene **5.79** & 1-(3,4,5-trimethoxyphenethyl)naphthalene **5.80**



5.78
$C_{21}H_{21}IO_3$ (448)

5.79, 46 %
$C_{21}H_{20}O_3$ (320)

5.80, 20 %
$C_{21}H_{22}O_3$ (322)

Iodide **5.78** (700 mg, 1.56 mmol), tributyltin hydride (505 μL, 545 mg, 1.88 mmol) and AIBN (50 mg 0.31 mmol) were heated in toluene (45 mL) at 90 °C for 20 hours with additional portions of tributyltin hydride (250 μL, 270 mg, 0.93 mmol) and AIBN (10 mg, 0.06 mmol) added after 8 and 16 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 30 mL) for 32 hours. The organic phase was diluted with ether (30 mL) then washed with water (2 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 % ether / petrol) yielded firstly dihydrochrysene **5.79** (230 mg, 0.72 mmol, 46 %) as a white solid and then alkane **5.80** (100 mg, 0.31 mmol, 20 %) as a yellow oil.

8,9,10-Trimethoxy-5,6-dihydrochrysene **5.79**

MP 167 – 168 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2931 w, 2822 w, 1593 m, 1447 m, 1363 m, 1319 m, 1142 m, 1110 s, 1023 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 311 (41000), 268 (120000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 8.47 (1H, d, *J* 8.8 Hz, Ar*H*), 8.16 (1H, app. ddt, *J* 8.4, 1.1, 0.9 Hz, Ar*H*), 7.87 (1H, dd, *J* 8.0, 1.6 Hz, Ar*H*), 7.79 (1H, d, *J* 8.8 Hz, Ar*H*), 7.53 (1H, td, *J* 8.0, 1.5 Hz, Ar*H*), 7.47 (1H, td, *J* 8.0, 1.2 Hz, Ar*H*), 6.69

(1H, s, Ar*H*), 3.98 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.27 – 3.22 (2H, m, CH_2), 2.89 – 2.84 (2H, m, CH_2) ppm.

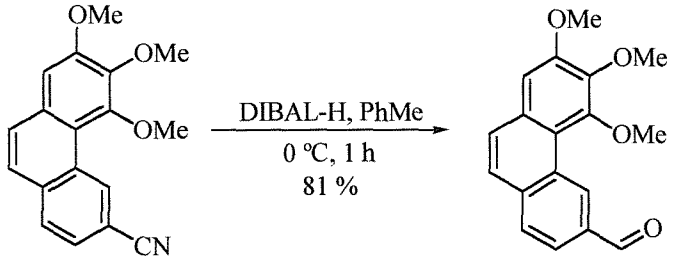
^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 152.5 (0, 2 × *C*O), 142.4 (0, *C*O), 135.0 (0, 2 × *C*), 133.2 (0, *C*), 132.7 (0, *C*), 131.5 (0, *C*), 130.3 (0, *C*), 128.5 (1, *C*H), 126.1 (1, *C*H), 126.0 (1, *C*H), 125.9 (1, *C*H), 125.3 (1, *C*H), 123.8 (1, *C*H), 107.2 (1, *C*H), 61.4 (3, O*C*H_3), 61.1 (3, O*C*H_3), 56.2 (3, O*C*H_3), 30.1 (2, *C*H_2), 24.4 (2, *C*H_2) ppm.

LRMS (M/z, CI) 321 (MH^+, 100 %), 191 (18 %) amu.

CHN $C_{21}H_{20}O_3$ requires: C 78.73, H 6.29; Found: C 78.58, H 6.28.

8.6 Experimental for Chapter 6

5,6,7-Trimethoxy-3-phenathrenecarbaldehyde **6.24**



5.11
$C_{18}H_{15}NO_3$ (293)

6.24
$C_{18}H_{16}O_4$ (296)

Aldehyde **6.24** was prepared by a modification of the method of Wen *et al.*[147] To a solution of benzonitrile **5.11** (650 mg, 2.22 mmol) in toluene (20 mL) at 0 °C was added diisobutylaluminium hydride (1.0 M in hexanes, 3.1 mL, 3.11 mmol) and the mixture was stirred at this temperature for 1 hour. Chloroform (20 mL) and then hydrochloric acid (10 % v/v, 10 mL) were added and the mixture stirred at room temperature for 1 hour. The organic phase was washed with water (20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded the title aldehyde **6.24** (535 mg, 1.81 mmol, 81 %) as a pale yellow solid.

MP 88 – 89 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2931 w, 2841 w, 1692 s, 1611 m, 1501 m, 1466 m, 1350 m, 1277 s, 1227 m, 1129 m, 1078 s, 1006 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 330 (12000), 263 (46000) nm.

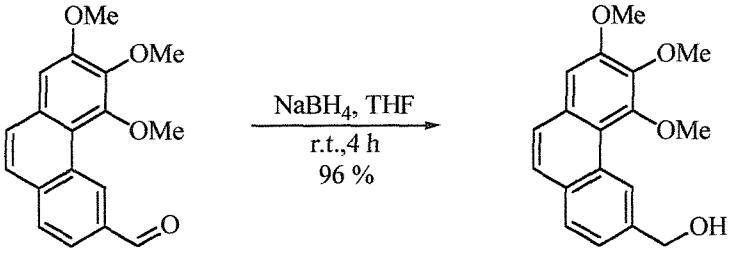
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 10.23 (1H, d, *J* 0.8 Hz, C*H*O), 10.05 - 10.04 (1H, m, Ar*H*), 8.05 (1H, dd, *J* 8.4, 1.7 Hz, Ar*H*), 7.93 (1H, d, *J* 8.4 Hz, Ar*H*), 7.77

(1H, d, *J* 8.9 Hz, Ar*H*), 7.71 (1H, d, *J* 8.9 Hz, Ar*H*), 7.15 (1H, s, Ar*H*), 4.09 (3H, s, OCH_3), 4.07 (3H, s, OCH_3), 4.05 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 193.4 (1, C*H*O), 153.6 (0, *C*O), 152.8 (0, *C*O), 143.9 (0, *C*O), 136.2 (0, *C*), 135.1 (0, *C*), 133.6 (1, *C*H), 130.6 (0, *C*), 130.3 (1, *C*H), 130.0 (0, *C*), 129.8 (1, *C*H), 127.0 (1, *C*H), 123.6 (1, *C*H), 119.4 (0, *C*), 105.9 (1, *C*H), 61.7 (3, O*C*H$_3$), 60.7 (3, O*C*H$_3$), 56.4 (3, O*C*H$_3$) ppm.

LRMS (M/z, CI) 297 (MH^+, 100 %), 167 (32 %) amu.

(5,6,7-Trimethoxy-3-phenanthryl)methanol **6.23**



6.24
$C_{18}H_{16}O_4$ (296)

6.23
$C_{18}H_{18}O_4$ (298)

Aldehyde **6.24** (500 mg, 1.69 mmol) was dissolved in tetrahydrofuran (20 mL) and cooled to 0 °C. Sodium borohydride (70 mg, 1.86 mmol) was added in two portions and the mixture stirred at room temperature for 4 hours. Ammonium chloride (sat. aq., 20 mL) was added and the mixture extracted with ether (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and purified by column chromatography (silica gel, 40 – 100 % ether / petrol) to yield the title compound **6.23** (485 mg, 1.63 mmol, 96 %) as a white solid.

MP 108 – 110 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3395 br. m, 2926 m, 2832 w, 1601 m, 1502 m, 1465 s, 1419 m, 1348 s, 1271 m, 1127 s, 1080 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 301 (21000), 257 (110000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 9.51 (1H, d, *J* 0.8 Hz, Ar*H*), 7.85 (1H, d, *J* 8.2 Hz, Ar*H*), 7.65 (1H, d, *J* 8.8 Hz, Ar*H*), 7.61 (1H, d, *J* 8.8 Hz, Ar*H*), 7.58 (1H, dd, *J* 8.2, 1.5 Hz, Ar*H*), 7.11 (1H, s, Ar*H*), 4.94 (2H, s, CH_2OH), 4.05 (6H, s, 2 × OCH_3), 4.03 (3H, s, OCH_3), 1.89 (1H, br. s, O*H*) ppm.

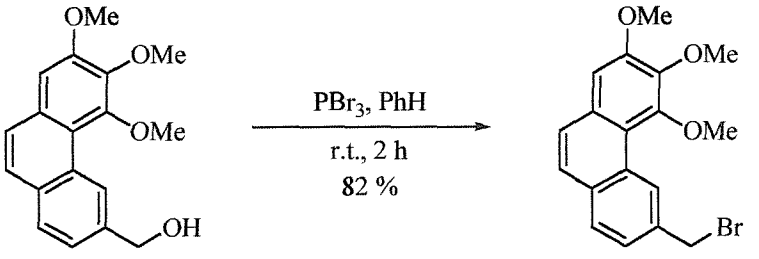
^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 153.0 (0, *C*O), 152.9 (0, *C*O), 143.3 (0, *C*O), 139.6 (0, *C*), 131.7 (0, *C*), 130.7 (0, *C*), 130.3 (0, *C*), 129.2 (1, *C*H), 127.3 (1, *C*H),

127.0 (1, *C*H), 125.5 (1, *C*H), 125.1 (1, *C*H), 119.3 (0, *C*), 105.7 (1, *C*H), 66.7 (2, CH_2OH), 61.7 (3, OCH_3), 60.7 (3, OCH_3), 56.3 (3, OCH_3) ppm.

LRMS (M/z, CI) 297 ($[M-H]^+$, 80 %), 296 (74 %), 224 (70 %), 207 (100 %), 191 (30 %), 154 (90 %) amu.

CHN $C_{18}H_{18}O_4$ requires: C 72.47, H 6.08; Found: C 72.34, H 6.02.

6-(Bromomethyl)-2,3,4-trimethoxyphenanthrene **6.64**



6.23
$C_{18}H_{18}O_4$ (298)

6.64
$C_{18}H_{17}BrO_3$ (361)

To a solution of alcohol **6.23** (435 mg, 1.46 mmol) in benzene (20 mL) at 0 °C was added phosphorus tribromide (50 μL, 140 mg, 0.52 mmol) and the mixture stirred at room temperature for 2 hours. After concentration *in vacuo*, the residue was diluted with dichloromethane (30 mL) and was washed with water (30 mL) then sodium hydrogen carbonate (sat. aq., 20 mL) and the organic phase was dried ($MgSO_4$). Concentration *in vacuo* yielded the title compound **6.64** (430 mg, 1.19 mmol, 82 %) as a pale brown oil that was used without further purification.

FT – IR (ν_{max}, neat) 2931 m, 2836 w, 1600 m, 1502 m, 1465 m, 1349 m, 1274 m, 1231 m, 1130s, 1082 s, 1013 m cm^{-1}.

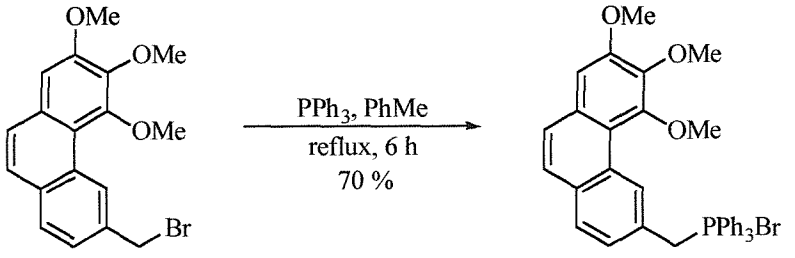
UV (λ_{max}, CH_2Cl_2) 300 (7700), 261 (35000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 9.60 (1H, d, *J* 1.5 Hz, Ar*H*), 7.84 (1H, d, *J* 8.1 Hz, Ar*H*), 7.67 – 7.60 (2H, m, 2 × Ar*H*), 7.58 (1H, dd, *J* 8.1, 1.5 Hz, Ar*H*), 7.11 (1H, s, Ar*H*), 4.80 (2H, s, CH_2Br), 4.07 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 4.03 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 152.8 (0, *C*O), 152.6 (0, *C*O), 143.1 (0, *C*O), 136.0 (0, *C*), 131.8 (0, *C*), 130.0 (0, *C*), 129.2 (1, *C*H), 128.5 (0, *C*), 127.6 (1, *C*H), 127.4 (1, *C*H), 126.9 (1, *C*H), 126.4 (1, *C*H), 118.8 (0, *C*), 105.4 (1, *C*H), 61.5 (3, OCH_3), 60.5 (3, OCH_3), 56.1 (3, OCH_3), 35.4 (2, CH_2Br) ppm.

LRMS (M/z, CI) 282 ($[MH-Br]^+$, 100 %), 267 (25 %), 224 (44 %), 207 (60 %), 154 (40 %) amu.

Triphenyl(5,6,7-trimethoxy-3-phenanthylmethyl)phosphonium bromide **6.22**



6.64
$C_{18}H_{17}BrO_3$ (361)

6.22
$C_{36}H_{32}BrO_3P$ (624)

Bromide **6.64** (405 mg, 1.12 mmol) and triphenylphosphine (310 mg, 1.18 mmol) were dissolved in toluene (20 mL) and the solution heated at reflux for 6 hours. The resulting solid was collected by filtration and washed with petrol (2 × 10 mL) to yield the title compound **6.22** (490 mg, 0.79 mmol, 70 %) as a white solid.

MP 253 – 254 °C (toluene).

FT – IR (ν_{max}, neat) 3002 w, 2931 w, 2841 w, 1597 m, 1493 m, 1465 s, 1438 s, 1350 m, 1274 m, 1131 s, 1111 m, 1081 s, 992 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 319 (11000), 262 (67000) nm.

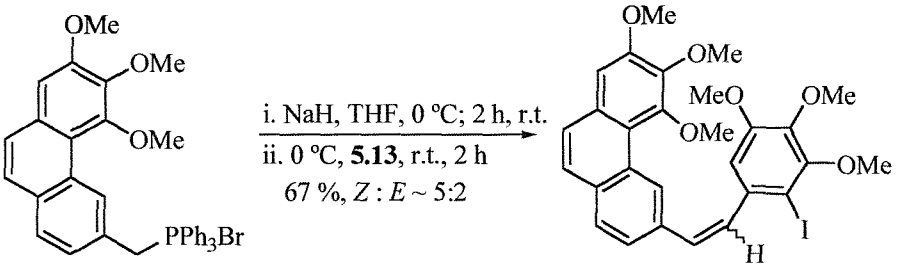
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 9.11 (1H, br. s, Ar*H*), 7.75 – 7.67 (9H, m, 9 × Ar*H*), 7.61 – 7.48 (9H, m, 9 × Ar*H*), 7.25 (1H, dt, *J* 8.3, 2.0 Hz, Ar*H*), 7.04 (1H, s, Ar*H*), 5.53 (2H, d, *J* 14.3 Hz, CH_2P), 3.98 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.73 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 152.9 (0, *C*O), 152.6 (0, *C*O), 142.9 (0, *C*O), 135.0 (1, d, *J* 2.9 Hz, 3 × *C*H), 134.5 (1, d, *J* 9.7 Hz, 6 × *C*H), 131.5 (0, d, *J* 3.4 Hz, *C*), 130.2 (0, d, *J* 8.3 Hz, *C*), 130.0 (1, d, *J* 12.6 Hz, 6 × *C*H), 129.8 (0, d, *J* 3.4 Hz, *C*), 129.6 (1, d, *J* 6.3 Hz, *C*H), 129.1 (1, d, *J* 2.9 Hz, *C*H), 128.6 (1, d, *J* 4.4 Hz, *C*H), 127.4 (1, d, *J* 1.5 Hz, *C*H), 126.7 (1, d, *J* 2.4 Hz, *C*H), 125.1 (0, d, *J* 8.7 Hz, *C*), 118.3 (0, d, *J* 1.5 Hz, *C*), 118.0 (0, d, *J* 85.5 Hz, 3 × *C*), 105.2 (1, *C*H), 61.2 (3, O*C*H$_3$), 60.6 (3, O*C*H$_3$), 56.1 (3, O*C*H$_3$), 32.3 (2, d, *J* 46.6 Hz, *C*H$_2$P) ppm.

^{31}P – NMR (121 MHz, $CDCl_3$) δ_P 23.3 ppm.

LRMS (M/z, ES+) 543 ($[M-Br]^+$, 100 %) amu.

6-((*Z*)-2-(2-Iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)-2,3,4-trimethoxyphenanthrene **6.21** &
6-((*E*)-2-(2-iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)-2,3,4-trimethoxyphenanthrene **6.25**



6.22
$C_{36}H_{32}BrO_3P$ (624)

(*Z*)-**6.21**
(*E*)-**6.25**
$C_{28}H_{27}IO_6$ (586)

To a cooled (0 °C) suspension of sodium hydride (60 % in mineral oil, 35 mg, 0.83 mmol) in tetrahydrofuran (20 mL) was added phosphonium bromide **6.22** (430 mg, 0.69 mmol) and the mixture stirred at room temperature for 2 hours. After cooling to 0 °C, 2-iodo-3,4,5-trimethoxybenzaldehyde **5.13** (205 mg, 0.63 mmol) was added as a solution in tetrahydrofuran (5 mL). The mixture was stirred at room temperature for a further 16 hours. After filtration through Celite, the filtrate was concentrated *in vacuo*. Purification by column chromatography (silica gel, 40 % ether / petrol) yielded firstly the **6.21** (160 mg, 0.27 mmol, 43 %) as a pale yellow oil then a mixture of isomers (90 mg, 0.15 mmol, 24 %, *Z*:*E* ~ 1:3) as a yellow oil.

6-((*Z*)-2-(2-Iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)-2,3,4-trimethoxyphenanthrene **6.21**

FT – IR (ν_{max}, neat) 2997 m, 2932 m, 2833 w, 1597 m, 1557 m, 1499 m, 1464 s, 1381 s, 1323 m, 1194 m, 1128 s, 1102 s, 1081 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 326 (24000), 277 (49000), 257 (63000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 9.42 (1H, d, *J* 1.3 Hz, Ar*H*), 7.66 (1H, d, *J* 8.3 Hz, Ar*H*), 7.59 (1H, d, *J* 8.0 Hz, Ar*H*), 7.56 (1H, d, *J* 8.0 Hz, Ar*H*), 7.35 (1H, dd, *J* 8.3 Hz, 1.3 Hz, Ar*H*), 7.08 (1H, s, Ar*H*), 6.88 (1H, d, *J* 12.0 Hz, C*H*=CH), 6.67 (1H, s, Ar*H*), 6.62 (1H, d, *J* 12.0 Hz, CH=C*H*), 4.01 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.32 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 153.8 (0, *C*O), 153.7 (0, *C*O), 153.0 (0, *C*O), 152.9 (0, *C*O), 143.3 (0, *C*O), 141.7 (0, *C*O), 137.4 (0, *C*), 135.1 (0, *C*), 134.0 (1, *C*H), 132.1 (1, *C*H), 131.4 (0, *C*), 130.7 (0, *C*), 130.2 (0, *C*), 128.5 (1, *C*H), 128.1 (1, *C*H), 127.2 (1, *C*H), 127.1 (1, *C*H), 126.8 (1, *C*H), 119.2 (0, *C*), 110.6 (1,

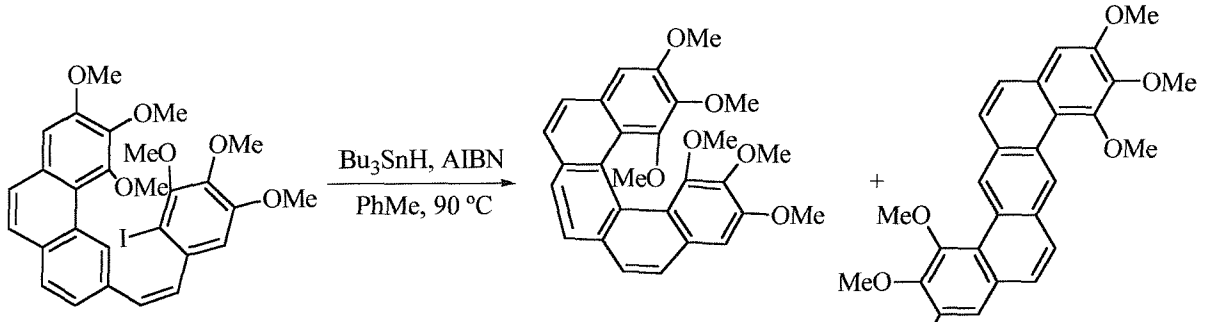
CH), 105.6 (1, *CH*), 87.9 (0, *CI*), 61.6 (3, OCH_3), 61.4 (3, OCH_3), 61.2 (3, OCH_3), 60.4 (3, OCH_3), 56.3 (3, OCH_3), 56.2 (3, OCH_3) ppm.

LRMS (M/z, ES+) 609 ($[M+Na]^+$, 15 %), 291 (32 %), 186 (100 %) amu.

HRMS (M/z, ES+) $C_{28}H_{27}IO_6Na^+$ requires: 609.0763; Found: $[M+Na]^+$ 609.0744.

6-((*E*)-2-(2-Iodo-3,4,5-trimethoxyphenyl)-1-ethenyl)-2,3,4-trimethoxyphenanthrene was not isolated.

1,2,3,12,13,14-Hexamethoxy[5]helicene **6.26** &
2,3,4,9,10,11-hexamethoxydibenzo[*a,h*]anthracene **6.27**



6.21
$C_{28}H_{27}IO_6$ (586)

6.26, 51 %
$C_{28}H_{26}O_6$ (458)

6.27, 17 %
$C_{28}H_{26}O_6$ (458)

Iodide **6.21** (150 mg, 0.26 mmol), tributyltin hydride (85 μL, 90 mg, 0.30 mmol) and AIBN (10 mg, 0.05 mmol) were heated in toluene (10 mL) at 90 °C for 16 hours with additional portions of tributyltin hydride (80 μL, 85 mg, 0.30 mmol) and AIBN (10mg, 0.05 mmol) added after 1, 2, and 4 hours. After cooling to room temperature the resulting solid was collected by filtration to yield 2,3,4,9,10,11-hexamethoxydibenzo[*a,h*]anthracene **6.27** (20 mg, 0.04 mmol, 17 %) as an off-white solid. The filtrate was stirred with a solution of potassium fluoride (10 % w/v, 20 mL) for 2 hours then the organic phase was washed with water (2 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 40 % ether / petrol) yielded the title [5]helicene **6.26** (60 mg, 0.13 mmol, 51 %) as an off-white solid.

1,2,3,12,13,14-Hexamethoxy[5]helicene **6.26**

MP 195 – 196 °C (ethanol).

FT – IR (ν_{max}, neat) 2931 m, 1603 m, 1466 s, 1422 s, 1346 s, 1274 s, 1247 m, 1138 m, 1094 s, 1014 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 315 (32000), 261 (24000), 237 (43000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.88 (2H, s, 2 × Ar*H*), 7.80 (2H, d, *J* 8.4 Hz, 2 × Ar*H*), 7.77 (2H, d, *J* 8.4 Hz, 2 × Ar*H*), 7.15 (2H, s, 2 × Ar*H*), 4.05 (6H, s, 2 × OCH_3), 3.83 (6H, s, 2 × OCH_3), 2.46 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 152.3 (0, 2 × *C*O), 151.7 (0, 2 × *C*O), 141.6 (0, 2 × *C*O), 130.9 (0, 2 × *C*), 129.2 (0, 2 × *C*), 126.9 (1, 2 × *C*H), 126.1 (1, 2 × *C*H), 125.3 (1, 2 × *C*H), 124.9 (0, 2 × *C*), 123.5 (0, 2 × *C*), 103.4 (1, 2 × *C*H), 62.7 (3, 2 × OCH_3), 59.9 (3, 2 × OCH_3), 56.2 (3, 2 × OCH_3) ppm.

LRMS (M/z, ES+) 529 (80 %), 481 ($[M+Na]^+$, 60 %), 459 (MH^+, 50 %), 291 (50 %), 168 (100 %) amu.

CHN $C_{28}H_{26}O_6$ requires: C 73.35, H 5.72; Found: C 73.23, H 5.84.

2,3,4,9,10,11-Hexamethoxydibenzo[*a,h*]anthracene **6.27**

MP 275 – 276 °C (toluene).

FT – IR (ν_{max}, neat) 2921 m, 1598 m, 1474 m, 1393 m, 1342 m, 1274 m, 1158 m, 1087 s, 1009 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 359 (8500), 345 (11000), 333 (14000), 303 (86000) nm.

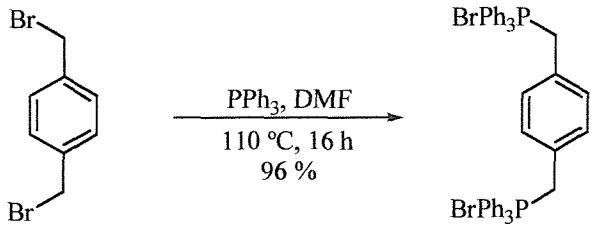
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 9.97 (2H, s, 2 × Ar*H*), 7.90 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.62 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.16 (2H, s, 2 × Ar*H*), 4.15 (6H, s, 2 × OCH_3), 4.10 (6H, s, 2 × OCH_3), 4.07 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 153.3 (0, 2 × *C*O), 153.0 (0, 2 × *C*O), 143.2 (0, 2 × *C*O), 131.6 (0, 2 × *C*), 130.5 (0, 2 × *C*), 129.0 (1, 2 × *C*H), 127.9 (0, 2 × *C*), 127.9 (1, 2 × *C*H), 126.7 (1, 2 × *C*H), 118.8 (0, 2 × *C*), 106.1 (1, 2 × *C*H), 61.8 (3, 2 × OCH_3), 60.7 (3, 2 × OCH_3), 56.4 (3, 2 × OCH_3) ppm.

LRMS (M/z, ES+) 522 ($[M+MeCN+Na]^+$, 21 %), 459 (MH^+, 12 %), 361 (55 %), 251 (55 %), 223 (100 %) amu.

CHN $C_{28}H_{26}O_6$ requires: C 73.35, H 5.72; Found: C 72.91, H 5.53.

(4-(1,1,1-Triphenylphosphonio)benzyl)triphenylphosphonium dibromide **6.30**



6.31
$C_8H_8Br_2$ (264)

6.30
$C_{44}H_{38}Br_2P_2$ (789)

α,α'-Dibromo-*p*-xylene **6.31** (3.00 g, 11.37 mmol) and triphenylphosphine (5.96 g, 22.73 mmol) were dissolved in *N*,*N*-dimethylformamide (30 mL) and the mixture heated at 90 –110 °C for 16 hours. After cooling to room temperature, the resulting solid was collected by filtration and washed with ether (2 × 20 mL) to yield the title compound **6.30** (8.57 g, 10.86 mmol, 96 %) as a white solid.[135,207]

MP >300 °C (DMF) lit. >360 °C (EtOH).[207]

FT – IR (ν_{max}, neat) 3045 w, 3006 w, 2861 w, 1435 m, 1405 w, 1112 s cm^{-1}.

UV (λ_{max}, MeCN) 260 (13000) nm.

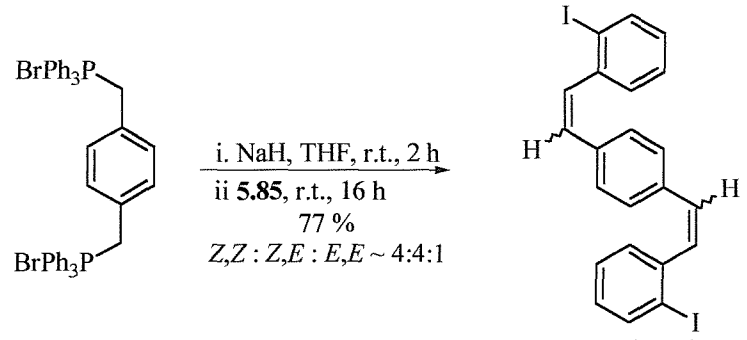
^{1}H – NMR (400 MHz, d_6-DMSO) δ_H 8.01 – 7.99 (6H, m, 6 × Ar*H*), 7.81 – 7.77 (24H, m, 24 × Ar*H*), 6.92 (4H, s, 4 × Ar*H*), 5.35 (4H, d, *J* 14.6 Hz, 2 × C*H*$_2$P) ppm.

^{13}C – NMR (100 MHz, d_6-DMSO) δ_C 135.6 (1, 6 × *C*H), 134.5 (1, d, *J* 10.2 Hz, 12 × *C*H), 134.6 (1, 4 × *C*H), 130.5 (1, d, *J* 12.6 Hz, 12 × *C*H), 128.6 (0, 2 × *C*), 118.1 (0, d, *J* 86.6 Hz, 6 × *C*), 28.2 (2, d, *J* 46.6 Hz, 2 × *C*H$_2$P) ppm.

^{31}P – NMR (121 MHz, d_6–DMSO) δ_P 24.6 ppm.

LRMS (M/z, ES+) 314 ([M-2Br]$^{2+}$, 100 %) amu.

1-Iodo-2-((*Z*)-2-(4-((*Z*)-2-(2-iodophenyl)-1-ethenyl)phenyl)-1-ethenyl)benzene **6.29**, 1-iodo-2-((*Z*)-2-(4-((*E*)-2-(2-iodophenyl)-1-ethenyl)phenyl)-1-ethenyl)benzene **6.32** and 1-iodo-2-((*E*)-2-(4-((*E*)-2-(2-iodophenyl)-1-ethenyl)phenyl)-1-ethenyl)benzene **6.33**



6.30

$C_{44}H_{38}Br_2P_2$ (789)

(*Z*,*Z*)-**6.29**
(*Z*,*E*)-**6.32**
(*E*,*E*)-**6.33**

$C_{22}H_{16}I_2$ (534)

To pre-washed (tetrahydrofuran, 10 mL) sodium hydride (60 % in mineral oil, 455 mg, 11.38 mmol) in tetrahydrofuran (70 mL) was added bisphosphonium dibromide **6.30** (3.74 g, 4.74 mmol) and the mixture stirred at room temperature for 2 hours before cooling to 0 °C. 2-Iodobenzaldehyde **5.85** (2.00 g, 8.62 mmol) was added as a solution in tetrahydrofuran (20 mL) and the mixture stirred at room temperature for a further 16 hours. The mixture was filtered though Celite and the filtrate concentrated *in vacuo*. The resulting yellow gum was purified by column chromatography (silica gel, dichloromethane) to yield the title compounds as a mixture of isomers (1.78 g, 3.33 mmol, 77 %, **6.29**:**6.32**:**6.33** ~ 4:4:1). The mixture was further purified by column chromatography (silica, gel, 5 % ether / petrol) to yield firstly **6.29** (370 mg, 0.69 mmol, 16 %) as a white solid, then **6.32** (200 mg, 0.37 mmol, 9 %) as colourless oil and finally **6.33** (50 mg, 0.09 mmol, 2 %) as a yellow solid.

1-Iodo-2-((*Z*)-2-(4-((*Z*)-2-(2-iodophenyl)-1-ethenyl)phenyl)-1-ethenyl)benzene **6.29**

MP 97 – 98 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3055 w, 3002 w, 2949 w, 1582 m, 1551 m, 1514 m, 1461 s, 1430 s, 1012 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 311 (40000), 274 (50000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.88 (2H, d, *J* 8.0 Hz, 2 × Ar*H*), 7.17 – 7.14 (4H, m, 4 × Ar*H*), 6.96 – 6.90 (6H, m, 6 × Ar*H*), 6.56 (2H, d, *J* 12.0 Hz, 2 × C*H*=CH), 6.48 (2H, d, *J* 12.0 Hz, 2 × CH=C*H*) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 142.1 (0, 2 × *C*), 140.1 (1, 2 × *C*H), 136.2 (0, 2 × *C*), 134.1 (1, 2 × *C*H), 131.1 (1, 2 × *C*H), 130.8 (1, 2 × *C*H), 129.4 (1, 4 × *C*H), 129.3 (1, 2 × *C*H), 127.1 (1, 2 × *C*H), 100.1 (0, 2 × *C*I) ppm.

LRMS (M/z, EI) 534 (M^+, 100 %), 408 ($[MH-I]^+$, 28 %), 279 (30 %), 293 (17 %), 139 (14 %) amu.

CHN $C_{22}H_{16}I_2$ requires: C 49.47, H 3.04; Found: C 49.65, H 3.10.

1-Iodo-2-((*Z*)-2-(4-((*E*)-2-(2-iodophenyl)-1-ethenyl)phenyl)-1-ethenyl)benzene **6.32**

FT – IR (ν_{max}, neat) 3050 w, 3006 w, 1582 m, 1507 m, 1460 s, 1431 s, 1264 m, 1010 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 332 (25000), 240 (12000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.92 (1H, d, *J* 8.2 Hz, Ar*H*), 7.87 (1H, dd, *J* 8.0, 1.2 Hz, Ar*H*), 7.60 (1H, dd, *J* 8.0, 1.6 Hz, Ar*H*), 7.41 – 7.30 (3H, m, 3 × Ar*H*), 7.28 (1H, d, *J* 16.0 Hz, *E*-C*H*=CH), 7.29 – 7.11 (4H, m, 4 × Ar*H*), 7.00 – 6.94 (2H, m, 2 × Ar*H*), 6.89 (1H, d, *J* 16.0 Hz, *E*-CH=C*H*), 6.65 (1H, d, *J* 12.2 Hz, *Z*-C*H*=CH), 6.56 (1H, d, *J* 12.2 Hz, *Z*-CH=C*H*) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 142.0 (0, *C*), 140.4 (0, *C*), 139.8 (1, *C*H), 139.3 (1, *C*H), 136.2 (0, *C*), 136.0 (0, *C*), 134.0 (1, *C*H), 132.6 (1, *C*H), 131.3 (1, *C*H), 130.7 (1, *C*H), 130.4 (1, *C*H), 129.6 (1, 2 × *C*H), 129.2 (1, *C*H), 129.0 (1, *C*H), 128.6 (1, *C*H), 128.3 (1, *C*H), 126.8 (1, 2 × *C*H), 126.4 (1, *C*H), 100.7 (0, *C*I), 99.8 (0, *C*I) ppm.

LRMS (M/z, EI) 534 (M^+, 100 %), 408 ($[MH-I]^+$, 10 %), 279 (30 %), 265 (14 %) amu.

1-Iodo-2-((*E*)-2-(4-((*E*)-2-(2-iodophenyl)-1-ethenyl)phenyl)-1-ethenyl)benzene **6.33**[208]

MP 166 – 168 °C (ether / petrol) (no literature value).

FT – IR (ν_{max}, neat) 3024 w, 1454 s, 1432 m, 1366 s, 1216 s, 1013 m cm^{-1}.

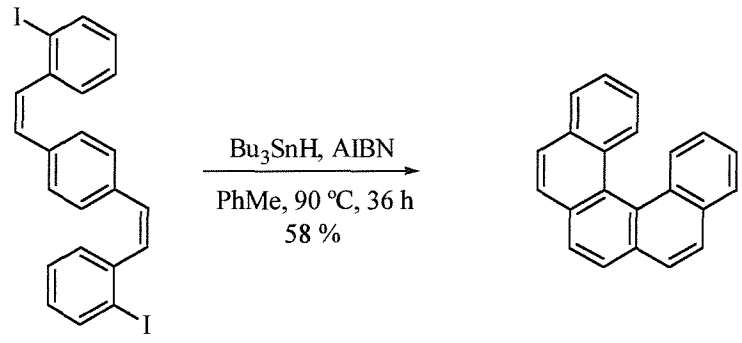
UV (λ_{max}, CH_2Cl_2) 344 (60000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.89 (2H, dd, *J* 7.7, 1.2 Hz, 2 × Ar*H*), 7.65 (2H, dd, *J* 7.8 Hz, 1.4 Hz, 2 × Ar*H*), 7.58 (4H, s, 4 × Ar*H*), 7.37 (2H, d, *J* 0.7 Hz, 2 × Ar*H*), 7.37 (2H, d, *J* 16.0 Hz, 2 × C*H*=CH), 6.99 (2H, d, *J* 16.0 Hz, 2 × CH=C*H*), 6.97 (2H, app. td, *J* 7.5, 1.6 Hz, 2 × Ar*H*) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 140.4 (0, 2 × *C*), 139.8 (1, 2 × *C*H), 136.9 (0, 2 × *C*), 132.8 (1, 2 × *C*H), 131.3 (1, 2 × *C*H), 129.2 (1, 2 × *C*H), 128.6 (1, 2 × *C*H), 127.4 (1, 4 × *C*H), 126.4 (1, 2 × *C*H), 100.7 (0, 2 × *C*I) ppm.

LRMS (M/z, EI) 534 (M^+, 100 %), 408 ($[MH-I]^+$, 10 %), 279 (28 %), 203 (12 %) amu.

[5]Helicene **6.1**



6.29
$C_{22}H_{16}I_2$ (534)

6.1
$C_{22}H_{14}$ (278)

Diiodide **6.29** (400 mg, 0.75 mmol), tributyltin hydride (480 μL, 525mg, 1.80 mmol) and AIBN (25 mg, 0.15 mmol) were heated in toluene (40 mL) at 90 °C for 36 hours with additional portions of tributyltin hydride (200 μL, 215 mg, 0.74 mmol) and AIBN (15 mg, 0.09 mmol) added after 16 and 24 hours. After cooling to room temperature, the mixture was stirred with a solution of potassium fluoride (10 % w/v, 30 mL) for 16 hours. The mixture was diluted with ether (30 mL) and the organic phase was washed with water (2 × 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5 % ether / petrol) yielded the title [5]helicene **6.1** (120 mg, 0.43 mmol, 58 %) as a white solid.[209]

MP 144 – 146 °C (ether / petrol) lit. 145 °C (no solvent stated).[209]

FT – IR (ν_{max}, neat) 3046 m, 1601 m, 1521 m 1437 m, 1253 m, 1223 m, 1123 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 327 (160000), 293 (35000), 259 (39000) nm.

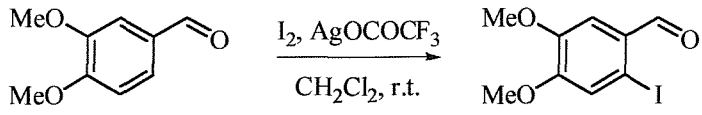
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 8.53 (2H, d, *J* 8.7 Hz, 2 × Ar*H*), 7.99 – 7.87 (8H, m, 8 × Ar*H*), 7.53 (2H, ddd, *J* 8.0, 6.8, 1.2 Hz, 2 × Ar*H*), 7.29 (2H, ddd, *J* 8.4, 7.0, 1.4 Hz, 2 × Ar*H*) ppm plus signals attributed to **6.34**.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 131.2 (0, 2 × *C*), 129.4 (0, 2 × *C*), 129.2 (0, 2 × *C*), 128.2 (1, 2 × *C*H), 127.9 (1, 2 × *C*H), 127.6 (1, 2 × *C*H), 127.4 (1, 2 × *C*H),

127.3 (0, 2 × *C*), 127.1 (1, 2 × *C*H), 127.0 (1, 2 × *C*H), 124.7 (1, 2 × *C*H) ppm plus signals attributed to **6.34**.

LRMS (M/z, EI) 278 (M^+, 83 %), 277 ($[M-H]^+$, 100 %), 276 (81 %), 138 (44 %) amu.

2-Iodo-4,5-dimethoxybenzyaldehyde **6.36**



6.35
$C_9H_{10}O_3$ (166)

6.36
$C_9H_9IO_3$ (292)

2-Iodo-4,5-dimethoxybenzaldehyde **6.36** was prepared by a modification of the method of Rafizadeh *et al.*[120] Thus, 3,4-dimethoxybenzaldehyde **6.35** (3.00 g, 18.05 mmol) was dissolved in dichloromethane (50 mL) and silver(I) trifluoroacetate (4.39 g, 19.86 mmol) was added. Iodine (4.81 g, 18.96 mmol) was added as a solution in dichloromethane (130 mL) over 40 minutes. After stirring for a further 16 hours, the mixture was filtered through Celite and the filtrate washed with sodium hydrogen carbonate (sat. aq., 50 mL) and sodium thiosulfate (sat. aq., 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound **6.36** (5.15 g, 17.64 mmol, 98 %) as a pale brown solid.[186,210]

MP 145 – 146 °C (EtOH) lit. 145 – 146 °C (MeOH).[210]

FT – IR (ν_{max}, neat) 2940 w, 2843 w, 1676 s, 1583 s, 1502 s, 1378 m, 1265 s, 1216 m, 1154 m cm^{-1}.

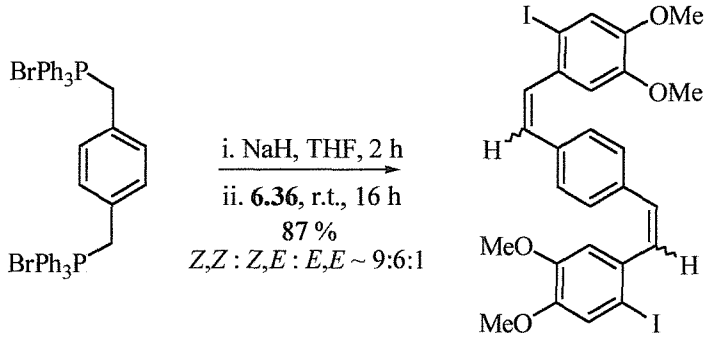
UV (λ_{max}, CH_2Cl_2) 322 (7000), 274 (12000), 235 (23000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 9.87 (1H, s, C*H*O), 7.43 (1H, s, Ar*H*), 7.32 (1H, s, Ar*H*), 3.97 (3H, s, OCH_3), 3.93 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 195.2 (1, *C*HO), 154.9 (0, *C*O), 150.2 (0, *C*O), 128.8 (0, *C*), 122.2 (1, *C*H), 111.5 (1, *C*H), 93.1 (0, *C*I), 56.9 (3, OCH_3), 56.5 (3, OCH_3) ppm.

LRMS (M/z, CI) 310 ($[M+NH_4]^+$, 10 %), 293 (MH^+, 100 %), 167 ($[M+2H-I]^+$, 74 %) amu.

1-Iodo-2-((*Z*)-2-(4-((*Z*)-2-(2-iodo-4,5-dimethoxyphenyl)-1-ethenyl)phenyl)-1-ethenyl)-4,5-dimethoxybenzene **6.37**, 1-iodo-2-((*Z*)-2-(4-((*E*)-2-(2-iodo-4,5-dimethoxyphenyl)-1-ethenyl)phenyl)-1-ethenyl)-4,5-dimethoxybenzene **6.38** and 1-iodo-2-((*E*)-2-(4-((*E*)-2-(2-iodo-4,5-dimethoxyphenyl)-1-ethenyl)phenyl)-1-ethenyl)-4,5-dimethoxybenzene **6.39**



6.30

$C_{44}H_{38}Br_2P_2$ (789)

(*Z*,*Z*)-**6.37**
(*Z*,*E*)-**6.38**
(*E*,*E*)-**6.39**
$C_{26}H_{24}I_2O_4$ (654)

To a suspension of pre-washed (tetrahydrofuran, 10 mL) sodium hydride (60 % in mineral oil, 360 mg, 9.05 mmol) in tetrahydrofuran (60 mL) was added bisphosphonium dibromide **6.30** (2.97 g, 3.77 mmol) and the mixture allowed to stir at room temperature for 16 hours. The mixture was cooled to 0 ° C and 2-iodo-4,5-dimethoxybenzaldehyde **6.36** (2.00 g, 6.85 mmol) was added as a solution in tetrahydrofuran (20 mL). The mixture was stirred at room temperature for a further 16 hours before filtration through Celite. The filtrate was concentrated *in vacuo* and purified by column chromatography (silica gel, dichloromethane) to yield the three title compounds as a yellow solid (1.95 g, 2.98 mmol, 87 %, *Z,Z*:*Z,E*:*E,E* ~ 9:6:1). The mixture was further purified by column chromatography (silica gel, 15 – 25 % ethyl acetate / petrol) to yield firstly **6.37** (705 mg, 1.08 mmol, 31 %) as a yellow solid then **6.38** (540 mg, 0.83 mmol, 24 %) as a yellow solid and finally **6.39** (120 mg, 0.18 mmol, 5 %) as a yellow solid.

1-Iodo-2-((*Z*)-2-(4-((*Z*)-2-(2-iodo-4,5-dimethoxyphenyl)-1-ethenyl)phenyl)-1-ethenyl)-4,5-dimethoxybenzene **6.37**

MP 195 – 196 °C (EtOH/toluene).

FT – IR (ν_{max}, neat) 3050 w, 2993 w, 2931 w, 2834 w, 1595 m, 1498 s, 1437 s, 1384 m, 1192 s, 1119 s, 1026 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 327 (19000), 301 (21000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.25 (2H, s, 2 × Ar*H*), 7.01 (4H, s, 4 × Ar*H*), 6.68 (2H, s, 2 × Ar*H*), 6.50 (2H, d, *J* 11.9 Hz, 2 × C*H*=CH), 6.42 (2H, d, *J* 11.9 Hz, 2 × CH=C*H*), 3.87 (6H, s, 2 × OCH_3), 3.52 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 149.3 (0, 2 × *C*O), 149.2 (0, 2 × *C*O), 135.9 (0, 2 × *C*), 134.1 (0, 2 × *C*), 133.9 (1, 2 × *C*H), 130.4 (1, 2 × *C*H), 129.3 (1, 4 × *C*H), 121.6 (1, 2 × *C*H), 113.3 (1, 2 × *C*H), 87.4 (0, 2 × *C*I), 56.6 (3, 2 × O*C*H$_3$), 56.1 (3, 2 × O*C*H$_3$) ppm.

LRMS (M/z, ES+) 677 ([M+Na]$^+$, 100 %), 361 (75 %) amu.

CHN $C_{26}H_{24}I_2O_4$ requires: C 47.73, H 3.70; Found: C 47.98, H 3.68.

1-Iodo-2-((*Z*)-2-(4-((*E*)-2-(2-iodo-4,5-dimethoxyphenyl)-1-ethenyl)phenyl)-1-ethenyl)-4,5-dimethoxybenzene **6.38**

MP 155 – 157 °C (EtOH/toluene).

FT – IR (ν_{max}, neat) 2997 w, 2936 w, 2834 w, 1745 w, 1595 w, 1516 m, 1506 s, 1432 m, 1260 s, 1198 s, 1158 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 347 (39000), 236 (34000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.38 (2H, d, *J* 8.4 Hz, 2 × ArH), 7.29 (1H, s, Ar*H*), 7.27 (1H, s, Ar*H*), 7.20 (1H, d, *J* 16.1 Hz, *E*-C*H*=CH), 7.18 (2H, d, *J* 8.4 Hz, 2 × Ar*H*), 7.11 (1H, s, Ar*H*), 6.79 (1H, d, *J* 16.1 Hz, *E*-CH=C*H*), 6.74 (1H, s, Ar*H*), 6.59 (1H, d, *J* 11.8 Hz, *Z*-C*H*=CH), 6.48 (1H, d, *J* 11.8 Hz, *Z*-CH=C*H*) 3.94 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.54 (3H, s, OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 149.7 (0, *C*O), 149.5 (0, *C*O), 149.0 (0, *C*O), 148.9 (0, *C*O), 136.2 (0, 2 × *C*), 133.9 (0, *C*), 133.7 (1, *C*H), 132.8 (0, *C*), 132.4 (1, *C*H), 130.1 (1, *C*H), 129.7 (1, 2 × *C*H), 129.4 (1, *C*H), 126.5 (1, 2 × *C*H), 121.7 (1, *C*H), 121.2 (1, *C*H), 113.0 (1, *C*H), 108.5 (1, *C*H), 89.6 (0, *C*I), 89.2 (0, *C*I), 56.3 (3, O*C*H$_3$), 56.3 (3, O*C*H$_3$), 56.1 (3, O*C*H$_3$), 55.9 (3, O*C*H$_3$) ppm.

LRMS (M/z, ES+) 677 ([M+Na]$^+$, 17 %), 307 (22 %), 251 (45 %), 223 (100 %) amu.

CHN $C_{26}H_{24}I_2O_4$ requires C 47.73, H 3.70; Found C 47.83, H 3.78.

1-Iodo-2-((*E*)-2-(4-((*E*)-2-(2-iodo-4,5-dimethoxyphenyl)-1-ethenyl)phenyl)-1-ethenyl)-4,5-dimethoxybenzene **6.39**

MP 232 – 233 °C (EtOAc/EtOH).

FT – IR (ν_{max}, neat) 3006 w, 2953 w, 2927 w, 2825 w, 1595 w, 1512 m, 1498 s, 1437 m, 1257 s, 1206 s, 1161 m, 1022 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 368 (47000), 242 (28000) nm.

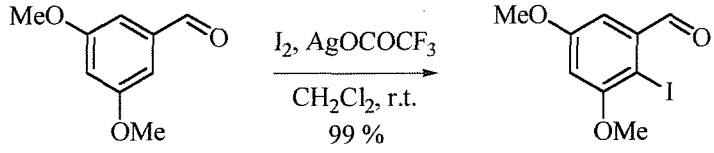
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.48 (4H, s, 4 × Ar*H*), 7.21 (2H, s, 2 × Ar*H*), 7.20 (2H, d, *J* 16.0 Hz, 2 × C*H*=CH), 7.07 (2H, s, 2 × Ar*H*), 6.79 (2H, d, *J* 16.0 Hz, 2 × CH=C*H*), 3.88 (6H, s, 2 × OCH_3), 3.82 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 150.0 (0, 2 × *C*O), 149.8 (0, 2 × *C*O), 137.0 (0, 2 × *C*), 133.2 (0, 2 × *C*), 132.7 (1, 2 × *C*H), 129.9 (1, 2 × *C*H), 127.4 (1, 4 × *C*H), 122.1 (1, 2 × *C*H), 108.9 (1, 2 × *C*H), 89.9 (0, 2 × *C*I), 56.6 (3, 2 × OCH$_3$), 56.4 (3, 2 × OCH$_3$) ppm.

LRMS (M/z, ES+) 677 ($[M+Na]^+$, 11 %), 391 (21 %), 307 (32 %), 251 (57 %), 223 (100 %) amu.

CHN $C_{26}H_{24}I_2O_4$ requires C 47.73, H 3.70; Found C 47.80, H 3.78.

2-Iodo-3,5-dimethoxybenzaldehyde **6.41**



6.40
$C_9H_{10}O_3$ (166)

6.41
$C_9H_9IO_3$ (292)

To a solution of 3,5-dimethoxybenzaldehyde **6.40** (2.01 g, 12.11 mmol) in dichloromethane (20 mL) was added silver(I) trifluoroacetate (2.92 g, 13.24 mmol). Iodine (3.21 g, 12.64 mmol) was added as a solution in dichloromethane (110 mL) over 40 minutes and the mixture was stirred for a further 3 hours. The resulting yellow solid was removed by filtration through Celite and the filtrate was washed with sodium hydrogen carbonate (sat. aq., 30 mL) and sodium thiosulfate (sat. aq., 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound **6.41** (3.53 g, 12.09 mmol, 99 %) as a pale yellow solid.[209]

MP 88 – 89 °C (EtOH) lit. 103 – 104.5 (petrol).[211]

FT – IR (ν_{max}, neat) 2967 w, 2918 w, 2834 w, 1690 s, 1582 s, 1445 m, 1330 s, 1287 s, 1198 m, 1161 s, 1075 m, 1009 m cm^{-1}.

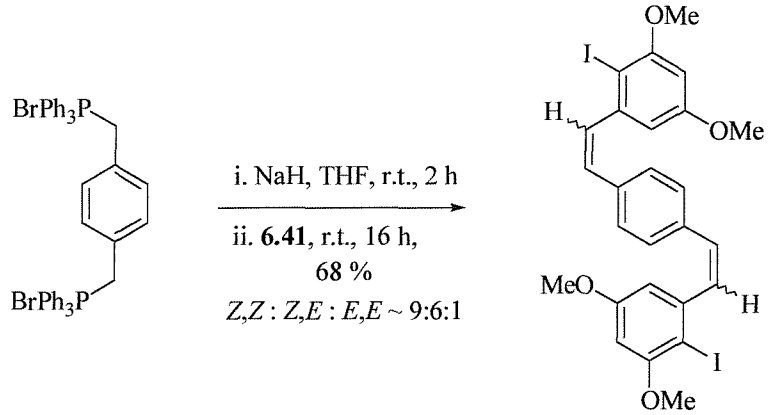
UV (λ_{max}, CH_2Cl_2) 339 (3700), 268 (4900) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 10.18 (1H, s, C*H*O), 7.07 (1H, d, *J* 2.8 Hz, Ar*H*), 6.67 (1H, d, *J* 2.8 Hz, Ar*H*), 3.91 (3H, s, OCH_3), 3.86 (3H, s, OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 196.6 (1, *C*HO), 161.7 (0, *C*O), 159.4 (0, *C*O), 137.0 (0, *C*), 105.4 (1, *C*H), 105.1 (1, *C*H), 84.5 (0, *C*I), 57.2 (3, OCH_3), 56.2 (3, OCH_3) ppm.

LRMS (M/z, CI) 310 ($[M+NH_4]^+$, 43 %), 293 (MH^+, 90 %), 167 ($[M+2H-I]^+$, 75 %), 166 ($[MH-I]^+$, 100 %), 153 (98 %), 139 (40 %).

1-Iodo-2-((*Z*)-2-(4-((*Z*)-2-(2-iodo-3,5-dimethoxyphenyl)-1-ethenyl)phenyl)-1-ethenyl)-3,5-dimethoxybenzene **6.42**, 1-iodo-2-((*Z*)-2-(4-((*E*)-2-(2-iodo-3,5-dimethoxyphenyl)-1-ethenyl)phenyl)-1-ethenyl)-3,5-dimethoxybenzene **6.43** and 1-iodo-2-((*E*)-2-(4-((*E*)-2-(2-iodo-3,5-dimethoxyphenyl)-1-ethenyl)phenyl)-1-ethenyl)-3,5-dimethoxybenzene **6.44**



6.30

$C_{44}H_{38}Br_2P_2$ (789)

(*Z*,*Z*)-**6.42**
(*Z*,*E*)-**6.43**
(*E*,*E*)-**6.44**

$C_{26}H_{24}I_2O_4$ (654)

To pre-washed (tetrahydrofuran, 10 mL) sodium hydride (60 % in mineral oil, 325 mg, 8.13 mmol) in tetrahydrofuran (50 mL) was added bisphosphonium dibromide **6.30** (2.92 g, 3.70 mmol) and the mixture stirred at room temperature for 2 hours before cooling to 0 °C. 2-Iodo-3,5-dimethoxybenzaldehyde **6.41** (1.60 g, 5.48 mmol) was added as a solution in tetrahydrofuran (20 mL) and the mixture stirred at room temperature for 16 hours. The mixture was filtered through Celite and the filtrate concentrated *in vacuo*. The resulting yellow gum was purified by column chromatography (silica gel, dichloromethane) to yield the title compounds as a yellow solid (1.21 g, 1.85 mmol, 68 %, **6.42**:**6.43**:**6.44** ~ 9:6:1). Recrystallisation from ethyl acetate yielded **6.42** (310 mg, 0.47 mmol, 17 %) as a yellow

solid. The remaining products were found to be inseparable by fractional recrystallisation and column chromatography.

1-Iodo-2-((*Z*)-2-(4-((*Z*)-2-(2-iodo-3,5-dimethoxyphenyl)-1-ethenyl)phenyl)-1-ethenyl)-3,5-dimethoxybenzene **6.42**

MP 196 – 198 °C (EtOH / EtOAc).

FT – IR (ν_{max}, neat) 3006 w, 2960 w, 2932 w, 2830 w, 1574 s, 1453 s, 1408 m, 1321 s, 1161 s, 1077 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 303 (25000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 6.97 (4H, s, 4 × Ar*H*), 6.54 (2H, d, *J* 12.0 Hz, 2 × C*H*=CH), 6.49 (2H, d, *J* 12.0 Hz, 2 × CH=C*H*), 6.36 (2H, d, *J* 2.6 Hz, 2 × Ar*H*), 6.31 (2H, d, *J* 2.6 Hz, 2 × Ar*H*), 3.88 (6H, s, 2 × OCH_3), 3.56 (6H, s, 2 × OCH_3) ppm.

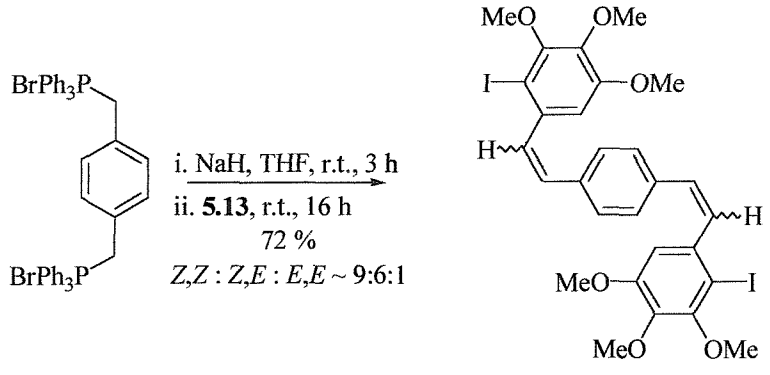
^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 161.1 (0, 2 × *C*O), 159.8 (0, 2 × *C*O), 144.0 (0, 2 × *C*), 135.7 (0, 2 × *C*), 134.4 (1, 2 × *C*H), 130.8 (1, 2 × *C*H), 129.9 (1, 4 × *C*H), 107.1 (1, 2 × *C*H), 98.4 (1, 2 × *C*H), 80.7 (0, 2 × *C*I), 56.8 (3, 2 × O*C*H$_3$), 55.8 (3, 2 × O*C*H$_3$) ppm.

LRMS (M/z, EI) 654 (M^+, 45 %), 527 ($[M-I]^+$, 28 %), 400 ($[M-2I]^+$, 100 %) amu.

CHN $C_{26}H_{24}I_2O_4$ requires: C 47.73, H 3.70; Found: C 47.70, H 3.70.

1-Iodo-2-((*Z*)-2-(4-((*E*)-2-(2-iodo-3,5-dimethoxyphenyl)-1-ethenyl)phenyl)-1-ethenyl)-3,5-dimethoxybenzene **6.43** and 1-iodo-2-((*E*)-2-(4-((*E*)-2-(2-iodo-3,5-dimethoxyphenyl)-1-ethenyl)phenyl)-1-ethenyl)-3,5-dimethoxybenzene **6.44** were not isolated.

2-Iodo-1-((*Z*)-2-(4-(2-(*Z*)-(2-iodo-3,4,5-trimethoxyphenyl)ethenyl)phenyl)ethenyl-3,4,5-trimethoxybenzene **6.45**, 2-iodo-1-((*E*)-2-(4-(2-(*Z*)-(2-iodo-3,4,5-trimethoxyphenyl)ethenyl)phenyl)ethenyl-3,4,5-trimethoxybenzene **6.46** and 2-iodo-1-((*E*)-2-(4-(2-(*E*)-(2-iodo-3,4,5-trimethoxyphenyl)ethenyl)phenyl)ethenyl-3,4,5-trimethoxybenzene **6.47**



6.30

$C_{44}H_{38}Br_2P_2$ (789)

(*Z*,*Z*)-**6.45**
(*Z*,*E*)-**6.46**
(*E*,*E*)-**6.47**
$C_{28}H_{28}I_2O_6$ (714)

To sodium hydride (60 % in mineral oil, 300 mg, 7.45 mmol) in tetrahydrofuran (30 mL) was added bisphosphonium dibromide **6.30** (2.69 g, 3.42 mmol) and the mixture stirred for 3 hours. After cooling to 0 °C, 2-iodo-3,4,5-trimethoxybenzaldehyde **5.13** (2.00 g, 6.21 mmol) was added as a solution in tetrahydrofuran (20 mL) and the mixture stirred at room temperature for 16 hours. The resulting yellow mixture was filtered through Celite and the filtrate concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded firstly **6.45** (740 mg, 1.04 mmol, 33 %) as a pale yellow solid then a mixture of **6.45** and **6.46** (360 mg, 0.50 mmol, 16 %, **6.45**:**6.46** ~ 1:1) and finally **6.46** (500 mg, 0.70 mmol, 23 %) as a yellow solid.

2-Iodo-1-((*Z*)-2-(4-(2-(*Z*)-(2-iodo-3,4,5-trimethoxyphenyl)ethenyl)phenyl)ethenyl-3,4,5-trimethoxybenzene **6.45**

MP 111 – 114 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2997 w, 2927 m, 2839 w, 1559 m ,1476 s, 1416 m, 1381 s, 1321 s, 1240 m, 1156 m, 1103 s, 1005 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 347 (15000), 315 (32000), 262 (56000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.02 (4H, s, 4 × Ar*H*), 6.58 (2H, s, 2 × Ar*H*), 6.52 (2H, d, *J* 12.1 Hz, 2 × C*H*=CH), 6.46 (2H, d, *J* 12.1 Hz, 2 × CH=C*H*), 3.91 (6H, s, 2 × OCH_3), 3.88 (6H, s, 2 × OCH_3), 3.52 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 153.5 (0, 2 × *C*O), 153.4 (0, 2 × *C*O), 141.4 (0, 2 × *C*O), 137.0 (0, 2 × *C*), 135.4 (0, 2 × *C*), 133.8 (1, 2 × *C*H=CH), 130.2 (1, 2 × CH=*C*H), 129.0 (1, 4 × *C*H), 109.6 (1, 2 × *C*H), 87.3 (0, 2 × *C*I), 61.2 (3, 2 × O*C*H$_3$), 61.0 (3, 2 × O*C*H$_3$), 56.1 (3, 2 × O*C*H$_3$) ppm.

LRMS (M/z, ES+) 737 ([M+Na]$^+$, 100 %), 251 (54 %), 223 (78 %) amu.

CHN $C_{28}H_{28}I_2O_6$ C 47.08, H 3.95; Found C 47.07, H 3.96.

2-Iodo-1-((*E*)-2-(4-(2-(*Z*)-(2-iodo-3,4,5-trimethoxyphenyl)ethenyl)phenyl)ethenyl-3,4,5-trimethoxybenzene **6.46**

MP 114 – 116 °C (ether / petrol).

FT – IR (ν_{max}, neat) 3001 w, 2937 m, 2844 w, 1550 m, 1476 s, 1423 m, 1381 s, 1320 m, 1194 m, 1102 s, 1004 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 347 (33000), 225 (43000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.39 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 7.34 (1H, d, *J* 16.1 Hz, *E*-C*H*=CH), 7.18 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 7.00 (1H, s, Ar*H*), 6.80 (1H, d, *J* 16.1 Hz, *E*-CH=C*H*), 6.63 (1H, s, Ar*H*), 6.60 (1H, d, *J* 12.0 Hz, *Z*-C*H*=CH), 6.53 (1H, d, *J* 12.0 Hz, *Z*-CH=C*H*), 3.93 (6H, s, 2 × OC*H*$_3$), 3.90 (6H, s, 2 × OC*H*$_3$), 3.90 (3H, s, OC*H*$_3$), 3.55 (3H, s, OC*H*$_3$) ppm.

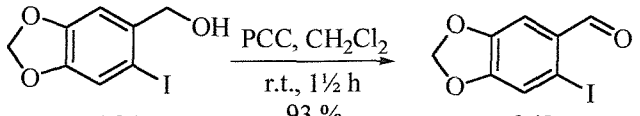
^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 154.3 (0, *C*O), 153.9 (0, *C*O), 153.8 (0, *C*O), 153.6 (0, *C*O), 142.4 (0, *C*O), 141.7 (0, *C*O), 137.3 (0, *C*), 136.5 (0, *C*), 136.4 (0, *C*), 136.3 (0, *C*), 134.3 (1, *C*H), 133.1 (1, *C*H), 130.8 (1, *C*H), 130.5 (1, *C*H), 129.9 (1, 2 × *C*H), 126.9 (1, 2 × *C*H), 110.1 (1, *C*H), 105.9 (1, *C*H), 89.4 (0, *C*I), 87.6 (0, *C*I), 61.5 (3, 2 × O*C*H$_3$), 61.3 (3, O*C*H$_3$), 61.2 (3, O*C*H$_3$), 56.6 (3, O*C*H$_3$), 56.4 (3, O*C*H$_3$) ppm.

LRMS (M/z, ES+) 737 ([M+Na]$^+$, 17 %), 307 (25 %), 251 (50 %), 223 (100 %) amu.

CHN $C_{28}H_{28}I_2O_6$ requires C 47.08, H 3.95; Found C 47.41, H 4.03.

2-Iodo-1-((*E*)-2-(4-(2-(*E*)-(2-iodo-3,4,5-trimethoxyphenyl)ethenyl)phenyl)ethenyl-3,4,5-trimethoxybenzene **6.47** was not isolated.

6-Iodobenzo[1,3]dioxole-5-carbaldehyde **6.48**[212]



4.24 $C_8H_7IO_3$ (278)

6.48 $C_8H_5IO_3$ (276)

6-Iodobenzo[1,3]dioxole-5-carbaldehyde **6.48** was prepared by the method of Padwa *et al.*[212] Alcohol **4.24** (4.00 g, 14.39 mmol) was dissolved in dichloromethane (150 mL) and cooled to 0 °C. Pyridinium chlorochromate (6.20 g, 28.78 mmol) was added and the mixture allowed to stir at room temperature for 1½ hours before removal of the chromium residues by filtration through silica (eluent: dichloromethane). The filtrate was concentrated *in vacuo* to yield the title compound **6.48** (3.70 g, 13.41 mmol, 93 %) as an off-white solid.[212]

MP 102 – 103 °C (EtOH) lit. 112 – 113 °C (EtOAc/pentane).[212]

FT – IR (ν_{max}, neat) 3099 w, 2967 w, 2900 w, 1663 s, 1609 m, 1489 m, 1388 m, 1251 m, 1113 s, 1035 m cm^{-1}.

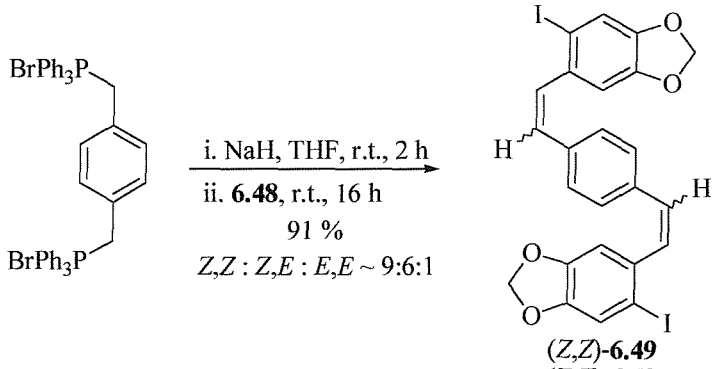
UV (λ_{max}, CH_2Cl_2) 322 (5500), 272 (6500), 236 (18000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 9.88 (1H, s, C*H*O), 7.37 (1H, s, Ar*H*), 7.34 (1H, s, Ar*H*), 6.09 (2H, s, OCH_2O) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 194.8 (1, *C*HO), 154.0 (0, *C*O), 149.6 (0, *C*O), 130.1 (0, *C*), 119.9 (1, *C*H), 109.3 (1, *C*H), 103.1 (2, OCH_2O), 93.7 (0, *C*I) ppm.

LRMS (M/z, CI) 294 ($[M+NH_4]^+$, 23 %), 277 (MH^+, 84 %), 168 (25 %), 151 ($[M+2H-I]^+$, 100 %), 135 (13 %) amu.

5-Iodo-6-((*Z*)-2-(4-((*Z*)-2-(6-iodo-1,3-benzodioxol-5-yl)-1-ethenyl)phenyl)-1-ethenyl)-1,3-benzodioxole **6.49**, 5-iodo-6-((*Z*)-2-(4-((*E*)-2-(6-iodo-1,3-benzodioxol-5-yl)-1-ethenyl)phenyl)-1-ethenyl)-1,3-benzodioxole **6.50** and 5-iodo-6-((*E*)-2-(4-((*E*)-2-(6-iodo-1,3-benzodioxol-5-yl)-1-ethenyl)phenyl)-1-ethenyl)-1,3-benzodioxole **6.51**



6.30

$C_{44}H_{38}Br_2P_2$ (789)

(*Z*,*Z*)-**6.49**
(*Z*,*E*)-**6.50**
(*E*,*E*)-**6.51**

$C_{24}H_{16}I_2O_4$ (622)

To pre-washed (tetrahydrofuran, 10 mL) sodium hydride (60 % in mineral oil, 385 mg, 9.58 mmol) in tetrahydrofuran (60 mL) was added bisphosphonium dibromide **6.30** (3.14 g, 3.99 mmol) and the mixture stirred at room temperature for 2 hours before cooling to 0 °C. Aldehyde **6.48** (2.00 g, 7.25 mmol) was added and the mixture stirred at room temperature for a further 16 hours. Filtration through Celite, concentration *in vacuo* and purification by column chromatography (silica gel, dichloromethane) yielded a mixture of the title compounds (2.04 g, 3.28 mmol, 91 %, **6.49**:**6.50**:**6.51** ~ 9:6:1) as a yellow foam. Further purification by column chromatography (silica gel, 5 – 10 % EtOAc / petrol) yielded firstly **6.49** (465 mg, 0.75 mmol, 21 %) as a yellow solid and then **6.50** (320 mg, 0.51 mmol, 14 %) as a yellow solid.

5-Iodo-6-((*Z*)-2-(4-((*Z*)-2-(6-iodo-1,3-benzodioxol-5-yl)-1-ethenyl)phenyl)-1-ethenyl)-1,3-benzodioxole **6.49**

MP 173 – 175 °C (EtOH/toluene).

FT – IR (ν_{max}, neat) 3072 w, 3011 w, 2892 w, 1500 m, 1472 s, 1423 m, 1228 s, 1097 m, 1034 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 301 (19000), 231 (24000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.29 (2H, s, 2 × Ar*H*), 7.00 (4H, s, 4 × Ar*H*), 6.65 (2H, s, 2 × Ar*H*), 6.49 (2H, d, *J* 12.0 Hz, 2 × C*H*=CH), 6.38 (2H, d, *J* 12.0 Hz, 2 × CH=C*H*), 5.93 (4H, s, 2 × OCH_2O) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 148.6 (0, 2 × *C*O), 148.1 (0, 2 × *C*O), 135.6 (0, 2 × *C*), 135.3 (0, 2 × *C*), 133.9 (1, 2 × *C*H), 130.7 (1, 2 × *C*H), 129.3 (1, 4 × *C*H), 118.7 (1, 2 × *C*H), 110.4 (1, 2 × *C*H), 102.0 (2, 2 × O*C*H_2O), 88.4 (0, 2 × *C*I) ppm.

LRMS (M/z, ES+) 391 ([M-2I+Na]$^+$, 20 %), 307 (30 %), 251 (60 %), 223 (100 %) amu.

CHN $C_{24}H_{26}I_2O_4$ requires: C 46.33, H 2.59; Found: C 46.83, H 2.69.

5-Iodo-6-((*Z*)-2-(4-((*E*)-2-(6-iodo-1,3-benzodioxol-5-yl)-1-ethenyl)phenyl)-1-ethenyl)-1,3-benzodioxole **6.50**

MP 186 – 188 °C (EtOH/toluene).

FT – IR (ν_{max}, neat) 3015 w, 2962 w, 2892 w, 1472 s, 1370 m, 1220 s, 1040 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 339 (44000), 272 (61000) nm.

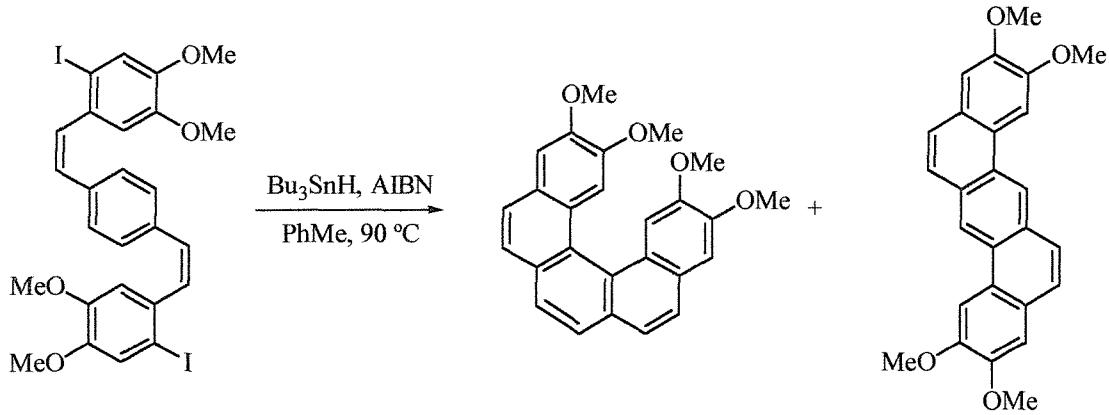
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.37 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 7.33 (1H, s, Ar*H*), 7.29 (1H, s, Ar*H*), 7.20 (1H, s, Ar*H*), 7.16 (2H, d, *J* 8.2 Hz, 2 × Ar*H*), 7.14 (1H, d, *J* 16.0 Hz, *E*-C*H*=CH), 6.76 (1H, d, *J* 16.0 Hz, *E*-CH=C*H*), 6.70 (1H, s, Ar*H*), 6.56 (1H, d, *J* 12.0 Hz, *Z*-C*H*=CH), 6.42 (1H, d, *J* 12.0 Hz, *Z*-CH=C*H*), 5.99 (2H, s, OCH_2O), 5.95 (2H, s, OCH_2O) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 149.3 (0, *C*O), 148.7 (0, *C*O), 148.5 (0, *C*O), 148.2 (0, *C*O), 136.4 (0, *C*), 136.2 (0, *C*), 135.4 (0, *C*), 134.3 (0, *C*), 134.0 (1, *C*H), 132.7 (1, *C*H), 130.6 (1, *C*H), 130.1 (1, *C*H), 129.9 (1, 2 × *C*H), 127.0 (1, 2 × *C*H), 119.1 (1, *C*H), 118.7 (1, *C*H), 110.4 (1, *C*H), 106.1 (1, *C*H), 102.2 (2, O*C*H_2O), 102.0 (2, O*C*H_2O), 89.7 (0, *C*I), 88.4 (0, *C*I) ppm.

LRMS (M/z, ES+) 391 ([M-2I+Na]$^+$, 22 %), 307 (30 %), 251 (45 %), 224 (100 %) amu.

5-Iodo-6-((*E*)-2-(4-((*E*)-2-(6-iodo-1,3-benzodioxol-5-yl)-1-ethenyl)phenyl)-1-ethenyl)-1,3-benzodioxole **6.51** was not isolated.

2,3,12,13-Tetramethoxy[5]helicene **6.52** and 2,3,9,10-tetramethoxydibenzo[*a,h*]anthracene **6.53**



6.37
$C_{26}H_{24}I_2O_4$ (654)

6.52, 40 %
$C_{26}H_{22}O_4$ (398)

6.53, 5 %
$C_{26}H_{22}O_4$ (398)

To a solution of diiodide **6.37** (500 mg, 0.76 mmol) in toluene (40 mL) was added tributyltin hydride (450 μL, 480 mg, 1.67 mmol) and AIBN (25 mg, 0.15 mmol). The mixture was heated at 90 °C for 36 hours with additional portions of tributyltin hydride (200 μL, 215 mg, 0.74 mmol) and AIBN (25 mg, 0.15 mmol) added after 8 and 20 hours. After cooling to 0 °C, the resulting solid was collected by filtration to yield a mixture of **6.52** and **6.53** (60 mg, 0.15 mmol, 20 %, **6.52**:**6.53** ~ 3:1). The filtrate was allowed to stir with a solution of potassium fluoride (10 % w/v, 30 mL) for 16 hours. The mixture was diluted with ether (30 mL) and the organic phase was washed with water (2 × 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % EtOAc / petrol) yielded the title [5]helicene **6.52** as an off white solid (75 mg, 0.19 mmol, 25 %).

2,3,12,13-Tetramethoxy[5]helicene **6.52**

MP 252-254 °C (ether / petrol).

FT – IR (ν_{max}, neat) 2958 w, 2922 w, 2825 w, 1622 w, 1514 m, 1464 m, 1260 s, 1224 m, 1164 m, 1135 m, 1066 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 301 (23000), 269 (21000), 237 (31000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.85 – 7.70 (8H, m, 8 × Ar*H*), 7.30 (2H, s, 2 × Ar*H*), 4.08 (6H, s, 2 × OCH_3), 3.61 (6H, s, 2 × OCH_3) ppm.

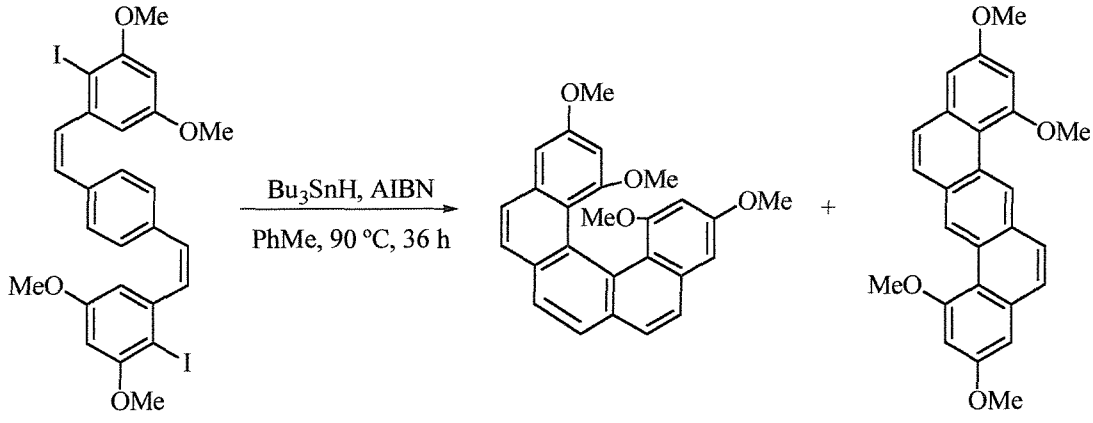
^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 148.9 (0, 2 × *C*O), 147.2 (0, 2 × *C*O), 131.3 (0, 2 × *C*), 128.4 (0, 2 × *C*), 126.7 (1, 2 × *C*H), 126.3 (1, 2 × *C*H), 126.0 (0, 2 × *C*), 125.2 (0, 2 × *C*), 125.1 (1, 2 × *C*H), 110.2 (1, 2 × *C*H), 107.3 (1, 2 × *C*H), 56.0 (3, 2 × OCH_3), 55.8 (3, 2 × OCH_3) ppm.

2,3,9,10-Tetramethoxydibenzo[*a,h*]anthracene **6.53**

Due to the insolubility of this compound and the inability to separate it from **6.52** only select ^{1}H-NMR data is reported.

^{1}H – NMR (300 MHz, d_6-DMSO) δ_H 9.42 (2H, s, 2 × Ar*H*), 8.48 (2H, s, 2 × Ar*H*), 7.86 (2H, d, *J* 9.2 Hz, 2 × Ar*H*), 4.20 (6H, s, 2 × OCH_3) plus signals obscured by **6.52**.

1,3,12,14-Tetramethoxy[5]helicene **6.54** and 2,4,9,11-tetramethoxydibenzo[*a,h*]anthracene **6.55**



6.42
$C_{26}H_{24}I_2O_4$ (654)

6.54, 47 %
$C_{26}H_{22}O_4$ (398)

6.55, 4 %
$C_{26}H_{22}O_4$ (398)

A solution of diiodide **6.42** (400 mg, 0.61 mmol), tributyltin hydride (395 μL, 425 mg, 1.47 mmol) and AIBN (25 mg, 0.15 mmol) in toluene (20 mL) were heated at 90 °C for 36 hours with additional tributyltin hydride (200 μL, 215 mg, 0.74 mmol) and AIBN (15 mg, 0.09 mmol) added after 8 and 20 hours. After cooling to room temperature, the resulting solid was collected by filtration to yield **6.55** (10 mg, 0.03 mmol, 4 %) as a yellow solid. The filtrate was stirred with a solution of potassium fluoride (10 % w/v, 20 mL) for 3 hours. The organic phase was washed with water (2 × 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 20 % ether / petrol) yielded the title [5]helicene **6.54** (115 mg, 0.29 mmol, 47 %) as a yellow solid.

1,3,12,14-Tetramethoxy[5]helicene **6.54**

MP 191 – 193 °C (EtOH/EtOAc).

FT – IR (ν_{max}, neat) 3002 w, 2953 w, 2931 w, 2926 w, 1607 s, 1561 s, 1460 m, 1273 m, 1211 s, 1162 s, 1067 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 341 (16000), 297 (48000) nm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.90 (2H, s, 2 × Ar*H*), 7.89 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 7.81 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 7.00 (2H, d, *J* 2.3 Hz, 2 × Ar*H*), 6.43 (2H, d, *J* 2.3 Hz, 2 × Ar*H*), 4.01 (6H, s, 2 × OCH_3), 2.97 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 158.0 (0, 2 × *C*O), 157.4 (0, 2 × *C*O), 133.3 (0, 2 × *C*), 130.8 (0, 2 × *C*), 127.3 (1, 2 × *C*H), 126.5 (1, 2 × *C*H), 125.7 (1, 2 × *C*H), 125.3 (0, 2 × *C*), 120.6 (0, 2 × *C*), 99.0 (1, 2 × *C*H), 96.5 (1, 2 × *C*H), 55.6 (3, 2 × O*C*H_3), 54.1 (3, 2 × O*C*H_3) ppm.

LRMS (M/z, ES+) 421 ([M+Na]$^+$, 50 %), 399 (MH$^+$, 100 %), 361 (98 %), 229 (70 %) amu.

CHN $C_{26}H_{22}O_4$ requires: C 77.37, H 5.57; Found: C 77.87, H 5.54.

2,4,9,11-Tetramethoxydibenzo[*a*,*h*]anthracene **6.55**

MP >280 °C (toluene).

FT – IR (ν_{max}, neat) 2997 w, 2958 w, 2925 w, 1606 m, 1555 m, 1445 m, 1216 m, 1159 s, 1064 s cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 347 (16000), 322 (31000), 296 (120000) nm.

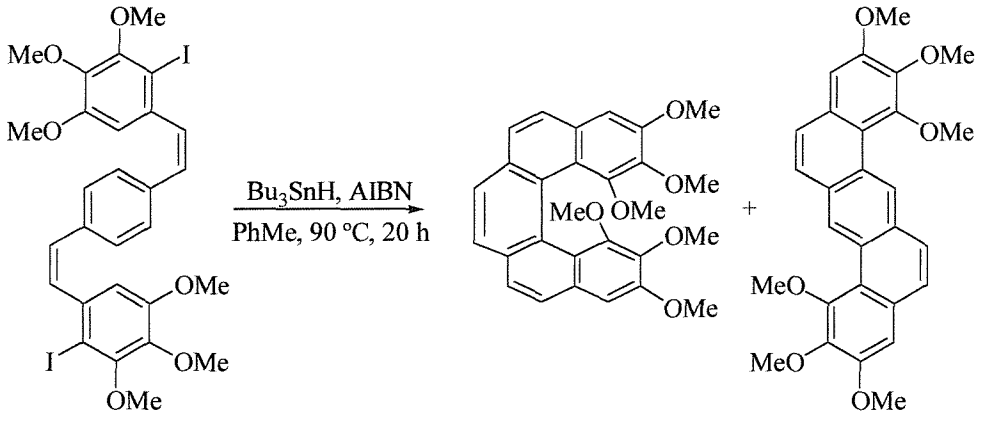
^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 9.78 (2H, s, 2 × Ar*H*), 7.76 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.43 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 6.77 (2H, d, *J* 2.5 Hz, 2 × Ar*H*), 6.65 (2H, d, *J* 2.5 Hz, 2 × Ar*H*), 4.01 (6H, s, 2 × OCH_3), 3.80 (6H, s, 2 × OCH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 160.6 (0, 2 × *C*O), 158.8 (0, 2 × *C*O), 135.9 (0, 2 × *C*), 131.5 (0, 2 × *C*), 130.5 (1, 2 × *C*H), 128.0 (0, 2 × *C*), 127.6 (1, 2 × *C*H), 127.0 (1, 2 × *C*H), 115.4 (0, 2 × *C*), 102.4 (1, 2 × *C*H), 99.5 (1, 2 × *C*H), 56.2 (3, 2 × O*C*H_3), 55.9 (3, 2 × O*C*H_3) ppm.

LRMS (M/z, EI) 398 (M$^+$, 100 %), 352 (10 %), 336 (22 %), 266 (8 %), 199 (9 %) amu.

1,2,3,12,13,14-Hexamethoxy[5]helicene **6.26** &

2,3,4,9,10,11-hexamethoxydibenzo[*a,h*]anthracene **6.27**



6.45
$C_{28}H_{28}I_2O_6$ (714)

6.26, 34%
$C_{28}H_{26}O_6$ (459)

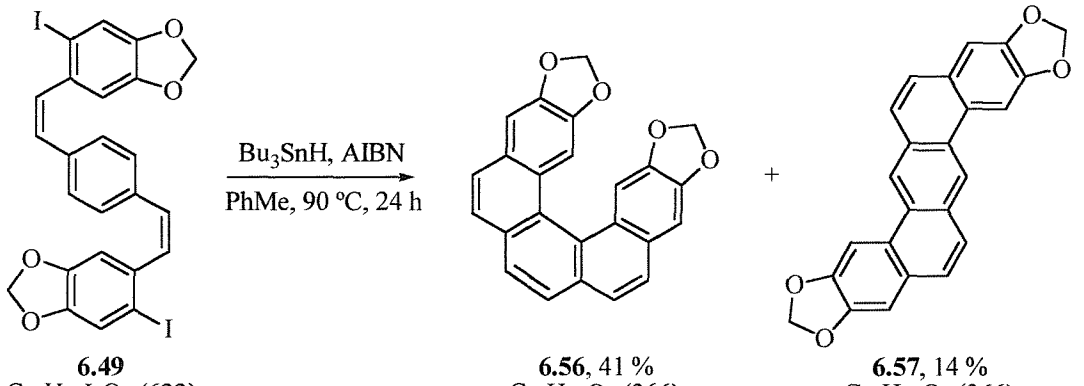
6.27, 28 %
$C_{28}H_{26}O_6$ (459)

Diiodide **6.45** (500 mg, 0.70 mmol), tributyltin hydride (450 μL, 490 mg, 1.68 mmol) and AIBN (50 mg, 0.30 mmol) were heated in toluene (20 mL) at 90 °C for 20 hours with additional portions of tributyltin hydride (200 μL, 215 mg, 0.74 mmol) and AIBN (15 mg, 0.09 mmol) added after 4 and 16 hours. After allowing the mixture to cool to room temperature, the resulting solid was collected by filtration to yield dibenzo[*a,h*]anthracene **6.27** (90 mg, 0.20 mmol, 28 %) as a pale yellow solid. The filtrate was stirred with a solution of potassium fluoride (10 % w/v, 20 mL) for 4 hours before diluting with ether (30 mL). The organic phase was washed with water (2 × 20 mL) then dried ($MgSO_4$) and concentrated *in vacuo* to yield the title [5]helicene **6.26** (110 mg, 0.24 mmol, 34 %) as an off-white solid.

The data were consistent with that reported earlier.

[1,3]Dioxolo[4',5':12,13][5]heliceno[2,3-*d*][1,3]dioxole **6.56** &

[1,3]dioxolo[4",5":6',7'naphtho[2',1':6,7]phenanthro[2,3-d][1,3]dioxole **6.57**



6.49
$C_{24}H_{16}I_2O_4$ (622)

6.56, 41 %
$C_{24}H_{14}O_4$ (366)

6.57, 14 %
$C_{24}H_{14}O_4$ (366)

Diiodide **6.49** (420 mg, 0.68 mmol), tributyltin hydride (435 μL, 470mg, 1.62 mmol) and AIBN (25 mg, 0.14 mmol) were heated in toluene (35 mL) for 24 hours with additional

tributyltin hydride (220 μL, 240 mg, 0.82 mmol) and AIBN (25 mg, 0.14 mmol) added after 8 and 16 hours. After cooling to room temperature, the resulting solid was collected by filtration to yield **6.57** (35 mg, 0.10 mmol, 14 %) as an off-white solid. The filtrate was concentrated *in vacuo* and the residue diluted with acetonitrile (60 mL), washed with petrol (3 × 30 mL) and the acetonitrile phase concentrated *in vacuo*. Purification by column chromatography (silica gel, 10 % ethyl acetate / petrol) yielded the title [5]helicene **6.56** (100 mg, 0.27 mmol, 40 %) as an off-white solid.

[1,3]Dioxolo[4',5':12,13][5]heliceno[2,3-*d*][1,3]dioxole **6.56**

MP 246 – 248 °C (EtOAc / petrol).

FT – IR (ν_{max}, neat) 2967 m, 1505 m, 1438 m, 1239 s, 1041 m cm^{-1}.

UV (λ_{max}, CH_2Cl_2) 326 (9300), 296 (23000), 267 (24000), 233 (35000) nm.

^{1}H – NMR (400 MHz, C_6D_6) δ_H 8.04 (2H, s, 2 × Ar*H*), 7.63 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 7.62 (2H, s, 2 × Ar*H*), 7.56 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 7.11 (2H, s, 2 × Ar*H*), 5.27 (2H, s, 2 × OC*H*HO), 5.17 (2H, s, 2 × OCH*H*O) ppm.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.77 – 7.73 (8H, m, 8 × Ar*H*), 7.26 (2H, s, 2 × Ar*H*), 6.12 (2H, d, *J* 1.2 Hz, 2 × OC*H*HO), 5.97 (2H, d, *J* 1.2 Hz, 2 × OCH*H*O) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 147.6 (0, 2 × *C*O), 147.1 (0, 2 × *C*O), 131.9 (0, 2 × *C*), 129.9 (0, 2 × *C*), 127.3 (0, 2 × *C*), 127.1 (1, 2 × *C*H), 127.0 (0, 2 × *C*), 126.8 (1, 2 × C*H*), 125.1 (1, 2 × *C*H), 107.2 (1, 2 × *C*H), 105.0 (1, 2 × *C*H), 101.6 (2, 2 × O*C*H_2O) ppm.

LRMS (M/z, ES+) 407 ([M+H_2O+Na]$^+$, 48 %), 323 (57 %), 294 (100 %).

[1,3]Dioxolo[4",5":6',7'naphtho[2',1':6,7]phenanthro[2,3-d][1,3]dioxole **6.57**

MP > 283 °C (toluene).

FT – IR (ν_{max}, neat) 3021 w, 2912 w, 1470 m, 1252 m, 1043 m cm^{-1}.

^{1}H – NMR (400 MHz, d_6-DMSO) δ_H 9.44 (2H, s, 2 × Ar*H*), 8.66 (2H, s, 2 × Ar*H*), 8.10 (2H, d, *J* 8.9 Hz, 2 × Ar*H*), 7.91 (2H, d, *J* 8.9 Hz, 2 × Ar*H*), 7.66 (2H, s, 2 × Ar*H*), 6.40 (4H, s, 2 ×O*C*H_2O) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 127.0 (1, 2 × *C*H), 126.0 (1, 2 × *C*H), 122.5 (1, 4 × *C*H), 106.5 (1, 2 × *C*H), 102.2 (2, 2 × O*C*H_2O) ppm.

6.57 was only sparing soluble in DMSO so that detection of quaternary carbons was not possible.

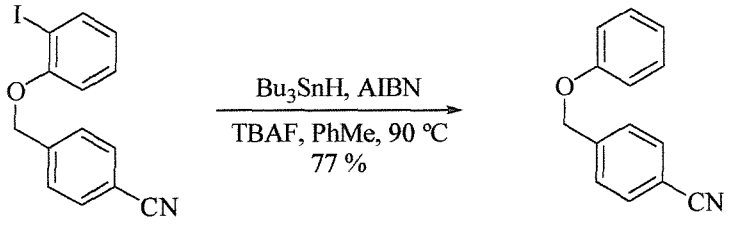
8.7 Experimental for Chapter 7

General methods for the reduction of aryl iodides or aryl bromides:

Method I: To a solution of aryl halide (1.00 mmol) in toluene (20 mL) was added tetrabutylammonium fluoride (1.1 M in tetrahydrofuran, 1.3 mL, 1.40 mmol) and tributyltin hydride (325 μL, 350 mg, 1.20 mmol). The solution was heated at 90 °C for 16 – 48 hours with additional portions of tributyltin hydride (135 μL, 145 mg, 0.50 mmol) and tetrabutylammonium fluoride (1.1 M in tetrahydrofuran, 0.5 mL, 0.60 mmol) added until reaction was complete (typically additional portions were added after 4 and 8 hours). After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue was purified by column chromatography.

Method II: To a solution of aryl halide (1.00 mmol) in tetrahydrofuran (20 mL) was added tetrabutylammonium fluoride (1.1 M in tetrahydrofuran, 1.3 mL, 1.40 mmol) and tributyltin hydride (325 μL, 350 mg, 1.20 mmol). The mixture was stirred at room temperature for 20 – 40 hours with additional portions of tributyltin hydride (135 μL, 145 mg, 0.50 mmol) and tetrabutylammonium fluoride (1.1 M in tetrahydrofuran, 0.5 mL, 0.60 mmol) added until reaction was complete (typically additional portions were added after 8 and 16 hours). The mixture was concentrated *in vacuo* and the residue was purified by column chromatography.

4-(Phenoxymethyl)benzonitrile **7.13**



2.3
$C_{14}H_{10}INO$ (335)

7.13
$C_{14}H_{11}NO$ (209)

Prepared by Method I in 77 % yield as a colourless oil.[213]

FT – IR (ν_{max}, neat) 2228 s, 1600 s, 1495, s, 1242, s, 1172, m, 1047 m cm^{-1}.

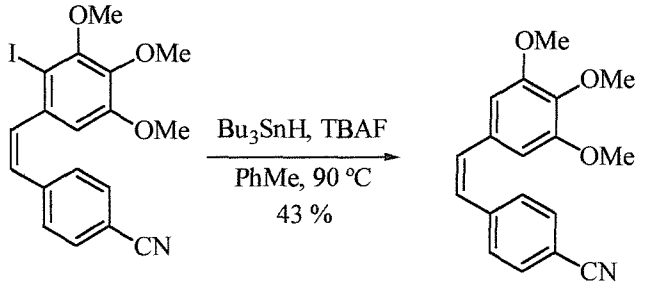
UV (λ_{max}, MeOH) 272 (2200), 228 (20000) nm.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* 7.4 Hz, 2 × Ar*H*), 7.59 (2H, d, *J* 7.4 Hz, 2 × Ar*H*), 7.30 (2H, dd, *J* 8.8, 7.7 Hz, 2 × Ar*H*), 6.99 (1H, t, *J* 7.7 Hz, Ar*H*), 6.95 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 5.16 (2H, s, OCH_2) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 158.3 (0, *C*O), 142.8 (0, *C*), 132.6 (1, 2 × *C*H), 129.8 (1, 2 × *C*H), 127.7 (1, 2 × *C*H), 121.7 (1, *C*H), 118.9 (0, *C*N), 114.9 (1, 2 × *C*H), 111.8 (0, *C*CN), 68.9 (2, O*C*H$_2$) ppm.

LRMS (M/z, CI) 227 ($[M+NH_4]^+$, 100 %), 209 (M^+, 72 %), 133 (32 %), 116 (44 %).

4-(2-(*Z*)-(3,4,5-Trimethoxyphenyl)ethenyl)benzonitrile **7.14**



5.10
$C_{18}H_{16}INO_3$ (421)

7.14
$C_{18}H_{17}NO_3$ (295)

Prepared by Method I in 43 % yield as a colourless oil.

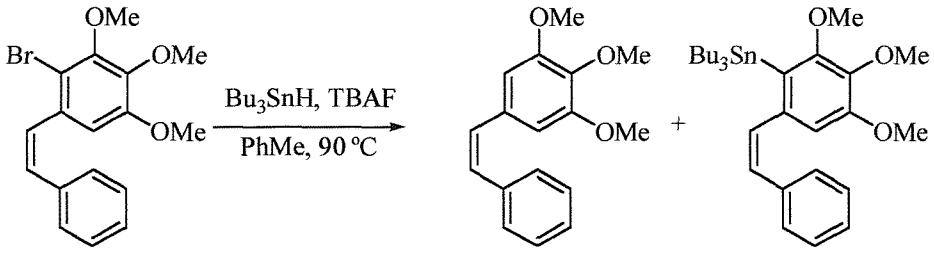
FT – IR (ν_{max}, neat) 3010 w, 2958 m, 2928 m, 2828 w, 2225 m, 1579 m, 1506 m, 1328 m, 1128 s cm^{-1}.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.53 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 7.38 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 6.67 (1H, d, *J* 12.2 Hz, C*H*=CH), 6.53 (1H, d, *J* 12.2 Hz, CH=C*H*), 6.41 (2H, s, 2 × Ar*H*), 3.85 (3H, s, OC*H*$_3$), 3.67 (6H, s, 2 × OC*H*$_3$) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 153.6 (0, 3 × *C*O), 142.7 (0, *C*), 133.5 (1, *C*H), 132.4 (1, 2 × *C*H), 131.9 (0, *C*), 130.1 (1, 2 × *C*H), 128.3 (1, *C*H), 119.3 (0, *C*N), 110.9 (0, *C*CN), 106.5 (1, 2 × *C*H), 61.4 (3, O*C*H$_3$), 56.4 (3, 2 × O*C*H$_3$) ppm.

1-(2-(*Z*)-Phenylethenyl)-3,4,5-trimethoxybenzene **5.110** &

1-(2-(*Z*)-phenylethenyl)-2-tributylstannyl-3,4,5-trimethoxybenzene **7.15**



5.39
$C_{17}H_{17}BrO_3$ (349)

5.110, 78 %
$C_{17}H_{18}O_3$ (270)

7.15, 6 %
$C_{29}H_{44}O_3Sn$ (559)

5.110 was prepared by Method I in 78 % yield as a colourless oil (data identical to that reported previously) along with **7.15** in 6 % yield as a colourless oil.

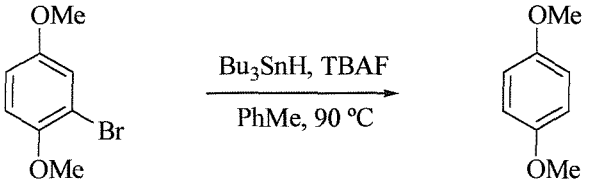
1-(2-(*Z*)-Phenylethenyl)-2-tributylstannyl-3,4,5-trimethoxybenzene **7.15**

FT – IR (ν_{max}, neat) 2954 s, 2927 s, 1548 m, 1464 m, 1306 m, 1102 s cm^{-1}.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.19 – 4.15 (5H, m, C_6H_5), 6.56 (1H, s, Ar*H*), 6.55 (1H, d, *J* 12.0 Hz, C*H*=CH), 6.49 (1H, d, *J* 12.0 Hz, CH=C*H*), 3.88 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.52 (3H, s, OCH_3), 1.57 – 1.42 (6H, m, 3 × CH_2), 1.38 – 1.24 (6H, m, 3 × CH_2), 1.08 – 1.02 (6H, m, 3 × CH_2), 0.86 (9H, t, *J* 7.3 Hz, 3 × CH_3) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 157.3 (0, *C*O), 155.7 (0, *C*O), 149.8 (0, *C*O), 140.8 (0, *C*), 137.4 (0, *C*), 133.5 (1, *C*H), 130.0 (1, *C*H), 129.8 (0, *C*), 129.6 (1, 2 × *C*H), 128.4 (1, 2 × *C*H), 127.3 (1, *C*H), 109.7 (1, *C*H), 61.1 (3, OCH_3), 61.0 (3, OCH_3), 56.1 (3, OCH_3), 29.6 (2, 3 × CH_2), 27.8 (2, 3 × CH_2), 14.1 (3, 3 × CH_3), 12.1 (2, 3 × CH_2) ppm.

1,4-Dimethoxybenzene **7.22**



7.21
$C_8H_9BrO_2$ (217)

7.22
$C_8H_{10}O_2$ (138)

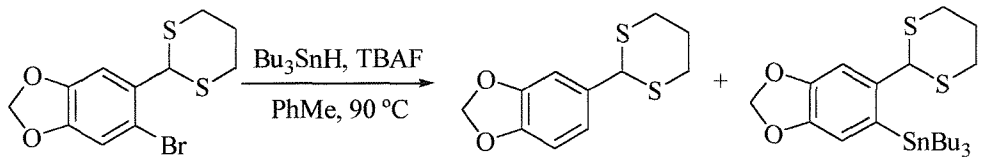
Prepared by Method I in 65 % yield as a white solid.[214-216]

MP 51 – 52 °C (petrol / ether) lit. 57 – 58 °C (benzene).[214]

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 6.82 (4H, s, 4 × Ar*H*), 3.78 (6H, s, 2 × OC*H*$_3$) ppm.

5-([1,3]Dithian-2-yl)benzo[1,3]dioxole **7.24** &

6-([1,3]dithian-2-yl)-5-tributylstannylbenzo[1,3]dioxole **7.25**



7.23
$C_{11}H_{11}BrO_2S_2$ (319)

7.24, 81 %
$C_{11}H_{12}O_2S_2$ (240)

7.25, 9 %
$C_{23}H_{38}O_2S_2Sn$ (529)

7.24 was prepared by Method I in 81 % yield as a white solid along with **7.25** in 9 % yield as a colourless oil.

5-([1,3]Dithian-2-yl)benzo[1,3]dioxole **7.24**[217]

MP 82 – 83 °C (petrol / ether) lit. 85 – 86 °C (no solvent stated).[217]

FT – IR (ν_{max}, neat) 2937 w, 2889 m, 1501 s, 1488 s, 1441 m, 1250 s, 1038 s, cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 6.99 (1H, d, *J* 1.8 Hz, Ar*H*), 6.94 (1H, dd, *J* 7.7, 1.8 Hz, Ar*H*), 6.76 (1H, d, *J* 7.7 Hz, Ar*H*), 5.96 (2H, s, OC*H*$_2$O), 5.12 (1H, s, SC*H*S), 3.04 (2H, ddd, *J* 14.3, 12.7, 2.6 Hz, 2 × SC*H*H), 2.90 (2H, ddd, *J* 14.3, 4.4, 3.3 Hz, 2 × SCH*H*), 2.16 (1H, dtt, *J* 14.1, 4.1, 2.2 Hz, SCH$_2$C*H*HCH$_2$S), 1.90 (1H, dtt, *J* 14.1, 12.1, 3.3 Hz, SCH$_2$CH*H*CH$_2$S) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 147.9 (0, *C*O), 147.8 (0, *C*O), 133.1 (0, *C*), 121.4 (1, *C*H), 108.5 (1, 2 × *C*H), 101.4 (2, O*C*H$_2$O), 51.3 (1, S*C*HS), 32.3 (2, 2 × S*C*H$_2$), 25.2 (2, *C*H$_2$) ppm.

6-([1,3]Dithian-2-yl)-5-tributylstannylbenzo[1,3]dioxole **7.25**

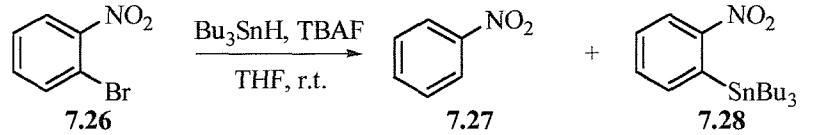
FT – IR (ν_{max}, neat) 2955 s, 2924 s, 1510 m, 1472 s, 1265 m, 1216 m, 1014 m cm^{-1}.

^{1}H – NMR (400 MHz, $CDCl_3$) δ_H 7.21 (1H, s, Ar*H*), 6.82 (1H, s, Ar*H*), 5.94 (2H, s, OC*H*$_2$O), 4.93 (1H, s, SC*H*S), 2.99 (2H, ddd, *J* 14.6, 12.3, 2.5 Hz, 2 × SC*H*H), 2.92 (2H, dt, *J* 14.5, 3.8 Hz, 2 × SCH*H*), 2.17 (1H, dtt, *J* 14.3, 4.0, 2.5 Hz, SCH$_2$C*H*HCH$_2$S), 1.93 (1H, dtt, *J* 14.3, 12.0, 3.5 Hz, SCH$_2$CH*H*CH$_2$S), 1.62 – 1.53 (6H, m, 3 × C*H*$_2$), 1.36 (6H, app. sext., *J* 7.3 Hz, 3 × C*H*$_2$), 1.16 – 1.11 (6H, m, 3 × C*H*$_2$), 0.92 (9H, t, *J* 7.3 Hz, 3 × C*H*$_3$) ppm.

^{13}C – NMR (100 MHz, $CDCl_3$) δ_C 148.9 (0, *C*O), 147.8 (0, *C*O), 139.9 (0, *C*), 134.4 (0, *C*), 115.3 (1, *C*H), 109.5 (1, *C*H), 101.3 (2, O*C*H$_2$O), 55.5 (1, S*C*HS), 32.9 (2,

2 × SCH_2), 29.5 (2, 3 × CH_2), 27.8 (2, 3 × CH_2), 25.4 (2, $SCH_2CH_2CH_2S$), 12.7 (3, 3 × CH_3), 11.0 (2, 3 × CH_2) ppm.

Nitrobenzene **7.27** & (2-nitrophenyl)tributylstannane **7.28**



7.26 $C_6H_4BrNO_2$ (202) | **7.27** $C_6H_5NO_2$ (123) | **7.28** $C_{18}H_{31}NO_2Sn$ (412)

7.27 was prepared by Method II in 37 % yield as a yellow oil along with **7.28** in 19 % yield as a colourless oil.

Nitrobenzene **7.27**[218]

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.24 (2H, dd, *J* 8.7, 1.2 Hz, 2 × Ar*H*), 7.72 (1H, br. t, *J* 8.7 Hz, Ar*H*), 7.56 (2H, t, *J* 8.5 Hz, 2 × Ar*H*) ppm.

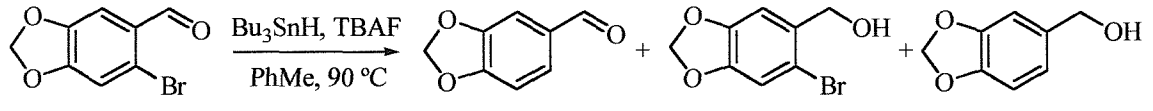
(2-Nitrophenyl)tributylstannane **7.28**

FT – IR (ν_{max}, neat) 2955 s, 2922 s, 2841 m,1522 s, 1453 m, 1339 m cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.32 (1H, d, *J* 7.8 Hz, Ar*H*), 7.66 (1H, td, *J* 7.8, 1.8 Hz, Ar*H*), 7.62 (1H, d, *J* 7.8 Hz, Ar*H*), 7.51 (1H, td, *J* 7.8, 1.8 Hz, Ar*H*), 1.58 – 1.45 (6H, m, 3 × CH_2), 1.33 (6H, app. sext. *J* 7.4 Hz, 3 × CH_2), 1.17 – 1.10 (6H, m, 3 × CH_2), 0.89 (9H, t, *J* 7.4 Hz, 3 × CH_3) ppm.

^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 140.3 (0, *C*), 137.8 (1, *C*H), 133.6 (1, *C*H), 133.6 (0, *C*), 129.3 (1, *C*H), 124.2 (1, *C*H), 29.2 (2, 3 × CH_2), 27.5 (2, 3 × CH_2), 13.8 (3, 3 × CH_3), 11.1 (2, 3 × CH_2) ppm.

Benzo[1,3]dioxole-5-carbaldehyde **7.30**, (6-bromobenzo[1,3]dioxol-5-yl)methanol **7.31** & (benzo[1,3]dioxol-5-yl)methanol **4.2**



7.29 $C_8H_5BrO_3$ (229) | **7.30**, 25 % $C_8H_6O_3$ (150) | **7.31**, 17 % $C_8H_7BrO_3$ (231) | **4.2**, 55 % $C_8H_8O_3$ (152)

4.2 was prepared by Method I in 55 % yield as an off-white solid along with **7.30** in 25 % yield as a white solid and **7.31** in 17 % yield as a white solid.

Benzo[1,3]dioxole-5-carbaldehyde **7.30**[219]

FT – IR (ν_{max}, neat) 2954 m, 2911 m, 1688 s, 1603 m, 1448 s, 1262 s, 1098 m, 1038 s cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 9.81 (1H, s, C*H*O), 7.42 (1H, dd, *J* 7.8, 1.6 Hz, Ar*H*), 7.34 (1H, d, *J* 1.6 Hz, Ar*H*), 6.93 (1H, d, *J* 7.8 Hz, Ar*H*), 6.08 (2H, s, OCH_2O) ppm.

6-Bromobenzo[1,3]dioxol-5-yl)methanol **7.31**[220]

FT – IR (ν_{max}, neat) 3418 br. w, 2967 w, 2898 m, 1501 m, 1480 s, 1242 s, 1039 s cm^{-1}.

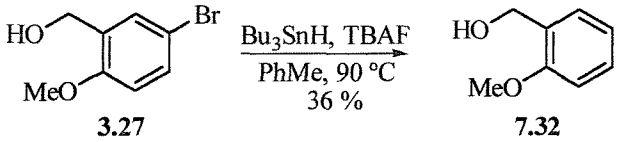
^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.01 (1H, s, Ar*H*), 6.98 (1H, s, Ar*H*), 5.99 (2H, s, OCH_2O), 4.65 (2H, d, *J* 6.4 Hz, CH_2OH), 1.97 (1H, t, *J* 6.4 Hz, O*H*) ppm.

(Benzo[1,3]dioxol-5-yl)methanol **4.2**[221]

FT – IR (ν_{max}, neat) 3384 br. m, 2957 m, 2863 m, 1490 m, 1443 m, 1248 s, 1040 m cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 6.88 (1H, s, Ar*H*), 6.82 (1H, d, *J* 8.0 Hz, Ar*H*), 6.78 (1H, d, *J* 8.0 Hz, Ar*H*), 5.95 (2H, s, OCH_2O), 4.58 (2H, s, CH_2OH), 2.40 (1H, br. s, O*H*) ppm.

2-Methoxybenzyl alcohol **7.32**



3.27
$C_8H_9BrO_2$ (217)

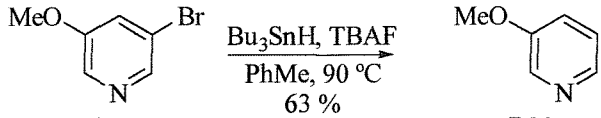
7.32
$C_8H_{10}O_2$ (138)

7.32 was prepared by Method I in 36 % yield as a colourless oil (46 % starting material **3.27** was recovered).[222]

FT – IR (ν_{max}, neat) 3379 br. m, 2932 w, 2836 w, 1602 m, 1492 s, 1463 m, 1242 s, 1030 m cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 7.35 – 7.30 (2H, m, 2 × Ar*H*), 7.00 (1H, td, *J* 7.5, 0.6 Hz, Ar*H*), 6.94 (1H, d, *J* 8.5 Hz, Ar*H*), 4.74 (2H, d, *J* 6.4 Hz, CH_2OH), 3.92 (3H, s, OCH_3), 2.39 (1H, t, *J* 6.4 Hz, O*H*) ppm.

3-Methoxypyridine **7.33**



4.8
C_6H_6BrNO (188)

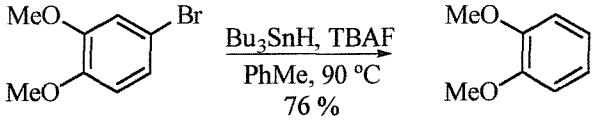
7.33
C_6H_7NO (109)

7.33 was prepared by Method I in 63 % yield as a colourless oil.

FT – IR (ν_{max}, neat) 2958 m, 2928 m, 1739 m, 1574 m, 1479 m,1425 m, 1283 s, 1231 m cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 8.33 (1H, dd, *J* 2.5, 0.8 Hz, Ar*H*), 8.23 (1H, dd, *J* 4.0, 1.9 Hz, Ar*H*), 7.23 – 7.19 (2H, m, 2 × Ar*H*) 3.86 (3H, s, OCH_3) ppm.

1,2-Dimethoxybenzene **7.35**



7.34
$C_8H_9BrO_2$ (217)

7.35
$C_8H_{10}O_2$ (138)

7.35 was prepared by Method I in 76 % yield as a colourless oil.[223]

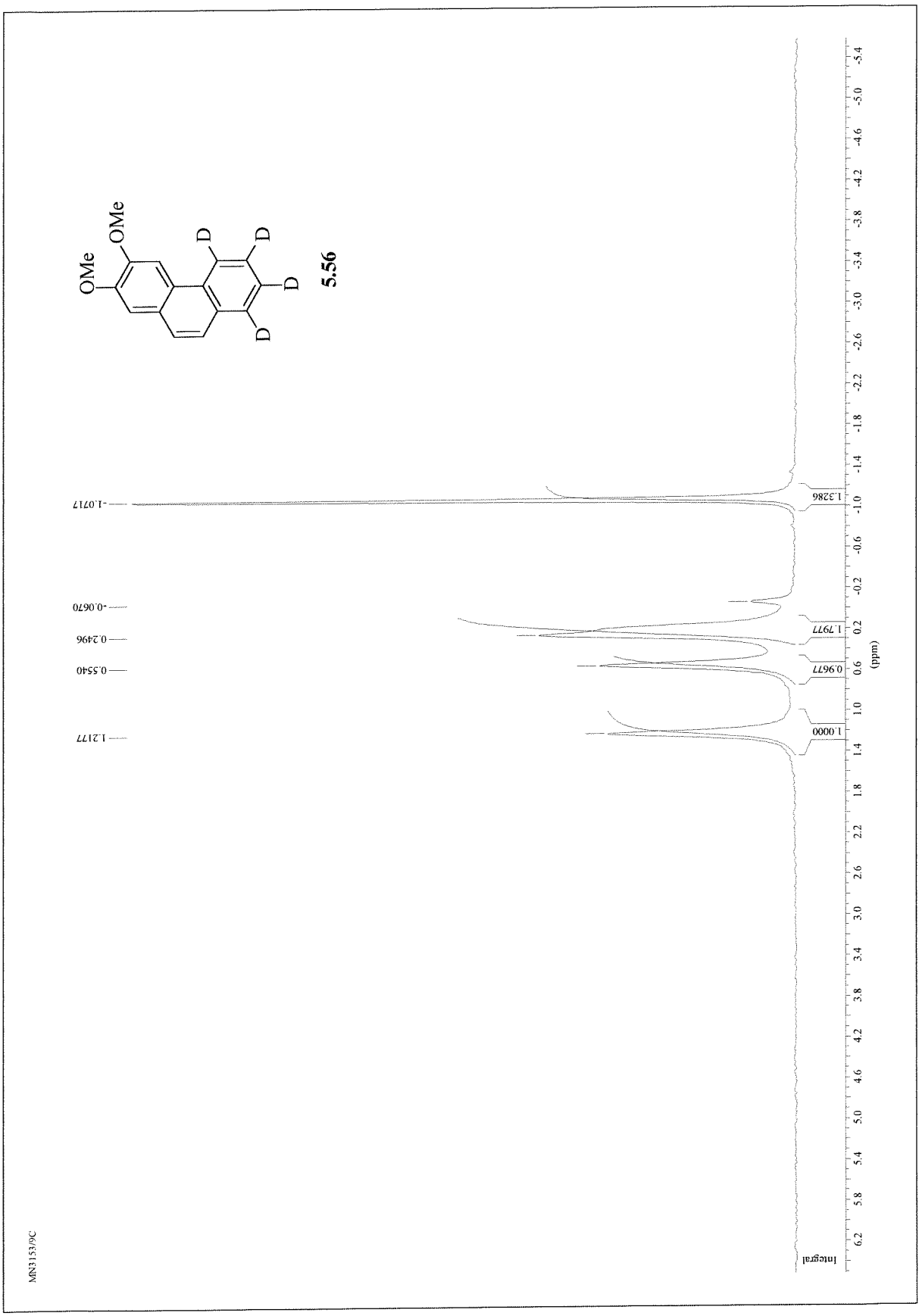
FT – IR (ν_{max}, neat) 2950 m, 2922 w, 2832 w, 1506 s, 1463 m, 1254 s, 1230 m, 1176 m, 1123 m, 1028 m cm^{-1}.

^{1}H – NMR (300 MHz, $CDCl_3$) δ_H 6.92 – 6.80 (4H, m, 4 ×Ar*H*), 3.92 (6H, s, 2 × OCH_3) ppm.

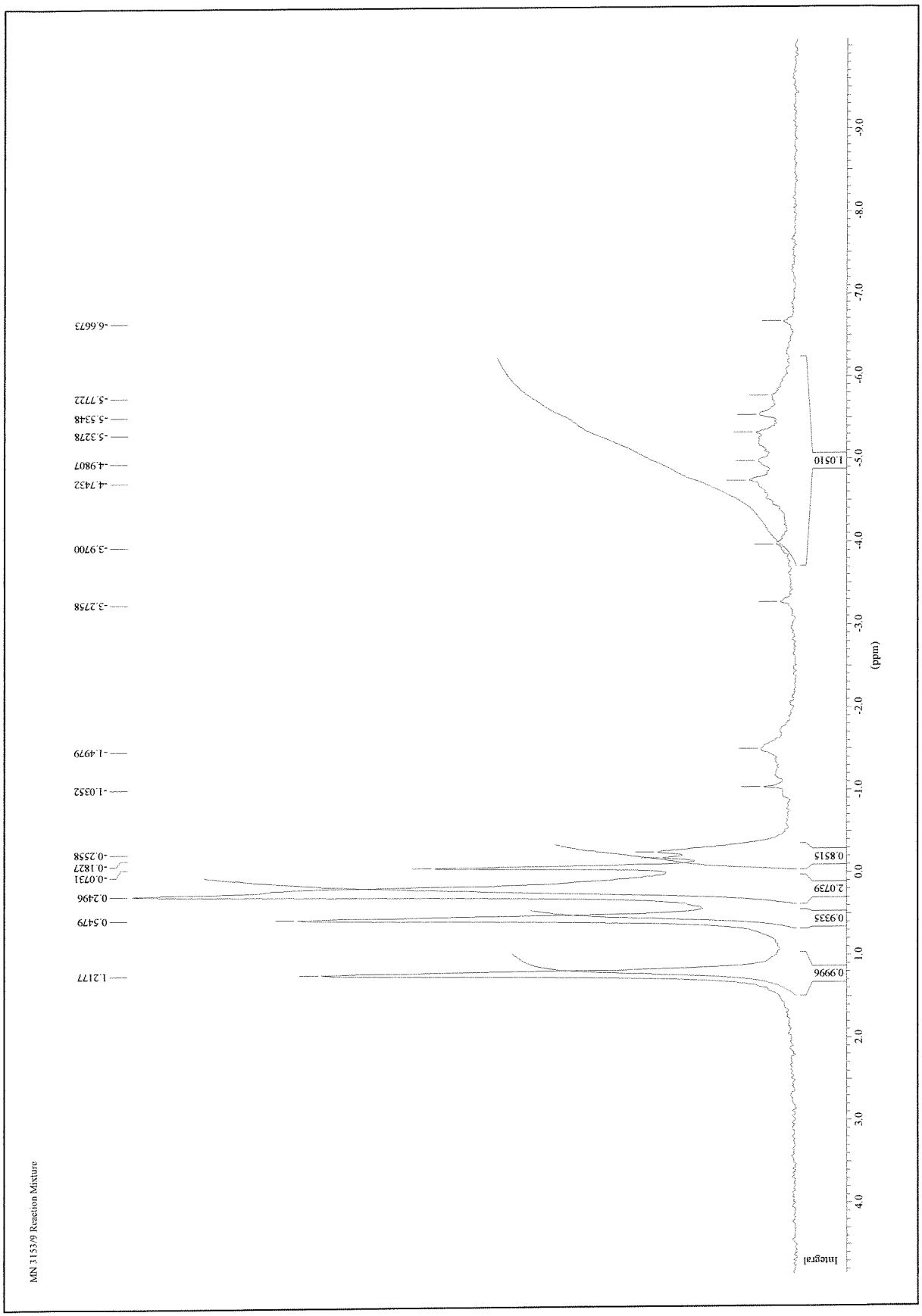
^{13}C – NMR (75 MHz, $CDCl_3$) δ_C 149.1 (2 × *C*O), 121.0 (1, 2 × *C*H), 111.4 (1, 2 × *C*H), 55.9 (3, 2 × OCH_3) ppm.

Appendix

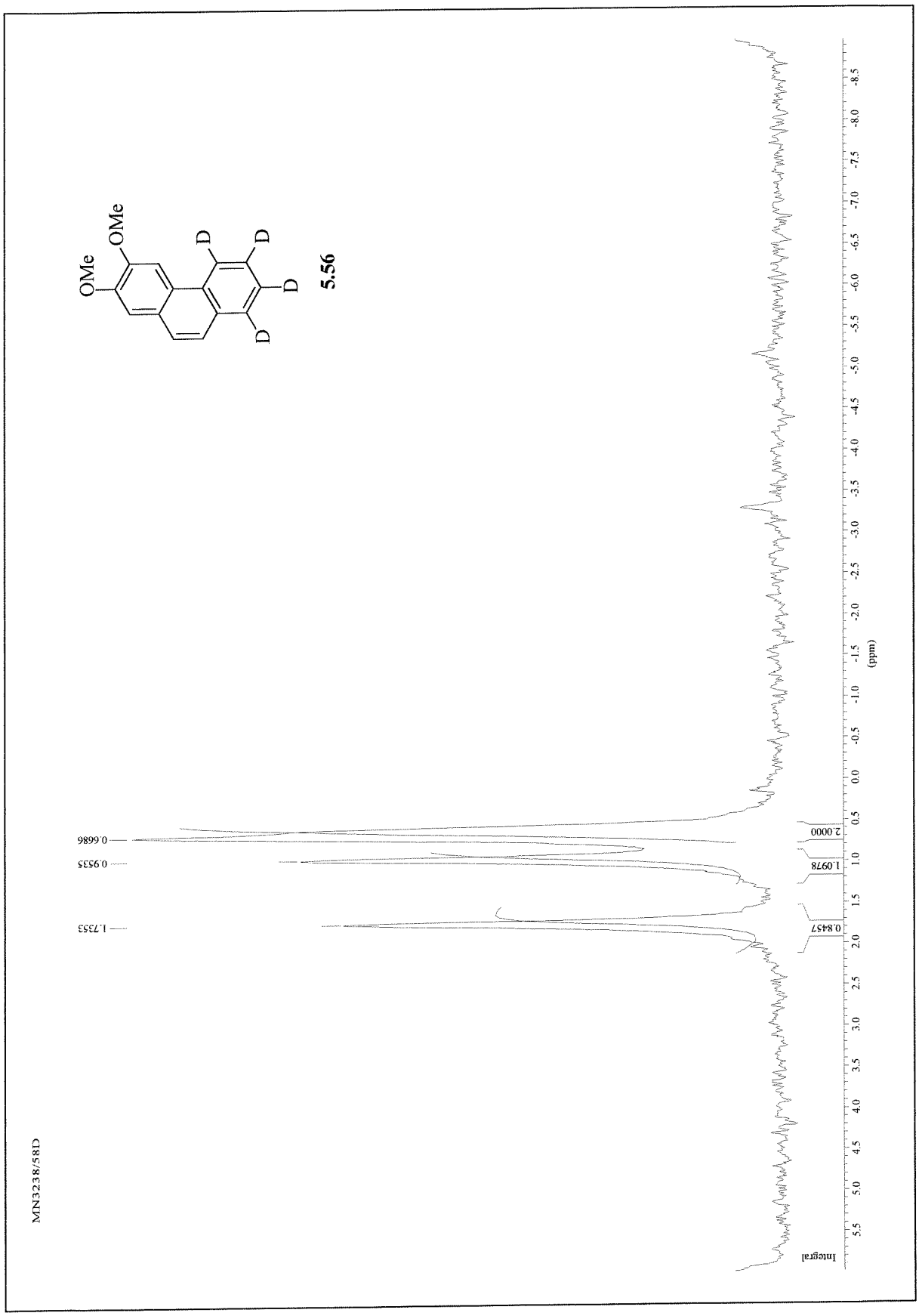
I. ^{2}H – NMR of Phenanthrene 5.56 in Benzene



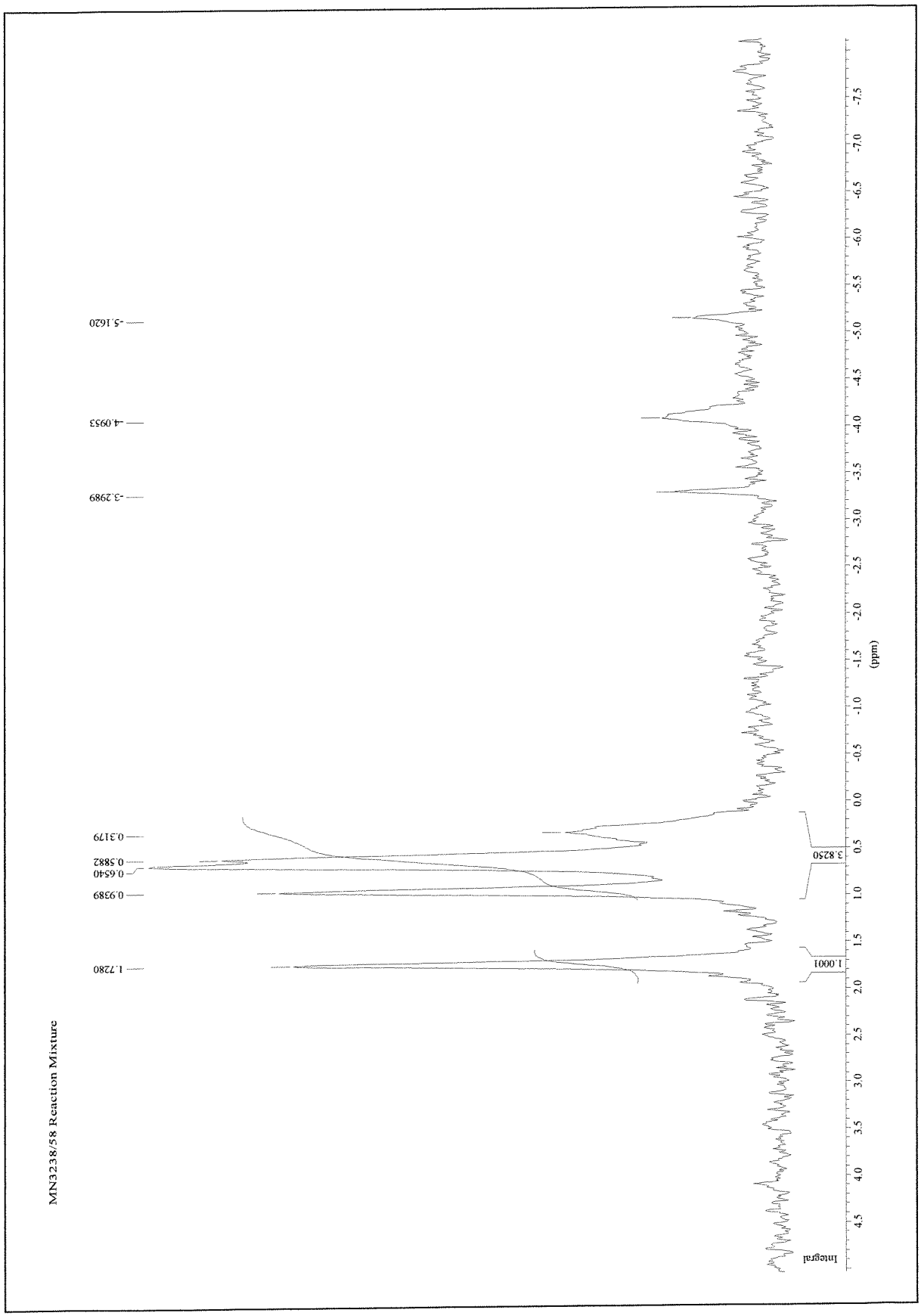
II. ^{2}H – NMR of Benzene Reaction Mixture



III. ^{2}H – NMR of Phenanthrene 5.56 in Tetrahydrofuran



IV. ^{2}H – NMR of Tetrahydrofuran Reaction Mixture



V. X – Ray Data for 1,2,3,12,13,14-hexamethoxy[5]helicene 6.26

EPSRC National Crystallography Service

Data Collection Summary

Summary report for Directory: diska/02srf004

Report generated Mar 05, 2002; 13:54:22

Unit cell

8514 reflections with 2.91°<theta<27.48° (resolution between 7.00A and 0.77A) were used for unit cell refinement

Symmetry used in scalepack	p1
a (Angstrom)	8.5741 +/- 0.0002
b (Angstrom)	9.6294 +/- 0.0003
c (Angstrom)	14.5220 +/- 0.0005
alpha (°)	84.6497 +/- 0.0009
beta (°)	78.5435 +/- 0.0010
gamma (°)	74.219 +/- 0.002
Volume (A3)**	1129.83 +/- 0.06
Mosaicity (°)	0.449 +/- 0.002

Data collection

Summary

Total number of images collected	204
Total exposure time	67.4 minutes
Data collection exposure time	66.1 minutes
Data collection wall-clock time	93.6 minutes

Experimental Conditions

Wavelength	0.71073 A
Generator setting	50kV 75mA
Crystal to detector distance	30.00 mm

Scans

Type	Name	# images	Total Rotation	Per frame Rotation	Exposure per frame	Used in scaling
data collection	s01f	179	358.0° phi	2.000°	20 seconds	Yes
data collection	s02f	17	34.0° omega	2.000°	20 seconds	Yes
Phi/Chi	i01f - i08f	8			10 seconds	

Scalepack Scaling

Deleted observations

Overload or incomplete profile	290
Sigma cutoff	16
High resolution limit	25

Final Data Set

Scale factor	10.00
Number of 'full' reflections	2844
Number of 'partial' reflections	18822
Total number of integrated reflections	15354
Total number of unique reflections	5003
Data completeness	97.2%
Resolution range	7.00-0.77 A
Theta range	2.91°-27.48°
Average Intensity	72.1
Average Sigma(I)	3.9
Overall R-merge (linear)	0.089

Crystal Information

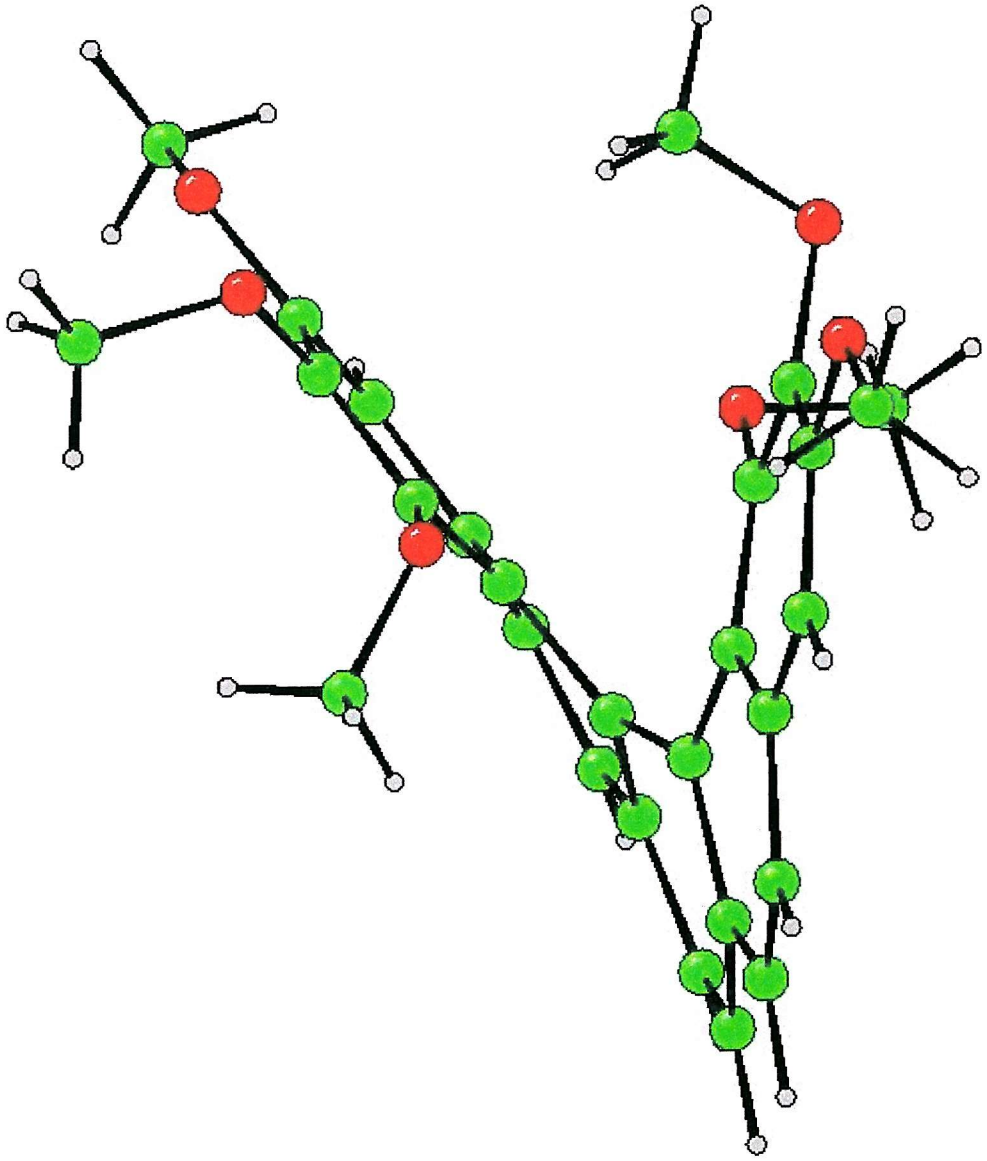
Collection Temperature	120 K
Crystal Size	x x
Crystal Colour	
Crystal Shape	

SORTAV Absorption correction

Max Transmission Factor	1.05091
Min Transmission Factor	0.90066

N.B. The scaling summary is redundant as outliers are treated during the absorption correction using SORTAV. The quoted data completeness is for the stated resolution ranges, and the Overall R-merge is that before the absorption correction. The SORTAV transmission factors are based on a crude approximation and the expected formula (not always correct!). For more information visit the service web site at: http://www.soton.ac.uk/~xservice/

X – Ray Data for 1,2,3,12,13,14-hexamethoxy[5]helicene 6.26



Chapter 9 – List of References

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