UNIVERSITY OF SOUTHAMPTON

Changing the Course of Radical Reactions Through Solid Phase Immobilisation:

Radical Reactions in Solution and on Solid Phase

BY

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A Thesis submitted for the degree of Doctor of Philosophy

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ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

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The work described in this thesis concerns our attempts to exploit a dichotomy between solid and solution phase reaction kinetics to develop new and useful radical cyclisation strategies. The thesis begins with a review of radical reactions conducted on solid supported substrates. 2-Bromostilbenes were subjected to tributyltin-mediated radical forming conditions with cyclisation occurring via 6-*exo/endo*-trig pathway to give the corresponding phenanthrenes in good yield. Similar reactions on solid phase showed that the desired phenanthrene was the *minor* product of the reaction - the *major* component being the *trans*-stilbene.

2-iodostilbenes are known to give poor results with a mixture of dihydrophenanthrene and direct reduction products present. When the PS-Wang immobilised analogue was subjected to the same reaction and then cleaved into solution with 95% TFA, we noted that the yield of dihydrophenanthrene was greatly improved and that no products derived from the direct reduction. Instead, another radical intermediate – a biaryl, was present as the *minor* component. Related examples and extensions will be discussed. Methods used to analyse our supported substrates will also be highlighted, together with new solid phase cyclisation results of stilbenes where there is at least one halo substituent on both rings.

Table Of Contents

Preface

The research described in this thesis was carried out under the supervision of Dr. David C. Harrowven and Prof. Mark Bradley at the University of Southampton between October 2001 and October 2004. No part of this thesis has previously been submitted for a degree.

Acknowledgements

A big thanks to Dr. David Harrowven who gave me the opportunity to explore the incredible world of organic chemistry. Thank you for the advice, encouragement, optimism during these years and a significant amount of proofreading. Also many thanks for the Christmas dinners!

I also want to thank Prof. Richard Whitby and Prof. Mark Bradley for their input and ideas.

Thanks to all the members of the Harrowven group, past and present, especially Stuart Flanagan, Michael Nunn and Peter May during the first year, for their advice and funny times in the lab.

Thanks to Finnish Chemical Societies and University of Southampton for conference funding.

Thanks to Dr. John Langley and Julie Herniman for the good MS service and Joan Street and Dr. Neil Wells for the NMR services.

Special thanks to Vicki and Sally for proofreading, and many thanks also to Thomas and Leo.

Particularly, I want to thank my blessed mother for supporting me in everything I have done so far. I thank my father for guidance, you always had advice when I needed it. Thanks to Anneli for staying strong!

Thanks to my friends, you have made these times happy, exciting and interesting, without you life could be boring. Femke, Alfons, Maurice thank you for the nice times spent together in Holland and elsewhere. Maurice, thanks for fixing my computer, which has been dying for all these years but still is alive.

Thanks to Adam for good squash matches, and Mat for the tennis. James, thanks for the great walking trips. Thanks to everybody at church and in both homegroups, it was good to get to know you all and share the good news. James, Helen, Kevin, thanks for the interesting discussions and for being a good friend. Warmest thanks to Eila Huotari, whose handling of matters during winter 2003-2004 made things a lot easier. Thanks also to Ritva Snellman in this regard.

Matti, Ville, Isabel, Femke, Alfons, Mika, Maurice, Cory, thanks for being such good friends for so many years despite the distance.

Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
amu	atomic mass units
approx.	approximately
aq.	aqueous
Ar	aryl
Bn	benzyl
br.	broad
Bu	*n*-butyl
Celite	Celite 521
CHN	combustion analysis
CI	chemical ionisation
conc.	concentrated
d	doublet
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DHP	3,4-dihydro-2*H*-pyran
DIAD	diisopropyl azodicarboxylate
DIEA	*N, N*-diisopropylethylamine
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine

DMF	*N,N*-dimethylformamide
DMSO	dimethylsufoxide
EI	electron ionisation
eq.	equivalents
ES	electrospray
Et	ethyl
ether	diethyl ether
FT	Fourier transform
GC	gas chromatography
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
hv	visible and ultraviolet radiation
Hz	hertz
IR	infrared
lit.	literature
LRMS	low resolution mass spectrometry
m	medium, multiplet
m	*meta*
M	mol dm^{-3}
Me	methyl
min.	minute(s)

Mol. Wt.	molecular weight
mp	melting point
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
petrol	petroleum ether (40/60)
Ph	phenyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
q	quartet
r.t.	room temperature
s	strong, singlet
sat.	saturated
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl
tol	toluene
Ts	*p*-toluenesulfonyl
UV	ultraviolet
w	weak

1 The Development of Radical Chemistry on the Solid Phase

1 The Development of Radical Chemistry on the Solid Phase

1.1. Introduction

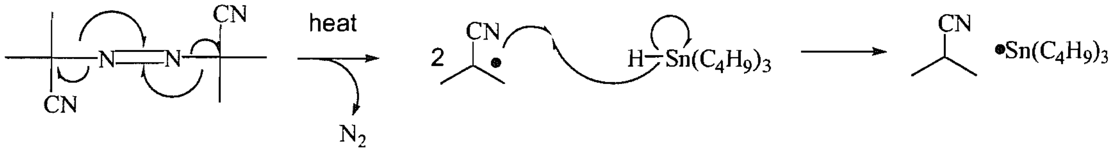
Organic synthesis is dominated by polar chemical reactions, where an electron-rich centre reacts with an electron-deficient centre. Homolytic processes involving organic radicals have been exploited to a lesser extent, having long been perceived to be unruly processes of little synthetic value. This attitude has changed in recent years. A better understanding of the kinetics of radical reactions has inspired the development of many new and useful synthetic procedures that have been exploited by synthetic chemists interested in the construction of complex molecules, including natural products. Indeed, radical reactions are now considered mainstream, providing powerful and versatile methods for the construction of mono- and polycyclic systems and often offering significant advantages over two-electron processes. Despite their high reactivity, radical reactions proceed under mild conditions, avoiding strongly acidic or basic reagents. The absence of bulky counterions or solvation spheres also permits the generation of bonds between sterically crowded centres.

Reactions conducted on immobilised substrates benefit from, amongst other things, a simplification of both purification and work-up procedures and the use of excess reagents to drive reactions to completion. The past decade has witnessed unparalleled growth in the use and applications of combinatorial chemistry. Solid phase library synthesis has been central to much of this development as it offers a means of generating large numbers of compounds within a short time-frame. Reactions that have been studied extensively on solid support include amide synthesis, aromatic substitution, cross-coupling and condensation reactions, cycloadditions, Grignard reactions, Michael additions, olefinations, oxidations and reductions. By contrast, radical chemistry has attracted only limited attention. The chapter overviews those transformations reported to date together with a brief summary of the methods used to analyse supported substrates.

We wondered if it might also be possible to exploit differences in the kinetics of solution phase and solid phase reactions. In particular, bimolecular reactions involving an immobilised substrate generally proceed more slowly than analogous solution phase reactions, a phenomenon attributed to a slowdown in the rate of diffusion of a reagent when it is encapsulated within the solid support. By contrast, unimolecular reactions conducted on a supported substrate ought to display similar reaction kinetics to analogous reactions conducted in solution. [1-3] Our aim was to exploit that dichotomy between solid and solution phase kinetics, reasoning that comparatively slow intramolecular radical reactions would be more efficient with immobilised substrates as they would be less likely to give intermolecular side reactions such as premature hydrogen atom abstraction from tributyltin hydride. [4]

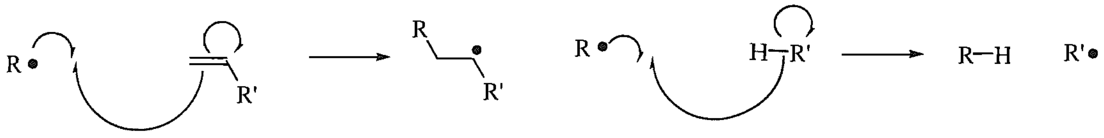
1.2. Background to Radical Reactions

Radical chain reactions are comprised of three basic steps: initiation, propagation and termination. The first of these is usually achieved by thermal or photochemical decomposition of an initiator such as azobisisobutyronitrile (AIBN) or dibenzoyl peroxide (DBP). For AIBN the extrusion of nitrogen provides a driving force for C-N bond homolysis leading to the creation of radical intermediates. Once a radical reaction has been initiated it must next be propagated. Usually this requires a mediator such as tributyltin hydride. This reagent readily donates a hydrogen atom to a carbon centred radical intermediate producing tributyltin radical (Scheme 1).



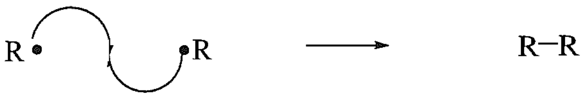
Scheme 1

In turn, tributyltin radical can interact with organic halides to produce tributylin halide and a carbon centred radical intermediate. The latter can react further with radical acceptors or be quenched by hydrogen atom abstraction from tributyltin hydride to complete the chain reaction (Scheme 2).



Scheme 2

The rates of these competing processes dictate the ratio of the products formed for any given reaction. Termination steps, leading to the loss of radical intermediates from the system (*e.g.* Scheme 3), also compete with propagation adding a further complication.



Scheme 3

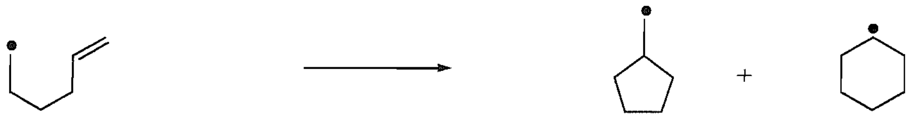
From a practical point of view, there are a number of issues to consider when conducting radical chain reactions. If the concentration of radical intermediates is too high, termination steps become significant leading to the production of unwanted side products. However, if the concentration of radical intermediates is too low, reaction times are increased and premature quenching of radicals by the solvent or impurities can lead to reduced yields.

1.3. Radical Cyclisation Reactions

In order to achieve synthetically useful radical cyclisation reactions, some basic requirements have to be fulfilled. Firstly, each of the reaction steps must be faster than unwanted side reactions, such as H-atom abstraction from the solvent or radical recombination. Secondly, the rate of ring closure of a radical intermediate must be faster than its reaction with the mediator. The regiochemistry of a radical cyclisation reaction is also important. Often, two competing pathways are possible. For example, a radical intermediate may add to either atom in a multiple bond leading to *endo* or *exo* cyclisation. For butenyl and pentenyl radicals the *endo*-cyclisation mode is strongly disfavoured (Baldwin's rules). 3- and 4-*exo* cyclisations are possible though of limited value in synthesis. This is due to ring strain, which slows of the rate of cyclisation and makes the reverse reaction more favourable. Indeed, the equilibrium usually favours the acyclic radical intermediate. The formation of cyclobutanes by 4-*exo* cyclisation of a pentenyl radical is slower than the formation of cyclopropanes by 3-*exo* cyclisation of a butenyl radical. It too is a reversible process (Scheme 4). [5]

Scheme 4

Formation of 5- and 6-membered rings represent the most useful class of radical reactions because they are generally exothermic and irreversible. For the parent 5-hexenyl radical, cyclisation proceeds to give a 98:2 ratio of products in favour of the 5-membered ring over the 6-membered ring (Scheme 5). [6,7]



Scheme 5

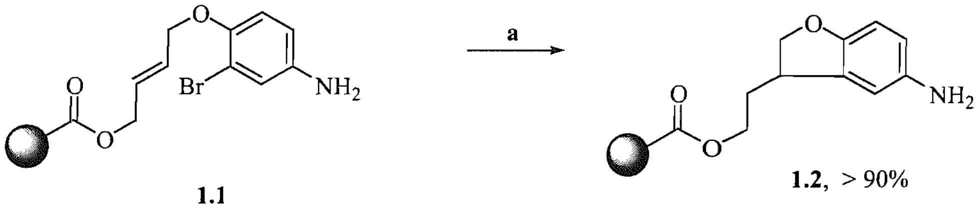
Formation of the thermodynamically disfavoured product (5-*exo*) from 5-hexenyl radical is best explained by inspecting the chair like transition state leading to both products (Scheme 6). The 5-*exo* arrangement reflects the favourable overlap between the SOMO of the radical and the LUMO of the alkene. The corresponding 6-*endo* transition state is energetically less favourable because of poorer overlap of the orbitals leading to ring strain. 6-Heptenyl radicals also prefer 6-*exo* cyclisation over 7-*endo* cyclisation, though the reaction is about 40 times slower than the corresponding 5-*exo*-trig cyclisation.

Scheme 6

Although hexenyl and heptenyl radicals prefer *exo* ring closure, the regioselectivity can be reversed by the character of the radical intermediate (alkyl, vinyl, aryl), the nature of the radical acceptor (*e.g.* double or triple bond) and the tether linking the radical intermediate to the radical acceptor.

1.4. Intramolecular Radical Cyclisations Carried Out on Solid Phase

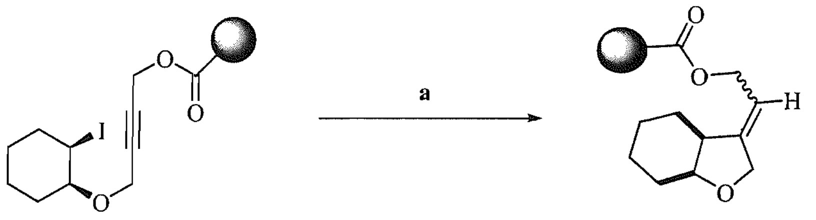
In recent years, the potential of radical reactions for combinatorial purposes has become apparent. Solid phase synthesis was born with the pioneering work of Bruce Merrifield, who developed the rapid production of peptides built up one amino acid at a time. [8] The first example of a radical induced carbon-carbon bond formation on a substrate immobilised on the solid phase was reported in 1997 by Balasubramanian and involved the reaction of an aryl radical with a double bond to form a dihydrobenzofuran ring (Scheme 7). [9]



a. Bu$_3$SnH, *t*-BuOH, AIBN, toluene, 70-80 °C.

Scheme 7

The radical was generated from the corresponding aryl halide **1.1** by tributyltin hydride and AIBN. The reaction was successful, with greater than 90% conversion to the expected 5-*exo*-trig cyclised product **1.2,** with no uncyclised product detected. The latter point is of great importance, since other workers have shown that uncyclised material can be a significant side product in analogous solution phase reactions when high concentrations of tributyltin hydride are employed. Beckwith *et al.* [6] showed that the cyclisation of an alkyl radical to a triple bond (5-*exo*-dig), is four times slower than the corresponding cyclisation of an aryl radical to a double bond. These slower cyclisation modes have a greater tendency to form byproducts when employing high concentrations of tributyltin hydride. [10] Nonetheless, cyclisations of **1.3**, and several related substrates, were blessed with success giving the (*E*)- and (*Z*)-alkylidene tetrahydrofuran rings **1.4**, reactions typically going to completion in two hours with no reduced material or byproducts observed (Scheme 8). Notably, the analogous reactions performed in solution resulted in a mixture of the isomeric iodoalkylidene furan rings contaminated with large amounts of tin residues.



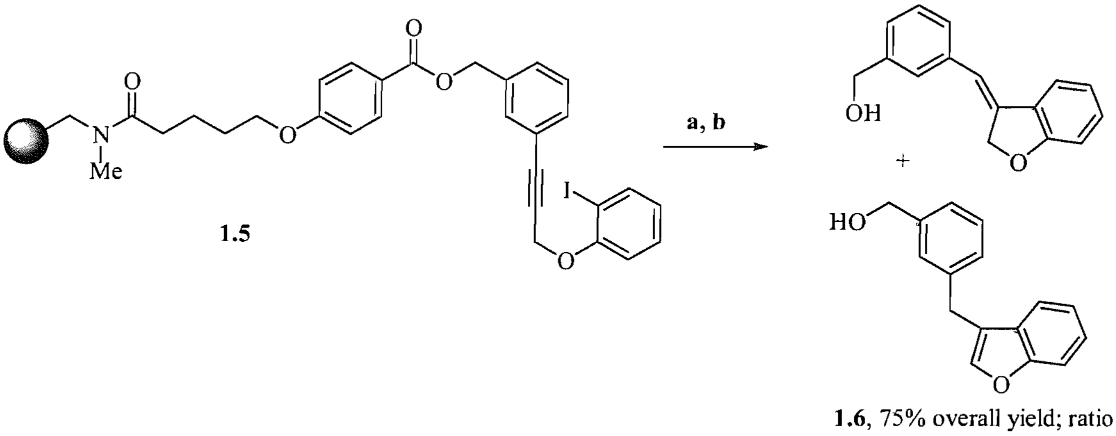
1.3

1.4, 69%
E : *Z*, 1.2 : 1

a. 20-25 eq. Bu_3SnH, 5 mol% AIBN, toluene, 70-80 °C.

Scheme 8

Another example of a cyclisation to an alkyne was reported by De Mesmaeker and Berteina in 1998. [11] The radical cyclisation of **1.5**, for example, led to a 75/25 mixture of *exo*- and *endo*-cyclic double bonds in 75% overall yield (Scheme 9). De Mesmaeker also reported a series of high yielding aryl radical cyclisations to alkenes **1.7** leading to dihydrobenzofurans **1.8** and **1.9**. [12] These substrates were immobilised on polystyrene resin through a Wang-like linker (Scheme 10), and the products cleaved by stirring the resin in a mixture of NaOMe in MeOH / dioxane.

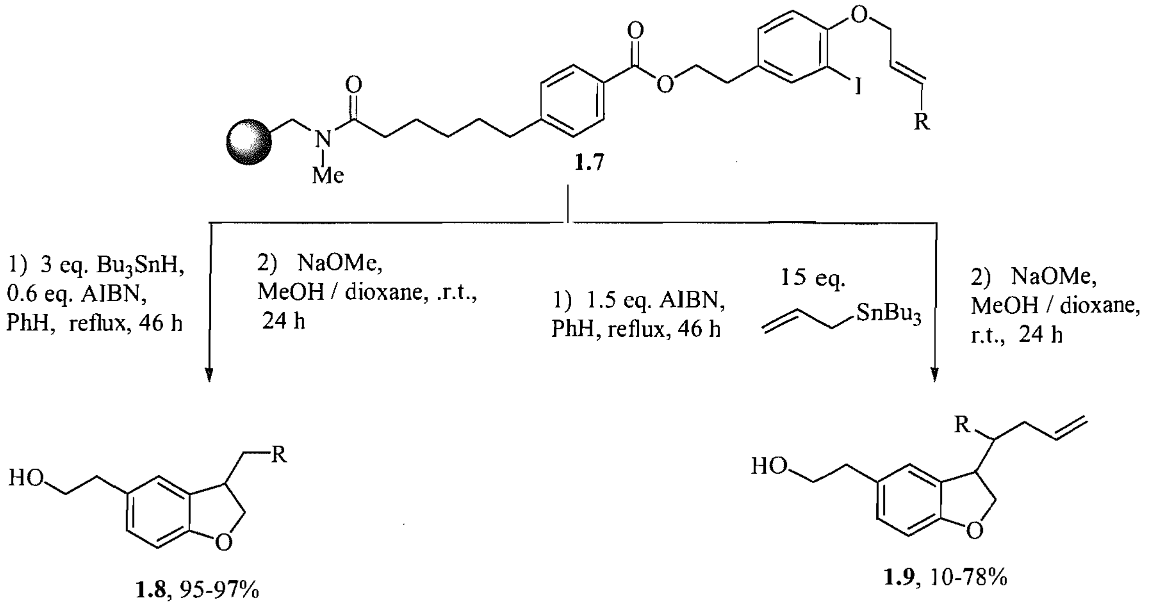


1.5

1.6, 75% overall yield; ratio 75/25

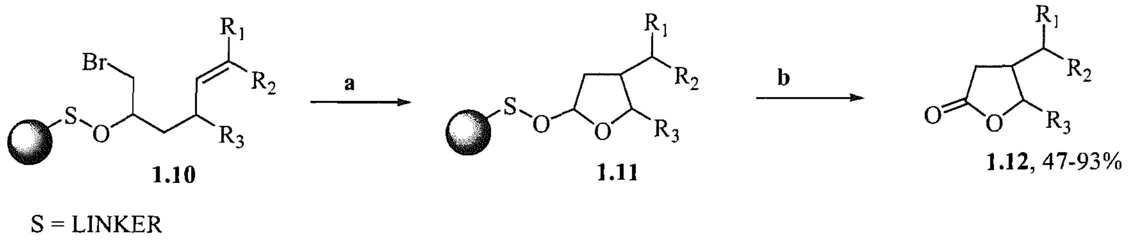
a. 3 eq. Bu_3SnH, 0.6 eq. AIBN, benzene (0.05 M), reflux, 46 h.; **b.** 6 eq. NaOMe, MeOH / dioxane (1 / 4), r.t., 24 h.

Scheme 9



Scheme 10

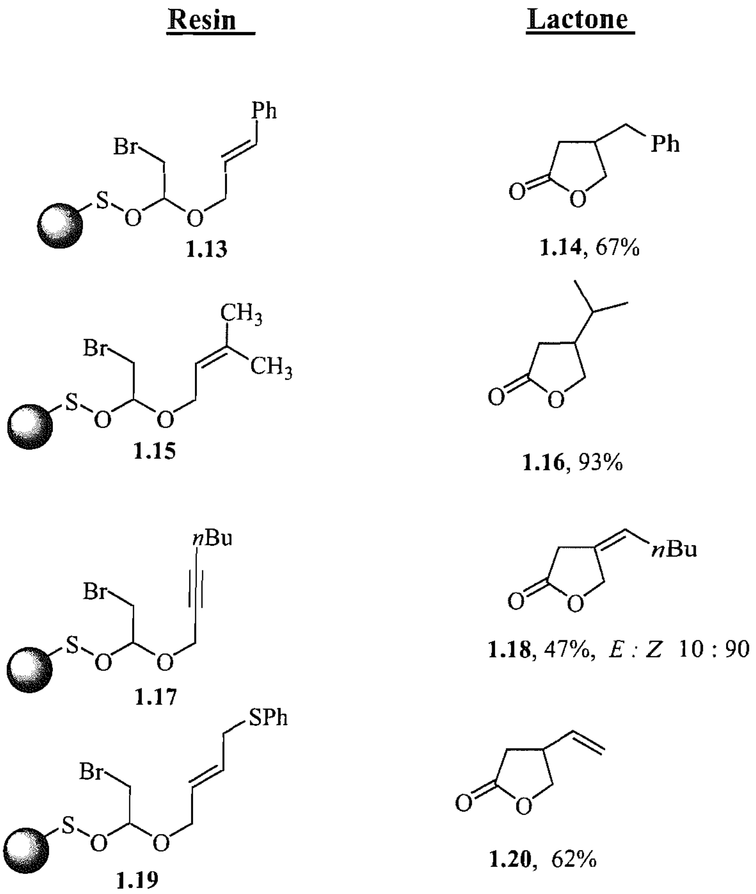
A convenient synthesis of γ-butyrolactones using radical cyclisation on solid-phase was achieved by Watanabe. [13] Here, polymer-supported β-bromoethylacetals **1.10** were treated with tributyltin hydride in the presence of AIBN to generate carbon centred radical intermediates which cyclised onto the vicinal carbon-carbon double bond. Subsequent cleavage of the cyclisation products from the solid phase by Jones oxidation released the γ-butyrolactones into solution (Scheme 11).



a. Bu_3SnH, AIBN, benzene, reflux; **b.** Jones reagent, 2 equiv. r.t., 3 h.

Scheme 11

Some specific examples are given below (Scheme 12). In each case cyclisation occurred to the internal carbon of the double bond. Cyclisation to an alkyne was also achieved, **1.17** leading to lactone **1.18** with a 1:9 *E*:*Z* ratio for the newly created alkene. For substrate **1.19**, cyclisation was followed by β-elimination of the phenylthiyl radical to give 3-vinyl-γ-butyrolactone **1.20** in a 62% yield after cleavage from the resin by Jones oxidation.



1.13 → **1.14**, 67%

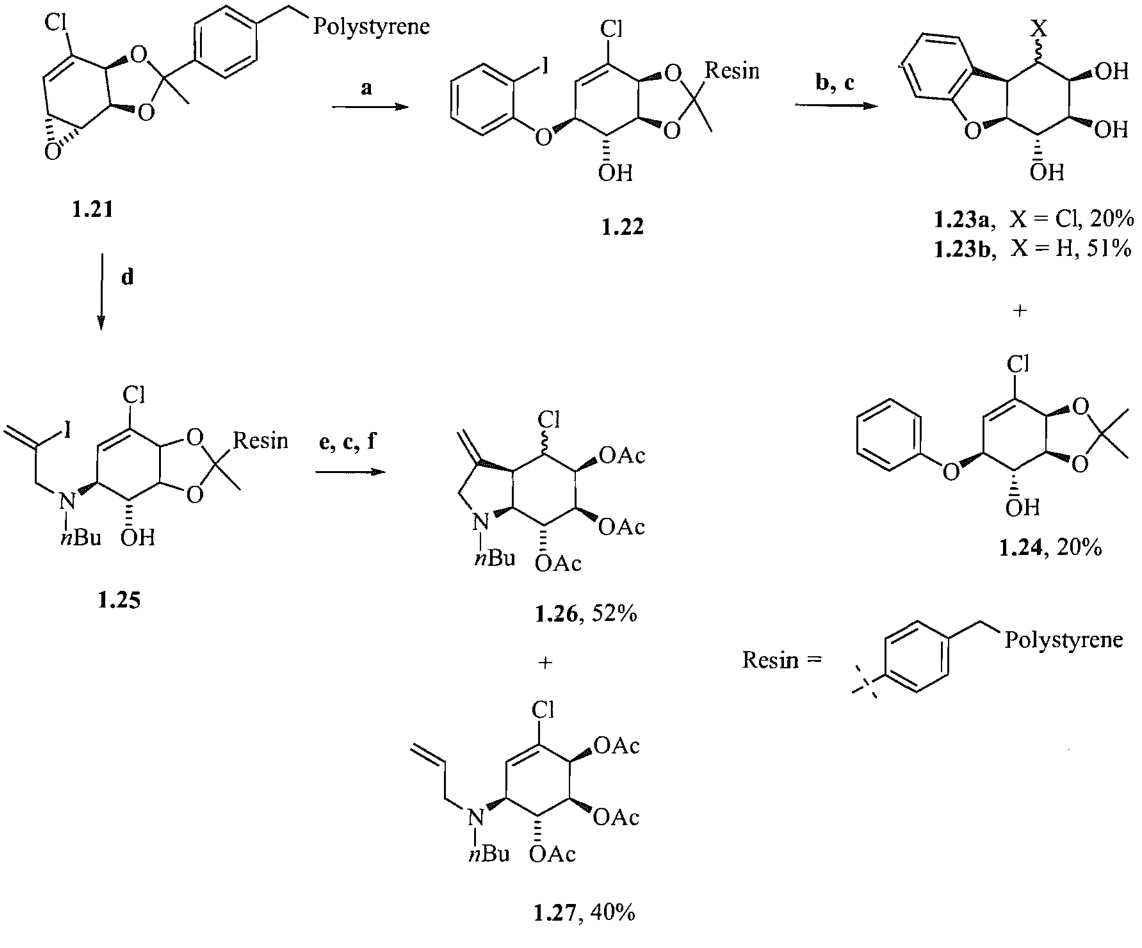
1.15 → **1.16**, 93%

1.17 → **1.18**, 47%, *E* : *Z* 10 : 90

1.19 → **1.20**, 62%

Scheme 12

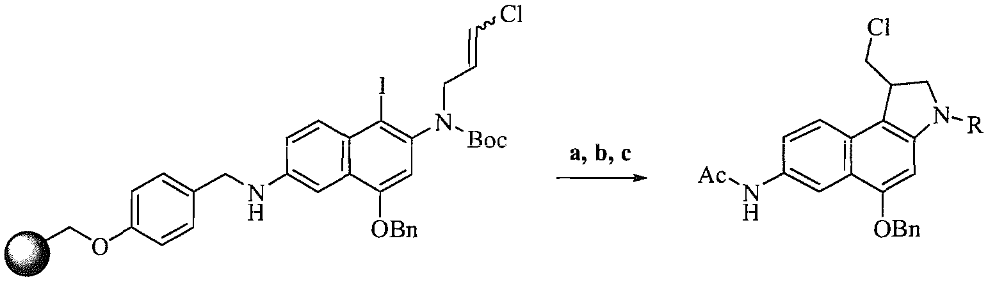
Berteina *et al.* [14] investigated radical cyclisation reactions involving cyclohexene diols. Polymer-bound substrate **1.22** (derived from epoxide **1.21**) was treated with AIBN and Bu_3SnH added in nine portions to produce, after acidic cleavage from the resin, a mixture of **1.23a** and **1.23b** (71%), together with non-cyclised compound **1.24** (20%). The cyclisation of **1.25**, which was synthesised from **1.21**, gave similar results.



a. 6 eq. 2-iodophenol, 6 eq. Schwesinger base, dioxane, 100 °C, 90 h; **b.** 14.5 eq. Bu_3SnH, 1.9 eq. AIBN, benzene, reflux, 80 h; **c.** TFA, r.t., 1 h; **d.** 5 eq. butyl-(-2-iodo-allyl)-amine, 50 mM $LiClO_4$, 2,6-lutidine, 50 °C, 21 h; **e.** 3 eq. Bu_3SnH, 0.6 eq AIBN, benzene, reflux, 48 h; **f.** 20 eq. Ac_2O, 10 eq. Et_3N, pyridine, r.t., 16 h.

Scheme 13

In 1999, Jia *et al.* [15] reported an intramolecular aryl radical cyclisation onto a vinyl chloride in the synthesis of 1-chloromethyl-1,2-dihydro-3*H*-benz[e]indole **1.29** (also known as *seco*-CBI, it closely resembles the pharmacophores of CC-1065 and duocarmycin SA). This class of cyclopropylindole antitumor antibiotics are extremely potent cytotoxins and have engendered great interest both as anticancer drugs and as targets for synthesis. [16,17] The reaction was monitored by acetylation and cleavage to yield **1.29**, which was formed as a mixture of free and Boc protected amines.



1.28

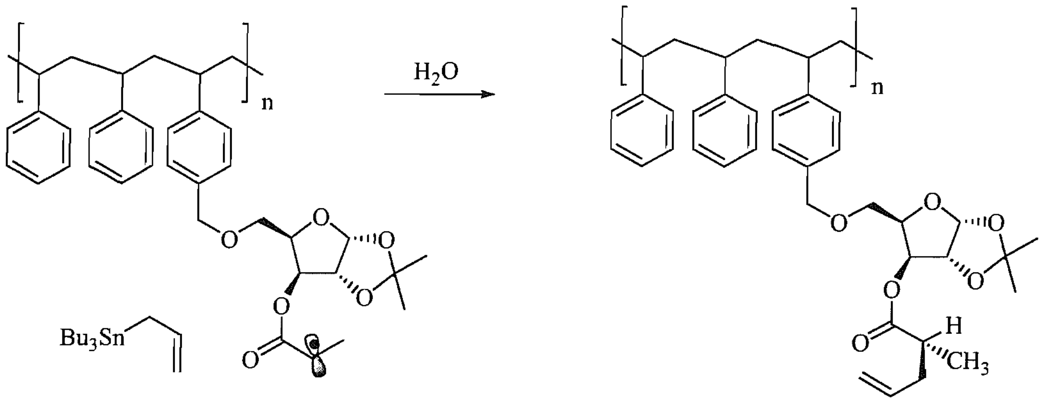
1.29, R = H, 46%; R = Boc, 28%

a. 1.3 eq. Bu_3SnH, AIBN, benzene, reflux 8 h; **b.** AcCl, DIEA; **c.** 95% TFA.

Scheme 14

1.5. Intermolecular Radical Reactions Using Tin

Enholm *et al.* [18] were the first to report a diastereoselective radical reaction on the solid phase using allyltributyltin (Scheme 15). Treatment of **1.30** with allyltributyltin, under free radical conditions, gave **1.31** in 93% yield with 97% diastereoselectivity using a removable carbohydrate based auxiliary attached to a non-crosslinked soluble polystyrene support. According to the group 'free radical reactions with allyltributyltin have great synthetic potential with these designer soluble supports, which differs markedly from the standard Merrifield 2-3% divinylbenzene cross-linked polystyrene polymers currently used extensively'.

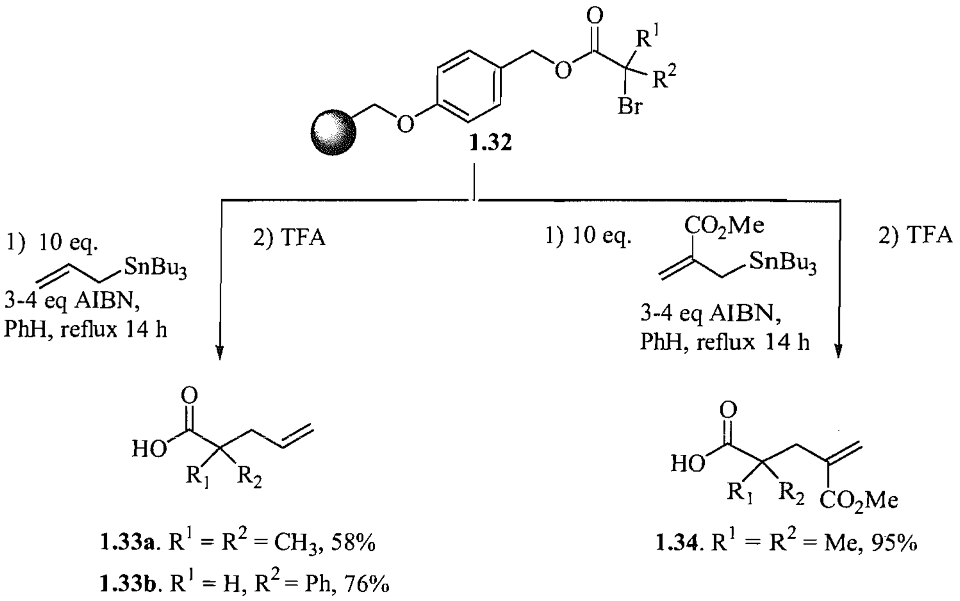


1.30

1.31, 93%

Scheme 15

The first examples of intermolecular free radical allylation reactions on solid support were reported by Sibi and Chandramouli in 1997. [19] Their choice of study was the free radical allylation of α-bromoesters on Wang resin using allyltributyltin. Refluxing the α-bromoesters in benzene with 10 eq. of allyltributyltin and 3-4 eq. of AIBN as initiator gave the allylated products **1.33** in 58-76% yield following cleavage with TFA (2 examples shown of 5). When the amount of either allylstannane or AIBN was reduced, the reaction gave lower yields. They also found that the electronic nature of substituent at the radical centre had some impact on the chemical efficiency of the reaction – with electron-withdrawing groups at the 2-position of the allylstannane improving the reaction yield, as in the formation of **1.34** (Scheme 16).



1.33a. $R^1 = R^2 = CH_3$, 58%
1.33b. $R^1 = H$, $R^2 = Ph$, 76%

1.34. $R^1 = R^2 = Me$, 95%

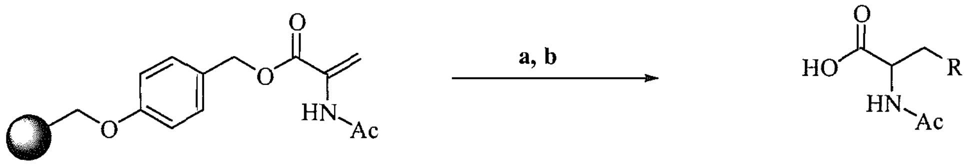
Scheme 16

1.6. The Disadvantages of Using Tin

The toxicity of organotin reagents is a significant drawback associated with many radical reactions. Organotin reagents are also moderately expensive and the removal of tin residues from product mixtures can be difficult, [20] and these too are highly toxic. This is of key importance since the alkyl chains solubilise the tin enabling it to pass the blood-brain barrier, where over time it may accumulate. The immobilisation of either the tin reagent or the substrate on a solid support allows the two to be separated at the end of the reaction by washing, providing a simple and effective means of purification. It is particularly important to wash the resin thoroughly when substrates are bound to the solid support as organotin compounds have a tendency to remain occluded within the resin matrix. These may then be released into solution upon clevage of the product.

1.7. Radical Conditions on Solid Phase Without Tin

Yim *et al.* [21] reported a synthesis of α-amino acids by the reductive homolysis of organomercurials in the presence of polymer-supported 2-acetamidoacrylic acid (Scheme 17). [22] Performing the reaction using tributyltin hydride had given only trace amounts (8%) of the desired product in the washings, together with starting material. Prolonged reaction times resulted in degradation of the dehydroamino acid **1.35**. The synthesis of *N*-acetyl–DL-leucine **1.36a** was performed at room temperature by dropwise addition of an excess of aqueous sodium borohydride to a mixture of **1.35** and isopropylmercury chloride to give **1.36a** in 49% isolated yield. Syntheses of *N*-acetyl-γ-methyl-DL-leucine **1.36b** and *N*-acetyl-DL-cyclohexylalanine **1.36c** were achieved under the same reaction conditions in isolated yields of 49% and 60%, respectively. The authors claim this methodology has wide potential in the synthesis of α-amino acids, given the wide variety of alkylmercury halides available.



1.35

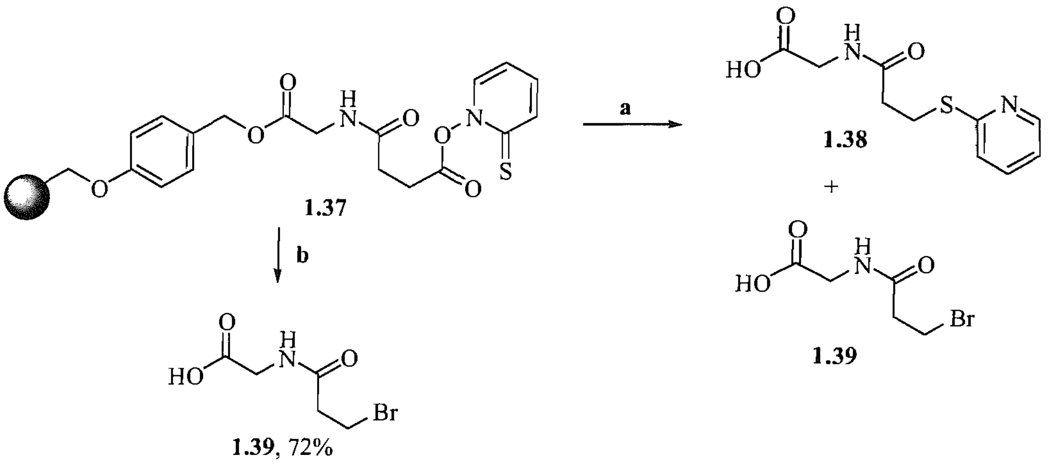
1.36a, R = *i*-Pr, 49%
1.36b, R = *t*-Bu, 49%
1.36c, R = *c*-C_6H_{11}, 60%

a. 3 eq. RHgCl, 8 eq. $NaBH_4$, CH_2Cl_2 / H_2O, 1.5 h; **b.** TFA / CH_2Cl_2, 30 min, r.t.

Scheme 17

1.7.1. Generation of Radicals *via* Barton Esters

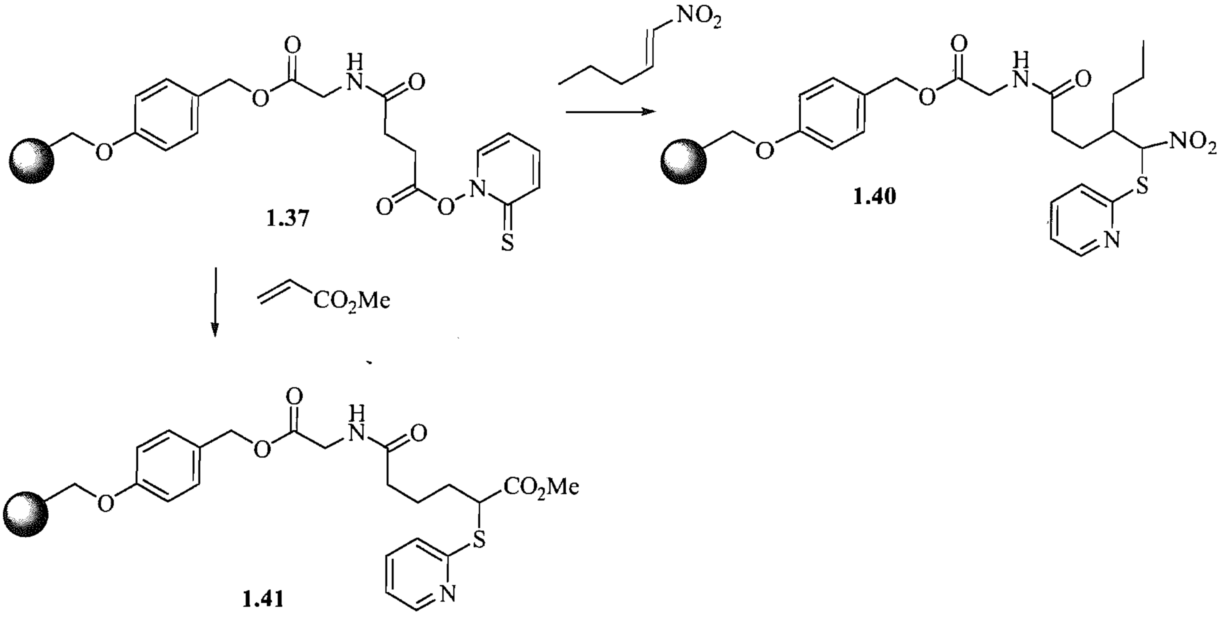
The contamination of organotin compounds, which are known to be toxic and very difficult to eliminate, is the major drawback of many of the above mentioned reactions. In order to overcome this problem, many research groups have explored other methods for generating radicals in solid-phase reactions. Among the various methods for producing alkyl radicals, those involving esters of *N*-hydroxy-2-thiopyridone, developed by Barton, offer some practical advantages. They are easily prepared from the corresponding carboxylic acid and readily fragment upon irradiation with an ordinary tungsten lamp. There is no need for elevated temperatures, and the group is itself the chain transfer species. Barton esters have been prepared on a solid support from carboxylic acids by Attardi and Taddei. [23] Irradiation of **1.37** was tried in the presence of $CBrCl_3$. When the reaction was carried out in THF or using $CBrCl_3$ as the solvent, a mixture of compounds **1.38** and **1.39** were obtained after cleavage from resin. When the irradiation was carried out in DMF in the presence of at least 50 eq. of $CBrCl_3$, compound **1.39** was obtained exclusively in 72% yield (Scheme 18).



a. 1) hv (200 W lamp), THF, 20 min.; 2) TFA / CH_2Cl_2 / Et_3SiH, r.t., 1 h; **b.** hv (200 W lamp), $CBrCl_3$ (50 eq.), DMF 20 min.; 2) TFA / CH_2Cl_2/Et_3SiH, r.t., 1 h.

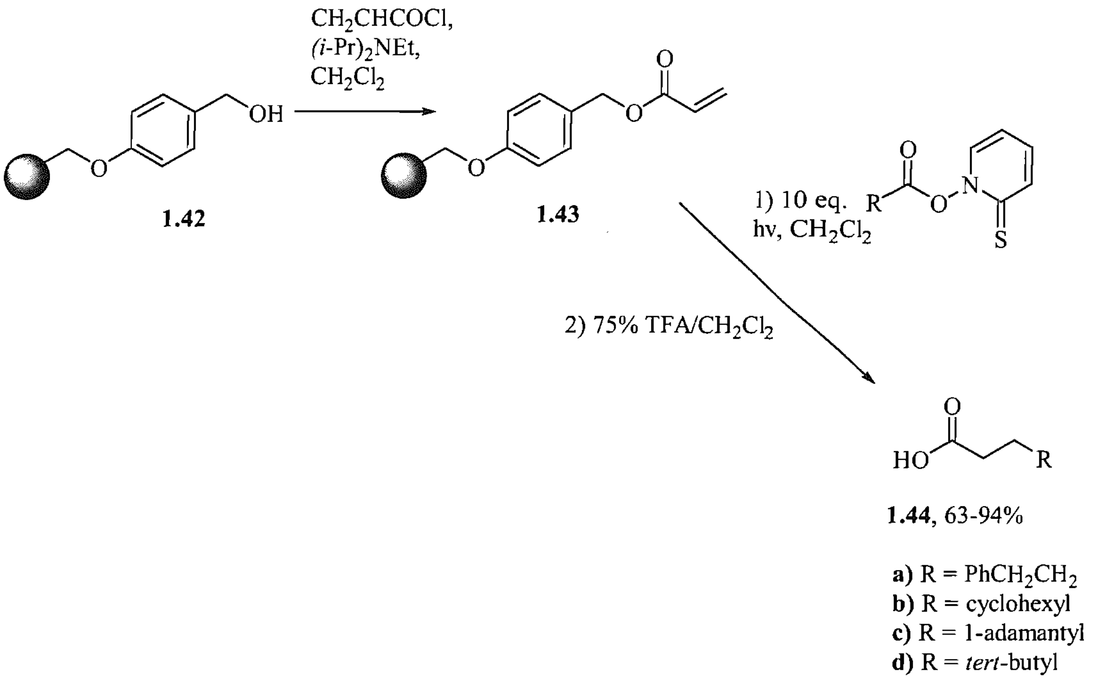
Scheme 18

Barton ester **1.37** was also reacted with electron-poor alkenes such as methyl acrylate or 1-nitropentene. Carrying out the reaction in DMF with 50 eq. of the radical acceptor produced **1.38** as the main product. The expected products **1.40** and **1.41** were given after addition of the R$^•$ and ArS$^•$ across an electron deficient alkene when these were employed in 100 fold excess (Scheme 19).



Scheme 19

Zhu and Ganesan have investigated the conjugate addition of alkyl radicals (generated from Barton esters) to acrylate immobilised on a solid support.[24] Acrylic acid was loaded with either the Wang or Rink linkers using cross-linked polystyrene. When irradiated in the presence of 10 eq. of a Barton ester, conjugate addition occurred giving alkylated products that were readily cleaved from the resin by hydrolysis with trifluoroacetic acid (Scheme 20).

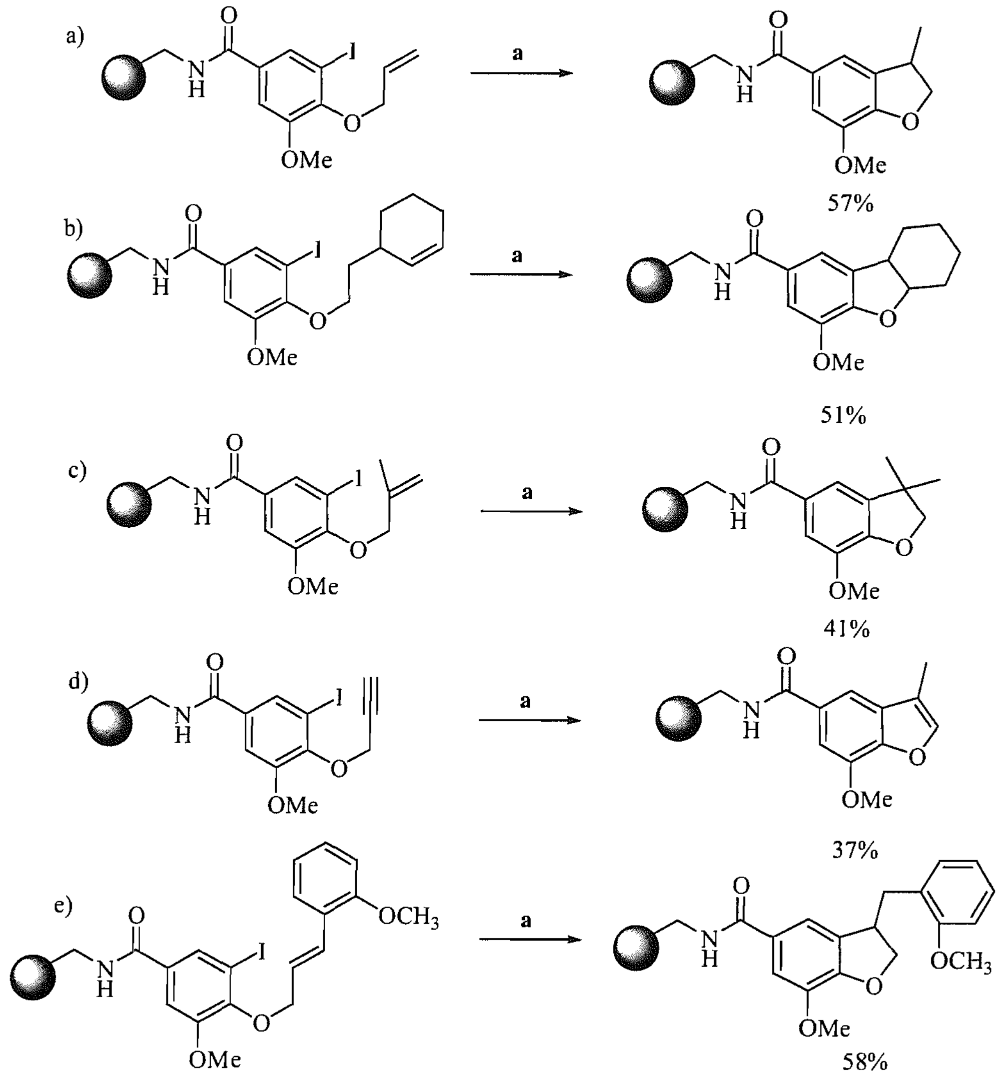


Scheme 20

Acids **1.44a** and **1.44b** were isolated in 91-94% yield, while addition of 1-adamantyl radical proved somewhat less efficient, giving **1.44c** in 63% yield. TentaGel-Wang resin gave consistently lower yields compared to the use of the Wang or Rink linker. This could be due to poorer loading efficiency, something that the authors were unable to compare due to the difficulty of isolating acrylic acid after TFA cleavage.

1.7.2. SmI_2- and Triethylborane mediated radical cyclisations

Du and Armstrong reported an alternative synthesis of various benzofuran derivatives through SmI_2-mediated radical cyclisations on solid support. [25] This mild and rapid cyclisation offers an advantage over tributyltin hydride-mediated routes to benzofuran derivatives, as they do not require high temperatures or long reaction times. They do however require the use of the carcinogenic solvent HMPA. Some of the cyclisations conducted are shown in Scheme 21.

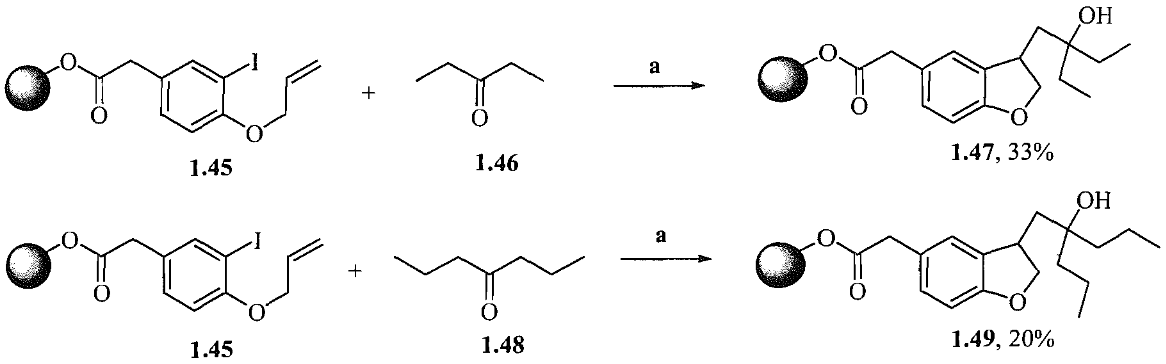


a. SmI$_2$, HMPA, THF, 1 h.

Scheme 21

The cyclisations generally proceeded cleanly, with the aryl substituents reacting in good yield and without any formation of products from radical disproportionation. The method was also applicable to the synthesis of fused heterocyclic systems as evidence by entry b).

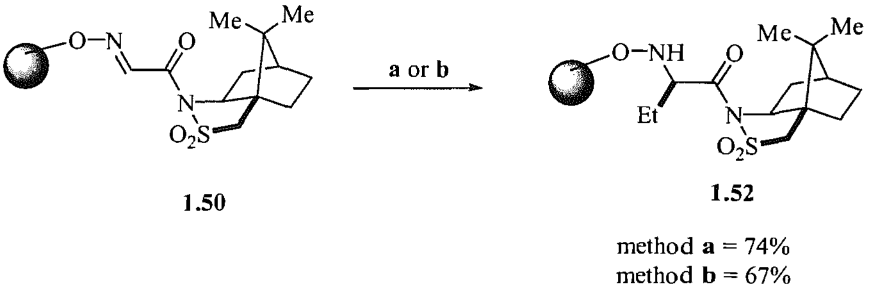
Further work [26] by the same authors, showed that these radical cyclisations could be followed by reduction to anionic species, which in turn could be trapped with electrophiles. These reactions were found to be highly substrate dependent, limiting the general utility of the method in combinatorial library construction. Reaction of TentaGel-bound **1.45** with SmI_2 in the presence of 3-pentanone generated captured product **1.47** in 33% yield (Scheme 23). With other acyclic ketones such as 4-heptanone **1.48**, acceptable yields were also realised. Comparison with the corresponding solution phase reactions indicated that the anionic species were generated more slowly on solid support than in solution. As a consequence, SmI_2 was largely consumed by reaction with the added ketone rather than in reaction with **1.45**. To generate the anionic species from **1.45** it was necessary to add SmI_2 some time before the introduction of the electrophile (ketone).



a. SmI_2, HMPA, THF, 1 h.

Scheme 22

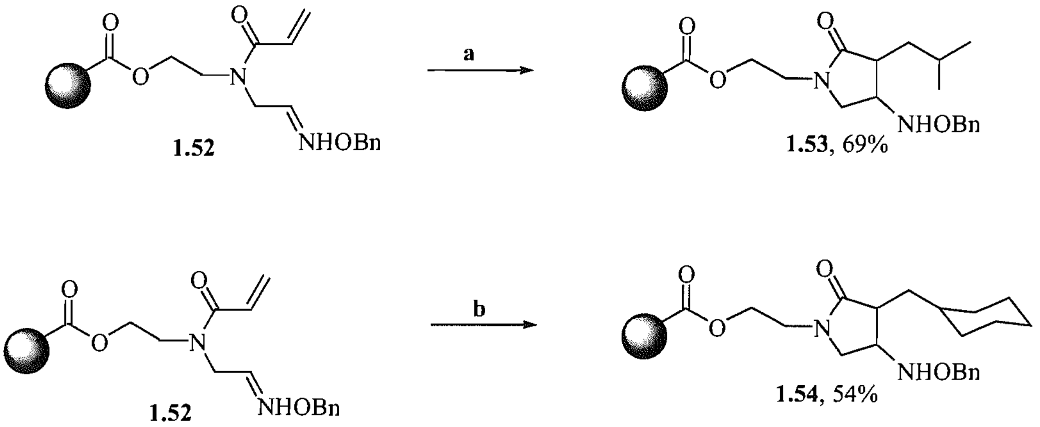
Studies using triethylborane as a radical chain carrier has been carried out by Naito. [27-30] In one study, ethyl radical addition to **1.50** using either triethylborane or diethylzinc as radical initiators and chain carriers was compared. Alkyl radical addition to Oppolzer's camphorsultam derivatives of oxime ether anchored to polymer support proceeded smoothly at a temperature of 0 °C to give α-amino acid derivatives with excellent diastereoselectivities. This was better than the analogous solution-phase reaction, suggesting lower reactivity of the immobilised oxime (Scheme 23).



a. Et_3B (5 eq.), -78 °C, DCM, 30 min; **b.** Et_2Zn (5 eq.), -78 °C, DCM, 30 min.

Scheme 23

Triethyborane also worked well as a radical mediator. Solid phase tandem C-C bond forming reactions of oxime ethers connected with α, β-unsaturated carbonyl groups proceeded effectively to give the corresponding γ-lactams in good yield (Scheme 24). However, these reactions had to be carried out at higher temperatures (100 °C).



1.52 → **1.53**, 69%

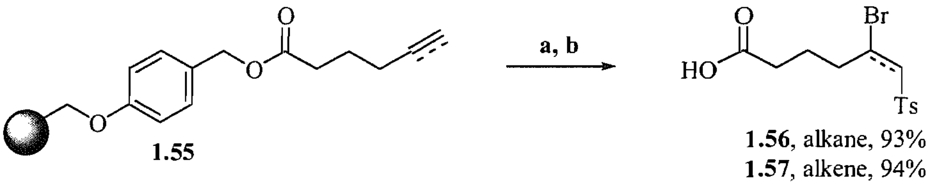
1.52 → **1.54**, 54%

a. *i*-PrI, Et_3B in hexane, toluene, 100 °C; **b.** *c*-hexylI, Et_3B in hexane, toluene, 100 °C.

Scheme 24

1.7.3. Sulfur Radicals

The addition of toluenesulfonyl radicals to solid supported alkenes and alkynes has been reported by Caddick *et al.* [31] Wang-type resin was used to deliver high yields (> 90%) of bromosulfonyl-alkanes and alkenes. The reaction was found to be highly sensitive to both the reaction solvent and linker; in some cases leading only to decomposition. In additions to alkynes, E-alkenes were the only products produced (Scheme 25).



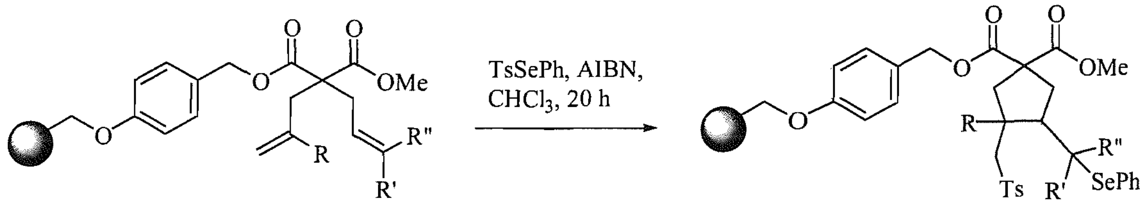
1.55

1.56, alkane, 93%
1.57, alkene, 94%

a. 6 eq. TsBr, 6 eq. AIBN, toluene, 65-70 C°, 16-22 h; **b.** 95% TFA, 90 min.

Scheme 25

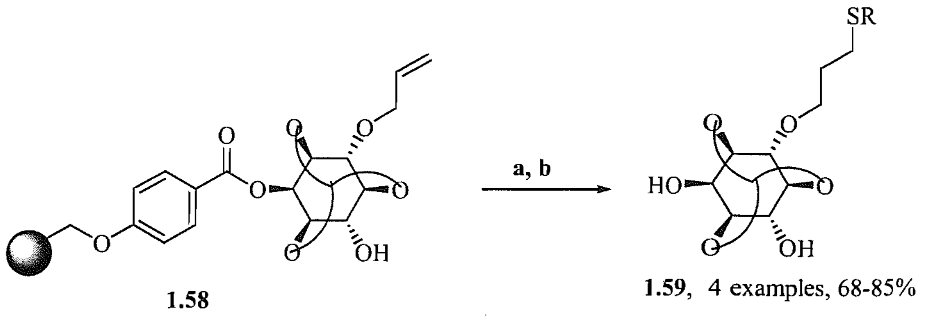
Later Harrowven *et al.* [32] reported the use of TsSePh to effect radical cyclisation reactions of dienes on solid phase (Scheme 26). Using resin-bound 1,6-dienes as substrates, it was shown that cyclisation could be readily effected when an excess of AIBN was added in two portions, one at the start of the reaction, the other after 5 hours. Addition of tosyl radical to the diene was a highly regioselective process, preferentially adding to any unsubstituted alkene carbon. After cyclisation the radical was trapped with SePh from TsSePh, regenerating the tosyl radical to propagate the chain reaction.



1. R, R', R" = H, 74%
2. R = H; R', R" = Me, 71%
3. R, R' = H; R" = Ph, 68%
4. R = Me; R' = H; R" = Ph, 69%
5. R, R', R" = Me, 68%

Scheme 26

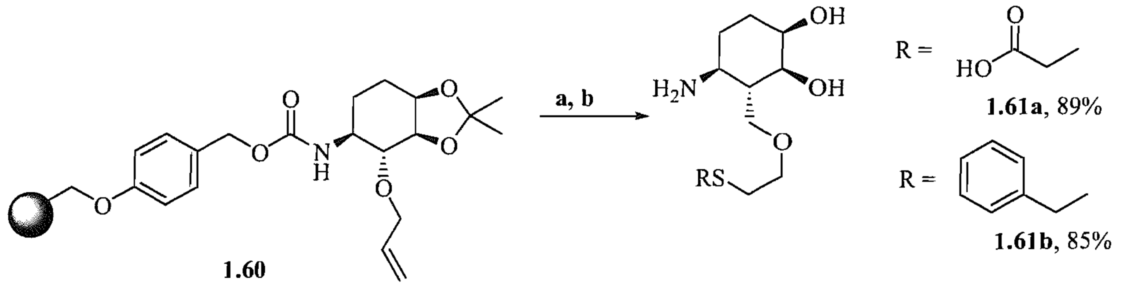
Plourde *et al.* [33] described the free radical addition of thiols to polymer supported allyl ethers with subsequent liberation of the resulting thioethers from the polymer. Using an orthoformate derivative attached to 1% divinylbenzene crosslinked carboxypolystyrene, the reaction was successful with alkyl thiols, as well as hydroxy, carboxy, and benzyl substituted thiols (4 examples, 68-85%, Scheme 27). It did not proceed to any significant degree with aryl or heteroaryl thiols.



a. RSH, AIBN, benzene, 80 °C, 24 h; **b.** K_2CO_3, THF-MeOH (2 : 1), 25 °C, 20 h.

Scheme 27

In an extension to the method, the reaction was performed with Wang resin bearing an aminocyclitol residue. Reaction with thioglycolic acid and benzyl mercaptan proceeded smoothly to give **1.61a** and **1.61b** in 89% and 85% yield, respectively (Scheme 28).

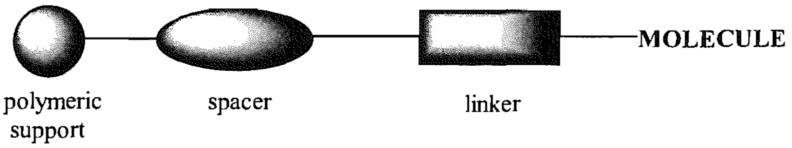


a. RSH, AIBN, DMF, 80 °C, 24 h; **b.** TFA-CH_2Cl_2 (1 : 1), r.t., 2 h.

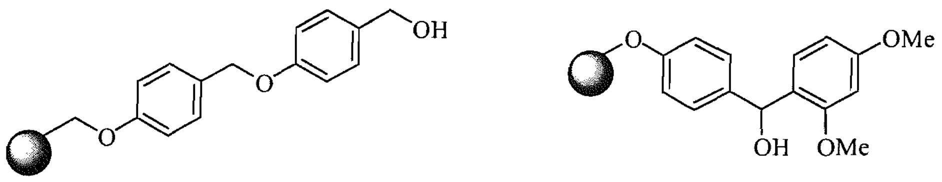
Scheme 28

1. 8. Choice of Linker for Solid Phase Synthesis

Large numbers of reactions have been translated from solution phase to solid phase and more continue to be developed. Attachment of the substrate to the solid phase is critical to the success of the process. A linker is usually employed, which can be thought of as a bifunctional protecting group. It facilitates attachment of the substrate to the polymer bead through a bond that becomes labile when subjected to the cleavage conditions. The functional group attaching the linker to the solid support is usually more robust and is unchanged upon exposure to the cleavage conditions. A linker should resist reaction through the synthetic sequence and must be compatible with the diverse structures to be prepared in the target library without compromising the chemical methodologies to be employed. Furthermore, the linker must be readily cleaved from the resin using mild conditions compatible with compounds synthesised.



The Wang and Rink linkers, **1.62** and **1.63**, respectively, are two of the most widely used in solid phase organic synthesis (Scheme 29).



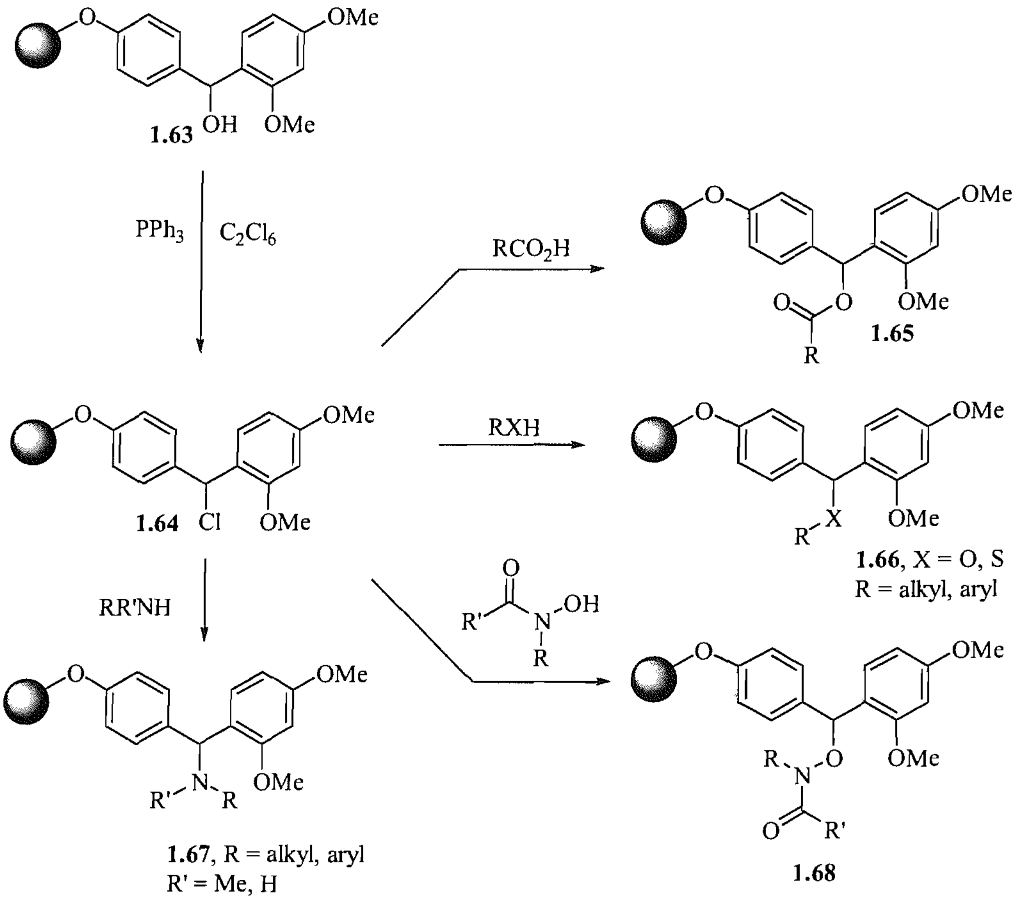
Wang Linker **1.62**

Rink Alcohol **1.63**

Scheme 29

1.8.1. Rink Linker

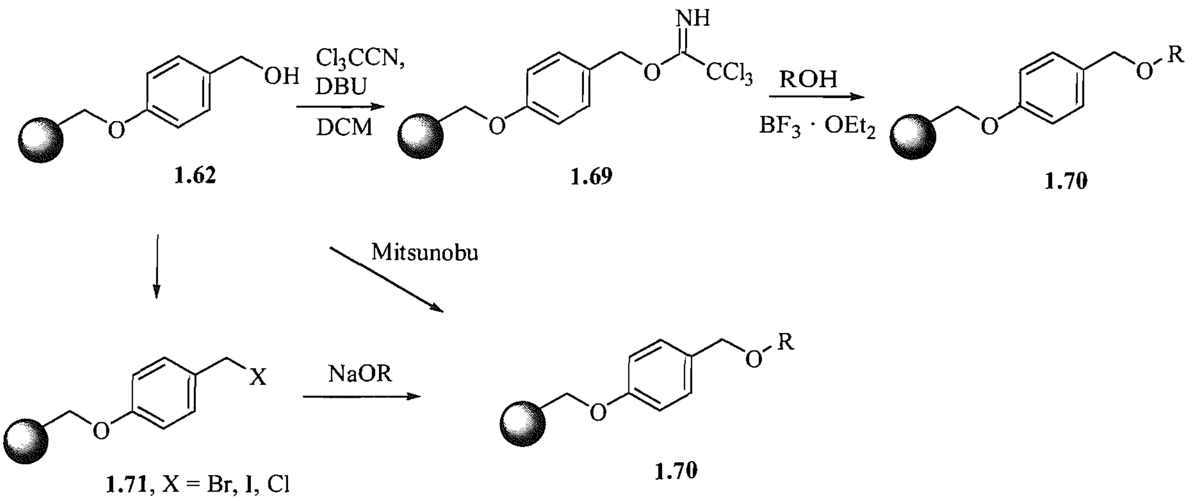
In 1987, Rink introduced a new resin that proved to be very useful for the solid-phase synthesis of protected peptide fragments and of acid sensitive peptide amides. [34] The three electron-donating alkoxy groups on the Rink linker, help to stabilise the cation formed upon cleavage, the reaction mixture turning to a deep red colour on treatment with TFA. Rink chloride **1.64** can be prepared from the Rink alcohol **1.63** by reaction with PPh_3 and hexachloroethane. [35,36] Treatment with a nucleophile then allows substrates to be attached through a range of functionalities, including alcohols, phenols, primary and secondary amines, anilines, thiols, thiophenols and carboxylic acids (Scheme 30).



Scheme 30

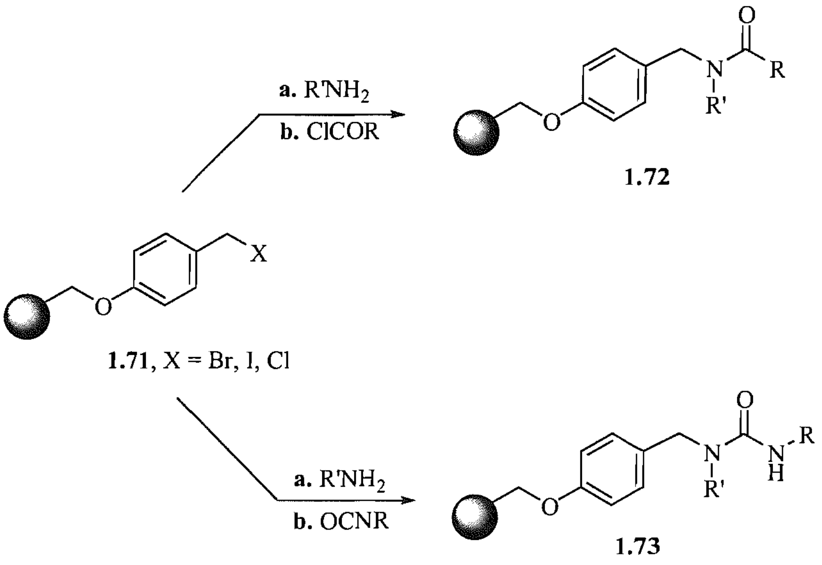
1.8.2. Wang Linker

The *p*-alkoxybenzyl linker **1.62** (commonly known as Wang linker) [37] is primarily used for the attachment of molecules possessing a free carboxyl group, but has been used to attach a range of functionalities. It can be converted to the corresponding bromide, [38] chloride, [39,38] iodide, [40] or trichloroacetimidate, [41] which in turn can be displaced with various nucleophilic functional groups. These may also be attached using the Mitsunobu reaction, though this is generally less reliable than attachments made *via* the trichloroacetimidate derivative **1.69** (Scheme 31). [42] TFA in DCM is commonly used to effect cleavage of Wang linked substrates.



Scheme 31

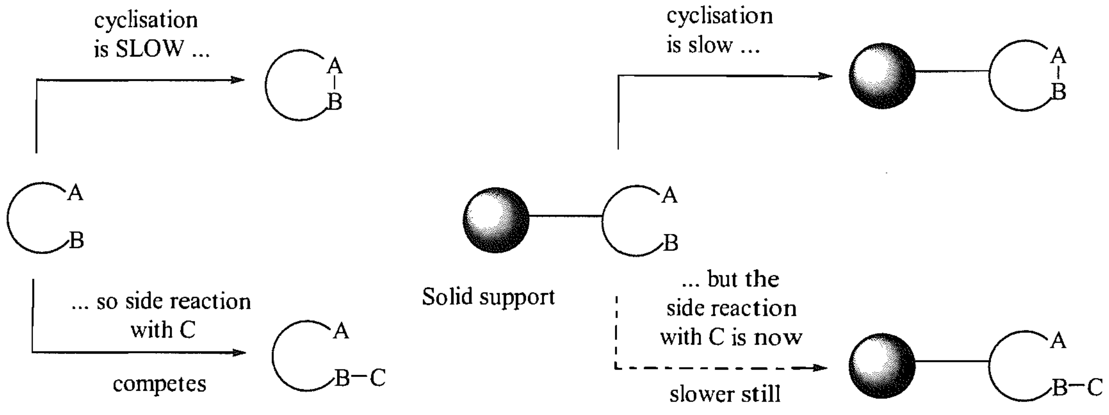
Displacement of **1.71** with an amine gives amide linker **1.72** after acylation. Acid labile urea linkers **1.73** also have been developed from Wang amines (Scheme 32).



Scheme 32

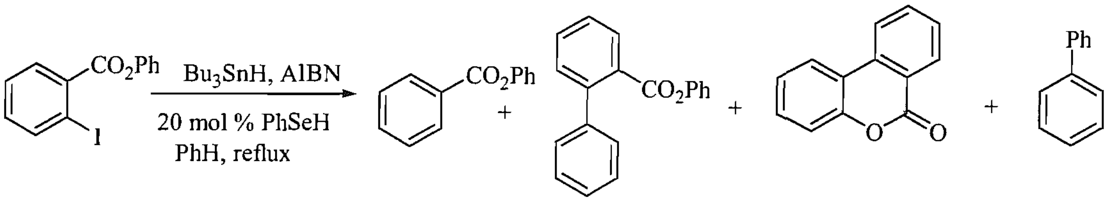
1.9. Cascade Radical Reactions on the Solid Phase. Can Slow Bimolecular Kinetics be Used to Advantage?

Our investigation sought to effect cascade radical reactions on solid support with the hope that differences between solution phase and solid phase kinetics might be exploited. Improving the efficiency of slow cyclisation reactions is one area where immobilisation might be helpful as bimolecular side reactions would be slowed when a substrate is immobilised on a solid support. This slowdown would not apply to unimolecular processes such as cyclisation reactions, so these ought to be more efficient. If this supposition holds true then any intramolecular reaction that is inefficient due to a competing intermolecular side reaction will benefit from immobilisation on a solid support (Scheme 33).



Scheme 33

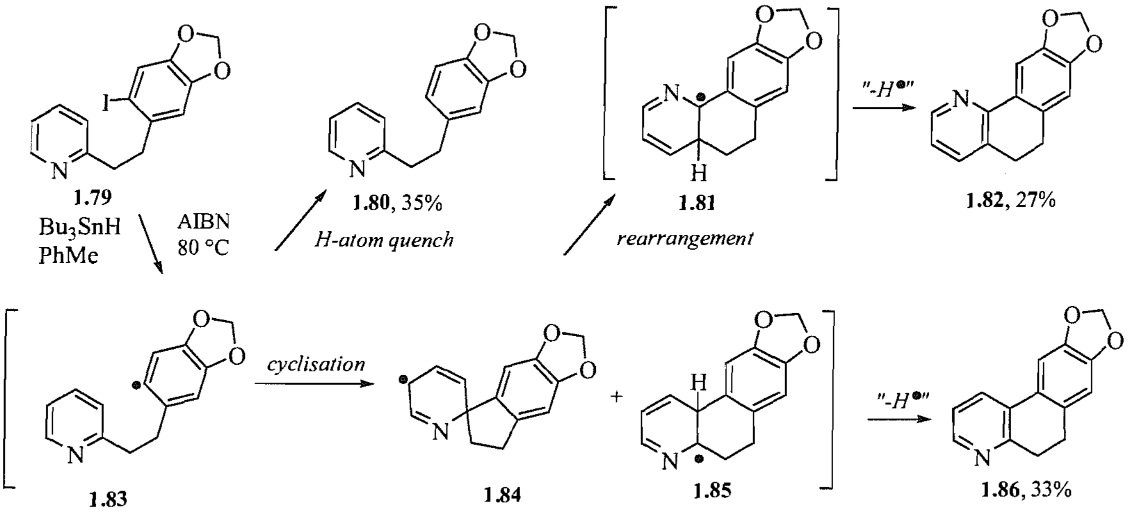
Intramolecular radical additions to electron rich and electron deficient arenes are known to proceed at a useful rate. [43-45] The inefficiency of these reactions has to do with the myriad of products that such reactions frequently give. [46] For example, treatment of aryl iodode **1.74** with tributyltin hydride led to a complex product mixture from which **1.75**, **1.76**, and **1.78** were formed along with the desired cyclised product **1.77** (Scheme 34).



1.74 **1.75**, 17% **1.76**, 35% **1.77**, 12% **1.78**, 21%

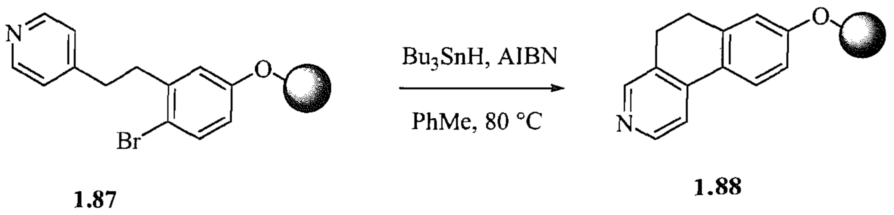
Scheme 34

The yield of **1.77** might be enhanced if intermolecular side reactions were slowed. This could be achieved by conducting the chemistry on solid phase, where unimolecular reactions would be promoted by the slowing down of competing bimolecular processes. A further example is the radical re-arrangement highlighted in Scheme 35. [47] Though the reaction is quite efficient for the production of benzoquinolines **1.82** and **1.86**, a large part of the remaining mass balance consists of the unwanted side product **1.80**.



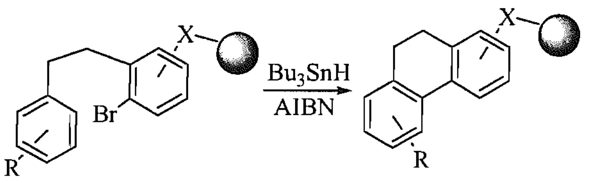
Scheme 35

Immobilisation on the solid phase may slow the intermolecular hydrogen atom abstraction from tributyltin hydride, thus helping to promote the cyclisation sequence leading to aryl ether **1.88**.

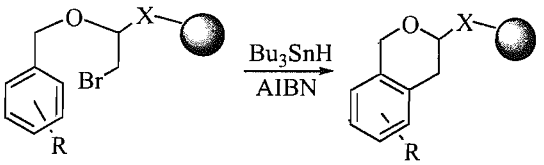


Scheme 36

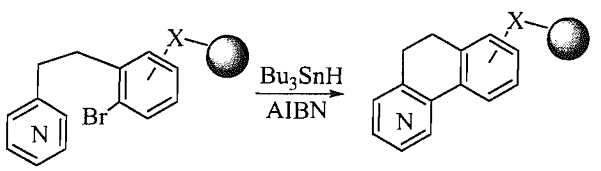
Success in this venture would allow us to target all manner of polycyclic structures using this simple methodology. It would also provide the basis for examining the effect of solid phase immobilisation on a host of other processes that are low yielding due to competitive intermolecular side reactions, e.g. schemes 37-40.



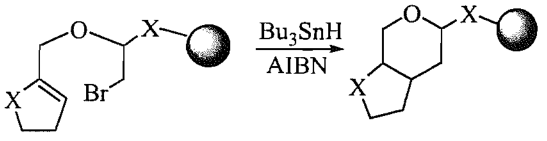
Scheme 37



Scheme 38



Scheme 39



Scheme 40

1.10. Conclusion

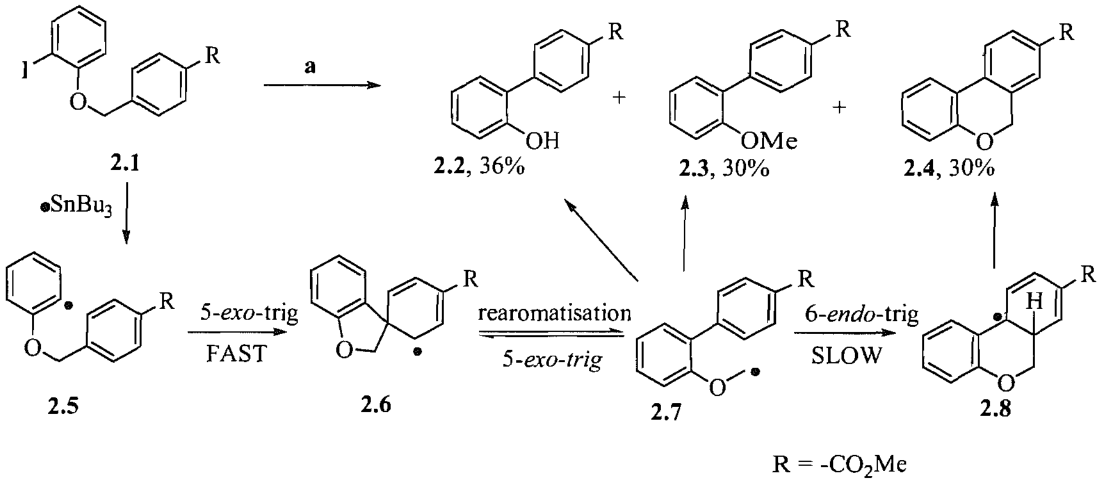
The development of organic synthesis on solid support allows libraries of compounds to be prepared, potentially useful in the discovery of new bioactive compounds, new catalysts and new materials. The development of carbon-to-carbon bond forming reactions on solid phase is an important task as these allow access to any number of organic products on the solid phase. Radical reactions have not been widely applied on solid supports, and have yet to be applied to the synthesis of large compound libraries. The feasibility of carrying out radical reactions on solid phase has been demonstrated, as detailed in the preceding discussion. If progress continues, they should soon become a significant addition to the combinatorial chemist's toolkit. Developments in polymer-supported reagents and scavenger resins have helped to facilitate the running of radical reactions in parallel and there is huge potential for the development of simplified work-up procedures and purification methodologies.

Chapter 2 – On the Search for a Suitable Coupling System for Our Study

2 On the Search for a Suitable Coupling System for Our Study

2.1. Background – Iodoaryl Ethers for Cyclisation

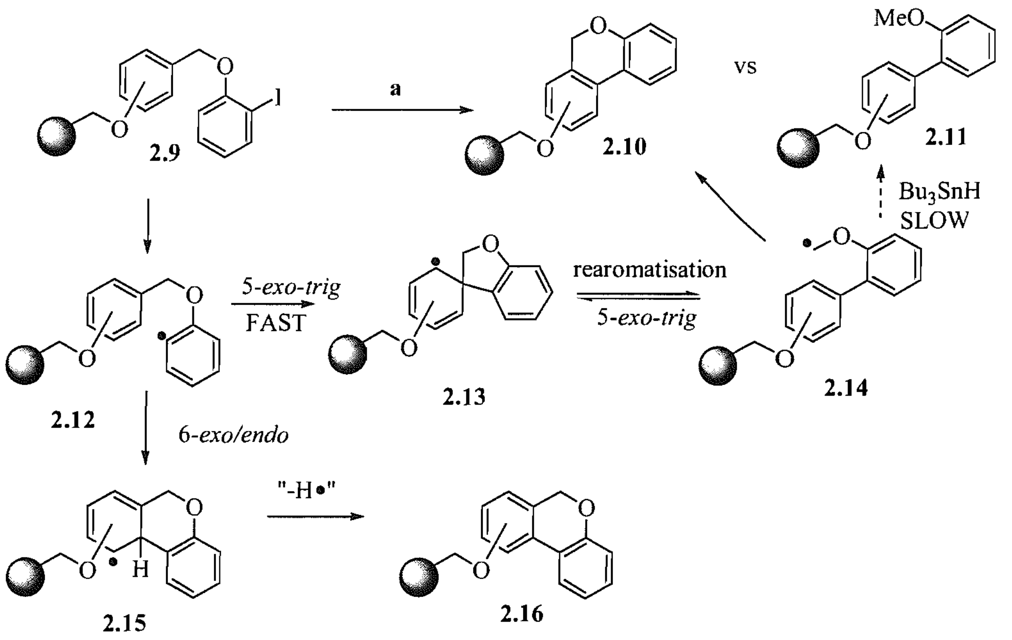
Radical additions to arenes in solution phase synthesis usually proceed at a useful rate but often give rise to complex product mixtures. In recent years a number of methodologies have been discovered that exploit the reaction. For example, tin-mediated intramolecular radical reactions involving benzyl iodoaryl ethers have been used to good effect in the synthesis of bi- and triaryls including isoaucuparin, a natural product found in the sapwood tissue of *Sorbus aucuparia.* [48,49] However, a major disadvantage is that the reactions often display poor selectivity, producing complex product mixtures that can be difficult to separate (Scheme 41).



a. Bu_3SnH, AIBN, 90 °C, PhMe, 28 h.

Scheme 41

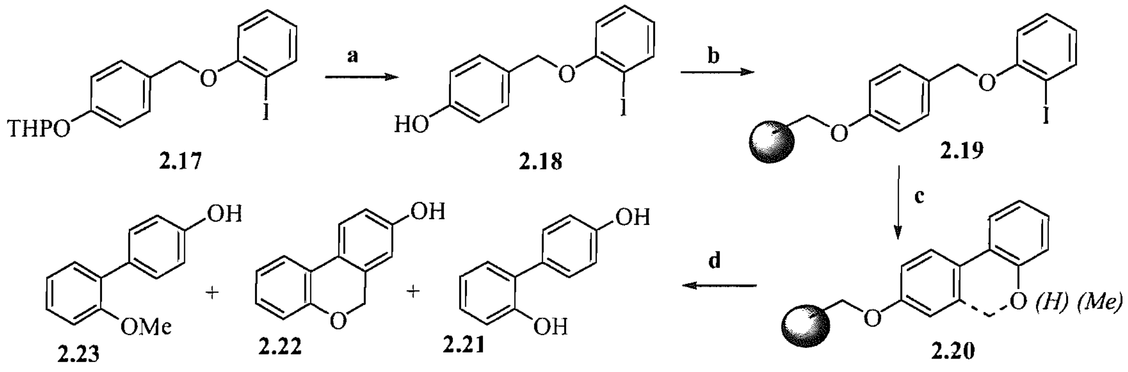
The reaction seemed ideal for our study as i) the substrates were suitable for attachment on solid phase and ii) some of the known byproducts would be lessened if our kinetic arguments were correct (Scheme 42). By slowing down the intermolecular H-atom abstraction from tributyltin hydride, the formation of the tricycle **2.10** should become efficient. The ratio of products derived by 5-*exo* and 6-*exo/endo* pathways ought be unaltered.



a. Bu_3SnH, AIBN, 90 °C, PhMe, 28 h.

Scheme 42

To investigate the reaction we first needed to prepare the iodoaryl ether precursors as shown in Section 2.2. We then proposed to attach the precursors (as exemplified with the iodoaryl ether **2.17**) to the solid support using the Mitsunobu reaction (Scheme 43).

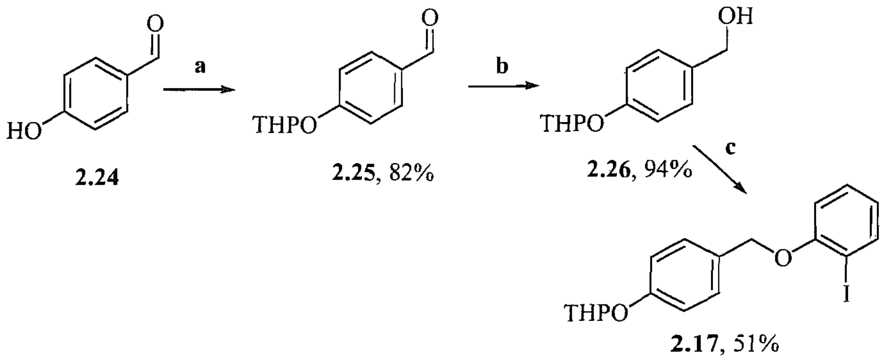


a. CBr_4 / MeOH, 65 °C, 3 h; **b.** DIAD, PPh_3, PS-Wang Resin, THF, r.t., 16 h; **c.** Bu_3SnH, AIBN, PhMe, reflux, 16 h; **d.** 95% TFA, 2.5% DCM, 2.5% $i\text{-}Pr_3SiH$, r.t., 1 h.

Scheme 43

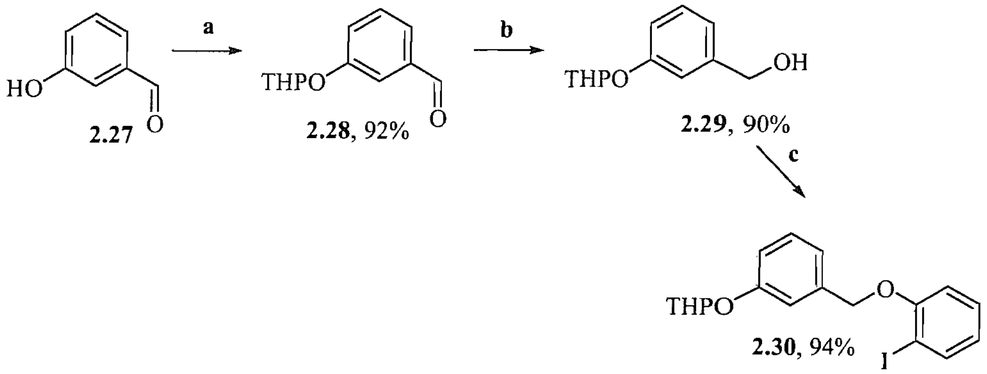
2.2. Preparation of Iodoaryl Ethers

Our first task was to synthesise benzyl iodoaryl ethers suitable for attachment on a solid support. Our starting points were 4-hydroxybenzaldehyde **2.24** and 3-hydroxybenzaldehyde **2.27**. Of the various methods available for the protection of hydroxy groups we decided to use the tetrahydropyranyl ether as it is generally easy to form and inert to most non-acidic conditions. Thus both starting materials were THP-protected, according to the method of Severi, [50] to yield aldehydes **2.25** and **2.28**. In turn, these were transformed by reduction to alcohols **2.26** (94%) and **2.29** (90%), respectively. A Mitsunobu-reaction with 2-iodophenol then yielded benzyl iodoaryl ethers **2.17** and **2.30**. With the product derived from 4-hydroxybenzaldehyde, purification proved troublesome and the yield was low (51%) compared to the 3-hydroxybenzaldehyde derivative (94%) (Schemes 44 and 45).



a. CH_2Cl_2, THF, 10 mol% PPTS, 3,4-dihydro-2*H*-pyran, r.t., 72 h; **b.** $NaBH_4$, MeOH, r.t., 1 h; **c.** DIAD, PPh_3, 2-iodophenol, THF, -10 °C, 2 h.

Scheme 44

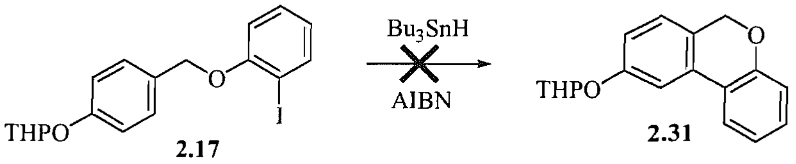


a. CH_2Cl_2, THF, 10 mol% PPTS, 3,4-dihydro-2*H*-pyran, r.t., 72 h; **b.** $NaBH_4$, MeOH, r.t., 1 h; **c.** DIAD, PPh_3, 2-iodophenol, THF, -10 °C, 2 h.

Scheme 45

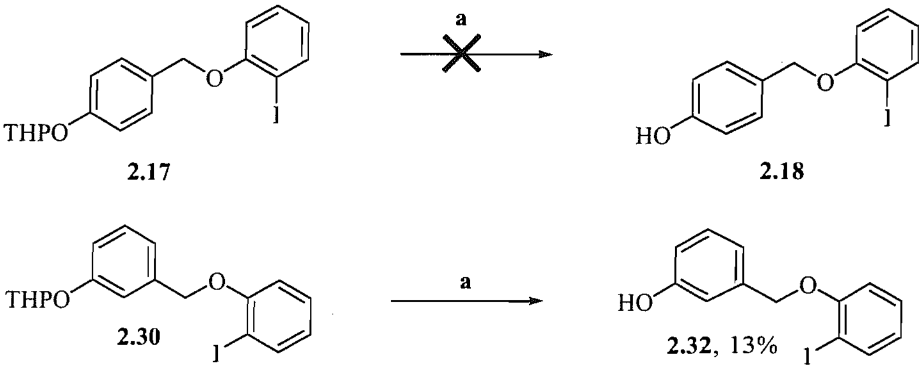
2.3. Radical Cyclisation Reaction and Cleavage of the THP-Group

Before embarking on the solid phase reactions, we thought it appropriate to effect the radical cyclisation of **2.17** in solution. Based on ^{1}H-NMR analysis of the products derived from the radical cyclisation, the reaction was unsuccessful, giving a complex mixture of unidentified products (Scheme 46).



Scheme 46

At this point our attention turned to the problem of removal of the THP-protecting group so that the substrate might be coupled to a solid support. A hydrolyzing system by Lee, [51] using CBr_4 in MeOH for reflux, failed to cleave tetrahydropyranyl ether **2.17** completely giving an inseparable mixture of starting material and the deprotected material. The reaction was repeated with addition of an excess of CBr_4 and with an increase in the reaction time. These had no beneficial effect on the outcome. Iodoaryl ether **2.30** was successfully deprotected to **2.32**, albeit in low yield (13%) (Scheme 47).



a. CBr_4 / MeOH, 65 °C, 3 h.

Scheme 47

2.4. Conclusion

Benzyl iodoaryl ethers suitable for attaching to the solid phase were prepared from 4-hydroxybenzaldehyde and 3-hydroxybenzaldehyde. Thus, THP-protection of the phenols according to the method of Severi and reduction to the corresponding alcohols facilitated a Mitsunobu-reaction with 2-iodophenol to yield the desired benzyl iodoaryl ethers. With the product derived from 4-hydroxybenzaldehyde, purification proved troublesome and the yield was low (54%) compared to that attained with the 3-hydroxybenzaldehyde derivative (94%). An attempt to effect the radical cyclisation of 2-[4-(2-iodo-phenoxymethyl)-phenoxy]-tetrahydro-pyran **2.17** was unsuccessful, giving unidentified products. Translation of this chemistry to the solid phase required removal of the THP-protecting group. The iodoaryl ether **2.17** could not be deprotected using CBr_4 in CH_3OH at reflux, producing an inseparable mixture of cleaved material and starting material. Iodoaryl ether **2.30** was successfully deprotected to **2.32**, but in a very low yield (13%). Consequently we decided that the reaction was unsuitable for the analogous resin bound substrates so we sought a more reliable method for THP hydrolysis.

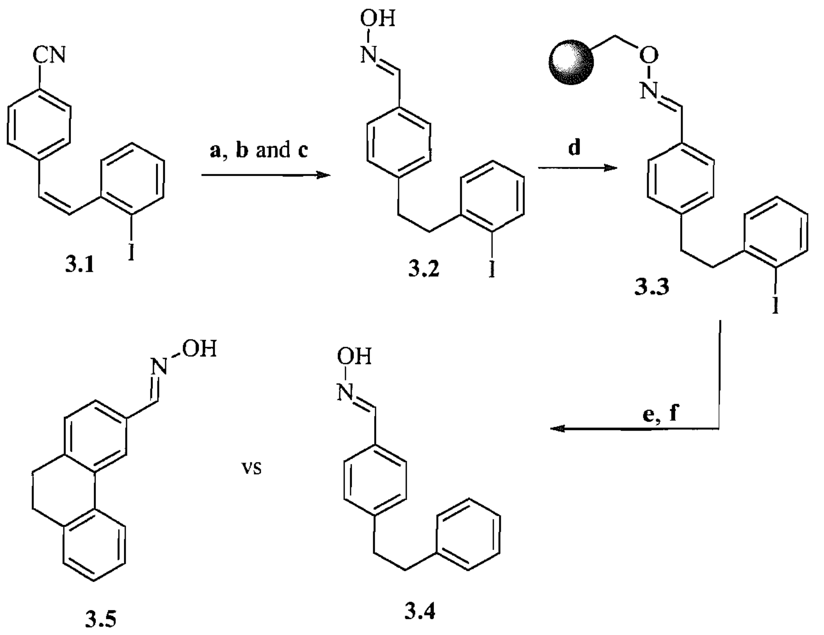
Chapter 3 - Using the DHP-Linker for Attaching Oximes

3 Using the DHP-Linker for Attaching Oximes

3. 1. Background

Research into the possibility of attaching oximes to a solid support *via* an ether linkage was then investigated. We hoped that the method would allow aldehydes to be attached to a solid support in a traceless fashion. This would be useful as Wittig methodology could give access to a series of cyclisation precursors with differing electronic characteristics. After the radical reaction, the product mixture could be cleaved from resin with TFA (Scheme 48).

A series of polystyrene-bound substituted benzophenone oximes were synthesised by Kaiser and Degrado in 1979. [52] The oxime containing resin, which was initially developed for solid phase peptide synthesis, has been used in the synthesis of ureas and hydroxamic acids on solid support. [53,54]

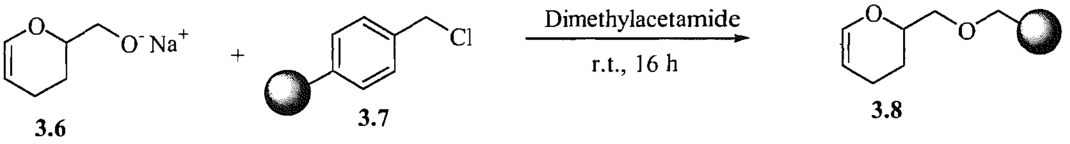


a. *p*-$TsNHNH_2$, NaOAc, THF / H_2O, 80 °C, 16 h; **b.** DIBAL-H, PhMe, 0 °C, 1 h, then $CHCl_3$ / HCl, r.t., 1 h; **c.** $NH_2OH \cdot HCl$, Na_2CO_3, EtOH / H_2O, 50 °C, 15 min.; **d.** DHP-resin, PPTS, 1,2-dichloroethane, 80 °C, 16 h; **e.** Bu_3SnH, AIBN, PhMe, reflux, 24 h; **f.** 95% TFA, 2.5% DCM, 2.5% (i-Pr)$_3$SiH, r.t., 1 h.

Scheme 48

3.2. The DHP-Linker

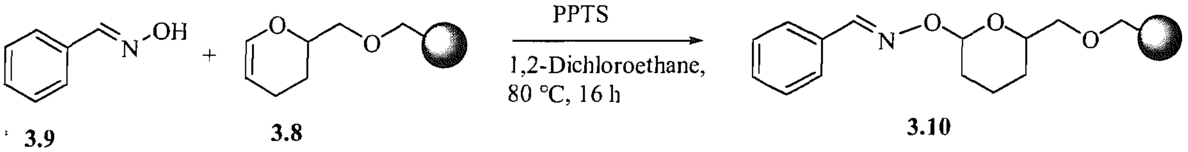
The dihydropyran (DHP) linker is an example of linker based on a common solution phase protecting group. Both primary and secondary alcohols, as well as phenols, have been reported to couple to a dihydropyran-functionalised support, [55] and the resulting tetrahydropyranyl (THP) protecting group is stable to strong bases. Attachment of an alcohol is catalysed with *p*-TsOH at 0 °C or PPTS in 1,2-dichloroethane at 80 °C. Cleavage is achieved with 95% TFA, or with PPTS in 1:1 butanol / 1,2-dichloroethane at 60 °C. The method has been used a number of times, and it has been found that the loading is highly dependent on the nature of the substrate. Loading can be very poor for highly hindered systems. The dihydropyran-functionalised support is synthesised in a single step as shown in Scheme 49, with Merrifield resin (chloromethylpolystyrene-1%-divinylbenzene) **3.7** being treated with the sodium salt of **3.6** in dry *N, N*-dimethylacetamide at room temperature for 16 hours.



Scheme 49

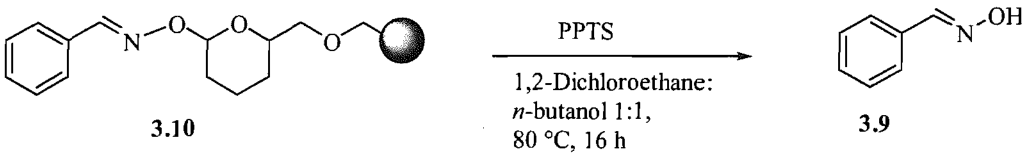
3. 3. Attachment of Benzyloximes on Solid Phase

Instead of coupling an alcohol, we wished to establish whether benzyloximes such as **3.9** (3 eq.) could be attached to the resin **3.8** employing pyridinium *para*-toluenesulfonate (PPTS) at 80 °C for 16 h (Scheme 50). Pleasingly, when **3.8** was treated with oxime **3.9** and PPTS, the resulting resin **3.10** gave an IR stretch at 1650 cm^{-1}, suggesting that a C=N had been formed and the reaction had been successful.



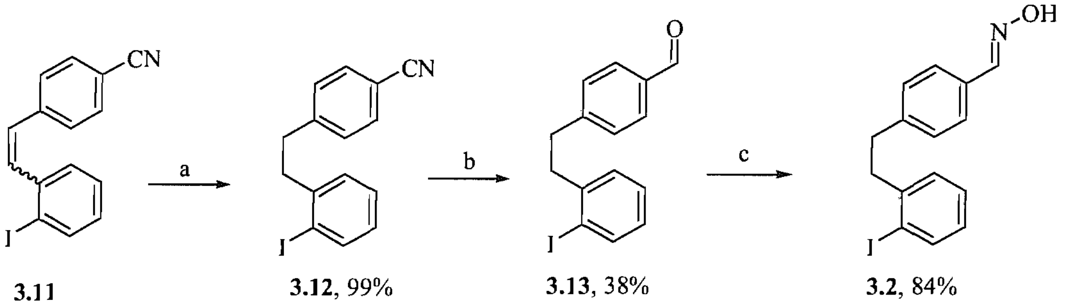
Scheme 50

The loading level was next determined by cleavage of the oxime from the resin using PPTS in 1 : 1 *n*-butanol / 1,2-dichloroethane at 60 °C for 16 hours (Scheme 51). From the isolated mass of **3.9** we determined a loading level of 0.52 mmol / g of resin.



Scheme 51

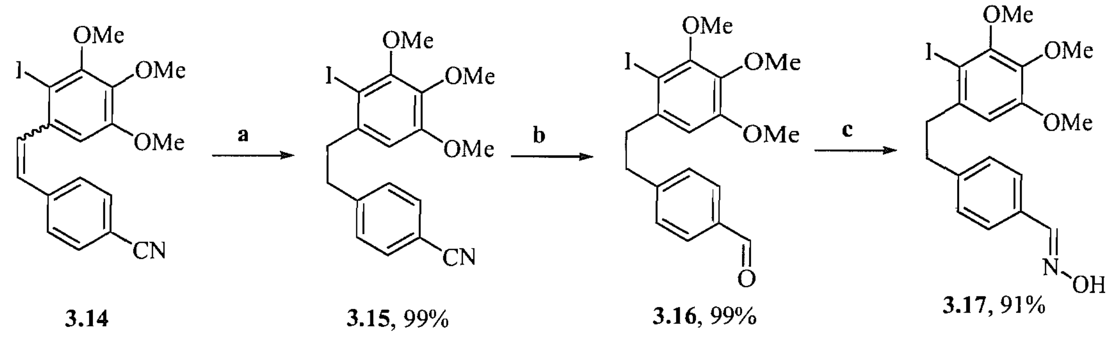
Our next task was to prepare oxime based substrates for attachment to the resin and radical cyclisation. The first substrate targeted was oxime **3.2**, which we hoped to prepare from cyanostilbene **3.11**. The alkene was reduced with diimide to the corresponding alkane **3.12** in quantitative yield (99%). Reduction of the nitrile-group with DIBAL-H then gave aldehyde **3.13** in a modest yield (38%). Condensation with hydroxylamine hydrochloride then resulted in oxime **3.2** (84%).



a. *p*-TsNHNH$_2$, NaOAc, THF / H$_2$O, 80 °C, 16 h; **b.** DIBAL-H, PhMe, 0 °C, 1 h, then CHCl$_3$ / HCl, r.t., 1 h.; **c.** NH$_2$OH · HCl, Na$_2$CO$_3$, EtOH / H$_2$O, 50 °C, 15 min.

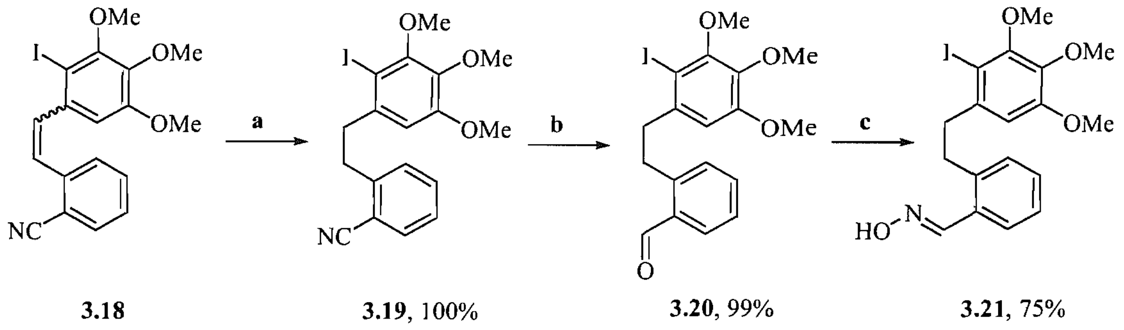
Scheme 52

The same sequence was then applied to the two trimethoxy derivatives **3.14** and **3.18** (Schemes 53 and 54). In each case, yields achieved were excellent, leading to four oxime precursors for our study.



a. *p*-TsNHNH$_2$, NaOAc, THF / H$_2$O, 80 °C, 16 h; **b.** DIBAL-H, PhMe, 0 °C, 1 h, then CHCl$_3$ / HCl, r.t., 1 h; **c.** NH$_2$OH · HCl, Na$_2$CO$_3$, EtOH / H$_2$O, 50 °C, 15 min.

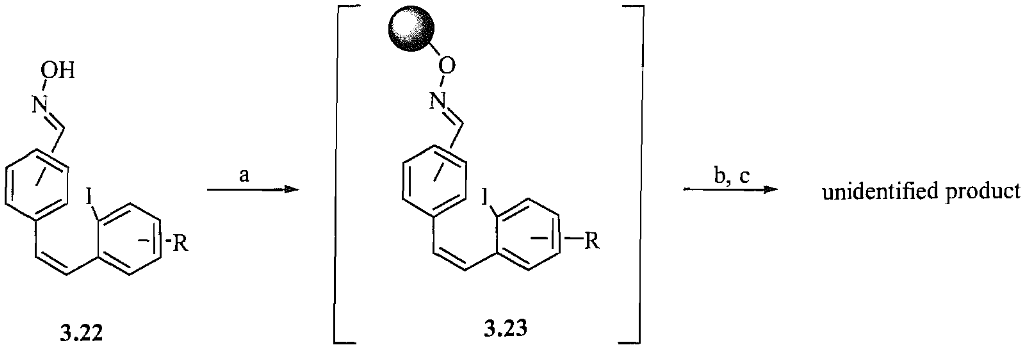
Scheme 53



a. *p*-TsNHNH$_2$, NaOAc, THF / H$_2$O, 80 °C, 16 h; **b.** DIBAL-H, PhMe, 0 °C, 1 h, then CHCl$_3$ / HCl, r.t., 1 h; **c.** NH$_2$OH · HCl, Na$_2$CO$_3$, EtOH / H$_2$O, 50 °C, 15 min.

Scheme 54

With these substrates to hand, we next sought to attach them to the DHP-resin **3.8**. But having performed the coupling reaction of the substrate, IR proved inconclusive as to whether we had successfully coupled our substrates onto the resin. Yet, we proceeded for cyclisation following cleavage. Unfortunately, in each case cleavage of the product mixture from the resin yielded insufficient material for analysis. This suggests inefficient loading of oxime to resin. This was disappointing, given that we had been able to attach **3.9**, albeit with low loading. Consequently, low loading would have made it expensive to proceed on this path.



a. DHP-resin, PPTS, 1,2-dichloroethane, 80 °C, 16 h; **b.** Bu_3SnH, AIBN, PhMe, reflux, 24 h; **c.** 95% TFA, 2.5% DCM, 2.5%, $(i\text{-Pr})_3SiH$, r.t., 1 h.

Scheme 55

3. 4. Conclusion

We have shown that the DHP resin can be used to attach oximes to a solid support, albeit with low loading, and that these may be cleaved from the resin using standard hydrolysis conditions. We were also able to prepare a series of oxime precursors in high yield in solution. However, attempts to attach these to the solid support, effect the key radical cyclisation and then cleave the resulting product into solution could not be realised. A key issue was the low quantity of material given on cleavage, which prevented proper characterisation of the product mixture. These disappointments led us to direct our efforts elsewhere in the hope of finding a suitable system to examine.

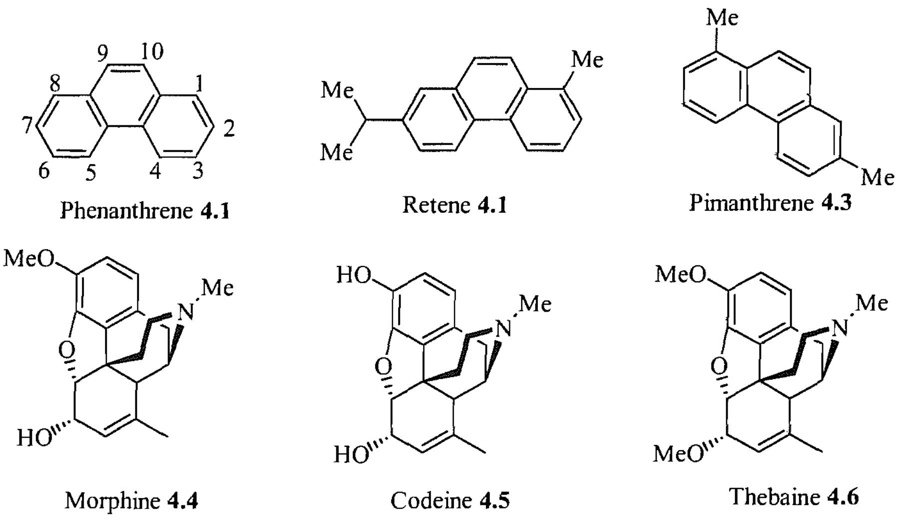
4 Radical Cyclisations of Stilbenes and Dihydrostilbenes on Solid Phase

4 Radical Cyclisations of Stilbenes and Dihydrostilbenes on Solid Phase

4. 1. Background

4. 1. 1. Biological Activity

Phenanthrene **4.1** is a polycyclic aromatic hydrocarbon composed of three fused benzene rings. Many phenanthrenes occur in nature, and saturated derivatives are numerous including the steroids and many classes of terpenes. Retene **4.2** is commonly found in technical oils produced industrially by distillation of resins and oleoresins, while pimanthrene **4.3** is a minor constituent of the resin from *Pinus Maritima.* Partially saturated phenanthrenes are also found as subunits in alkaloids, including the morphine group with important analgesic, hypnotic and calmative properties (*e.g.* **4.4** to **4.6**). Morphine, the most prevalent and important alkaloid in opium, binds to and activates μ-opiate receptors in the brain, spinal cord and gut. Regular use, even for a few days, invariably leads to physical tolerance and dependence, and a characteristic and highly unpleasant withdrawal syndrome occurs when the dosage is suddenly reduced. Yet, in spite of their dangerous habit-forming character, the alkaloids of the morphine group are indispensable in modern medical practice (Scheme 56).[56]



Phenanthrene **4.1**

Retene **4.1**

Pimanthrene **4.3**

Morphine **4.4**

Codeine **4.5**

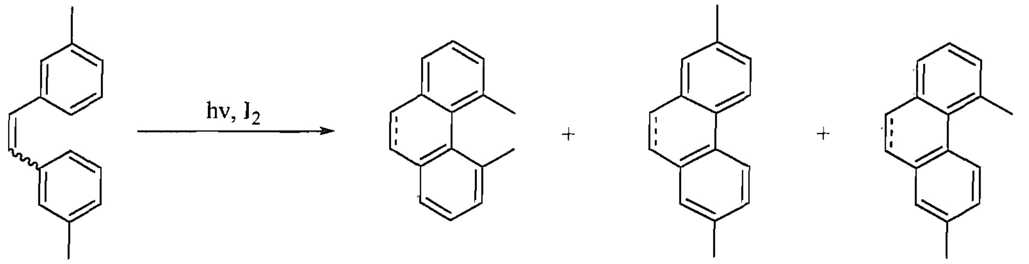
Thebaine **4.6**

Scheme 56

4. 2. Radical Cyclisations of 2-Halostilbenes

4. 2. 1. Methods for the Synthesis of Phenanthrenes in Solution

Aryl-aryl bond forming reactions have been known for more than a century and they form an important class of reactions in of modem organic synthesis. The formation of phenanthrenes and related polynuclear aromatics by ultraviolet light irradiation of stilbenes or stilbene derivatives in the presence of an oxidant such as iodine has been extensively studied. In 1971, Mallory *et al.* [57] studied the photocyclisation of *m, m'*-dimethylstilbene **4.7** and showed that each of the three possible cyclisation modes leading to **4.8-4.10** were observed, with a modest preference for the formation of 4,5-dimethylphenanthrene **4.8**. In this system three ground-state conformers are in equilibrium, with each able to undergo photocyclisation to the corresponding dihydrophenanthrenes. These, in turn, are oxidised with the iodine to 4,5-dimethylphenanthrene **4.8**, 2,7-dimethylphenanthrene **4.9** and 2,5-dimethylphenanthrene **4.10** (Scheme 57).

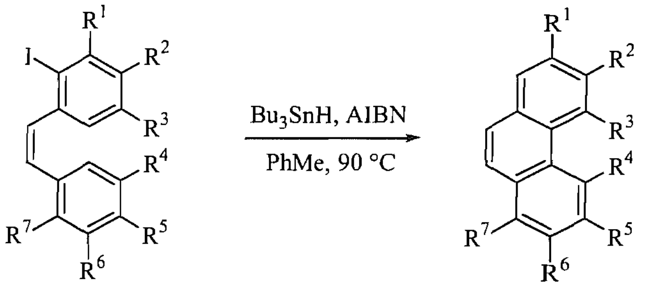


4.7 **4.8**, 54% **4.9**, 28% **4.10**, 18%

Scheme 57

4. 2. 2. Previous Radical Cyclisations of 2-Halostilbenes and 2-Iododihydrostilbenes

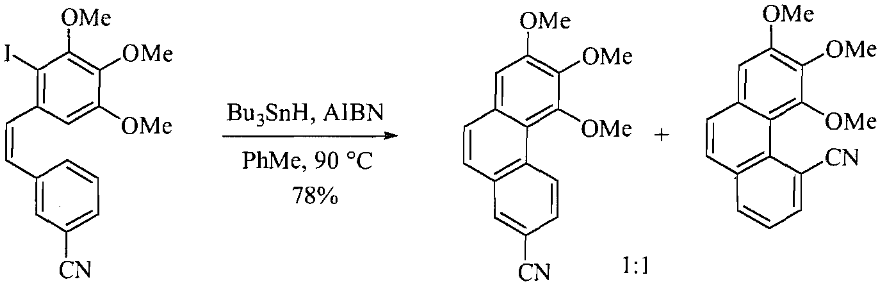
Regiocontrol is often poor in such photocyclisation reactions leading to stilbenes. Moreover, little can be done to bias reactions in favour of a particular cyclisation mode should the desired outcome be disfavoured. Indeed, if the wrong product is given a different method of preparing the phenanthrene has to be used or a cumbersome strategy involving blocking groups employed. A solution to this regiochemical problem was developed in our group by Michael Nunn and involved a radical cyclisation strategy. He showed that 2-halostilbenes are useful precursors of phenanthrenes through tributyltin hydride mediated radical cyclisations. Yields ranging from good to excellent were achieved in each case, with the precursors formed by simple Wittig reactions (Scheme 58). [58] Changing the electronics of the haloaromatic had little effect on the course of the reaction with electron rich and unsubstituted arenes each displaying useful reactivity. A separable 1:1 mixture of regioisomers **4.14** and **4.15** was formed in the case of **4.13** (Scheme 59), whereas cyclisation of **4.19**, gave a separable 5:1 mixture of **4.20** and **4.21** in favour of the less encumbered product (Scheme 60). Similarly, exposure of **4.11d** to standard radical forming conditions produced only **4.12d**, indicating that the electronic character of the radical donor and acceptor each have a significant impact on the regiochemical course of the reaction.



4.11 **4.12**

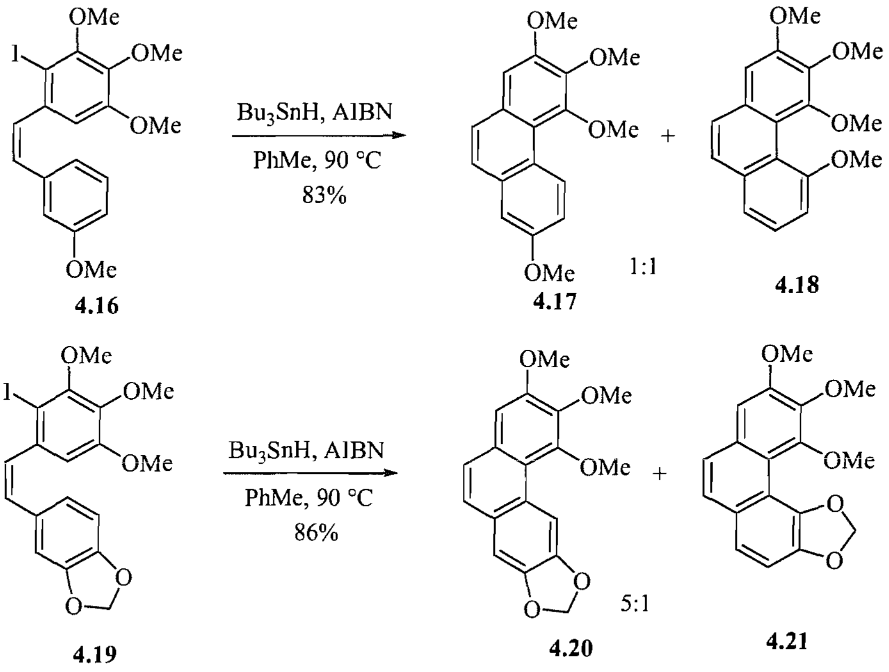
a) R^5 = CN, 90%.
b) R^1-R^3 = OMe, R^7 = CN, 92%.
c) R^1-R^3 = OMe, 89%.
d) R^1-R^3 = OMe, R^5-R^6 = OMe, 81%.

Scheme 58



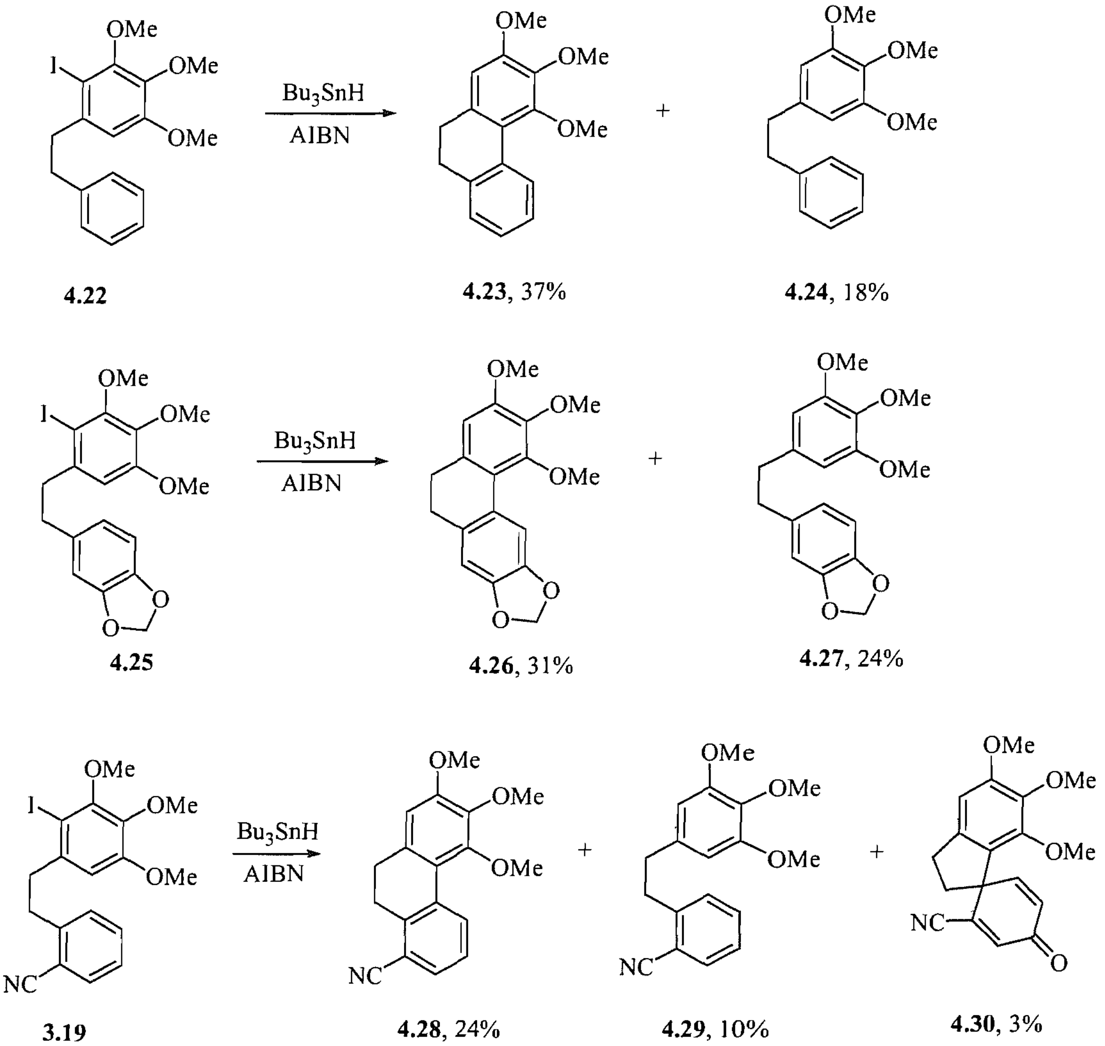
4.13 **4.14** **4.15**

Scheme 59



Scheme 60

Reaction of 2-iodohydrostilbenes with tributyltin hydride and AIBN proved less efficient. In each of the cases examined, the corresponding dihydrophenanthere was formed in modest yield together with the product of direct reduction of the halide. This system seemed ideal for translation to solid support as the unwanted byproduct is formed by intermolecular hydrogen-atom abstraction, a process that should be slowed when the substrate is immobilised on a resin (Scheme 61).

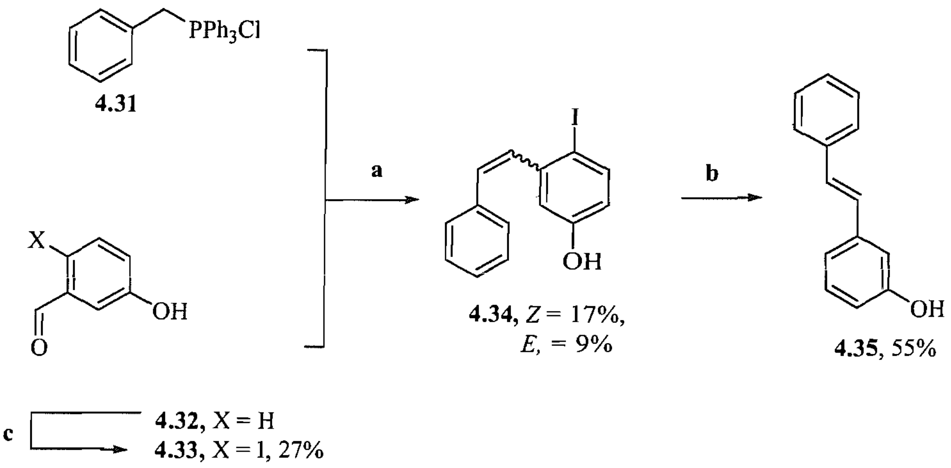


Scheme 61

4. 3. Synthesis of Phenanthrenes: Investigation with Iodostilbenes

Before we could investigate the hypothesis, we first needed to develop a route to the iodostilbene precursors. *cis*-Iodostilbenes were required for efficient cyclisation, and we hoped that a Wittig reaction might give us the desired stereochemical outcome. To that end, phosphonium salt **4.31** was deprotonated with sodium hydride and conjoined with aldehyde **4.33**, yielding a separable

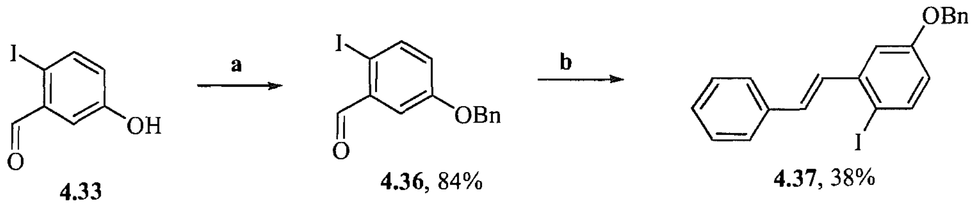
2:1 mixture of *cis*- and *trans*-iodostilbenes **434**(*E* & *Z*). Subjecting *cis*-iodostilbene **4.34**(*Z*) to standard tributyltin mediated radical forming conditions yielded only the isomerised and reduced *trans*-stilbene **4.35** in 55% yield (Scheme 62). None of the anticipated phenanthrene was formed, indicating that alkene isomerisation outpaced carbon-to-iodine bond homolysis in this case.



a. NaH, THF, r.t., 2 h; **4.33**, r.t., 16 h. **b.** Bu$_3$SnH, AIBN, PhMe, 90 °C, 16 h; **c.** KI, I$_2$, NH$_3$, r.t., 1 h, conc. HCl, r.t., 3 h.

Scheme 62

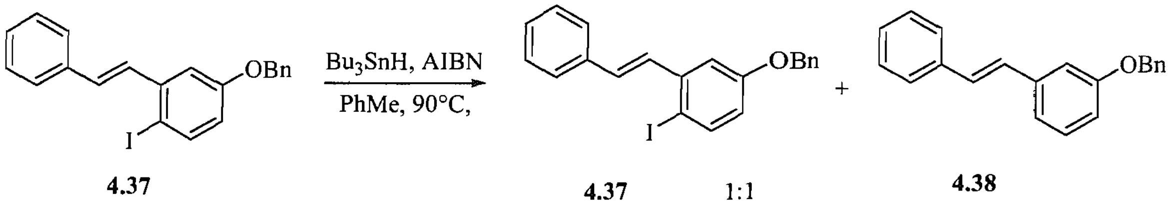
The observation led us to conclude that the free phenol was adversely affecting the course of the reaction. Consequently, **4.33** was protected as its benzyl ether **4.36** in 84% yield. A Wittig reaction between **4.36** and benzyltriphenylphosphonium chloride gave only the *trans*-stilbene **4.37** in a disappointing 38% yield (Scheme 63).



a. K_2CO_3, BnBr, $(CH_3)_2CO$; **b.** NaH, benzyltriphenylphosphonium chloride, THF, r.t., 2 h; **4.36**, r.t., 16 h.

Scheme 63

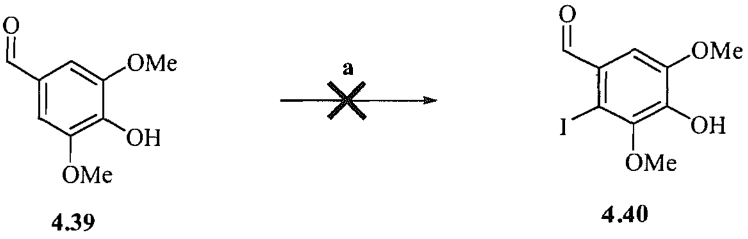
Stilbene **4.37** was then treated with Bu_3SnH and AIBN. ^1H, ^{13}C-NMR and MS results of the cyclisation attempt suggested that a mixture of starting material **4.37** and reduced product **4.38** had been given in 1:1 ratio (Scheme 64). Given the poor results attained with this substrate, we decided to try another approach for the synthesis of phenanthrenes.



Scheme 64

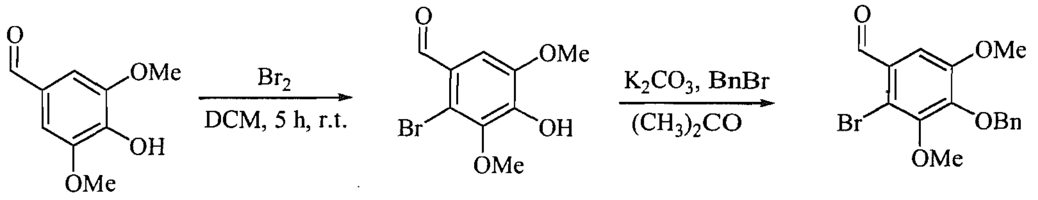
4. 4. Synthesis of Phenanthrenes: Investigation with Bromostilbenes

Attempts to effect the iodination of syringaldehyde **4.39** to **4.40** using silver trifluoroacetate and an iodinating agent failed.



a. I_2, $AgOCOCF_3$, CH_2Cl_2, r.t., 1.5 h.

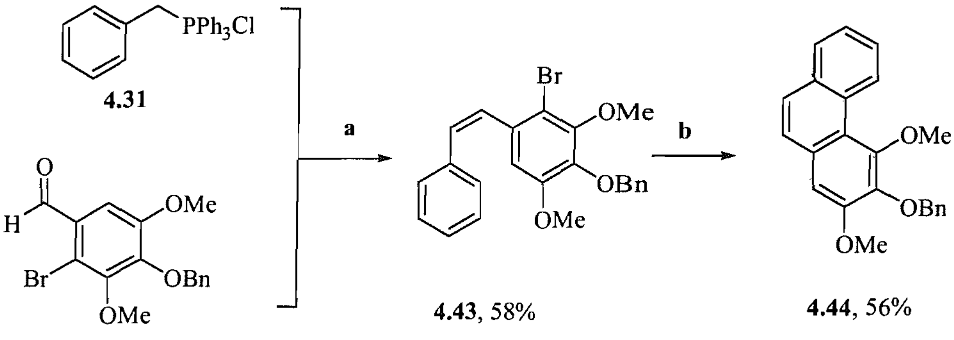
As an alternative approach it was decided to investigate the use of bromostilbenes for the cyclisation. Though the homolysis of the carbon-halogen bond in aryl bromides is much harder to effect than the corresponding reaction with aryl iodides, they have often been employed as substrates for radical reactions and are much easier to prepare. Bromination of syringaldehyde **4.39** to **4.41**, and subsequent protection of the phenol with a benzyl group was successful and gave us **4.42** (Scheme 65).



4.39 **4.41**, 88% **4.42**, 42%

Scheme 65

We next needed to install the acceptor arene using a Wittig reaction. Deprotonation of **4.31** with sodium hydride followed by addition of **4.42**, yielded *cis*-stilbene **4.43** in 58% yield. Pleasingly, warming a toluene solution of this material to 80 °C in the presence of tributyltin hydride and AIBN gave the expected product 3-benzyloxy-2,4-dimethoxyphenanthrene **4.44** in 56% yield (Scheme 66).



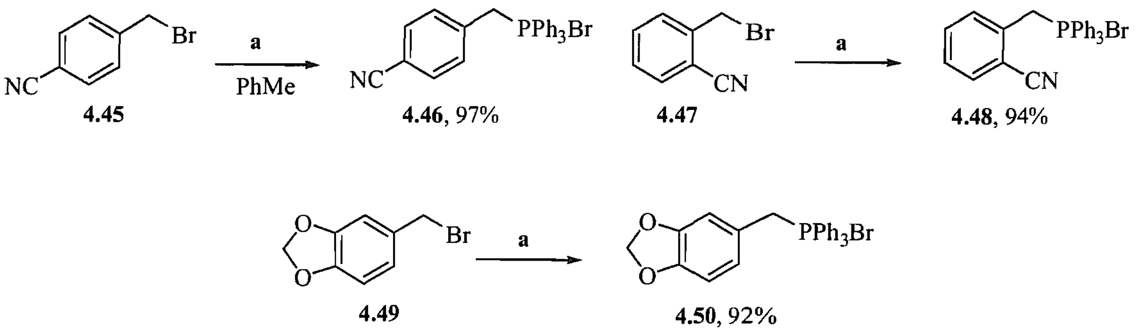
4.31 **4.42** **4.43**, 58% **4.44**, 56%

a. NaH, THF, r.t., 2 h; **4.42**, r.t., 2 h; **b.** Bu_3SnH, AIBN, PhMe, 80 °C, 16 h.

Scheme 66

4. 5. Preparation of Solid Phase Precursors

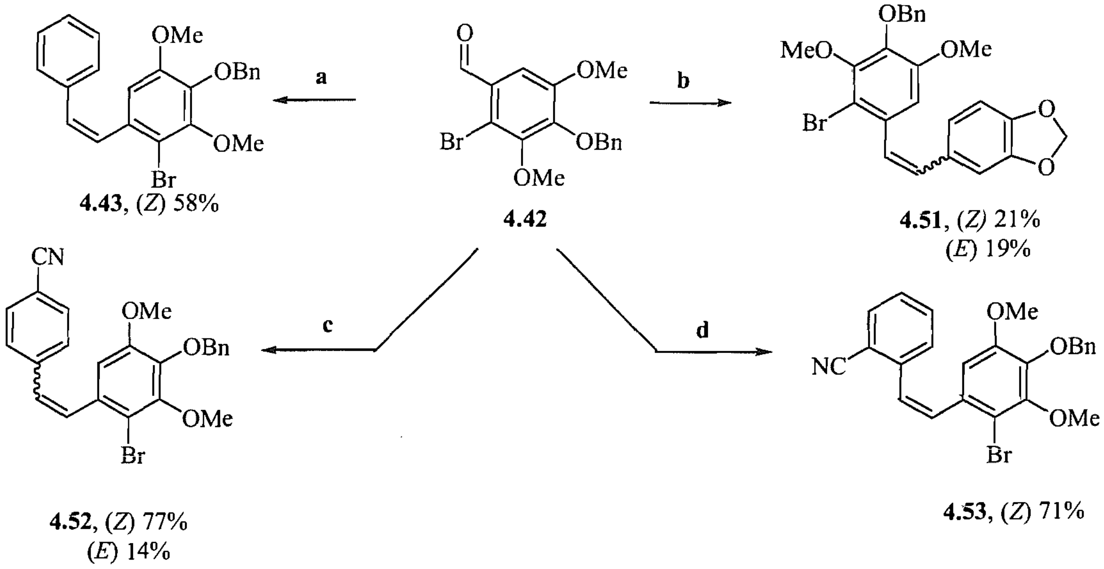
A range of different phosphonium salts, **4.46, 4.48** and **4.50**, was prepared by treatment of benzyl bromide substrates **4.45, 4.47** and **4.49**, respectively, with triphenylphosphine in toluene (Scheme 67).



a. PPh$_3$, PhMe, 90 °C, 5 h.

Scheme 67

The precursors for our study were the *cis*-stilbenes **4.51, 4.52, 4.53** and **4.43** and the saturated analogues derived from reduction of the respective alkenes with diimide. These were conveniently prepared by a series of Wittig reactions with the benzyl-protected bromosyringaldehyde **4.42** (Scheme 68). Each of the Wittig reactions gave a mixture of *cis*- and *trans*-stilbenes in ratios of between 6:1 and 1:1. These isomers were readily separated by column chromatography. For **4.43** and **4.53** (reactions **a** and **d**), the *trans*-isomers were formed in trace amounts and could not be isolated in sufficient purity for proper characterisation.

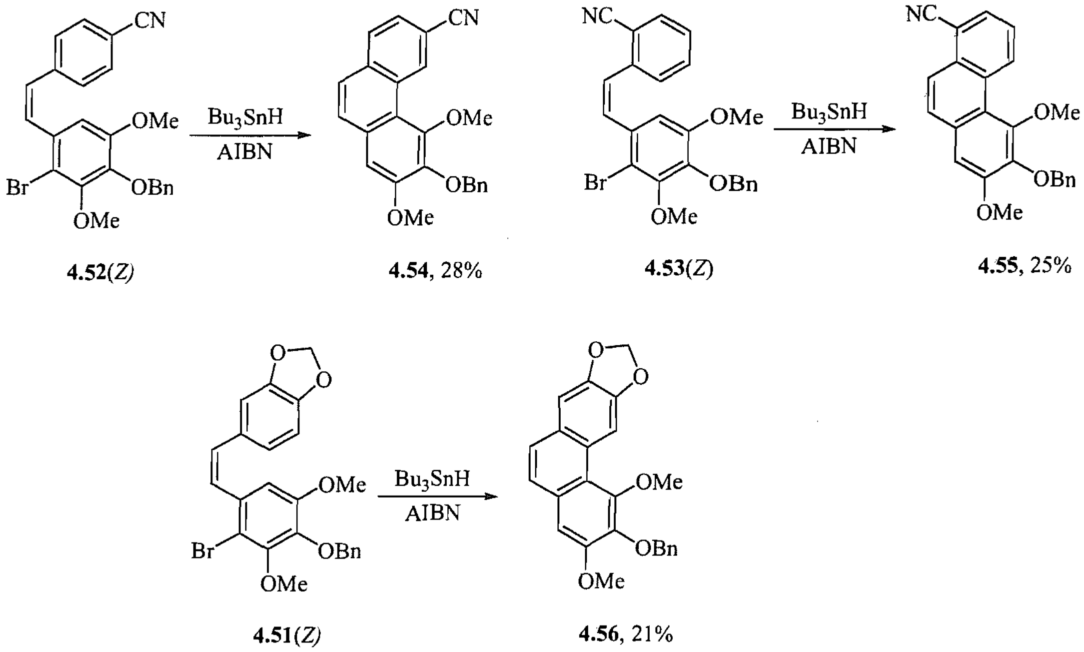


a. $ArCH_2PPh_3Br$, NaH, THF, 0 °C, 2 h, then **4.42**, r.t., 16 h; **b.** $ArOCH_2OCH_2PPh_3Br$, NaH, THF, 0 °C, 2 h, then **4.42**, r.t., 16 h; **c.** 4-CN-C_6H_4-CH_2PPh_3Br, NaH, THF, 0 °C, 2 h, then **4.42**, r.t., 16 h; **d.** 2-CN-C_6H_4-CH_2PPh_3Br, NaH, THF, 0 °C, 2 h, then **4.42**, r.t., 16 h.

Scheme 68

4. 6. Radical Cyclisation Reactions

In the reactions highlighted below, cyclisation of *cis*-stilbenes **4.52(*Z*), 4.53(*Z*)** and **4.51(*Z*)** by treatment with tributyltin hydride and AIBN in toluene to phenanthrenes **4.54, 4.55** and **4.56** were each achieved, although yields were modest (Scheme 69). From these studies it was clear that changing the substitution pattern on the acceptor arene had little effect on the outcome of the reaction. Thus 2-bromo-4-stilbene **4.52(*Z*)** and 2-bromo-2-stilbene **4.53(*Z*)** yielded the phenanthrenes **4.54** and **4.55** in 28% and 25% yield, respectively. The cyclisation of stilbene **4.51(*Z*)** to phenanthrene **4.56** also proceeded successfully in 21% yield.

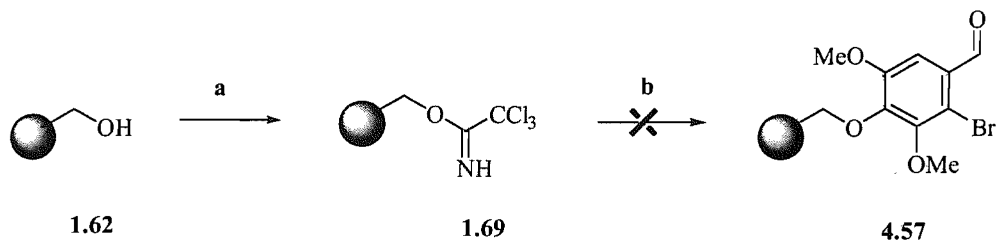


Scheme 69

4.7. Reactions on Solid Support

For a solid phase synthesis to be realised it is essential to couple the substrates to the solid support efficiently. We required an acid labile linker with an appropriate balance of stability and reactivity. It needed to have a reasonable shelf life for convenient use, and yet the linker had to be reactive enough to be displaced under mild conditions once our reaction sequence was complete. To that end, PS-Wang-trichloroacetimidate resin **1.69** was prepared. However, all attempts to effect the desired coupling to our phenol precursor **4.41** met with failure, despite considerable effort (Scheme 70). The formation of the polymer bound acetimidate **1.69** was monitored by IR, and this showed the expected appearance of new absorption bands at 1664 cm^{-1} and 3500 cm^{-1} for the acetimidate group. However, the expected change in the IR on addition of phenol **4.41** under a range of conditions did not materialise. Since it was plausible that the aldehyde in resin bound **4.57** might also give a stretching frequency at ~1664 cm^{-1} we employed

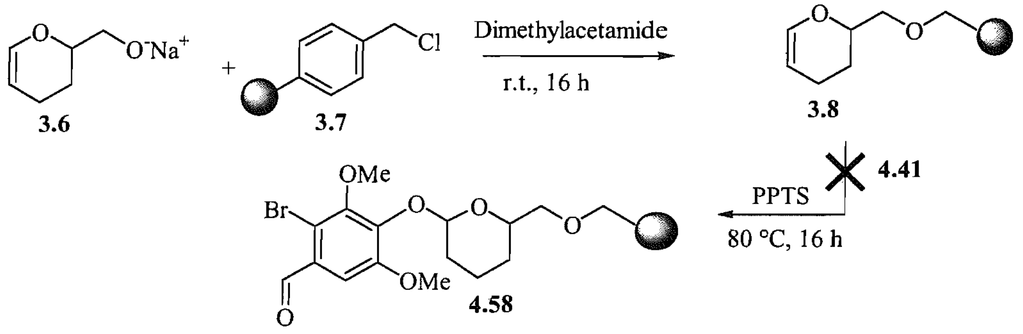
^{1}H NMR-solid bead analysis as a second method of analysis. This confirmed our suspicion that the coupling reaction to form **4.57** had failed.



a. Cl_3CCN, DBU, CH_2Cl_2, 0 °C, 20-40 min.; **b. 4.41**, CH_2Cl_2, $BF_3 \cdot OEt_2$, cyclohexane.

Scheme 70

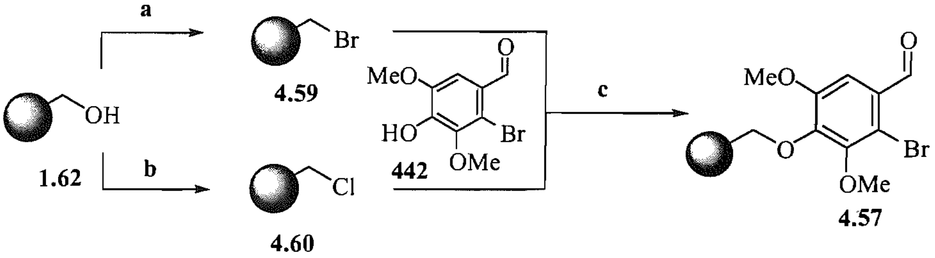
The dihydropyran-functionalized resin **3.8**, which has been used to attach alcohols to the Merrifield solid support, was therefore selected as a possible alternative as this mirrored our earlier THP protection of the phenol moiety. However, coupling of this resin **3.8** to phenol **4.41** could not be achieved (Scheme 71).



Scheme 71

These failures led us to consider alternative methods to attach our substrate to a solid support. An ideal resin should bear a linker with similar properties to a protecting group, *i.e.* have stability under the conditions required to advance the substrate to product, while possessing some reactivity to allow for its cleavage. The 95% TFA labile Wang resin seemed to fulfil these criteria.

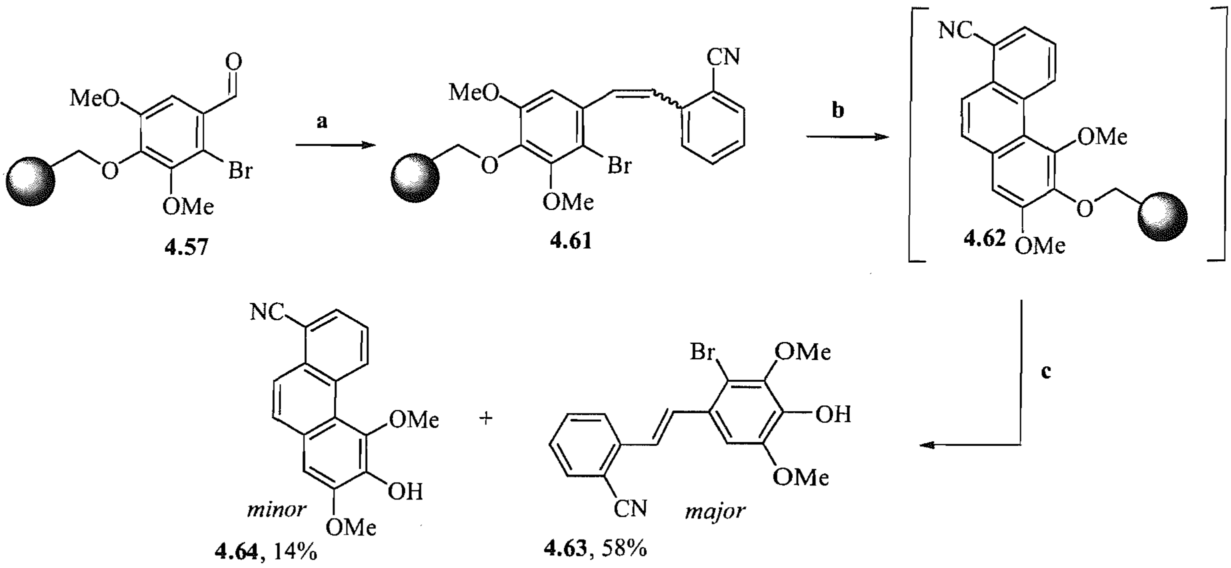
The terminal hydroxyl group in PS-Wang resin was first activated by conversion to chloro- and bromo Wang, according to the method of Raju *et al.* [59] In turn, each was reacted with phenol **4.41** in the presence of cesium carbonate according to the method of Grosche *et al.* [60] Pleasingly, coupling was achieved with both bromo- and chloro-PS-Wang to give our substrate **4.57**. Coupling was confirmed by IR and gel phase ^{13}C-NMR, the signals for the aldehyde being observed at ν_{max} 1685 cm^{-1} and δ_C 191.1 ppm, respectively (Scheme 72).



a. 5 eq. PBr$_3$, CH$_2$Cl$_2$, 0 °C, 45 min.; **b.** 4 eq. SOCl$_2$, CH$_2$Cl$_2$, 0 °C, 45 min.; **c.** Cs$_2$CO$_3$, **4.41**, DMF, 80 °C, 16 h.

Scheme 72

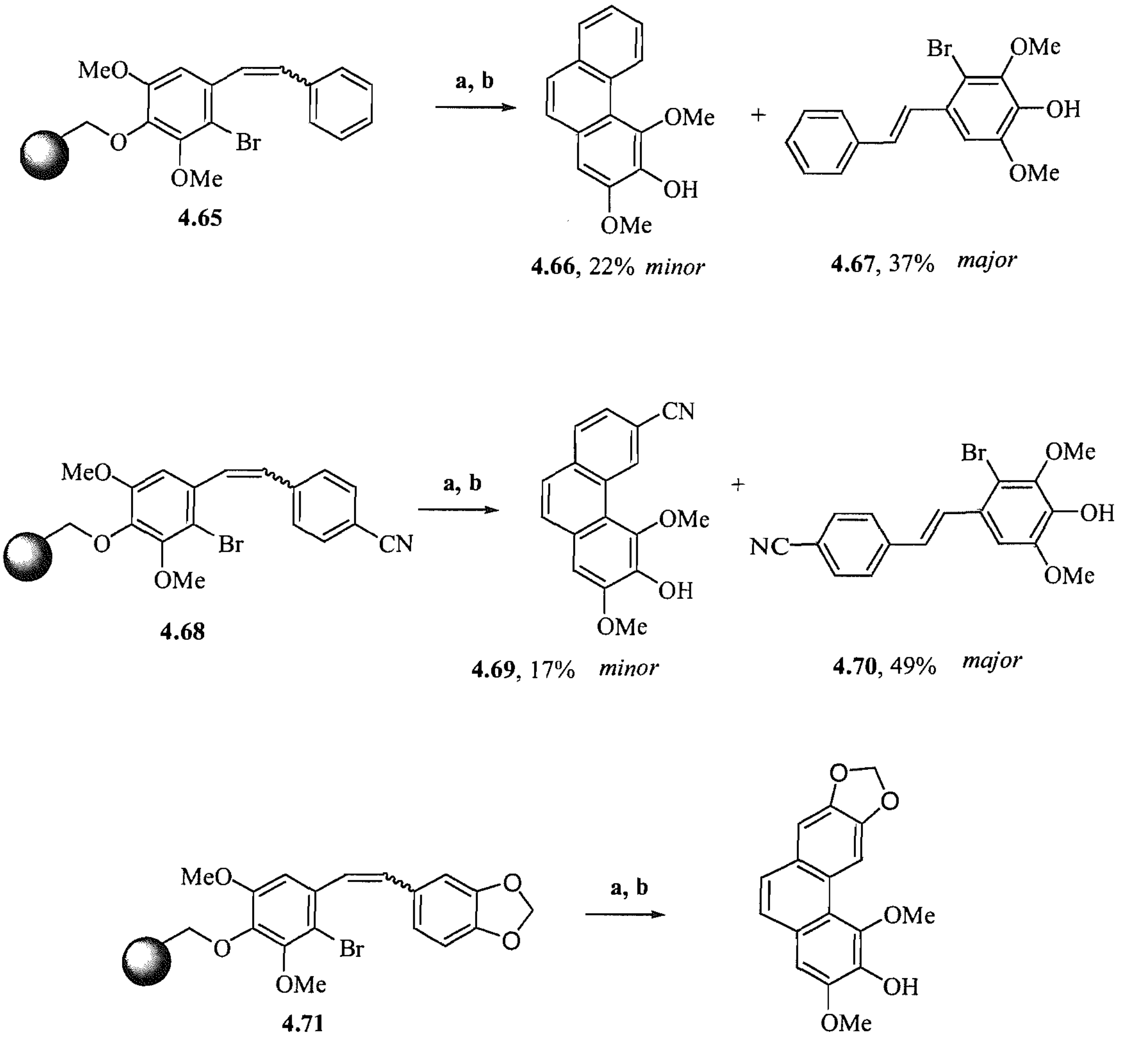
We next required to effect the Wittig reaction leading to stilbene **4.61**. Deprotonation of phosphonium bromide **4.48** (5 eq.) with excess sodium hydride (6 eq.) followed by addition of resin bound aldehyde **4.57** yielded bromostilbene **4.61**. We were able to infer that the reaction had been successful by the disappearance of the aldehyde signals at ν_{max} 1685 cm^{-1} in the IR and δ_C 191.1 ppm in the gel phase ^{13}C-NMR. The product resin was next subjected to standard tin mediated radical forming conditions then the 'product mixture' was cleaved from the resin using 95% TFA. Both reactions proceeded efficiently. However, analysis of the cleaved material showed that the desired phenanthrene **4.64** was the minor product of the reaction - the major component being the *trans*-stilbene **4.63** (Scheme 73). It seems likely that this is, at least in part, due to poor *Z*-selectivity in the Wittig reaction, though it could also be as a result of alkene isomerisation during the radical cyclisation phase.



a. Ar-CH_2PPh_3Br, NaH, THF, 0 °C, 2 h, then **462**, r.t., 16 h; **b.** Bu_3SnH, AIBN, PhMe, reflux, 16 h; **c.** 95% TFA, 2.5% DCM, 2.5% (*i*-Pr)$_3$SiH, r.t., 1 h.

Scheme 73

Encouraged by these result, a range of substrates (**4.65, 4.68 and 4.71**) for cyclisation was then prepared using the Wittig methodology. Changing the substitution pattern and electronics on the radical acceptor had minimal effect on the cyclisation reaction. In most cases, the desired phenathrene was formed as the minor product with the corresponding *trans*-stilbene being the dominant product (Scheme 74). For stilbene **4.71**, however, only the desired phenanthrene was recovered as the byproduct could not be isolated in sufficient yield and purity for reliable characterisation.



4.65

4.66, 22% *minor*

4.67, 37% *major*

4.68

4.69, 17% *minor*

4.70, 49% *major*

4.71

4.72, 19%

a. Bu_3SnH, AIBN, PhMe, reflux, 16 h; **b.** 95% TFA, 2.5% DCM, 2.5% $(i\text{-}Pr)_3SiH$, r.t., 1 h.

Scheme 74

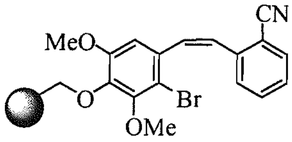
4. 8. Analysis

The lack of convenient methods of analysis for resin bound substrates is arguably the biggest drawback to resin based organic synthesis. To assist us in the development of this chemistry, we mimicked each of the key reactions in solution using a benzyl-protecting group in place of the polystyrene resin. This technique, though labour intensive, also provided us with a direct comparison of the solid phase and solution phase results. This comparison was especially useful when analysing the resin bound substrates. As discussed previously, we had found gel phase ^{13}C-NMR to be a useful, if slow, method to monitor reactions on the solid phase. Importantly there was excellent correlation between the ^{13}C-NMR-signals obtained by gel phase analysis on resin bound substrates and those obtained in solution with the analogous benzyl ether.

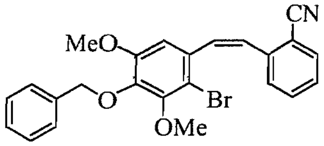
In Table 1, some resin IR and gel phase ^{13}C-NMR signals of resin bound stilbene **4.61** are compared to those of the corresponding benzyl ether **453**(*Z*) prepared in solution.

IR, Resin 4.61	**IR, 453(*Z*)**	**^{13}C NMR,Resin 4.61**	**^{13}C NMR, 4.53(*Z*)**
Absence of 1685 (s)	Absence of 1681 (s)	Absence of 191.1	Absence of 191.3
1390 (m)	1388 (s)	141.7	141.8
1106 (vs)	1100 (s)	117.5	117.9
		109.1	109.6
		61.2	61.3
		55.8	55.9

Table 1. IR values in cm^{-1}, ^{13}**C NMR** (Gel-phase, δ_C ppm (75 MHz, $CDCl_3$)).



Resin **4.61**

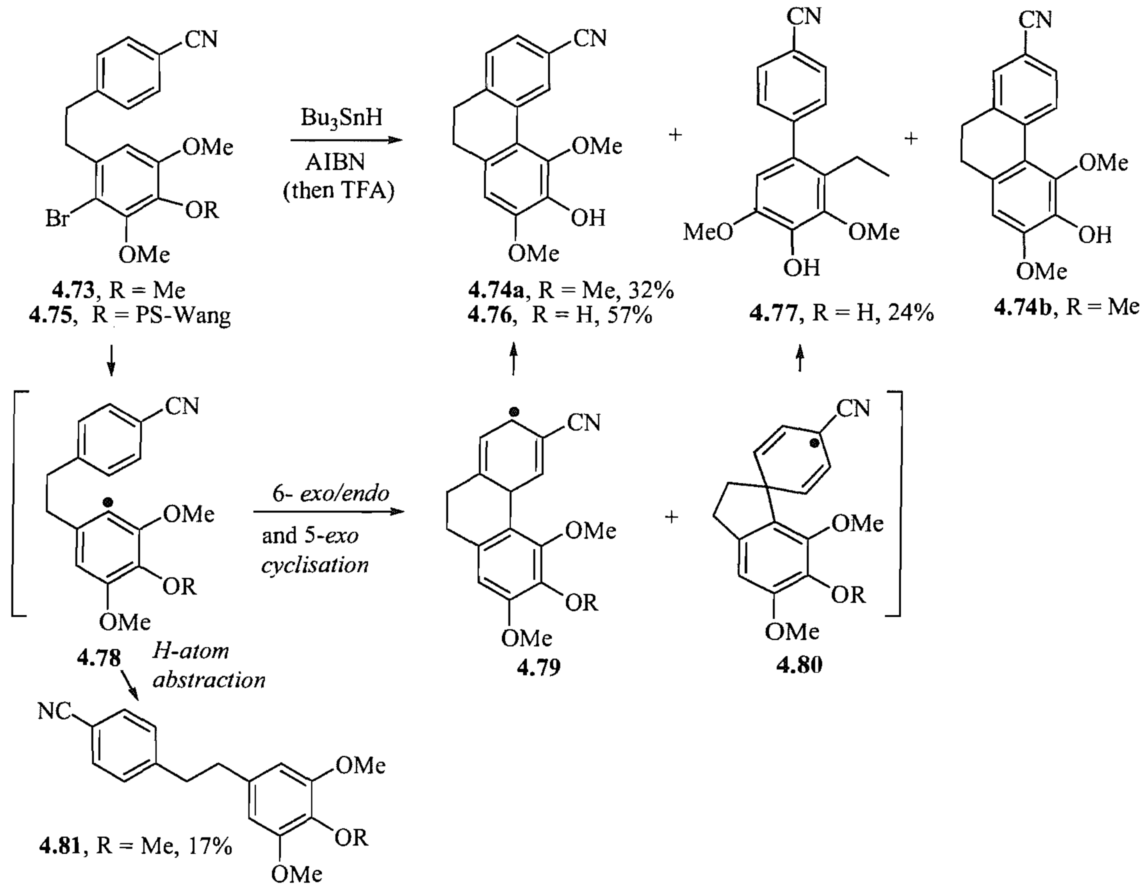


Benzyl ether **4.53(*Z*)**

4. 9. Changing the Course of Kinetics by Solid Phase Immobilisation

It is known that intermolecular reactions involving immobilised substrates are slower than analogous solution phase reactions due to the slow diffusion of reagents through the solid support. By contrast, related intramolecular reactions generally display very similar reaction kinetics. Our aim was to exploit this dichotomy as it offered a way of making slow radical cyclisation reactions more efficient than those conducted in solution.[49] We had now arrived at a point where this hypothesis could be tested. For proof of concept we chose to compare the radical cyclisation reactions of dihydrostilbenes **4.73** and **4.75**. These were each prepared by reduction of the corresponding stilbene **4.52** and **4.68** with diimide.

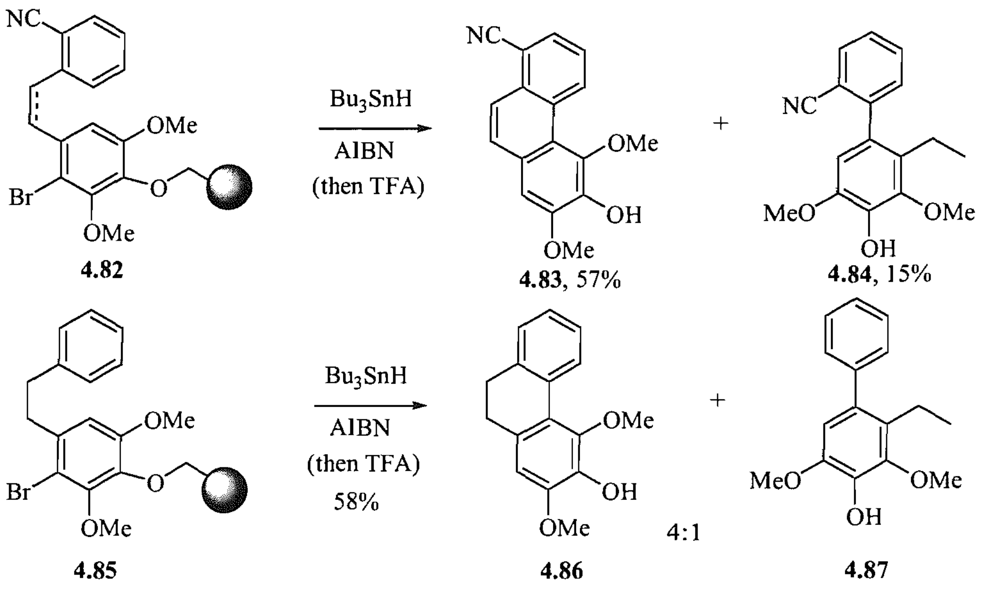
Research previously executed in our laboratories had shown that treatment of **4.73** with tributyltin hydride under standard radical forming conditions led to a complex mixture of products from which only dihydrophenanthrene **4.74a** (32%), dihydrophenanthrene **4.74b** and dihydrostilbene **4.81** (17%) could be isolated and properly characterised. Notably, when the PS-Wang immobilised analogue **4.75** was subjected to the same reaction, the product mixture after cleavage from the resin with 95% TFA, contained only products derived from cyclisation of the aryl intermediate to the vicinal arene. These were dihydrophenanthrene **4.76** (57%) and biaryl **4.77** (24%) (Scheme 75). Biaryl **4.77** was presumably formed through fragmentation of the spirocyclic radical intermediate **4.80** followed by H-atom abstraction from tributyltin hydride.



Scheme 75

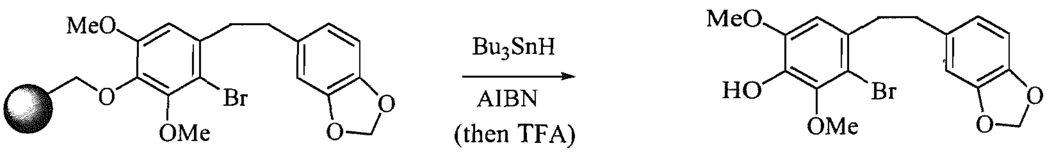
We similarly performed radical cyclisations of **4.82** and **4.85** with excess Bu_3SnH (18 eq.) and AIBN (9 eq.) (Scheme 77). Pleasingly, analysis of the product mixtures given after cleavage showed that each substrate had followed the radical pathway outlined above. Resin bound **4.82**, for example, gave phenanthrene **4.83** (57%) and biaryl **4.84** (15%). The former suggests that diimide reduction of the polymer bound stilbene was incomplete. Dihydrostilbene **4.85** produced an inseparable mixture of **4.86** and **4.87** in a 4:1 ratio.

Based on these results, it is clear that substrates immobilised on solid phase display different reaction profiles to their solution phase analogues. The rate of carbon-to-bromine homolysis is slower with immobilised substrates, which require large excesses of tributyltin hydride and the initiator to achieve complete reaction. The subsequent intramolecular reaction is, however, much faster than H-atom abstraction from tributyltin radical leading to direct reduction of the substrate. This large difference in the relative rates of reaction means that reactions on solid supported substrates give the intramolecular reactions with excellent efficiency compared to the analogous solution phase substrates. Indeed, only products arising from collapse of the spirocyclic intermediate were observed for resin bound substrates, in stark contrast to those reactions conducted in solution.



Scheme 77

Performing the reaction with resin coupled 4-(2-benzo[1,3]dioxol-5-yl-ethyl)-3-bromo-2,6-dimethoxy-phenol **4.88** produced the uncyclised product **4.89** (30%) following TFA-induced cleavage (Scheme 78). For reasons that remain nuclear C-Br homolysis did not occur in this case, even though a large excess of Bu_3SnH (18 eq.) and AIBN (9 eq.) was used. The reaction was performed two times and on both occasions dehydrostilbene **4.89** was the only compound identified in the product mixture.



4.88

4.89, 46%

Scheme 78

4. 10. Conclusion

Our initial attempts to effect the radical cyclisation of iodostilbenes failed. Subjecting *cis*-iodostilbene **4.34** to standard tributyltin mediated radical forming conditions gave only the isomerised and reduced *trans*-stilbene **4.35** in 55% yield (Scheme 62). None of the anticipated phenanthrene was formed, indicating that alkene isomerisation outpaced carbon-to-iodine bond homolysis in this case. Iodostilbene **4.37** produced a mixture of starting material **4.37** and reduced product **4.38** in 1 : 1 ratio (Scheme 64). By contrast, cyclisation of *cis*-bromostilbenes such as **4.52, 4.53** and **4.51** to phenanthrenes **4.54, 4.55** and **4.56** were achieved in modest yield (Scheme 69). Changing the substitution pattern on the radical acceptor had little effect on the course of the reaction. While the chemistry could easily be put into practice in solution, conducting the same reactions on solid phase proved to be a much greater challenge. Coupling of alcohols such as **4.41** to trichloroacetimidate resin proved unsuccessful, and a reasonable method for analysing the resin beads following reactions was lacking. New suggestions were needed. The first important achievement in the solid phase part of the program was the coupling of our substrates to PS-bromo- and PS-chloro-Wang. A method to monitor reactions was found in gel phase ^{13}C-NMR. This enabled us to reliably compare the ^{13}C-NMR signals obtained on solid phase chemistry to those of the analogous benzyl ether products prepared in solution phase. Also, a significant achievement for us was that we were able to successfully conduct Wittig reactions on solid phase using an excess of sodium hydride and the phosphonium salt. Due to poor *Z*-selectivity during the Wittig reaction, cyclisations of these solid supported stilbenes produced the desired phenanthrenes as minor products- the major component being the *trans*-stilbene. Reactions conducted on the corresponding dihydrostilbenes led to dihydrophenanthrenes and biaryls *via* cyclisation of the aryl radical intermediates to the vicinal arene. Notably, no side products arising from direct reduction were observed. As expected, the rate of intramolecular reaction was much faster than H-atom abstraction from hydride and the course of these reactions did indeed change through solid phase immobilisation.

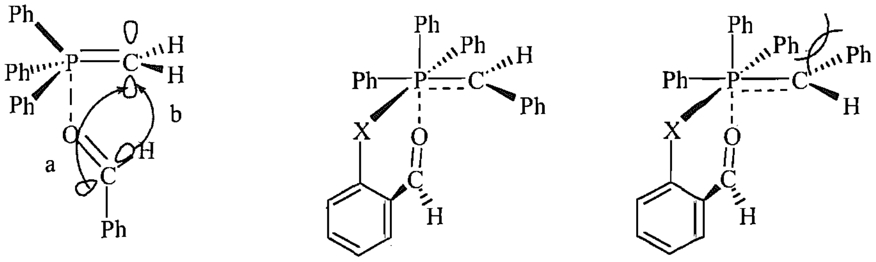
5 *Phenanthrene Synthesis Using Ortho-Halo Substituted Substrates as Precursors*

5 *Phenanthrene Synthesis Using Ortho-Halo Substituted Substrates as Precursors*

5.1. Background

Gilheany *et al.* [61] recently introduced the term 'co-operative *ortho*-effects' to describe an interesting phenomenon observed in solution phase Wittig reactions leading to stilbenes. Whereas reactions of this type generally give rise to mixtures of *cis*- and *trans*-stilbenes, they become remarkably selective when both the ylide and aldehyde bear an *ortho*-halo-substituent and have the other *ortho*-carbon unsubstituted. In such cases the diastereomeric ratio attained is generally 10 : 1 or better in favour of the *cis*-stilbene. Cushman *et al.* [62] and Yamataka *et al.* [63] had also noted that *ortho*-methoxy and *ortho*-halo substituted benzaldehydes gave predominantly *cis*-stilbenes in reactions with benzylidenetriphenylphosphorane. Yamataka and co-workers suggested that this selectivity was due to a chelation of both the filled p-orbitals on the heteroatom and the carbonyl oxygen with the phosphorus atom in the initial δ-complex formed between the aldehyde and ylide (Scheme 79). In case of the parent system **5.1**, the aldehyde phenyl group should point away from the ylide to avoid steric repulsion. When an MeO or Cl substituent is on the *ortho* carbon of benzaldehyde, the δ-complex favours adoption of a different conformation. The phosphorus atom takes a hypervalent octahedral structure accepting two lone pairs of electrons, one from the carbonyl oxygen, the other from the *ortho*-heteroatom (*c.f.* **5.2**). The phenyl group of the benzylidene moiety now prefers to be oriented on the same side as the phenyl group of the benzaldehyde in order to reduce steric repulsion with the phenyl ligands on P (**5.2a** over **5.2b**). Conformation **5.2a** is favourable for the *cis*-oxaphosphetane formation. Stabilisation of this type can also be envisaged when *o*-MeO or *o*-Cl substituent are present on the benzaldehyde moiety. Consequently, these substrates too are likely to afford *cis*-stilbenes preferentially.

As we suspected that many of our Wittig reactions on solid supported substrates resulted in the formation of a substantial amount of the undesired *trans*-stilbene, which could not be separated without cleaving the product from the resin, it seemed appropriate to exploit the co-operative *ortho* effect for the preparation of solid supported substrates. This required nothing more than for us to introduce an *ortho*-halo or *ortho*-alkoxy substituent to each of the reacting partners.

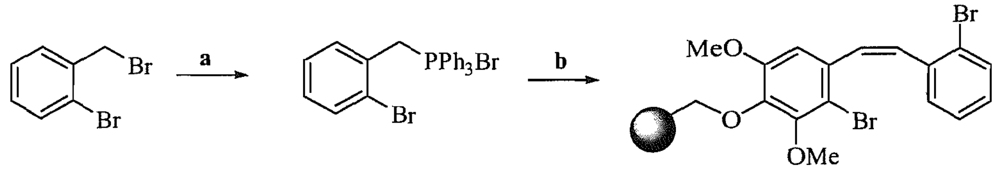


5.1 **5.2a** **5.2b**

Scheme 79

5. 2. Radical Cyclisations of *Ortho*-Halo Stilbenes on Solid Phase

We started our study with *ortho*-bromobenzyl bromide **5.3**, which was treated with triphenylphosphine in toluene to yield the corresponding phosphonium bromide **5.4**. Deprotonation with sodium hydride and union with resin bound aldehyde **4.57** yielded the phosphonium salt **5.5** (Scheme 80).

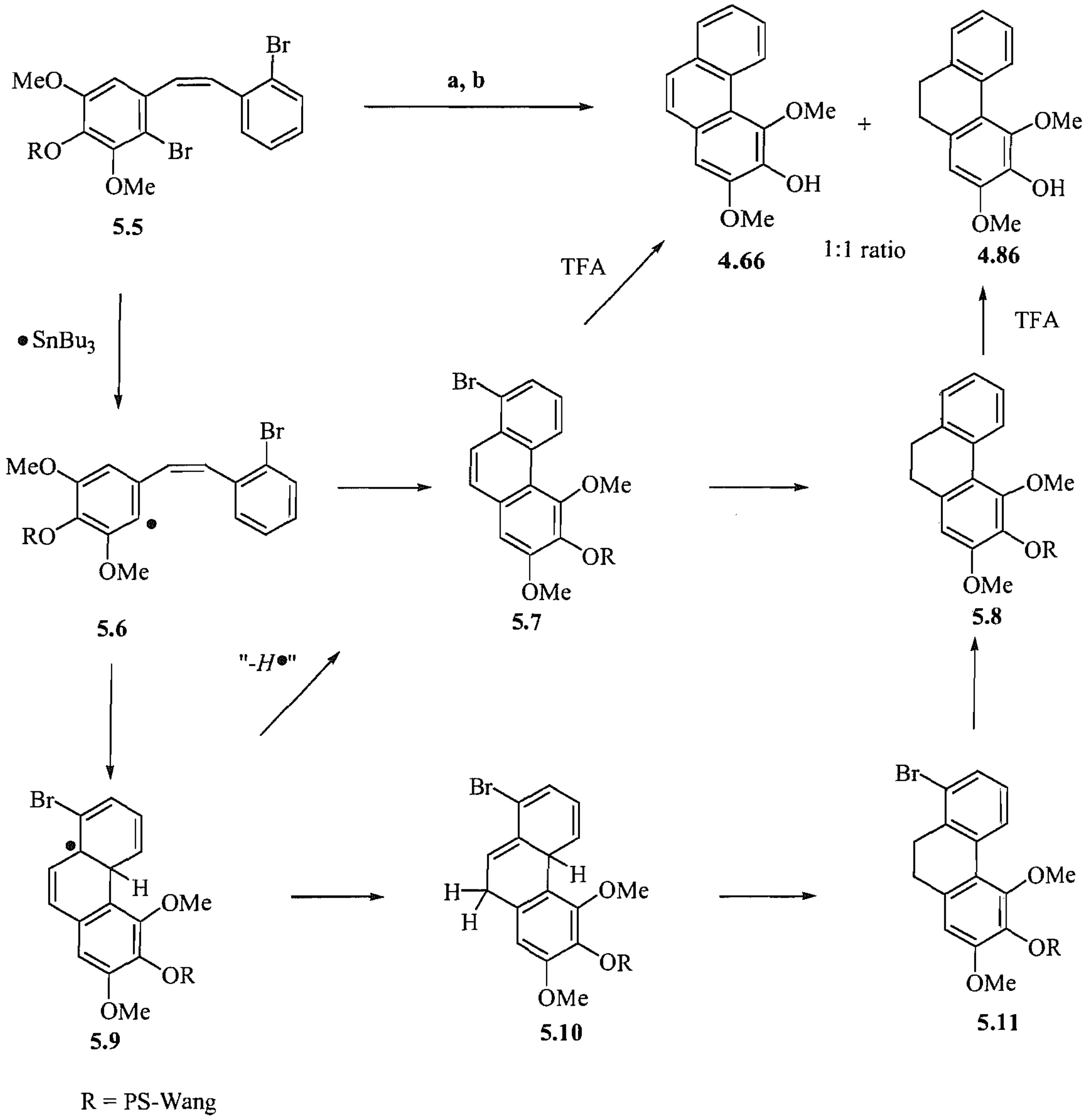


5.3 **5.4**, 93% **5.5**

a. PPh_3, PhMe, reflux, 5 h; **b.** 3. NaH, THF, 0 °C, 2 h, then **4.57**, r.t., 16 h.

Scheme 80

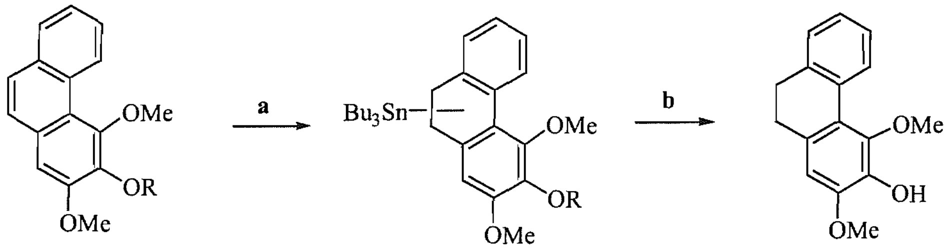
The stage was now set for us to conduct the key radical cyclisation reaction. This was carried out using an excess of tributyltin hydride (18 eq.) and AIBN (9 eq.). Analysis of the product mixture after cleavage with TFA revealed that the expected phenanthrene **4.66** had been formed together with dihydrophenanthrene **4.86** (Scheme 81). These were produced in a 1:1 ratio. At this time we are unsure as to how **4.86** was formed. One explanation is that cyclisation is followed by hydrogen atom abstraction from tributyltin hydride and tautomerism.



a. Bu_3SnH, AIBN, PhMe, reflux, 24 h; **b.** 95% TFA, 2.5% CH_2Cl_2, 2.5% (i-Pr)$_3$SiH, r.t., 1 h.

Scheme 81

Alternatively, phenanthrene **5.12** may have undergone hydrostannylation to **5.13** *in situ*, which then underwent protodestannylation on treatment with TFA. Such a process was observed within our group during work leading to the total synthesis of cavicularin.

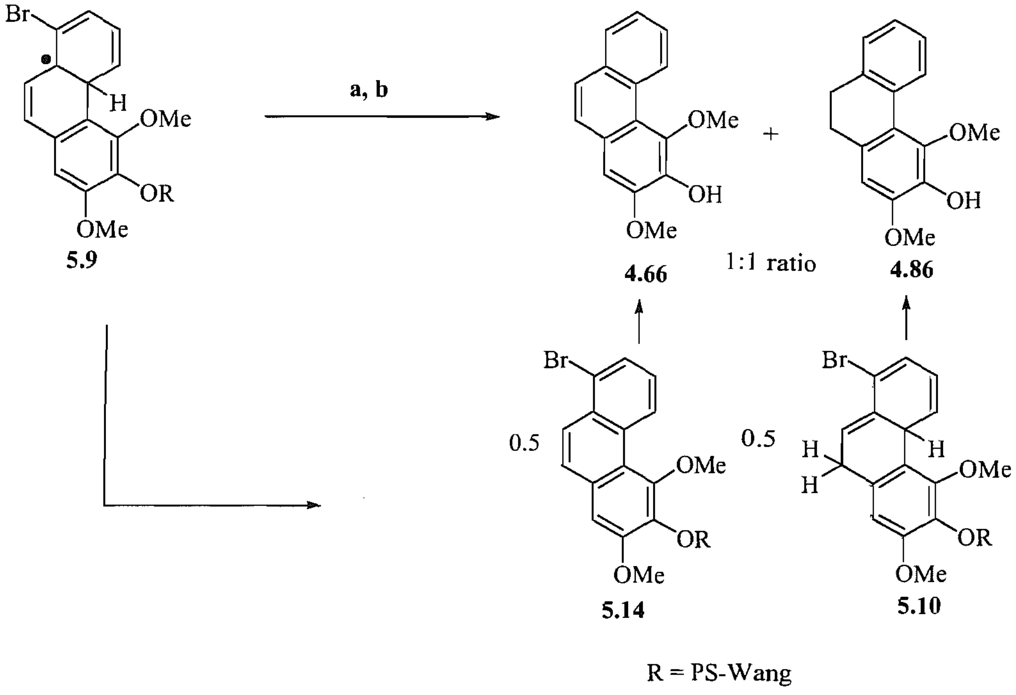


5.12 **5.13** **4.86**

a. Bu_3SnH, AIBN, PhMe, reflux, 24 h; **b.** 95% TFA, 2.5% CH_2Cl_2, 2.5% $(i\text{-}Pr)_3SiH$, r.t., 1 h.

Scheme 82

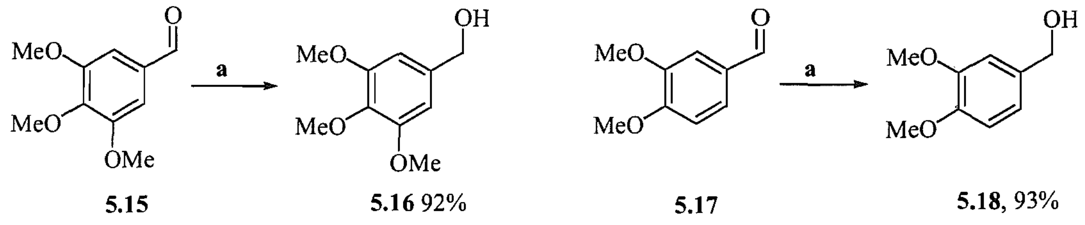
A third possibility is that **5.9** disproportionates to give equimolar quantities of **5.14** and **5.10**, a mechanism that has been suggested to explain the rearomatisation of the arene in radical reactions (Scheme 83). In this way equal amounts of intermediates **5.14** and **5.10** would be expected from radical intermediate **5.9**: the first as a result of hydrogen atom loss, the second as a result of gaining a hydrogen atom.



a. Bu_3SnH, AIBN, PhMe, reflux, 24 h; **b.** 95% TFA, 2.5% CH_2Cl_2, 2.5% $(i\text{-}Pr)_3SiH$, r.t., 1 h.

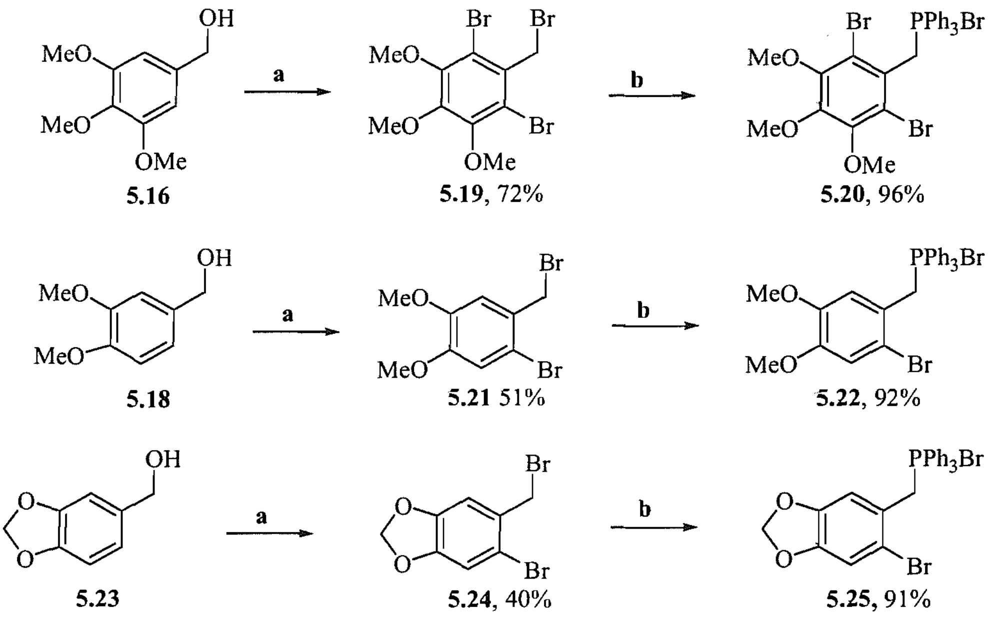
Scheme 83

To gain a better understanding of the reaction with supported substrates, a range of phosphonium salts (**5.20**, **5.22** and **5.25**) was prepared (Schemes 84 and 85). Thus reduction of aldehydes **5.15** and **5.17** with sodium borohydride gave alcohols **5.16** and **5.18** in excellent yields (92-93%). Bromination in acetic acid then produced the corresponding benzyl bromides **5.19**, **5.21** and **5.24** in modest to good yields (40-72%). These were then transformed into phosphonium salts in excellent yields by heating them in solution with triphenylphosphine (92-96%).



a. $NaBH_4$, MeOH, 0 °C, 30 min.

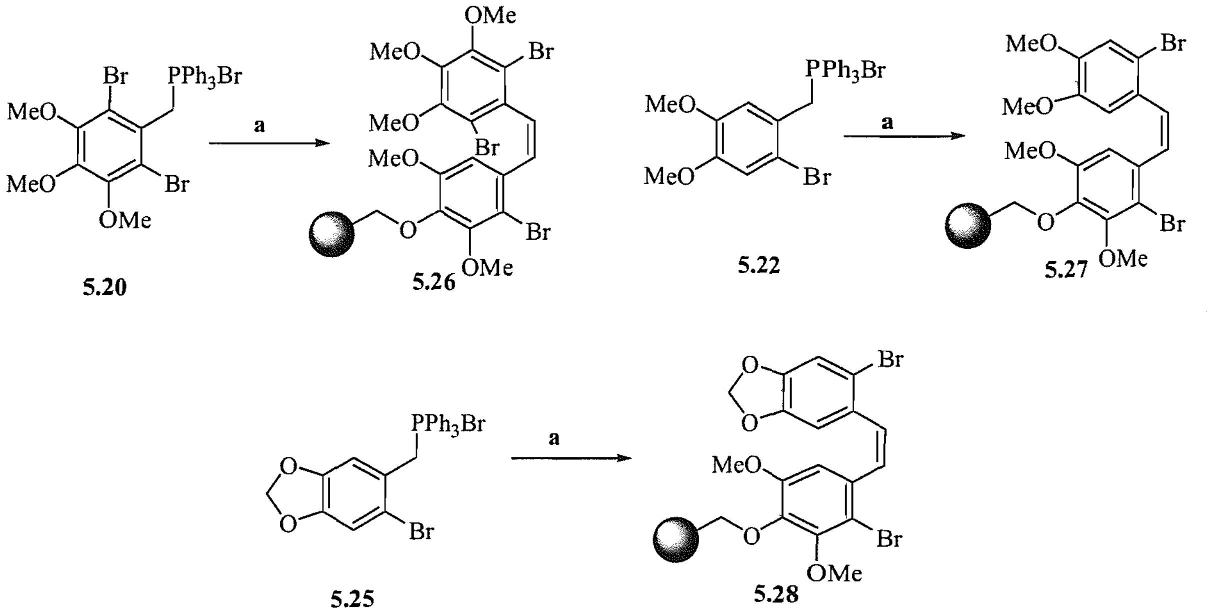
Scheme 84



a. Br_2, AcOH, 0 °C, r.t., 2 h.; **b.** PPh_3, PhMe, reflux, 6 h.

Scheme 85

Once again, Wittig methodology was used to produce a range of substrates with differing steric and electronic characteristics (Scheme 86). KOtBu was used to effect deprotonation of the phosphonium salts.

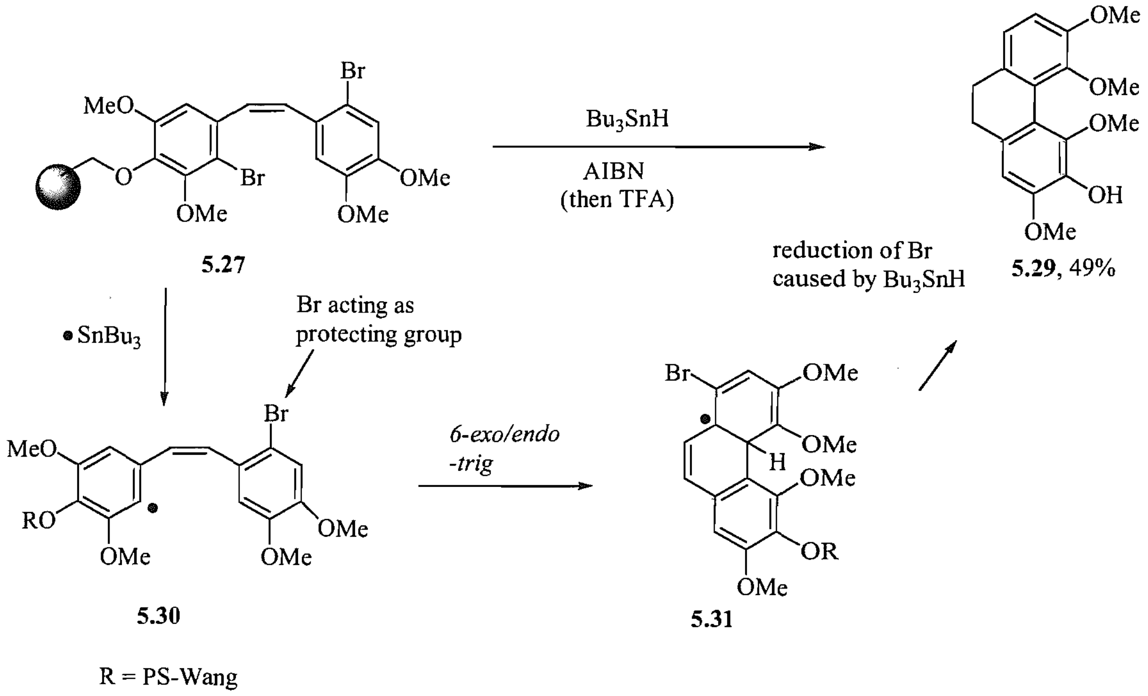


a. KOtBu, THF, 0 °C, 4 h, then **4.57**, r.t., 24 h.

Scheme 86

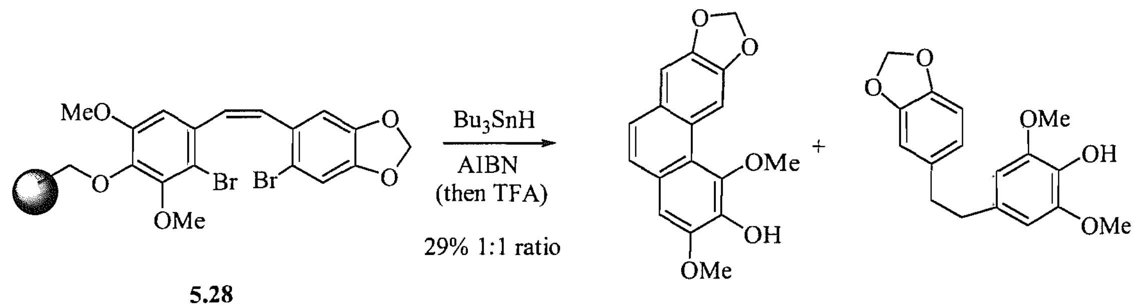
5. 3. Radical Reactions of our Solid Supported Substrates

The stage was now set for us to investigate the radical cyclisation of these resin bound stilbene substrates. In particular, we were keen to see if these would give a consistent pattern of reactivity and whether they would give both the expected phenanthrene and the 'unexpected' dihydrophenathrene. Pleasingly, the reaction of **5.27** proved to be highly regioselective, giving only 2,4,5,6-tetramethoxy-9,10-dihydrophenathrene **5.29**. From this we can conclude that C-Br bond homolysis was selective for the aryl bromide had occurred exclusively and in the preference to the other bromide in the substrate. Moreover, the halide that remained acted as a protecting group in the subsequent cyclisation, directing formation of the new carbon-to-carbon bond to the other *ortho*-carbon in the arene acceptor (Scheme 87). The fact that we already observed dihydrophenathrene **5.29** as a product, suggests that phenanthrene reduction occurs rather than disproportionation (Scheme 83) or H-atom abstraction from Bu_3SnH (Scheme 81).



Scheme 87

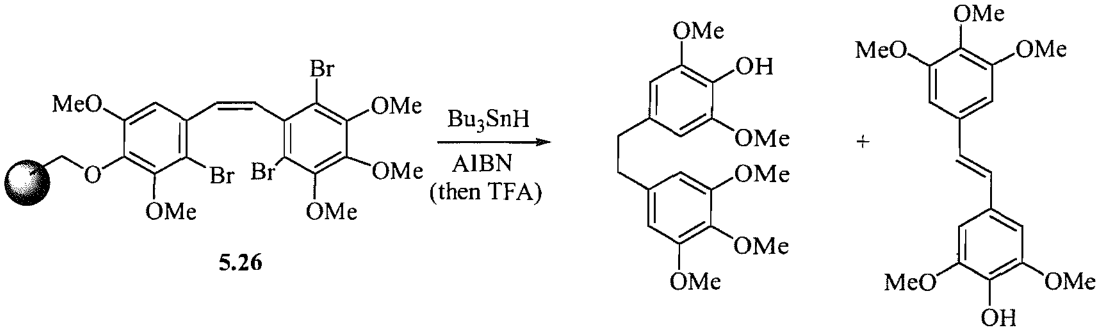
This was further borne out by our observation that stilbene **5.28** yielded a 1:1 mixture of phenanthrene **4.72** and dihydrostilbene **5.32** (Scheme 88). Indeed this result is more consistent with the hydrostannylation mechanism as it is known that minor changes in the nature of substituents can have a profound impact on the efficiency of addition of tributyltin radical to stilbenes. [64]



5.28 **4.72** **5.32**

Scheme 88

Alas, the fickle nature of these reactions was further demonstrated with an attempt to induce cyclisation of **5.26** to the corresponding phenanthrene/dihydrophenanthrene. On this occasion, only dihydrostilbene **5.33** and stilbene **5.34** were isolated following cleavage with TFA (Scheme 89).



5.26 **5.33**, 16% **5.34**, 8%

Scheme 89

5. 4. Conclusion

The synthesis of a wide range of precursors, where each of the two reacting partners (both ylid and aldehyde) contain an *ortho*-halo substituent, was synthesised in good yield, and successfully coupled to a solid support. Our first cyclisation (Scheme 81) using excess Bu$_3$SnH and AIBN produced the expected phenanthrene **4.66** and an unexpected dihydrophenanthrene **4.86**. It is unclear how **4.86** was formed, though it seems likely that phenanthrene **4.66** underwent hydrostannylation *in situ*, with protodestannylation then occurring on treatment with TFA. Cyclisation and cleavage of a related stilbene **5.27** in similar conditions produced a single cyclised compound. The reaction proved to be highly regioselective with C-Br bond homolysis occurring in the pentasubstituted arylbromide **5.27** exclusively and leaving the other bromine intact. The latter then acted as a protecting group in the subsequent cyclisation which displayed excellent regioselectivity.

Stilbene **5.28** yielded a mixture of phenanthrene **4.72** and dihydrostilbene **5.32** (Scheme 88). While the formation of the phenanthrene **4.72** was expected, formation of dihydrostilbene **5.32** suggest that hydrostannylation of stilbene **5.28** occurred prior to homolysis of the C-Br bond in this case.

One further cyclisation was attempted using stilbene **5.26**. Alas, this gave a mixture of dihydrostilbene **5.33** and stilbene **5.34** in a 16% and 8% (2 : 1 ratio) yield, respectively (Scheme 89). Given the modest amount of material obtained from the two last reactions, we are hesitant to draw any meaningful conclusions from these experiments. They do however demonstrate the fickle nature of solid phase synthesis, which has been a major frustration throughout this program of research.

Chapter 6   Experimental Section

6 Experimental Section

6.1. General

Infra red spectra of samples were recorded on a Bio Rad FT-IR Goldengate spectrometer or Thermo Mattson Satellite FT-IR spectrometer. Positions of absorption maxima are quoted in cm^{-1}. Maxima are reported υ_{max} followed by the signal intensity (described using the abbreviations s, strong; m, medium; w, weak; v, very; br; broad). UV- spectra were measured on on either a Pye Unicam SP8-400 spectrophotometer or Afilent 8453 spectrophotometer as solutions in dichloromethane or methanol as indicated in the script. Maxima are reported as λ_{max} followed in parentheses by the extinction coefficient ε_{max} (dm^3, mol^{-1}, dm^{-1}).

^1H and ^{13}C NMR spectroscopy was performed on a Bruker AC300 (300 MHz) or DPX-400 (400 MHz) spectrometer. Chemical shifts (δ) are reported as parts per million (ppm). Multiplicities are described using the abbreviations s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad. Mass spectrometric data are reported as values in atomic mass units and are followed in parentheses by the peak intensity relative to the base peak (100%).

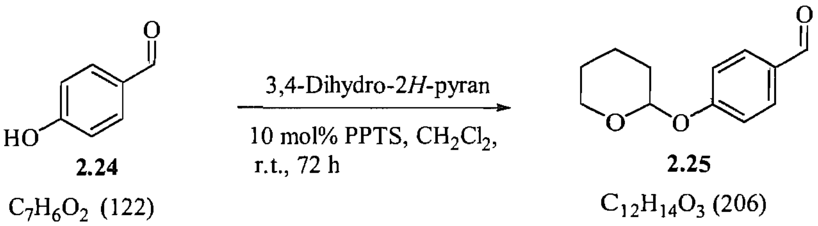
Flash column chromatography was performed using MN Kieselgel 60, 0.04 – 0.063 mm 230 – 400 mesh ASTM silica. Thin layer chromatography was performed on aluminium backed sheets coated with Sil G / UV_{254} 0.25 mm Silica gel 60. Merrifield resin used was 200 – 400 mesh, 1% cross-linked supplied by NovaBiochem. Wang resin was supplied by NovaBiochem, and the beads were 50-100 mesh and 100-200 mesh. Bromo-Wang and chloro-Wang was prepared from PS-Wang by the method of Raju. [38] Yields quoted for products cleaved from a resin are for the overall reaction sequence of loading and subsequent cleavage. Where molar quantities for a resin-bound substrate are reported, these indicate the theoretical maximum loading, assuming a 100% loading of the resin was achieved.

HPLC was performed using a Kontron Instruments pump with a 10 mm x 250 mm Biosyl D 90 / 10 column eluting at 3 mL / min. Chemical ionosation (CI) and electron ionization (EI) mass spectrometry was performed using a Thermoquest Trace GCMS spectrometer. Electrospray (ES) mass spectrometry was performed using a Micromass Platform (MP) spectrometer. High resolution EIMS was performed on a VG analytical 70-250-SE spectrometer and high resolution ESMS was performed on a Bruker Apex III spectrometer. Combustion analysis was performed by Medac Ltd. Melting points were carried out using a Griffin melting point apparatus and are uncorrected.

Dichloromethane was distilled from calcium hydride. Chloroform was distilled from calcium carbonate. Tetrahydrofuran was dried and degassed by distillation from sodium / benzophenone. Toluene was distilled from sodium. Petroleum ether 40-60° was freshly distilled. Other solvents were used directly from the bottle as supplied except where stated otherwise. All Wittig, radical cyclisation, sodium borohydride reactions were carried out under an athmosphere of nitrogen.

6.2. Experimental for Chapter 2

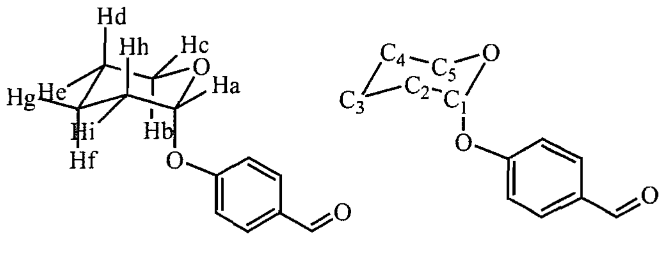
4-(Tetrahydro-pyran-2-yloxy)-benzaldehyde **2.25**



2.24
$C_7H_6O_2$ (122)

2.25
$C_{12}H_{14}O_3$ (206)

This procedure was performed according to the method of Severi.[65] 4-Hydroxybenzaldehyde (5.00 g, 41.0 mmol) was dissolved in tetrahydrofuran (50 mL), where after dichloromethane (100 mL) was added. 3,4-Dihydro-2*H*-pyran (9.4 mL 49.20 mmol) was added *via* syringe, followed by pyridinium *para*-toluene sulfonate (1.03 g 2.05 mmol) in one portion. After stirring for 72 hours at ambient temperature, the reaction mixture was washed with saturated potassium carbonate solution (3 x 100 mL) and the combined aqueous layers were extracted with dichloromethane (100 mL). The combined organic phases were then dried with $MgSO_4$ and concentrated *in vacuo* to yield a dark brown oil. Purification by column chromatography (silica gel, 20-30% ether/petrol) yielded the product as a pale yellow oil **2.25** (6.98 g, 33.8 mmol, 82%).[66]



IR (ν_{max}, neat) 2941 (w), 1692 (s), 1597 (vs), 1512 (m), 1247 (vs), 1200 (m), 1162 (s), 1124 (m), 1039 (s), 959 (vs), 916 (vs) cm^{-1}.

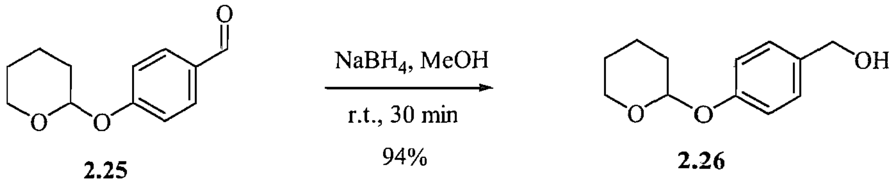
UV λ_{max} (ε_{max}, CH_3OH): 212 (13000), 266 (17000) nm.

^{1}H NMR δ_H ppm (300 MHz, $CDCl_3$) 9.90 (1H, s, ArC$\underline{H}$O), 7.83 (2H, d, J = 8.8 Hz, Ar$\underline{H}$), 7.16 (2H, d, J = 8.8 Hz, Ar$\underline{H}$), 5.55 (1H, t, J = 2.9 Hz, $\underline{H}_a$), 3.85 (1H, ddd, J = 11.4, 9.9, 3.0 Hz, $\underline{H}_b$), 3.64 (1H, dtd, J = 11.2, 3.7, 1.0 Hz, $\underline{H}_c$), 1.50-2.10 (6H, m, $\underline{H}_{d\text{-}I}$).

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 191.0 (Ar$\underline{C}$HO), 162.1 ($\underline{C}$ (Ar)), 131.8 (2 x $\underline{C}$H (Ar), 130.6 ($\underline{C}$ (Ar)), 116.5 (2 x $\underline{C}$H (Ar)), 96.1 ($\underline{C}_1$), 62.1 (C_5), 30.0 ($\underline{C}_2$), 25.0 ($\underline{C}_4$), 18.4 ($\underline{C}_3$).

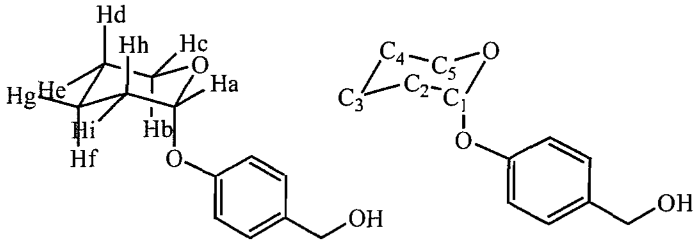
LRMS (CI, m/z) 207 (MH^+, 28%), 85 ($C_5H_9O^+$, 100%) amu.

[4-(Tetrahydro-pyran-2-yloxy)-phenyl]-methanol **2.26**



2.25 $C_{12}H_{14}O_3$ (206) **2.26** $C_{12}H_{16}O_3$ (208)

Sodium borohydride (530 mg, 14.00 mmol) was added portionwise *via spatula* over 10 minutes to a stirred solution of 4-(tetrahydro-pyran-2-yloxy)-benzaldehyde **2.25** (2.61 g, 12.67 mmol) in methanol (50 mL) at 0 °C under nitrogen. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour until effervescence had ceased. Saturated ammonium chloride solution (25 mL) was then carefully added and the reaction mixture extracted with diethyl ether (3 x 100 mL). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (silica gel, 50-60% ether in petrol) to give the product **2.26** as a clear yellow oil (2.48 g, 11.92 mmol, 94%).[67]

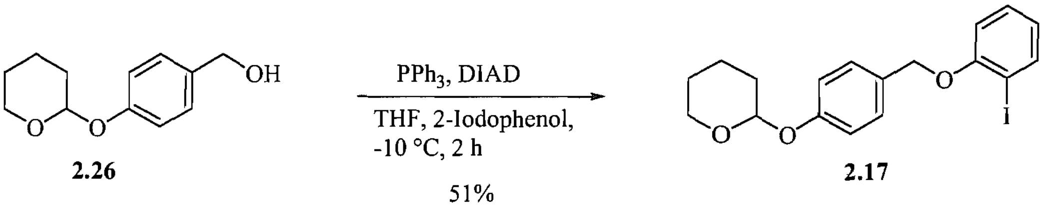


IR (ν_{max}, neat) 3450 (br. m), 2941 (w), 1607 (w), 1512 (s), 1356 (w), 1219 (vs), 1039 (vs), 911 (s) cm^{-1}.

UV λ_{max} (ε_{max}, CH_2Cl_2) 268 (2200), 225 (6700) nm.

^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 7.29 (2H, d, J = 8.7 Hz, Ar$\underline{H}$), 7.05 (2H, d, J = 8.7 Hz, Ar$\underline{H}$), 5.42 (1$\underline{H}$, t, J = 3.2 Hz, $\underline{H}_a$), 4.61 (2H, s, $ArC\underline{H}_2OH$), 3.90 (1H, ddd, J = 11.4, 9.2, 3.0 Hz, $\underline{H}_b$), 3.60 (1H, dtd, J = 11.4, 4.2, 1.5 Hz, $\underline{H}_c$), 1.50 - 2.10 (7H, m, $\underline{H}_{d\text{-}I}$, and O$\underline{H}$).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 156.8 ($\underline{C}$ (Ar)), 134.2 ($\underline{C}$ (Ar)), 128.7 (2 x $\underline{C}$H (Ar)), 116.7 (2 x $\underline{C}$H (Ar)), 96.5 ($\underline{C}_1$), 65.2 ($Ar\underline{C}H_2OH$), 62.2 ($\underline{C}_5$), 30.5 ($\underline{C}_2$), 25.3 ($\underline{C}_4$), 18.9 ($\underline{C}_3$).
LRMS	(CI, m/z) 124 ($[MH\text{-}C_5H_9O]^+$, 18%), 107 ($[MH\text{-}C_5H_9O\text{-}H_2O]^+$, 100%) amu.

2-[4-(2-Iodo-phenoxymethyl)-phenoxy]-tetrahydro-pyran **2.17**



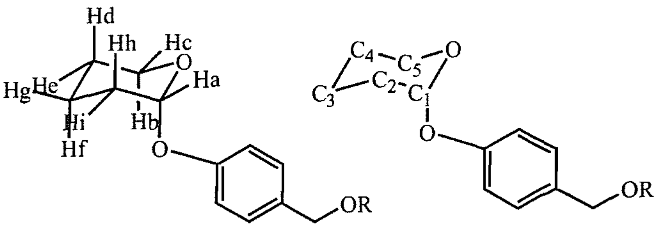
2.26

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

2.17

$C_{18}H_{19}IO_3$ (410)

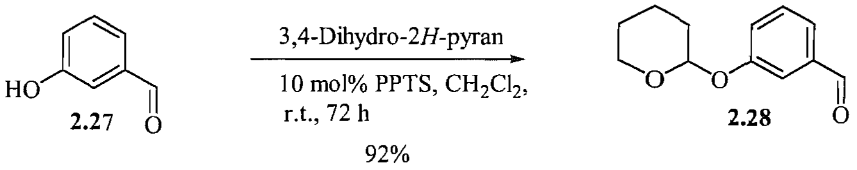
[4-(Tetrahydro-pyran-2-yloxy)-phenyl]-methanol **2.26** (1.00 g, 4.80 mmol) was dissolved in tetrahydrofuran (40 mL) under nitrogen with stirring. 2-Iodophenol (1.27 g, 5.76 mmol) and triphenylphosphine (1.51 g, 5.76 mmol) were added, then the reaction mix was cooled to −10 °C and di-isopropyl azodicarboxylate (DIAD) (1.04 mL, 5.28 mmol) added dropwise over 10 minutes via syringe. After two hours at −10 °C the reaction mixture was concentrated *in vacuo* to yield a pale yellow oil. Purification by column chromatography (silica gel, 10-20% ether in petrol) gave an oil that was purified further by column chromatography to yield the product **2.17** as a white solid (1.00 mg, 2.44 mmol, 51%).



MP	79-81 °C (ether/petrol).
IR	(ν_{max}, neat) 2950 (w), 1574 (w), 1502 (m), 1460 (m), 1440 (m), 1356 (w), 1219 (s), 1285 (m), 1110 (m), 1007 (s), 916 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 273 (4000), 204 (27200) nm.

^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 7.81 (1H, dd, *J* = 6.6, 0.9 Hz, Ar$\underline{H}$), 7.42 (2H, d, *J* = 8.3 Hz, Ar$\underline{H}$), 7.28 (1H, td, *J* = 7.9, 0.9 Hz, Ar$\underline{H}$), 7.04 (2H, d, *J* = 8.6 Hz, Ar$\underline{H}$), 6.87 (1H, dd, *J* = 8.2, 1.2 Hz, Ar$\underline{H}$), 6.70 (1H, td, *J* = 7.8, 1.2 Hz, Ar$\underline{H}$), 5.44 (1H, t, *J* = 2.7 Hz $\underline{H}_a$), 5.09 (2H, s, ArC$\underline{H}_2$OH), 3.93 (1H, ddd, *J* = 12.4, 9.2, 2.5 Hz, $\underline{H}_b$), 3.62 (1H, dtd, *J* = 11.4, 5.5, 1.9 Hz, $\underline{H}_c$), 1.50-2.10 (6H, m, $\underline{H}_{d\text{-}I}$).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 156.9 ($\underline{C}$ (Ar)), 154.9 ($\underline{C}$ (Ar)), 139.5 ($\underline{C}$H (Ar)), 129.8 ($\underline{C}$H (Ar)), 129.5 ($\underline{C}$ (Ar)), 128.5 (2 x $\underline{C}$H (Ar)), 122.9 ($\underline{C}$H (Ar)), 116.6 (2 x $\underline{C}$H (Ar)), 113.0 ($\underline{C}$H (Ar)), 96.5 ($\underline{C}_1$), 87.0 ($\underline{C}$I (Ar)), 70.8 (Ar$\underline{C}H_2$O), 62.3 ($\underline{C}_5$), 30.5 ($\underline{C}_2$), 25.4 ($\underline{C}_4$), 19.0 ($\underline{C}_3$).
LRMS	(CI, m/z) 220 (100%), 94 (30%), 65 (48%) amu.
CHN	Found: C, 52.74; H, 4.69; $C_{18}H_{19}IO_3$ requires: C, 52.70; H, 4.67.

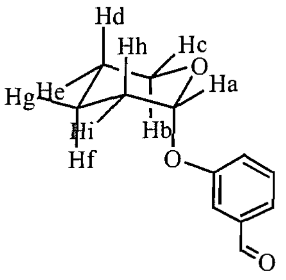
3-(Tetrahydro-pyran-2-yloxy)-benzaldehyde **2.28**

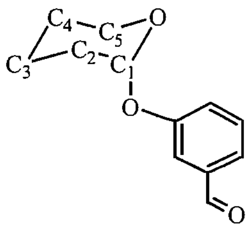


$C_7H_6O_2$ (122)

$C_{12}H_{14}O_3$ (206)

This procedure was performed according to the method of Severi. [65] 3-Hydroxybenzaldehyde **2.27** (5.00 g, 41.0 mmol) was dissolved in tetrahydrofuran (50 mL), where after dichloromethane (100 mL) was added. 3,4-Dihydro-2*H*-pyran (9.4 mL 49.20 mmol) was added via syringe, followed by pyridinium *para*-toluene sulfonate (1.03 g, 2.05 mmol) in one portion. After stirring for 72 hours at ambient temperature, the reaction mixture was washed with saturated sodium carbonate solution (3 x 100 mL) and the combined aqueous layers were extracted with dichloromethane (100 mL). The combined organic phases were then dried with $MgSO_4$ and concentrated *in vacuo* to yield a dark brown oil. Purification by column chromatography (silica gel, 20-30% ether in petrol) yielded the product **2.28** as a dark yellow oil (7.76 g, 37.67 mmol, 92%). [66]





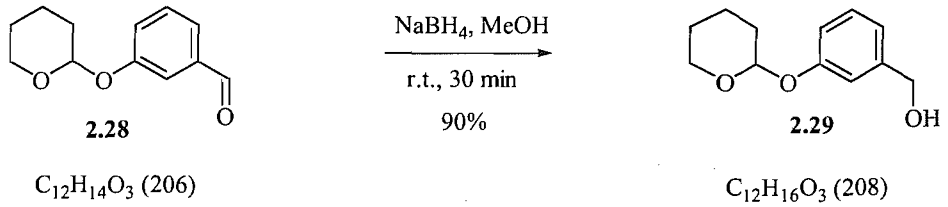
IR	(ν_{max}, neat) 2945 (w), 1697 (vs), 1588 (m), 1489 (m), 1384 (w), 1252 (vs), 1204 (m), 1110 (m), 1044 (s), 954 (m), 868 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_3OH) 246 (10600), 209 (22000) nm.

^{1}H NMR δ_H ppm (300 MHz, $CDCl_3$) 9.98 (1H, s, ArC$\underline{H}$O), 7.57 (1H, dd, J = 2.5, 1.0 Hz, Ar$\underline{H}$), 7. 51 (1H, dt, J = 7.4, 1.5, Ar$\underline{H}$), 7.45 (1H, t, J = 7.4 Hz, Ar$\underline{H}$), 7.32 (1H, ddd, J = 7.9, 2.5, 1.0 Hz, Ar$\underline{H}$), 5.50 (1H, t, J = 3.5 Hz, $\underline{H}_a$), 3.89 (1H, ddd, J = 12.4, 9.4, 3.0 Hz, $\underline{H}_b$), 3.63 (1H, m, $\underline{H}_c$), 1.50-2.10 (6H, m, $\underline{H}_{d\text{-}1}$).

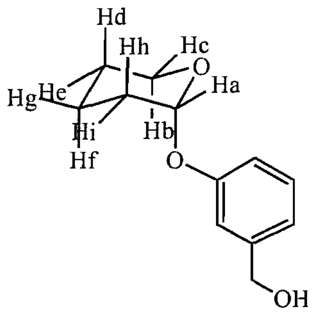
^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 192.3 (Ar$\underline{C}$HO), 157.7 ($\underline{C}$ (Ar)), 137.9 ($\underline{C}$ (Ar)), 130.2 ($\underline{C}$H (Ar)), 123.6 ($\underline{C}$H (Ar)), 123.1 ($\underline{C}$H (Ar)), 116.6 ($\underline{C}$H (Ar)), 96.5 ($\underline{C}_1$), 63.5 (C_5), 31.1 ($\underline{C}_2$), 25.6 ($\underline{C}_4$), 19.9 ($\underline{C}_3$).

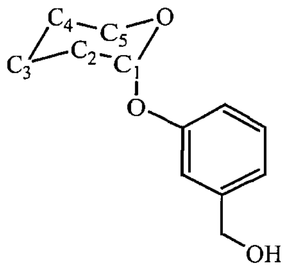
LRMS (CI, m/z) 207 (MH^+, 2%), 85 ($C_5H_9O^+$, 100%) amu.

[3-(Tetrahydro-pyran-2-yloxy)-phenyl]-methanol **2.29**



Sodium borohydride (530 mg, 14.0 mmol) was added portionwise *via spatula* over time to a stirred solution of 3-(tetrahydro-pyran-2-yloxy)-benzaldehyde **2.28** (2.61 g, 12.60 mmol) in methanol (50 mL) at 0 °C under nitrogen. After complete addition, the reaction mixture was allowed to warm to ambient temperature and stirred for 1 hour until effervescence had ceased. Saturated ammonium chloride solution (25 mL) was then carefully added and the reaction mixture extracted with diethyl ether (3 x 100 mL). The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by column chromatography (silica gel, 50-60% diethyl ether in petrol) to give the product as a clear yellow oil **2.29** (2.35 g, 11.30 mmol, 90%).



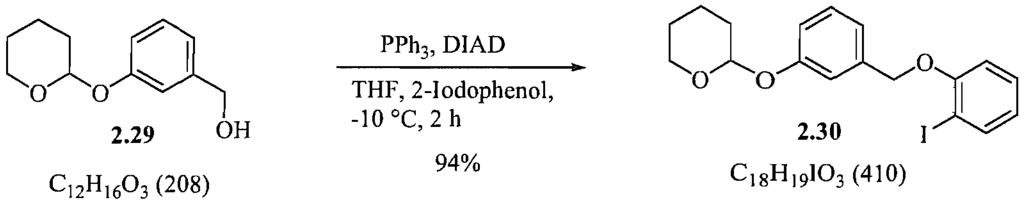


IR (ν_{max}, neat) 3452 (br. m), 2941 (w), 1593 (w), 1489 (w), 1357 (w), 1252 (s), 1034 (s), 959 (s), 869 (m) cm^{-1}.

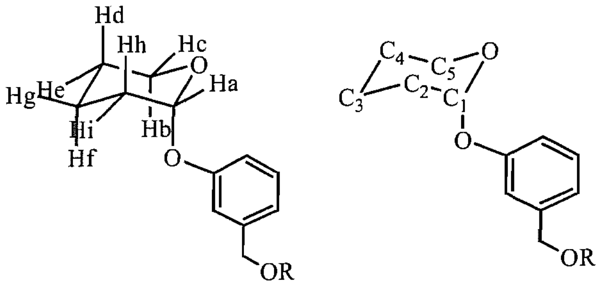
UV λ_{max} (ε_{max}, CH_2Cl_2) 268 (2600), 223 (4400) nm.

^{1}H NMR	δ_H ppm (300 MHz, CDCl$_3$) 7.27 (1H, t, J = 8.1 Hz, Ar$\underline{H}$), 6.95 - 7.08 (3H, Ar$\underline{H}$), 5.45 (1H, t, J = 3.5 Hz, $\underline{H}_a$), 4.67 (2H, s, ArC$\underline{H}_2$OH), 3.92 (1H, ddd, J = 11.9, 9.4, 3.0 Hz, $\underline{H}_b$), 3.61 (1H, dtd, J = 10.9, 4.0, 1.5 Hz, $\underline{H}_c$), 1.50-2.10 (7H, m, $\underline{H}_{d-I}$ and O$\underline{H}$).
^{13}C NMR	δ_C ppm (75 MHz, CDCl$_3$) 157.4 ($\underline{C}$ (Ar)), 142.6 ($\underline{C}$ (Ar)), 129.7 ($\underline{C}$H (Ar)), 120.2 ($\underline{C}$H (Ar)), 115.8 (2 x $\underline{C}$H (Ar)), 115.1 ($\underline{C}$H (Ar)), 96.4 ($\underline{C}_1$), 65.4 ($\underline{C}$H$_2$OH), 62.2 ($\underline{C}_5$), 30.5 ($\underline{C}_2$), 25.4 ($\underline{C}_4$), 18.9 ($\underline{C}_3$).
LRMS	(CI, m/z) 124 ([MH-C$_5$H$_9$O]$^+$, 100%), 107 ([MH-C$_5$H$_9$O-H$_2$O]$^+$, 30%) amu.
HRMS	(ES+, m/z) Found: ([M + Na]$^+$: 231.0992; C$_{12}$H$_{16}$O$_3$Na$^+$ requires: 231.0991.

2-[3-(2-Iodo-phenoxymethyl)-phenoxy]-tetrahydro-pyran **2.30**



To [3-(tetrahydro-pyran-2-yloxy)-phenyl]-methanol **2.29** (1.00 g, 4.80 mmol) in THF (40 mL) and under nitrogen was added 2-iodophenol (1.27 g, 5.76 mmol) and triphenylphosphine (1.51 g, 5.76 mmol). The reaction mix was cooled to −10 °C and di-isopropyl azodicarboxylate (1.04 mL, 5.28 mmol) added dropwise over 10 minutes *via* syringe. After stirring for a further two hours at −10 °C, the reaction mixture was concentrated *in vacuo* and a pale yellow oil obtained. Purification by column chromatography (silica gel, 10-20% ether in petrol) yielded the product **2.30** as a pale yellow oil (1.85 g, 4.51 mmol, 94%).



IR (ν$_{max}$, neat) 2945 (w), 1583 (m), 1470 (m), 1432 (m), 1271 (m), 1120 (m), 1016 (vs), 964 (m), 745 (vs) cm^{-1}.

UV $\lambda_{max}(\varepsilon_{max}$, CH_2Cl_2) 274 (4100), 205 (27400) nm.

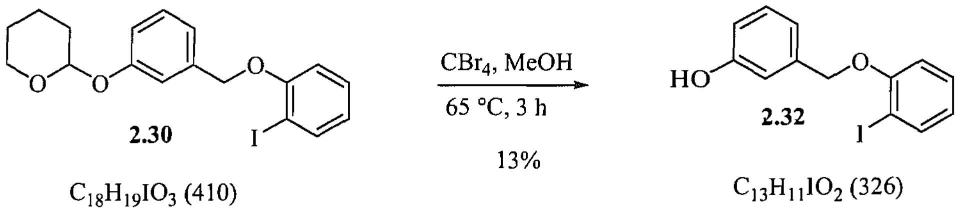
^{1}H NMR δ_H ppm (300 MHz, CDCl$_3$) 7.82 (1H, dd, J = 7.9, 1.5 Hz, ArH), 7.66 (1H, dd, J = 7.9, 1.5 Hz, ArH), 7.31 (1H, t, J = 7.9 Hz, ArH), 7.26 (1H, td, J = 6.0, 1.5 Hz, ArH), 7.13 (1H, d, J = 7.4 Hz, ArH), 7.01 (1H, dt, J = 8.2, 1.5 Hz, ArH), 6.86 (1H, dd, J = 8.4, 1.5 Hz, ArH), 6.73 (1H, td, J = 7.9, 1.5 Hz, ArH), 5.45 (1H, t, J = 3.2 Hz, H$_a$), 5.14 (2H, s, ArCH$_2$O), 3.94 (1H, ddd, J = 11.9, 8.9, 3.5 Hz, H$_b$), 3.63 (1H, dtd, J = 11.9, 4.2 , 2.0 Hz, H$_c$), 1.50-2.10 (6H, m, H$_{d\text{-}I}$).

^{13}C NMR δ_C ppm (75 MHz, CDCl$_3$) 157.7 ((C (Ar)), 157.6 (C (Ar)), 139.9 (CH (Ar)), 130.3 (CH (Ar)), 129.9 (C (Ar)), 129.8 (2 x (CH (Ar)), 123.2 (CH (Ar)), 115.6 (2 x (CH (Ar)), 113.2 (CH (Ar)), 96.9 (C$_1$), 87.3 (CI (Ar)), 70.8 (ArCH$_2$O), 62.7 (C$_5$), 30.8 (C$_2$), 25.6 (C$_4$), 19.3 (C$_3$).

LRMS (CI, m/z) 220 (8%), 107 (100 %), 124 (20%) amu.

HRMS (ES+, m/z) Found: ([2M+ Na]$^+$: 843.0628; $C_{36}H_{38}I_2O_6Na^+$ requires: 843.0649.

3-(2-Iodo-phenoxymethyl)-phenol **2.32**



2.30 $C_{18}H_{19}IO_3$ (410)

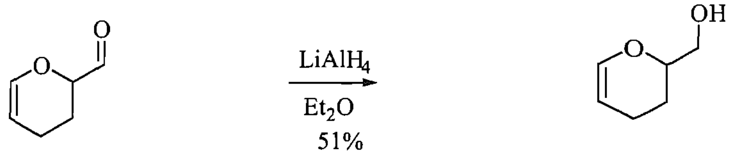
2.32 $C_{13}H_{11}IO_2$ (326)

230 (1.80 g, 4.39 mmol) was mixed with anhydrous methanol (5 mL), whereafter carbon tetrabromide was added and the mixture refluxed at 65 °C for 3 hours. After stirring for a further seven hours at 65 °C and addition of carbontetrabromide (728 mg, 2.20 mmol), the reaction mixture was concentrated *in vacuo* and a dark brown oil obtained. Purification by column chromatography (silica gel, 10-20% ether in petrol) yielded the product **232** as a green oil, which turned red on standing at room temperature (190 mg, 0.58 mmol, 13%).

IR	(ν_{max}, neat) 3456 (br. m), 1744 (w), 1589 (m), 1474 (m), 1276 (m), 1248 (s), 1051 (s) cm^{-1}.
UV	$\lambda_{max}(\varepsilon_{max}$, CH_2Cl_2) 272 (6000), 205 (30800) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 7.85 (1H, dd, J = 7.8, 1.5 Hz, ArH), 7.35-7.25 (2H, m, ArH), 7.11-7.01 (2H, m, ArH), 6.89 (1H, dd, J = 8.3, 1.3 Hz, ArH), 6.84 (1H, J = 8.0, 2.3 Hz, ArH), 6.78 (1H, dt, J = 7.5, 1,5 Hz, ArH), 5.17 (2H, s, CH_2), 5.02 (1H, s, ArOH).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 174.2 (CH_2OC (Ar)), 157.2 (COH (Ar)), 155.9 (C (Ar)), 139.7 (CH (Ar)), 130.0 (CH (Ar)), 129.6 (CH (Ar)), 123.0 (CH (Ar)), 119.3 (CH (Ar)), 115.0 (CH (Ar)), 113.9 (CH (Ar)), 112.9 (CH (Ar)), 86.9 (CI), 70.5 (CH_2).
LRMS	(CI, m/z) 326 (M^+, 8%), 200 ([M-I], 16%) amu.
HRMS	(ES+, m/z) Found: M^+: 325.9802; $C_{13}H_{11}IO_2^+$ requires: 325.9804.

6.3. Experimental for Chapter 3

2-Hydroxymethyl-3,4-dihydro-2*H*-pyran

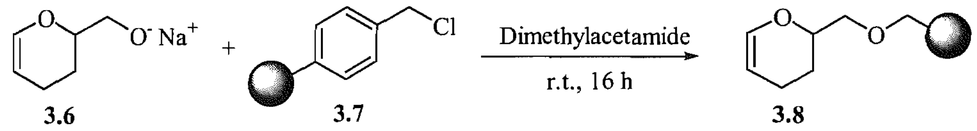


$C_6H_8O_2$ (112) $C_6H_{10}O_2$ (114)

2-Hydroxymethyl-3,4-dihydro-2*H*-pyran was prepared according a reported procedure by Buffet *et al.* [68] Lithium aluminium hydride (1 M in ether, 0.050 mol) was added slowly over 30 min to a cooled (0 °C) solution of acrolein dimer (2.80 g, 24.92 mmol) in anhydrous ether (20 mL). The resultant solution was stirred at 0 °C for a further 30 minutes and at room temperature for 1 hour and finally heated at reflux for 1 hour. The mixture was cooled to 0 °C and ethyl acetate (15 mL) was added slowly to consume the excess $LiAlH_4$. Stirring was continued as the mixture warmed to room temperature over 30 minutes, and the reaction was quenched by careful sequential addition of water (2 mL), sodium hydroxide (2 mL, 2.5 M) and water (6 mL). The solution was filtered and the residual solid was washed with ether (40 mL). The organic phase was washed with water (40 mL and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give alcohol 2-hydroxymethyl-3,4-dihydro-2*H*-pyran as a colourless oil (1.44 g, 12.63 mmol, 51%). [68]

IR	(ν_{max}, neat) 3391 (br. m), 2924 (w), 1649 (vs), 1240 (vs), 998 (m), 726 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 229 (800) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 6.43 (1H, br d, J = 6.0 Hz, =C$\underline{H}$), 4.72 – 4.78 (1H, m, =C$\underline{H}$), 3.95 (2H, m, C$\underline{H}_2$), 3.67 – 3.76 (2H, m, C$\underline{H}_2$OH), 1.68 – 2.19 (4H, m).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 143.7 (=$\underline{C}$H), 101.2 (=$\underline{C}$H), 75.9 ($\underline{C}$H), 65.9 ($\underline{C}H_2$), 24.3 ($\underline{C}H_2$), 19.8 ($\underline{C}H_2$).
LRMS	(CI, m/z) 115 (MH^+, 100 %), 83 (14 %), 55 (8 %) amu.

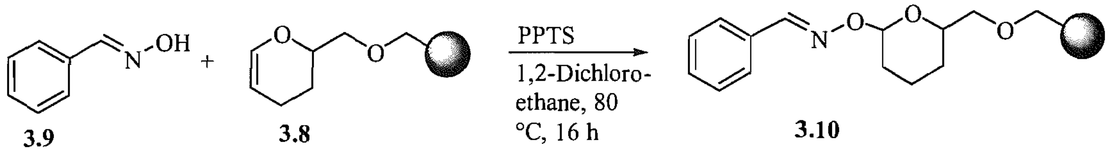
Dihydropyran functionalised resin **3.8**



This method was adapted from a reported procedure by Huang *et al.* [69] To a nitrogen-purged flask were added THF (50 mL), 2-(hydroxymethyl)-3,4-dihydro-2*H*-pyran (1.44 g, 12.63 mmol), and NaH (560 mg, 13.89 mmol). The mixture was stirred at room temperature for 2 hours and then concentrated. To the residue were added dimethylacetamide (100 mL) and Merrifield's resin **3.7** (2.63 g, 4.20 mmol, 1.60 mmol / g). The mixture was stirred at room temperature for 16 hours. The polymer was then washed in to a filter using dichloromethane. The beads were washed sequentally with dichloromethane (40 mL), DMF / H_2O (40 mL), DMF (40 mL) and dichloromethane (50 mL) and dried *in vacuo* for 16 hours to afford 2.90 g of the dihydropyran functionalized resin **3.8**.

IR (ν_{max}, solid phase) 2923 (w), 2164 (w), 1650 (w), 1493 (m), 1452 (m), 1241 (w), 1070 (m) cm^{-1}.

Resin coupled (*E*)-benzaldehyde oxime **3.10**

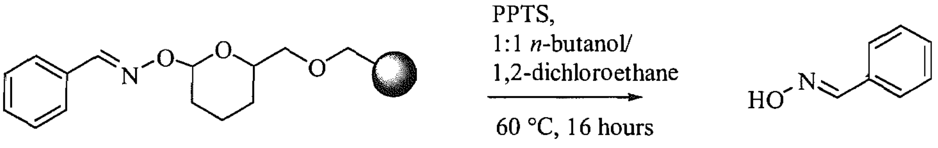


C_7H_7NO (121)

This method was adapted from a reported procedure by Ellman *et al.* [70] Resin **3.8** (1.05 g, 0.780 mmol) was swelled in of 1,2-dichloroethane (8 mL). (*E*)-benzaldehyde oxime **3.9** (500 mg, 4.13 mmol) and PPTS (390 mg, 1.60 mmol) were added. The mixture was stirred at 80 °C for 16 hours. The resin was then washed with dichloromethane (40 mL), DMF / H_2O (40 mL), DMF (40 mL) and dichloromethane (50 mL) and dried *in vacuo*.

IR	(ν_{max}, solid phase) 2925 (w), 1661 (w), 1494 (m), 1450 (m), 1314 (m), 1116 (w), 948 (m), 757 (m), 698 (s) cm^{-1}.

(*E*)-Benzaldehyde oxime **3.9**



3.10

3.9

C_7H_7NO (121)

This method was adapted from a reported procedure by Ellman *et al.* [70] Oxime derivatised support **3.10** (800 mg) was swelled in 1 : 1 *n*-butanol / 1,2-dichloroethane (20 mL), then PPTS (370 mg, 1.48 mmol) was added. The flask was stoppered and heated to 60 °C for 16 hours. The resulting solution was filtered, concentrated in *vacuo* and purified by column chromatography (silica gel, 20% ether in petrol) to yield a pale yellow oil **3.9** of 41 mmol. By implication, the resin **3.10** had a loading of 0.52 mmol / g.

IR of the resin beads following cleavage:

IR (ν_{max}, solid phase) 2923 (w), 2358 (w), 1602 (w), 1493 (m), 1452 (m), 1108 (m), 1031 (m) cm^{-1}.

3.9:

IR (ν_{max}, neat) 3322 (br. w), 2924 (w), 1705 (m), 1493 (m), 1446 (m), 1288 (m), 1288 (m), 1210 (m), 948 (vs) cm^{-1}.

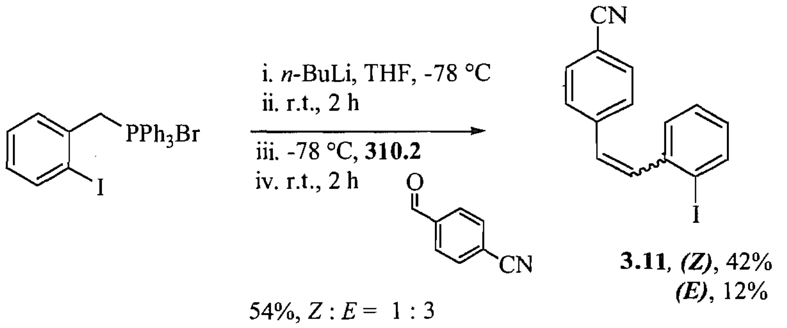
UV λ_{max} (ε_{max}, CH_2Cl_2) 252 (16900) nm.

^{1}H NMR δ_H ppm (400 MHz, C_6D_6) 8.62 (1H, s, N-O$\underline{H}$), 8.12 (1H, s, C$\underline{H}$), 7.50 – 7.53 (2H, m, Ar$\underline{H}$), 7.26 (1H, s, Ar$\underline{H}$), 7.11 – 7.13 (2H, m, Ar$\underline{H}$).

^{13}C NMR δ_C ppm (100 MHz, C_6D_6) 150.5 (N=$\underline{C}$H), 133.1 ($\underline{C}$ (Ar)), 130.3 ($\underline{C}$H (Ar)), 128.4 (2 x $\underline{C}$H (Ar)), 128.2 (2 x $\underline{C}$H (Ar)).

LRMS (CI, m/z) 122 (MH^+, 80%), 106 (100%), 78 (2%) amu.

(*Z*)-4-[2-(2-Iodo-phenyl)-vinyl]-benzonitrile **3.11(*Z*)** & (*E*)-4-[2-(2-Iodo-phenyl)-vinyl]-benzonitrile **3.11(*E*)**



3.11, *(Z)*, 42%
(E), 12%

$C_{25}H_{21}BrIP$ (559)

$C_{15}H_{10}IN$ (331)

To a cooled (0 °C) suspension of phosphonium bromide (7.68 g, 13.74 mmol) in tetrahydrofuran (30 mL) was added the *n*-butyllithium (6.8 mL 2.35 M, 16.03 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to -78 °C and 4-formyl-benzonitrile (1.50 g, 11.45 mmol) added as a solution in tetrahydrofuran (10 mL). After stirring at room temperature for 16 hours, water (20 mL) was added. Extraction with ether (3 x 40 mL) and concentration of the combined organic phases *in vacuo* yielded a white solid, which was purified by column chromatography (silica gel, 5-10% ether in petrol) to give firstly the *cis*-isomer as a white solid **3.11(*Z*)** (1.60 g, 4.83 mmol, 42%) and then the *trans*-isomer **3.11(*E*)** as a white solid (450 mg, 1.36 mmol, 12%).

3.11(*Z*):

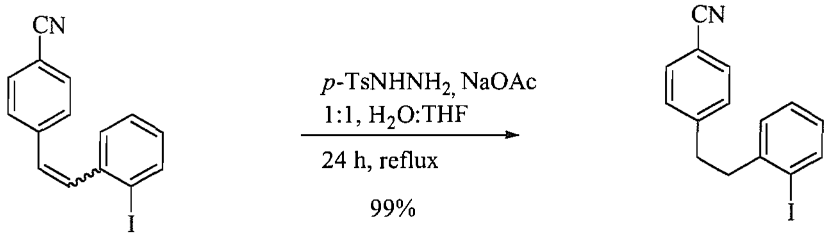
MP	75-77 °C (ether / petrol).
IR	(ν_{max}, neat) 3051 (w), 2227 (s), 1604 (m), 1503 (m), 1408 (m), 1178 (m), 1012 (vs), 887 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 289 (33700), 231 (47000) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 7.95 (1H, d, *J* = 8.0 Hz, Ar<u>H</u>), 7.50 (2H, d, *J* = 8.0 Hz, Ar<u>H</u>), 7.23 (2H, d, *J* = 8.0 Hz, Ar<u>H</u>), 7.24 – 7.20 (1H, m, Ar<u>H</u>), 7.10 (1H, d, *J* = 7.0 Hz, Ar<u>H</u>), 7.02 (1H, t, *J* = 8.0 Hz, Ar<u>H</u>), 6.74 (1H, d, *J* = 12.0 Hz, =C<u>H</u>), 6.67 (1H, d, *J* = 12.0 Hz, =C<u>H</u>).

^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 139.8 (C (Ar)), 139.7 (C (Ar)), 138.2 (CH (Ar)), 135.6 (CH (Ar)), 130.8 (2 x CH (Ar)), 128.8 (=CH), 128.4 (2 x CH (Ar)), 128.3 (CH (Ar)), 128.1 (=CH), 127.1 (CH (Ar)), 117.7 (CN), 109.5 (CCN), 98.1 (CI).
LRMS	(CI, m/z) 349 ($[M+NH_4]^+$, 4%), 331 (M^+, 100%), 203 ($[M-H-I]^+$, 96%).
HRMS	(EI, m/z) Found [M^+]: 330.9858; $C_{15}H_{10}IN^+$ requires 330.9858.

3.11(*E*):

MP	110-112 °C (ether / petrol).
IR	(ν_{max}, neat) 3040 (w), 2357 (w), 2223 (s), 1601 (s), 1505 (m), 1431 (m), 1328 (m), 1174 (s), 1008 (vs) cm^{-1}.
UV-Vis	λ_{max} (ε_{max}, CH_2Cl_2) 231 (23950), 317 (45000) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 7.92 (1H, dd, J = 7.7, 1.1 Hz, ArH), 7.71 – 7.60 (5H, m, ArH), 7.45 (1H, d, =CH, J = 16.5 Hz, ArH), 7.38 (1H, dd, J = 7.3, 0.8 Hz, ArH), 7.03 (1H, td, J = 7.7, 1.5 Hz, ArH), 6.97 (1H, d, J = 16.5 Hz, =CH).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 141.8 (C (Ar)), 140.2 (CH (Ar)), 139.8 (C (Ar)), 136.5 (CH (Ar)), 133.0 (2 x CH (Ar)), 130.3 (=CH), 130.0 (CH (Ar)), 128.9 (=CH), 127.6 (2 x CH (Ar)), 126.9 (CH (Ar)), 119.3 (CN), 111.5 (CCN), 101.1 (CI).
LRMS	(CI, m/z) 331 (M^+, 100%), 204 ($[M-I]^+$, 70%), 177 (24%).
HRMS	(EI, m/z) Found [M^+]: 330.9848; $C_{15}H_{10}IN^+$ requires 330.9858.
CHN	Found: C, 54.81; H, 3.12; N, 4.24; $C_{15}H_{10}IN$ requires C, 54.41; H, 3.04; N, 4.23.

4-[2-(2-Iodo-phenyl)-ethyl]-benzonitrile **3.12**



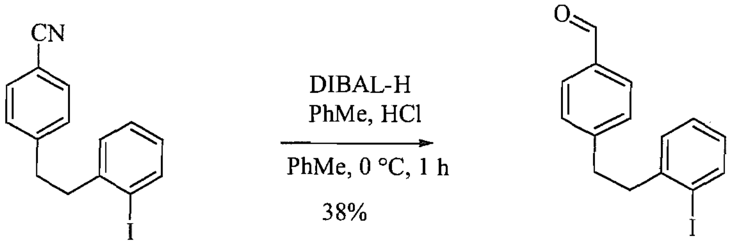
3.11(*E* & *Z*), **3.12**

$C_{15}H_{10}IN$ (331) $C_{15}H_{12}IN$ (333)

A rapidly stirred suspension of **3.11***(E & Z)* (1.60 g, 4.85 mmol), *para*-toluene-sulfonyl hydrazide (9.03 g, 48.5 mmol), and sodium acetate (3.98 g, 48.5 mmol), in THF (30 mL) and water (30 mL) was heated at reflux for 24 hours under nitrogen. The mixture was then cooled to room temperature, extracted with ether (3 x 40 mL) and concentrated *in vacuo* to yield a yellow oil, which was purified by column chromatography (silica gel, 20% ether in petrol) to give the product as a white solid **3.12** (1.60 g, 4.80 mmol, 99%).

MP	62-64 °C (ether / petrol).
IR	(ν_{max}, neat) 3054 (w), 2930 (w), 2225 (w), 1605 (s), 1505 (s), 1178 (w), 1009 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 236 (52700) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 7.76 (2H, dd, *J* = 7.5, 1.0 Hz, Ar$\underline{H}$), 7.53 (2H, d, *J* = 7.5 Hz, Ar$\underline{H}$), 7.23 (1H, d, *J* = 8.0 Hz, Ar$\underline{H}$), 7.16 (1H, dd, *J* = 7.5, 1.5 Hz, Ar$\underline{H}$), 7.03 (1H, td, *J* = 7.5, 1.5 Hz, Ar$\underline{H}$), 6.84 (1H, td, *J* = 8.0, 1.5 Hz, Ar$\underline{H}$), 2.85 – 2.96 (4H, m, 2 x C$\underline{H}_2$).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 147.2 ($\underline{C}$ (Ar)), 143.5 ($\underline{C}$ (Ar)), 140.1 ($\underline{C}$H (Ar)), 132.6 (2 x $\underline{C}$H (Ar)), 130.0 ($\underline{C}$H (Ar)), 129.8 (2 x $\underline{C}$H (Ar)), 128.9 ($\underline{C}$H (Ar)), 128.6 ($\underline{C}$H (Ar)), 119.4 ($\underline{C}$N), 110.5 ($\underline{C}$CN), 100.8 ($\underline{C}$I), 42.7 ($\underline{C}H_2$), 37.0 ($\underline{C}H_2$).
LRMS	(CI, m/z) 351 ($[M+NH_4]^+$, 100%), 333 (M^+, 62%), 223 (86%) amu.
HRMS	(EI, m/z) Found: M^+: 333.0011; $C_{15}H_{12}NI^+$ requires: 333.0015.

4-[2-(2-Iodo-phenyl)-ethyl]-benzaldehyde **3.13**



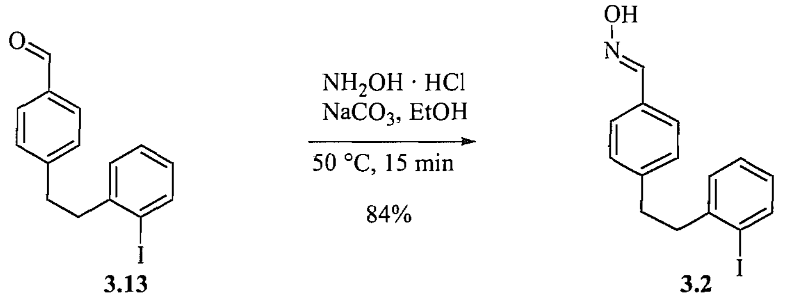
3.12 $C_{15}H_{12}IN$ (333)

3.13 $C_{15}H_{13}IO$ (336)

A stirred solution of 4-[2-(2-iodo-phenyl)-ethyl]-benzonitrile **3.12** (1.50 g, 4.50 mmol) in toluene (40 mL) was treated with DIBAL-H (1 M solution in hexanes 5.0 mL, 4.95 mmol) at 0 °C under nitrogen. After 1 hour, chloroform (20 mL), and hydrochloric acid (2 M, 10 mL) were added and reaction mixture stirred for 1 hour. The phases were then separated and the organic phase dried ($MgSO_4$), filtered and concentrated in *vacuo* to yield a pale yellow oil **3.13** (570 mg, 1.70 mmol, 38%).

IR	(ν_{max}, neat) 2924 (w), 2324 (w), 1605 (m), 1465 (m), 1305 (m), 1212 (s), 1168 (s), 1011 (s), 749 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 259 (41800) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 9.91 (1H, s, CHO), 7.77 (2H, dd, J = 8.0, 1.1 Hz, ArH), 7.74 (2H, d, J = 8.0, ArH), 7.31 (1H, d, J = 8.0, ArH), 7.15 – 7.19 (1H, m, ArH), 7.06 (1H, td, J = 7.5, 1.5 Hz, ArH), 6.83 (1H, td, J = 8.0, 2.0 Hz, ArH), 1.36 – 2.99 (4H, m, 2 x CH_2).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 192.3 (CHO), 149.5 (C (Ar)), 143.8 (C (Ar)), 141.3 (CH (Ar)), 130.4 (CH (Ar)), 130.0 (CH (Ar)), 129.7 (2 x CH (Ar)), 128.8 (CH (Ar)), 128.5 (CH (Ar)), 126.6 (C (Ar)), 125.7 (CH (Ar)), 100.8 (CI), 42.9 (CH_2), 37.1 (CH_2).
LRMS	(CI, m/z) 354 ($[M+NH_4]^+$, 20%) 337 (MH^+, 76%), 217 (100%) amu.
HRMS	(EI, m/z) Found: M^+: 335.9999, $C_{15}H_{13}IO^+$ requires 336.0011.

4-[2-(2-Iodo-3,4,5-trimethoxy-phenyl)-ethyl]-benzaldehyde oxime **3.2**



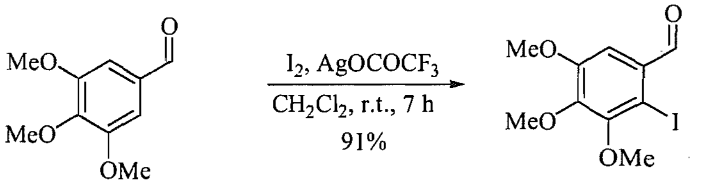
3.13 $C_{15}H_{13}IO$ (336)

3.2 $C_{15}H_{14}INO$ (351)

This method was adapted from a reported procedure by Kutschy *et al.* [71] To a stirred solution of 4-[2-(2-iodo-3,4,5-trimethoxy-phenyl)-ethyl]-benzaldehyde **3.13** (560 mg, 1.66 mmol) in ethanol (15 mL) was added a solution of hydroxylamine hydrochloride (182 mg, 2.62 mmol) and sodium carbonate (127 mg, 1.2 mmol) in water (2.5 mL). The mixture was heated to 50 °C for 15 minutes then the ethanol removed by distillation *in vacuo*. Water (20 mL) was added and the product extracted with ether (3 x 40 mL). The combined ether phases were concentrated *in vacuo* yielding a pale yellow oil, which was purified by column chromatography (silica gel, 20% ether in petrol) to give the **3.2** as a white solid (488 mg, 1.39 mmol, 84%).

MP	121-123 °C (ethanol).
IR	(ν_{max}, neat) 3244 (br. m), 2926 (w), 1915 (w), 1612 (w), 1452 (m), 1300 (m), 1213 (m), 1014 (w), 931 (w), 868 (w) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 260 (44600) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 8.05 (1H, s, N-O$\underline{H}$), 7.76 (2H, dd, J = 8.0, 1.0 Hz, Ar$\underline{H}$), 7.51 (1H, s, N=C$\underline{H}$), 7.43 (2H, d, J = 8.0 Hz, Ar$\underline{H}$), 7.15 – 7.20 (2H, m, Ar$\underline{H}$), 7.07 (1H, td, J = 7.5, 1.5 Hz, Ar$\underline{H}$), 6.82 (1H, td, J = 7.5, 1.5 Hz, Ar$\underline{H}$), 2.93 - 2.96 (2H, m, C$\underline{H}_2$), 2.81 - 2.92 (2H, m, C$\underline{H}_2$).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 149.9 (N=$\underline{C}$H), 143.3 ($\underline{C}$ (Ar)), 143.0 ($\underline{C}$ (Ar)), 139.1 ($\underline{C}$H (Ar)), 129.5 ($\underline{C}$ (Ar)), 129.1 ($\underline{C}$H (Ar)), 128.5 (2 x $\underline{C}$H (Ar)), 128.5 ($\underline{C}$H (Ar)), 128.0 ($\underline{C}$H (Ar)), 126.6 (2 x $\underline{C}$H (Ar)), 100.0 ($\underline{C}$I), 42.2 ($\underline{C}H_2$), 35.9 ($\underline{C}H_2$).
LRMS	(CI, m/z) 351 (M$^+$, 2%), 333 [M-NH$_4$]$^+$, 40%), 116 (78%).
CHN	Found: C, 51.66; H, 4.05; N, 4.04 $C_{15}H_{14}INO$ requires C, 51.30; H, 4.02; N, 3.99.

2-Iodo-3,4,5-trimethoxy-benzaldehyde



5.15

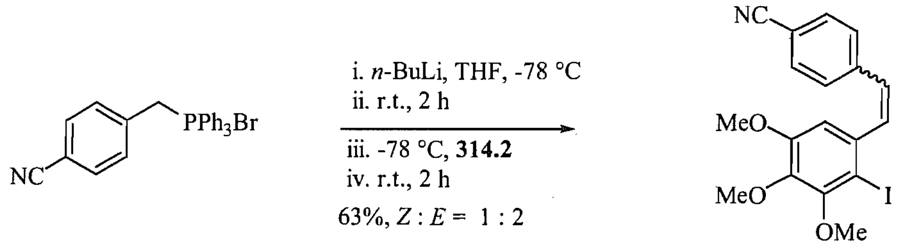
$C_{10}H_{12}O_4$ (212)

$C_{10}H_{11}IO_4$ (322)

2-Iodo-3,4,5-trimethoxy-benzaldehyde was prepared by the method of Bradley *et al.* [72] To a solution of **5.15** (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. Silver(I) trifluoroacetate was added until the reaction mixture turned yellow. The resulting solid was removed by filtration through Celite and the filtrate concentrated *in vacuo* to yield the title compound (9.00 g, 28.0 mmol, 91%) as a light yellow solid. [72]

MP	60-62 °C (ether / petrol), lit. 66-66.5. [72]
IR	(ν_{max}, neat) 3078 (w), 2937 (w), 2853 (w), 1682 (s), 1573 (s), 1378 (s), 1319 (s), 1159 (w), 919 (s), 862 (s), 722 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 333 (3300), 284 (9700), 234 (23800) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 10.03 (1H, s, C$\underline{H}$O), 7.33 (1H, s, Ar$\underline{H}$), 3.96 (3H, s, OC$\underline{H}_3$), 3.91 (3H, s, OC$\underline{H}_3$), 3.89 (3H, s, OC$\underline{H}_3$).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 195.2 ($\underline{C}$HO), 154.0 ($\underline{C}$ (Ar)), 153.0 ($\underline{C}$ (Ar)), 147.7 ($\underline{C}$ (Ar)), 130.5 ($\underline{C}$ (Ar)), 108.6 ($\underline{C}$H (Ar)), 91.6 ($\underline{C}$I), 61.2 (O$\underline{C}H_3$), 61.0 (O$\underline{C}H_3$), 56.3 (O$\underline{C}H_3$).
LRMS	(CI, m/z) 322 (M$^+$, 100 %), 196 ([MH-I]$^+$, 46 %), 116 (100 %), 89 (88 %) amu.

(*Z*)-4-[2-(2-Iodo-3,4,5-trimethoxy-phenyl)-vinyl]-benzonitrile **3.14(*Z*)** & (*E*)-4-[2-(2-Iodo-3,4,5-trimethoxy-phenyl)-vinyl]-benzonitrile **3.14(*E*)**



314, ***(Z)***, 20%
(E), 43%

$C_{25}H_{19}BrNP$ (444)

$C_{18}H_{16}INO_3$ (421)

To a cooled (-78 °C) suspension of phosphonium bromide (2.18 g, 4.91 mmol) in tetrahydrofuran (30 mL) was added the *n*-butyllithium (1.91 mL 2.35 M, 4.50 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to -78 °C and 2-iodo-3,4,5-trimethoxy-benzaldehyde (1.32 g, 4.1 mmol) added as a solution in tetrahydrofuran (10 mL). After stirring at room temperature for 16 hours, water (20 mL) was added. Extraction with ether (3 x 40 mL) and concentration of the combined organic phases *in vacuo* yielded a yellow solid, which was purified by column chromatography (silica gel, 20% ether in petrol) to give the *cis*-isomer as a white solid [73] **3.14(*Z*)** (350 mg, 0.83 mmol, 20%) and the *trans*-isomer **3.14(*E*)** as a yellow solid (750 mg, 1.75 mmol, 43%).

3.14(*Z*):

MP	88-90 °C (ethanol), lit. 86-87 °C (ethanol). [73]
IR	(ν_{max}, neat) 2963 (w), 2230 (s), 1604 (w), 1551 (w), 1480 (s), 1418 (s), 1382 (s), 1319 (s), 1243 (m), 1202 (m), 1154 (m), 1033 (m), 925 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 301 (18700), 230 (52600) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$): 7.49 (2H, d, *J* = 8.5 Hz, ArH), 7.24 (2H, d, *J* = 8.5 Hz, ArH), 6.67 (1H, d, *J* = 12.0 Hz, =CH), 5.58 (1H, d, *J* = 12.0 Hz, =CH), 6.44 (1H, s, ArH), 3.92 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.51 (3H, s, OCH_3).

^{13}C NMR δ_{C} ppm (100 MHz, $CDCl_3$): 153.7 ($\underline{\mathrm{C}}$ (Ar)), 141.7 ($\underline{\mathrm{C}}$ (Ar)), 141.2 ($\underline{\mathrm{C}}$ (Ar)), 136.8 ($\underline{\mathrm{C}}$ (Ar)), 135.9 ($\underline{\mathrm{C}}$ (Ar)), 132.0 (2 x $\underline{\mathrm{C}}$H (Ar)), 129.6 (2 x $\underline{\mathrm{C}}$H (Ar)), 129.6 ($\underline{\mathrm{C}}$H=CH), 128.7 ($\underline{\mathrm{C}}$H=CH), 118.8 ($\underline{\mathrm{C}}$N), 110.6 ($\underline{\mathrm{C}}$CN), 109.4 ($\underline{\mathrm{C}}$H (Ar)), 86.9 ($\underline{\mathrm{C}}$I (Ar)), 61.1 (O$\underline{\mathrm{C}}$$H_3$), 60.9 (O$\underline{\mathrm{C}}$$H_3$), 56.0 (O$\underline{\mathrm{C}}$$H_3$).

LRMS (CI, m/z) 439 ($[M+NH_4]^+$, 20%), 421 (M^+, 40%), 294 (100%), 311 (46%) amu.

3.14(*E*):

MP 170-172 °C (ethanol).

IR (ν_{max}, neat) 2936 (w), 2222 (s), 1603 (w), 1556 (m), 1472 (s), 1384 (s), 1342 (s), 1235 (m), 1162 (m), 1095 (vs), 1005 (m), 809 (m) cm^{-1}.

UV λ_{max} (ε_{max}, CH_2Cl_2): 301 (18700), 230 (52600) nm.

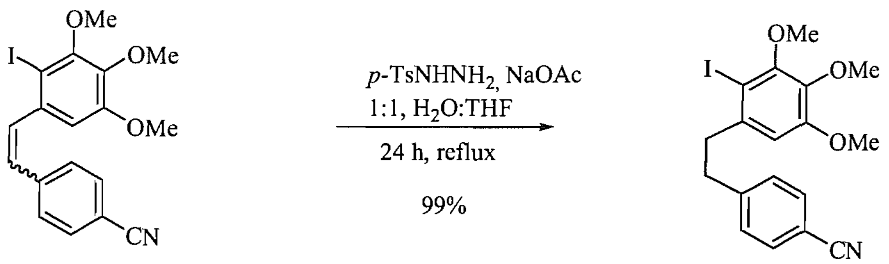
^{1}H NMR δ_{H} ppm (400 MHz, $CDCl_3$) 7.66 (2H, d, J = 8.5 Hz, Ar$\underline{\mathrm{H}}$), 7.61 (2H, d, J = 8.5 Hz, Ar$\underline{\mathrm{H}}$), 7.48 (1H, d, J = 16.1 Hz, C$\underline{\mathrm{H}}$=CH), 7.01 (1H, s, Ar$\underline{\mathrm{H}}$) 6.84 (1H, d, J = 16.1 Hz, C$\underline{\mathrm{H}}$=CH), 3.91 (3H, s, OC$\underline{\mathrm{H}}_3$), 3.91 (3H, s, OC$\underline{\mathrm{H}}_3$), 3.90 (3H, s, OC$\underline{\mathrm{H}}_3$).

^{13}C NMR δ_{C} ppm (75 MHz, $CDCl_3$) 154.6 ($\underline{\mathrm{C}}$ (Ar)), 143.2 ($\underline{\mathrm{C}}$ (Ar)), 142.0 ($\underline{\mathrm{C}}$ (Ar)), 137.0 ($\underline{\mathrm{C}}$ (Ar)), 135.7 ($\underline{\mathrm{C}}$ (Ar)), 133.1 (2 x $\underline{\mathrm{C}}$H (Ar)), 129.6 (2 x $\underline{\mathrm{C}}$H=CH (Ar)), 127.7 (2 x $\underline{\mathrm{C}}$H (Ar)), 119.5 ($\underline{\mathrm{C}}$N), 111.6 ($\underline{\mathrm{C}}$CN), 106.4 ($\underline{\mathrm{C}}$H (Ar)), 90.9 ($\underline{\mathrm{C}}$I), 61.7 (O$\underline{\mathrm{C}}$$H_3$), 61.4 (O$\underline{\mathrm{C}}$$H_3$), 56.9 (O$\underline{\mathrm{C}}$$H_3$).

LRMS (CI, m/z) 439 ($[M+NH_4]^+$, 6%), 421 (M^+, 12%), 294 (100%), 311 (46%) amu.

HRMS (ES+, m/z): Found: $[M+Na]^+$: 444.0070; $C_{18}H_{16}INO_3Na^+$ requires: 444.0067.

4-[2-(2-Iodo-3,4,5-trimethoxy-phenyl)-ethyl]-benzonitrile **3.15**



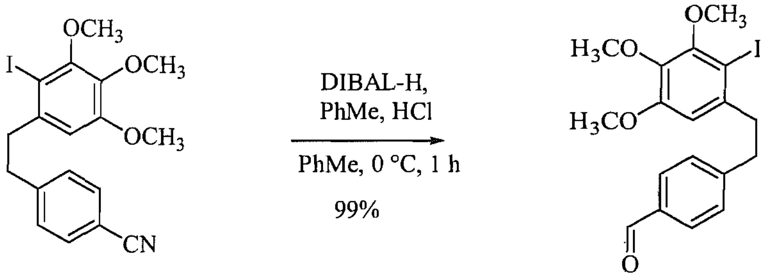
3.14(*Z* & *E*) **3.15**

$C_{18}H_{16}INO_3$ (421) $C_{18}H_{18}INO_3$ (423)

A rapidly stirred suspension of alkene **3.14** (***Z* & *E***) (600 mg, 1.43 mmol), *para*-toluene-sulfonyl hydrazide (2.66 g, 14.26 mmol), and sodium acetate (1.17 g, 14.26 mmol), in THF (20 mL) and water (20 mL) was heated at reflux for 24 hours. The mixture was then cooled to room temperature, and extracted with diethyl ether (3 x 40 mL). Concentration of the combined organic phases *in vacuo* yielded a colourless oil, which was purified by column chromatography (silica gel, 20% ether in petrol) to give the product as colourless oil **3.15** (600 mg, 1.42 mmol, 99%).

IR	(ν_{max}, neat) 2939 (w), 2361 (w), 2224 (m), 1606 (m), 1479 (s), 1449 (s), 1388 (s), 1332 (m), 1240 (m), 1197 (m), 1097 (vs), 1009 (vs), 826 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2): 235 (58450) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$): 7.60 (2H, d, J = 8.1 Hz, Ar$\underline{H}$), 7.34 (2H, d, J = 8.1 Hz, Ar$\underline{H}$), 6.50 (1H, s, Ar$\underline{H}$), 3.90 (3H, s, OC$\underline{H}_3$), 3.87 (3H, s, OC$\underline{H}_3$), 3.79 (3H, s, OC$\underline{H}_3$), 3.03-2.99 (2H, m, C$\underline{H}_2$), 2.96-2.93 (2H, m, C$\underline{H}_2$).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$): 153.6 ($\underline{C}$ (Ar)), 153.3 ($\underline{C}$ (Ar)), 146.9 ($\underline{C}$ (Ar)), 140.7 ($\underline{C}$ (Ar)), 138.8 ($\underline{C}$ (Ar)), 132.2 (2 x $\underline{C}$H (Ar)), 129.4 (2 x $\underline{C}$H (Ar)), 119.0 ($\underline{C}$N), 110.1 ($\underline{C}$CN), 109.0 ($\underline{C}$H (Ar)), 88.0 ($\underline{C}$I (Ar)), 61.0 (O$\underline{C}$H$_3$), 60.8 (O$\underline{C}$H$_3$), 56.1 (O$\underline{C}$H$_3$), 42.7 ($\underline{C}$H$_2$), 36.7 ($\underline{C}$H$_2$).
LRMS	(CI, m/z) 441 ([M+NH$_4$]$^+$, 10%), 424 (MH$^+$, 8%), 298 ([MH-I]$^+$, 100%).
HRMS	(ES+, m/z) Found: [M+Na]$^+$: 423.0329; $C_{18}H_{18}O_3INNa^+$ requires: 423.0332.

4-[2-(2-Iodo-3,4,5-trimethoxy-phenyl)-ethyl]-benzaldehyde **3.16**



3.15

$C_{18}H_{18}INO_3$ (423)

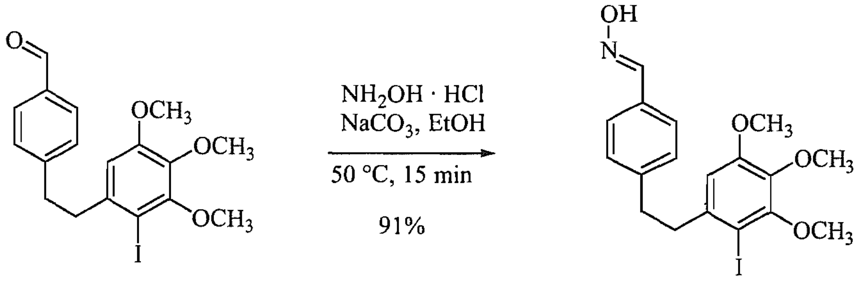
3.16

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

A stirred solution of nitrile **3.15** (500 mg, 1.18 mmol) in toluene (20 mL) was treated with DIBAL-H (1 M solution in hexanes 1.3 mL, 1.30 mmol) at 0 °C under nitrogen. After 1 hour, chloroform (20 mL), and hydrochloric acid (2M, 10 mL) were added and reaction mixture stirred for 1 hour. The phases were then separated and the organic phase dried ($MgSO_4$), filtered and concentrated in *vacuo* to yield a pale yellow oil **3.16** (500 mg, 1.17 mmol, 99%).

IR	(ν_{max}, neat) 2934 (w), 2851 (w), 1698 (s), 1605 (m), 1479 (s), 1386 (s), 1166 (s), 1100 (vs), 731 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 242 (14800) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 9.99 (1H, s, C$\underline{H}$O), 7.82 (2H, d, J = 8.5 Hz, Ar$\underline{H}$), 7.40 (2H, d, J = 8.5 Hz, Ar$\underline{H}$), 6.51 (1H, s, Ar$\underline{H}$), 3.89 (3H, s, OC$\underline{H}_3$), 3.86 (3H, s, OC$\underline{H}_3$), 3.77 (3H, s, OC$\underline{H}_3$), 3.07-3.02 (2H, m, C$\underline{H}_2$), 2.98-2.94 (2H, m, C$\underline{H}_2$).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 192.3 ($\underline{C}$HO), 153.9 ($\underline{C}$ (Ar)), 153.6 ($\underline{C}$ (Ar)), 149.1 ($\underline{C}$ (Ar)), 141.0 ($\underline{C}$ (Ar)), 139.5 ($\underline{C}$ (Ar)), 135.2 ($\underline{C}$ (Ar), 130.4 (2 x $\underline{C}$H (Ar)), 129.7 (2 x $\underline{C}$H (Ar)), 109.4 ($\underline{C}$H (Ar)), 88.3 ($\underline{C}$I), 61.4 (O$\underline{C}H_3$), 61.2 (O$\underline{C}H_3$), 56.5 (O$\underline{C}H_3$), 43.2 ($\underline{C}H_2$), 37.1 ($\underline{C}H_2$).
LRMS	(CI, m/z) 444 ([M+NH$_4$]$^+$, 4 %) 301 ([MH-I]$^+$, 100 %), 181 (54 %) amu.
HRMS	(ES+, m/z) Found: [M + Na]$^+$: 449.0216; $C_{18}H_{19}O_4INa^+$ requires: 449.0220.

4-[2-(2-Iodo-3,4,5-trimethoxy-phenyl)-ethyl]-benzaldehyde oxime **3.17**



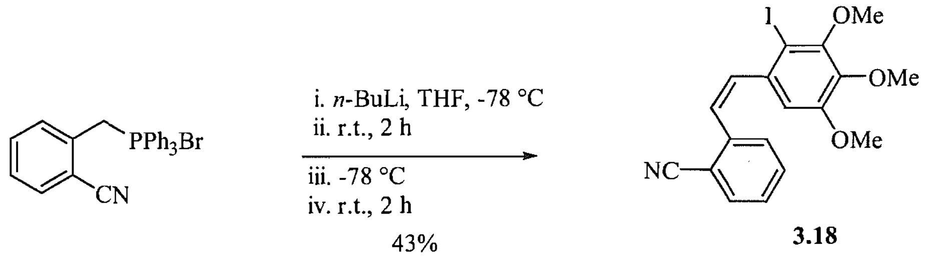
3.16 $C_{18}H_{19}IO_4$ (426)

3.17 $C_{18}H_{20}INO_4$ (441)

This method was adapted from a reported procedure by Kutschy *et al.* [71] To a stirred solution of aldehyde **3.16** (400 mg, 0.94 mmol) in ethanol (15 mL) was added a solution of hydroxylamine hydrochloride (102 mg, 1.47 mmol) and sodium carbonate (72 mg, 0.68 mmol) in water (2.5 mL), and the mixture stirred with heating (50 °C) for 15 minutes. After evaporation of ethanol *in vacuo* and addition of water (20 mL) the resulting product was extracted with ether (3 x 40 mL). The ether phases were combined and concentrated *in vacuo* to yield a pale yellow oil, which was purified by column chromatography (20% diethyl ether in petrol) to give the **3.17** as a colourless oil (377 mg, 0.86 mmol, 91%).

IR	(ν_{max}, neat) 3422 (br. w), 2934 (w), 1561 (w), 1479 (s), 1386 (s), 1327 (s), 1197 (m), 1099 (vs), 1004 (m), 958 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 242 (23700) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$): δ_H ppm (400 MHz, $CDCl_3$): 8.12 (1H, s, N-OH), 7.51 (2H, d, J = 8.0 Hz, ArH), 7.44 (1H, s, N=CH), 7.25 (2H, d, J = 8.0 Hz, ArH), 6.51 (1H, s, ArH), 3.89 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.03-3.00 (2H, m, CH_2), 2.91-2.87 (2H, m, CH_2).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$): δ_C ppm (75 MHz, $CDCl_3$): 153.9 (C (Ar)), 153.6 (C (Ar)), 150.7 (N=CH), 143.9 (C (Ar)), 140.9 (C (Ar)), 139.9 (C (Ar)), 130.4 (C (Ar), 129.4 (2 x CH (Ar)), 127.5 (2 x CH (Ar)), 109.5 (CH (Ar)), 88.3 (CI), 61.4 (OCH_3), 61.2 (OCH_3), 56.5 (OCH_3), 43.4 (CH_2), 36.8 (CH_2).
LRMS	(CI, m/z) 441 (M^+, 10%), 313 (100%), 116 (78%) amu.
HRMS	(ES+, m/z) Found: $[M+Na]^+$: 464.0338; $C_{18}H_{20}O_4INNa^+$ requires: 464.0329.

2-[2-(5-Iodo-2,3,4-trimethoxy-phenyl)-vinyl]-benzonitrile **3.18**



3.18

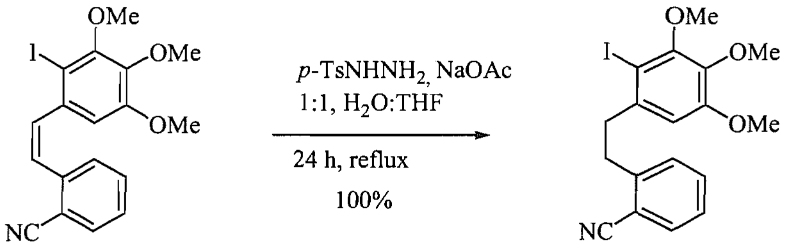
$C_{25}H_{19}BrNP$ (444)

$C_{18}H_{16}INO_3$ (421)

To a cooled (-78 °C) suspension of phosphonium bromide (2.18 g, 4.91 mmol) in tetrahydrofuran (30 mL) was added the *n*-butyllithium (1.92 mL 2.35 M, 4.50 mmol). After stirring at ambient temperature for 2 hours, the mixture was cooled to -78 °C and 2-iodo-3,4,5-trimethoxy-benzaldehyde (1.32 g, 4.09 mmol) added as a solution in tetrahydrofuran (10 mL). After stirring at room temperature for 16 hours, water (20 mL) was added. Extraction with diethyl ether (3 x 40 mL) and concentration *in vacuo* of the combined organic phases yielded a yellow solid, which was purified by column chromatography (silica gel, 20% diethyl ether in petrol) to give the *cis*-isomer as a white solid [74] **3.18** (750 mg, 1.78 mmol, 43%).

MP	128-130 °C (ether-petrol), lit. 94-96 °C (ether/petrol). [74]
IR	(ν_{max}, neat) 2935 (w), 2222 (s), 1554 (w), 1472 (s), 1383 (s), 1320 (s), 1236 (m), 1156 (m), 1041 (w), 775 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2): 231 (16300), 309 (45800) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$): 7.65 (1H, dd, J = 8.1, 1.1 Hz, ArH), 7.38-7.28 (2H, m, ArH), 7.15 (1H, d, J = 7.7 Hz, ArH), 6.86 (1H, d, J = 11.8 Hz, CH=CH), 6.79 (1H, d, J = 11.8 Hz, CH=CH), 6.36 (1H, s, ArH), 3.91 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.45 (3H, s, OCH_3).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$): 153.6 (C (Ar)), 141.7 (C (Ar)), 140.4 (C (Ar)), 138.0 (C (Ar)), 135.7 (C (Ar)), 133.0 (CH (Ar), 132.3 (CH (Ar)), 129.9 (CH x 2 (Ar)), 127.7 (CH=CH), 126.6 (CH=CH), 117.9 (CN), 112.4 (CCN), 109.7 (CH (Ar)), 87.4 (CI), 61.3 (OCH_3), 61.0 (OCH_3), 56.0 (OCH_3).
LRMS	(CI, m/z) 439 ($[M+NH_4]^+$, 62%), 421 (M^+, 55%), 294 (100%).

2-[2-(2-Iodo-3,4,5-trimethoxy-phenyl)-ethyl]-benzonitrile **3.19**



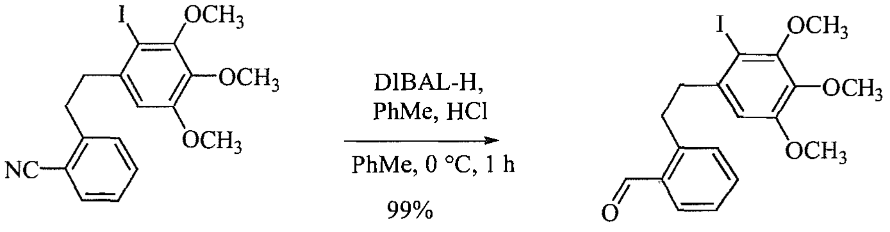
3.18 $C_{18}H_{16}INO_3$ (421)

3.19 $C_{18}H_{18}INO_3$ (423)

A rapidly stirred suspension of alkene **3.18** (700 mg, 1.66 mmol), *para*-toluenesulfonylhydrazide (3.09 g, 16.62 mmol), and sodium acetate (1.36 g, 16.62 mmol), in THF (20 mL) and water (20 mL) was heated at reflux for 24 hours under nitrogen. The mixture was then cooled to room temperature and extracted with diethyl ether (3 x 40 mL). Concentration of the combined organic phases *in vacuo* yielded a yellow oil, which was purified by column chromatography (20% ether in petrol) to give the product as a yellow oil **3.19** (700 mg, 1.65 mmol, 100%).

IR	(ν_{max}, neat) 2936 (w), 2361 (s), 2222 (w), 1561 (s), 1383 (s), 1480 (s), 1387 (s), 1199 (m), 1102 (vs), 762 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 231 (32300) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 7.65 (1H, dd, J = 7.7, 1.1 Hz, ArH), 7.52 (1H, td, J = 7.7, 1.5 Hz, ArH), 7.38 – 7.30 (2H, m, ArH), 6.60 (1H, s, ArH), 3.90 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.11-3.09 (4H, m, CH_2).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 155.0 (C (Ar)), 154.0 (C (Ar)), 145.5 (C (Ar)), 141.1 (C (Ar)), 139.1 (C (Ar)), 133.2 (2 x CH (Ar), 130.3 (CH (Ar)), 127.2 (CH (Ar)), 118.5 (CN), 112.4 (CCN), 109.0 (CH (Ar)), 88.3 (CI), 61.4 (OCH_3), 61.2 (OCH_3), 56.5 (OCH_3), 42.6 (CH_2), 35.6 (CH_2).
LRMS	(CI, m/z) 441 ($[M+NH_4]^+$, 14%), 423 (M^+, 10%), 298 ($[MH-I]^+$, 100%).
HRMS	(EI, m/z) Found: M^+: 423.03387; $C_{18}H_{18}O_3IN$ requires 423.03315.

2-[2-(2-Iodo-3,4,5-trimethoxy-phenyl)-ethyl]-benzaldehyde **3.20**



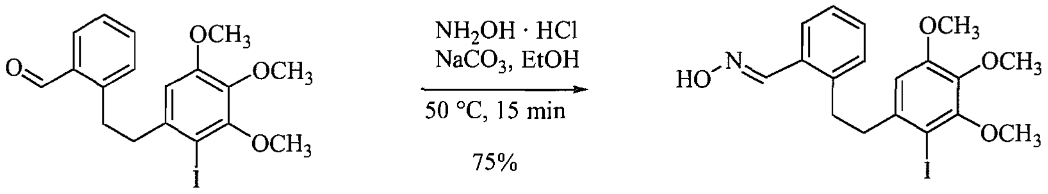
3.19
$C_{18}H_{18}INO_3$ (423)

3.20
$C_{18}H_{19}IO_4$ (426)

A stirred solution of **3.19** (500 mg, 1.18 mmol) in toluene (20 mL) was treated with DIBAL-H (1 M solution in hexanes 1.3 mL, 1.30 mmol) at 0 °C. After 1 hour, chloroform (20 mL), and hydrochloric acid (2 M, 10 mLl) were added and reaction mixture stirred for 1 hour. The phases were then separated and the organic phase dried ($MgSO_4$), filtered and concentrated in *vacuo* to yield a pale yellow oil **3.20** (500 mg, 1.17 mmol, 99%).

IR	(ν_{max}, neat) 2934 (w), 2845 (w), 1692 (s), 1479 (s), 1385 (s), 1320 (s), 1196 (s), 1004 (s), 757 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2): 238 (39845) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$): 10.23 (1H, s, CHO), 7.83 (1H, dd, *J* = 7.5, 1.0 Hz, ArH), 7.52 (1H, td, *J* = 7.5, 1.5 Hz, ArH), 7.41 (1H, td, *J* = 7.5, 1.0 Hz, ArH), 7.33 (1H, d, *J* = 7.5 Hz, ArH), 6.56 (1H, s, ArH), 3.89 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.31-3.27 (2H, m, CH_2), 3.04-3.00 (2H, m, CH_2).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$): 191.9 (CHO), 153.1 (C (Ar)), 152.6 (C (Ar)), 143.3 (C (Ar)), 140.1 (C (Ar)), 138.8 (C (Ar)), 133.6 (C (Ar), 133.3 (CH (Ar), 131.8 (CH (Ar)), 130.9 (CH (Ar)), 126.0 (CH (Ar)), 108.8 (CH (Ar)), 87.5 (CI), 60.5 (OCH_3), 60.3 (OCH_3), 55.6 (OCH_3), 42.5 (CH_2), 32.7 (CH_2).
LRMS	(CI, m/z) 444 ($[M+NH_4]^+$, 4%), 298 ($[MH-I]^+$, 78%), 285 (100%) amu.
HRMS	(ES+, m/z) Found $[M + Na]^+$: 449.0226; $C_{18}H_{19}O_4INa^+$ requires 449.0220.

2-[2-(2-Iodo-3,4,5-trimethoxy-phenyl)-ethyl]-benzaldehyde oxime **3.21**



3.20
$C_{18}H_{19}IO_4$ (426)

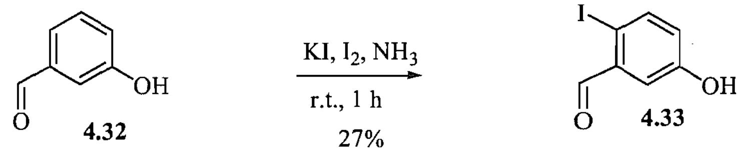
3.21
$C_{18}H_{20}INO_4$ (441)

This method was adapted from a reported procedure by Kutschy *et al.* [71] To a stirred solution of aldehyde **3.20** (300 mg, 0.70 mmol) in ethanol (15 mL) was added a solution of hydroxylamine hydrochloride (77 mg, 1.11 mmol) and sodium carbonate (54 mg, 0.51 mmol) in water (2.5 mL), and the mixture stirred with heating (50 °C) for 15 minutes. After evaporation of ethanol and addition of water (20 mL) the resulting product was extracted with ether (3 x 40 mL). Concentration of the combined organic phases *in vacuo* yielded a clear oil, which was purified by column chromatography (silica gel, 20% ether in petrol) to give **3.21** as a colourless oil (232 mg, 0.53 mmol, 75%).

IR	(ν_{max}, neat) 3446 (br. w), 2937 (m), 1738 (s), 1561 (m), 1561 (m), 1429 (s), 1385 (s), 1200 (m), 757 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 230 (35700) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 8.39 (1H, s, N-O$\underline{H}$), 7.69 (1H, s, N=C$\underline{H}$), 7.31 (1H, td, *J* = 7.5, 1.5 Hz, Ar$\underline{H}$), 7.26-7.21 (3H, m, Ar$\underline{H}$), 6.37 (1H, s, Ar$\underline{H}$), 3.89 (3H, s, O$\underline{CH_3}$), 3.85 (3H, s, O$\underline{CH_3}$), 3.72 (3H, s, O$\underline{CH_3}$), 3.01-2.99 (4H, m, 2 x $\underline{CH_2}$).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 153.8 ($\underline{C}$ (Ar)), 153.6 ($\underline{C}$ (Ar)), 149.4 (N=$\underline{C}$H), 141.4 ($\underline{C}$ (Ar)), 140.4 ($\underline{C}$ (Ar)), 139.6 ($\underline{C}$ (Ar), 130.8 ($\underline{C}$H (Ar)), 130.7 ($\underline{C}$ (Ar)), 130.3 ($\underline{C}$H (Ar)), 127.2 ($\underline{C}$H (Ar)), 127.0 ($\underline{C}$H (Ar)), 109.7 ($\underline{C}$H (Ar)), 88.3 ($\underline{C}$I), 61.4 (O$\underline{C}H_3$), 61.2 (O$\underline{C}H_3$), 56.5 (O$\underline{C}H_3$), 43.3 ($\underline{C}H_2$), 33.7 ($\underline{C}H_2$).
LRMS	(CI, m/z) 441 (M^+, 8%), 313 ($[M-2H-I]^+$, 28%), 298 (100%) amu.
HRMS	(ES+, m/z) Found: $[M+Na]^+$: 464.0340; $C_{18}H_{20}O_4INNa^+$ requires: 464.0329.

6.4. Experimental for Chapter 4

5-Hydroxy-2-iodo-benzaldehyde **4.33**



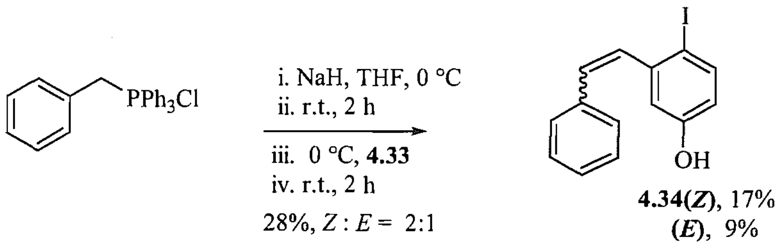
4.32 $C_8H_{10}O_2$ (138)

4.33 $C_7H_5IO_2$ (248)

Using the procedure of Pandya and Counsell, [75,76] a solution of iodine (37.20 g in 250 mL of 28% aqueous KI solution) was added dropwise over 15 minutes to a stirred solution of 3-hydroxybenzaldeyde (16.00 g, 0.131 M) in ammonia (150 mL) at ambient temperature. A dark, gummy residue appeared toward the end of the addition procedure. The reaction mixture was stirred an additional 1 hour then acidified with concentrated hydrochloric acid (100 mL) where upon precipitation occured. The resulting gum was dissolved in ether (80 mL) and washed with aqueous saturated sodium thiosulfate solution (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Recrystallisation from benzene – petroleum ether (40 mL) yielded the product **4.33** as a light brown solid [76] (4.37 g, 17.6 mmol, 27%).

MP	129-131 °C (benzene / petrol), lit. 131.5-133.5 °C. [76]
IR	(ν_{max}, neat) 3228 (br. m), 1675 (s), 1577 (s), 1492 (w), 1421 (m), 1398 (s), 1355 (w), 1267 (s), 1204 (m), 1160 (s), 1120 (w), 1017 (s), 979 (w), 868 (w), 754 (vs) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_3OH) 315 (8400), 271 (16000) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 9.94 (1H, s, J = 8.7 Hz, ArCHO), 7.89 (1H, d, J = 8.1 Hz, ArH), 7.46 (1H, d, J = 1.9 Hz, ArH), 7.20 (1H, dd, J = 8.1, 1.9 Hz, ArH), 5.69 (1H, s, ArOH).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 191.3 (ArCHO), 155.7 (C (Ar)), 139.3 (CH (Ar)), 138.3 (C (Ar)), 123.1 (CH (Ar)), 114.9 (CH (Ar)), 94.0 (CI (Ar)).
LRMS	(CI, m/z) 248 (M^+, 100%), 119 (12%), 92 (20%) amu.

(*Z*)-4-Iodo-3-styryl-phenol **4.34(*Z*)** & (*E*)-4-Iodo-3-styryl-phenol **4.34(*E*)**



$C_{25}H_{22}ClP$ (388)

$C_{14}H_{11}IO$ (322)

Sodium hydride (277 mg, 11.50 mmol) was washed with tetrahydrofuran (15 mL) then suspended in tetrahydrofuran (40 mL) and cooled to 0 °C. Benzyltriphenylphosphonium chloride (2.24 g, 57.60 mmol) was added and the mixture stirred at ambient temperature for 2 hours. On cooling to 0 °C 5-hydroxy-2-iodo-benzaldehyde **4.33** (1.30 g, 52.42 mmol) was added as a solution in tetrahydrofuran (10 mL). The reaction mixture was stirred at room temperature for 16 hours then partitioned between water (20 mL) and ether (80 mL). The aqueous phase was extracted with diethyl ether (3 x 80 mL) and the combined ether phases were concentrated to a dark brown oil. Purification by column chromatography (silica gel, 20-50% ether in petrol) gave firstly the *cis*-isomer **4.34(*Z*)** (280 mg, 0.87 mmol, 17%) as a pale yellow oil; then the *trans*-isomer **4.34(*E*)** (160 mg, 0.49 mmol, 9%) as a white solid.

4.34(*Z*):

IR	(ν_{max}, neat) 3477 (w), 1555 (s), 1492 (m), 1446 (m), 1407 (s), 1289 (s), 1253 (w), 1173 (s), 1138 (w), 1072 (w), 1013 (s), 967 (w), 946 (m), 918 (m), 876 (s) cm^{-1}.
UV	λ_{max}(ε_{max}, CH_3OH): 276 (14000), 208 (28000) nm.
^{1}H NMR	δ_H ppm (300MHz, $CDCl_3$): 7.49 (1H, d, J = 8.2 Hz, Ar$\underline{H}$), 7.10-7.40 (5H, m, Ar$\underline{H}$), 6.89 (1H, d, J = 1.9 Hz, Ar$\underline{H}$), 6.65 (1H, d, J = 12.2 Hz, =C$\underline{H}$), 6.58 (1H, ddd, J = 8.2, 2.0, 0.5 Hz, Ar$\underline{H}$), 6.49 (1H, d, J = 12.2 Hz, =C$\underline{H}$), 5.27 (1H, s, ArO$\underline{H}$).
^{13}C NMR	δ_C ppm (75MHz, $CDCl_3$): 154.6 ($\underline{C}$ (Ar), 139.6 ($\underline{C}$ (Ar)), 137.9 ($\underline{C}$H (Ar)), 131.4 ($\underline{C}$ (Ar)), 128.8 (2 x $\underline{C}$H (Ar)), 128.3 ($\underline{C}$H (Ar)), 127.4 (2 x $\underline{C}$H (Ar)), 123.1 (2 x =$\underline{C}$H), 115.4 ($\underline{C}$H (Ar)), 115.3 ($\underline{C}$H (Ar)), 83.8 ($\underline{C}$I (Ar)).

LRMS (CI, m/z) 322 (M$^+$, 100 %), 196 ([MH-I]$^+$, 32 %) amu.

HRMS (EI, m/z) Found: M$^+$: 321.9852; C$_{14}$H$_{11}$IO$^+$ requires: 321.9855.

4.34(*E*):

MP 130-131 °C (ether/petrol).

IR (ν_{max}, neat) 3448 (br. w), 1576 (m), 1496 (m), 1448 (m), 1404 (s), 1292 (s), 1200 (s), 1016 (s), 967 (vs), 873 (s) cm^{-1}.

UV-Vis λ_{max} (ε_{max}, CH$_3$OH): 204 (24600), 310 (35400) nm.

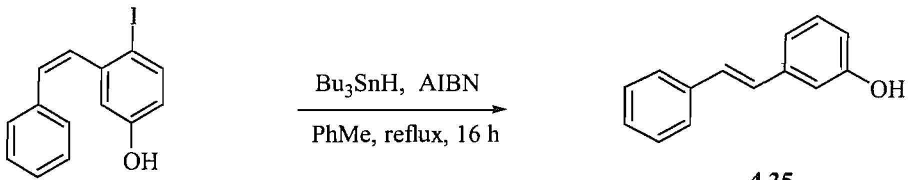
^{1}H NMR δ_H ppm (300 MHz, CDCl$_3$) 7.63 (1H, d, *J* = 8.2 Hz, Ar$\underline{H}$), 7.52 (2H d, *J* = 7.9 Hz, Ar$\underline{H}$), 7.38 (2H, t, *J* = 7.5 Hz, Ar$\underline{H}$), 7.32 - 7.26 (1H, m, Ar$\underline{H}$), 7.13 (1H, d, *J* = 16.6 Hz, =C$\underline{H}$), 7.01 (1H, d, *J* = 16.6 Hz, =C$\underline{H}$), 6.88 (1H d, *J* = 2.3, Ar$\underline{H}$), 6.85 (1H, d, *J* = 2.0, Ar$\underline{H}$), 5.29 (1H, s, ArO$\underline{H}$).

^{13}C NMR δ_C ppm (75 MHz, CDCl$_3$) 155.1 ($\underline{C}$ (Ar)), 140.0 ($\underline{C}$ (Ar)), 138.4 ($\underline{C}$H (Ar)), 137.0 ($\underline{C}$ (Ar)), 130.2 ($\underline{C}$H (Ar)), 128.9 (2 x $\underline{C}$H (Ar)), 128.2 ($\underline{C}$H=CH), 127.4 ($\underline{C}$H=CH), 126.8 (2 x $\underline{C}$H), 120.9 ($\underline{C}$H (Ar)), 112.8 ($\underline{C}$H (Ar)), 84.3 ($\underline{C}$I).

LRMS (CI m/z) 322 (M$^+$, 100%), 194 ([MH-I]$^+$, 36%) amu.

HRMS (EI, m/z) Found: M$^+$: 321.9854; C$_{14}$H$_{11}$IO$^+$ requires: 321.9855.

(*E*)-3-Styryl-phenol **4.35**



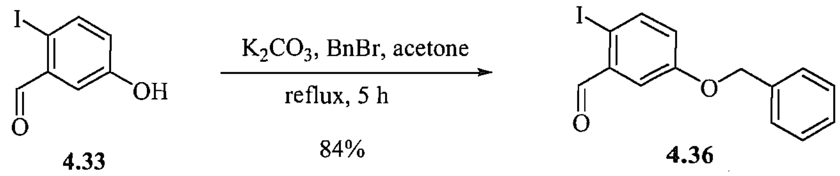
4.34(*Z*)
$C_{14}H_{11}IO$ (322)

4.35
$C_{14}H_{12}O$ (196)

A solution of (*Z*)-4-Iodo-3-styryl-phenol **4.34(*Z*)** (110 mg, 0.34 mmol), tributyltin hydride (120 µL, 0.41 mmol) and AIBN (11 mg, 0.068 mmol) in toluene (16 mL) was heated at reflux for 16 hours then cooled to room temperature. Potassium fluoride solution (10%) was added and the resulting biphasic mixture was stirred vigorously for 24 hours. Extraction with diethyl ether (3 x 30 mL) and concentration of the combined organic phases *in vacuo* yielded white crystals. Purification by column chromatography (silica gel, 10-20% ether in petrol) gave the product **4.35** (37 mg, 0.18 mmol, 55%) as a white solid. [77]

MP	119-121 °C (ether / petrol), lit. 121-122 (ethanol). [77]
IR	(ν_{max}, neat) 3541 (s), 3037 (w), 1589 (s), 1451 (s), 1151 (s), 789 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_3OH) 232 (14700), 302 (28800) nm.
^{1}H NMR	δ_H ppm (300 MHz, d_6-DMSO) 7.50 (2H, d, J = 7.5 Hz, Ar$\underline{H}$), 7.35 (1H, t, J = 7.5 Hz, Ar$\underline{H}$), 7.27-7.20 (2H, m, Ar$\underline{H}$), 7.12-7.06 (3H, m, Ar$\underline{H}$), 7.08 (1H, d, J = 16.1 Hz, ArH), 7.03 (1H, d, J = 16.1 Hz, Ar$\underline{H}$), 6.73 (1H, d, J = 8.0, 2.5 Hz, Ar$\underline{H}$), 4.67 (1H, s, ArO$\underline{H}$).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 154.3 ($\underline{C}$ (Ar)), 137.7 ($\underline{C}$ (Ar)), 135.7 ($\underline{C}$ (Ar)), 128.4 ($\underline{C}$H (Ar)), 127.8 ($\underline{C}$H (Ar)), 127.2 (2 x $\underline{C}$H (Ar)), 126.8 ($\underline{C}$H (Ar)), 126.3 ($\underline{C}$H (Ar)), 125.1 (2 x $\underline{C}$H (Ar)), 118.6 ($\underline{C}$H (Ar)), 113.2 ($\underline{C}$H (Ar)), 111.5 ($\underline{C}$H (Ar)).
LRMS	(CI m/z) 197 (MH$^+$, 100%), 165 (26%), 152 (14%) amu.

5-Benzyloxy-2-iodo-benzaldehyde **4.36**



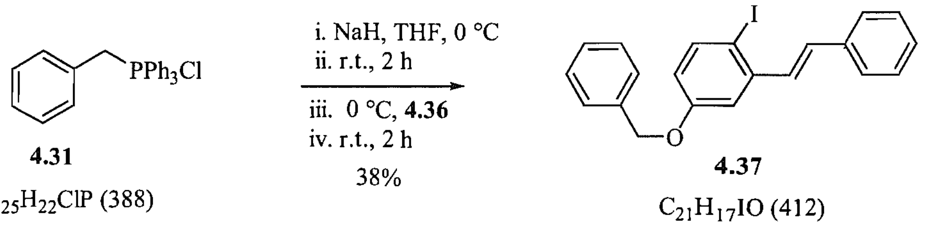
4.33 $C_7H_5IO_2$ (248)

4.36 $C_{14}H_{11}IO_2$ (338)

Adapted from a reported procedure by Counsell *et al.* [76] **4.33** (1.00 g, 4.03 mmol), potassium carbonate (780 mg, 5.64 mmol) and benzyl bromide (530 μL, 2.35 g, 4.43 mmol) in acetone (30 mL) were heated at reflux for 5 hours. The resulting white precipitate was filtered off, and the filtrate reduced *in vacuo* to yield a pale yellow oil. Purification of the oil by column chromatography (silica gel, 10-20% ether in petrol) gave the product **4.36** as a pale yellow solid (1.14 g, 3.37 mmol, 84%). [76]

MP	80-82 °C (ether / petrol), lit 81.5-83 °C (ethanol). [76]
IR	(ν_{max}, neat) 1681 (vs), 1567 (m), 1475 (m), 1419 (s), 1371 (vs), 1283 (s), 1170 (s), 1119 (s), 1025 (vs), 831 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2): 312 (9600), 274 (17000), 222 (20000) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 9.94 (1H, s, ArCHO), 8.05 (1H, d, J = 7.7 Hz, ArH), 7.46-7.38 (5H, m, ArH), 7.27 (1H, s, ArH), 7.21 (1H, dd, J = 7.9, 1.8 Hz, ArH), 5.24 (2H, s, CH_2).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 191.5 (ArCHO), 158.1 (C (Ar)), 140.5 (C (Ar)), 137.9 (C (Ar)), 135.9 (CH (Ar)), 128.8 (2 x CH (Ar)), 128.3 (CH (Ar)), 127.2 (2 x CH (Ar)), 125.3 (CH (Ar)), 110.3 (CH (Ar)), 96.1 (CI (Ar)), 71.2 (CH_2).
LRMS	(CI, m/z) 338 (M^+, 48%), 211 ($[M-I]^+$, 96%), 91 ($C_7H_7^+$, 100%) amu.

(*E*)-4-Benzyloxy-iodo-2-styryl-benzene **4.37**



4.31
$C_{25}H_{22}ClP$ (388)

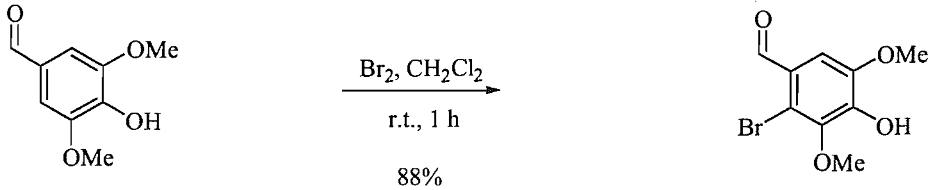
4.37
$C_{21}H_{17}IO$ (412)

To a cooled (0 °C) suspension of sodium hydride (150 mg, 3.80 mmol) in tetrahydrofuran (40 mL) was added benzyltriphenylphosphonium chloride (1.26 g, 3.25 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to 0 °C and 5-benzyloxy-2-iodo-benzaldehyde **4.36** (1.00 g, 2.96 mmol) as a solution in tetrahydrofuran (10 mL) was added. After stirring at room temperature for 16 hours, water (20 mL) was added. Extraction with diethyl ether (3 x 50 mL) and concentration *in vacuo* yielded a dark brown oil, which was purified by column chromatography (silica gel, 5-10% ether in petrol) to a white solid **4.37** (460 mg, 1.13 mmol, 38%).

MP	129-132 °C (ether / petrol).
IR	(ν_{max}, neat) 3024 (w), 1576 (m), 1561 (w), 1496 (w), 1473 (m), 1446 (m), 1408 (s), 1383 (s), 1336 (m), 1284 (s), 1262 (w), 1238 (m), 1171 (m), 1047 (s), 1030 (s), 956 (s), 794 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2): 226 (24000), 320 (40000) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$): 7.77 (1H, d, *J* = 8.1 Hz, Ar$\underline{H}$), 7.57-7.50 (4H, m, Ar$\underline{H}$), 7.46-7.41 (4H, m, Ar$\underline{H}$), 7.33-7.25 (2H, m, Ar$\underline{H}$), 7.10 (1H, d, *J* = 16.3 Hz, =C$\underline{H}$), 7.02 (1H, d, *J* = 16.2 Hz, =C$\underline{H}$), 7.0 (1H, s, Ar$\underline{H}$), 6.92 (1H, dd, *J* = 8.1, 1.4 Hz, Ar$\underline{H}$), 5.22 (2H, s, C$\underline{H}_2$).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$): 157.6 ($\underline{C}$ (Ar)), 139.7 ($\underline{C}$ (Ar)), 139.2 ($\underline{C}$ (Ar)), 137.0 ($\underline{C}$H (Ar)), 136.6 ($\underline{C}$ (Ar)), 129.8 ($\underline{C}$H (Ar)), 128.9 (2 x $\underline{C}$H (Ar)), 128.8 (2 x $\underline{C}$H (Ar)), 128.1 (2 x $\underline{C}$H (Ar)), 127.9 ($\underline{C}$H (Ar)), 127.2 (2 x $\underline{C}$H (Ar)), 126.8 (2 x =$\underline{C}$H), 121.2 ($\underline{C}$H (Ar)), 110.7 ($\underline{C}$H (Ar)), 85.7 ($\underline{C}$I (Ar)), 71.1 ($\underline{C}H_2$).
LRMS	(CI, m/z) 413 (MH$^+$, 6%), 287 ([M-I+2H]$^+$, 100%), 91 ($C_7H_7^+$, 66%) amu.
HRMS	(EI, m/z) Found: M$^+$: 412.03135; $C_{21}H_{17}IO^+$ requires: 412.03130.

CHN Found: C, 61.27; H, 4.19; $C_{21}H_{17}IO$ requires: C, 61.18; H, 4.16.

2-Bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.41**



4.39 $C_9H_{10}O_4$ (182)

4.41 $C_9H_9BrO_4$ (261)

This procedure was performed according to the method of Rouessac. [78] A solution of bromine (1.12 mL, 3.20 g, 20 mmol) in dichloromethane (35 mL) was added dropwise over 10 min to a solution of syringaldehyde (4.00 g, 21.97 mmol) in dichloromethane (35 mL). After 1 hour, the resulting precipitate was collected by filtration and the mother liquors were concentrated. The resulting solids were combined and recrystallised from ethylacetate / cyclohexane to give the product as a white solid **442** (5.02 g, 19.23 mmol, 88%). [78]

MP 186-189 °C (ethyl acetate), lit. 189 °C (ethyl acetate). [78]

IR (ν_{max}, neat) 3135 (br. w), 1662 (s), 1460 (s), 1413 (s), 1388 (s), 1233 (w), 1167 (s), 1087 (s), 1045 (s), 985 (w), 910 (s), 852 (s), 732 (s), 662 (s) cm^{-1}.

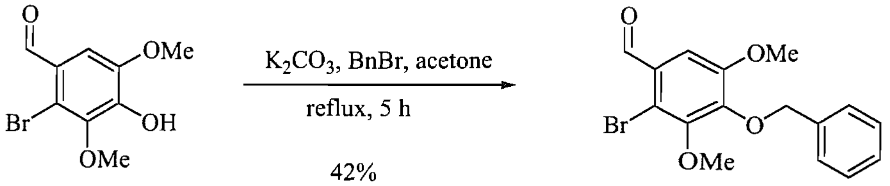
UV λ_{max} (ε_{max}, CH_3OH) 293 (15700), 229 (29800), 207 (30000) nm.

^{1}H NMR δ_H ppm (300 MHz, d_6-DMSO) 10.18 (1H, s, $ArC\underline{H}O$), 7.33 (1H, s, $Ar\underline{H}$), 3.96 (3H, s, OCH_3), 3.86 (3H, s, $ArOC\underline{H}_3$). ($ArO\underline{H}$ not visible).

^{13}C NMR δ_C ppm (75 MHz, d_6-DMSO) 190.2 ($Ar\underline{C}HO$), 148.4 ($\underline{C}OCH_3$), 147.2 ($\underline{C}OCH_3$), 144.8 ($\underline{C}$ (Ar)), 124.0 ($\underline{C}$ (Ar)), 115.3 ($\underline{C}Br$), 107.4 ($\underline{C}H$ (Ar)), 60.2 ($O\underline{C}H_3$), 56.2 ($O\underline{C}H_3$).

LRMS (CI m/z) 263 ($MH^+[^{81}Br]$, 86%), 261 ($MH^+[^{79}Br]$, 72%), 183 ($[MH-Br]^+$, 10%), 154 ($[MH-Br-CO]^+$, 4%) amu.

4-Benzyloxy-2-bromo-3,5-dimethoxy-benzaldehyde **4.42**



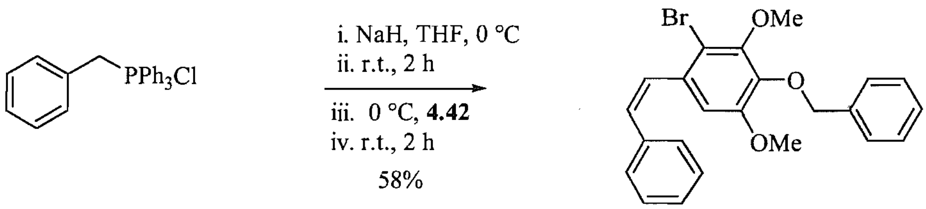
4.41
$C_9H_9BrO_4$ (261)

4.42
$C_{16}H_{15}BrO_4$ (351)

Following the procedure of Counsell *et al.* [76] 2-Bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.41** (1.00 g, 3.83 mmol), potassium carbonate (780 mg, 5.36 mmol) and benzyl bromide (500 µL, 2.20 g, 4.21 mmol) in acetone (40 mL) were heated to reflux for 5 hours. The resulting white precipitate was filtered off, and the filtrate was concentrated *in vacuo* to a pale yellow oil. The oil was purified by column chromatography (silica gel, 10-20% ether in petrol) to give the product **4.42** as a colourless oil (560 mg, 1.61 mmol, 42%).

IR	(ν_{max}, neat) 3164 (w), 3033 (w), 2937 (w), 2886 (s), 1681 (s), 1570 (s), 1443 (s), 1377 (s), 1316 (s), 1107 (s), 955 (s), 909 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 207 (39300), 279 (11400) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 10.31 (1H, s, ArC$\underline{H}$O), 7.49 (2H, dd, J = 8.0, 1.7 Hz, Ar$\underline{H}$), 7.42-7.34 (3H, m, Ar$\underline{H}$), 7.32 (1H, s, Ar$\underline{H}$), 5.16 (2H, s, C$\underline{H}_2$), 3.92 (3H, s, ArOC$\underline{H}_3$), 3.90 (3H, s, ArOC$\underline{H}_3$).
^{13}C NMR	δ_C ppm (75MHz, $CDCl_3$) 191.3 ($\underline{C}$HO), 153.5 ($\underline{C}$ (Ar)), 151.4 ($\underline{C}$ (Ar)), 147.8 ($\underline{C}$ (Ar)), 136.9 ($\underline{C}$ (Ar)), 129.2 ($\underline{C}$ (Ar)), 128.5 (2 x $\underline{C}$H (Ar)), 128.4 ($\underline{C}$H (Ar)), 128.3 (2 x $\underline{C}$H (Ar)), 115.7 ($\underline{C}$Br), 107.7 ($\underline{C}$H (Ar)), 75.7 ($\underline{C}H_2$), 61.5 (O$\underline{C}H_3$), 56.4 (O$\underline{C}H_3$).
LRMS	(CI, m/z) 353 ($MH^+[^{81}Br]$, 44%), 351 ($MH^+[^{79}Br]$, 48%), 271 ($[M-Br]^+$, 18%), 91 ($C_7H_7^+$, 100%) amu.
HRMS	(EI, m/z) Found: M^+: 350.0152; $C_{16}H_{15}O_4{}^{79}Br^+$ requires: 350.0154.

2-Benzyloxy-4-bromo-1,3-dimethoxy-5-styryl-benzene **4.43**



4.31 **4.43**

$C_{25}H_{22}ClP$ (388) $C_{23}H_{21}BrO_3$ (425)

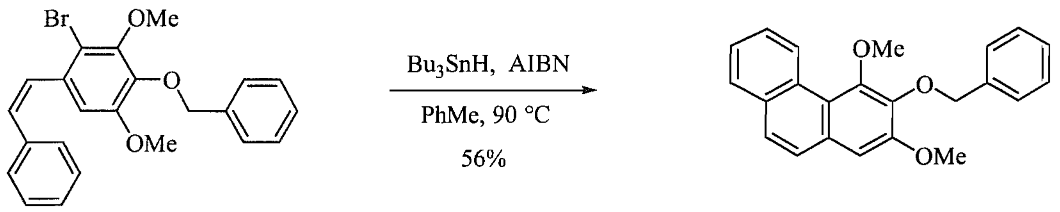
To a cooled (0 °C) suspension of sodium hydride (74 mg, 1.90 mmol) in tetrahydrofuran (12 mL) was added phosphonium chloride **4.31** (610 mg, 1.80 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to 0 °C and 4-benzyloxy-2-bromo-3,5-dimethoxy-benzaldehyde **4.42** (500 g, 1.4 mmol) as a solution in tetrahydrofuran (10 mL) was added. The reaction mixture was stirred at room temperature for 26 hours then water (20 mL) was added. Extraction with diethyl ether (3 x 40 mL) and concentration of the combined organic phases *in vacuo* yielded white crystals. Purification by column chromatography (silica gel, 10-20% ether in petrol) gave the product **4.43** (390 mg, 0.92 mmol, 58%) as a white solid.

MP	80-82 °C (ether / petrol).
IR	(ν_{max}, neat) 2934 (w), 1556 (w), 1492 (w), 1388 (s), 1236 (m), 1178 (m), 1103 (vs), 984 (m), 854 (m), 731 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 280 (23300), 224 (42300) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$): 7.50 (2H, dd, J = 8.1, 1.6 Hz, Ar$\underline{H}$), 7.41-7.33 (3H, m, Ar$\underline{H}$), 7.23-7.17 (5H, m, Ar$\underline{H}$), 6.69 (1H, d, J = 12.1 Hz, =$\underline{C}$H), 6.63 (1H, d, J = 12.1 Hz, =$\underline{C}$H), 6.54 (1H, s, Ar$\underline{H}$), 5.01 (2H, s, C$\underline{H_2}$), 3.94 (3H, s, OC$\underline{H_3}$), 3.43 (3H, s, O$\underline{C}H_3$).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 152.6 ($\underline{C}$ (Ar)), 151.5 ($\underline{C}$ (Ar)), 141.3 ($\underline{C}$ (Ar)), 137.5 ($\underline{C}$ (Ar)), 136.6 ($\underline{C}$ (Ar)), 133.3 ($\underline{C}$ (Ar)), 131.1 ($\underline{C}$H (Ar)), 129.6 ($\underline{C}$H (Ar)), 129.0 (2 x $\underline{C}$H (Ar)), 128.3 (2 x $\underline{C}$H (Ar)), 128.3 (2 x $\underline{C}$H (Ar)), 128.2 (2 x $\underline{C}$H (Ar)), 128.0 (=$\underline{C}$H), 127.3 (=$\underline{C}$H), 110.3 ($\underline{C}$Br), 109.7 ($\underline{C}$H (Ar)), 75.4 ($\underline{C}H_2$), 61.1 (O$\underline{C}H_3$ (Ar)), 55.7 (O$\underline{C}H_3$ (Ar)).

LRMS (CI, m/z) 336 ([MH [^{81}Br]-C_7H_7]$^+$, 96%), 334 ([MH [^{79}Br]-C_7H_7]$^+$, 98%), 256 ([MH-C_7H_7 - Br]$^+$, 100%), 91 ($C_7H_7^+$, 22%) amu.

HRMS (ES+, m/z) Found: [2M+Na]$^+$: 871.1252; $C_{46}H_{42}O_6{}^{79}Br_2Na^+$ requires: 871.1240

3-Benzyloxy-2,4-dimethoxy-phenanthrene **4.44**



4.43

$C_{23}H_{21}BrO_3$ (425)

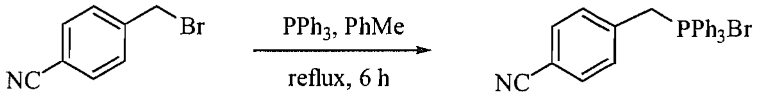
4.44

$C_{23}H_{20}O_3$ (344)

A solution of the alkene 2-benzyloxy-4-bromo-1,3-dimethoxy-5-styryl-benzene **4.43** (350 mg, 0.85 mmol), tributyltin hydride (270 µL, 1.02 mmol) and AIBN (28 mg, 0.17 mmol) in toluene (16 mL) was heated at reflux for 16 hours then cooled to room temperature. Potassium fluoride solution (30 mL, 10% solution) was added and the resulting biphasic mixture was stirred vigorously for 24 hours. Extraction with ether (3 x 30 mL) and concentration of the combined organic phases *in vacuo* yielded white crystals. Purification by column chromatography (silica gel, 10-20% ether in petrol) gave the product **4.44** (390 mg, 0.48 mmol, 56%) as a white solid.

MP	92-95 °C (ethanol).
IR	(ν_{max}, neat) 3024 (w), 1608 (w), 1576 (m), 1446 (s), 1384 (m), 1285 (m), 1171 (m), 1047 (s), 958 (vs), 765 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 254 (14400) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 9.56 (1H, d, *J* = 8.3 Hz, Ar$\underline{H}$), 7.88 (1H, d, *J* = 7.7 Hz, Ar$\underline{H}$), 7.71-7.55 (6H, m, Ar$\underline{H}$), 7.48-7.34 (3H, m, Ar$\underline{H}$), 7.13 (1H, s, Ar$\underline{H}$), 5.22 (2H, s, $C\underline{H}_2$), 4.08 (3H, s, $OC\underline{H}_3$), 4.02 (3H, s, $OC\underline{H}_3$).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 152.9 ($\underline{C}$ (Ar)), 142.5 ($\underline{C}$ (Ar)), 137.9 ($\underline{C}$ (Ar)), 131.8 ($\underline{C}$ (Ar)), 130.4 ($\underline{C}$ (Ar)), 129.9 ($\underline{C}$ (Ar)), 128.5 ($\underline{C}$ (Ar)), 128.4 (2 x $\underline{C}$H (Ar)), 128.3 (2 x $\underline{C}$H (Ar)), 128.0 ($\underline{C}$H (Ar)), 127.2 ($\underline{C}$H (Ar)), 126.8 (2 x $\underline{C}$H (Ar)), 126.7 ($\underline{C}$H (Ar)), 126.5 ($\underline{C}$H (Ar)), 125.5 ($\underline{C}$H (Ar)), 119.1 ($\underline{C}$ (Ar)), 105.4 ($\underline{C}$H (Ar)), 75.8 ($\underline{C}H_2$), 60.6 ($O\underline{C}H_3$), 56.0 ($O\underline{C}H_3$).
HRMS	(EI, m/z) Found: M$^+$: 344.1415; $C_{23}H_{20}O_3^+$ requires: 344.1413

(4-Cyanobenzyl)triphenylphosphonium bromide **4.46**



4.45

C_8H_6BrN (196)

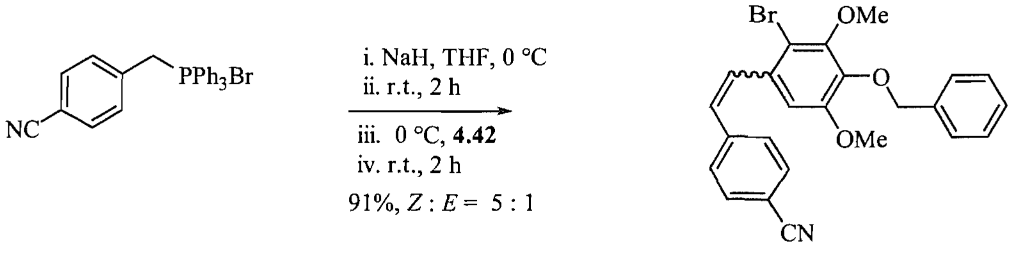
4.46

$C_{26}H_{21}BrNP$ (458)

(4-Cyanobenzyl)triphenylphosphonium bromide was prepared by the method of Rafizadeh *et al.* [79] 4-(Bromomethyl)benzonitrile (3.00 g, 15.31 mmol) and triphenylphosphine (4.82 g, 18.37 mmol) were dissolved in toluene (50 mL) and the mixture heated at reflux for 6 hours. The resulting solid was collected by filtration to yield the title compound as a white solid [79] (6.77 g, 14.78 mmol, 97%).

MP	>265 °C (toluene). Lit. 315-316 °C ($CHCl_3$ / toluene). [79]
IR	(ν_{max}, neat) 3007 (w), 2848 (m), 2770 (m), 2359 (m), 2230 (w), 1588 (m), 1500 (m), 1436 (s), 1319 (w), 1176 (m), 1112 (s), 996 (m), 864 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2): 270 (4500) 232 (49000) nm.
^{1}H NMR	δ_H ppm (300 MHz, d_6-DMSO) 7.30-7.18 (3H, m, ArH), 7.13-6.80 (12H, m, ArH), 6.90 (2H, d, J = 7.9 Hz, ArH), 6.56 (2H, dd, J = 8.6, 2.4 Hz, ArH), 4.15 (2H, s, CH_2).
^{13}C NMR	δ_C ppm (75 MHz, d_6-DMSO): 136.6 (d, J = 2.8 Hz, 3 x CH (Ar)), 135.4 (d, J = 9.6 Hz, 6 x CH (Ar)), 134.8 (d, J = 9.1 Hz, C (Ar)), 133.7 (d, J = 3.4 Hz, 2 x CH (Ar)), 133.2 (d, J = 5.7 Hz, 2 x CH (Ar)), 131.5 (d, J = 12.4 Hz, 6 x CH (Ar)), 119.0 (d, J = 2.8 Hz, CN), 118.5 (d, J = 86.5 Hz, 3 x C (Ar)), 113.6 (d, J = 4.0 Hz, CCN), 28.7 (d, J = 46.0 Hz, CH_2P).
^{31}P NMR	δ_P ppm (121 MHz, $CDCl_3$) 24.9.
LRMS	(CI, m/z) 309 ($[M-PPh_3Br]^+$, 28%), 181 (55%), 103 (54%).

(*Z*)-4-[2-(4-Benzyloxy-2-bromo-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile **4.52(*Z*)** & (*E*)-4-[2-(4-Benzyloxy-2-bromo-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile **4.52(*E*)**



4.46

$C_{26}H_{21}BrNP$ (458)

4.52*(Z)*, 77%
(E), 14%

$C_{24}H_{20}BrNO_3$ (450)

To a cooled (0 °C) suspension of sodium hydride (148 mg, 3.71 mmol) in tetrahydrofuran (30 mL) was added (4-cyanobenzyl)triphenylphosphonium bromide **4.46** (1.44 g, 3.13 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to 0 °C and 4-benzyloxy-2-bromo-3,5-dimethoxy-benzaldehyde **4.42** (1.00 g, 2.85 mmol) as a solution in tetrahydrofuran (10 mL) was added. The reaction mixture was stirred at room temperature for 26 hours then water (20 mL) was added. Extraction with ether (3 x 40 mL) and concentration of the combined organic phases *in vacuo* yielded white crystals. Purification by column chromatography (silica gel, 10-20% ether in petrol) gave the *cis*-isomer **4.52(*Z*)** (970 mg, 2.20 mmol, 77%) as a colourless oil and the *trans*-isomer **4.52(*E*)** (180 mg, 0.40 mmol, 14%) as a white solid.

4.52(*Z*):

IR (ν_{max}, neat) 2936 (w), 2230 (s), 1610 (m), 1554 (s), 1478 (vs), 1392 (vs), 1239 (s), 1163 (m), 985 (m), 853 (m) cm^{-1}.

UV λ_{max} (ε_{max}, CH_2Cl_2) 292 (13500), 218 (30700) nm.

^{1}H NMR δ_H ppm (300 MHz, $CDCl_3$) 7.49 (5H, m, ArH), 7.42-7.34 (2H, m, ArH), 7.28-7.24 (2H, m, ArH), 6.78 (1H, d, *J* = 12.1 Hz, =CH), 6.65 (1H, d, *J* = 12.1 Hz, =CH), 6.41 (1H, s, ArH), 5.07 (2H, s, CH_2), 3.94 (3H, s, OCH_3), 3.47 (3H, s, OCH_3).

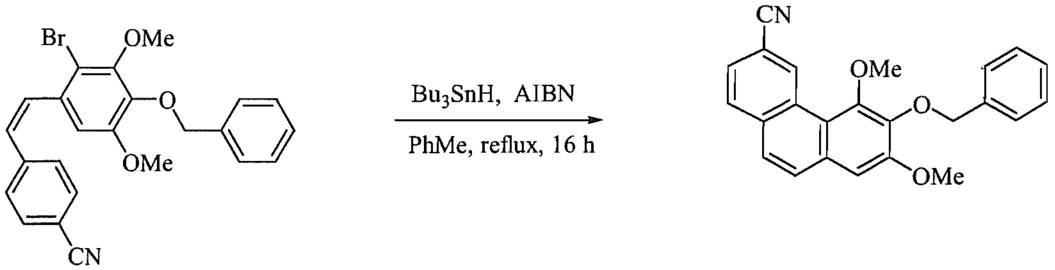
^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 152.8 (C (Ar)), 151.6 (C (Ar)), 141.6 (C (Ar)), 141.3 (2 x C (Ar)), 137.1 (C (Ar)), 132.7 (CH (Ar)), 132.2 (CH (Ar)), 131.9 (2 x CH (Ar)), 129.6 (2 x CH (Ar)), 129.2 (CH (Ar)), 128.4 (CH (Ar)), 128.3 (=CH), 128.2

	(=CH), 128.2 (CH (Ar)), 118.9 (CN), 110.6 (CCN), 110.2 (CH (Ar)), 109.2 (CBr), 75.4 (CH_2), 61.2 (OCH_3), 55.9 (OCH_3).
LRMS	(EI, M/z) 451 ($M^+[^{81}Br]$, 6%), 449 ($M^+[^{79}Br]$, 6%), 370 ($[M-Br]^+$, 38%), 91 ($C_7H_7^+$, 100%) amu.
HRMS	(EI, m/z) Found: M^+: 449.06375; $C_{24}H_{20}NO_3{}^{79}Br^+$ requires: 449.06265.

4.52(*E*):

MP	158 - 160 °C (ether/petrol).
IR	(ν_{max}, neat) 2942 (w), 2363 (w), 2220 (s), 1605 (m), 1468 (s), 1387 (s), 1178 (s), 1107 (vs), 1011 (vs), 741 (vs) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 217 (16000), 321 (29300) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 7.64 (2H, m, ArH), 7.61 (1H, d, *J* = 16.4 Hz, =CH), 7.52 (2H, d, *J* = 8.0, ArH), 7.43 – 7.34 (5H, m, ArH), 7.02 (1H, s, ArH), 6.95 (1H, d, *J* = 16.2 Hz, =CH), 5.09 (2H, s, CH_2), 3.93 (6H, s, 2 x OCH_3).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 153.2 (C (Ar)), 151.4 (C (Ar)), 142.6 (C (Ar)), 141.5 (C (Ar)), 137.2 (C (Ar)), 132.6 (C (Ar)), 132.6 (2 x CH (Ar)), 132.0 (CH (Ar)), 131.3 (CH (Ar)), 128.7 (CH (Ar)), 128.4 (CH (Ar)), 128.4 (2 x CH (Ar)), 128.2 (CH (Ar)), 127.3 (=CH), 127.1 (=CH), 119.0 (CN), 111.8 (CCN), 110.9 (CBr), 105.4 (CH (Ar)), 75.6 (CH_2), 61.1 (OCH_3), 56.3 (OCH_3).
LRMS	(EI, m/z) 451 ($M^+[^{81}Br]$, 13%), 449 ($M^+[^{79}Br]$, 13 %), 370 ($[M-Br]^+$, 48%), 91 ($C_7H_7^+$, 100%) amu.
HRMS	(EI, m/z) Found M^+: 449.0626; $C_{24}H_{20}NO_3{}^{79}Br^+$ requires: 449.0627.
CHN	Found: C, 64.49; H, 4,54; N, 3.20; $C_{24}H_{20}NO_3$ requires C, 64.01; H, 4.48; N, 3.11.

6-Benzyloxy-5,7-dimethoxy-phenanthrene-3-carbonitrile **4.54**



4.52(*Z*)

$C_{24}H_{20}BrNO_3$ (450)

4.54

$C_{24}H_{19}NO_3$ (369)

A solution of the alkene **4.52(*Z*)** (800 mg, 1.78 mmol), tributyltin hydride (620 mg, 0.57 mL, 2.13 mmol) and AIBN (58 mg, 0.36 mmol) in toluene (20 mL) was heated at reflux for 16 hours then cooled to room temperature. Potassium fluoride solution (10% solution, 30 mL) was added and the resulting biphasic mixture was stirred vigorously for 24 hours. Extraction with ether (3 x 40 mL) and concentration of the combined organic phases *in vacuo* yielded white crystals. Purification by column chromatography (silica gel, 10% ether in petrol) and recrystallisation from ethanol gave the product **4.54** (190 mg, 0.50 mmol, 28%) as a yellow solid.

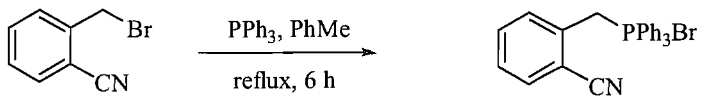
MP	118 - 120 °C (ethanol).
IR	(ν_{max}, neat) 2215 (s), 1600 (m), 1463 (s), 1341 (s), 1265 (s), 1128 (s), 1077 (vs), 990 (m), 853 (vs) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 313 (21400), 218 (51500), 257 (92700) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 9.96 (1H, s, Ar$\underline{H}$), 7.91 (1H, d, J = 8.2 Hz), 7.77 (1H, d, J = 8.8 Hz, Ar$\underline{H}$), 7.72 (2H, dd, J = 8.2, 1.7 Hz, Ar$\underline{H}$), 7.67 (1H, d, J = 8.8 Hz, Ar$\underline{H}$), 7.61 (1H, d, J = 8.2 Hz, Ar$\underline{H}$), 7.46 – 7.37 (3H, m, Ar$\underline{H}$), 7.14 (1H, s, Ar$\underline{H}$), 5.21 (2H, s, C$\underline{H}_2$), 4.09 (3H, s, OC$\underline{H}_3$), 4.03 (3H, s, OC$\underline{H}_3$).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 153.9 ($\underline{C}$ (Ar)), 152.9 ($\underline{C}$ (Ar)), 142.5 ($\underline{C}$ (Ar)), 137.5 ($\underline{C}$ (Ar)), 134.1 ($\underline{C}$ (Ar)), 132.6 ($\underline{C}$ (Ar)), 130.6 ($\underline{C}$ (Ar)), 130.0 ($\underline{C}$H (Ar)), 129.6 ($\underline{C}$H (Ar)), 129.4 (2 x $\underline{C}$H (Ar)), 128.6 (2 x $\underline{C}$H (Ar)), 128.3 (2 x $\underline{C}$H (Ar)), 127.1 ($\underline{C}$H (Ar)), 126.5 ($\underline{C}$H (Ar)), 120.4 ($\underline{C}$N), 118.1 ($\underline{C}$CN), 109.8 ($\underline{C}$ (Ar)), 105.6 ($\underline{C}$H (Ar)), 75.9 ($\underline{C}H_2$), 60.7 (O$\underline{C}H_3$), 56.1 (O$\underline{C}H_3$).

LRMS (EI, m/z) 369 (M^+, 13 %), 278 ([M- $C_7H_7^+$], 100 %), 91 ($C_7H_7^+$, 30 %) amu.

HRMS (EI, m/z) Found M^+: 369.1366; $C_{24}H_{19}NO_3^+$ requires: 369.1365.

CHN Found: C, 77.78; H, 5.23; $C_{21}H_{17}IO$ requires C, 78.03; H, 5.18.

(2-Cyanobenzyl)triphenylphosphonium bromide **4.48**



4.47 94% **4.48**

C_8H_6BrN (196) $C_{26}H_{21}BrNP$ (458)

(2-Cyanobenzyl)triphenylphosphonium bromide was prepared by the method of Rafizadeh *et al.*[79] 2-(Bromomethyl)benzonitrile (3.16 g, 16.12 mmol) and triphenylphosphine (4.23 g, 16.12 mmol) were dissolved in toluene (50 mL) and the mixture heated at reflux for 6 hours. The resulting solid was collected by filtration to yield the title compound **4.48** as a white solid[80] (6.97 g, 15.22 mmol, 94%).

MP >265 °C (toluene), no literature melting point.[80]

IR (ν_{max}, neat) 3015 (w), 2826 (m), 2766 (m), 2361 (w), 2219 (m), 2037 (w), 1988 (w), 1737 (w), 1587 (w), 1485 (m), 1439 (vs), 995 (w) cm^{-1}.

UV λ_{max} (ε_{max}, CH_2Cl_2) 270 (4500), 232 (46500) nm.

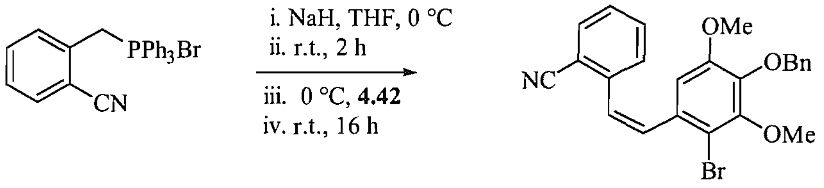
^{1}H NMR δ_H ppm (300 MHz, $CDCl_3$) 7.80-7.52 (16H, m, ArH), 7.45-7.29 (3H, m, ArH), 5.62 (2H, d, J = 14.7 Hz, CH_2).

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 135.7 (d, J = 3.4 Hz, 3 x CH (Ar)), 134.4 (d, J = 9.6 Hz 6 x CH (Ar)), 133.9 (d, J = 3.4 Hz, CH (Ar)), 132.8 (CH (Ar), 131.7 (CH (Ar)), 131.6 (C (Ar)), 130.5 (d, J = 12.1 Hz, 6 x CH (Ar)), 129.4 (d, J = 3.4 Hz, CH (Ar)), 117.0 (d, J = 36.7 Hz, 3 x C (Ar)), 116.1 (CN), 114.7 (CCN), 29.9 (d, J = 48.0 Hz, CH_2P).

^{31}P NMR δ_P ppm (121 MHz, $CDCl_3$) 24.5.

LRMS (CI, m/z) 309 ($[M-PPh_3Br]^+$, 14%), 181 (52%), 131 (88%) amu.

(*Z*)-2-[2-(4-Benzyloxy-2-bromo-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile **4.53(*Z*)**



4.48 $C_{26}H_{21}BrNP$ (458)

4.53(*Z*) $C_{24}H_{20}BrNO_3$ (449)

To a cooled (0 °C) suspension of sodium hydride (196 mg, 4.89 mmol) in tetrahydrofuran (30 mL) was added phosphonium bromide **4.48** (1.72 g, 3.76 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to 0 °C and 4-benzyloxy-2-bromo-3,5-dimethoxy-benzaldehyde **4.42** (1.20 g, 3.42 mmol) as a solution in tetrahydrofuran (10 mL) was added. The reaction mixture was stirred at room temperature for 24 hours then water (20 mL) was added. Extraction with diethyl ether (3 x 40 mL) and concentration of the combined organic phases *in vacuo* yielded white crystals. Purification by column chromatography (silica gel, 10-20% ether in petrol) gave the *cis*-isomer **4.53(*Z*)** (1.10 g, 2.42 mmol, 71%) as a white solid.

MP	130-132 °C (ether / petrol).
IR	(ν_{max}, neat) 2938 (w), 2223 (s), 1561 (m), 1463 (s), 1388 (s), 1324 (s), 1239 (s), 1164 (s), 1100 (vs), 968 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 306 (10200), 232 (24100) nm.
^{1}H NMR	δ_H ppm (300 MHz, C_6D_6) 7.40 (1H, d, J = 7.4 Hz, ArH), 7.17-6.93 (5H, m, ArH), 7.04 (1H, dd, J = 7.6, 1.4 Hz, ArH), 7.03 (1H, d, J = 12.2 Hz, =CH), 6.98 (1H, d, J = 12.2 Hz, =CH), 6.56 (1H, td, J = 7.6, 1.3 Hz, ArH), 6.47 (1H, td, J = 7.6, 1.3 Hz, ArH), 6.21 (1H, s, ArH), 5.01 (2H, s, CH_2), 3.72 (3H, s, OCH_3), 2.85 (3H, s, OCH_3).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 152.8 (C (Ar)), 151.7 (C (Ar)), 141.8 (C (Ar)), 140.6 (C (Ar)), 137.3 (C (Ar)), 134.0 (C (Ar)), 133.0 (CH (Ar)), 132.3 (CH (Ar)), 132.2 (CH x 2 (Ar)), 130.0 (CH (Ar)), 128.5 (2 x CH (Ar)), 128.3 (=CH), 127.8 (= CH),

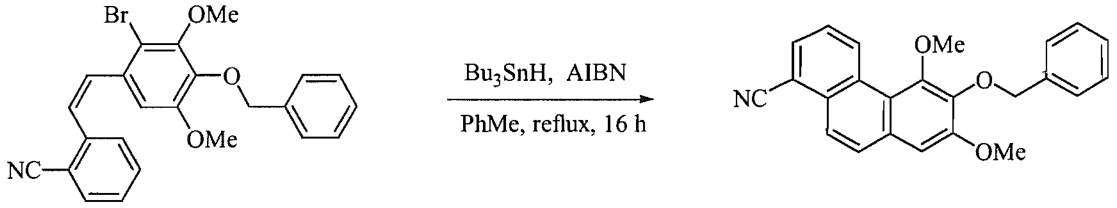
127.1 (CH x 2 (Ar)), 117.9 (CN), 112.5 (CCN), 110.6 (CH (Ar)), 109.6 (CBr), 75.6 (CH_2), 61.3 (OCH_3), 55.9 (OCH_3).

LRMS (CI m/z) 451 ($M^+[^{81}Br]$, 6 %), 449 ($M^+[^{79}Br]$, 6 %), 370 ([M^+-Br], 38 %), 91 ($C_7H_7^+$, 100 %) amu.

HRMS (EI, m/z) Found: M^+, 449.0638, $C_{24}H_{20}NO_3{}^{79}Br^+$ requires: 449.0627.

CHN Found: C, 64.13; H, 4.53; N, 3.09 $C_{24}H_{20}BrNO_3$ requires: C, 64.01; H, 4.48; 3.11.

6-Benzyloxy-5,7-dimethoxy-phenanthrene-1-carbonitrile **4.55**



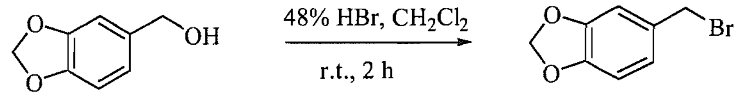
4.53(*Z*)
$C_{24}H_{20}BrNO_3$ (450)

4.55
$C_{24}H_{19}NO_3$ (369)

A solution of the alkene **4.53(*Z*)** (800 mg, 1.78 mmol), tributyltin hydride (620 mg, 570 μL, 2.13 mmol) and AIBN (58 mg, 0.36 mmol) in toluene (20 mL) was heated at reflux for 16 hours then cooled to room temperature. Potassium fluoride solution (10%, 30 mL) was added and the resulting biphasic mixture was stirred vigorously for 24 hours. Extraction with diethyl ether (3 x 40 mL) and concentration of the combined organic phases *in vacuo* yielded white crystals. Purification by column chromatography (silica gel, 5-20% ether in petrol) and recrystallisation from ethanol gave the product **4.55** (170 mg, 0.50 mmol, 25%) as a yellow solid.

MP	173-175 °C (ethanol).
IR	(ν_{max}, neat) 2931 (w), 2216 (m), 1605 (m), 1463 (s), 1350 (s), 1272 (s), 1156 (s), 1008 (s), 952 (vs), 840 (vs), 734 (vs) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 366 (5120), 324 (21000), 236 (63000), 264 (82000) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$): 9.86 (1H, dd, *J* = 8.7, 1.0 Hz, Ar$\underline{H}$), 8.14 (1H, dd, *J* = 8.9, 0.7 Hz, Ar$\underline{H}$), 7.95 (1H, dd, *J* = 7.3, 1.1 Hz, Ar$\underline{H}$), 7.85 (1H, d, *J* = 9.1 Hz, Ar$\underline{H}$), 7.71-7.60 (3H, m, Ar$\underline{H}$), 7.47-7.36 (3H, m, Ar$\underline{H}$), 7.18 (1H, s, Ar$\underline{H}$), 5.22 (2H, s, $C\underline{H}_2$), 4.06 (3H, s, $OC\underline{H}_3$), 4.04 (3H, s, $OC\underline{H}_3$).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 153.8 ($\underline{C}$ (Ar)), 153.0 ($\underline{C}$ (Ar)), 142.6 ($\underline{C}$ (Ar)), 137.6 ($\underline{C}$ (Ar)), 131.9 ($\underline{C}$ (Ar)), 131.3 ($\underline{C}$ (Ar)), 130.5 ($\underline{C}$H (Ar)), 130.4 ($\underline{C}$ (Ar)), 129.9 ($\underline{C}$H (Ar)), 128.4 ($\underline{C}$H x 2 (Ar)), 128.4 ($\underline{C}$H (Ar)), 128.3 ($\underline{C}$H x 2 (Ar)), 128.1 ($\underline{C}$H (Ar)), 126.1 ($\underline{C}$H (Ar)), 123.3 ($\underline{C}$H (Ar)), 118.8 ($\underline{C}$N), 118.5 ($\underline{C}$CN), 110.3 ($\underline{C}$ (Ar)), 105.7 ($\underline{C}$H (Ar)), 75.9 ($\underline{C}H_2$), 60.7 ($O\underline{C}H_3$), 56.1 ($O\underline{C}H_3$).
LRMS	(CI, m/z) 369 (M^+, 13%), 278 ([M^+- $C_7H_7^+$], 100%), 91 ($C_7H_7^+$, 30%) amu.
HRMS	(EI, m/z) Found: M^+; 369.1366; $C_{24}H_{19}NO_3^+$ requires: 369.1365.

5-Bromomethyl-benzo[1,3]dioxole **4.49**



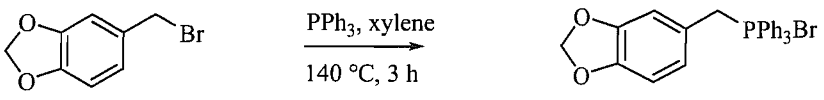
4.49

$C_8H_8O_3$ (152) $C_8H_7BrO_2$ (215)

The title compound was prepared by the method of Beard *et al.* [81] Piperonyl alcohol (5.00 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 x 20 mL). The combined organic phases were washed with water (2 x 20 mL), then dried ($MgSO_4$). Concentration *in vacuo* provided the title **4.49** compound as a white solid [81] (6.72 g, 31.2 mmol, 95%).

MP	45-47 °C (petrol), lit. 46-48 °C. [81]
IR	(ν_{max}, neat) 3000 (w), 2907 (w) 1607 (w), 1484 (vs), 1442 (vs), 1360 (s), 1248 (vs), 1034 (vs), 921 (vs), 808 (vs) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 230 (6500), 296 (6500), 256 (6700) nm.
^{1}H NMR	δ_H ppm (300 MHz, C_6D_6) 6.90 (1H, s, ArH), 6.87 (1H, m, ArH), 6.77 (1H, dd, J = 6.6, 0.7 Hz, ArH), 5.98 (2H, s, OCH_2O), 4.48 (2H, s, CH_2Br).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 148.1 (C (Ar)), 148.0 (C (Ar)), 131.7 (C (Ar)), 122.9 (CH (Ar)), 109.6 (CH (Ar)), 108.5 (CH (Ar)), 101.5 (OCH_2O), 34.4 (CH_2Br).
LRMS	(CI, m/z) 216 (M^+ [^{81}Br], 6%), 214 (M^+ [^{79}Br], 6%), 135 ($[M-Br]^+$, 100%), 105 (18%), 77 (30%), 77 (30%), 51 (20%) amu.

(1,3-Benzodioxol-5-ylmethyl)triphenylphosphonium bromide **4.50**



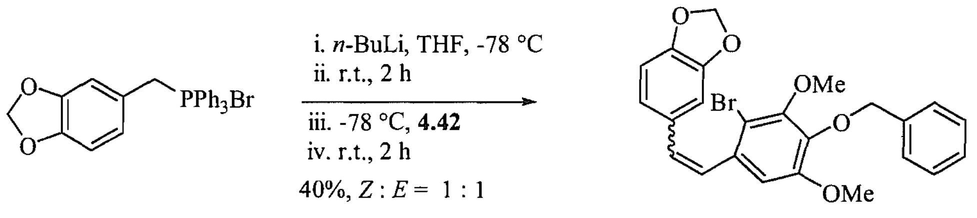
4.49 92% **4.50**

$C_8H_7BrO_2$ (215) $C_{26}H_{22}BrO_2P$ (477)

5-Bromomethyl-benzo[1,3]dioxole **4.49** (4.00 g, 18.60 mmol), and triphenylphosphine (5.86 g, 2.23 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 x 20 mL) and petrol (3 x 20 mL) to yield the title compound [82] **4.50** (8.13 g, 17.04 mmol, 92%).

MP	226-229 °C (xylene), lit. 235-238.5 °C. [82]
IR	(ν_{max}, neat) 3037 (w), 2784 (w), 1588 (w), 1488 (vs), 1438 (vs), 1249 (vs), 1110 (vs), 1036 (s), 924 (m), 866 (m), 749 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 292 (10100), 270 (12000), 232 (53000) nm.
^{1}H NMR	δ_H ppm (300 MHz, C_6D_6) 7.79-7.58 (18H, m, ArH), 5.85 (2H, s, OCH_2O), 5.29 (2H, d, *J* = 13.6 Hz, CH_2P).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 147.7 (2 x CO (Ar)), 135.0 (3 x CH (Ar)), 134.4 (d, *J* = 10.1 Hz, 6 x CH (Ar)), 130.2 (d, *J* = 12.4 Hz, 6 x CH (Ar)), 125.5 (d, *J* = 5.6 Hz), CH (Ar)), 120.1 (d, *J* = 9.0 Hz, C (Ar)), 117.7 (d, *J* = 85.4 Hz, 3 x C (Ar)), 111.4 (CH (Ar)), 108.6 (CH (Ar)), 101.3 (OCH_2O), 30.6 (d, *J* = 46.1 Hz, CH_2P).
^{31}P NMR	δ_P ppm (121 MHz, $CDCl_3$) 23.1.
LRMS	(ES+, m/z) 397 ([M-Br]$^+$, 100 %), 114 (13 %) amu.

(*Z*)-5-[2-(4-Benzyloxy-2-bromo-3,5-dimethoxy-phenyl)-vinyl]-benzo[1,3]dioxole **4.51(*Z*)** & (*E*)-5-[2-(4-Benzyloxy-2-bromo-3,5-dimethoxy-phenyl)-vinyl]-benzo[1,3]dioxole **4.51(*E*)**



4.50

$C_{26}H_{22}BrO_2P$ (477)

4.51, *(Z)* 21%
(E) 19%

$C_{24}H_{21}BrO_5$ (469)

To a cooled (-78 °C) suspension of phosphonium bromide **4.50** (3.26 g, 6.83 mmol) in tetrahydrofuran (30 mL) was added *n*-butyllithium (2.5 mL 2.49 M, 6.26 mmol). After stirring at ambient temperature for 2 hours, the mixture was cooled to -78 °C and aldehyde **4.42** (2.00 g, 5.69 mmol) as a solution in tetrahydrofuran (10 mL) was added. The reaction mixture was stirred at room temperature for 24 hours. Extraction with diethyl ether (3 x 40 mL) and concentration of the combined organic phases *in vacuo* yielded white crystals. Purification by column chromatography (silica gel, 10-20% ether in petrol) gave the *cis*-isomer **4.51(*Z*)** (560 mg, 1.18 mmol, 21%) as a white solid, and the *trans*-isomer **4.51(*E*)** (490 mg, 1.10 mmol, 19%).

4.51(*Z*):

MP	92-94 °C (ether / petrol).
IR	(ν_{max}, neat) 2909 (w), 1557 (m), 1484 (s), 1440 (vs), 1378 (s), 1329 (m), 1256 (s), 1223 (s), 1171 (m), 1012 (s), 923 (s), 855 (s), 817 (vs), 730 (vs) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2): 296 (14000) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 7.50 (1H, d, *J* = 7.5 Hz, Ar$\underline{H}$), 7.41 – 7.33 (5H, m, Ar$\underline{H}$), 6.72 (1H, dd, *J* = 8.0, 1.0 Hz, Ar$\underline{H}$), 6.69 (1H, d, *J* = 7.5 Hz, Ar$\underline{H}$), 6.62 (1H, s, Ar$\underline{H}$), 6.57 (1H, d, *J* = 12.4 Hz, =C$\underline{H}$), 6.50 (1H, d, *J* = 12.4 Hz, =C$\underline{H}$), 5.92 (2H, s, OC$\underline{H}_2$O), 5.07 (2H, s, C$\underline{H}_2$Ph), 3.93 (3H, s, OC$\underline{H}_3$), 3.60 (3H, s, OC$\underline{H}_3$).

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 152.7 (C (Ar)), 151.4 (C (Ar)), 147.4 (C (Ar)), 146.8 (C (Ar)), 141.2 (C (Ar)), 137.4 (C (Ar)), 133.4 (C (Ar)), 130.5 (C (Ar)), 128.3 (CH (Ar) x 3), 128.0 (CH (Ar)), 127.4 (CH (Ar)), 127.2 (CH (Ar)), 126.7 (=CH), 125.9 (=CH), 123.3 (CH (Ar)), 109.6 (CH (Ar)), 108.6 (CH (Ar)), 105.4 (CBr), 100.9 (OCH_2O), 75.5 (CH_2), 61.1 (3H, s, OCH_3), 56.0 (3H, s, OCH_3).

HRMS (ES+, m/z) Found: $[M+Na]^+$: 491.0465; $C_{24}H_{21}O_5Br^{79}BrNa^+$ requires: 491.0464.

CHN Found: C, 61.91; H, 4.58; $C_{24}H_{21}BrO_5$ requires C, 61.42; H, 4.51.

4.51(*E*):

IR (ν_{max}, neat) 2935 (w), 2890 (m), 1558 (m), 1488 (vs), 1445 (s), 1391 (m), 1336 (m), 1173 (s), 1105 (m), 1039 (s), 929 (s), 801 (s), 814 (vs) cm^{-1}.

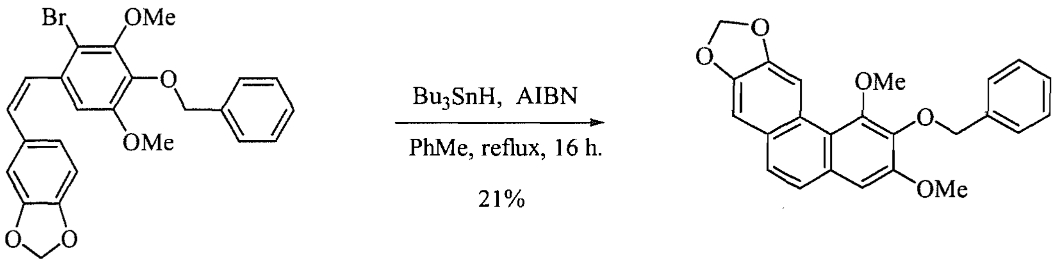
UV λ_{max} (ε_{max}, CH_2Cl_2) 296 (24000), 334 (33000), 232 (46000) nm.

^{1}H NMR δ_H ppm (300 MHz, $CDCl_3$) 7.52 (1H, d, *J* = 6.4 Hz, ArH), 7.44 – 7.30 (5H, m, ArH), 7.38 (1H, d, *J* = 16.2 Hz, =CH), 7.13 (1H, s, ArH), 7.00 (1H, dd, *J* = 7.8, 1.4 Hz, ArH), 6.98 (1H, d, *J* = 16.2 Hz, =CH), 6.82 (1H, s, ArH), 6.01 (2H, s, OCH_2O), 5.08 (2H, s, CH_2), 3.94 (3H, s, OCH_3), 3.92 (3H, s, OCH_3).

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 153.3 (C (Ar)), 151.5 (C (Ar)), 148.4 (C (Ar)), 147.8 (C (Ar)), 141.8 (C (Ar)), 137.5 (C (Ar)), 133.3 (C (Ar)), 131.7 (C (Ar)), 130.6 (CH (Ar)), 128.5 (3 x CH (Ar)), 128.2 (=CH), 126.1 (=CH), 122.0 (CH (Ar)), 111.1 (CBr), 108.6 (CH (Ar)), 105.9 (CH (Ar)), 105.2 (CH (Ar)), 101.4 (CH (Ar)), 101.0 (OCH_2O), 75.8 (CH_2), 61.2 (3H, s, OCH_3), 56.4 (3H, s, OCH_3).

HRMS (ES+, m/z) Found: $[2M+Na]^+$: 959.1034; $C_{48}H_{42}O_{10}Br_2{}^{79}BrNa^+$ requires: 959.1036.

2-Benzyloxy-1,3-dimethoxy-phenanthro[2,3][1,3]dioxole **4.56**



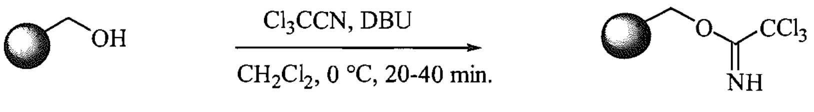
4.51(*Z*)
$C_{24}H_{21}BrO_5$ (469)

4.56
$C_{24}H_{20}O_5$ (388)

A solution of the alkene **4.51** (***Z***) (500 mg, 1.07 mmol), tributyltin hydride (370 mg, 350 µL, 1.28 mmol) and AIBN (35 mg, 0.21 mmol) in toluene (20 mL) was heated at reflux for 16 hours then cooled to room temperature. Potassium fluoride solution (10% solution, 30 mL) was added and the resulting biphasic mixture was stirred vigorously for 24 hours. Extraction with diethyl ether (3 x 40 mL) and concentration of the combined organic phases *in vacuo* yielded white crystals. Purification by column chromatography (silica gel, 5-20% ether in petrol) and recrystallization from ethanol gave the product **4.56** (120 mg, 0.23 mmol, 21%) as a yellow solid.

MP	111-113 °C (ethanol).
IR	(ν_{max}, neat) 3157 (w), 2892 (w), 2165 (w), 1736 (w), 1604 (s), 1503 (s), 1462 (vs), 1377 (m), 1287 (s), 1099 (vs), 981 (m), 843 (vs) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 286 (3700), 232 (11400) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 9.03 (1H, s, ArH), 7.61 (1H, d, J = 7.5 Hz, ArH), 7.55 (1H, m, ArH), 7.43 – 7.33 (5H, m, ArH), 7.21 (1H, s, ArH), 7.08 (1H, s, ArH), 6.11 (2H, s, OCH_2O), 5.19 (2H, s, CH_2Ph), 4.04 (3H, s, OCH_3), 4.00 (3H, s, OCH_3).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 153.0 (C (Ar)), 152.3 (C (Ar)), 148.0 (C (Ar)), 146.4 (C (Ar)), 141.6 (C (Ar)), 137.9 (C (Ar)), 129.8 (C (Ar)), 128.5 (2 x CH (Ar)), 128.4 (3 x CH (Ar)), 128.0 (CH (Ar)), 126.0 (CH (Ar)), 125.8 (C (Ar)), 125.0 (CH (Ar)), 119.2 (C (Ar)), 105.7 (CH (Ar)), 105.2 (CH (Ar)), 105.1 (C (Ar)), 101.2 (OCH_2O), 75.7 (CH_2), 60.6 (3H, s, OCH_3), 55.9 (3H, s, OCH_3).
HRMS	(ES+, m/z) Found $[M+Na]^+$: 411.1208; $C_{24}H_{20}O_5{}^{79}BrNa^+$ requires: 411.1203.

PS-Wang trichloroacetimidate resin **1.69**



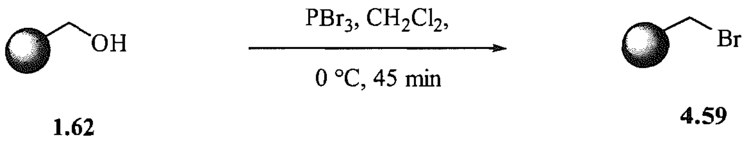
1.62 **1.69**

PS-Wang trichloroacetimidate resin was prepared according to the procedure of Hanessian, *et al.* [41] To a suspension of Merrifield resin (1.47 mmol / g resin, 1.70 g, 2.50 mmol) in dry dichloromethane (32 mL, 2.09 mmol) was added trichloroacetonitrile (4.69 mL, 46.8 mmol). The reaction mixture was then cooled to 0 °C and 1,8-diazobicyclo[5.4.0]undec-7-ene (313 µl, 2.09 mmol) was added dropwise over a period of 5 minutes. The reaction was stirred for 40 minutes, then the resin was collected on a sintered glass filter and washed with dichloromethane (50 mL), DMSO (50 mL), tetraydrofuran (50 mL) and again with dichloromethane (100 mL) before being air-dried for 1 hour. Exposing the resin to high vacuum for 6 hours completed the drying process.

Monitoring the reaction by infrared spectroscopy showed the disappearance of the hydroxyl stretching band at 3500 cm^{-1} and the appearance of a strong C=N stretching band at 1663 cm^{-1}.

IR (ν_{max}, solid phase) 3338 (w), 3027 (w), 2921 (w), 1663 (s), 1585 (w), 1512 (s), 1493 (s), 1452 (s), 1376 (m), 1299 (m), 1220 (m), 1174 (w), 1069 (s), 979 (s) cm^{-1}.

PS-bromo-Wang resin **4.59**

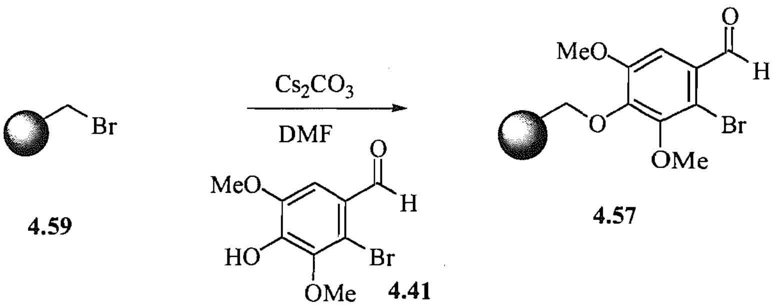


PS-bromo-Wang resin was prepared according to the procedure of Raju *et al.* [83] To a suspension of the PS-Wang resin (1.00 g, 1.70 mmol / g resin) in anhydrous dichloromethane (25 mL) (0 °C) was added phosphorous tribromide (650 μL, 6.80 mmol) dropwise over 10 minutes. The reaction mixture was stirred for 1 hour where after the resin was filtered, washed with dichloromethane (3 x 40 mL) and dried *in vacuo.*

Monitoring the reaction by infrared spectroscopy showed the disappearance of the OH-stretching band at 3500 cm^{-1}.

IR (ν_{max}, solid phase) 3082 (vs), 3059 (vs), 3027 (vs), 2852 (vs), 2361 (w), 1945 (m), 1609 (vs), 1511 (vs), 1377 (s), 907 (s), 701 (vs) cm^{-1}.

Resin bound 2-Bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.57**



Following the procedure of Grosche *et al.*, [60] PS-bromo-Wang resin (50 mg, 0.0750 mmol, 1.50 mmol / g resin) was swelled in DMF (5 mL) for 30 minutes. After this time, cesium carbonate (50 mg, 0.150 mmol) and the phenol **4.41** (98 mg, 0.38 mmol) were added. The reaction was heated at 80 °C for 16 hours then allowed to cool. The resin beads were isolated by filtration, washed with 1 : 1 DMF : H_2O (3 x 10 mL), methanol (3 x 10 mL) and dichloromethane (3 x 20 mL), then dried *in vacuo.*

Monitoring the reaction by infrared spectroscopy showed the appearance of the C=O-stretching band at 1685 cm^{-1}

IR (ν_{max}, solid phase) 3025 (w), 2920 (w), 2360 (m), 1685 (s), 1510 (s), 1450 (s), 1379 (s), 1218 (w), 1164 (s), 1104 (s), 821 (m), 757 (m) cm^{-1}.

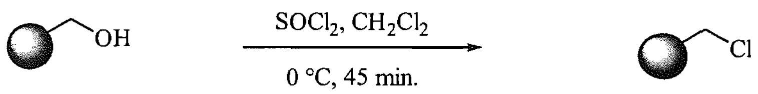
Gel phase:

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) **191.1 (CHO (Ar)**, 129.0 (PS), 114.7 (C (Ar)), **107.6 (CH (Ar)), 61.3 (OCH_3), 56.3 (OCH_3)**.

These data showed a good correlation with those obtained for the analogous benzylether 4-benzyloxy-2-bromo-3,5-dimethoxy-benzaldehyde **4.42**

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) **191.3 (CHO)**, 153.5 (C (Ar)), 151.4 (C (Ar)), 147.8 (C (Ar)), 136.9 (C (Ar)), 129.2 (C (Ar)), 128.5 (2 x CH (Ar)), 128.4 (CH (Ar)), 128.3 (2 x CH (Ar)), 115.7 (CBr), **107.7 (CH (Ar))**, 75.7 (CH_2), **61.5 (OCH_3), 56.4 (OCH_3)**.

PS-chloro-Wang resin **4.60**



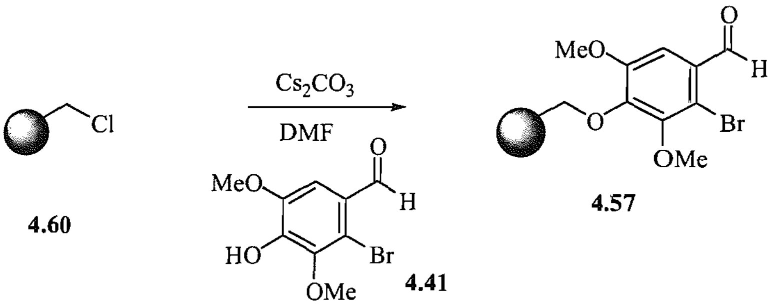
1.62 **4.60**

PS-chloro-Wang resin was prepared according to the procedure of Raju *et al.* [83] To a suspension of PS-Wang resin (1.00 g, 1.70 mmol / g resin) in anhydrous dichloromethane (20 mL) at 0 °C was added thionyl chloride (740 μL, 8.50 mmol) dropwise over 5 minutes. The reaction mixture was stirred for 1 hour then the resin was collected by filtration, washed with dichloromethane (100 mL) and methanol (50 mL), then dried *in vacuo*.

Monitoring the reaction by infrared spectroscopy showed the disappearance of the OH-stretching band at 3500 cm^{-1}.

IR (ν_{max}, solid phase) 3082 (vs), 3060 (vs), 3027 (vs), 2852 (vs), 1945 (m), 1611 (vs), 1586 (vs), 1511 (vs), 1304 (vs), 1243 (vs), 1176 (vs), 907 (s), 702 (vs), 669 (vs) cm^{-1}.

Resin bound 2-Bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.57**

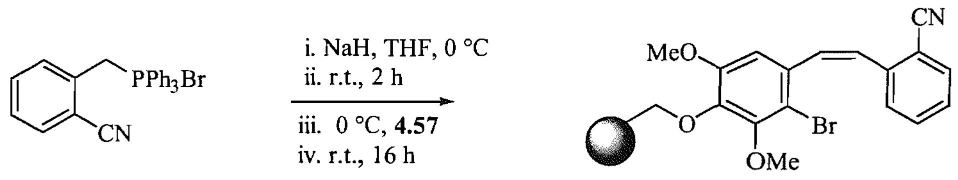


Following the procedure of Grosche *et al.*, [60] PS-chloro-Wang resin (50 mg, 0.080 mmol, 1.60 mmol / g resin) was swelled in DMF (5 mL) for 30 minutes. After this time, cesium carbonate (51 mg, 0.16 mmol) and 2-bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.41** (110 mg, 0.41 mmol) was added. The reaction was heated at 80 °C for 16 hours then allowed to cool. The resin beads were isolated by filtration, washed with 1:1 DMF:H_2O (3 x 10 mL), methanol (3 x 10 mL) and dichloromethane (3 x 20 mL), then dried *in vacuo*.

Monitoring the reaction by infrared spectroscopy showed the appearance of the C=O-stretching band at 1685 cm^{-1}.

IR (ν_{max}, solid phase) 3025 (w), 2922 (w), 1685 (s), 1610 (m), 1511 (s), 1451 (s), 1326 (s), 1165 (s), 986 (m), 821 (w), 734 (m), 698 (vs) cm^{-1}.

Resin bound 2-[2-(2-Bromo-4-hydroxy-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile **4.61**



4.48

$C_{26}H_{21}BrNP$ (458)

4.61

To prewashed sodium hydride (310 mg, 6.48 mmol) in tetrahydrofuran (20 mL) cooled to 0 °C was added the phosphonium bromide **4.48** (2.48 g, 5.40 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to 0 °C and the resin coupled 2-bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.57** (1.00 g, 1.08 mmol / g resin) was added as a suspension in tetrahydrofuran (10 mL). The reaction mixture was stirred at room temperature for 24 hours. The resin beads were isolated by filtration, washed with THF (3 x 20 mL), methanol (3 x 20 mL) and dichloromethane (3 x 20 mL), then dried *in vacuo*.

IR (ν_{max}, solid phase) 3024 (w), 2933 (w), 1738 (m), 1603 (m), 1511 (m), 1451 (m), 1390 (m), 1172 (m), 1106 (s), 983 (m), 758 (s) cm^{-1}.

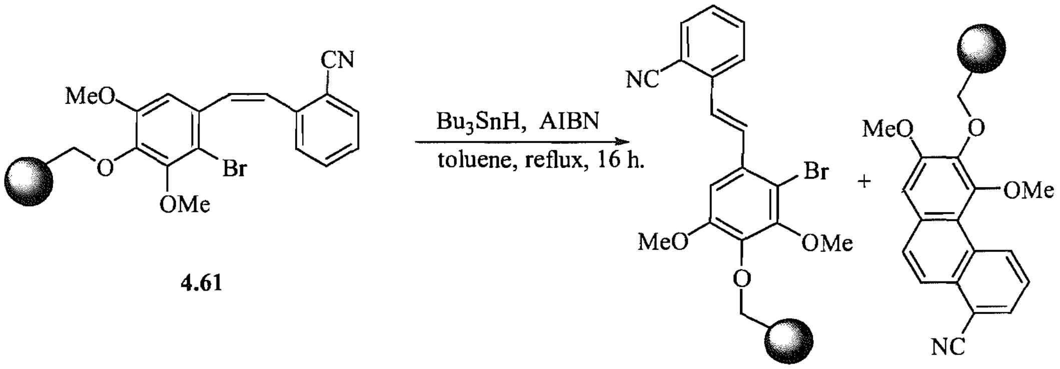
Gel phase:

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 152.6 (C (Ar)), 141.7 (C (Ar)), 137.0-124.0 (PS), **117.5** (CN), 114.0 (CCN), 111.5 (CH (Ar)), **109.1 (CBr)**, **61.2 (OCH_3)**, **55.8 (OCH_3)**.

These data showed a good correlation with those obtained for the analogous benzylether (*Z*)-2-[2-(4-benzyloxy-2-bromo-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile **4.53(*Z*)**

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 152.8 (C (Ar)), 151.7 (C (Ar)), 141.8 (C (Ar)), 140.6 (C (Ar)), 137.3 (C (Ar)), 134.0 (C (Ar)), 133.0 (CH (Ar)), 132.3 (CH (Ar)), 132.2 (CH x 2 (Ar)), 130.0 (CH (Ar)), 128.5 (2 x CH (Ar)), 128.3 (=CH), 127.8 (= CH), 127.1 (CH x 2 (Ar)), **117.9 (CN)**, 112.5 (CCN), 110.6 (CH (Ar)), **109.6 (CBr)**, 75.6 (CH_2), **61.3 (OCH_3)**, **55.9 (OCH_3)**.

Resin bound (*E*)-2-[2-(2-Bromo-4-hydroxy-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile & 6-Hydroxy-5,7-dimethoxy-phenanthrene-1-carbonitrile



4.61

A stirred suspension of resin **4.61** (870 mg, 0.20 mmol, 0.23 mmol / g resin) containing tributyltin hydride (1.23 g, 1.14 mL, 4.24 mmol) and AIBN (348 mg, 2.12 mmol) in toluene (15 mL) was heated at reflux for 16 hours. The mixture was cooled to room temperature, the resin beads were isolated by filtration, washed with toluene (3 x 40 mL), methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), and dried *in vacuo*.

IR (ν_{max}, solid phase) 3026 (w), 2923 (w), 2359 (m), 1604 (m), 1511 (m), 1452 (s), 1390 (m), 1327 (m), 1221 (s), 1106 (s), 983 (m), 822 (w), 758 (s) cm^{-1}.

Gel phase:

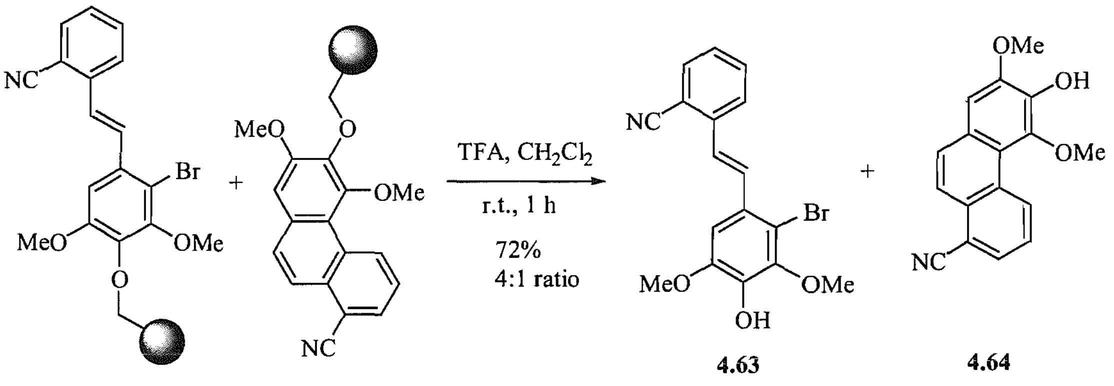
^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 152.8 (C (Ar)), 145.4 (C (Ar)), 140.9 ((C (Ar)), 137.0-124.0 (PS), **118.2 (CN)**, 114.8 (CH (Ar)), **109.7 (C (Ar)), 61.4 (OCH_3), 55.9 (OCH_3)**.

These data showed a good correlation with those obtained for the 6-Benzyloxy-5,7-dimethoxy-phenanthrene-3-carbonitrile **4.55**

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 153.8 (C (Ar)), 153.0 (C (Ar)), 142.6 (C (Ar)), 137.6 (C (Ar)), 131.9 (C (Ar)), 131.3 (C (Ar)), 130.5 (CH (Ar)), 130.4 (C (Ar)), 129.9 (CH (Ar)), 128.4 (CH x 2 (Ar)), 128.4 (CH (Ar)), 128.3 (CH x 2 (Ar)), 128.1

($\underline{C}$H (Ar)), 126.1 ($\underline{C}$H (Ar)), 123.3 ($\underline{C}$H (Ar)), **118.8 ($\underline{C}$N)**, 118.5 ($\underline{C}$CN), **110.3 ($\underline{C}$ (Ar))**, 105.7($\underline{C}$H (Ar)), 75.9 ($\underline{C}H_2$), **60.7 (O$\underline{C}H_3$)**, **56.1 (O$\underline{C}H_3$)**.

(*E*)-2-[2-(2-Bromo-4-hydroxy-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile **4.63** & 6-Hydroxy-5,7-dimethoxy-phenanthrene-1-carbonitrile **4.64**



4.63 $C_{17}H_{14}BrNO_3$ (360)

4.64 $C_{17}H_{13}NO_3$ (279)

Resin from the aforementioned experiment (769 mg, 0.23 mmol / g resin, 0.18 mmol), was swelled in dichloromethane (5 mL) for 20 minutes, where after the cleavage coctail consisiting of 95% distilled trifluoroacetic acid (4.75 mL), 2.5% dichloromethane (125 μL) and 2.5% triisopropylsilane (125 μL) was added, and stirred for 1 hour. The reaction mixture was filtered and the resin washed with dichloromethane (30 mL). Reduction *in vacuo* yielded a yellow oil, which was dissolved in dichloromethane (10 mL) and washed with saturated sodium bicarbonate solution (3 x 40 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica gel, 5-10% ether in petrol) yielding a yellow oil **4.64** (7 mg, 2.51 x 10^{-5} mol, 14%) and a white solid **4.63** (29 mg, 1.04 x 10^{-4} mol, 58%).

IR of the resin beads following cleavage:

IR (ν_{max}, solid phase) 3025 (w), 2929 (w), 2360 (vs), 1735 (w), 1508 (s), 1451(s), 1217 (s), 1017 (w), 758 (s) cm^{-1}.

4.64:

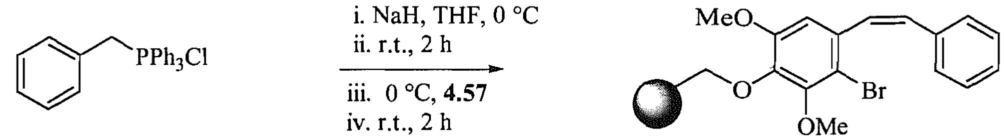
IR (ν_{max}, neat) 3481 (br. w), 2942 (w), 2841 (w), 2361 (s), 2341 (s), 2217 (m), 1578 (w), 1507 (w), 1473 (s), 1257 (vs), 1079 (s), 958 (s) cm^{-1}.

UV	λ_{max} (ε_{max}, CH_2Cl_2) 327 (9500), 274 (28800), 232 (31770), 254 (36300) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 9.69 (1H, d, J = 8.5 Hz, ArH), 7.99 (1H, d, J = 9.5 Hz, ArH), 7.86 (1H, dd, J = 7.0, 1.3 Hz, ArH) 7.74 (1H, d, J = 9.0, ArH), 7.57 (1H, dd, J = 9.0, 7.3 Hz, ArH), 7.19 (1H, s, ArH), 6.10 (1H, s, ArOH), 4.12 (3H, s, OCH_3), 4.01 (3H, s, OCH_3).
LRMS	(CI, m/z) 279 (M^+, 100%), 264 (55%), 232 (25%) amu.
HRMS	(EI, m/z) Found M^+: 279.0893; $C_{17}H_{13}NO_3^+$ requires: 279.0895.

4.63:

MP	192-194 °C (ether/petrol).
IR	(ν_{max}, neat) 3148 (br. m), 2940 (w), 2221(m), 1594 (m), 1491 (s), 1261 (m), 1192 (s), 915 (s), 865 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 252 (25000), 230 (31000) nm.
^{1}H NMR	δ_H ppm (300 MHz, $CDCl_3$) 7.89 (1H, d, J = 8.0 Hz, ArH), 7.72-7.63 (2H, m, ArH), 7.69 (1H, d, J = 16.1 Hz, =CH), 7.40 (1H, t, J = 7.0 Hz, ArH) 7.30 (1H, d, J = 16.1 Hz, =CH), 7.08 (1H, s, ArH), 5.81 (1H, s, ArOH), 4.02 (3H, s, OCH_3), 3.95 (3H, s, OCH_3).
^{13}C NMR	δ_C ppm (75 MHz, $CDCl_3$) 147.6 (C (Ar)), 144.9 (C (Ar)), 140.9 (C (Ar)), 140.7 (C (Ar)), 133.5 (CH (Ar)), 133.3 (CH (Ar)), 132.7 (CH (Ar)), 128.1 (CH (Ar)), 127.9 (C (Ar)), 125.9 (=CH), 125.2 (=CH), 118.4 (CN), 112.6 (CCN), 111.6 (CBr), 105.0 (CH (Ar)), 61.1 (OCH_3), 56.9 (OCH_3).
LRMS	(CI, m/z) 361 ($M^+[^{81}Br]$, 100%), 359 ($M^+[^{79}Br]$, 98%), 280 ($[M\text{-}Br]^+$, 10%), 265 (23%) amu.
HRMS	(EI, m/z) Found: M^+: 359.0151; $C_{17}H_{14}O_3N^{79}Br^+$ requires 359.0157.

Resin bound 3-Bromo-2,6-dimethoxy-4-styryl-phenol **4.65**



4.31

$C_{25}H_{22}ClP$ (388)

4.65

To prewashed sodium hydride (51 mg, 1.30 mmol) in tetrahydrofuran (8 mL) cooled to 0 °C was added the phosphonium bromide **4.31** (0.427 g, 1.10 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to 0 °C and the resin coupled 2-bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.57** (200 mg, 0.22 mmol, 1.07 mmol / g resin) was added as a suspension in THF (3 mL) following swelling for 30 minutes. The reaction mixture was stirred at room temperature for 16 hours. The resin beads were isolated by filtration, washed with THF (3 x 20 mL), methanol (3 x 20 mL) and dichloromethane (3 x 20 mL), then dried *in vacuo*.

IR (ν_{max}, solid phase) 3024 (w), 2922 (w), 2361 (s), 1602 (w), 1509 (m), 1474 (m), 1325 (m), 1219 (m), 1104 (s), 925 (w), 696 (vs) cm^{-1}.

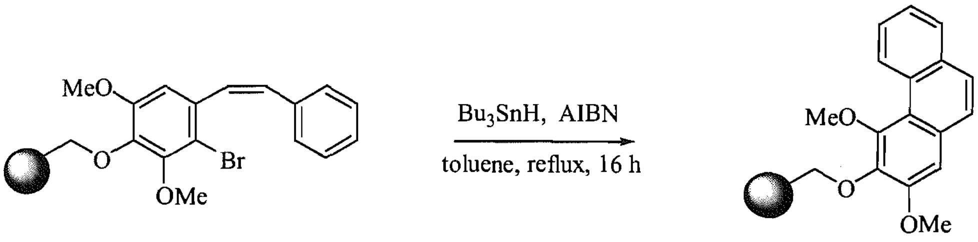
Gel phase:

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 131.9 (PS), 114.7 ($\underline{C}$ (Ar)), **61.3 (O$\underline{C}H_3$), 56.3 (O$\underline{C}H_3$).**

These data showed a good correlation with those obtained for the analogous benzyl ether 2-benzyloxy-4-bromo-1,3-dimethoxy-5-styryl-benzene **4.43**

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$): 152.6 ($\underline{C}$ (Ar)), 151.5 ($\underline{C}$ (Ar)), 141.3 ($\underline{C}$ (Ar)), 137.5 ($\underline{C}$ (Ar)), 136.6 ($\underline{C}$ (Ar)), 133.3 ($\underline{C}$ (Ar)), 131.1 ($\underline{C}$H (Ar)), 129.6 ($\underline{C}$H (Ar)), 129.0 (2 x $\underline{C}$H (Ar)), 128.3 (2 x $\underline{C}$H (Ar)), 128.3 (2 x $\underline{C}$H (Ar)), 128.2 (2 x $\underline{C}$H (Ar)), 128.0 (=$\underline{C}$H), 127.3 (=$\underline{C}$H), 110.3 ($\underline{C}$Br), 109.7 ($\underline{C}$H (Ar)), 75.4 ($\underline{C}H_2$), **61.1 (O$\underline{C}H_3$ (Ar)), 55.7 (O$\underline{C}H_3$ (Ar)).**

Resin bound 2,4-Dimethoxy-phenanthren-3-ol



4.65

Swelled resin from the aforementioned experiment (150 mg, 0.0345 mmol, 0.23 mmol / g resin) containing tributyltin hydride (220 mg, 0.20 µl, 0.75 mmol) and AIBN (61 mg, 0.37 mmol) in toluene (10 mL) was heated to reflux for 16 hours. The mixture was cooled to room temperature, the resin beads were isolated by filtration, washed with toluene (3 x 20 mL), methanol (3 x 20 mL) and dichloromethane (3 x 20 mL), and dried *in vacuo.*

IR (ν_{max}, solid phase) 3028 (w), 2922 (w), 1595 (m), 1443 (m), 1219 (m), 1168 (w), 1102 (m), 960 (w), 807 (w), 746 (m), 691 (vs) cm^{-1}.

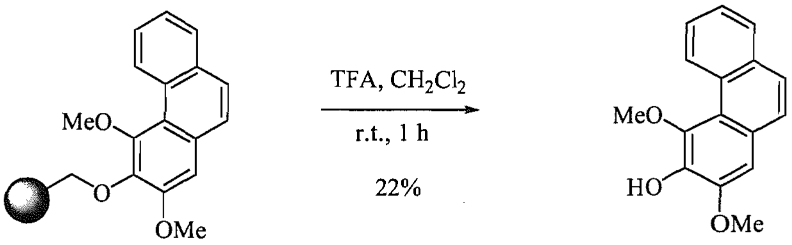
Gel phase:

^{13}C NMR δ_C ppm (75 MHz, CDCl$_3$) 129.7 (PS), 115.3 ($\underline{C}$ (Ar)), **61.3 (O$\underline{C}$H$_3$), 56.3 (O$\underline{C}$H$_3$).**

These data showed a good correlation with those obtained for 3-benzyloxy-2,4-dimethoxy-phenanthrene **4.44**

^{13}C NMR δ_C ppm (75 MHz, CDCl$_3$) 152.9 ($\underline{C}$ (Ar)), 142.5 ($\underline{C}$ (Ar)), 137.9 ($\underline{C}$ (Ar)), 131.8 ($\underline{C}$ (Ar)), 130.4 ($\underline{C}$ (Ar)), 129.9 ($\underline{C}$ (Ar)), 128.5 ($\underline{C}$ (Ar)), 128.4 (2 x $\underline{C}$H (Ar)), 128.3 (2 x $\underline{C}$H (Ar)), 128.0 ($\underline{C}$H (Ar)), 127.2 ($\underline{C}$H (Ar)), 126.8 (2 x $\underline{C}$H (Ar)), 126.7 ($\underline{C}$H (Ar)), 126.5 ($\underline{C}$H (Ar)), 125.5 ($\underline{C}$H (Ar)), 119.1 ($\underline{C}$ (Ar)), 105.4 ($\underline{C}$H (Ar)), 75.8 ($\underline{C}$H$_2$), **60.6 (O$\underline{C}$H$_3$), 56.0 (O$\underline{C}$H$_3$)**.

2,4-Dimethoxy-phenanthren-3-ol **4.66**

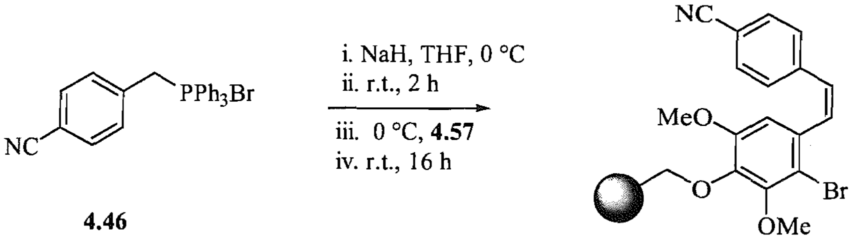


4.66
$C_{16}H_{14}O_3$ (254)

Resin from the aforementioned experiment (769 mg, 0.23 mmol / g resin, 0.18 mmol) was swelled in dichloromethane (5 mL) for 20 minutes, where after the cleavage cocktail consisting of 95% distilled trifluoroacetic acid (4.75 mL), 2.5% dichloromethane (125 μL) and 2.5% triisopropylsilane (125 μL) was added. After 1 hour, the reaction mixture was filtered and the resin washed with dichloromethane (30 mL). Reduction *in vacuo* yielded a yellow oil, which was dissolved in dichloromethane (10 mL) and washed with saturated sodium bicarbonate solution (3 x 40 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica gel, 5-10% ether in petrol) and recrystallised to a white solid **4.66** (10 mg, 0.039 mmol, 22%).

IR	(ν_{max}, neat) cm^{-1}. 3481 (br. w), 2934 (w), 1727 (w), 1505 (s), 1472 (s), 1289 (s), 1214 (s), 1126 (s), 974 (w) cm^{-1}.
UV	λ_{max} (ε_{max}, CH$_2$Cl$_2$) 313 (21400), 218 (51500), 257 (92700) nm.
^{1}H NMR	δ_H ppm (300 MHz, CDCl$_3$) 9.79 (1H, d, J = 8.6 Hz, Ar$\underline{H}$), 7.75 (1H, d, J = 7.9 Hz, Ar$\underline{H}$), 7.65-7.35 (4H, m, 4 x Ar$\underline{H}$), 6.76 (1H, s, Ar$\underline{H}$), 5.63 (1H, s, ArO$\underline{H}$), 3.70 (3H, s, OC$\underline{H}_3$), 3.29 (3H, s, OC$\underline{H}_3$).
LRMS	(EI, m/z) 254 (M$^+$, 100%), 239 (46%), 168 (24%) amu.
HRMS	(EI, m/z) Found M$^+$: 254.0947; $C_{16}H_{14}O_3^+$ requires: 254.0943.

Resin bound 4-[2-(2-Bromo-4-hydroxy-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile **4.68**



4.46

$C_{26}H_{21}BrNP$ (458)

4.68

To prewashed sodium hydride (310 mg, 6.48 mmol) in tetrahydrofuran (8 mL) cooled to 0 °C was added the phosphonium salt **4.46** (2.47 g, 5.40 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to 0 °C and the resin bound 2-bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.57** (1.00 g, 1.08 mmol / g resin) was added as a suspension in tetrahydrofuran (15 mL) following swelling for 30 minutes. The reaction mixture was stirred at room temperature for 16 hours. The resin beads were isolated by filtration, washed with THF (3 x 20 mL), methanol (3 x 20 mL) and dichloromethane (3 x 20 mL), then dried *in vacuo*.

IR (ν_{max}, solid phase) 3025 (w), 2927 (w), 2361 (w), 2226 (w), 1604 (m), 1512 (m), 1452 (s), 1390 (m), 1222 (m), 1106 (vs), 982 (w), 826 (m) cm^{-1}.

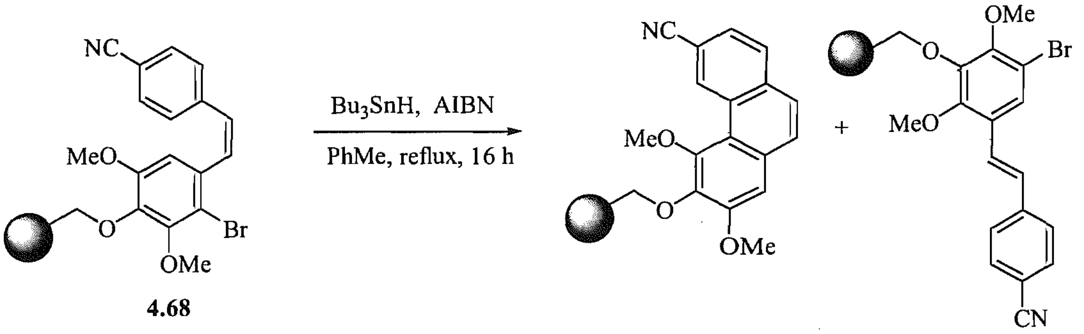
Gel phase:

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) **141.0 (C (Ar))**, 135.4 – 125.5 (PS), 114.6 (CN), **109.3 (CBr), 75.2 (CH_2), 61.2 (OCH_3), 55.9 (OCH_3)**.

These data showed a good correlation with those obtained for the analogous benzylether (*Z*)-4-[2-(4-benzyloxy-2-bromo-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile **4.52(*Z*)**

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 152.8 (C (Ar)), 151.6 (C (Ar)), **141.6 (C (Ar))**, 141.3 (2 x C (Ar)), 137.1 (C (Ar)), 132.7 (CH (Ar)), 132.2 (CH (Ar)), 131.9 (2 x CH (Ar)), 129.6 (2 x CH (Ar)), 129.2 (CH (Ar)), 128.4 (CH (Ar)), 128.3 (=CH), 128.2 (=CH), 128.2 (CH (Ar)), 118.9 (CN), 110.6 (CCN), 110.2 (CH (Ar)), **109.2 (CBr)**, 75.4 (CH_2), **61.2 (OCH_3), 55.9 (OCH_3)**.

Resin bound 6-Hydroxy-5,7-dimethoxy-phenanthrene-3-carbonitrile & (*E*) 4-[2-(2-Bromo-4-hydroxy-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile



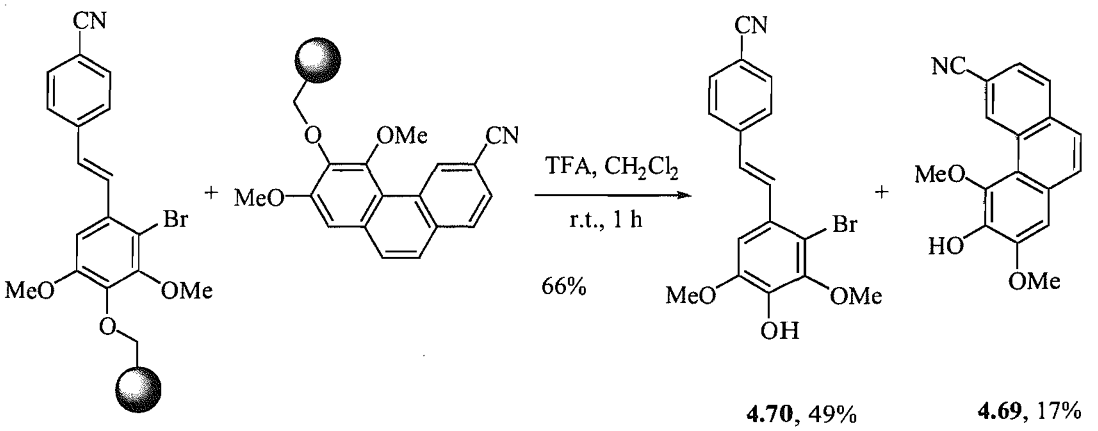
Resin **4.68** from the aforementioned experiment (800 mg, 0.18 mmol, 0.23 mmol / g resin) containing tributyltin hydride (1.14 g, 1.05 mL, 3.91 mmol) and AIBN (321 mg, 1.95 mmol) in toluene (15 mL) was heated to reflux for 16 hours. The mixture was cooled to room temperature, the resin beads were isolated by filtration, washed with toluene (3 x 40 mL), methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), and dried *in vacuo*.

IR (ν_{max}, solid phase) 3025 (w), 2928 (w), 2362 (w), 2226 (w), 1711 (s), 1604 (m), 1512 (m), 1452 (s), 1363 (m), 1220 (s), 1106 (s), 827 (m) cm^{-1}.

Gel phase:

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 135.1 – 125.4 (PS), 115.5 ($\underline{C}CN$), 110.2 ($\underline{C}$ (Ar)), 105.2 ($\underline{C}H$ (Ar)), 76.0 ($\underline{C}H_2$), 62.0 ($O\underline{C}H_3$), 57.0 ($O\underline{C}H_3$), 41.3 (PS).

(*E*)-4-[2-(2-Bromo-4-hydroxy-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile **4.70** & 6-Hydroxy-5,7-dimethoxy-phenanthrene-3-carbonitrile **4.69**



4.70, 49% $C_{17}H_{14}BrNO_3$ (360)

4.69, 17% $C_{17}H_{13}NO_3$ (279)

Resin from the aforementioned experiment (800 mg, 0.23 mmol/g resin, 0.18 mmol), was swelled in dichloromethane (18 mL) for 20 minutes, whereafter the cleavage cocktail consisiting of 95% distilled trifluoroacetic acid (4.75 mL), 2.5% dichloromethane (125 μL) and 2.5% triisopropylsilane (125 μL) was added, and stirred for 1 hour. The reaction mixture was filtered and the resin washed with dichloromethane (30 mL). Reduction *in vacuo* yielded a yellow oil, which was dissolved in dichloromethane (10 mL) and washed with saturated sodium bicarbonate solution (3 x 40 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica gel, 5-10% ether in petrol) yielding two white solids, stilbene **4.70** (9 mg, 0.03 mmol, 49%) and phenanthrene **4.69** (25 mg, 0.09 mmol, 17%).

IR of the resin beads following cleavage:

IR (ν_{max}, solid phase) 3025 (w), 2923 (w), 2360 (s), 1784 (w), 1602 (w), 1493 (s), 1452 (s), 1172 (m), 1028 (w), 758 (vs) cm^{-1}.

4.69:

MP 155-158 °C (ether / petrol).

IR (ν_{max}, neat) 3473 (br. w), 2946 (w), 2218 (s), 1620 (m), 1473 (s), 1195 (w), 959 (s), 796 (s) cm^{-1}.

UV λ_{max} (ε_{max}, CH_2Cl_2) 328 (8500), 288 (25100), 254 nm (28300) nm.

^{1}H NMR δ_H ppm (300 MHz, $CDCl_3$) 9.89 (1H, s, ArH), 7.93 (1H, d, J = 8.1, ArH), 7.76 (2H, m, ArH), 7.65 (1H, d, J = 8.6 Hz, ArH), 7.16 (1H, s, ArH), 6.09 (1H, s, ArOH), 4.11 (3H, s, OCH_3), 4.11 (3H, s, OCH_3).

HRMS (ES+, m/z) Found: $[2M + Na]^+$; 581.1685, $C_{34}H_{26}N_2O_6Na^+$ requires: 581.1685.

4.70:

MP 208-210 °C (ether / petrol).

IR (ν_{max}, neat) 3451 (w. br), 2938 (w), 2360 (vs), 2221 (s), 1560 (s), 1491 (s), 1401(s), 1311 (vs), 1176 (s), 1050 (m), 948 (m) cm^{-1}.

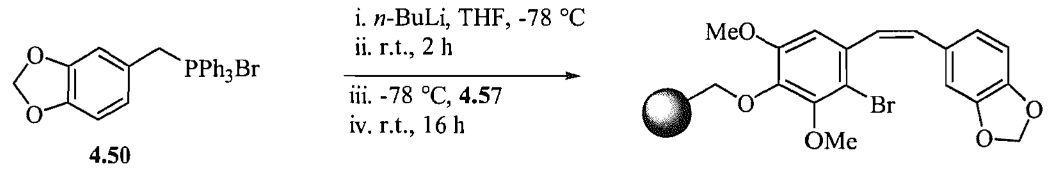
UV λ_{max} (ε_{max}, CH_2Cl_2) 326 (2600), 232 (4100) nm.

^{1}H NMR δ_H ppm (300 MHz, $CDCl_3$) 7.65 (2H, d, J = 8.5 Hz, ArH), 7.61 (2H, d, J = 8.5 Hz, ArH), 7.58 (1H, d, J = 16.1 Hz, =CH), 7.00 (1H, s, ArH), 6.89 (1H, d, J = 16.1 Hz, =CH), 5.76 (1H, s, ArOH), 3.99 (3H, s, OCH_3), 3.94 (3H, s, OCH_3).

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 147.6 (C (Ar)), 144.9 (C (Ar)), 142.9 (C (Ar)), 140.6 (C (Ar)), 132.9 (CH x 2 (Ar)), 131.7 (CH (Ar)), 128.1 (C (Ar)), 127.9 (CH (Ar)), 127.4 (=CH x 2), 119.4 (CN), 112.5 (CCN), 111.2 (CBr), 104.9 (CH (Ar)), 61.1 (OCH_3), 56.9 (OCH_3).

HRMS (EI, m/z) Found: M^+: 359.01511, $C_{17}H_{14}BrNO_3^+$ requires 359.01570.

Resin coupled 4-(2-Benzo[1,3]dioxol-5-yl-vinyl)-3-bromo-2,6-dimethoxy-phenol **4.71**



4.50

$C_{26}H_{22}BrO_2P$ (477)

4.71

To a cooled suspension of phosphonium salt **4.50** (2.55 g, 5.35 mmol) in tetrahydrofuran (20 mL) cooled to -78 °C was added *n*-butyllithium (2.58 mL 2.49 M, 6.42 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to 0 °C and resin bound 2-bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.57** (1.00 g, 1.07 mmol / g resin) was added as a suspension in tetrahydrofuran (15 mL). The reaction mixture was stirred at room temperature for 24 hours. The resin beads were isolated by filtration, washed with THF (3 x 20 mL), methanol (3 x 20 mL) and dichloromethane (3 x 20 mL), then dried *in vacuo*.

IR (ν_{max}, solid phase) 3026 (w), 2925 (w), 2360 (m), 1605 (m), 1489 (s), 1447 (s), 1390 (w), 1235 (s), 1171 (w), 1038 (s), 930 (w) cm^{-1}.

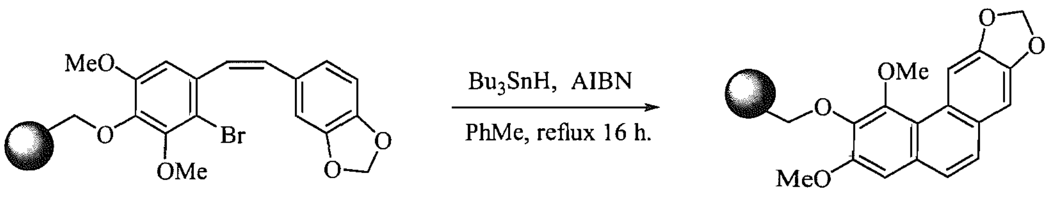
Gel phase:

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 153.3 (C (Ar)), 147.5 (C (Ar)), 141.3 (C (Ar)), 135.0-125.0 (PS), **109.2 (CH (Ar)), 106.0 (CBr), 101.2 (OCH$_2$O), 61.2 (3H, s, OCH$_3$), 56.4 (3H, s, OCH$_3$)**, 35.9.

These data showed a good correlation with those obtained for the analogous benzyl ether (*Z*)-5-[2-(4-Benzyloxy-2-bromo-3,5-dimethoxy-phenyl)-vinyl]-benzo[1,3]dioxole **4.51(*Z*)**

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$): 152.7 (C (Ar)), 151.4 (C (Ar)), 147.4 (C (Ar)), 146.8 (C (Ar)), 141.2 (C (Ar)), 137.4 (C (Ar)), 133.4 (C (Ar)), 130.5 (C (Ar)), 128.3 (CH (Ar) x 3), 128.0 (CH (Ar)), 127.4 (CH (Ar)), 127.2 (CH (Ar)), 126.7 (=CH), 125.9 (=CH), 123.3 (CH (Ar)), **109.6 (CH (Ar))**, 108.6 (CH (Ar)), **105.4 (CBr), 100.9 (OCH$_2$O)**, 75.5 (CH$_2$), **61.1 (3H, s, OCH$_3$), 56.0 (3H, s, OCH$_3$)**.

Resin coupled 1,3-Dimethoxy-phenanthro[2,3-d][1,3]dioxol-2-ol



4.71

A stirred suspension of the swelled resin **4.71** (1.36 g, 0.31 mmol, 0.23 mmol / g resin) containing tributyltin hydride (1.75 g, 1.61 mL, 6.00 mmol) and AIBN (493 mg, 3.00 mmol) in toluene (15 mL) was heated to reflux for 16 hours. The mixture was cooled to room temperature, the resin beads were isolated by filtration, washed with toluene (3 x 40 mL), methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), and dried *in vacuo*.

IR (ν_{max}, solid phase) 2925 (w), 1602 (m), 1502 (s), 1451 (s), 1238 (s), 1126 (s), 1038 (s), 818 (m), 758 (m) cm^{-1}.

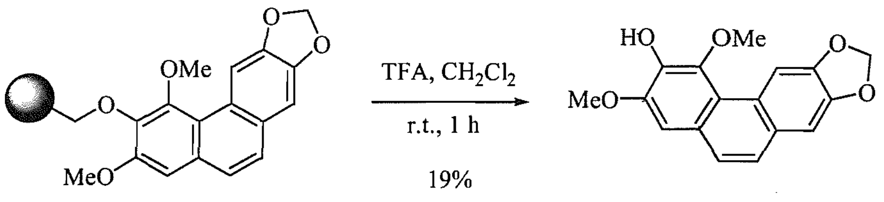
Gel phase:

^{13}C NMR δ_C ppm (75 MHz, CDCl$_3$) **153.0 (C (Ar)), 148.4 (C (Ar))**, 135.0-125.0 (PS), **106.1 (CH (Ar)), 101.3 (OCH$_2$O), 61.5 (3H, s, OCH$_3$), 56.6 (3H, s, OCH$_3$)**.

These data showed a good correlation with those obtained for the analogous benzyl ether 2-benzyloxy-1,3-dimethoxy-phenanthro[2,3][1,3]dioxole **4.56**

^{13}C NMR δ_C ppm (75 MHz, CDCl$_3$) **153.0 (C (Ar))**, 152.3 (C (Ar)), **148.0 (C (Ar))**, 146.4 (C (Ar)), 141.6 (C (Ar)), 137.9 (C (Ar)), 129.8 (C (Ar)), 128.5 (2 x CH (Ar)), 128.4 (3 x CH (Ar)), 128.0 (CH (Ar)), 126.0 (CH (Ar)), 125.8 (C (Ar)), 125.0 (CH (Ar)), 119.2 (C (Ar)), **105.7 (CH (Ar))**, 105.2 (CH (Ar)), 105.1 (C (Ar)), **101.2 (OCH$_2$O)**, 75.7 (CH$_2$), **60.6 (3H, s, OCH$_3$), 55.9 (3H, s, OCH$_3$)**.

1,3-Dimethoxy-phenanthro[2,3-d][1,3]dioxol-2-ol **4.72**



4.72

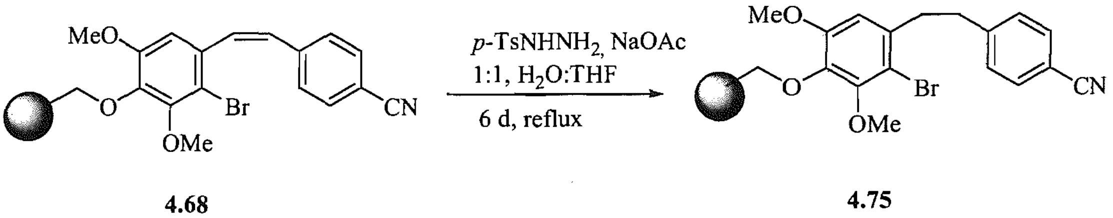
$C_{17}H_{14}O_5$ (298)

Resin from the aforementioned experiment (769 mg, 0.23 mmol / g resin, 0.18 mmol) was swelled in dichloromethane (5 mL) for 20 minutes, where after the cleavage cocktail consisting of 95% distilled trifluoroacetic acid (4.75 mL), 2.5% dichloromethane (125 μL) and 2.5% triisopropylsilane (125 μL) was added. After 1 hour, the reaction mixture was filtered and the resin washed with dichloromethane (30 mL). Reduction *in vacuo* yielded a yellow oil, which was dissolved in dichloromethane (10 mL) and washed with saturated sodium bicarbonate solution (3 x 40 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica gel, 5-10% ether in petrol) and recrystallised to a white solid **4.72** (10 mg, 0.034 mmol, 19%).

IR of the resin beads following cleavage:

IR	(ν_{max}, solid phase) 3027 (w), 2922 (w), 2360 (w), 1782 (w), 1604 (w), 1493 (s), 1452 (s), 1215 (m), 1038 (m), 759 (m) cm^{-1}.
4.72:	
MP	178-180 °C (benzene).
IR	(ν_{max}, neat) 3409 (br. w), 2920 (w), 2361 (w), 1621 (w), 1509 (m), 1460 (vs), 1374 (w), 1301 (s), 1095 (s), 973 (w), 926 (m), 878 (s), 810 (m), 642 (w) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 285 (22100), 259 (55500) nm.
^{1}H NMR	δ_H ppm (400 MHz, C_6D_6) 8.92 (1H, s, Ar$\underline{H}$), 7.52 (1H, d, J = 9.4 Hz, Ar$\underline{H}$), 7.49 (1H, d, J = 8.5 Hz, ArH), 7.20 (1H, s, ArH), 7.07 (1H, s, ArH), 6.10 (2H, s, $OC\underline{H}_2O$), 5.92 (1H, s, ArO$\underline{H}$), 4.06 (3H, s, $OC\underline{H}_3$), 3.96 (3H, s, $OC\underline{H}_3$).
LRMS	(ES+, m/z) 298 (M^+ 100%), 283 (68%), 73 (25%).

Resin coupled 4-[2-(2-Bromo-4-hydroxy-3,5-dimethoxy-phenyl)-ethyl]-benzonitrile **4.75**



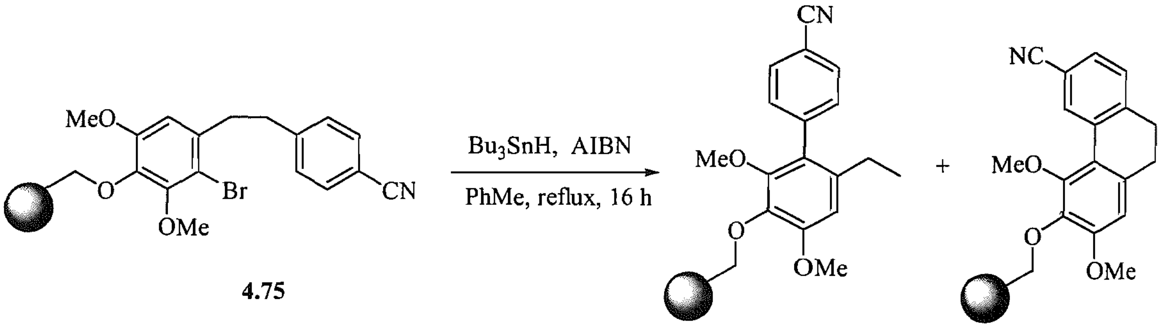
A rapidly stirred solution of alkene resin **4.68** (1.00 g, 0.23 mmol / g resin), *para*-toluenesulfonylhydrazide (3.02 g, 16.20 mmol) and sodium acetate (1.33, 16.20 mmol) in THF (20 mL) and water (20 mL) was heated at reflux for 6 days. The mixture was cooled to room temperature, the resin beads were isolated by filtration, then washed with methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), and dried *in vacuo*.

IR (ν_{max}, solid phase) 3025 (w), 2926 (w), 2225 (w), 2169 (w), 1979 (w), 1738 (w), 1603 (m), 1452 (s), 1395 (m), 1227 (m), 1105 (s), 823 (m) cm^{-1}.

Gel phase:

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 150.7 ($\underline{C}$ (Ar)), 140.5 (C (Ar)), 135.0-125.0 (PS), 114.9 ($\underline{C}$N), 109.4 ($\underline{C}$Br), 60.9 (O$\underline{C}H_3$), 56.0 (O$\underline{C}H_3$), 53.1 ($\underline{C}H_2$).

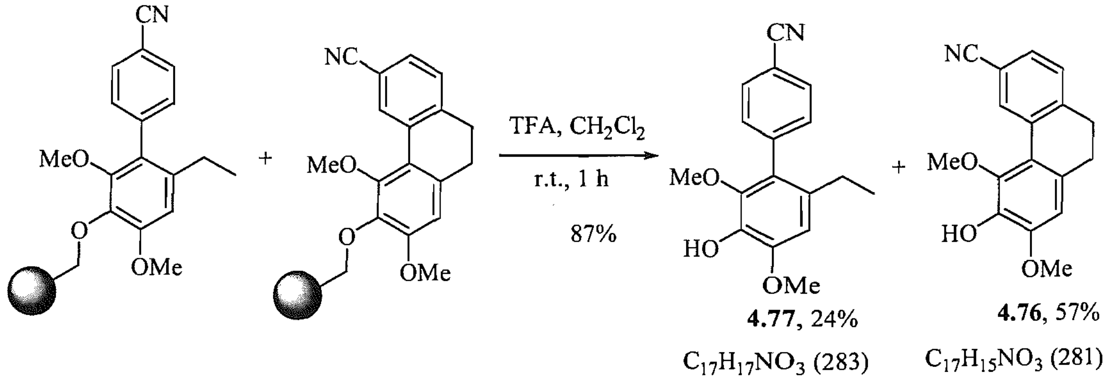
Cyclisation of resin coupled 4-[2-(2-Bromo-4-hydroxy-3,5-dimethoxy-phenyl)-ethyl]-benzonitrile **4.75**



A stirred suspension of the swelled resin **4.75** (780 mg, 0.18 mmol, 0.23 mmol / g resin) containing tributyltin hydride (940 mg, 870 μL, 3.23 mmol) and AIBN (266 mg, 1.62 mmol) in toluene (10 mL) was heated to reflux for 16 hours. The mixture was cooled to room temperature, the resin beads were isolated by filtration, washed with toluene (3 x 40 mL), methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), and dried *in vacuo*.

IR	(ν_{max}, solid phase) 3025 (w), 2926 (w), 1602 (w), 1511 (s), 1452 (s), 1395 (s), 1326 (s), 1224 (m), 1105 (s), 823 (m) cm^{-1}.
Gel phase:	
^{13}C NMR	δ_C ppm (75 MHz, CDCl$_3$) 135.0-125.0 (PS), 115.0 ($\underline{C}$N), 110.1 ($\underline{C}$Br), 61.1 (3H, s, O$\underline{C}$H$_3$), 56.1 (3H, s, O$\underline{C}$H$_3$).

6'-Ethyl-3'-hydroxy-2',4'-dimethoxy-biphenyl-4-carbonitrile **4.77** & 6-Hydroxy-5,7-dimethoxy-9,10-dihydro-phenanthrene-3-carbonitrile **4.76**



4.77, 24%
$C_{17}H_{17}NO_3$ (283)

4.76, 57%
$C_{17}H_{15}NO_3$ (281)

Resin from the aforementioned experiment (700 mg, 0.23 mmol / g resin, 0.16 mmol) was swelled in dichloromethane (15 mL) for 20 minutes, whereafter the cleavage cocktail consisting of 95% distilled trifluoroacetic acid (4.75 mL), 2.5% dichloromethane (125 μL) and 2.5% triisopropylsilane (125 μL) was added. After 1 hour, the reaction mixture was filtered and the resin washed with dichloromethane (30 mL). Reduction *in vacuo* yielded a yellow oil, which was dissolved in dichloromethane (10 mL) and washed with saturated sodium bicarbonate solution (3 x 40 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica gel, 10-20% ether in petrol) to a yellow solid which was recrystallised from benzene to give **4.77** (11 mg, 3.88×10^{-5} mol, 24%) and a yellow oil **4.76** (26 mg, 9.25×10^{-5} mol, 57%).

IR of the resin beads following cleavage:

IR (ν_{max}, solid phase) 3026 (w), 2924 (w), 1782 (w), 1603 (w), 1493 (m), 1452 (m), 1310 (w), 1214 (m), 1168 (s), 758 (m) cm^{-1}.

4.77:

MP 133-137 °C (benzene).

IR (ν_{max}, neat) 3359 (br. w), 2938 (w), 2236 (s), 1612 (s), 1495 (s), 1460 (s), 1307 (vs), 1151 (vs), 1073 (m), 914 (s) cm^{-1}.

UV λ_{max} (ε_{max}, CH_2Cl_2) 266 (19000), 230 (74000) nm.

^{1}H NMR δ_H ppm (300 MHz, C_6D_6) 7.05 (2H, dd, J = 6.6, 1.8 Hz, ArH), 6.91 (2H, dd, J = 6.6, 1.8 Hz, ArH), 6.30 (1H, s, ArH), 5.29 (1H, s, ArOH), 3.36 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 2.19 (2H, q, J = 7.5 Hz, CH_2), 0.91 (3H, t, J = 7.5 Hz, CH_3).

LRMS (CI, m/z) 283 (M^+, 100 %), 236 (12 %), 253 (22 %).

HRMS (EI, m/z) Found M^+: 283.1211; $C_{17}H_{17}NO_3^+$ requires: 283.1208.

4.76:

IR (ν_{max}, neat) 3423 (w), 2938 (w), 2839 (w), 2225 (s), 1601 (m), 1498 (s), 1454 (m), 1328 (m), 1304 (s), 1123 (s), 904 (w), 828 (m) cm^{-1}.

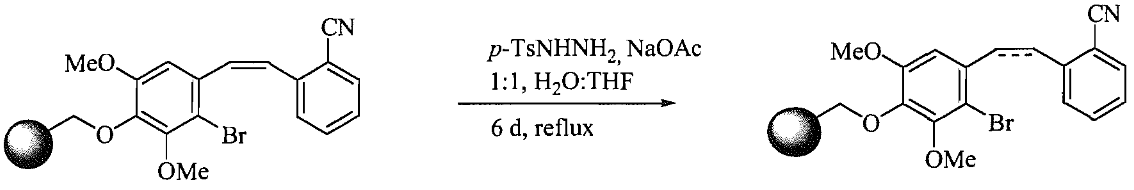
UV λ_{max} (ε_{max}, CH_2Cl_2): 266 (12900), 231 (23700) nm.

^{1}H NMR δ_H ppm (300 MHz, C_6D_6): 8.72 (1H, d, J = 1.8 Hz, ArH), 8.28 (1H, d, J = 8.1 Hz, ArH), 6.63 (1H, d, J = 8.1 Hz, ArH), 6.14 (1H, s, ArOH), 5.33 (1H, s, ArOH), 3.40 (3H, s, OCH_3), 3.22 (3H, s, OCH_3), 2.40 - 2.20 (4H, m, CH_2).

LRMS (CI, m/z) 281 (M^+, 100 %), 206 (6 %), 166 (40 %) amu.

HRMS (EI, m/z) Found M^+: 281.1052; $C_{17}H_{15}NO_3^+$ requires: 281.1052.

Resin coupled 2-[2-(2-Bromo-4-hydroxy-3,5-dimethoxy-phenyl)-ethyl]-benzonitrile & 2-[2-(2-Bromo-4-hydroxy-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile **4.82**



4.61

4.82

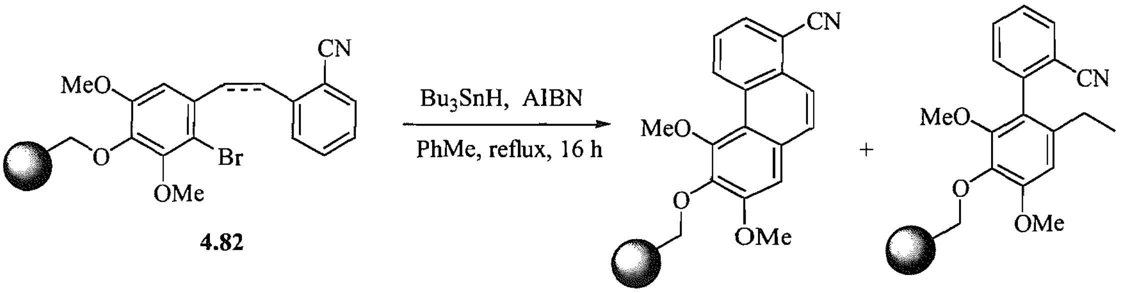
A rapidly stirred solution of alkene resin **4.61** (1.00 g, 0.23 mmol / g resin), *para*-toluene-sulfonyl-hydrazide (3.02 g, 16.20 mmol) and sodium acetate (1.33, 16.20 mmol) in THF (20 mL) and water (20 mL) was heated at reflux for 6 days. The mixture was cooled to room temperature, the resin beads were isolated by filtration then washed with methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), and dried *in vacuo*.

IR (ν_{max}, solid phase) 3026 (w), 2929 (w), 2224 (w), 2050 (w), 1737 (m), 1602 (m), 1451 (s), 1394 (m), 1327 (w), 1107 (s), 984 (m), 822 (w), 759 (s) cm^{-1}.

Gel phase:

^{13}C NMR δ_C ppm (75 MHz, CDCl$_3$) 135.5 – 125.5 (PS), 117.8 ($\underline{C}$N), 112.4 ($\underline{C}$CN) 109.4 ($\underline{C}$Br), 61.1 (O$\underline{C}$H$_3$), 56.1 (O$\underline{C}$H$_3$), 34.8 ($\underline{C}$H$_2$).

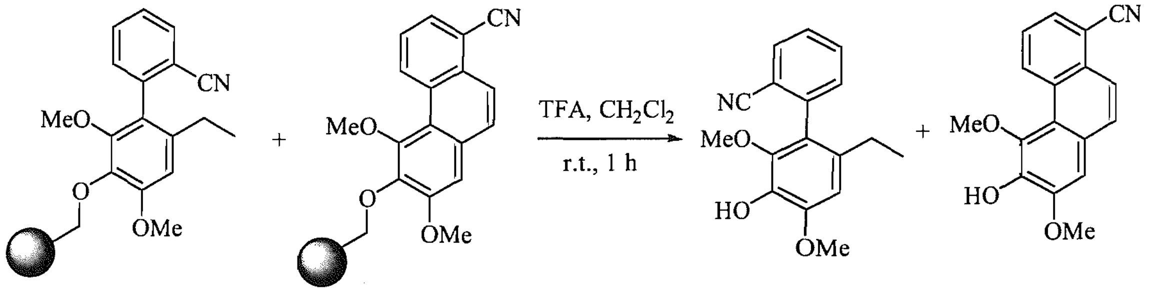
Cyclisation of 2-[2-(2-Bromo-4-hydroxy-3,5-dimethoxy-phenyl)-ethyl]-benzonitrile & 2-[2-(2-Bromo-4-hydroxy-3,5-dimethoxy-phenyl)-vinyl]-benzonitrile **4.82**



A stirred suspension of the swelled resin **4.82** from the aforementioned experiment (780 mg, 0.18 mmol, 0.23 mmol / g resin) containing tributyltin hydride (940 mg, 870 μL, 3.23 mmol) and AIBN (266 mg, 1.62 mmol) in toluene (10 mL) was heated to reflux for 16 hours. The mixture was cooled to room temperature, the resin beads were isolated by filtration, washed with toluene (3 x 40 mL), methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), and dried *in vacuo.*

IR (ν_{max}, solid phase) 2925 (w), 1981 (w), 1489 (s), 1451 (s), 1243 (s), 1105 (s), 1038 (s) cm^{-1}.

6'-Ethyl-3'-hydroxy-2',4'-dimethoxy-biphenyl-2-carbonitrile **4.84** & 6-Hydroxy-5,7-dimethoxy-9,10-dihydro-phenanthrene-1-carbonitrile **4.83**



4.84, 15% $C_{17}H_{17}NO_3$ (283)

4.83, 57% $C_{17}H_{15}NO_3$ (281)

Resin from the aforementioned experiment (700 mg, 0.23 mmol / g resin, 0.16 mmol) was swelled in dichloromethane (5 mL) for 20 minutes, whereafter the cleavage cocktail consisting of 95% distilled trifluoacetic acid (4.75 mL), 2.5% dichloromethane (125 μL) and 2.5% triisopropylsilane (125 μL) was added. After 1 hour, the reaction mixture was filtered and the resin washed with dichloromethane (30 mL). Reduction *in vacuo* yielded a yellow oil, which was dissolved in DCM (10 mL) and washed with saturated sodium bicarbonate solution (3 x 40 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica, 10-20% ether in petrol) to a colourless oil **4.84** (7 mg, 2.47 x 10^{-5} mol, 15%) and a white solid **4.83** (26 mg, 9.25 x 10^{-5} mol, 57%).

IR of the resin beads following cleavage:

IR (ν_{max}, solid phase) 3025 (w), 2921 (w), 1783 (w), 1602 (w), 1602 (w), 1493 (m), 1452 (m), 1217 (m), 1170 (m), 758 (m) cm^{-1}.

4.84:

IR (ν_{max}, neat) 3415 (br. w), 2226 (m), 1611 (m), 1500 (s), 1461 (w), 1307 (s), 1154 (s), 911 (w) cm^{-1}.

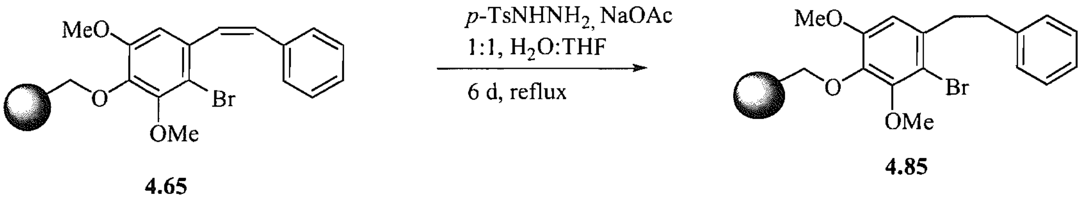
UV λ_{max} (ε_{max}, CH_2Cl_2) 284 (3200), 230 (10000) nm.

^{1}H NMR	δ_H ppm (300 MHz, C_6D_6) 8.49 (1H, dd, J = 8.1, 1.1 Hz, Ar$\underline{\text{H}}$), 7.06 (1H, dd, J = 7.7, 1.1 Hz, Ar$\underline{\text{H}}$), 6.69 (1H, dt, J = 7.6, 1.5 Hz, Ar$\underline{\text{H}}$), 6.73 (1H, dt, J = 7.7, 1.5 Hz, Ar$\underline{\text{H}}$), 6.06 (1H, s, Ar$\underline{\text{H}}$), 5.27 (1H, s, Ar$\underline{\text{O}}$H), 3.45 (3H, s, OC$\underline{\text{H}}_3$), 3.17 (3H, s, OC$\underline{\text{H}}_3$), 2.34 – 2.20 (2H, m, C$\underline{\text{H}}_2$), 0.99 (3H, t, J = 7.7 Hz, C$\underline{\text{H}}_3$).
LRMS	(CI, m/z) 283 (M^+, 100%), 268 (24%), 120 (14%) amu.
HRMS	(CI, m/z) Found: M^+: 283.1211; $C_{17}H_{17}NO_3^+$ requires: 283.1208.

4.83:

MP	186-188 °C (benzene).
IR	(ν_{max}, neat) 3481 (br.m), 2948 (m), 2217 (m), 1619 (s), 1510 (s), 1473 (vs), 1442 (s), 1196 (s), 959 (w) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 387 (11800), 232 (48800) nm.
^{1}H NMR	δ_H ppm (300 MHz, C_6D_6) 9.74 (1H, d, J = 8.5 Hz, Ar$\underline{\text{H}}$), 8.24 (1H, d, J = 8.8 Hz, Ar$\underline{\text{H}}$), 7.39 (2H, m, 2 x Ar$\underline{\text{H}}$), 7.05 (1H, dd, J = 8.4, 7.4 Hz, Ar$\underline{\text{H}}$), 6.55 (1H, s, Ar$\underline{\text{H}}$), 5.60 (1H, s, ArO$\underline{\text{H}}$), 3.59 (3H, s, OC$\underline{\text{H}}_3$), 3.19 (3H, s, OC$\underline{\text{H}}_3$).
LRMS	(CI, m/z) 279 (M^+, 100%), 164 (44%), 264 (30%) amu.

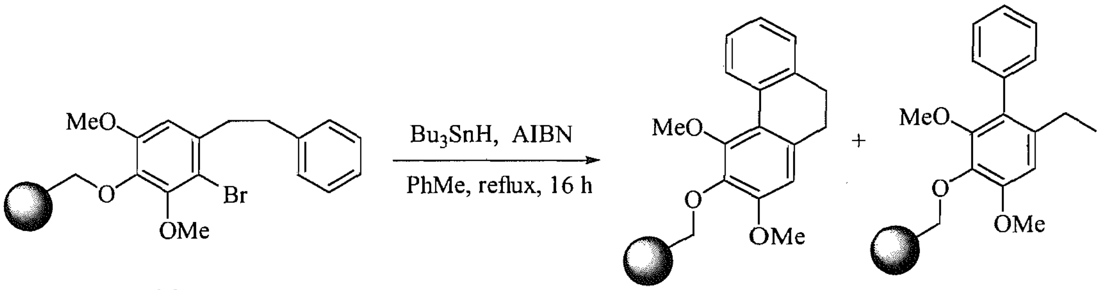
Resin coupled 3-Bromo-2,6-dimethoxy-4-phenethyl-phenol **4.85**



A rapidly stirred solution of alkene resin **4.65** (1.00 g, 0.23 mmol / g resin), *para*-toluene-sulfonyl-hydrazide (3.02 g, 16.20 mmol) and sodium acetate (1.33, 16.20 mmol) in THF (20 mL) and water (20 mL) was heated at reflux for 5 days. The mixture was cooled to room temperature, the resin beads were isolated by filtration then washed with methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), and dried *in vacuo*.

IR (ν_{max}, solid phase) 3028 (w), 2917 (w), 2056 (w), 1730 (m), 1602 (m), 1482 (s), 1392(m), 1320 (w), 1125 (s), 985 (m), 826 (w). cm^{-1}.

Cyclisation of resin coupled 3-Bromo-2,6-dimethoxy-4-styryl-phenol **4.85**



4.85

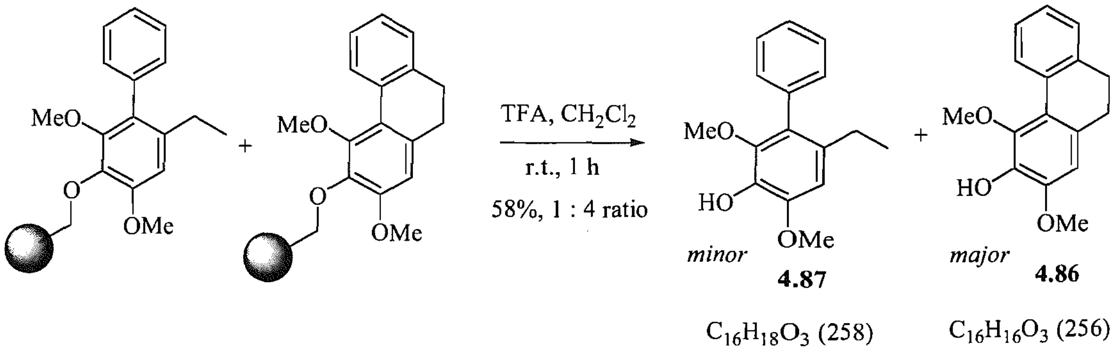
A stirred suspension of the swelled resin **4.85** (650 mg, 0.23 mmol / g resin, 0,18 mmol) containing tributyltin hydride (780 mg, 720 μL, 2.69 mmol) and AIBN (220 mg, 1.35 mmol) in toluene (10 mL) was heated to reflux for 16 hours. The mixture was cooled to room temperature, the resin beads were isolated by filtration, washed with toluene (3 x 40 mL), methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), and dried *in vacuo*.

IR (ν_{max}, solid phase) 3026 (w), 2923 (w), 1784 (m), 1603 (m), 1494 (s), 1453 (m), 1213 (s), 1169 (s), 1018 (m), 907 (w) cm^{-1}.

Gel phase:

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 135.5 – 125.5 (PS), 114.9 ($\underline{C}$ (Ar)), 109.4 ($\underline{C}Br$), 60.9 ($O\underline{C}H_3$), 55.9 ($O\underline{C}H_3$), 36.3 ($\underline{C}H_2$).

6-Ethyl-2,4-dimethoxy-biphenyl-3-ol **4.87** & 2,4-Dimethoxy-9,10-dihydro phenanthren-3-ol **4.86**



Resin from the aforementioned experiment (600 mg, 0.14 mmol, 0.23 mmol / g resin) was swelled in dichloromethane (5 mL) for 20 minutes, whereafter the cleavage coctail consisting of 95% distilled trifluoroacetic acid (4.75 mL), 2.5% dichloromethane (125 μL) and 2.5% triisopropylsilane (125 μL) was added. After 1 hour, the reaction mixture was filtered and the resin washed with dichloromethane (30 mL). Reduction *in vacuo* yielded a yellow oil, which was dissolved in dichloromethane (10 mL) and washed with saturated sodium bicarbonate solution (3 x 40 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica, 10-20% ether in petrol) to a white solid. Spectral analysis showed this to be an inseparable 1 : 4 mixture of **4.87** and **4.86** (21 mg, 0.082 mmol, 58%).

IR of the resin beads following cleavage:

IR (ν_{max}, solid phase) 3025 (w), 2923 (w), 1783 (m), 1603 (m), 1494 (s), 1453 (s), 1213 (s) cm^{-1}.

4.87:

IR (ν_{max}, neat) 3399 (br. w), 2935 (w), 1611 (m), 1494 (w), 1453 (m), 1304 (m), 1194 (m), 1147 (s), 837 (m), 754 (m) cm^{-1}.

UV λ_{max} (ε_{max}, CH$_2$Cl$_2$) 282 (10200), 231 (16900) nm.

^{1}H NMR δ_H ppm (300 MHz, C_6D_6) 7.32 – 7.11 (5H, m, Ar$\underline{H}$), 6.40 (1H, s, Ar$\underline{H}$), 5.35 (1H, s ArO$\underline{H}$), 3.41 (3H, s, $OC\underline{H}_3$), 3.29 (3H, s, $OC\underline{H}_3$), 2.42 (2H, q, J = 7.7 Hz, $C\underline{H}_2$), 1.05 (3H, t, *J* = 7.7 Hz, $C\underline{H}_3$).

LRMS (CI, m/z) 258 (M^+, 100%), 211 (34%), 128 (25%) amu.

HRMS (EI, m/z) Found: M^+: 258.1249; $C_{17}H_{18}O_3^+$ requires: 258.1256.

4.86:

IR (ν_{max}, neat) 3399 (br. w), 2935 (w), 1611 (m), 1494 (w), 1453 (m), 1304 (m), 1194 (m), 1147 (s), 837 (m), 754 (m) cm^{-1}.

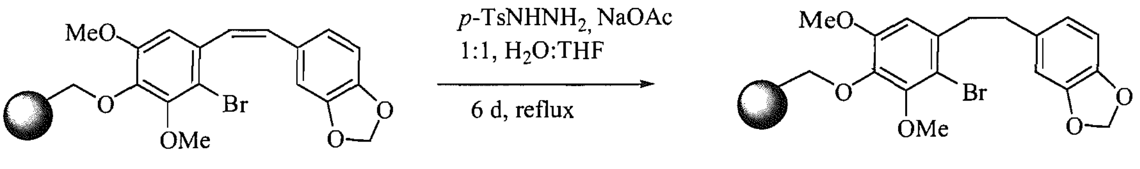
UV λ_{max} (ε_{max}, CH_2Cl_2) 282 (10200), 231 (16700) nm.

^{1}H NMR δ_H ppm (300 MHz, C_6D_6) 8.61 (1H, d, *J* = 7.7 Hz, Ar$\underline{H}$), 7.32 – 7.20 (3H, m, Ar$\underline{H}$), 6.26 (1H, s, Ar$\underline{H}$), 5.35 (1H, s ArO$\underline{H}$), 3.51 (3H, s, $OC\underline{H}_3$), 3.27 (3H, s, $OC\underline{H}_3$), 2.66 – 2.61 (2H, m, $C\underline{H}_2$), 2.52 – 2.48 (2H, m, $C\underline{H}_2$)

LRMS (CI, m/z) 256 (M^+, 100%), 141 (42 %), 152 (29%) amu.

HRMS (EI, m/z) Found: M^+: 256.1095; $C_{16}H_{16}O_3^+$ requires 256.1099.

Resin coupled 4-(2-Benzo[1,3]dioxol-5-yl-ethyl)-3-bromo-2,6-dimethoxy-phenol **4.88**



4.71 **4.88**

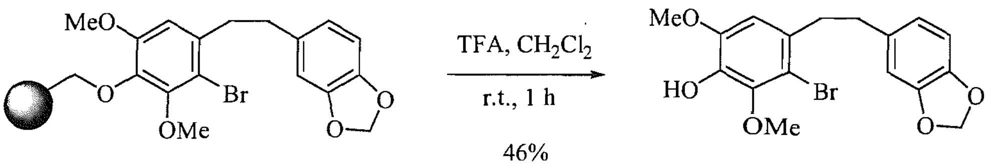
A rapidly stirred solution of alkene resin **471** (1.00 g, 0.23 mmol / g resin), *para*-toluene-sulfonyl hydrazide (2.73 g, 14.68 mmol) and sodium acetate (1.20 g, 14.68 mmol) in THF (20 mL) and water (20 mL) was heated at reflux for 6 days. The mixture was cooled to room temperature, the resin beads were isolated by filtration, washed with methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), and dried *in vacuo*.

IR (ν_{max}, solid phase) 3026 (w), 2927 (w), 1980 (w), 1605 (w), 1488 (s), 1449 (s), 1243 (s), 1038 (s), 928 (w), 813 (m) cm^{-1}.

Gel phase:

^{13}C NMR δ_C ppm (75 MHz, $CDCl_3$) 153.3 ($\underline{C}$ (Ar)), 147.5 ($\underline{C}$ (Ar)), 141.3 ($\underline{C}$ (Ar)), 135.0-125.0 (PS), 109.2 ($\underline{C}H$ (Ar)), 101.2 (OCH_2O), 61.2 (3H, s, $O\underline{C}H_3$), 56.0 (3H, s, $O\underline{C}H_3$), 35.9 ($\underline{C}H_2$).

4-(2-Benzo[1,3]dioxol-5-yl-ethyl)-3-bromo-2,6-dimethoxy-phenol **4.89**



4.88

4.89

$C_{17}H_{17}BrO_5$ (381)

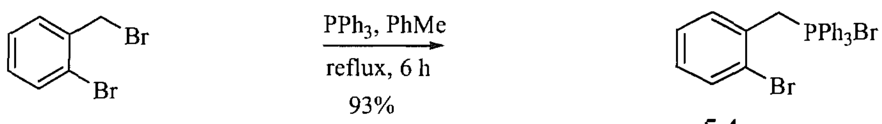
Resin **4.88** from the aforementioned experiment (570 mg, 0.23 mmol / g resin, 0.13 mmol) was swelled in dichloromethane (5 mL) for 20 minutes, whereafter the cleavage cocktail consisting of 95% distilled trifluoroacetic acid (4.75 ml), 2.5% dichloromethane (125 μL) and 2.5 % triisopropylsilane (125 μL) was added. After 1 hour, the reaction mixture was filtered and the resin washed with dichloromethane (30 mL). Reduction *in vacuo* yielded a yellow oil, which was dissolved in dichloromethane (10 mL) and washed with saturated sodium bicarbonate solution (3 x 40 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica gel, 5-10% ether in petrol) and recrystallised to a white solid **4.89** (23 mg, 0.06 mmol, 46%).

IR of the resin beads following cleavage:

IR	(ν_{max}, solid phase) 2919 (w), 1782 (w), 1603 (w), 1492 (vs), 1452 (m), 1308 (w), 1172 (m), 1038 (m), 757 (m) cm^{-1}.
4.89:	
MP	74 – 76 °C (ether / petrol).
IR	(ν_{max}, neat) 3400 (br. w), 2936 (w), 2358 (w), 1601 (w), 1498 (vs), 1310 (s), 1183 (vs), 1038 (vs), 929 (s), 847 (s), 808 (vs) cm^{-1}.
^{1}H NMR	δ_H ppm (300 MHz, C_6D_6): 6.72 (1H, d, J = 1.5 Hz, ArH), 6.64 (1H, d, J = 7.7 Hz, ArH), 6.51 (1H, dd, J = 8.1, 1.5 Hz, ArH), 6.12 (1H, s, ArH), 5.34 (2H, s, OCH_2O), 5.27 (1H, s, ArOH), 3.73 (3H, s, OCH_3), 3.12 (3H, s, OCH_3), 2.94 - 2.88 (2H, m, CH_2), 2.77 - 2.72 (2H, m, CH_2).
LRMS	(CI, m/z) 382 (M^+ [^{81}Br], 6%), 380 (M^+ [^{79}Br], 6%), 301 ($[M-Br]^+$, 40%), 245 (100%), 135 (100%) amu.
HRMS	(CI, m/z) Found: M^+: 380.0259; $C_{17}H_{17}O_5{}^{79}Br^+$ requires: 380.0259.

6.5. Experimental for Chapter 5

(2-Bromo-benzyl)-triphenyl-phosphonium bromide **5.4**



5.3

$C_7H_6Br_2$ (249)

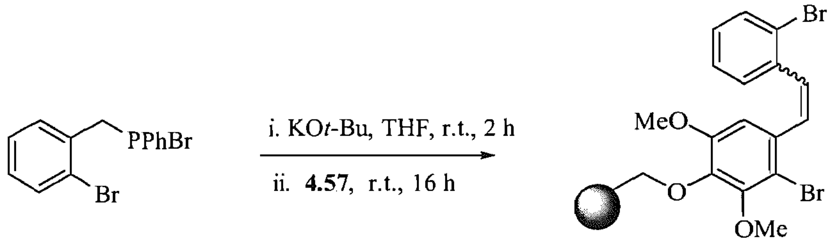
5.4

$C_{25}H_{21}Br_2P$ (572)

1-Bromo-2-bromomethyl-benzene (5.00 g, 20.00 mmol), and triphenylphosphine (5.77 g, 22.00 mmol), were dissolved in toluene (40 mL) and the mixture stirred at reflux for 6 hours. After cooling to ambient temperature, the resulting white solid was collected by filtration and washed with cold toluene (2 x 40 mL) and petrol (3 x 20 mL) to yield the title compound **5.4** as a white solid [84] (10.59 g, 18.51 mmol, 93%).

MP	189-191 °C (petrol), lit. 193-195. [84]
IR	(ν_{max}, neat) 3463 (w), 1588 (w), 1436 (s), 1108 (s), 1026 (w), 841 (w), 758 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 270 (9000), 231 (59300) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 7.79 (3H, t, J = 7.0 Hz, Ar$\underline{H}$), 7.70-7.60 (12H, m, 12 x Ar$\underline{H}$), 7.53 (1H, dt, J = 7.5, 2.5 Hz, Ar$\underline{H}$), 7.40 (1H, d, J = 7.5 Hz, Ar$\underline{H}$), 7.17 (1H, t, J = 7.5 Hz, Ar$\underline{H}$), 7.12 (2H, tt, J = 7.5, 2.0 Hz, Ar$\underline{H}$), 5.67 (2H, d, J = 14.6 Hz, $C\underline{H}_2P$).
^{31}P-NMR	δ_P ppm (121 MHz, $CDCl_3$) 22.7
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 135.6 (3 x $\underline{C}$H (Ar)), 134.8 (6 x $\underline{C}$H (Ar)), d, J = 9.7 Hz, 6 x $\underline{C}$H (Ar)), 133.6 (2 x $\underline{C}$H (Ar)), 133.4 (2 x $\underline{C}$H (Ar)), 128.8 ($\underline{C}$Br (Ar)), 128.1 (s, $\underline{C}$ (Ar)), 117.8 (d, J = 85.5 Hz, 3 x $\underline{C}$ (Ar)), 31.4 (d, J = 48.6 Hz, $\underline{C}H_2P$).
LRMS	(ES+, m/z) 433 (M^+-[^{81}Br], 100%), 431 (M^+-[^{79}Br], 92 %).

Resin coupled 3-Bromo-4-[2-(2-bromo-phenyl)-vinyl]-2,6-dimethoxy-phenol **5.5(*Z*)** & 3-Bromo-4-[2-(2-bromo-phenyl)-vinyl]-2,6-dimethoxy-phenol **5.5(*E*)**



5.4

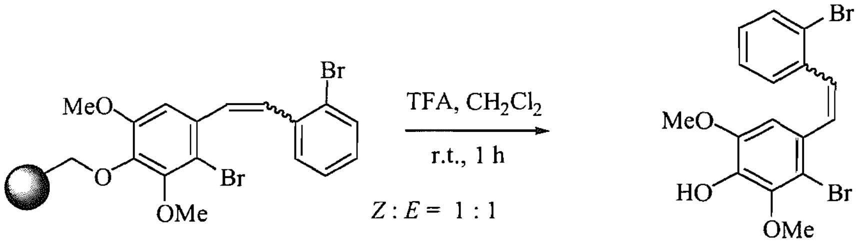
$C_{25}H_{21}Br_2P$ (572)

5.5

To a cooled (0 °C) suspension of phosphonium bromide **5.4** (5.99 g, 11.70 mmol) in tetrahydrofuran (20 mL) was added the potassium *tert*-butoxide (1.58 g, 14.08 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to 0 °C and the resin coupled 2-bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.57** (2.00 g, 3.50 mmol) was added as a suspension in tetrahydrofuran (15 mL). The reaction mixture was stirred at room temperature for 24 hours. The resin beads were isolated by filtration, washed with THF (3 x 20 mL), methanol (3 x 20 mL) and dichloromethane (3 x 20 mL), then dried *in vacuo*.

IR (ν_{max}, solid phase) 3054 (w), 2836 (w), 2764 (w), 1591 (w), 1510 (s), 1438 (vs), 1377 (m), 1218 (s), 1011 (m), 961 (m) cm^{-1}.

(*Z*)-3-Bromo-4-[2-(2-bromo-phenyl)-vinyl]-2,6-dimethoxy-phenol & (*E*)-3-Bromo-4-[2-(2-bromo-phenyl)-vinyl]-2,6-dimethoxy-phenol



5.5(*Z&E*)

$C_{16}H_{14}Br_2O_3$ (414)

In order to determine the loading, the aforementioned resin **5.5(*Z/E*)** (500 mg), was swelled in dichloromethane (5 mL) for 20 minutes, whereafter the cleavage cocktail consisting of 95% distilled trifluoroacetic acid (4.75 mL), 2.5% dichloromethane (125 μL) and 2.5% triisopropylsilane (125 μL) was added. After 1 hour, the reaction mixture was filtered and the resin washed with dichloromethane (30 mL). Concentration *in vacuo* yielded a yellow oil, which was dissolved in dichloromethane (10 mL) and washed with saturated sodium bicarbonate solution (3 x 40 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica gel, 5-10% ether in petrol) to an inseparable 1:1 mixture of *cis*- and and *trans*-isomer as a white solid (125 mg, 0.30 mmol). From this we established the resin loading to be 0.15 mmol / g.

IR of the resin beads following cleavage:

IR	(ν_{max}, solid phase) 2928 (w), 1601 (w), 1494 (w), 1452 (m), 1242 (w), 1083 (w) cm^{-1}.

(*Z*)-3-Bromo-4-[2-(2-bromo-phenyl)-vinyl]-2,6-dimethoxy-phenol:

IR	(ν_{max}, neat) 3497 (br. m), 1590 (w), 1492 (vs), 1402 (s), 1254 (w), 1196 (s), 1024 (m), 850 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 241 (55100), 320 (56900) nm.

^{1}H NMR δ_H ppm (400 MHz, CDCl$_3$) 7.45 (1H, d, J = 7.5 Hz, ArH), 7.11 (1H, d, J = 7.5 Hz, ArH), 7.02 (1H, t, J = 7.5 Hz, ArH), 6.94 (1H, d, J = 12.0 Hz, =CH), 6.78 (1H, d, J = 12.0 Hz, =CH), 6.70 (1H, m, ArH), 6.29 (1H, s, ArH), 5.34 (1H, s, ArOH), 3.22 (3H, s, OCH$_3$), 2.92 (3H, s, OCH$_3$).

^{13}C NMR δ_C ppm (100 MHz, CDCl$_3$) 145.5 (COCH$_3$), 140.9 (COCH$_3$), 138.5 (C (Ar)), 133.1 (C (Ar)), 131.6 (CH (Ar)), 130.3 (CH (Ar)), 129.0 (CH (Ar)), 128.6 (CH (Ar)), 128.2 (=CH), 128.1 (=CH), 124.8 (COH), 112.8 (CBr), 112.0 (CBr), 105.2 (CH (Ar)), 60.5 (OCH$_3$), 55.6 (OCH$_3$).

HRMS (ES+, m/z) Found: [M+Na]$^+$: 434.9208, C$_{16}$H$_{14}$O$_3$^{79}Br$_2$ requires: 434.9202.

(*E*)-3-Bromo-4-[2-(2-bromo-phenyl)-vinyl]-2,6-dimethoxy-phenol :

IR (ν_{max}, neat) 3497 (br. m), 1590 (w), 1492 (vs), 1402 (s), 1254 (w), 1196 (s), 1024 (m), 850 (m) cm^{-1}.

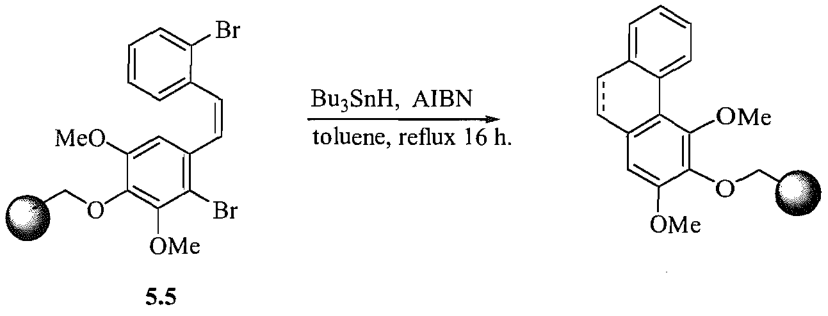
UV λ_{max} (ε_{max}, CH$_2$Cl$_2$) (55100) 320 (56900) nm.

^{1}H NMR δ_H ppm (400 MHz, CDCl$_3$) 7.73 (1H, d, J = 16.1 Hz, =CH), 7.64 (1H, d, J = 8.0 Hz, ArH), 7.53 (1H, d, J = 16.1 Hz, =CH), 7.11 (1H, d, J = 7.5 Hz, ArH), 7.02 (1H, t, J = 7.5 Hz, ArH), 6.82-6.76 (1H, m, ArH), 6.38 (1H, s, ArH), 5.48 (1H, s, ArOH), 3.84 (3H, s, OCH$_3$), 3.82 (3H, s, OCH$_3$)

^{13}C NMR δ_C ppm (100 MHz, CDCl$_3$) 147.1 (COCH$_3$), 146.9 (COCH$_3$), 140.1 (C (Ar)), 133.7 (C (Ar)), 124.8 (COH), 131.8 (CH (Ar)), 129.5 (CH (Ar)), 128.7 (CH (Ar)), 128.4 (=CH), 127.7 (=CH), 127.6 (CH (Ar)), 112.8 (C (Br)), 112.0 (C (Br)), 109.2 (CH (Ar)), 60.5 (OCH$_3$), 55.9 (OCH$_3$).

HRMS (ES+, m/z) Found: [M+Na]$^+$: 434.9208; C$_{16}$H$_{14}$O$_3$^{79}Br$_2$Na$^+$ requires: 434.9202.

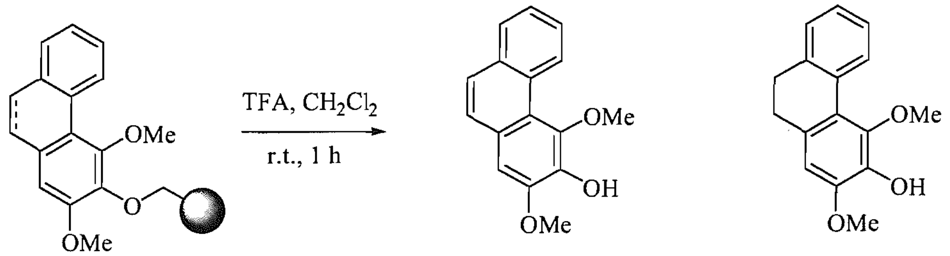
Cyclisation of resin coupled 3-Bromo-4-[2-(2-bromo-phenyl)-vinyl]-2,6-dimethoxy-phenol **5.11**



A stirred suspension of the aforementioned resin **5.5** (1.50 g, 0.23 mmol, 0.15 mmol / g resin) pre-swelled in toluene (10 mL) was heated to reflux for 16 hours with tributyltin hydride (0.94 g, 0.87 mL, 3.23 mmol) and AIBN (266 mg, 1.62 mmol). The mixture was cooled to room temperature, and the resin beads isolated by filtration, washed with toluene (3 x 40 mL), methanol (3 x 40 mL) and DCM (3 x 40 mL), and dried *in vacuo*.

IR (ν_{max}, solid phase) 3512 (br. w), 2934 (w), 1590 (w), 1492 (s), 1401 (m), 1196 (s), 1024 (m), 849 (w) cm^{-1}.

2,4-Dimethoxy-phenanthren-3-ol **4.66** & 2,4-Dimethoxy-9,10-dihydro-phenanthren-3-ol **4.86**



4.66 $C_{16}H_{14}O_3$ (254)

4.86 $C_{16}H_{16}O_3$ (256)

The aforementioned resin (1.53 g, 0.15 mmol / g resin, 0.23 mmol) was swelled in dichloromethane (10 mL) for 20 minutes, whereafter the cleavage cocktail consisting of 95% distilled trifluoroacetic acid (19 mL), 2.5% dichloromethane (0.5 mL) and 2.5% triisopropylsilane (0.5 mL) was added. After 1 hour, the reaction mixture was filtered and the resin washed with dichloromethane (30 mL). The combined organic phases were concentrated *in vacuo* to yield a yellow oil, which was dissolved in dichloromethane (125 μL) and washed with saturated sodium bicarbonate solution (3 x 40 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica gel, 20-40% ether in petrol) yielding a colourless oil **4.66** (20 mg, 0.079 mmol, 34%) and **4.86** as a yellow oil (20 mg, 0.079 mmol, 34%).

IR of the resin beads following cleavage:

IR (ν_{max}, solid phase) 3026 (w), 2923 (w), 1602 (w), 1452 (m), 1218 (m), 757 (s) cm^{-1}.

4.66:

IR (ν_{max}, neat) 3508 (br. w), 2936 (w), 1615 (w), 1473 (s), 1289 (s), 1126 (s), 894 (m) cm^{-1}.

UV λ_{max} (ε_{max}, CH_2Cl_2): 307 (17100), 258 (103600) nm.

^{1}H NMR δ_H ppm (400 MHz, $CDCl_3$): 9.87 (1H, d, J = 8.5 Hz, ArH), 7.87 (1H, d, J = 7.5 Hz, ArH), 7.68-7.51 (4H, m, 4 x ArH), 6.85 (1H, s, ArH), 5.80 (1H, s, ArOH), 3.81 (3H, s, OCH_3), 3.40 (3H, s, OCH_3).

LRMS (CI, m/z) 254 (M^+, 100%), 239 (60%), 139 (66%) amu.

HRMS (ES+, m/z) Found: MH^+: 255.1016; $C_{16}H_{14}O_3^+$ requires: 255.1015

4.86:

IR (ν_{max}, neat) 3225 (w), 1611 (m), 1496 (s), 1496 (s), 1328 (s), 1260 (m), 835 (s) cm^{-1}.

UV λ_{max} (ε_{max}, CH_2Cl_2) 282 (40000), 231 (46300) nm.

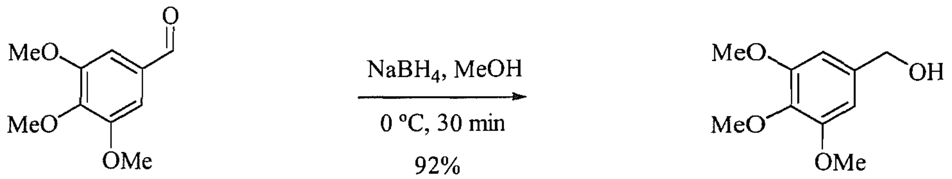
^{1}H NMR δ_H ppm (400 MHz, $CDCl_3$): 8.71 (1H, d, J = 8.0 Hz, ArH), 7.37 (1H, td, J = 8.0, 2.5 Hz, ArH), 7.26-7.22 (2H, m, 2 x ArH), 6.39 (1H, s, ArH), 5.50 (1H, s, ArOH), 3.64 (3H, s, OCH_3), 3.41 (3H, s, OCH_3), 2.77-2.73 (2H, m, CH_2), 2.63-2.60 CH_2).

^{13}C NMR δ_C ppm (100 MHz, $CDCl_3$) 147.1 (C (Ar)), 146.4 (C (Ar)), 138.9 (C (Ar)), 138.1 (C (Ar)), 133.5 (C (Ar)), 130.9 (C (Ar)), 128.4 (CH (Ar)), 128.1 (CH (Ar)), 127.9 (CH (Ar)), 126.9 (CH (Ar)), 121.2 (C (Ar)), 107.4 (CH (Ar)), 60.0 (OCH_3), 55.8 (OCH_3), 30.6 (CH_2), 30.5 (CH_2).

LRMS (ES+ m/z) 256 (M^+, 100%), 241 (36%), 139 (54%).

HRMS (ES+, m/z) Found $[M+Na]^+$: 279.0993; $C_{16}H_{16}O_3Na^+$ requires: 279.0991

(3,4,5-Trimethoxy-phenyl)-methanol **5.16**



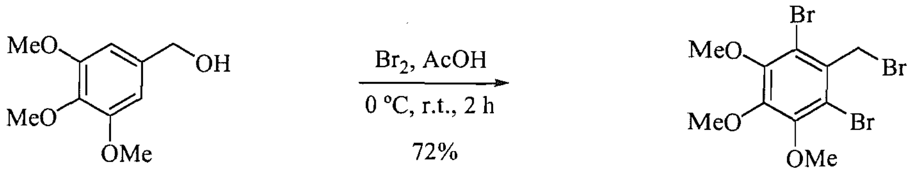
5.15 **5.16**

$C_{10}H_{12}O_4$ (196) $C_{10}H_{14}O_4$ (198)

3,4-Dimethoxy-benzaldehyde **5.15** (20.00 g, 0.10 mol) was stirred in methanol (200 mL) at 0 °C. NaBH$_4$ (4.25 g, 0.11 mol) was added portionwise over 20 minutes and the mixture stirred for 30 minutes. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (70 mL), washed with brine (70 mL), dried (MgSO$_4$), filtered and concentrated in *vacuo* to yield the product as a pale yellow oil **5.16** (18.67 g, 94.29 mmol, 92%). [85]

IR	(ν_{max}, neat) 3449 (br. w), 2940 (w), 1591 (s), 1537 (s), 1329 (s), 1100 (vs), 827 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH$_2$Cl$_2$) 231 (21700) nm.
^{1}H NMR	δ_H ppm (400 MHz, CDCl$_3$) 6.62 (2H, s, 2 x (C$\underline{H}$ (Ar)), 5.31 (1H, s, ArO$\underline{H}$), 4.66 (2H, s, C$\underline{H}_2$), 3.89 (6H, s, 2 x OC$\underline{H}_3$), 3.86 (3H, s, OC$\underline{H}_3$).
^{13}C NMR	δ_C ppm (100 MHz, CDCl$_3$) 153.8 (2 x $\underline{C}$ (Ar)), 137.8 ($\underline{C}$ (Ar)), 137.0 ($\underline{C}$ (Ar)), 104.3 (2 x $\underline{C}$H (Ar)), 65.9 ($\underline{C}$H$_2$), 61.2 (O$\underline{C}$H$_3$), 56.5 (2 x O$\underline{C}$H$_3$).
LRMS	(CI, m/z) 198 (MH$^+$, 72%), 181 (100%), 127 (26%).

1,3-Dibromo-2-bromomethyl-4,5,6-trimethoxy-benzene **5.19**



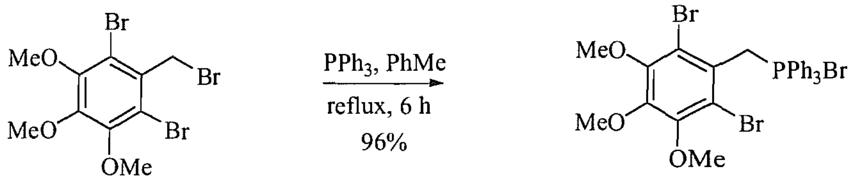
5.16
$C_{10}H_{14}O_4$ (198)

5.19
$C_{10}H_{11}Br_3O_3$ (418)

1,3-Dibromo-2-bromomethyl-4,5,6-trimethoxy-benzene **5.19** was prepared by the method of Padwa *et al.* [86] To a stirred solution of (3,4,5-trimethoxy-phenyl)-methanol **5.16** (7.80 g, 39.39 mmol) in glacial acetic acid (12 mL) at 0 ° C was added bromine (2.42 mL) in glacial acetic acid (12 mL) dropwise over 30 min. After 16 hours at room temperature, the suspended creamy solid formed was isolated via suction filtration and washed with water (40 mL). The crude material was re-crystallised from petrol to afford the product **5.19** as a white solid (11.80 g, 28.30 mmol, 72%).

MP	68-70 °C (petrol).
IR	(ν_{max}, neat) 2942 (w), 1562 (w), 1464 (s), 1383 (vs), 1209 (s), 1081 (s), 831 (w) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 231 (30600) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 4.88 (2H, s, $C\underline{H}_2$), 3.95 (3H, s, $OC\underline{H}_3$), 3.91 (6H, s, 2 x $OC\underline{H}_3$).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 151.1 ($\underline{C}OCH_3$ (Ar)), 148.1 ($\underline{C}OCH_3$ (Ar)), 131.9 ($\underline{C}$ (Ar)), 116.0 (2 x $\underline{C}Br$), 61.5 ($O\underline{C}H_3$), 61.1 (2 x $O\underline{C}H_3$), ($\underline{C}H_2Br$).
LRMS	(CI, m/z) 341 (MH^+-[^{81}Br]$^+$, 100%), 339 (MH^+-[^{79}Br], 98 %), 297 (20%).
HRMS	(EI, m/z) Found M^+: 415.82496; $C_{10}H_{11}O_3{}^{79}Br_3{}^+$ requires 415.82496

(1,3-Dibromo-3,4,5-trimethoxy-benzyl)-triphenyl-phosphonium bromide **5.20**



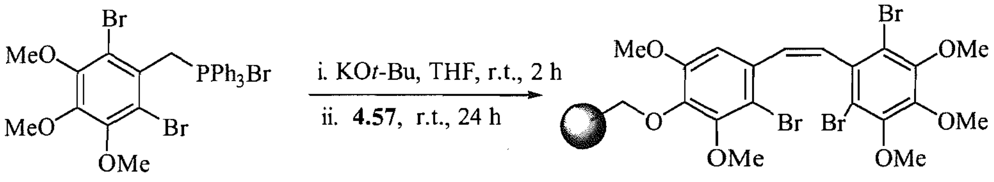
5.19 **5.20**

$C_{10}H_{11}Br_3O_3$ (418) $C_{28}H_{26}Br_3O_3P$ (681)

1,3-Dibromo-2-bromomethyl-4,5,6-trimethoxy-benzene **5.19** (5.00 g, 11.96 mmol) and triphenyl-phosphine (3.45 g, 13.16 mmol) were dissolved in toluene (40 mL), and the mixture stirred at reflux for 5 hours. After cooling, the resulting white solid was collected by filtration and washed with cold toluene (2 x 40 mL) and petrol (3 x 20 mL) to yield the title compound **5.20** (7.80 g, 11.45 mmol, 96%) as a white solid.

MP	215-217 °C (toluene).
IR	(ν_{max}, neat) 2993 (w), 1589 (w), 1468 (m), 1435 (s), 1384 (s), 1329 (m), 951 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 270 (16200), 231 (75300) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 7.80-7.74 (9H, m, 9 x Ar$\underline{H}$), 7.66-7.61 (6H, m, 6 x Ar$\underline{H}$), 5.55 (2H, d, *J* = 13.7 Hz, C$\underline{H}_2$P), 3.89 (3H, s, OC$\underline{H}_3$), 3.72 (6H, s, 2 x OC$\underline{H}_3$).
^{31}P-NMR	δ_P ppm (121 MHz, $CDCl_3$) 20.7.
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 151.3 (2 x ($\underline{C}OCH_3$), 148.0 ($\underline{C}OCH_3$), 135.2 (s, 3 x ($\underline{C}$H (Ar)), 134.5 (s, 6 x $\underline{C}$H (Ar)), 130.2 (d, *J* = 11.7 Hz, 6 x $\underline{C}$H (Ar)), 118.5 (s, $\underline{C}$ (Ar)), 118.1 (d, *J* = 85.5 Hz, 3 x $\underline{C}$ (Ar)), 117.5 (s, 2 x $\underline{C}$Br), 61.7 (s, O$\underline{C}H_3$), 61.2 (2 x O$\underline{C}H_3$), 35.3 (d, *J* = 48.6 Hz, $\underline{C}H_2$P).
LRMS	(ES+, m/z) 602 (M^+-[^{81}Br], 100%), 600 (M^+-[^{79}Br], 92 %) amu.
HRMS	(ES+, m/z) Found M^+: 598.9986; $C_{28}H_{26}O_3P^{79}Br_2^+$ requires 598.9981.

Resin coupled 3-Bromo-4-[2-(2,6-dibromo-3,4,5-trimethoxy-phenyl)-vinyl]-2,6-dimethoxy-phenol



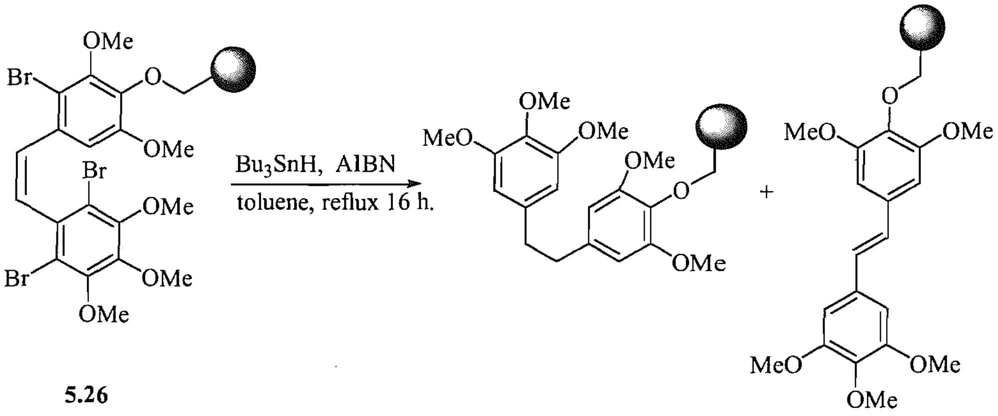
5.20 **5.26**

$C_{28}H_{26}Br_3O_3P$ (681)

To a cooled (0 °C) suspension of phosphonium salt **5.20** (7.24 g, 12.02 mmol) in tetrahydrofuran (20 mL) was added potassium *tert*-butoxide (1.89, 16.83 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to 0 °C and the resin coupled 2-bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.57** (3.30 g, 0.71 mmol / g resin, 2.34 mmol, swelled for 30 minutes) was added as a suspension in tetrahydrofuran (40 mL). The reaction mixture was stirred at room temperature for 24 hours. The resin beads were then isolated by filtration, washed with THF (3 x 20 mL), methanol (3 x 20 mL) and dichloromethane (3 x 20 mL), then dried *in vacuo*.

IR (ν_{max}, solid phase) 2918 (w), 1600 (w), 1493 (m), 1452 (m), 1222 (w), 1105 (m) cm^{-1}.

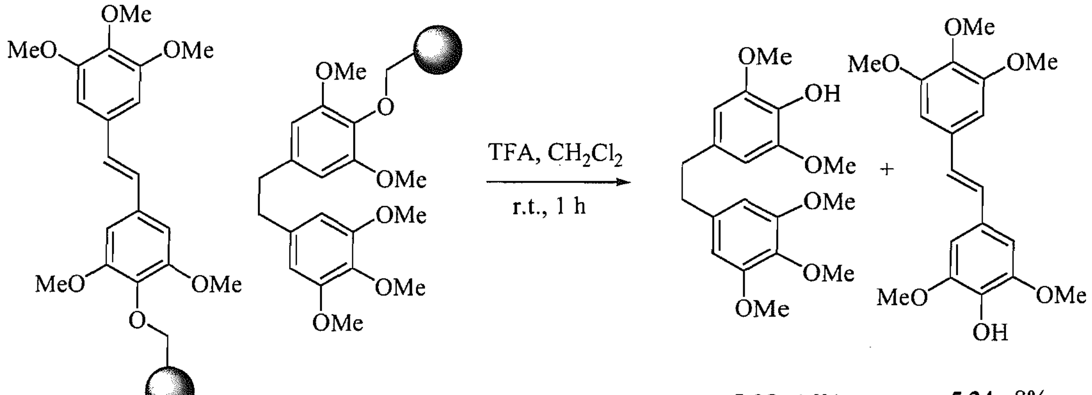
Cyclisation of resin coupled 3-Bromo-4-[2-(2,6-dibromo-3,4,5-trimethoxy-phenyl)-vinyl]-2,6-dimethoxy-phenol **5.26**



A stirred suspension of the swelled resin **5.26** (3.67 g, 0.55 mmol, 0.15 mmol / g resin) containing tributyltin hydride (4.20 g, 3.89 mL, 14.45 mmol) and AIBN (1.19 g, 7.23 mmol) in toluene (10 mL) was heated to reflux for 16 hours. The mixture was then cooled to room temperature, and the resin beads isolated by filtration, washed with toluene (3 x 40 mL), methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), and dried *in vacuo*.

IR (ν_{max}, solid phase) 2922 (w), 1601 (w), 1494 (m), 1452 (m), 1209 (w), 1030 (w), 757 (m) cm^{-1}.

2,6-Dimethoxy-4-[2-(3,4,5-trimethoxy-phenyl)-ethyl]-phenol **5.33** & (*E*)-2,6-Dimethoxy-4-[2-(3,4,5-trimethoxy-phenyl)-vinyl]-phenol **5.34**



5.33, 16%
$C_{19}H_{24}O_6$ (348)

5.34, 8%
$C_{19}H_{22}O_6$ (346)

The aforementioned resin (3.65 g, 0.15 mmol / g resin, 0.55 mmol) was swelled in dichloromethane (5 mL) for 20 minutes, whereafter the cleavage cocktail consisting of 95% distilled trifluoroacetic acid (19 mL), 2.5% dichloromethane (0.5 mL) and 2.5% triisopropylsilane (0.5 mL) was added. After 1 hour, the reaction mixture was filtered and the resin washed with dichloromethane (30 mL). Concentration of the combine organic phases *in vacuo* yielded a yellow oil, which was dissolved in dichloromethane (10 mL) and washed with saturated sodium bicarbonate solution (3 x 40 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica gel, 10-20% ether in petrol) yielding **5.33** as a yellow solid (31 mg, 0.089 mmol, 16%) and **5.34** as a white solid (15 mg, 0.043 mmol, 8%).

IR	(ν_{max}, solid phase) 2923 (w), 1784 (w), 1603 (w), 1494 (m), 1168 (w) cm^{-1}.

5.33:

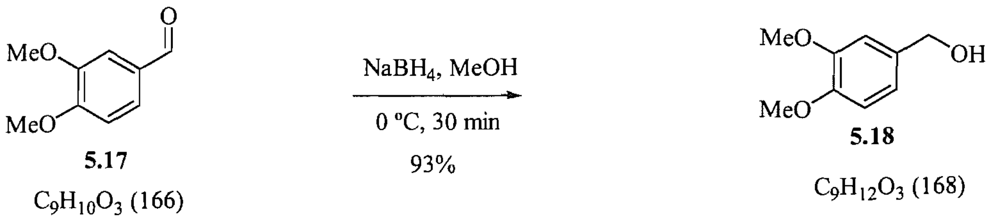
MP	94-96 °C (ether / petrol).
IR	(ν_{max}, neat) 3420 (br. m), 2934 (w), 1589 (m), 1512 (m), 1333 (m), 1219 (s), 998 (w) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 273 (30000), 231 (40000) nm.

^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 6.37 (4H, s, Ar$\underline{H}$), 5.39 (1H, s, ArO$\underline{H}$), 4.06 (3H, s, OC$\underline{H}_3$), 3.86 (6H, s, 2 x OC$\underline{H}_3$), 3.82 (6H, s, 2 x OC$\underline{H}_3$), 2.84 (4H, s, 2 x C$\underline{H}_2$).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 153.2 (2 x $\underline{C}OCH_3$ (Ar)), 147.0 ((2 x $\underline{C}OCH_3$ (Ar)), 137.5 ($\underline{C}$ (Ar)), 136.4 ($\underline{C}$ (Ar)), 133.1 ($\underline{C}$ (Ar)), 132.8 ($\underline{C}OCH_3$ (Ar)), 105.7 (2 x $\underline{C}H$ (Ar)), 105.4 (2 x $\underline{C}H$ (Ar)), 61.0 (O$\underline{C}H_3$), 56.4 (2 x O$\underline{C}H_3$), 56.2 (2 x O$\underline{C}H_3$), 38.7 ($\underline{C}H_2$), 38.3 ($\underline{C}H_2$).
LRMS	(CI, m/z) 366 ($[M+NH_4]^+$, 16%), 349 (MH^+, 100%).

5.34:

MP	202–204 °C (ether/petrol).
IR	(ν_{max}, neat) 3495 (br. w), 2936 (w), 2839 (w), 1608 (m), 1515 (s), 1455 (s), 1339 (s), 1210 (s), 1102 (vs), 999 (s), 838 (m).
UV	λ_{max} (ε_{max}, CH_2Cl_2): 230 (5900), 334 (13200) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 6.94 (1H, d, J = 16.0 Hz, =C$\underline{H}$), 6.89 (1H, d, J = 16.0 Hz, =C$\underline{H}$), 6.76 (2H, s, Ar$\underline{H}$), 6.74 (2H, s, Ar$\underline{H}$), 5.56 (1H, s, ArO$\underline{H}$), 3.96 (6H, s, 2 x OC$\underline{H}_3$), 3.93 (6H, s, 2 x OC$\underline{H}_3$), 3.88 (3H, s, OC$\underline{H}_3$).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 154.5 (2 x $\underline{C}OCH_3$ (Ar)), 148.9 (2 x $\underline{C}OCH_3$ (Ar)), 137.0 ($\underline{C}$ (Ar)), 134.5 (2 x $\underline{C}$ (Ar)), 129.3 ($\underline{C}OH$), 129.2 ($\underline{C}H$=CH), 127.1 ($\underline{C}H$=CH), 104.9 (2 x $\underline{C}H$ (Ar)), 104.5 (2 x $\underline{C}H$ (Ar)), 60.6 (O$\underline{C}H_3$), 56.6 (2 x O$\underline{C}H_3$), 56.4 (2 x O$\underline{C}H_3$).
LRMS	(CI, m/z) 346 (M^+, 100%, 331 (62%) amu.
HRMS	(EI, m/z) Found: M^+: 346.1412, $C_{19}H_{22}O_6^+$ requires: 346.1416.

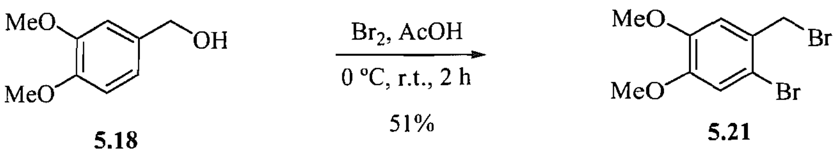
(3,4-Dimethoxy-phenyl)-methanol **5.18**



3,4-Dimethoxy-benzaldehyde (10.00 g, 60.24 mmol) was stirred in methanol (120 mL) at 0 °C. $NaBH_4$ (2.50 g, 66.09 mmol) was added portionwise and the mixture stirred for 30 min. The solvent was removed under reduced pressure and the residue diluted in dichloromethane (50 mL), washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo* to yield the product as a pale yellow oil **5.18** (9.43 g, 56.13 mmol, 93%). [87]

IR	(ν_{max}, neat) 3413 (br. m), 1593 (w), 1514 (s), 1419 (m), 1259 (vs), 1153 (s), 809 (w) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 281 (8100), 235 (20100) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 6.93-6.87 (3H, m, 3 x Ar$\underline{H}$), 5.31 (1H, s, ArO$\underline{H}$), 4.64 (2H, s, $C\underline{H}_2$), 3.91 (6H, s, 2 x $OC\underline{H}_3$).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 149.6 ($\underline{C}$ (Ar)), 149.0 ($\underline{C}$ (Ar)), 134.1 ($\underline{C}$ (Ar)), 119.8 ($\underline{C}$H (Ar)), 111.6 ($\underline{C}$H (Ar)), 111.0 ($\underline{C}$H (Ar)), 65.7 ($\underline{C}H_2$), 56.4 ($O\underline{C}H_3$), 56.3 ($O\underline{C}H_3$).
LRMS	(CI, m/z) 168 (M^+, 68%), 151 (100 %), 139 (18%).

1-Bromo-2-bromomethyl-4,5-dimethoxy-benzene **5.21**



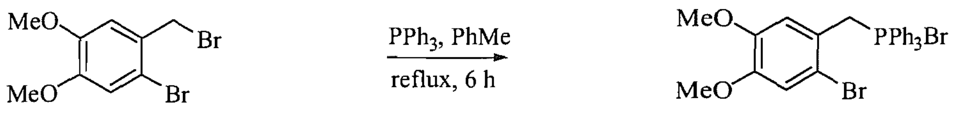
5.18 $C_9H_{12}O_3$ (168)

5.21 $C_9H_{10}Br_2O_2$ (310)

1-Bromo-2-bromomethyl-4,5-dimethoxy-benzene **5.21** was prepared by the method of Padwa *et al.* [86] To a stirred solution of (3,4-dimethoxy-phenyl)-methanol **5.18** (8.43g, 50.12 mmol) in glacial acetic acid (15.27 mL) at 0 ° C was added bromine (3.09 mL, 9.61 g, 6.15 mmol, 3.09 mL) in glacial acetic acid (9.16 mL) dropwise over 30 min. After stirring for a further 2 hours at room temperature, the suspended creamy solid formed was isolated by suction filtration and washed with water (50 mL). The crude material was re-crystallised from petrol to afford the product as an orange solid [88] **5.21** (7.89 g, 25.45 mmol, 51%).

MP	81-83 °C (petrol), lit. 82-84 °C (ether). [88]
IR	(ν_{max}, neat) 2932 (w), 2839 (w), 1599 (m), 1501 (vs), 1343 (m), 1259 (vs), 1206 (vs), 1165 (vs), 968 (m), 797 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 230 (16700) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 7.07 (1H, s, ArH), 6.94 (1H, s, ArH), 4.60 (2H, s, CH_2), 3.90 (3H, s, OCH_3), 3.86 (3H, s, OCH_3).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 149.9 (C (Ar)), 148.7 (C (Ar)), 128.8 (C (Ar)), 116.2 (CH (Ar)), 115.9 (CBr (Ar)), 115.2 (CH (Ar)), 56.7 (2 x OCH_3), 34.5 (CH_2).
LRMS	(CI, m/z) 231 (M-[^{81}Br]$^+$, 26%), 229 (M-[^{79}Br]$^+$, 98 %), 108 (46%) amu.

(2-Bromo-4,5-dimethoxy-benzyl)-triphenyl-phosphonium bromide **5.22**



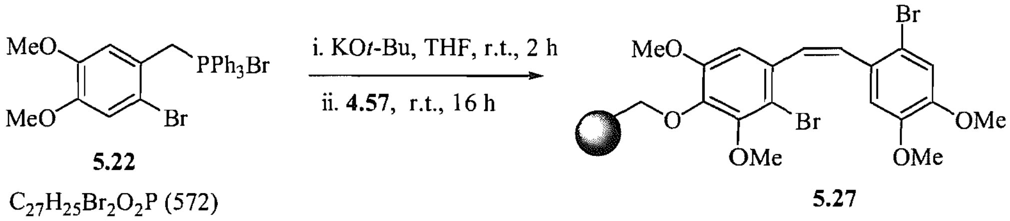
5.21
$C_9H_{10}Br_2O_2$ (310)

5.22
$C_{27}H_{25}Br_2O_2P$ (572)

1-Bromo-2-bromomethyl-4,5-dimethoxy-benzene **5.21** (5.00 g, 16.13 mmol), and triphenylphosphine (4.65 g, 17.74 mmol), were dissolved in toluene (40 mL), and the mixture stirred at reflux for 6 hours. After cooling, the resulting white solid was collected by filtration and washed with cold toluene (2 x 40 mL) and petrol (3 x 20 mL) to yield the title compound **5.22** (8.50 g, 14.86 mmol, 92%) as a white solid.

MP	255-257 °C (toluene).
IR	(ν_{max}, neat) 3054 (w), 2836 (w), 2764 (w), 1591 (w), 1510 (s), 1438 (vs), 1377 (m), 1218 (s), 1011 (m), 961 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 295 (13600), 232 (98200) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 7.80 (3H, J = 7.8 Hz, ArH), 7.75-7.62 (12H, m, 12 x CH (Ar)), 7.17 (1H, s, ArH), 6.80 (1H, s, ArH), 5.50 (2H, d, J = 14.1 Hz, CH_2), 3.81 (3H, s, OCH_3), 3.58 (3H, s, OCH_3).
^{31}P-NMR	δ_P ppm (121 MHz, $CDCl_3$) 22.0.
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$): 149.9 (s, $COCH_3$), 148.9 (s, $COCH_3$), 135.2 (3 x CH (Ar)), 134 (d, J = 11.7 Hz, 6 x CH (Ar)), 134.7 (d, J = 11.7 Hz, 6 x CH (Ar)), 130.3 (d, J = 13.6 Hz, 6 x CH (Ar)), 118.9 (s, C (Ar)), 117.7 (d, J = 85.5 Hz, 3 x C (Ar)), 117.1 (s, CH (Ar)), 116.1 (s, CH (Ar)), 115.2 (CBr (Ar)), 56.6 (s, OCH_3), 56.4 (s, OCH_3), 30.8 (d, J = 48.3 Hz, CH_2P).
LRMS	(ES+, m/z) 493 ([M^+-[^{81}Br]], 100%), 491 ([M^+-[^{79}Br]], 100%).
HRMS	(ES+, m/z) Found M^+: 491.0766; $C_{27}H_{25}O_2P^{79}Br^+$ requires 491.0770.

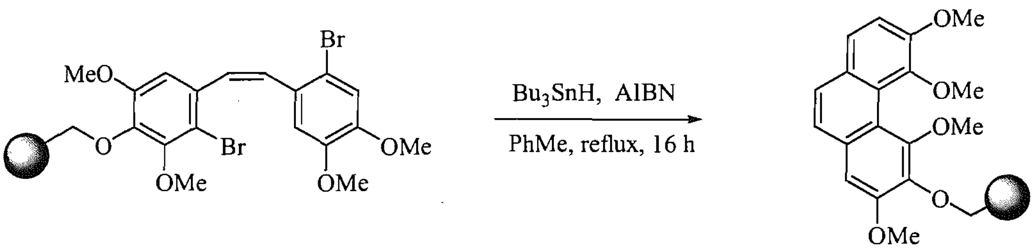
Resin coupled 3-Bromo-4-[2-(2-bromo-4,5-dimethoxy-phenyl)-vinyl]-2,6-dimethoxy-phenol **5.27**



To a suspension of phosphonium bromide **5.22** (6.88 g, 12.12 mmol) in tetrahydrofuran (20 mL) cooled to 0 °C was added potassium *tert*-butoxide (1.89 g, 16.83 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to 0 °C and the pre-swelled resin coupled 2-bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.57** (3.30 g, 0.50 mmol, 0.15 mmol / g resin) was added as a suspension in tetrahydrofuran (3 mL). The reaction mixture was stirred at room temperature for 24 hours. The resin beads were isolated by filtration, washed with THF (3 x 20 mL), methanol (3 x 20 mL) and dichloromethane (3 x 20 mL), then dried *in vacuo*.

IR	(ν_{max}, solid phase) 2922 (w), 1601 (w), 1494 (m), 1386 (w), 1209 (w), 1030 (w), 757 (s), 697 (vs) cm^{-1}.

Cyclisation of resin coupled 3-Bromo-4-[2-(2-bromo-4,5-dimethoxy-phenyl)-vinyl]-2,6-dimethoxy-phenol **5.27**

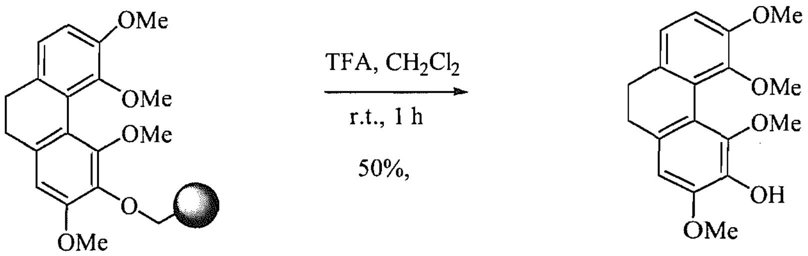


5.27

A stirred suspension of the swelled resin **5.27** from the aforementioned experiment (3.72 g, 0.56 mmol, 0.15 mmol /g resin) was heated at reflux with tributyltin hydride (4.20 g, 3.89 mL, 14.44 mmol) and AIBN (1.20 g, 7.32 mmol) in toluene (mL) for 16 hours. The mixture was then cooled to room temperature. The resin beads were isolated by filtration, washed with toluene (3 x 40 mL), methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), then dried *in vacuo*.

IR (ν_{max}, solid phase) 3026 (w), 1600 (w), 1493 (m), 1452 (m), 1343 (w), 1222 (m), 1127 (m), 757 (s) cm^{-1}.

2,4,5,6-Tetramethoxy-9,10-dihydro-phenanthren-3-ol **5.29**



5.29

$C_{18}H_{20}O_5$ (316)

Resin from the aforementioned experiment (3.42 g, 0.51 mmol, 0.15 mmol / g resin) was swelled in dichloromethane (15 mL) for 20 minutes, whereafter the cleavage coctail consisting of 95% distilled trifluoroacetic acid (19 mL), 2.5% dichloromethane (500 μL) and 2.5% triisopropylsilane (500 μL) was added. After 1 hour, the reaction mixture was filtered and the resin washed with dichloromethane (30 mL). The combined organic phases were concentrated *in vacuo* to a yellow oil, which was dissolved in DCM (20 mL) and washed with saturated sodium bicarbonate solution (3 x 60 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica gel, 5-10% ether in petrol) to a white solid **5.29** (80 mg, 0.25 mmol, 49%).

IR of the resin beads following cleavage:

IR	(ν_{max}, solid phase) 2924 (w), 1738 (w), 1493 (w), 1167 (w), 756 (w) cm^{-1}.

532:

MP	130-132 °C (ether / petrol).
IR	(ν_{max}, neat) 3359 (br. m), 2940 (w), 1600 (w), 1455 (s), 1266 (m), 1193 (m), 966 (m), 807 (w) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 279 (35900), 232 (52000) nm.

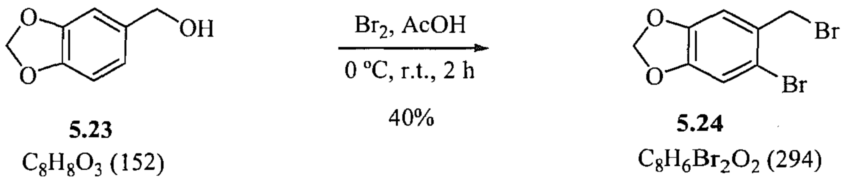
^{1}H NMR δ_H ppm (400 MHz, $CDCl_3$) 6.98 (1H, d, J = 8.5 Hz, ArH), 6.74 (1H, d, J = 8.0 Hz, ArH), 6.48 (1H, s, ArH), 5.67 (1H, ArOH), 3.82 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.48 (3H, s, OCH_3), 2.68-2.66 (2H, m, CH_2), 2.61-2.58 (2H, m, CH_2).

^{13}C NMR δ_C ppm (100 MHz, $CDCl_3$) 152.9 ($COCH_3$ (Ar)), 148.9 ($COCH_3$ (Ar)), 147.5 ($COCH_3$ (Ar)), 147.2 ($COCH_3$ (Ar)), 138.7 (C (Ar)), 133.8 (C (Ar)), 132.2 (C (Ar)), 127.4 (COH (Ar)), 121.9 (CH (Ar)), 119.1 (C (Ar)), 112.1 (CH (Ar)), 106.7 (CH (Ar)), 60.7 (OCH_3), 60.5 (OCH_3), 56.3 (OCH_3), 56.2 (OCH_3), 32.0 (2 H, s, CH_2), 31.5 (2H, s, CH_2).

LRMS (CI, m/z) 317 (MH^+, 100%), 269 (12%) amu.

HRMS (ES+, m/z) Found: $[M+Na]^+$: 339.1208, $C_{18}H_{20}O_5Na^+$ requires: 339.1209.

5-Bromo-6-bromomethyl-benzo[1,3]dioxole **5.24**



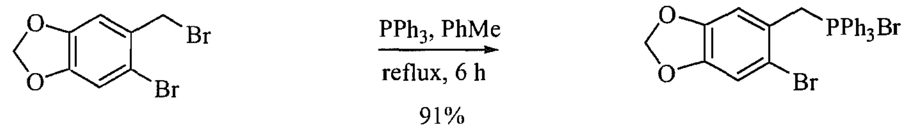
5.23
$C_8H_8O_3$ (152)

5.24
$C_8H_6Br_2O_2$ (294)

5-Bromo-6-bromomethyl-benzo[1,3]dioxole **5.24** was prepared by the method of Padwa *et al.* [86] To a stirred solution of piperonyl alcohol **5.23** (10.24 g, 67.37 mmol) in glacial acetic acid (20.53 mL) at 0 ° C was added bromine (4.15 mL) in glacial acetic acid (12.31 mL) dropwise over 30 min. After 2 hours at room temperature, the suspended creamy solid formed was isolated by suction filtration and washed with water (60 mL). The crude material was re-crystallised from petrol to afford the product as an orange solid [86,89] **5.24** (7.96 g, 27.05 mmol, 40%).

MP	81-83 °C (petrol), lit. 88-89 °C (hexanes). [86]
IR	(ν_{max}, neat) 2898 (w), 1619 (w), 1480 (vs), 1387 (s), 1236 (s), 1123 (s), 1033 (vs), 929 (vs), 665 (s) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 230 (18800), 264 (10700), 302 (9200).
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$) 7.02 (1H, s, ArH), 6.92 (1H, ArH), 6.00 (2H, OCH_2O), 4.56 (2H, s, CH_2).
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 149.2 (C (Ar)), 148.0 (C (Ar)), 130.4 (C (Ar)), 116.0 (CBr (Ar)), 113.5 (CH (Ar)), 110.9 (CH (Ar)), 102.5 (OCH_2O), 34.5 (CH_2).
LRMS	(CI, m/z) 295 ($M^+[^{81}Br]$, 26%), 293 ($M^+[^{79}Br]$, 24 %).

(6-Bromo-benzo[1,3]dioxol-5-ylmethyl)-triphenyl-phosphonium bromide **5.25**



5.24
$C_{26}H_{21}Br_2O_2P$ (556)

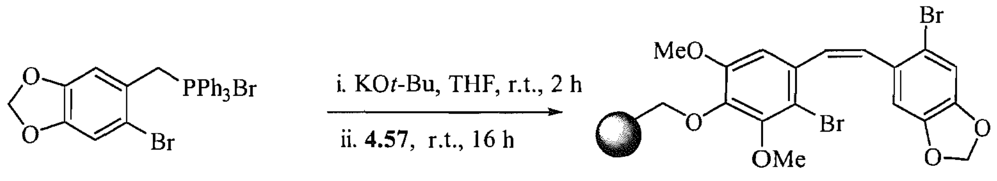
5.25
$C_{26}H_{21}Br_2O_2P$ (556)

5.24 (5.00g, 17.01 mmol), and triphenylphosphine (4.91g, 18.7 mmol), were dissolved in toluene (40 mL), and the mixture stirred at reflux for 6 hours. After cooling, the resulting white solid was collected by filtration and washed with cold toluene (2 x 40 mL) and petrol (3 x 20 mL) to yield the title compound **5.25** as a white solid [89] (8.84 g, 15.45 mmol, 91%).

MP	> 250 °C (toluene), lit. 278-280 °C (MeOH). [89]
IR	(ν_{max}, neat) 3010 (w), 2867 (w), 1586 (w), 1476 (s), 1431 (s), 1246 (s), 1110 (vs), 1033 (s), 920 (m) cm^{-1}.
UV	λ_{max} (ε_{max}, CH_2Cl_2) 302 (16200), 270 (19600), 231 (90800) nm.
^{1}H NMR	δ_H ppm (400 MHz, $CDCl_3$): 7.80 (3H, t, *J* = 7.5 Hz, ArH), 7.75-7.62 (12 H, m, 12 x ArH), 7.03 (1H, s, ArH), 6.80 (1H, s, ArH), 5.94 (2H, s, OCH_2O), 5.62 (2H, d, *J* = 13.6 Hz, CH_2P).
^{31}P-NMR	δ_P ppm (121 MHz, $CDCl_3$) 22.0
^{13}C NMR	δ_C ppm (100 MHz, $CDCl_3$) 149.4 (s, CO), 148.4 (s, CO), 135.5 (3 x CH (Ar)), 134.8 (d, *J* = 9.7 Hz, 6 x CH (Ar)), 130.7 (d, *J* = 13.6 Hz, 6 x CH (Ar)), 120.5 (d, *J* = 9.7 Hz, C (Ar)), 118.6 (d, *J* = 7.8, CH (Ar)), 118.0 (d, *J* = 85.5 Hz, 3 x C (Ar)), 113.0 (CBr (Ar)), 112.7 (s, CH (Ar)), 102.7 (OCH_2O), 31.6 (d, *J* = 48.6 Hz, CH_2P).
LRMS	(ES+, m/z) 477 ([M^+-[^{81}Br]], 100%), 475 ([M^+-[^{79}Br]], 97%).

Resin coupled 3-Bromo-4-[2-(6-bromo-benzo[1,3]dioxol-5-yl)-vinyl]-2,6-dimethoxy-phenol

5.28



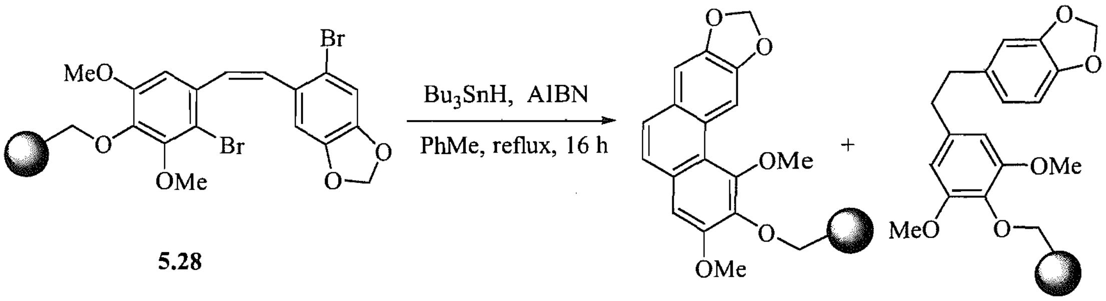
5.25 **5.28**

$C_{26}H_{21}Br_2O_2P$ (556)

To a suspension of phosphonium salt **5.25** (6.67 g, 12.02 mmol) in tetrahydrofuran (30 mL) cooled to -78 °C was added the potassium *tert*-butoxide (1.89 g, 16.83 mmol). After stirring at ambient temperature for 3 hours, the mixture was cooled to 0 °C and the pre-swelled resin coupled 2-bromo-4-hydroxy-3,5-dimethoxy-benzaldehyde **4.57** (3.30 g, 0.71 mmol / g resin, 2.34 mmol) was added as a suspension in tetrahydrofuran (30 mL). After 24 hours at room temperature the resin beads were isolated by filtration, washed with THF (3 x 20 mL), methanol (3 x 20 mL) and dichloromethane (3 x 20 mL), then dried *in vacuo*.

IR (ν_{max}, solid phase) 2931 (w), 1592 (w), 1473 (s), 1279 (w), 1240 (w), 1016 (m), 808 (w), 749 (m) cm^{-1}.

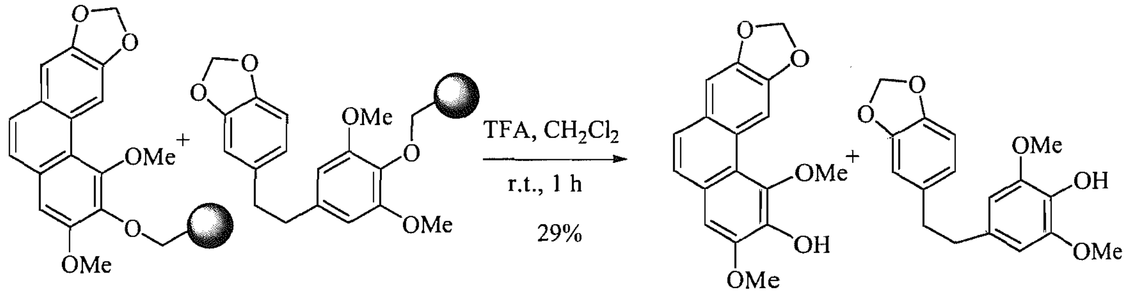
Cyclisation of 3-Bromo-4-[2-(6-bromo-benzo[1,3]dioxol-5-yl)-vinyl]-2,6-dimethoxy-phenol **5.28**



A stirred suspension of the aforementioned resin **5.28** (3.60 g, 0.54 mmol, 0.15 mmol / g resin), pre-swelled for 30 minutes in toluene (10 mL) with tributyltin hydride (4.20 g, 3.89 mL, 14.45 mmol) and AIBN (1.19 g, 7.23 mmol) was heated to reflux for 16 hours then mixture was cooled to room temperature. The resin beads were isolated by filtration, washed with toluene (3 x 40 mL), methanol (3 x 40 mL) and dichloromethane (3 x 40 mL), and dried *in vacuo*.

IR (ν_{max}, solid phase) 2921 (w), 1603 (w), 1494 (m), 1452 (m), 1221 (w), 1104 (w), 757 (m) cm^{-1}.

1,3-Dimethoxy-phenanthro[2,3-d][1,3]dioxol-2-ol **4.72** and 4-(2-Benzo[1,3]-dioxol-5-yl-ethyl)-2,6-dimethoxy-phenol **5.32**



4.72 **5.32**

$C_{17}H_{14}O_5$ (298) $C_{17}H_{18}O_5$ (302)

Resin from the aforementioned experiment (3.37 g, 0.15 mmol / g resin, 0.51 mmol) was swelled in dichloromethane (5 mL) for 20 minutes, whereafter the cleavage cocktail consisting of 95% distilled trifluoroacetate (19 mL), 2.5% dichloromethane (0.5 mL) and 2.5% triisopropylsilane (0.5 mL) was added. After 1 hour, the reaction mixture was filtered and the resin washed with dichloromethane (30 mL). Concentration of the combined organic phases *in vacuo* yielded a yellow oil, which was dissolved in DCM (10 mL) and washed with saturated sodium bicarbonate solution (3 x 40 mL). Concentration *in vacuo* yielded a yellow oil, which was purified by column chromatography (silica gel, 10-20% ether in petrol) to a white solid which contained both products **4.72** and **5.32** in a 1:1 ratio (46 mg, 0.15 mmol, 29%). These products proved inseparable by HPLC.

IR of the resin beads following cleavage:

IR (ν_{max}, solid phase) 2924 (w), 1738 (w), 1493 (w), 1167 (w), 756 (w) cm^{-1}.

4.72:

IR (ν_{max}, neat) 3427 (br. m), 2931 (w), 1618 (w), 1461 (vs), 1234 (m), 1095 (m), 925 (m) cm^{-1}.

UV λ_{max} (ε_{max}, CH_2Cl_2) 285 (29000), 258 (67000) nm.

^{1}H NMR δ_H ppm (400 MHz, $CDCl_3$) 8.83 (1H, s, Ar$\underline{H}$), 7.41 (1H, s, Ar$\underline{H}$), 7.17 (2H, s, Ar$\underline{H}$), 6.65 (1H, s, Ar$\underline{H}$), 6.01 (2H, s, OC$\underline{H}_2$O), 5.89 (1H, s, ArO$\underline{H}$), 3.96 (3H, s, OC$\underline{H}_3$), 3.87 (3H, s, OC$\underline{H}_3$).

^{13}C NMR δ_C ppm (100 MHz, $CDCl_3$) 146.8 ($\underline{C}OCH_3$), 146.4 ($\underline{C}OCH_3$), 146.3 ($\underline{C}$ (Ar)), 143.8 ($\underline{C}$ (Ar)), 135.5 ($\underline{C}$ (Ar)), 128.5 ($\underline{C}$ (Ar)), 125.2 ($\underline{C}$H (Ar)), 125.0 ($\underline{C}$H (Ar)), 118.0 ($\underline{C}$ (Ar)), 108.9 ($\underline{C}$ (Ar)), 105.1 ($\underline{C}$H (Ar)), 104.7 ($\underline{C}$H (Ar)), 101.1 (O$\underline{C}H_2$O), 100.7 ($\underline{C}$ (Ar)), 59.9 (O$\underline{C}H_3$), 56.0 (O$\underline{C}H_3$).

LRMS (CI, m/z) 298 ([M$^+$, 100%), 283 (44%), 126 (20%).

HRMS (ES+, m/z) Found: [M+Na]$^+$: 321.0733; $C_{18}H_{20}O_5$ Na$^+$ requires: 321.0733.

5.32:

IR (ν_{max}, neat) 3427 (br. w), 2931 (w), 1618 (w), 1461 (vs), 1234 (m), 1095 (m), 925 (m) cm^{-1}.

UV λ_{max} (ε_{max}, CH_2Cl_2) 285 (29000), 258 (68000) nm.

^{1}H NMR δ_H ppm (400 MHz, $CDCl_3$) 7.11 (1H, s, Ar$\underline{H}$), 6.98 (1H, s, Ar$\underline{H}$), 6.65-6.51 (1H, m, Ar$\underline{H}$), 6.28 (2H, s, Ar$\underline{H}$), 6.01 (2H, s, OC$\underline{H}_2$O), 5.83 (1H, s, ArO$\underline{H}$), 3.87 (3H, s, OC$\underline{H}_3$), 3.77 (3H, s, OC$\underline{H}_3$), 2.72 (4H, s, C$\underline{H}_2$).

^{13}C NMR δ_C ppm (100 MHz, $CDCl_3$) 147.7 ($\underline{C}$ (Ar)), 146.8 ($\underline{C}$ (Ar)), 138.8 ($\underline{C}$ (Ar)), 132.7 ($\underline{C}$ (Ar)), 126.4 ($\underline{C}$ (Ar)), 121.7 ($\underline{C}$H (Ar)), 121.2 ($\underline{C}$ (Ar)), 108.9 ($\underline{C}$ (Ar)), 105.4 (2 x $\underline{C}$H (Ar)), 105.1 ($\underline{C}$H (Ar)), 104.7 ($\underline{C}$H (Ar)), 101.1 (O$\underline{C}H_2$O), 59.9 (O$\underline{C}H_3$), 56.2 (O$\underline{C}H_3$), 38.3 ($\underline{C}H_2$), 37.9 ($\underline{C}H_2$).

LRMS (CI, m/z) 302 (M$^+$, 18%), 154 (100%), 207 (70%).

HRMS (ES+, m/z) Found: [M+Na]$^+$: 325.1046; $C_{17}H_{18}O_5Na^+$ requires: 325.1046.

Chapter 7 List of References

7 *References*

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