University of Southampton

Intramolecular Radical Additions to Aromatic Compounds

By

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A Thesis submitted for the degree of Doctor of Philosophy

Department of Chemistry
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ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

Intramolecular radical additions to aromatic compounds

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This thesis is concerned with the development of cyclisation strategies that allow entry to polycyclic heterocycles and medium sized ring systems. Radical additions to pyridines are developed and methodologies explore the differences between the homolysis of C-Br and C-I bonds. Mechanisms are described for the unexpected *ipso* additions to the pyridines.

Work towards the synthesis of the stegnans and dimethylgomisin illustrates the attempts to utilise the *ipso* addition to form medium sized ring systems.

A new method of synthesising these medium sized ring systems is discussed. Progress towards a general methodology is described and shows the opportunities for which it could be utilised.

A literature review of the synthesis of heterocycles via radical cyclisations is presented.

Contents

Preface

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

Acknowledgements

Firstly I would like to thank David Harrowven and the University of Southampton for the opportunity to do this research and for having faith in my abilities when I had so many doubts myself. I would like to thank David and John Mellor for all their advice and help during the past three years.

Four people that I need to thank for all their hard work are Neil Wells, Joan Street, John Langley and Julie Herniman for everything they do. I can't thank them enough for the time they have spent keeping the spectrometers running and helping me.

Thanks also need to be said to my family for all their support during my extended time at university. Sorry it took so long but we are almost there now and hopefully I can back all of the time and patience expended on me.

Finally I wish to thank some very important people. The group I have worked in and the friends around me. I especially wish to mention Michael Nunn, Mathieu Carpentier, Ben Sutton, Heather Bourne, Stuart Flanagan, Melloney Tyte, Tim Woodcock. Thanks to them for all of the great times we have spent together over the years.

Thank you also to all of my friends especially the guys down the Gate. I hope that they're still winning.

There are some other people that I should thank for their encouragement and help. Firstly I would like to thank Maugan Higgins for his help and advice over the years. I would also like to thank two mentors of mine, Dr Spencer and Farid Azizian. Both of them have helped me to fulfil a dream that they helped to form in my mind. Thank you for being there even when I wasn't.

"It is a strange fate that we should suffer so much fear and doubt over so small a thing. Such a little thing."

Boromir, The Fellowship of the Ring

Abbreviations

AIBN	azo-*iso*-butyronitrile
amu	atomic mass units
APCI	atmospheric pressure chemical ionisation
aq.	aqueous
Ar	aryl
Bn	benzyl
Bu	butyl
CHN	combustion analysis
CI	chemical ionisation
conc.	concentration
COSY	correlated spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EI	electron impact
eq.	equivalents
Et	ethyl
FT	Fourier Transform
h	hours
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectra
IR	infra red
lit.	literature
LRMS	low resolution mass spectra
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
M	molar
mmol	millimoles
Me	methyl
min	minutes
NMR	nuclear magnetic resonance

Ph	phenyl
ppm	parts per million
py	pyridine
THF	tetrahydrofuran
TBDMS	*tert*-butyldimethylsilyl
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
UV	ultra violet

Chapter 1

Introduction

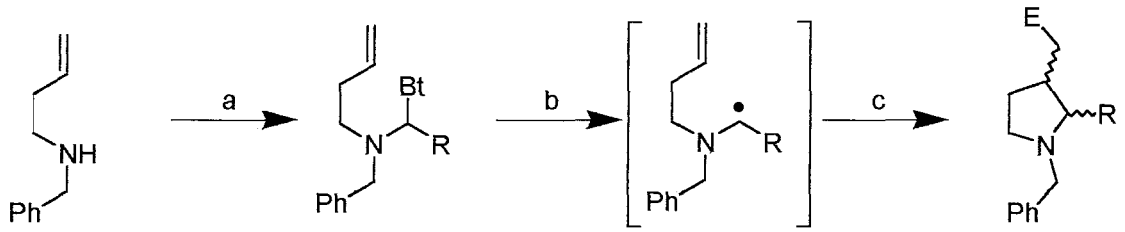
1.0 Introduction

Radical cyclisation strategies for the synthesis of heterocycles are now a well established and commonly used. The vast majority of radical cyclisations use tributyltin hydride as a mediator but other methods are becoming more common. This review focuses on the use of radical cyclisations to form nitrogen-containing heterocycles. [1,2]

1.1 Synthesis of heterocycles by radical cyclisation

1.1.1 Synthesis of pyrrolidines and piperidines

The synthesis of pyrrolidines by 5-*exo*-trig radical cyclisation, provides a common route to these ring systems. The radical can be formed at various positions in relation to the *N*-heteroatom. Cyclisation of radicals α- to the *N*-heteroatom have been widely studied and a range of pyrrolidines have been prepared in this way. For example by samarium diiodide mediated 5-*exo*-trig cyclisation *N*-(α-benzotriazolylalkyl)alkenylamines, generally proceed smoothly (Scheme 1).

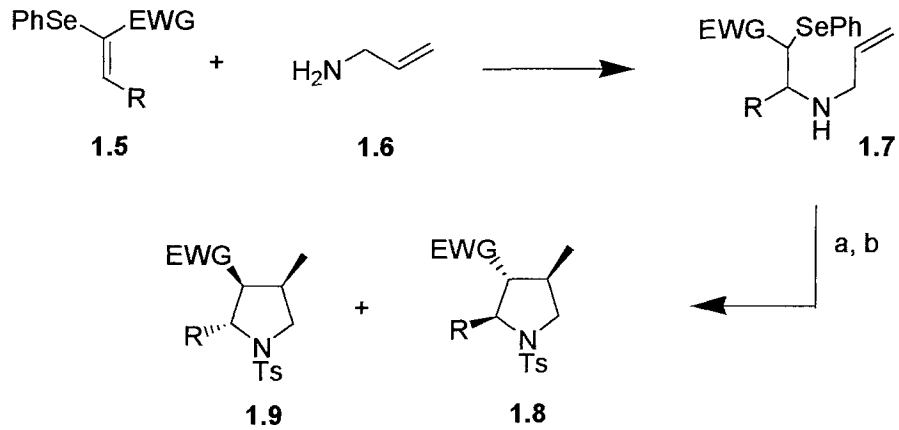


1.1 **1.2** **1.3** **1.4**

Reagents and Conditions: **a.** RCHO, BtH; **b.** SmI_2, THF, HMPA; **c.** E^+
Bt = 1- or 2- Benzotriazolyl

Scheme 1: Cyclisation of (benzotriazolylalkyl)alkenylamines

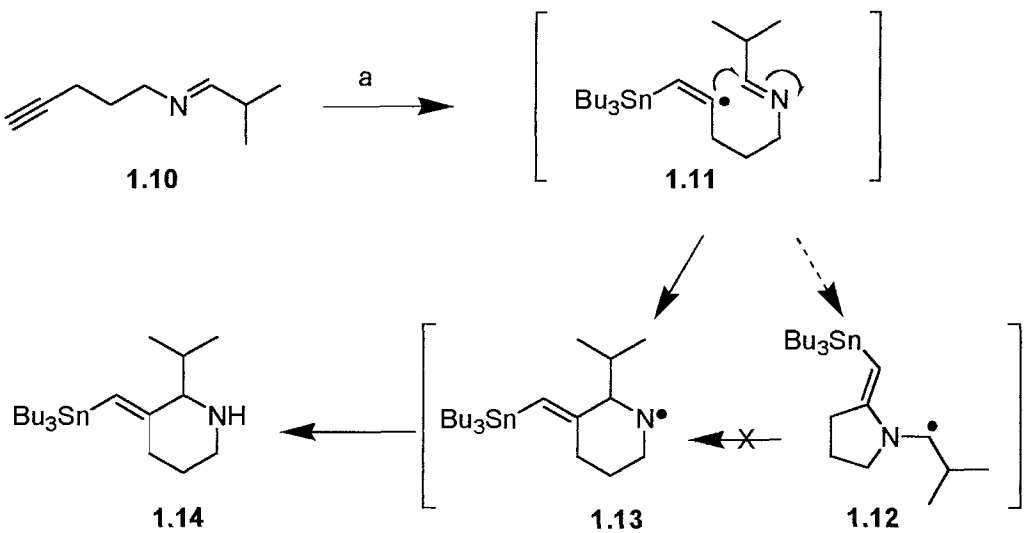
More popular are radical reactions from the carbon centre β to the nitrogen atom. For instance, a useful synthetic procedure uses Michael type addition reactions of allyl or propargyl-amines to α-phenylselenide-α,β-unsaturated esters, amides, ketones, nitriles and sulfones to yield radical precursors. The phenylselenide group may then be abstracted by tris(trimethylsilyl)silane with triethylborane as initiator. The resulting radical intermediates then undergo 5-*exo*-trig (or 5-*exo*-dig) cyclisations to give the corresponding pyrrolidine (or dihydropyrrole) derivatives (Scheme 2).[3]



Reagents and Conditions: **a.** $(TMS)_3SiH$, Et_3B, O_2, PhMe;
b. TsCl, Et_3N, two diastereoisomers, 36 - 89 %

Scheme 2: Radical cyclisation using phenylselenide groups

An example of *endo* cyclisation leading to piperidines has been reported involving the cyclisation of alkenyl radicals onto an imine.[4] The alkenyl radical was generated by addition of $Bu_3Sn^{\bullet}$ to a terminal alkyne. The resulting alkenyl radical then underwent a 6-*endo* cyclisation leading to **1.13**. The alternative pathway, 5-*exo*-trig cyclisation to **1.12** and rearrangement to **1.13** was ruled out as cyclisation to the imine nitrogen is disfavoured (Scheme 3).

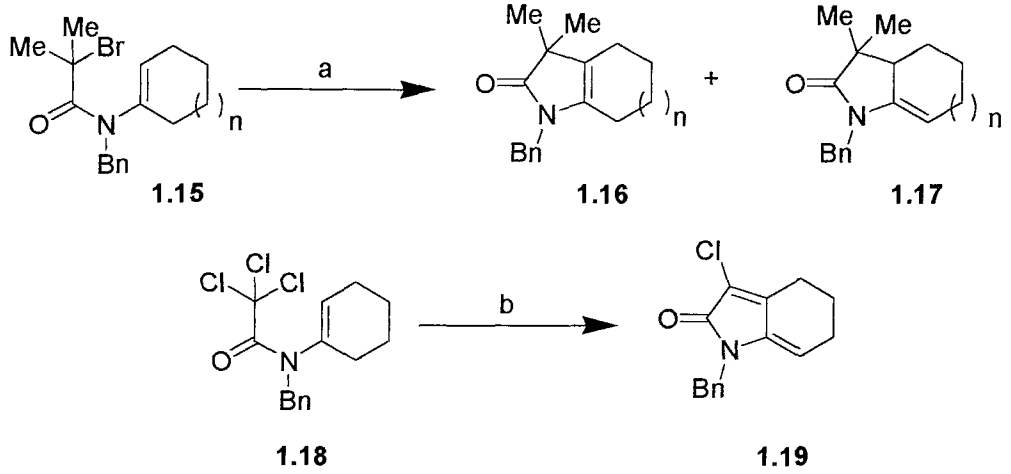


Reagents and Conditions: **a.** Bu_3SnH, AIBN, PhH, Δ, 27 - 43 %

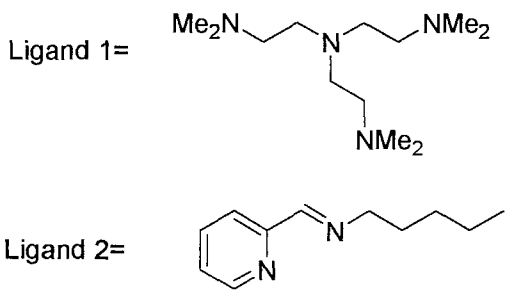
Scheme 3: Radical cyclisation using the addition of tributyltin radical

Clark *et al.* have shown that copper(I) reagents can may be used instead of toxic tributyltin hydride in some instances. Formation of di- and tetrahydroindanones by 5-

endo-trig radical cyclisation provides an excellent illustration of this powerful methodology (Scheme 4).[5]

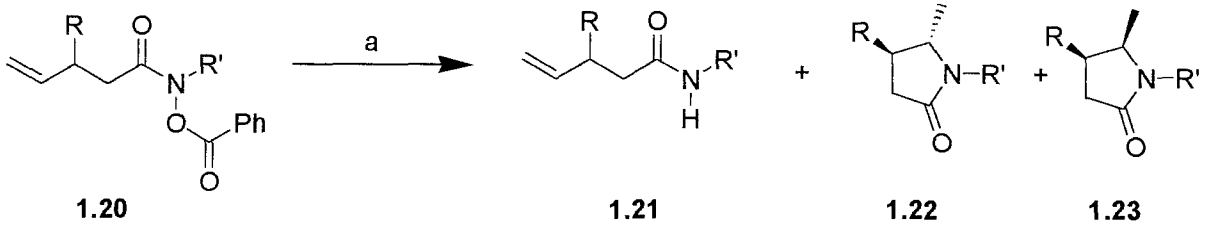


Reagents and Conditions: **a.** 30 mol% CuBr(*ligand 1*), DCM, rt, 20 mins; **b.** 1 eq. CuCl (*ligand 2*), DCM, 40°C, 48 hrs



Scheme 4: Use of copper mediated reactions

Cyclisation involving *N*-centered radicals have also been investigated by Clark *et al.* In most cases only a small amount of reduced material is isolated.[6] Yields are moderate in most cases but the stereoselectivity of these reactions show up effectiveness of radical cyclisation reactions.



Reagents and Conditions: **a.** Bu_3SnH, AIBN, PhMe, 110°C, 8 hrs

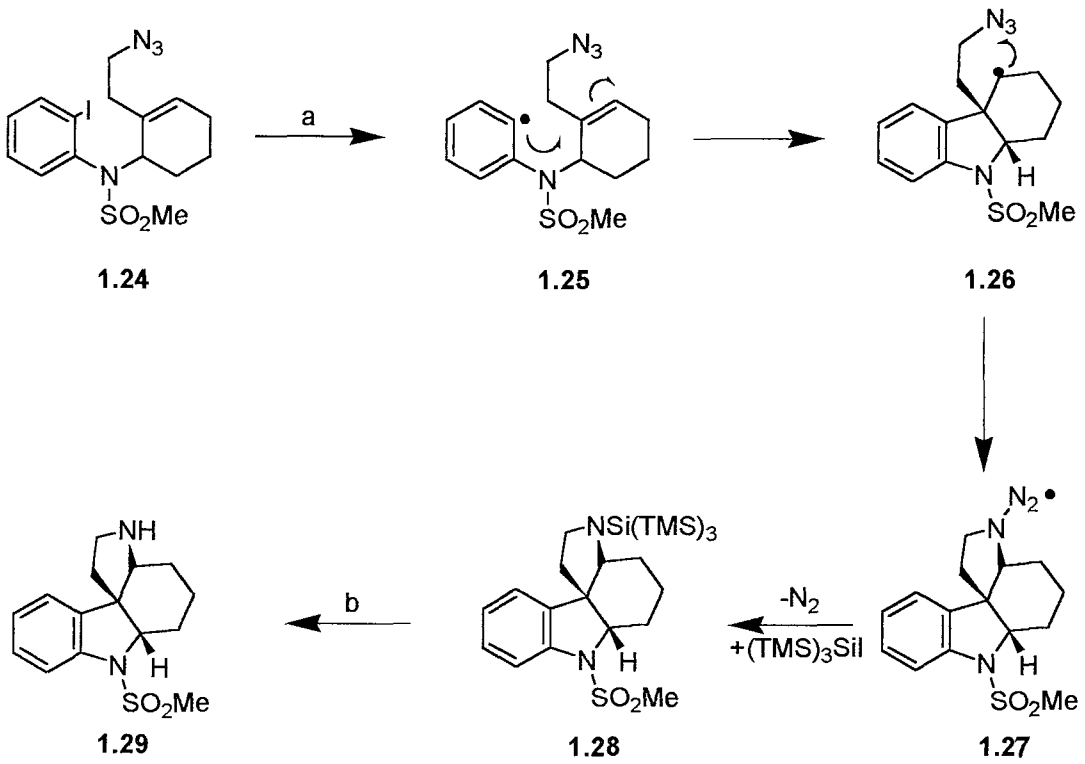
Scheme 5: 5-*exo*-trig cyclisations involving *N*-centered radicals

R	R'	Cyclised/reduced	Yield of **1.22** +**1.23**	d.e.
Me	Me	17:1	47%	17%
Me	Bn	12:1	53%	23%
Ph	Me	3.5:1	22%	43%

Table 1: Results of radical cyclisation

1.1.2 Synthesis of related condensed heterocycles

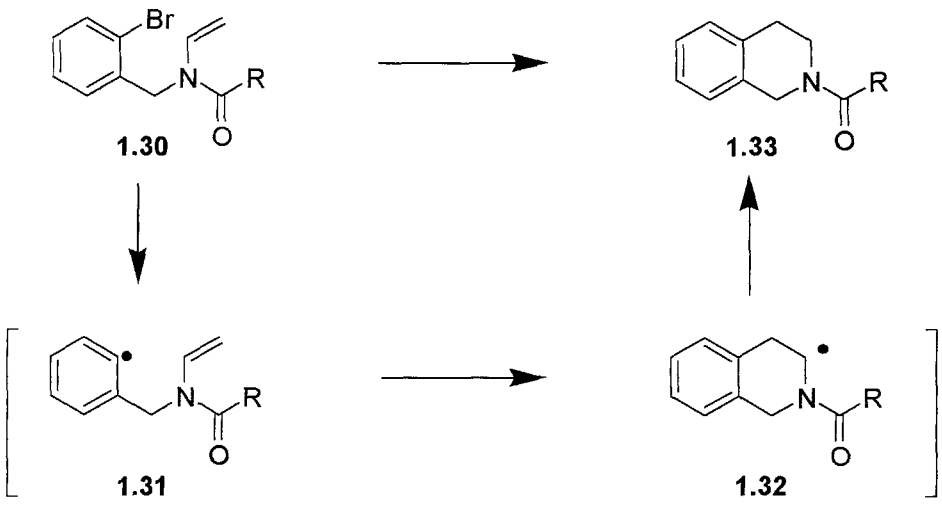
The cyclisation of aryl radicals onto unsaturated side chains containing nitrogen provides one of the most commonly used radical methodologies for the synthesis of nitrogen heterocycles. An interesting example has been reported for the stereoselective synthesis of the tetracyclic core of the *Aspidosperma* alkaloids. [7,8] This procedure produces the two nitrogen heterocycles, in a single step, and three stereogenic centres with the correct relative stereochemistry. This cyclisation of aryl radical **1.25** leads to alkyl radical **1.26**. A second 5-*exo*-trig cyclisation to the proximal azide then provides radical **1.27**. Lose of nitrogen and the addition of water leads to the product **1.29** (Scheme 6). This methodology has been exploited in the synthesis of (±)-γ-lycorane and (+)-7-dexoypancrastistatin.



Reagents and Conditions: **a.** $(TMS)_3SiH$, AIBN, PhH, Δ; b) H_2O, 83 %

Scheme 6: Formation of the aspidosperma skeleton

Aryl radical cyclisation reactions to form small rings normally display a strong preference for the *exo* mode rather than the *endo* mode.[9,10] However this is reversed when two or more adjacent sp^2 hybridised atoms are placed in the chain tethering the radical donor and acceptor. An example of this switch occurs where *N*-(*o*-bromobenzyl)enamide precursor are subjected to radical forming conditions. Thus, on treatment with tributyltin hydride the precursor **1.30** undergoes a 6-*endo*-trig cyclisation to yield the α-aminoalkyl radical **1.32**. The only cyclised products observed in this case was tetrahydroisoquinoline **1.33** (Scheme 7). Indeed the authors found no evidence of products derived form the 5-*exo*-trig cyclisation mode in many related examples.

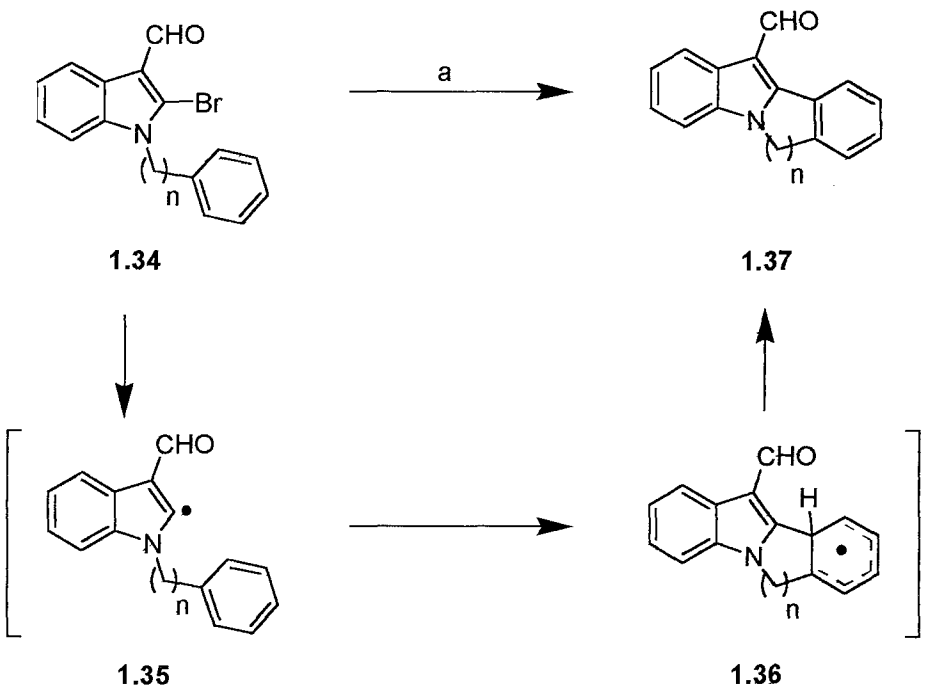


Reagents and Conditions: **a.** Bu_3SnH , 1,1' - azobis(cyclohexanecarbonitrile), PhMe, Δ

R = Et (80 %) and R = H (43 %)

Scheme 7: 6-*endo* cyclisation

Cyclisations of 2-indolyl radicals onto arenes have been used to good effect in the synthesis of many tetracyclic ring systems. For example Jones *et al.* showed that 5-, 6- and 7-membered rings could be constructed in this way through cyclisation of an indolyl radical to the *ortho* carbon of a pendant arene. Notably, in each case the radical intermediate **1.36** underwent rearomatisation to **1.37** through loss of a hydrogen atom even though tributyltin hydride was used as the mediator. In each reaction some uncyclised material, *N*-(phenylalkyl)indole-3-carbaldehyde, was observed in the product mixture.[11-13]

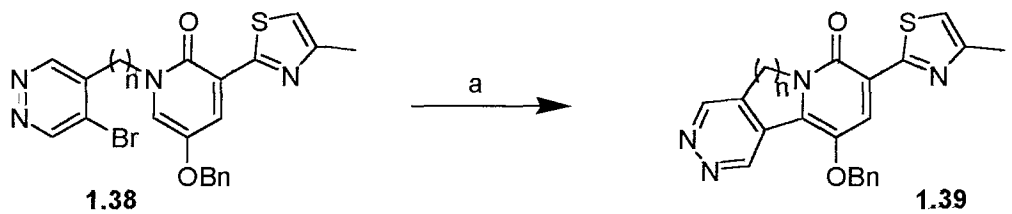


Reagents and Conditions: **a.** Bu_3SnH (syringe pump addition), AIBN, MeCN, Δ

n = 1, 25 %; n = 2, 65 %; n = 3, 37 %

Scheme 8: Cyclisation of indol-2-yl radicals to proximal arenes

In a related series of cyclisations leading to tricyclic pyridones, Bu_3SnH-mediated cyclisations facilitate by 5-, 6- and 7- *exo*-trig ring closure reactions of pyridazinyl radicals onto the pyridone ring (Scheme 9). [14,15]



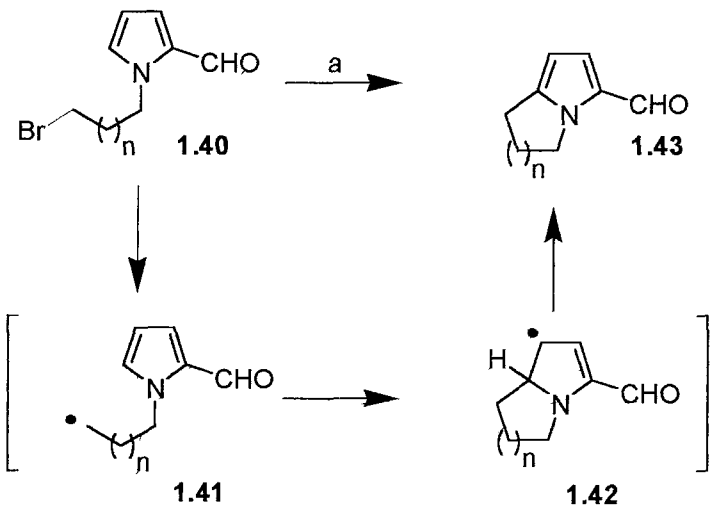
Reagents and Conditions: **a.** Bu_3SnH, AIBN, PhH, Δ

n = 1, 37 %; n = 2, 35 %; n = 3, 50 %

Scheme 9: Radical cyclisation to pyridones

Cyclisation of *N*-(ω-alkyl) radicals onto heteroarenes has been used to annulate pyrroles, imidazoles and indoles.[16-18] The synthesis of [1,2-α]fused pyrroles, *viz* **1.40** to **1.41**, provides an example of such a reducing radical cyclisations mediated by Bu_3SnH. Homolysis of the alkyl bromide **1.40** with Bu_3SnH first gives *N*-(ω-

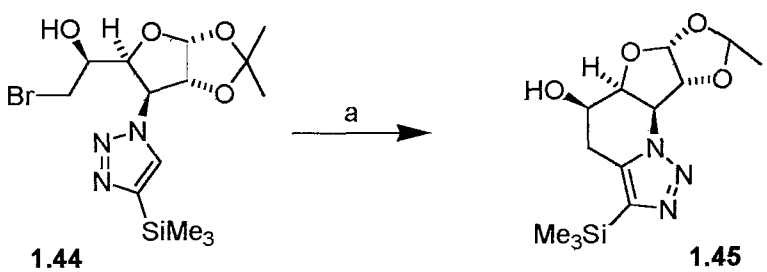
alkyl)pyrrole radical **1.41**. This undergoes cyclisation onto the pyrrole ring to form the allyl radical **1.42**. A hydrogen atom is then lost to yield the [1,2]-α-fused pyrroles **1.43** in moderate yields (28 – 55 %) (Scheme 10).



Reagents and Conditions: **a.** Bu_3SnH (syringe pump addition), AIBN, MeCN, Δ, (n = 1, 28 %; n = 2, 55 %; n = 3, 40 %)

Scheme 10: Cyclisation onto pyrroles

This methodology has been extended to triazines. Thus, a 6-*exo*-trig cyclisation of sugar derived bromide **1.44** onto the proximal 1,2,3–triazole yielded tetracycle **1.45** (Scheme 11).

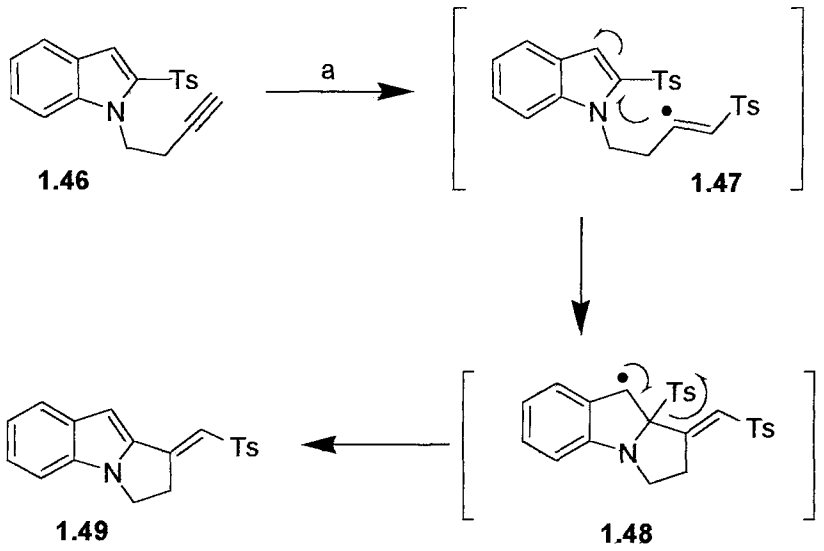


Reagents and Conditions: **a.** $(TMS)_3SiH$, AIBN, PhMe, Δ, 36 %

Scheme 11: Cyclisation onto triazines

The synthesis of [1,2]-α-fused indoles from *N*-(ω-alkynyl)indoles can be effected using catalytic tosyl radicals. Conversion of the alkynyl precursor starts with the addition of tosyl radical to the alkyne, *viz* **1.46** to **1.47**. This addition is followed by the cyclisation of the vinyl radical **1.47** to the indole leading to benzyl radical **1.48**. Loss of a tosyl radical then leads to rearomatisation and propagation of the chain

reaction. The protocol was also used for 6-membered ring cyclisations and with *N*-(ω-alkenyl)indoles (Scheme 12).

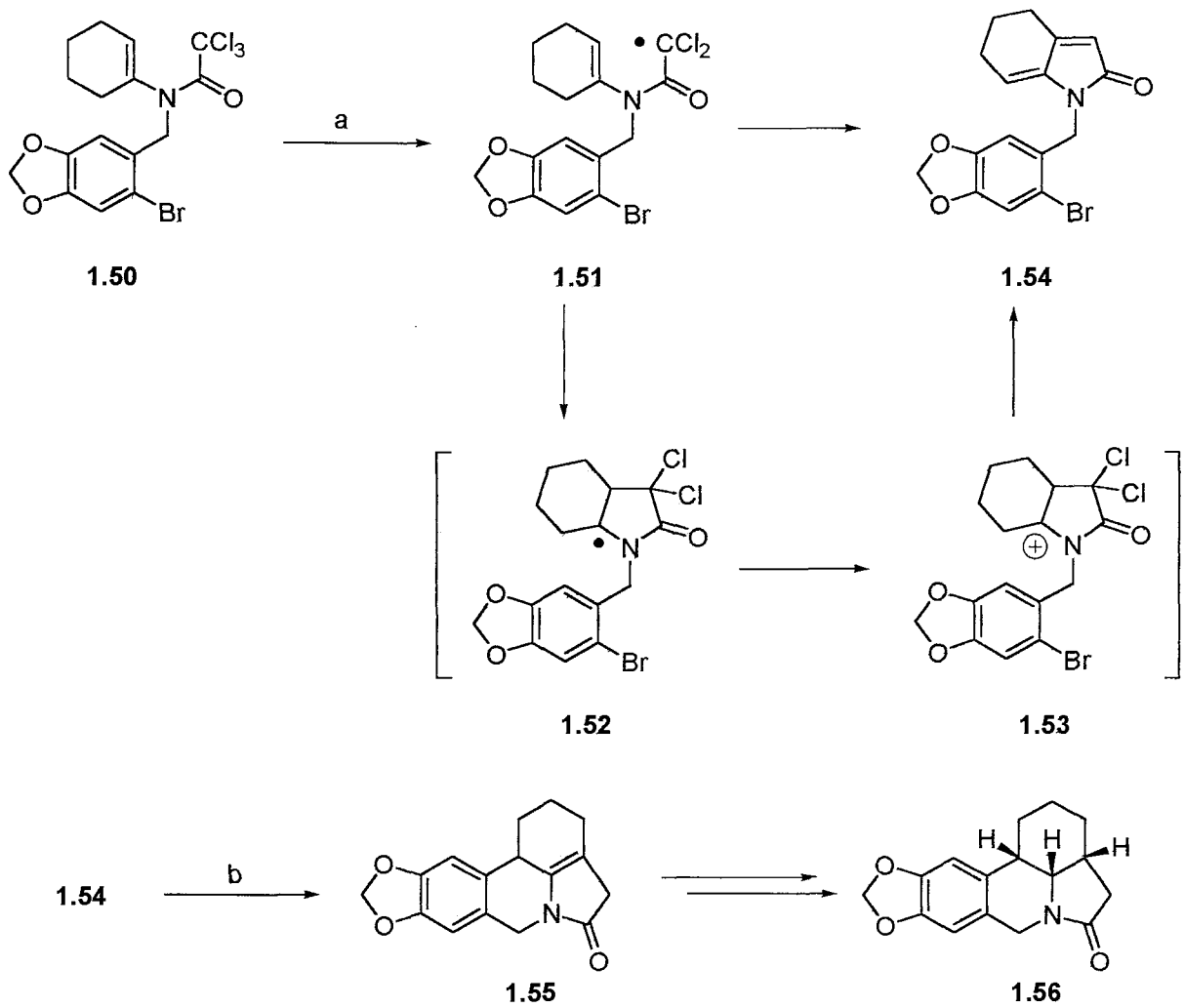


Reagents and Conditions: **a.** TsSePh (0.25 eq.), AIBN, PhH, Δ, 72 -89 %

Scheme 12: Formation of fused indoles

1.1.3 Natural Product Total Synthesis

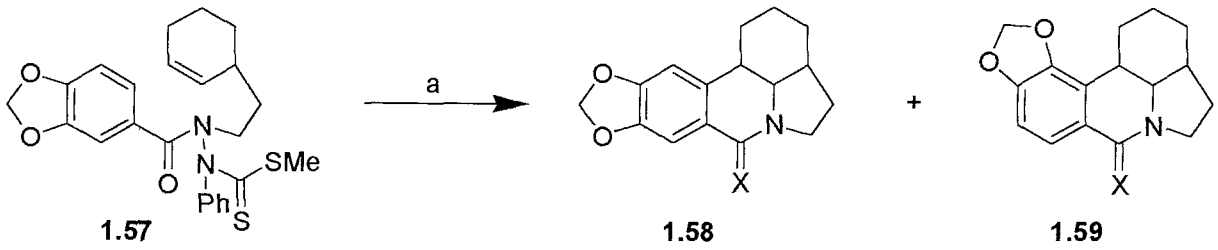
The challenge of natural product total synthesis has continued to inspire imaginative and ingenious routes to a host of complex ring systems. Radical cyclisation strategies can frequently be used to circumvent tedious functional group interconversions or problems of racemisations. Zard *et al.* exploited two radical cyclisation reactions in a synthesis of (±)-γ-lycorane.[19,20] In their first cyclisation they used nickel to generate the α-amidyl radical **1.51** from the precursor **1.50**. Unusually, this underwent a 5-*endo*-trig cyclisation to the proximal alkene to form product **1.54**. The second cyclisation used tributyltin hydride to induce a 6-*endo*-trig cyclisation of **1.54** to pyrrolidone **1.55** (Scheme 13).



Reagents and Conditions: **a.** Ni, NaOAc, propan-2-ol, Δ, 60%; **b.** Bu_3SnH, AIBN, PhMe, Δ, 65%

Scheme 13:Formation of (±)-γ-lycorane

Zard *et al.* also looked into an alternative route to this compound, which still exploited two radical cyclisations. In this case they found that the reaction proceeded but with a second regioisomer competing with their target material (Scheme 14).



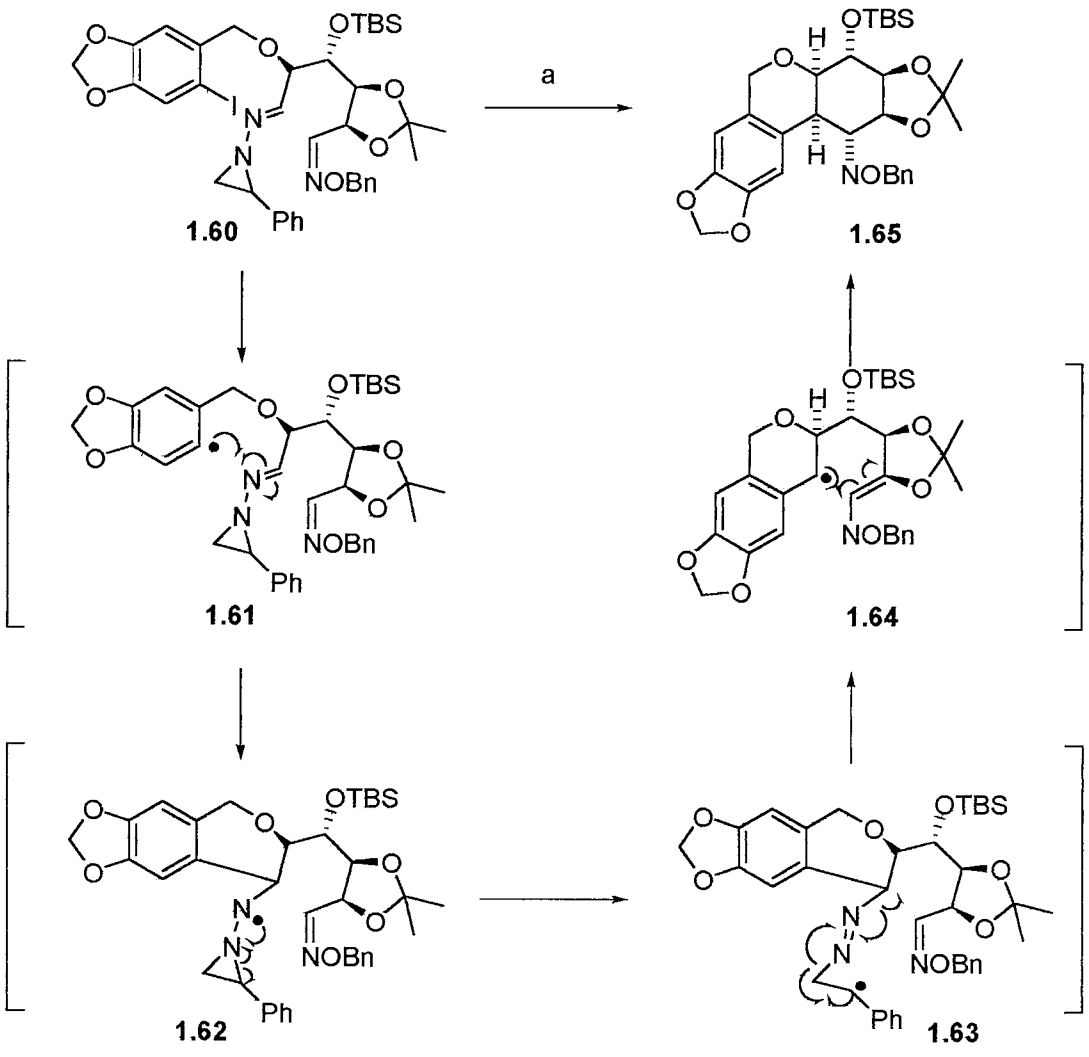
1.57 1.58 1.59

Reagents and Conditions: **a.** Bu_3SnH (1.2 eq.), 1,1'-azobis(cyclohexane)carbonitrile (1 eq.), PhMe, Δ,

X=O (63%)
$X=CH_2$ (100%)

Scheme 14: Alternative route to (±)-γ-lycorane

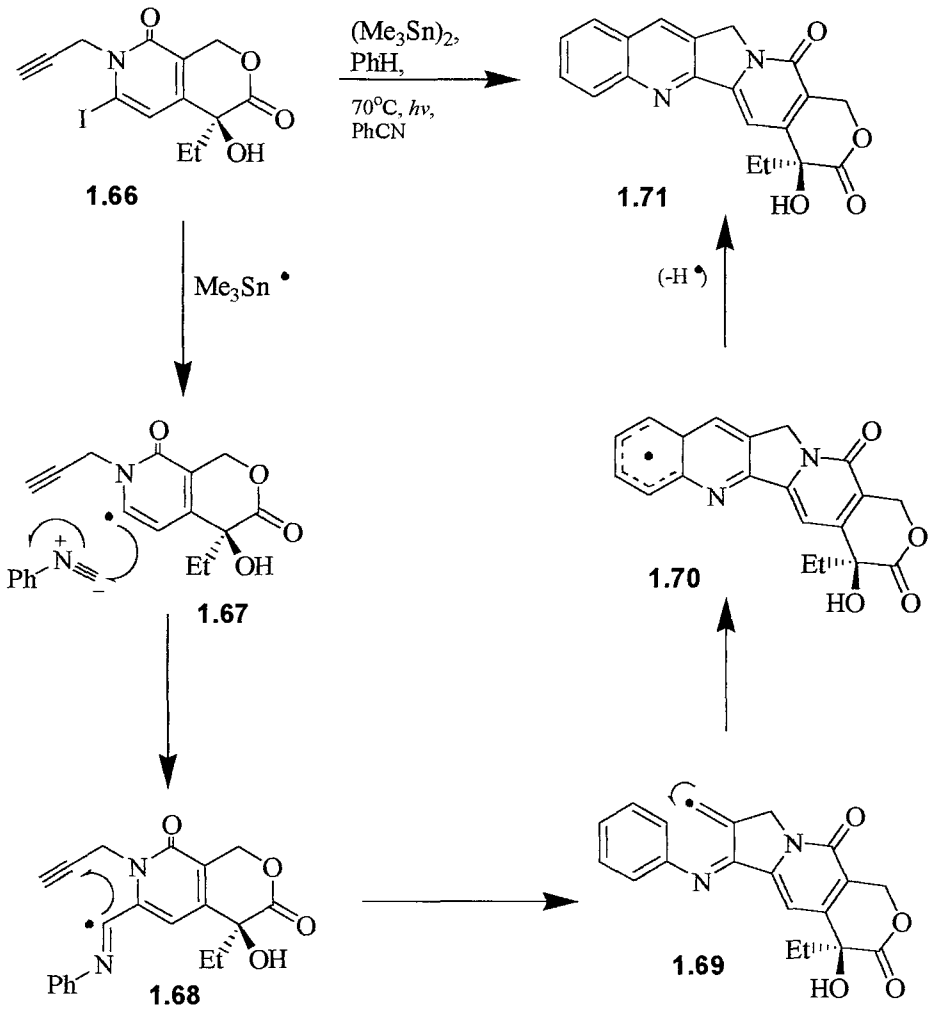
A Ph_3SnH-mediated radical cyclisation is used as a key step in the synthesis of the naturally occurring alkaloid (+)-7-deoxypancrastistatin.[21] The synthesis exploits a protocol developed by Kim *et al.* in which an aryl radical **1.61** cyclises onto the imine bond of an arizidinyl hydrazone to yield the *N*-centered radical intermediate **1.62**. This intermediate breaks down with loss of nitrogen and styrene to yield a new *C*-centered radical **1.64**. cyclise again. Cyclisation to the proximal alkene, and hydrogen atom abstraction, yield **1.65** (Scheme 15).



Reagents and Conditions: **a.** Ph_3SnH, AIBN, PhH, Δ, loss of N_2, and styrene, 78%

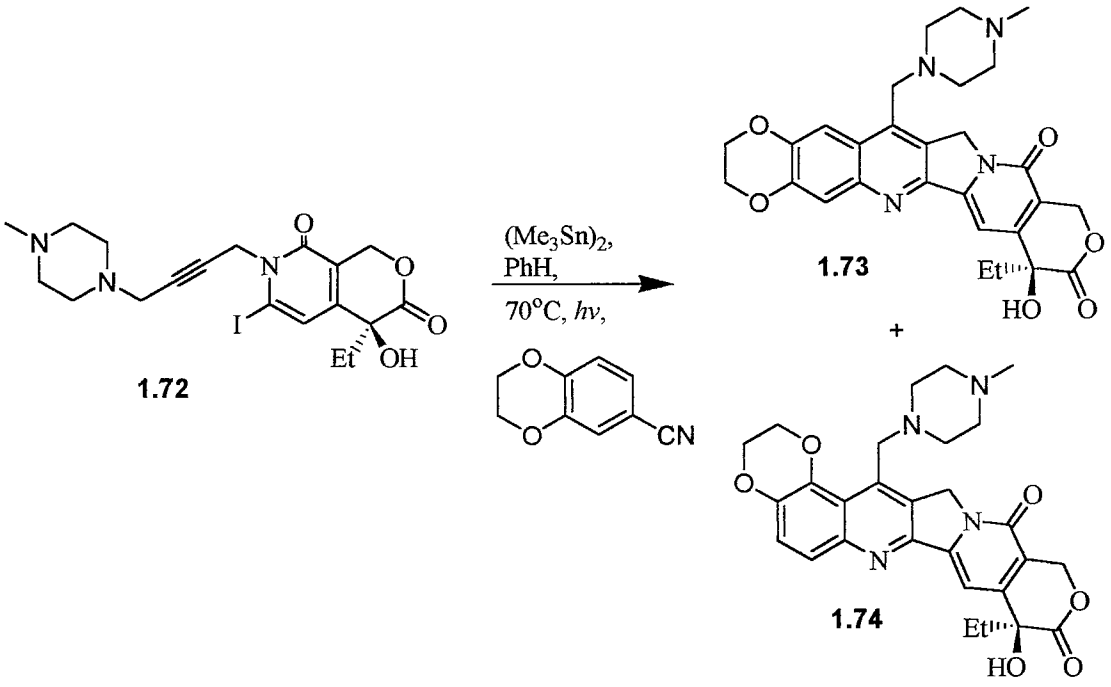
Scheme 15: A tandem radical cyclisation en route to (+)-7- deoxypancrastistatin

To provide an entry to the camptothecin family of alkaloids, Curran *et al.* developed a novel radical annulation protocol employing isonitriles.[22] This allowed the target and a number of analogs to be synthesised by a short and efficient route (Scheme 16).



Scheme 16: Formation of camptothecin

This elegant route was also applied successfully in a synthesis of GI – 147211C by modifying the alkyne and the isonitrile used. **1.72** provided an inseparable 3:2 mixture of the desired product **1.73** and its regioisomer **1.74** in a conjoined 57 % yield (Scheme 17).



Scheme 17: Formation of GI – 147211C

1.2 Medium sized heterocycles

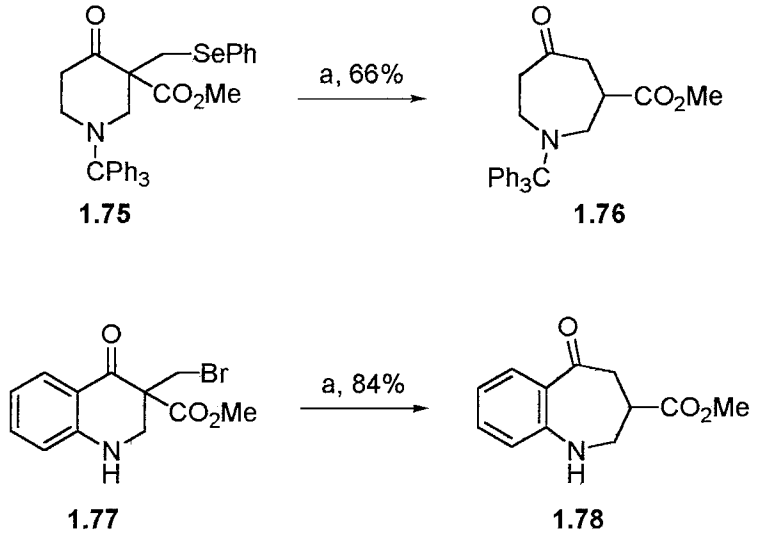
1.2.1 Introduction

Many five and six membered ring systems have been formed by radical cyclisation but many natural products contain rings of other sizes, in particular larger rings. In this short review we shall discuss some of the ways in which medium ring synthesis has been addressed using radical cyclisation reactions.[23] Much of this area involves oxygen heterocycles but some work towards nitrogen containing heterocycles is also highlighted.

1.2.2 Alkoxy Radical Fragmentations

Alkoxy radicals may be generated by cyclisation of a reactive carbon centered radical with a carbonyl group. Fragmentation of the alkoxy radical is generally favourable as it leads to the carbonyl group and a more stable carbon centered radical. When the alkoxy radical is situated at a ring fragmentation may induce ring enlargement. Groups such as esters, halogens and even alkyl groups can help to direct and promote fragmentation as these stabilise the product radical formed.

Dowd *et al* have used this process to great effect to form seven – membered nitrogen heterocycles (Scheme 18). [24-26]



1.75 **1.76**

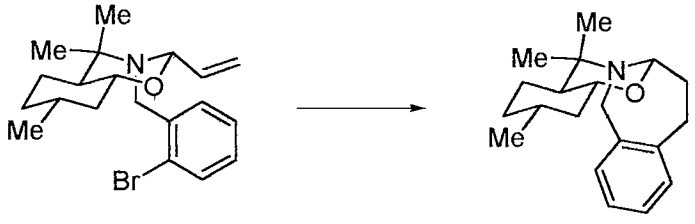
1.77 **1.78**

Reagents and Conditions: **a.** Bu_3SnH (1.1 eq.), AIBN, PhH, 80°C

Scheme 18: Formation of seven membered rings

1.2.3 Aromatic Radical Cyclisations

Aryl radicals, because they have greater s-character, are very reactive radicals and rapidly react with unsaturated carbon atoms. Aryl radicals are widely employed for the formation of benzo–fused ring systems due to their high cyclisation rates. Pedrosa have reported an unusual 7-*endo*-trig aryl radical cyclisation to form the benzazepine derivative **1.80** from precursor **1.79**.[27] No product derived from a 6-*exo*-trig cyclisation was isolated in this case (Scheme 19).



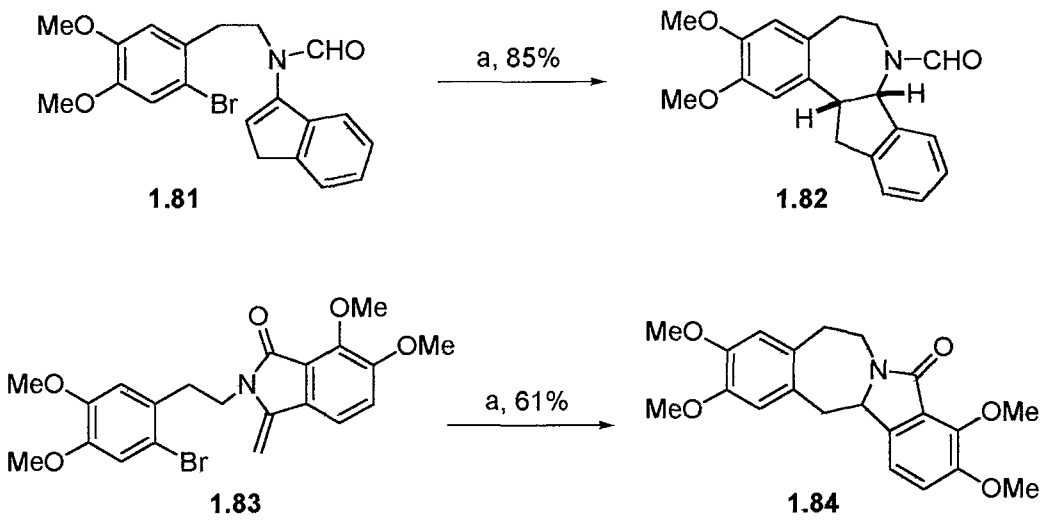
1.79 **1.80**

Reagents and Conditions: **a.** Bu_3SnH (1.1 eq.), AIBN, PhH, 80°C, 70%

Scheme 19: Formation of benzazepine derivative

Domingeuz *et al.* reported a regioselective intramolecular 7-*endo*-trig cyclisation of aryl bromide onto an enamide double bond to give benzazepine **1.82**. [28] He also

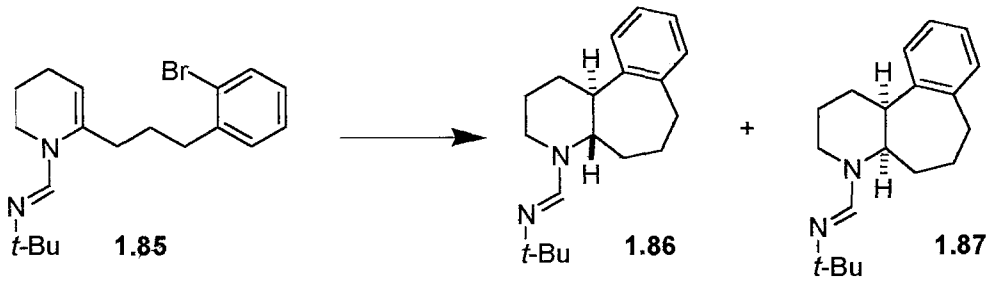
utilised this process to form the alkaloid lennoxamine **1.84**. These examples show the wide tolerance of functional groups in radical cyclisation reactions, the formamide being unaffected by the process (Scheme 20).



Reagents and Conditions: **a.** Bu_3SnH (2.0 eq.), AIBN (0.2 eq.), PhH, 80°C

Scheme 20: Methodology and formation of lennoxamine

Recently, Hallberg showed that enamide participated in a 7-*endo*-trig aryl radical cyclisation to give *trans*- and *cis*- fused octahydrobenzo[*f*]quinolines (Scheme 21). [29]

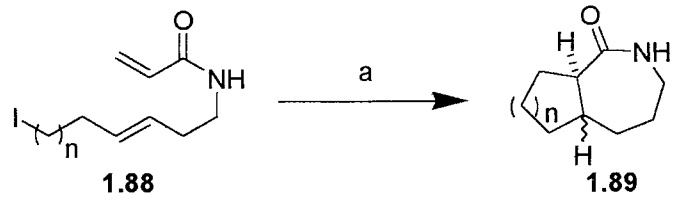


Reagents and Conditions: **a.** Bu_3SnH (1.5 eq.), AIBN (0.1 eq.), PhH, 80°C, 66%, trans:cis 3:1

Scheme 21: 7-*endo* cyclisation

1.2.4 Tandem Radical Cyclisations

A valuable method for the construction of bi- and polycyclic systems involves tandem reaction sequences in which two or more radical reactions are connected in a single reaction sequence. An example from Pattenden *et al.* involved the treatment of amide **1.88** with tributyltin hydride to form the 5,7-fused bicyclic lactam **1.89** *via* consecutive 10-*endo*-trig, 5-*exo*-trig radical cyclisations (Scheme 22). [30]



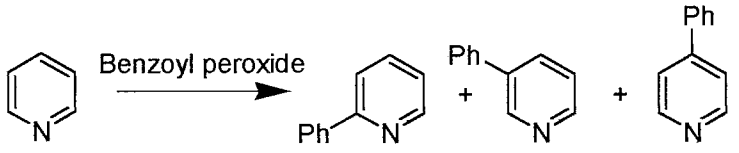
Reagents and Conditions: **a.** Bu_3SnH , AIBN, PhH, 80°C

n=1 *cis*, no yield reported
n=2 *trans*, 45%

Scheme 22: Tandem radical cyclisation

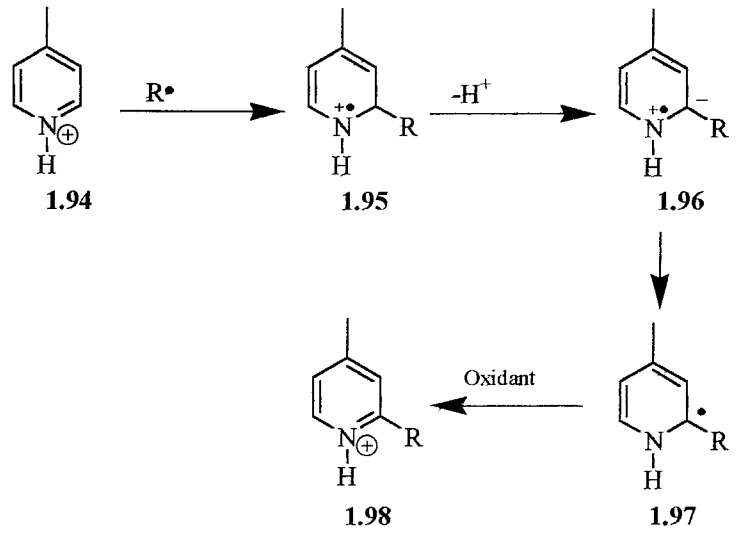
1.3 Radical Additions to Pyridines

Radical additions to pyridines were known to be difficult. In the literature there are a number of examples of how difficult these additions were found to be.[31,32] Hey *et al.* found that the addition of a phenyl group to pyridines resulted in a statistical mixture of products.[33]



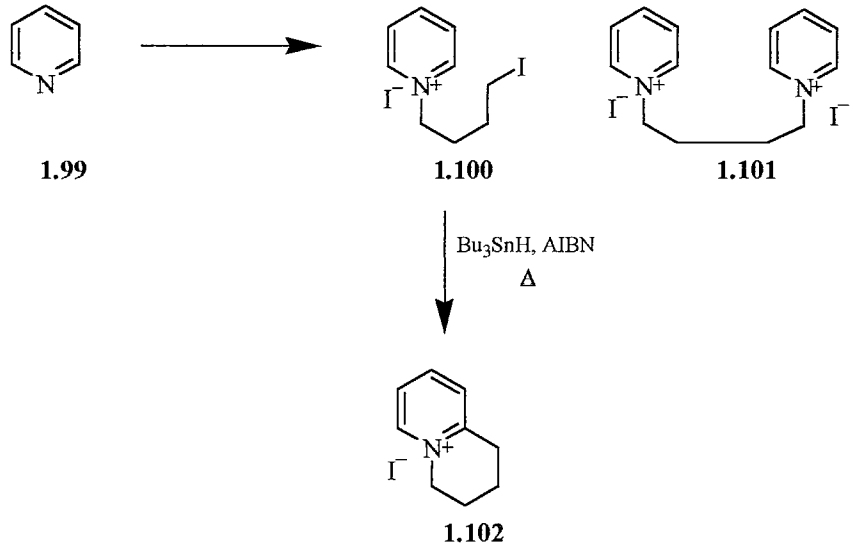
Scheme 23: Radical additions to pyridines

Intermolecular and intramolecular radical additions onto pyridinium salts have been widely reported. Minisci *et al.* did much pioneering work on the addition of carbon centered radical intermediates to protonated pyridines.[34] Early work showed that a variety of selective reactions could be achieved by taking advantage of polar effects arising from the nucleophilic character of carbon-centered radicals in reactions with electron deficient substrates. From these findings the use of protonated pyridines as acceptors of carbon-centered radicals was developed. Minisci found that radicals generated from alkyl iodides could give highly selective reactions with good conversion rates and chemical yields (Scheme 24).



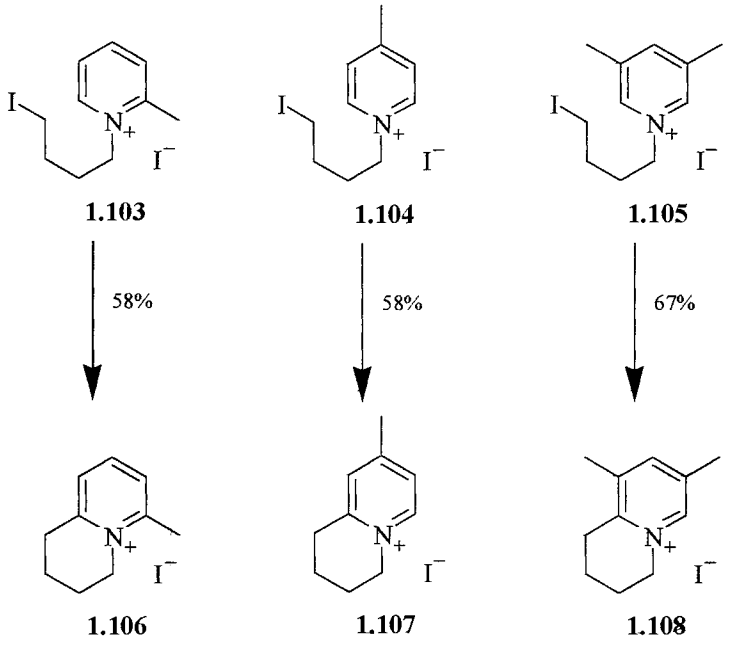
Scheme 24: Typical Minisci Reactions

More recently Murphy *et al.* developed an intramolecular variant of the reaction.[35-37] Murphy used reductive conditions instead of the oxidative conditions developed by Minisci. Their study began with substrate **1.100** in order to form the [6,6] fused ring system **1.102**. They isolated **1.100** and **1.101** when they attempted to alkylate pyridine. However, when the cyclisation was attempted with **1.100** under standard radical forming conditions poor yields were obtained. They had expected to observe some dihydropyridines but none were apparent upon isolation. This result led to suggestions that rearomatization is swift in the reaction medium (Scheme 25).



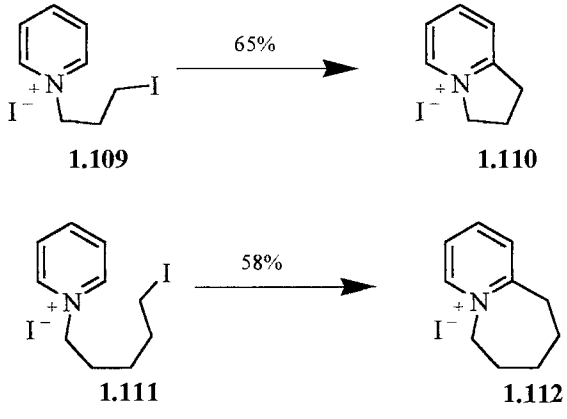
Scheme 25: Cyclisation reactions leading to [6,6] fused ring systems

The effect of substituents on the cyclisation was also investigated. Good yields were obtained from substrates **1.103**, **1.104** and **1.105** giving **1.106**, **1.107** and **1.108** respectively in about 60% yield. Thus, the reaction was both robust and synthetically useful.



Scheme 26: Effect of Substituents

That this procedure could be used in the construction of [6,5]- and [6,7]- ring systems was also demonstrated. Good yields were obtained for these systems with methyl groups at C-2, C-3 and C-4 as well as with the parent ring systems shown in scheme 27.



Scheme 27: [6,5] and [6,7] fused ring systems

1.4 Conclusions

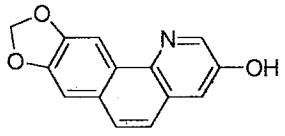
In conclusion, radical additions to pyridines have largely focused on pyridinium salts and are rather limited. The work that has been conducted illustrates some of the advantages of radical additions and cyclisation reactions and the efficency with which they can be employed.

Chapter 2

Intramolecular Radical Additions to Pyridines

2.1 Introduction

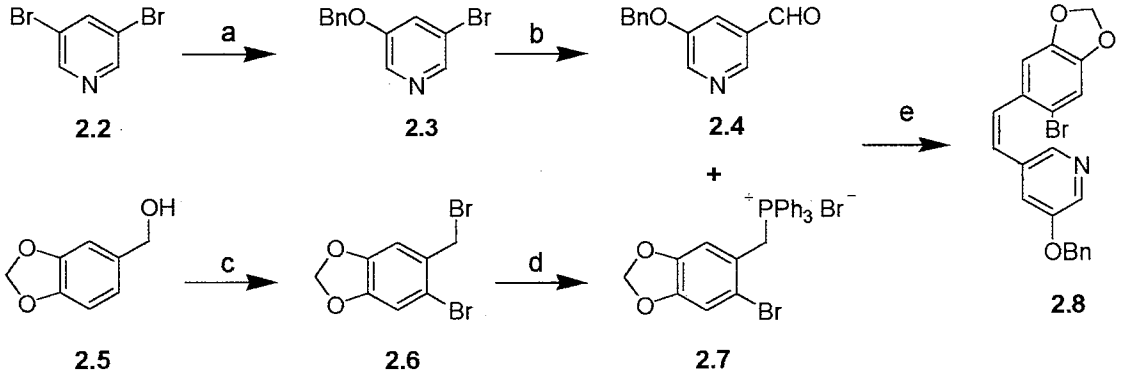
Formosan *toddalia asiatica* has been used in Asian folk medicine for centuries. In 1993 Chen and co-workers discovered a new alkaloid within this plant and named it toddaquinoline **2.1**.[38] Characterisation of the compound showed that it was based on a unique tetracyclic skeleton (Figure 1). Due to the lack of material available, no biological testing of the compound could be conducted. It therefore seemed to be a reasonable target for synthesis.



2.1

Figure 1: Toddaquinoline

In work previously conducted in the group we were able to synthesis toddaquinoline starting from 3,5–dibromopyridine **2.2** and 3,4–methylenedioxybenzyl alcohol **2.5**.[39] From these starting materials we formed the aldehyde **2.4** and phosphonium salt **2.7**. Next a Wittig reaction conjoined these materials to form alkene **2.8** in 81 % yield as a separable 5:2 mixture of *Z*- and *E*- isomers.

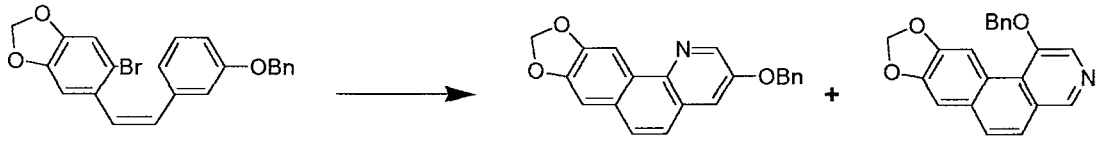


Reagents and Conditions: **a.** 2 eq. NaOBn, DMF, 65°C, 90 min, 57%; **b.** *n*-BuLi, THF, -90°C, 1h; DMF, -90°C to -60°C, 30 min, 81%; **c.** Br_2, AcOH, 0°C, 2h, 70%; **d.** PPh_3, xylene, 80°C, 5h, 88%; **e.** NaH, THF, rt, 2h; **4**, rt, 2h, 81% (*E*:*Z*, 2:5)

Scheme 1: Towards the Total Synthesis of Toddaquinoline

During the course of this work a number of methods were examined to accomplish the cyclisation of azastilbene **2.8** to toddaquinoline benzyl ether **2.9**.[40,41] With tributyltin hydride as a mediator cyclisation of **2.8** led to a 1:1 mixture of toddaquinoline benzyl ether **2.9** and a regioisomer **2.10** (Scheme 2). However, conducting the reaction with sodium cobalt(I) salophen gave **2.9** in 61% yield. The Lewis acidic nature of

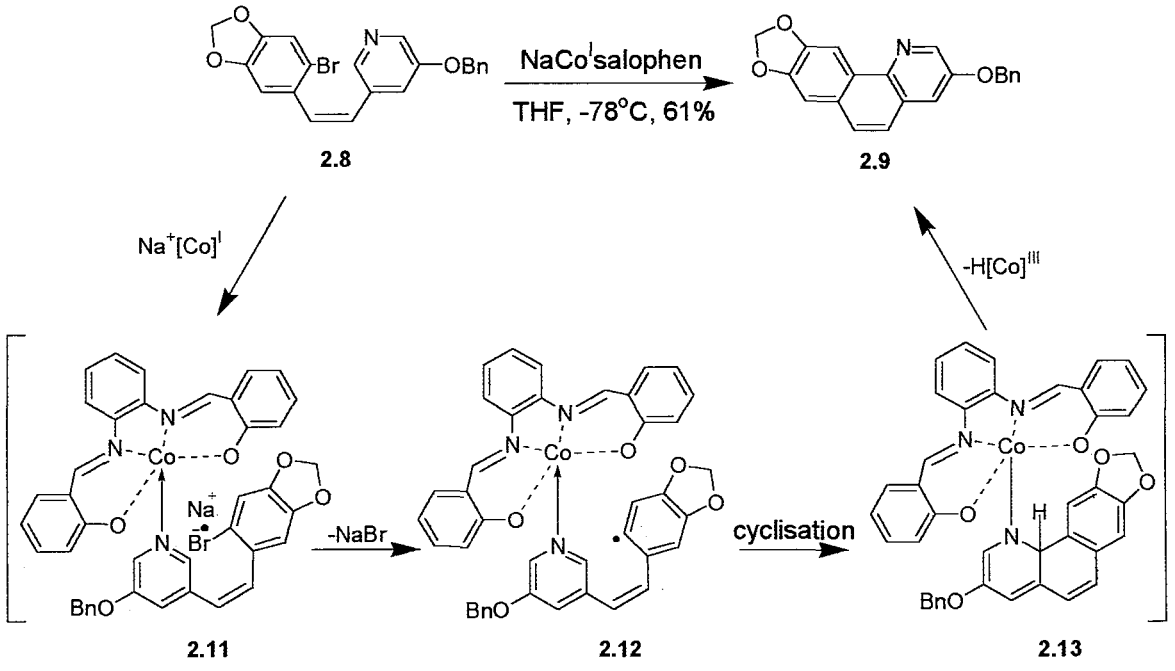
cobalt(II) salophen may explain the different courses of the tin and cobalt(I) mediated cyclisations. Thus, single electron transfer from cobalt(I) salophen leads to the formation of the Lewis acid – Lewis base complex **2.11**. This complexation enhances electrophilicity at the C-6 position of the pyridine moiety. On collapse of **2.11** to **2.12**, the "nucleophilic" aryl radical preferentially adds to this carbon centre (Scheme 3).



2.8 **2.9** **2.10**

Reagent	**2.9**	**2.10**
Bu_3SnH, AIBN, PhMe, 80°C, 4h	29%	30%

Scheme 2: Tin mediated radical cyclisation of **2.8**

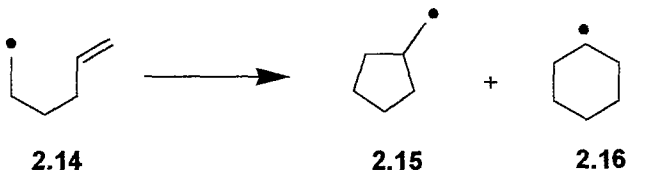


2.8 **2.9** **2.11** **2.12** **2.13**

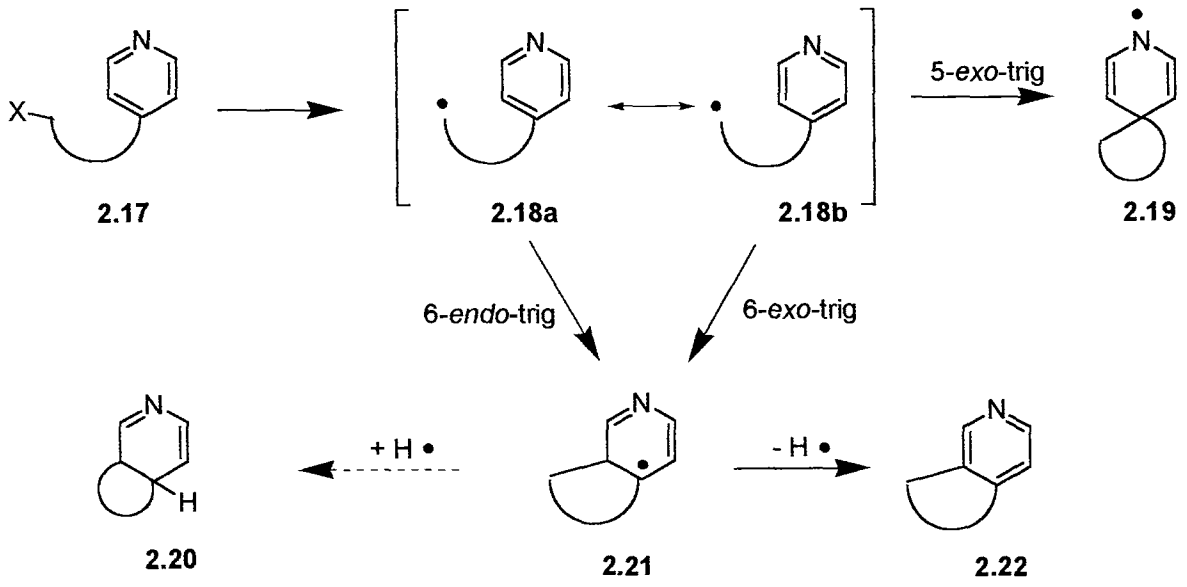
Scheme 3: Cyclisation leading to toddaquinoline benzyl ether **2.9**

Deprotection of the benzyl ether **2.9** under standard conditions using hydrogen and palladium to remove the protecting group completed the first total synthesis of toddaquinoline.[41] More importantly, the synthesis had exposed a dichotomy between tin and cobalt(I)-mediated radical additions to pyridines and demonstrated that such processes are viable at neutral pH. The synthesis also highlights some other interesting observations. It is well known that hexenyl radical **2.14** undergoes both 5-

exo-trig and 6-*endo*-trig cyclisation and that the former course dominates (98:2) (Scheme 4). However, in the toddaquinoline work, cyclisation followed the 6-*exo/endo*-trig course exclusively. Moreover, even in the presence of tributyltin hydride the product formed by loss of a hydrogen atom (**2.21** to **2.22**) rather than the more usual hydrogen atom abstraction pathway (**2.21** to **2.20**) occurs (Scheme 5).



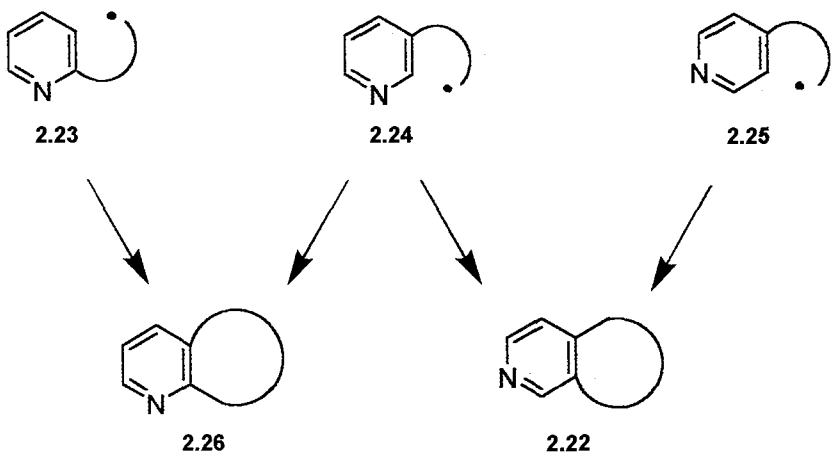
Scheme 4: Cyclisation of 5-hexenyl radical



Scheme 5: Radical Cyclisation Pathways

2.2 Aim of Investigation

The aim of this investigation was to extend the utility of radical cyclisations onto pyridines. We wished to determine the factors influencing both the mode of cyclisation and the regiochemical outcome of such reactions. In particular, we wished to determine whether cyclisation to C-3 of a pyridine could be effected and to delineate the role the tether plays in determining the course of said reactions (Scheme 6).

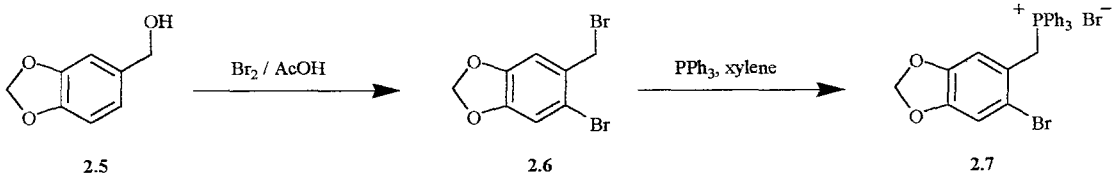


Scheme 6: Radical Cyclisations to Pyridines

2.3 Intramolecular Additions to Pyridines

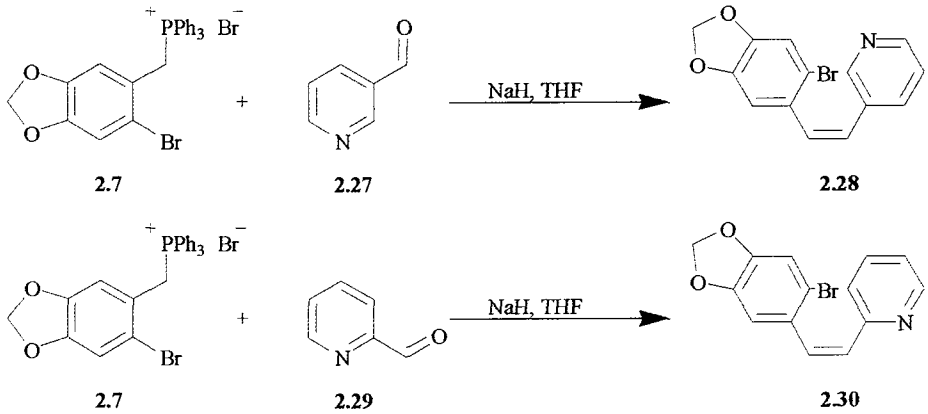
2.3.1 Bromides

It was a simple task to form the phosphonium salt **2.7** from piperonyl alcohol. Thus treatment of **2.5** with bromine and acetic acid gave dibromide **2.6**, which on heating with triphenylphosphine in xylene gave **2.7**, a key building block for the substrates we wished to examine.



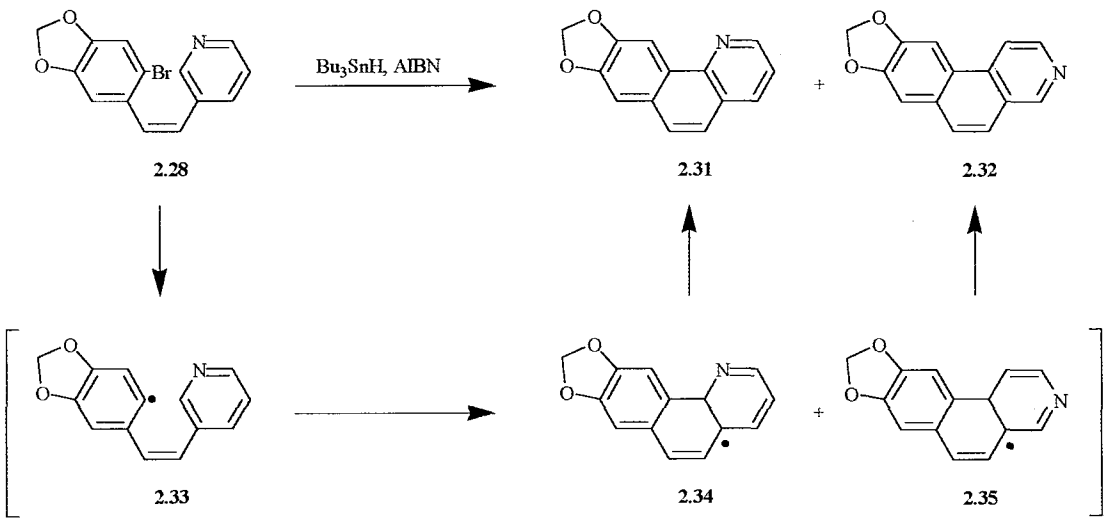
Scheme 6: Formation of phosphonium salt **2.7**

Exposure of **2.7** to sodium hydride, followed by addition of aldehyde **2.27** led to alkene **2.28** in a 3:1 ratio of *Z:E* isomers in 64% yield. Similarly, using aldehyde **2.29** led to a 12:1 mixture of *Z:E* azastilbenes **2.30** in 36% yield. These isomers were separated by column chromatography.



Scheme 7: Formation of alkenes **2.28** and **2.30**

Treatment of azastilbene **2.28** with tributyltin hydride under standard radical forming conditions, using 20 mol % AIBN as an initiator, gave a 3:1 mixture of **2.31** and **2.32** in 64% yield. In the cyclisation the aryl radical is added directly to either the C-2 or C-4 centre of the proximal pyridine giving rise to **2.34** and **2.35**. These intermediates each collapse with loss of a hydrogen atom to give **2.31** and **2.32** respectively. An important facet of this reaction is the absence of products derived from a 5-*exo*-trig cyclisation. The radical addition only appears to go through the 6-*exo*/*endo*-trig pathway and the aromaticity of the pyridine is regenerated in the products (Scheme 8).



Scheme 8: Radical cyclisation of alkene **2.28**

To optimise this reaction we decided to investigate the initiator, concentration effects and the solvent. Firstly we looked at the type of initiator we were using since AIBN does not dissolve very well in toluene. Therefore we looked at VAZO and benzoyl peroxide. As shown in table 2.1 we can see that AIBN is still the best initiator for this reaction.

Initiator	Yield of **2.31** + **2.32**
AIBN	64
VAZO	52
Benzoyl Peroxide	43

Table 2.1: Use of Initiator

Next we turned to the concentration and found that as the concentration increased more of the reduced starting material was being obtained. If the concentration was too low we recovered more starting material (Table 2.2). It was found that 1.2 mmol of tributyltin hydride to 1 mmol of substrate at a concentration of 32.5 x 10^{-6}M was the best conditions for this reaction.

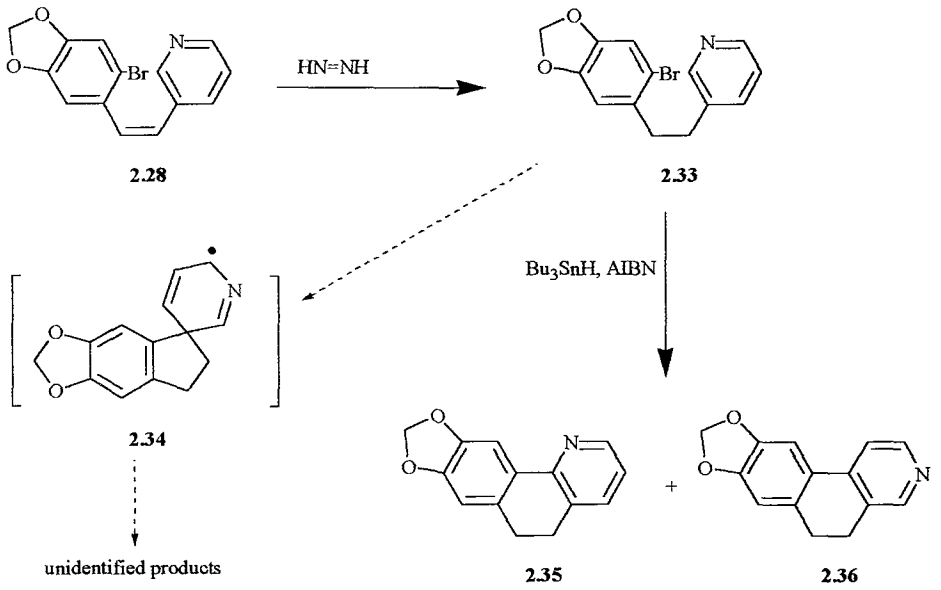
Tributyltin Hydride (eq.)	Substrate (eq.)	Concentration (x10^{-6} M)	Reduced SM	Yield **2.31** + **2.32**
1.0	1.0	50.0	0	42
1.2	1.0	50.0	0	52
1.5	1.0	50.0	12	43
2.0	1.0	50.0	22	37
1.0	1.0	25.0	0	22
1.2	1.0	25.0	0	26
1.5	1.0	25.0	0	37
1.0	1.0	32.5	0	46
1.2	1.0	32.5	0	55

Table 2.2: Concentration effects

Overall in optimising this reaction we were able to show that the concentration of tributyltin hydride is critical. Best results were realised with slow dropwise addition of AIBN and 1.2 mmol of tributyltin hydride to 1 mmol of substrate were heated at 80 °C for 72 h in toluene.

The tin mediated radical cyclisation of bromide **2.33**, prepared in 74% yield by diimide reduction of **2.28**, has also been examined. Aryl bromide **2.33** gave cyclisation products **2.35** and **2.36** in 25% yield as a separable 1:1 mixture together with 50% recovered starting material. This result was disappointing and it was clear that C-Br bond homolysis was very slow. The rest of the mass balance was made up

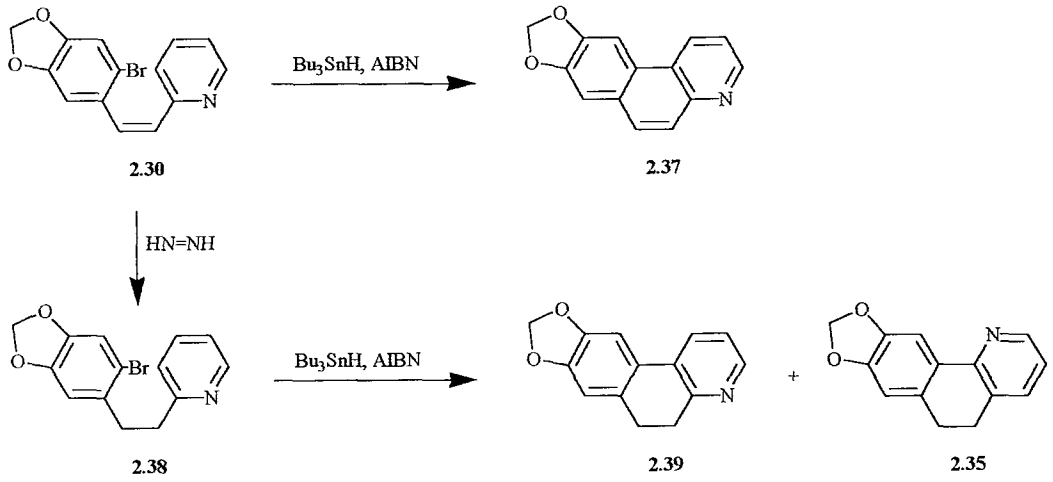
of unidentifiable products. We suspect that these are derived from the spirocycle **2.34** formed from *ipso* addition of the aryl radical to C-3 of the pyridine.



2.28 **2.33** **2.34** **2.35** **2.36**

Scheme 9: Formation and cyclisation of alkane **2.33**

Our attention next turned to radical additions to the C-3 centre of a pyridine. Cyclisation of aryl bromide **2.30** was conducted and the cyclised product **2.37** was obtained in 36% yield with 33% of the starting material recovered (Scheme 10). The low yield in this case is not surprising since the "nucleophilic" aryl radical is no longer adding to an electrophilic centre.

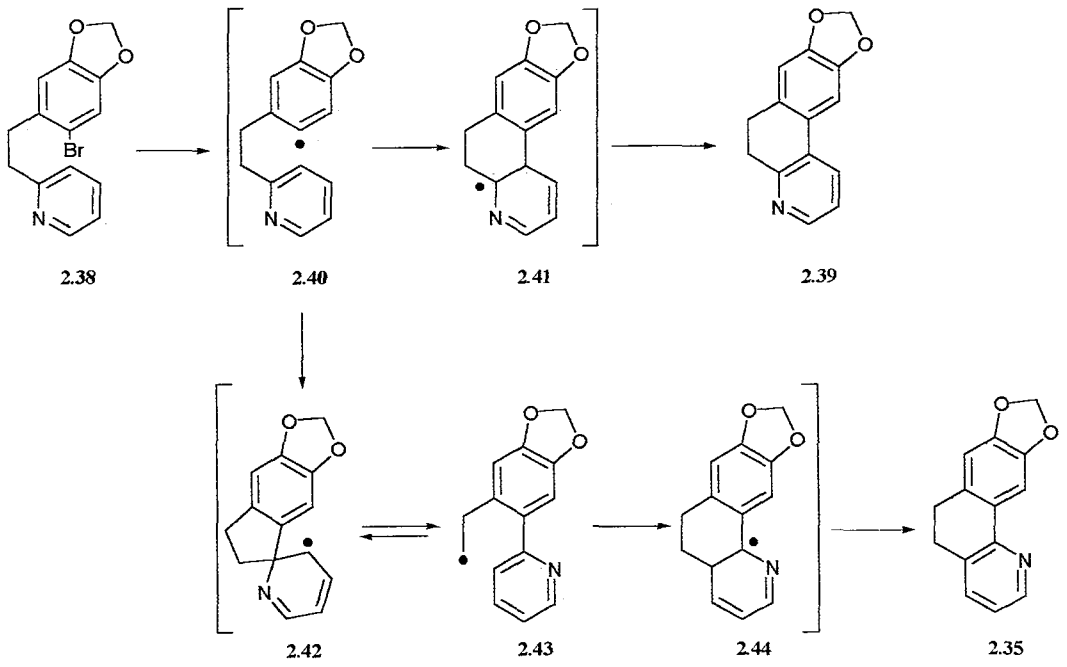


2.30 **2.37** **2.38** **2.39** **2.35**

Scheme 10: Radical cyclisation of alkene **2.30**

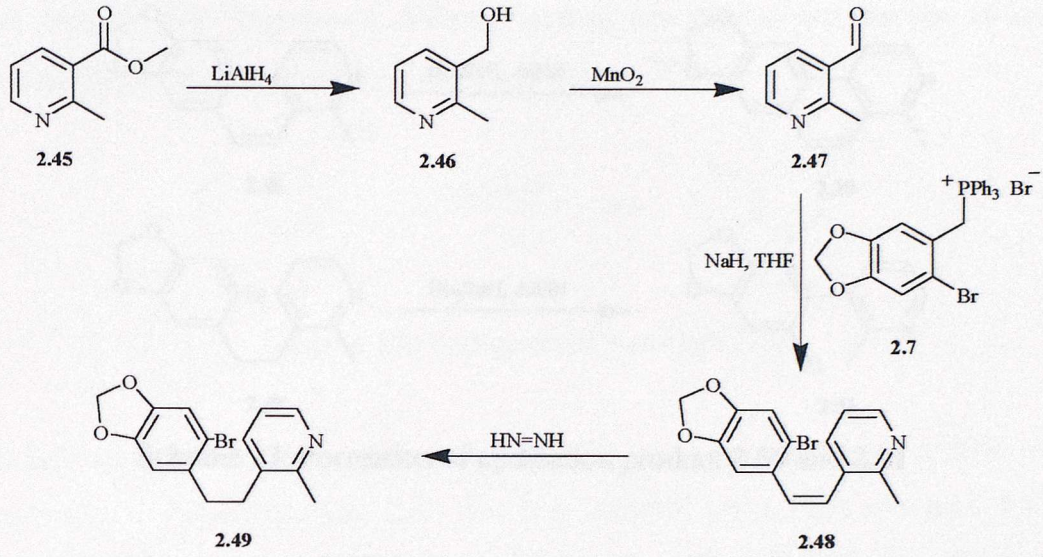
Cyclisation of aryl bromide **2.38** was then examined, having been prepared from alkene **2.30** in 76% yield by diimide reduction. In this case, tetracycles **2.39** and **2.35**

were obtained as a separable 1:1 mixture in 44% yield together with 41% recovered starting material. Formation of the rearrangement product **2.35** was quite unexpected. We presume that aryl radical **2.40** can undergo a 6-*exo*/*endo*-trig cyclisation to C-3 leading to **2.39**. It may also undergo a 5-*exo*-trig cyclisation leading to spirocycle **2.42**. Rearomatisation of the pyridine is now achieved by fragmentation of the newly formed ring giving **2.43**. A 6-*exo*/*endo*-trig cyclisation of **2.43** to **2.44** and loss of a hydrogen atom then gives **2.35** (Scheme 11).



Scheme 11: Radical cyclisation of alkane **2.38**

At this juncture we decided to investigate whether cyclisation to C-2 or C-4 could be blocked by a substituent placed at one of these centres. To this end we prepared aldehyde **2.47** in which the C-2 position is blocked by a methyl group. First, lithium aluminium hydride was used to reduce methyl ester **2.45** to alcohol **2.46**. Alcohol **2.46** was then treated with activated manganese dioxide to form aldehyde **2.47**. Coupling with bromide **2.7** next gave aryl bromide **2.48** in 83% yield in an inseparable 3:1 mixture of *Z* and *E* diastereoisomers. To complete the series the reduced aryl bromide **2.49** was also prepared by diimide reduction of **2.48** (Scheme 12) in 23% yield.



2.45 2.46 2.47 2.7 2.48 2.49

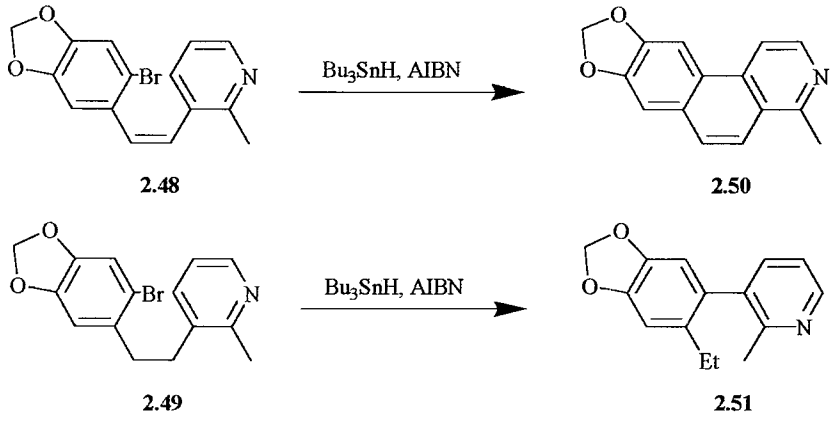
Scheme 12: Formation of alkene **2.48** and alkane **2.49**

Cyclisation of bromide **2.48** with tributyltin hydride under standard radical forming conditions gave isoquinoline **2.50** in 94% yield. In this case using THF as the solvent was found to be beneficial as it eased the workup considerably. The solvent we chose also seemed to have an effect since the purification of the product was more efficient with THF. This was probably due to how we removed the tin residues since the tributyltin fluoride we formed with our KF wash dissolved partially in toluene making purification more difficult (Table 2.3).

Solvent	Isolated Yield of **2.50**
Toluene	76
THF	94

Table 2.3: Solvent effects

Thus, blocking of the C-2 position with a methyl group had been successful and it was hoped that the reduced product would also prove effective. The cyclisation of **2.49** was conducted in toluene and gave 3-(6-ethyl-1,3-benzodioxol-5-yl)-2-methylpyridine **2.51** in 7% yield with 62% recovered starting material. No other products could be isolated and identified (Scheme 13).

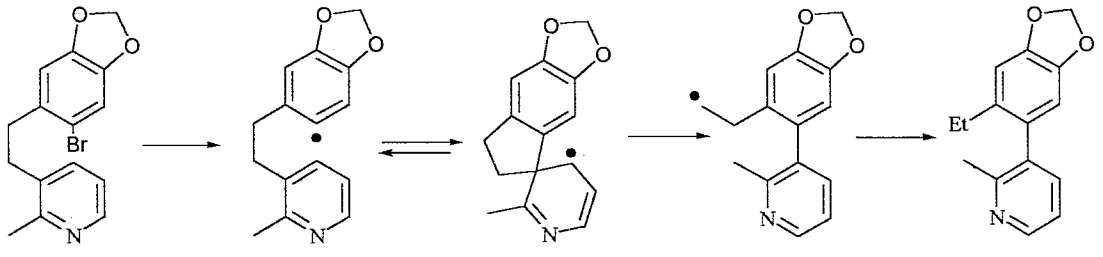


2.48 2.50

2.49 2.51

Scheme 13: Formation of cyclisation product **2.50** and **2.51**

We suspect that product **2.51** is formed *via* spirocycle **2.53**, which collapses by fragmentation to **2.54** with the regeneration of the pyridine ring. Hydrogen atom abstraction from tributyltin hydride then gives **2.51**. The product **2.51** is very interesting since it ties in with the products observed in the transformation of **2.38** into tetracycle **2.35**.



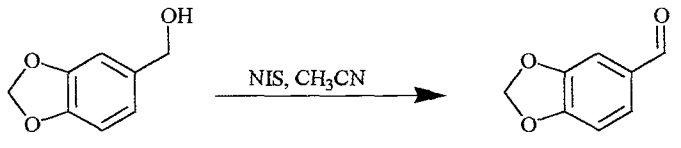
2.49 2.52 2.53 2.54 2.51

Scheme 14: Radical cyclisations of alkane **2.49**

2.3.2 Iodides

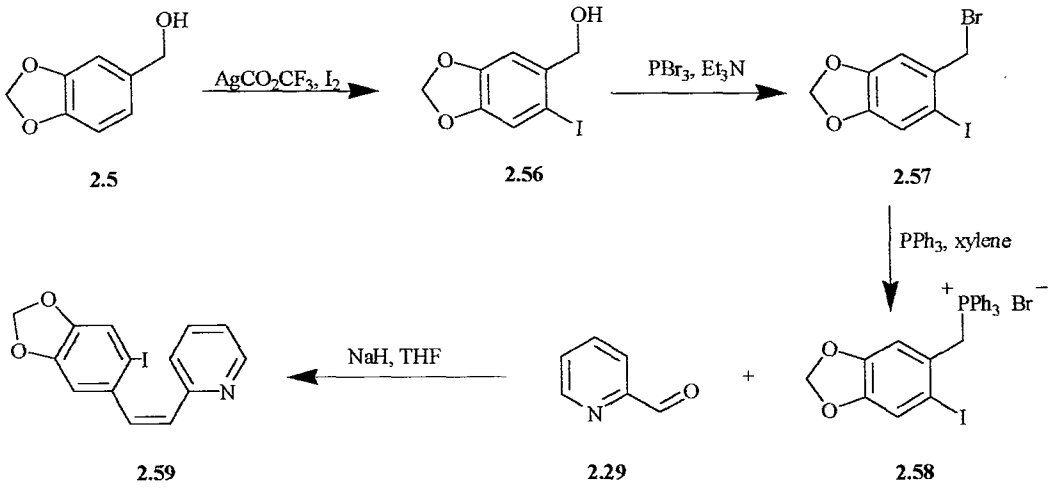
It was clear that homolysis of the C-Br bond was not as effective as we would like as on many occasions recovered starting material was still present after extended reaction times. Through the use of the corresponding iodides we hoped that radical generation would be more facile. In order to investigate this we needed to synthesise iodide **2.58**. ICl, [42-44] I_2 in THF and NIS in acetonitrile[45] were all investigated for the conversion of piperonyl alcohol **2.5** to aryl iodide **2.56**. The first two procedures gave a complex mixture of products that were very difficult to separate. While treatment with NIS led to the oxidation of piperonyl alcohol **2.5** to piperonal **2.55** in moderate

yield (Scheme 17). Therefore a different method was needed and the use of iodine activated by silver or mercury salts was investigated. [46,47]



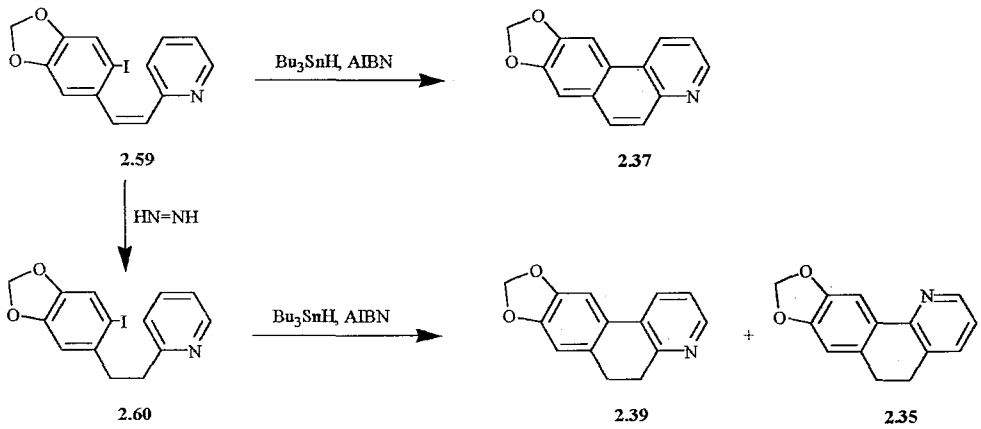
Scheme 15: Formation of piperonal **2.55**

The iodination of **2.5** using iodine and silver trifluoroacetate proceeded in 93% yield. Conversion to benzyl bromide **2.57** was then effected using PBr_3 and gave **2.57** in 45% yield. However, using 40% HBr the desired bromide **2.57** was formed in a more pleasing 86% yield. Treatment of **2.57** with triphenylphosphine in xylene at 80°C gave phosphonium salt **2.58** in 82% yield.



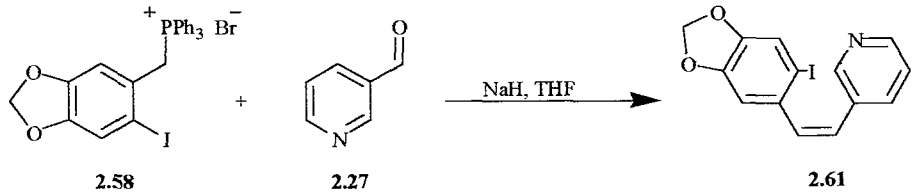
Scheme 16: Formation of alkene **2.59**

It was now a simple matter to access the precursors we required using Wittig chemistry. Thus, conjoining aldehyde **2.29** and phosphonium salt **2.58** led to *cis*-azastilbene **2.59** in 60% yield. Cyclisation of this aryl iodide using tributyltin hydride gave tetracycle **2.61** in 35% yield. Unfortunately this was not an improvement on the cyclisation of bromide **2.30**. It was hoped that the reduced compound might give more encouraging results.



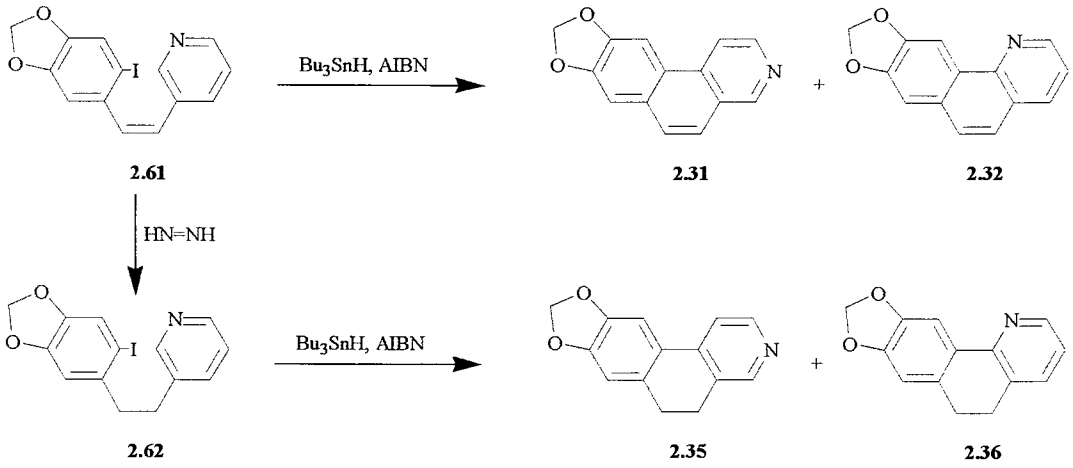
Scheme 17: Radical Cyclisation of alkene **2.59** and alkane **2.60**

Reduction of **2.59** with diimide gave aryl iodide **2.60** in 97% yield and the cyclisation with tributyltin hydride gave tetracycles **2.39** and **2.35** in a combined yield of 98% in a 2:1 ratio (Scheme 15). This encouraging result led us to examine other cyclisations in this series. Aldehyde **2.27** was conjoined with **2.58** to form precursor **2.61** in 70% yield as a 2:1 ratio of *Z:E* isomers. The cyclisation of **2.61** was conducted using tributyltin hydride and gave **2.31** and **2.32** as the isolated products of the reaction in a combined yield of 79% in a 2:1 ratio (Scheme 19).



Scheme 18: Formation of alkene **2.61**

Azastilbene **2.61** was reduced with diimide to give precursor **2.62** in 83% yield. Cyclisation of this substrate was conducted using the standard tributyltin hydride procedure to give **2.35** and **2.36** in 1:1 ratio in 49% yield.

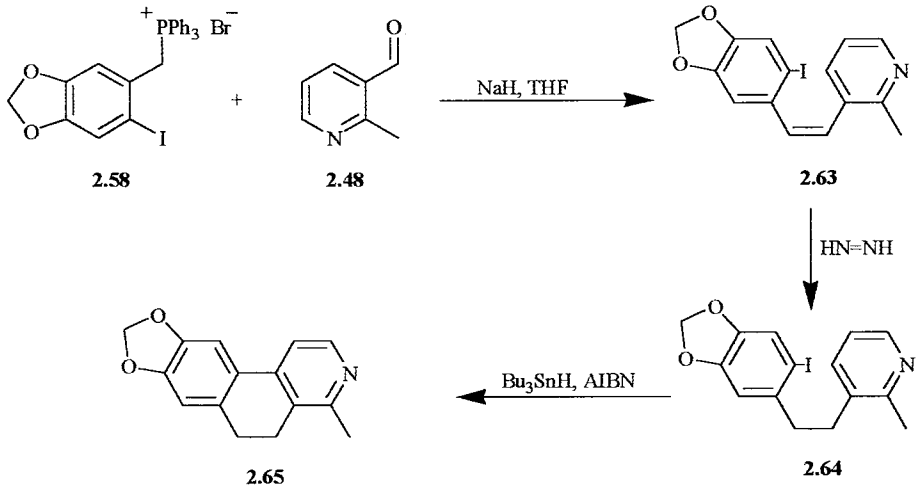


2.61 2.31 2.32

2.62 2.35 2.36

Scheme 19: Radical cyclisations of alkene **2.61** and alkane **2.62**

Next we formed (*Z*)-**2.63** in 52% yield from aldehyde **2.48** and phosphonium salt **2.58**. Reduction of **2.63** with diimide gave **2.64** in 72% yield. Cyclisation of **2.64** gave tetracycle **2.65** in 37% yield with 27% recovered starting material. The rest of the mass balance was made up of unidentifiable products that we suspect are formed from the spirocycle **2.66** presumed to be an intermediate in this reaction (Scheme 20).

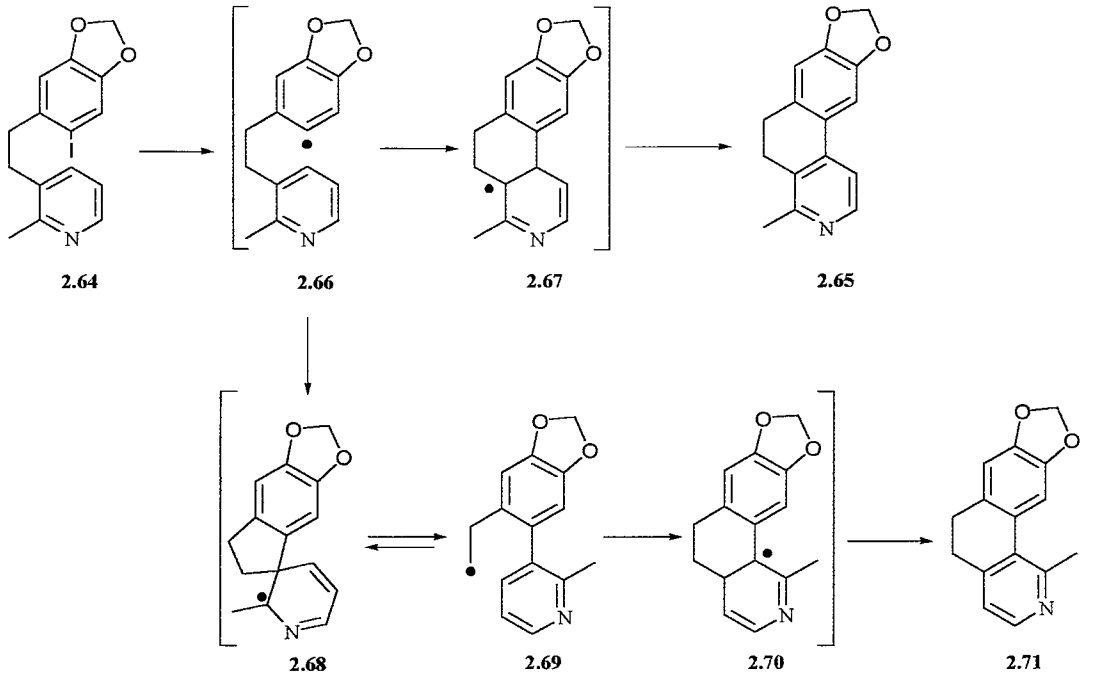


2.58 2.48 2.63

2.65 2.64

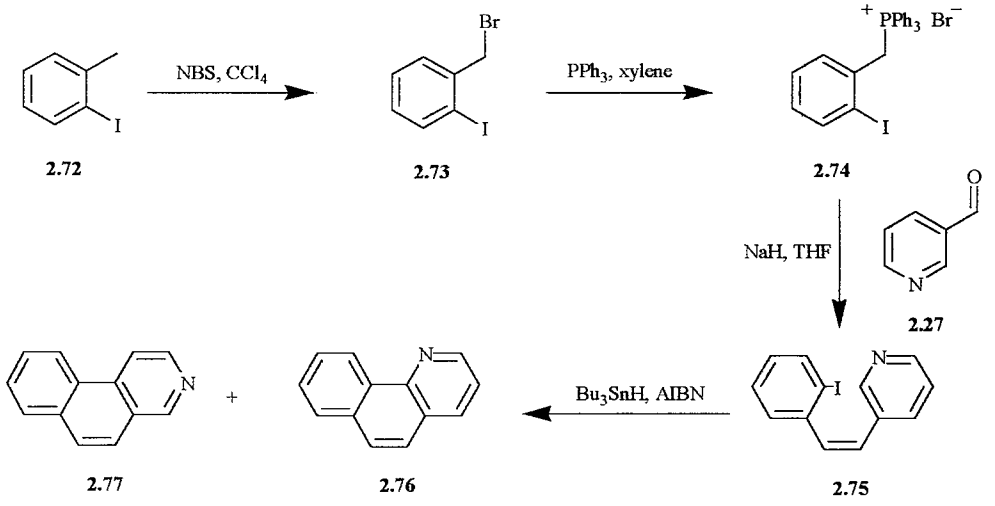
Scheme 20: Radical cyclisation of alkane **2.64**

We presume that aryl radical **2.66** can undergo a 6-*exo*/*endo*-trig cyclisation to C-3 leading to **2.65**. It may also undergo a 5-*exo*-trig cyclisation leading to spirocycle **2.68** however the formation of this spirocycle does not appear to be a competing factor in this reaction. (Scheme 21).



Scheme 21: Cyclisation pathways for **2.64**

To extend this investigation further we decided to form the phosphonium salt **2.74**. The formation of the bromide **2.73** by bromination of 2-iodotoluene **2.72** with NBS proceeded in 42% yield. Treatment with triphenylphosphine then gave phosphonium salt **2.74** in 93% yield (Scheme 22).



Scheme 22: Formation of tetracycles **2.76** and **2.77**

Aldehyde **2.27** was then conjoined with phosphonium salt **2.74** to give alkene **2.75** in 74% yield as 1:1 separable mixture of *Z:E* isomers. Cyclisation of alkene **2.75** was conducted with tributyltin hydride and tricycles **2.76** and **2.77** were formed in a 1:1 ratio in 94% yield.

2.4 Conclusions

From the results detailed above we can see that radical additions to C-2, C-3 and C-4 of a pyridine can all be achieved at neutral pH when conducted intramolecularly. For cyclisations involving *cis*-azastilbenes, addition of the radical intermediate to the pyridine centre *ortho* to the point of tether occurs with varying degrees of success. The additions of aryl radical intermediates to pyridines appear to be influenced by the electrophilicity of the carbon centre to which they add. Aryl iodides were generally found to be better substrates for the reaction than aryl bromides. In most cases complete homolysis of the C-I bond was observed. An interesting facet of this work is that dihydropyridines were never observed as products. Using tributyltin hydride as a mediator we would normally expect to see radical intermediates abstract a hydrogen atom from the reagent rather than suffer loss of a hydrogen atom.

When we look at the dihydroazastilbene (alkane) series, products derived from *ipso* cyclisation accompany those derived from *ortho* cyclisation. Moreover, where 5-*exo*-trig radical cyclisation is facile, a rearrangement of the thus formed spirocycle occurs.

The method is useful for the synthesis of many condensed heteroaromatics and work within the group has extended the methodology to quinolines, isoquinolines and indoles with good effect.

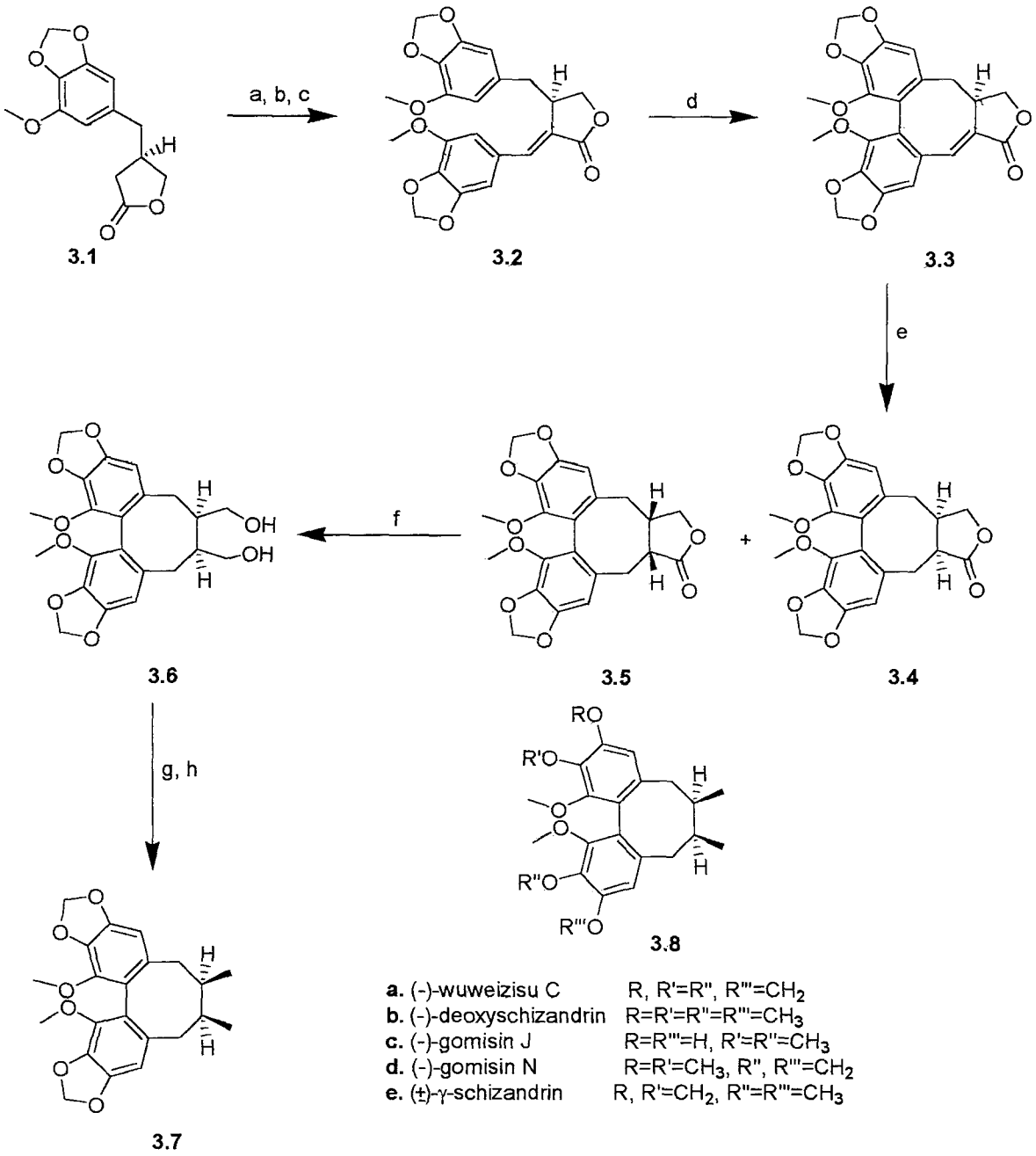
Chapter 3

The Formation of Medium Ring Systems: an Intramolecular Radical Approach

3.1 Background

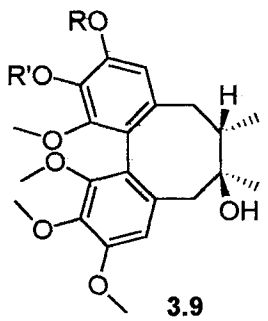
Many approaches have been developed to address the synthesis of the stegnanes series of natural products. Most of the approaches developed to date involve oxidative coupling of biaryls as a method of effecting the closure of the 8-membered ring.

For example, Tanaka *et al.* targeted a number of these biologically active dibenzocyclooctene lignans starting from the optically pure lactone **3.1**, formed by Robin *et al.*[48] in their synthesis of (±)–deoxyschizandrin.[49,50] Aldol condensation with 3-methoxy-4,5-(methylendioxy)benzaldehyde and lactone **3.1** gave **3.2** after reduction of the alcohol in 86% yield. Oxidative coupling allowed entry towards (-)-wuweizisu C **3.7**. [51] From intermediate **3.3** hydrogenation gave the isomers **3.4** and **3.5**. The *cis* relationship between C-6 and C-7 position was confirmed by the fact that both **3.4** and **3.5** gave a single diol by the reduction of the lactone moiety. Methanesulfonylation of **3.6** followed by reduction afforded the optically pure (-)-wuweizisu C **3.7** (Scheme 1).[51] Using similar procedures Tanaka *et al.* were able to construct (-)–gomisin J **3.8c**,[51] (-)–gomisin N **3.8d** [51] and (±)–γ–schizandrin **3.8e**.[51] *Via* intermediate **3.3**, Tanaka was also able to access (+) – gomisin A **3.9a**, [52] kadsurin **3.10** [53] and (+)-schizandrin **3.9b** (Scheme 2).[53]

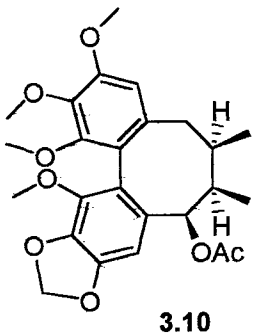


Reagents and Conditions: **a.** LDA, 3-methoxy-4,5-(methylenedioxy)benzaldehyde, THF, -78°C; **b.** Ac_2O, Et_3N, DMAP; **c.** DBU, PhMe; **d.** $Fe(ClO_4)_3$, CF_3CO_2H, CH_2Cl_2; **e.** H_2, Pd-C, AcOEt; **f.** DIBAL-H, THF; **g.** MsCl, pyr.; **h.** $LiBHEt_3$, THF

Scheme 1: Total Synthesis of lignans isolated from *schisandra chinensis*



3.9

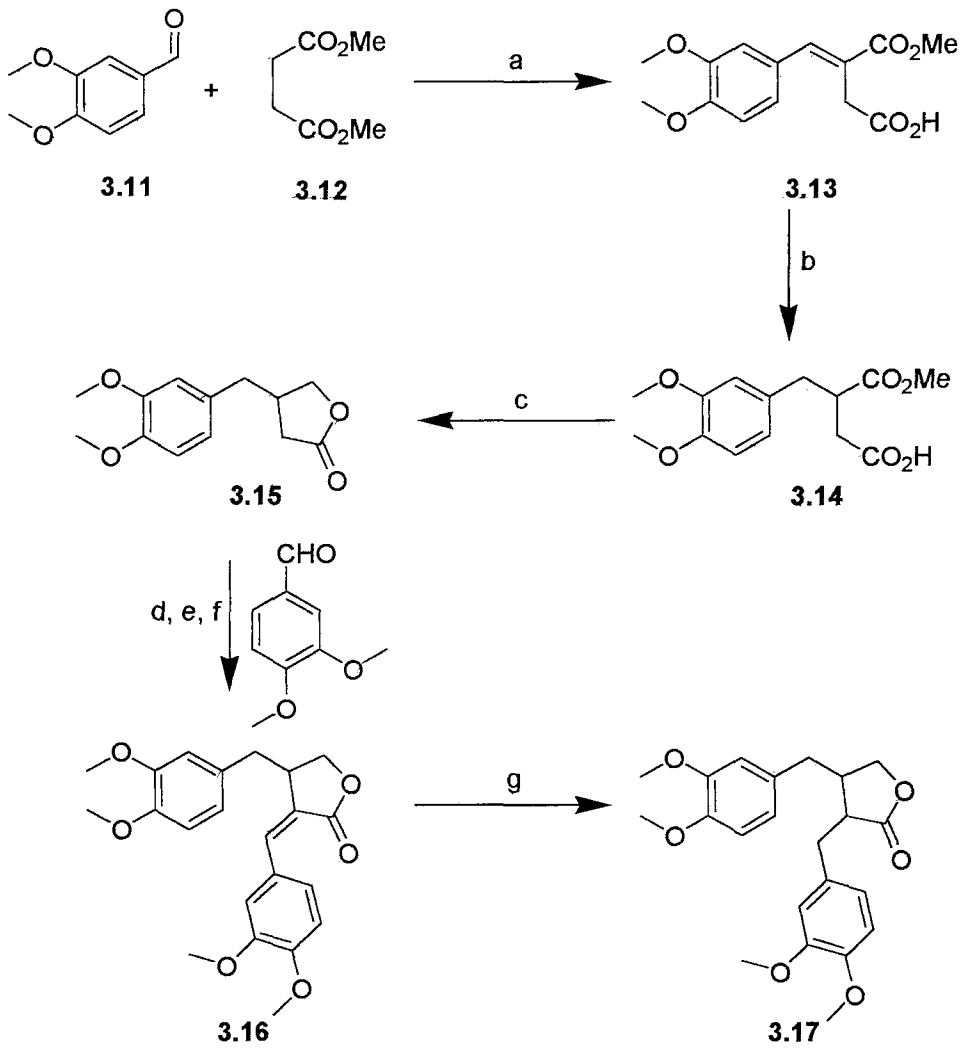


3.10

a. (+)-gomisin A R, R'=CH_2
b. (+)-schizandrin R=R'=CH_3

Scheme 2: Natural products isolated by Tanaka *et al.*

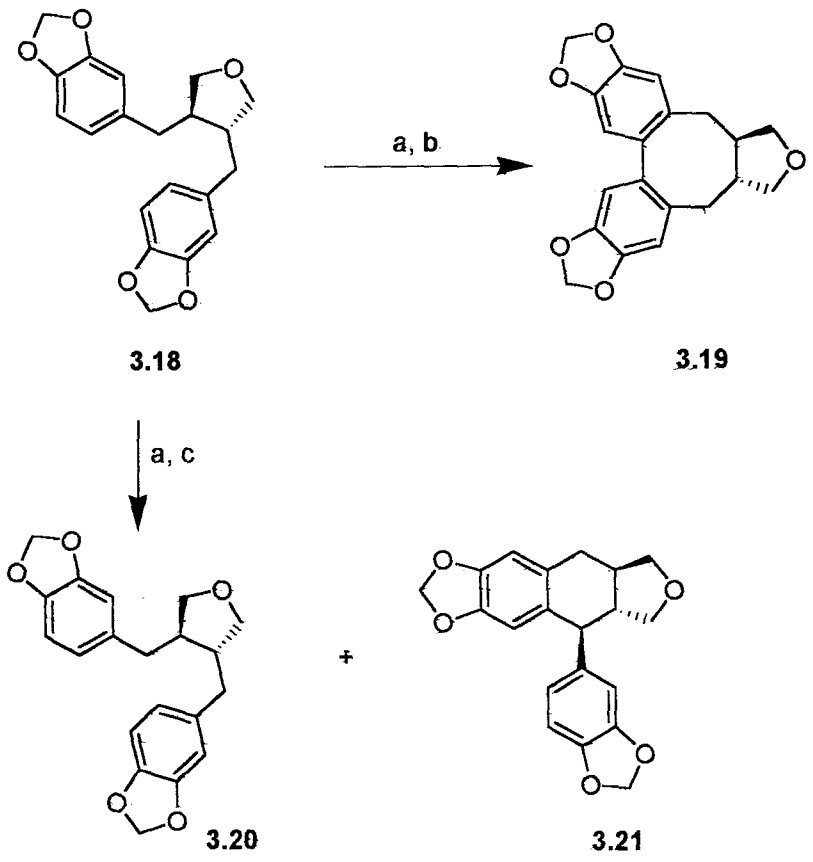
Ward *et al.* used a similar approach to access dibenzocyclooctene lignans.[54,55] To access the series they used a Stobbe condensation to provide them with the acid **3.13** (Scheme 3). Hydrogenation and the use of calcium borohydride provided the lactone **3.15**. An aldol condensation and elimination of the alcohol provided them with the alkene **3.16**. Hydrogenation then gave lactone **3.17** from which they hoped to gain an insight into the methodology of the oxidative coupling.



Reagents and Conditions: **a.** *t*-BuOK, *t*-BuOH; **b.** H_2 / Pd-C, MeOH; **c.** $CaCl_2$, EtOH, $NaBH_4$; **d.** LDA, THF; **e.** Ac_2O, Et_3N, DMAP, THF; **f.** NaH, THF; **g.** H_2 / Pd-C, THF / MeOH

Scheme 3: Synthesis of Precursor **3.17**

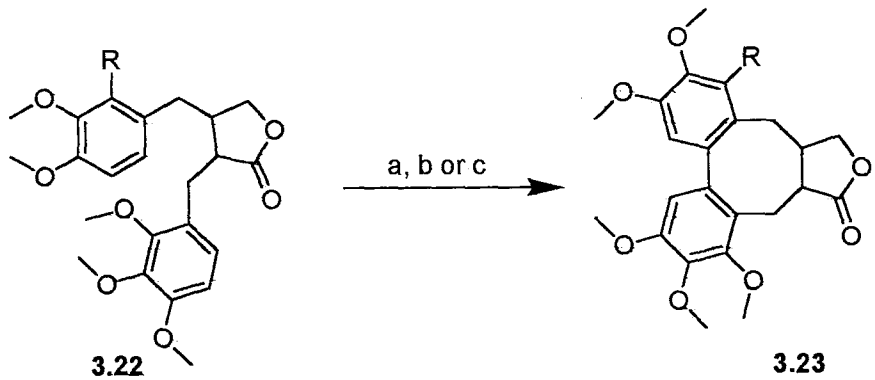
In previous work by Ward *et al.* using tetrahydrofurans instead of butyrolactones they found that biaryls were formed in low yield when DDQ and TFA were employed. However, when acetic acid was used instead of TFA they isolated the acetate **3.20** and the aryl tetralin **3.21** (Scheme 4). Unfortunately this approach could not be utilised with the lactone substrates.



Reagents and Conditions: **a.** DDQ; **b.** TFA; **c.** HOAc

Scheme 4: Use of DDQ and acid for formation of stegnacins

Ward *et al.* sought to use the methodology developed to access steganacin and related compounds. Using ruthenium tetra(trifluoracetate), ruthenium dioxide or thallium oxide they were able to isolate the dibenzocyclooctene lignans in moderate to good yields.



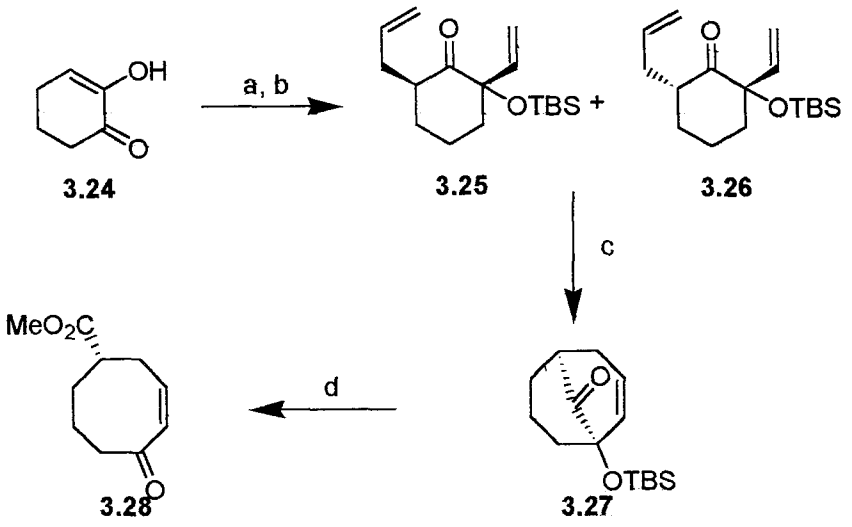
Reagents and Conditions: **a.** $RuO_2.2H_2O$, TFA-TFAA, $BF_3.Et_2O$; **b.** Tl_2O_3, TFA-TFAA, $BF_3.Et_2O$; **c.** VOF_3, TFA-TFAA
R = H or OMe

Scheme 5: Formation of dibenzocyclooctene lignans

3.2 Formation of Medium Sized Rings

The synthesis of medium sized rings often requires special consideration due to adverse transannular interactions. They are present in the core of numerous biologically important natural products. They can be difficult to construct by conventional cyclisation techniques due to enthalpic and entropic reasons. In fact the number of procedures developed to access these carbon frameworks is relatively small. In this review we will look at a small number of approaches towards these ring systems. Some of the approaches undertaken include oxy–Cope rearrangements,[56,57] Wharton/Grob fragmentations,[58,59] metathesis reactions,[60,61] transition metal-catalysed cycloadditions and a variety of SmI_2 sequenced reactions.[62]

Mascarenas *et al.* were able to use a RCM in order to construct eight and nine membered rings in four operationally simple steps. [63]



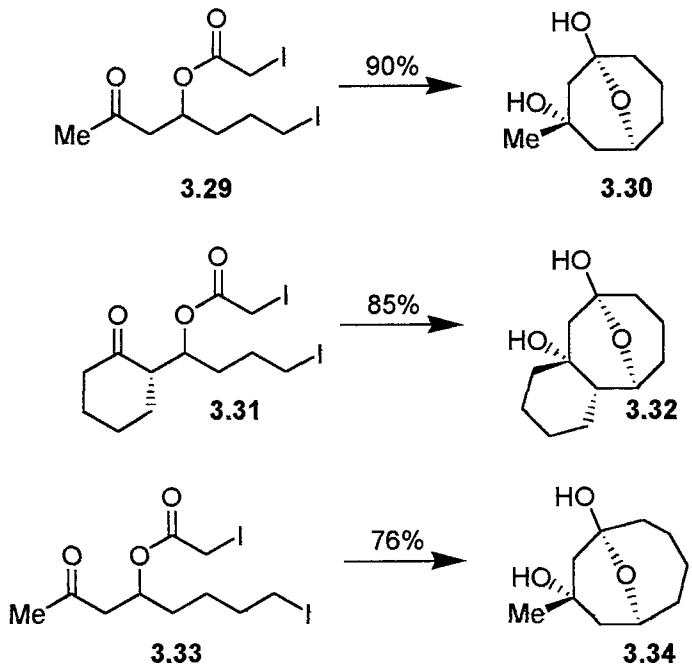
Reagents and Conditions: **a.** TBSCl, imidazole, CH_2Cl_2; **b.** CH_2CHLi, THF, -78°C, then allyl bromide; **c.** Grubb's catalyst (5 mol%), CH_2Cl_2, 40°C; **d.** $Pb(OAc)_4$, MeOH, 20°C

Scheme 6: Synthesis of medium sized ring systems using ring closing metathesis

An interesting part of their work is that the rigid bicyclic framework provides an excellent stereocontrolling element for the cyclisation that takes place. However this procedure uses a catalyst that is expensive and the oxidative cleavage of the ketone is accomplished with lead tetraacetate which is toxic and harmful to the environment.

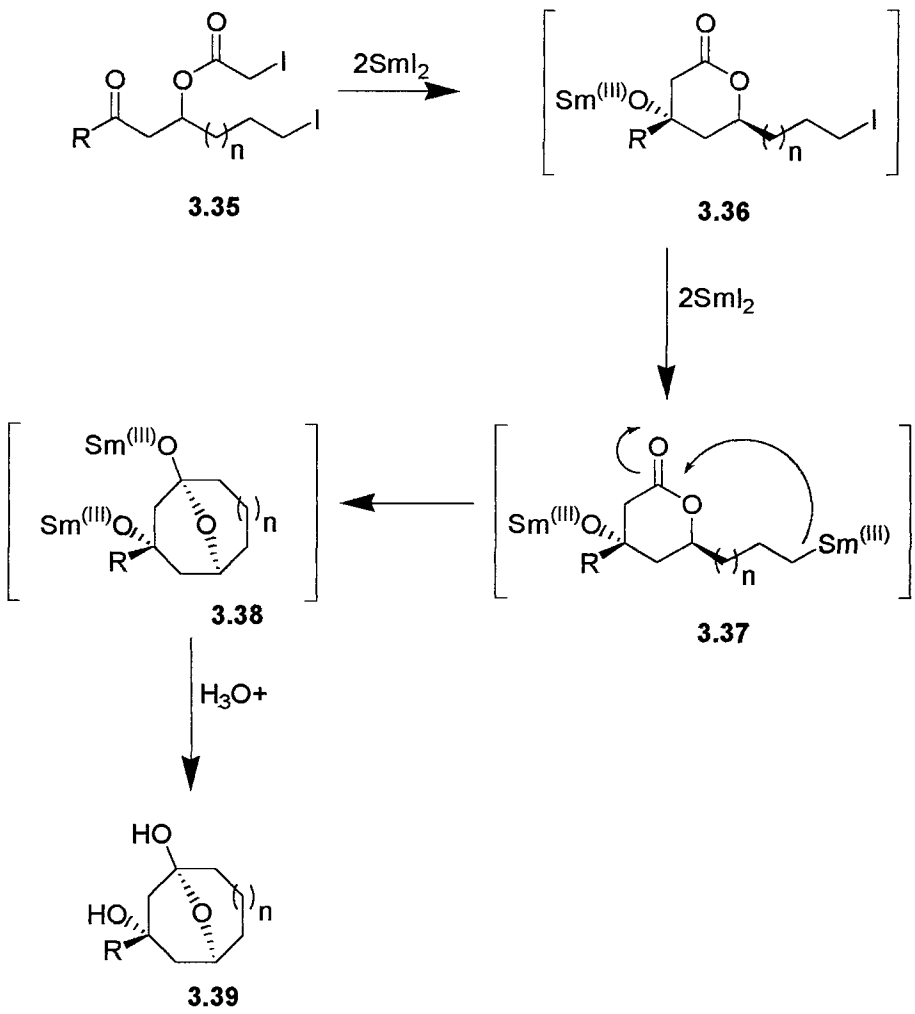
Molander *et al.* used SmI_2 in order to form eight and nine membered ring systems.[64] Using their sequential Reformatsky/nucleophilic acyl substitution reactions they

obtained good yields for cyclooctanes and cyclononanes. The ring systems formed are fused bicycles until the epoxide is removed. Samarium diiodide is also difficult to manipulate and use and 5 equivalents of this expensive reagent are needed to bring about the reaction. In this procedure it was necessary to use diiodides since the corresponding dibromides and dichlorides gave poor yields. They were unable to form ten membered rings by this method.



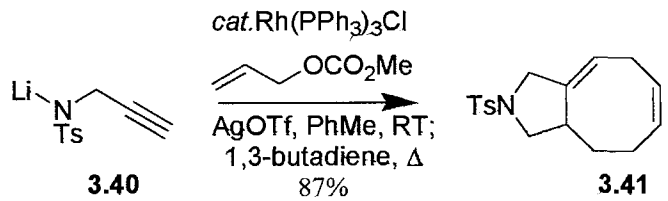
Scheme 7: Formation of ring systems using samarium diiodide

Each of these approaches attempts to overcome the problems of medium ring synthesis by forming bicyclic products, which can then be cleaved to reveal the carbocycle.



Scheme 8: Mechanism for Molander's intermediate

Evans *et al.* used a transition metal-catalysed [4 + 2 + 2] cycloaddition to access the eight membered ring systems.[65] They treated the lithium salt of *N*-tosylpropargylamine with allyl carbonate in the presence of Wilkinson's catalyst at room temperature. The enyne thus formed was heated at reflux for about 12h under an atmosphere of 1,3-butadiene to afford the cycloaddition adduct in 87 % yield.



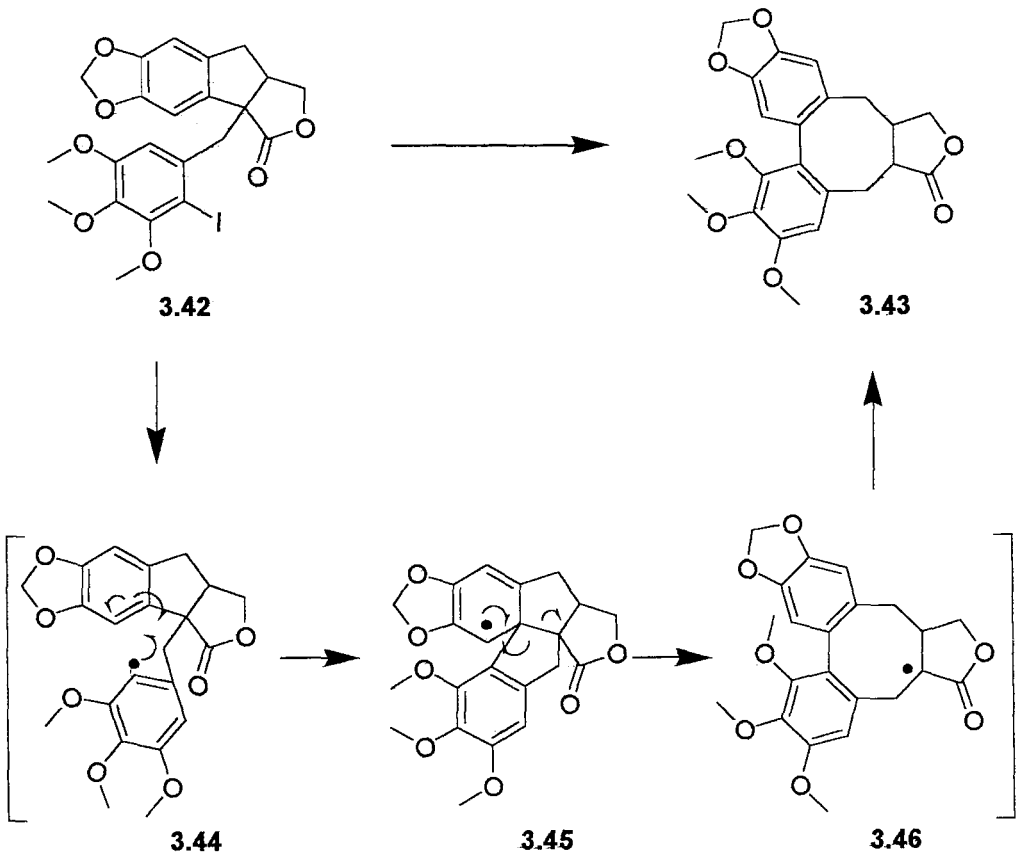
Scheme 9: Two component system

They found that their procedure needed an additive of silver trifluoroacetate in 20 mol % which makes it a rather expensive route. The reaction has also been shown to give

good yields for propargyl ethers and propargyl sulfones. The procedure provides an excellent entry into these ring systems.

3.3 Aims of Investigation

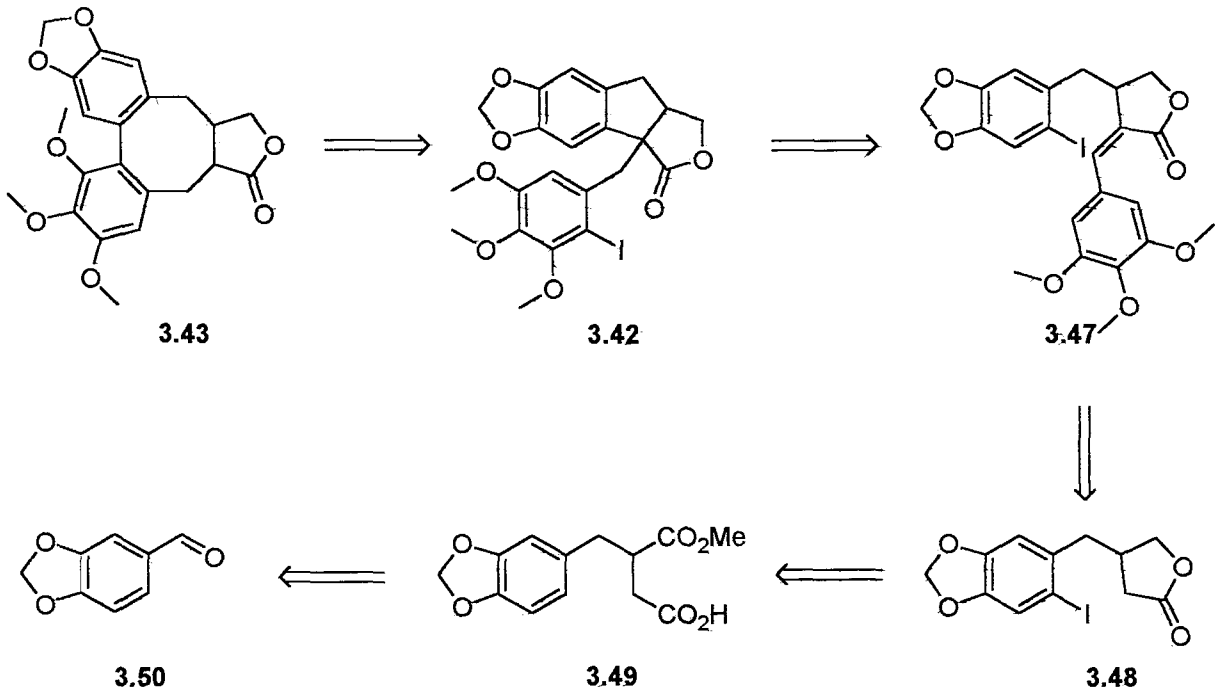
We hoped to access the stegnane series of natural products through the use of an intramolecular radical addition and fragmentation sequence. We planned to form precursor **3.42** and hoped that on treatment with tributyltin hydride that the resulting radical **3.44** would add to the aryl ring forming intermediate **3.45**. This radical would then fragment to the more stable tertiary radical in order to regenerate the aromatic ring. Addition of a hydrogen atom from tributyltin hydride would then give the cyclooctane **3.43** and propagate the chain reaction (Scheme 10).



Scheme 10: Proposed Key Step

We hoped to follow some work by Ward to prepare the requisite starting material **3.42**. Therefore, after a Stobbe condensation and hydrogenation we could access the acid **3.49**. From this we hoped to form the lactone **3.48** couple in the second arene via

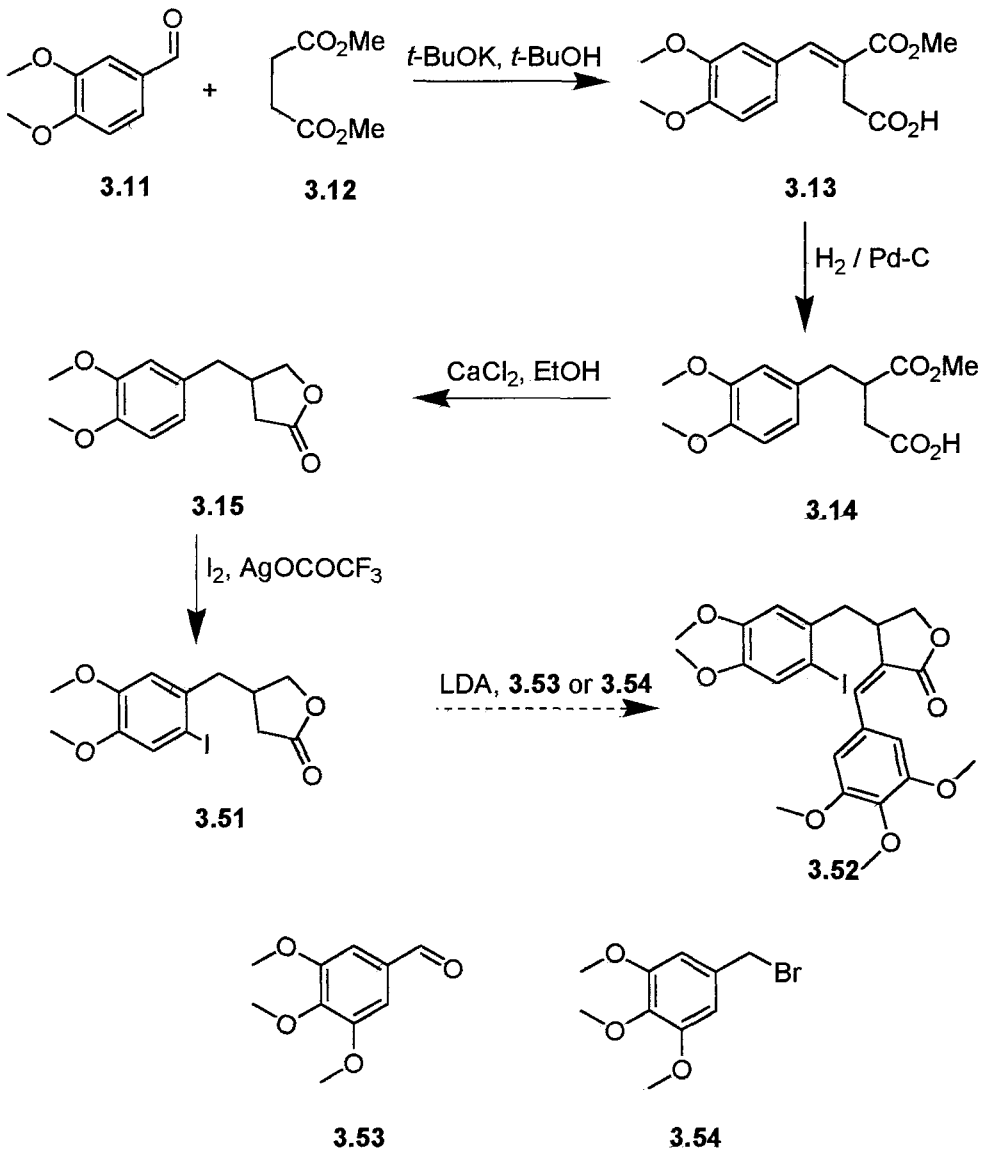
an aldol condensation. A radical cyclisation would then give the tricyclic precursor which could be iodinated to give our precursor **3.42** (Scheme 11).



Scheme 11: Proposed retrosynthesis for stegnans

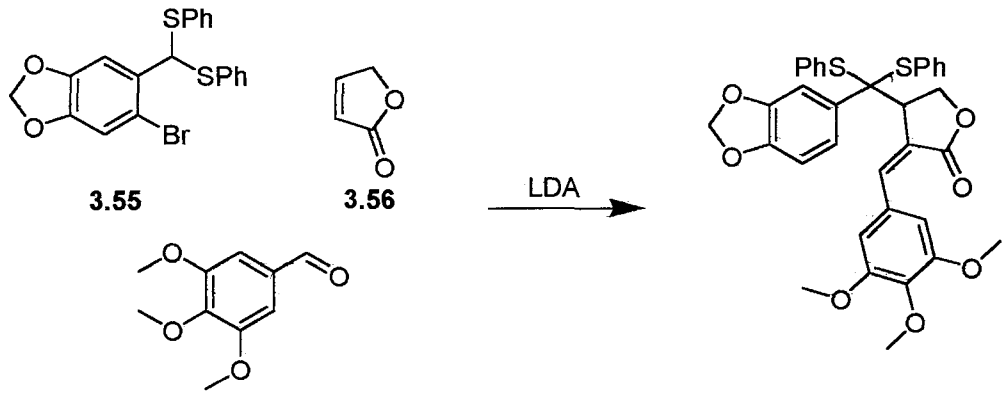
3.4 Stegnans

The acid **3.13** was formed in 70% yield via a Stobbe condesation then hydrogenated to give **3.14** in 66 % yield. Reduction of the ester moiety with calcium borohydride, formed *in situ* from calcium chloride and sodium borohydride, then gave lactone **3.15** in 95% yield. Iodination of this material using silver trifluoroacetate as a mediator gave iodide **3.51** in 98 % yield (Scheme 12). Attempts to alkylate iodide **3.51** did not furnish us with any alkylated product **3.52**. We assumed that this was because of a retro aldol occurring during the reaction. Therefore we attempted to acetylate the alcohol so that we could form **3.52** when the acetylated product was treated with sodium hydride.[54] However no acetylated product could be isolated. We tried a number of bases including lithium diisopropylamine, lithium hexamethyldisilazide and sodium hydride but still found none of the desired product upon purification. We also attempted to use both aryl aldehyde **3.53** and benzyl bromide **3.54** but to no product could be isolated only recovered starting material.



Scheme 12: Synthesis of iodolactone **3.52**

Thus we embarked on a different strategy. Using furanone **3.55**, bromide **3.56** and aldehyde **3.53** we hoped to effect a Michael additon / condensation sequence to **3.57**. This three component reaction would, in principle, allow us to construct the desired skeleton **3.57** quickly and efficiently (Scheme 13). Alas the reaction did not proceed as hoped and we recovered only starting material from the reaction when we attempted the reaction with lithium diisopropylamine in THF after 18 hours.

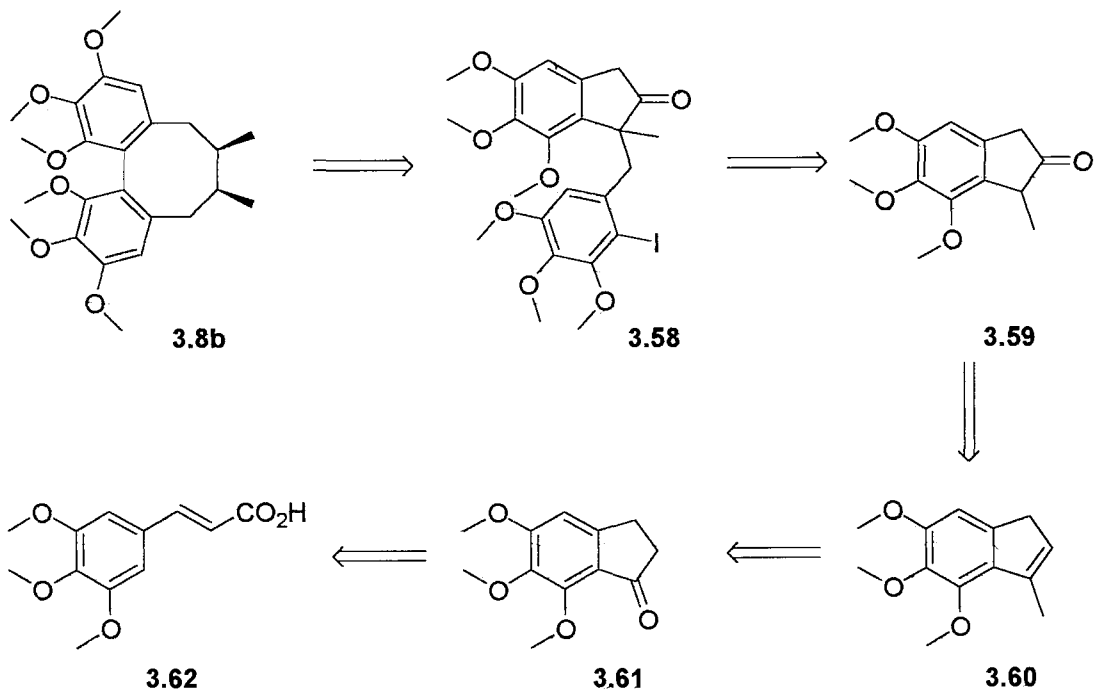


3.55 **3.56** **3.53** **3.57**

Scheme 13: Attempted synthesis of precursor **3.57**

3.5 Dimethylgomisin

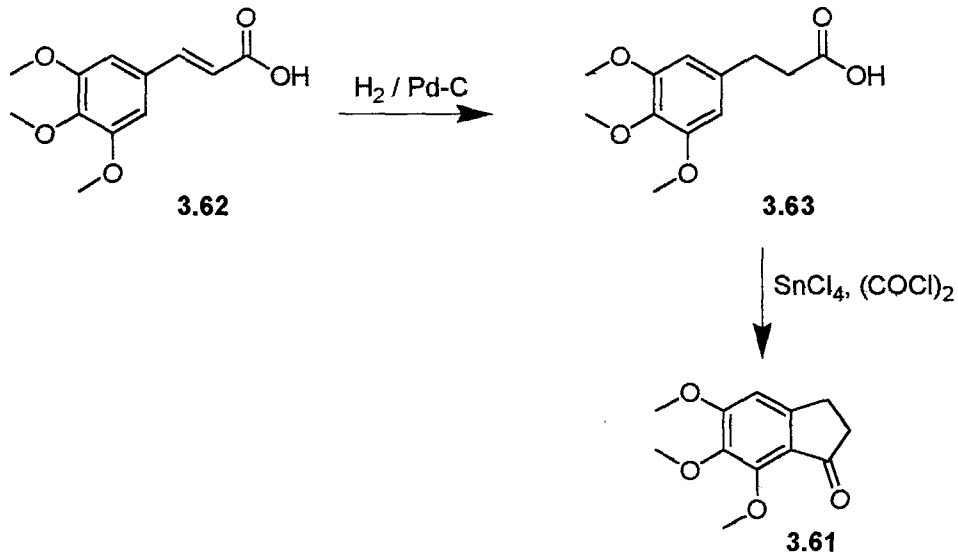
Since we were having so many difficulties with the stegnans we decided to leave that route and try to form dimethylgomisin.



3.8b **3.58** **3.59** **3.62** **3.61** **3.60**

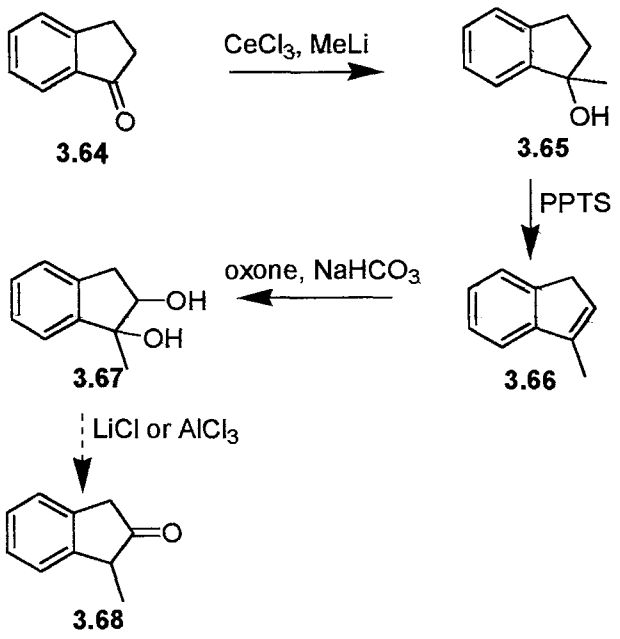
Scheme 14: Retrosynthesis of dimethylgomisin

We started this work by forming hydrocinnamic acid **3.63** through hydrogenation of **3.62** (96 % yield). Treatment with tin tetrachloride then gave indanone **3.61** in 83 % yield.



Scheme 15: Synthesis of indanone **3.61**

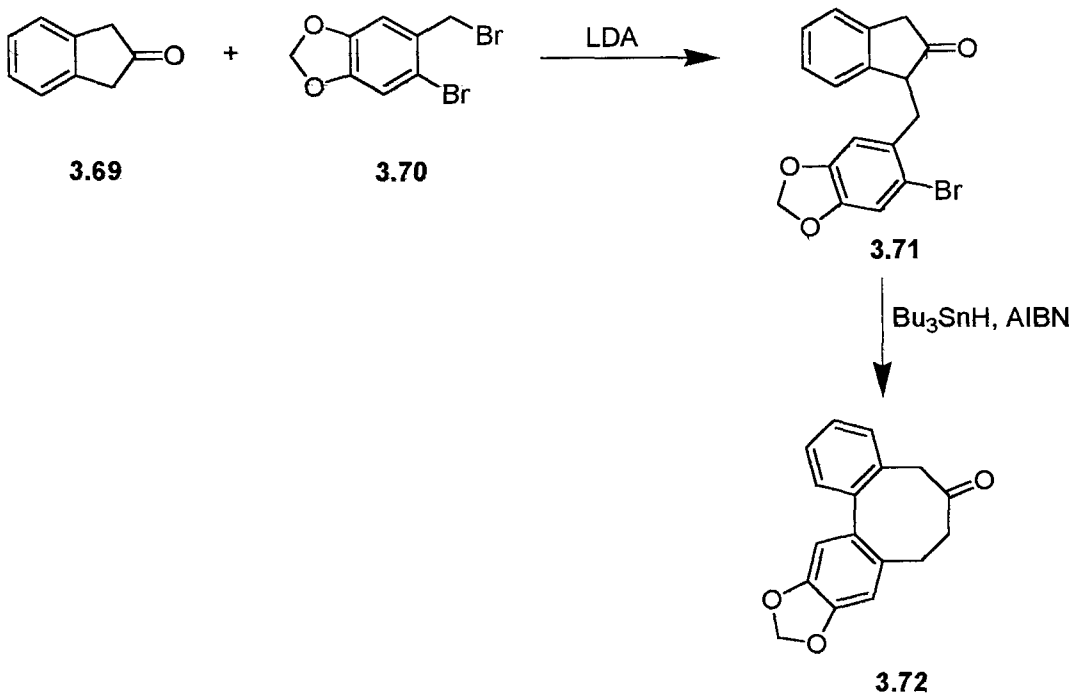
We now needed to transform indanone **3.61** into indene **3.60**. This turned out not to be as simple as first envisioned. We attempted to react **3.61** with methylmagnesium iodide in THF but without success since the grignard formed a complex with THF to form a solid mass. Conducting the reaction in ether was more rewarding but led to an inseparable mixture of products on attempted isolation. This led us to consider the use of cerium trichloride and methyllithium. We were still unable to isolate the desired alcohol but rather a mixture of products. Because of the problems encountered we decided to conduct a model study on 1 – indanone. We found that the alcohol formed using the cerium trichloride / methyllithium procedure but was unstable and we were unable to isolate it for any length of time. Therefore we decided that it was best to react the alcohol immediately with PPTS in DCM. This provided us with the alkene **3.66** in 42 % yield over the two steps (Scheme 17). We treated the alkene with DDO and we were able to form the diol **3.67** in 40 % yield. From this diol **3.67** we were unable to form the desired ketone **3.68** using lithium chloride or aluminium trichloride. Since progress was again slow we decided to leave this natural product and investigate the methodology.



Scheme 17: Synthesis of indanone **3.68**

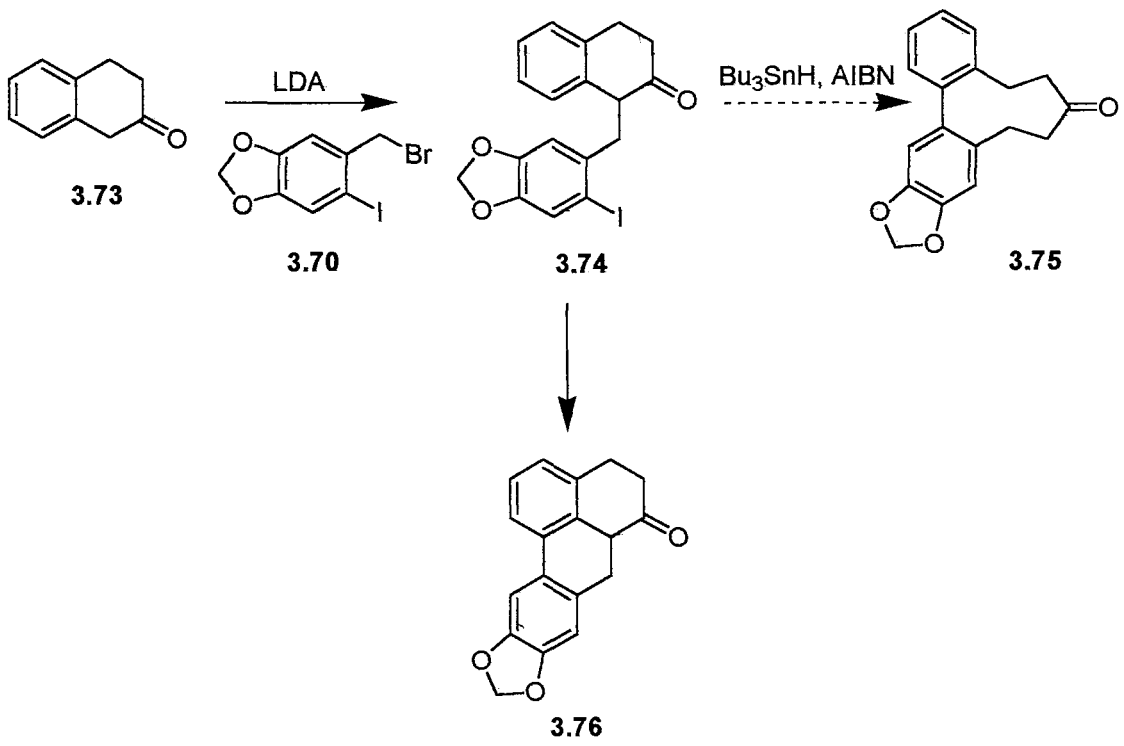
3.6 Intramolecular Radical Approach to Medium Sized Rings

Our study began with the preparation of **3.71** by alkylation of 2 – indanone **3.69** with benzyl bromide **3.70**. We obtained the alkylated product **3.71** in 47 % yield. Pleasingly, on exposure of this product to tributyltin hydride under standard radical forming conditions we were able to isolate the eight membered ring system **3.72** in 37 % yield.



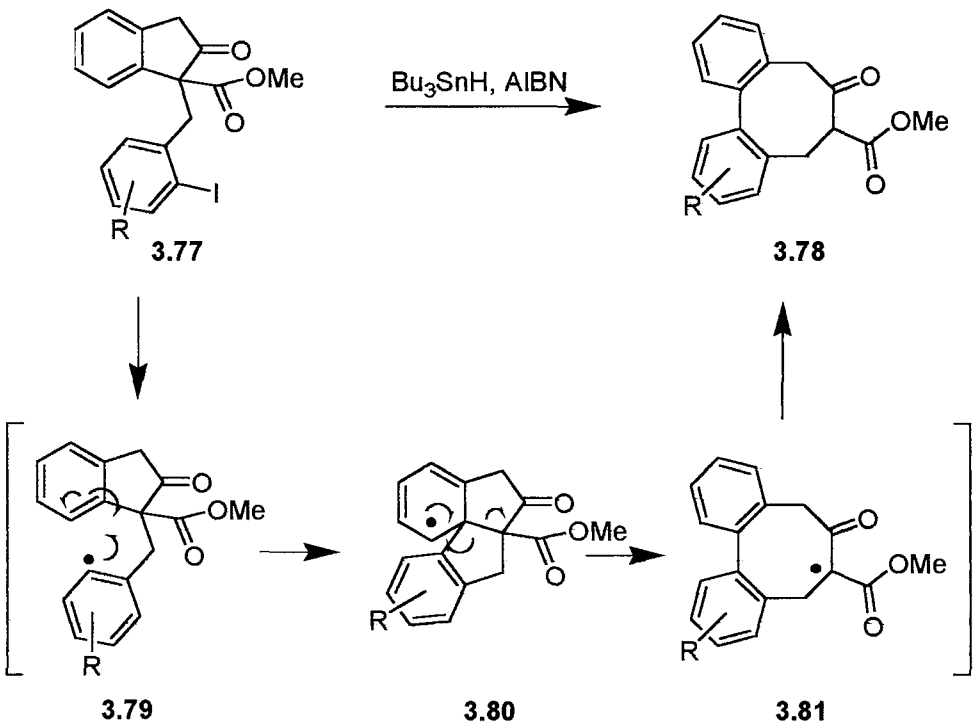
Scheme 18: Synthesis of dibenzocyclooctene **3.72**

This was an encouraging result and we decided to extend our study to tetralins. Tetralone **3.73** was treated sequentially with LDA and benzyl bromide **3.70** to give precursor **3.74** in a disappointing 23% yield. Attempts to transform this product into cyclononane proved unrewarding (Scheme 19). A number of attempts formed a number of products that could not be identified at the time. However when the results from the tetralins were obtained we suspect that the one of the products is the tetracycle **3.76**.



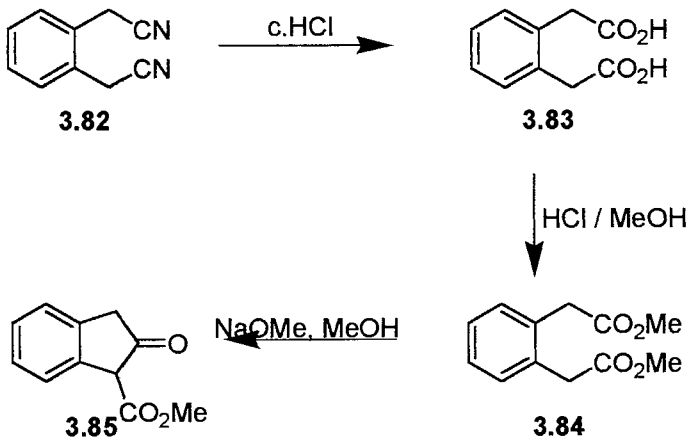
Scheme 19: Synthesis of precursor **3.75**

Since these cyclisation reactions were not giving us good yields of our desired product we went back to consider the mechanism. We envisaged that by adding an ester group adjacent to the ketone we would be able to promote both the alkylation reaction and the fragmentation step **3.80** to **3.81** (Scheme 20).



Scheme 20: Improved mechanism

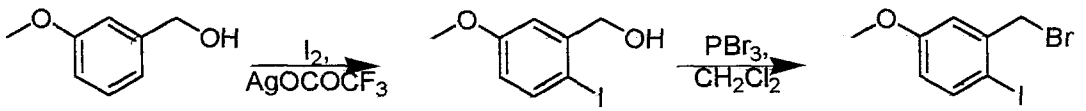
To investigate this idea we needed to form indanone **3.85**. This was achieved by refluxing the *bis*-acetonitrile **3.82** in concentrated hydrochloric acid to give acid **3.83** in 98 % yield. Acid **3.83** was then treated with methanolic hydrochloric acid to give the *bis*-ester **3.84** in 78 % yield. Exposure of this material to sodium methoxide provided the desired indanone **3.85** in 96 % yield (Scheme 21).



Scheme 21: Synthesis of indanone **3.85**

A number of 2-iodobenzyl bromides were now required in order to investigate the scope of our key step. Benzyl bromide **3.88** was formed from 3-methoxybenzyl alcohol via silver trifluoroacetate promoted iodination to the iodide **3.87** (86 % yield).

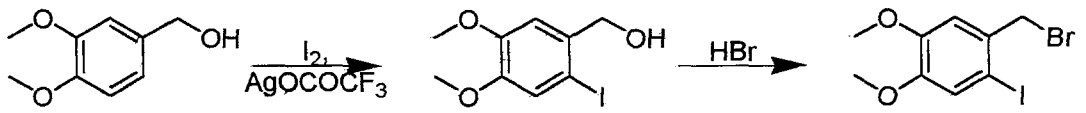
Brominating **3.87** with PBr_3 then gave the benzyl bromide **3.88** in 80 % yield (Scheme 22). The hydrobromic acid route to the bromide proved troublesome in this case.



3.86 **3.87** **3.88**

Scheme 22: Synthesis of bromide **3.88**

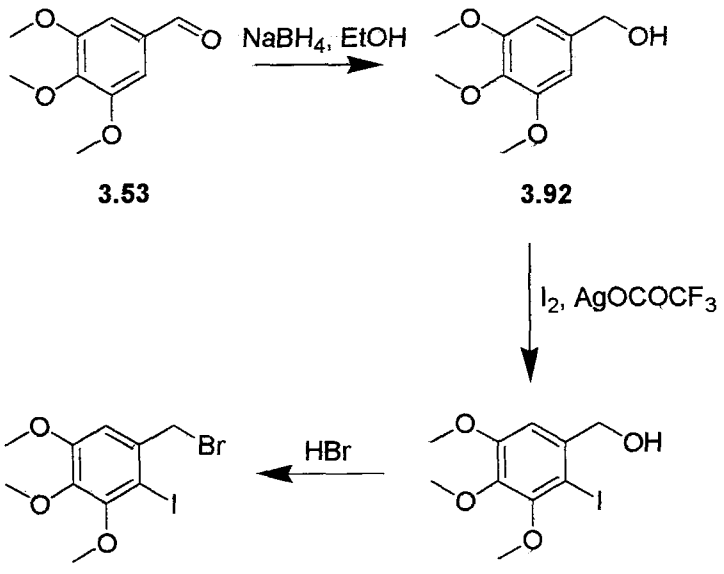
Benzyl bromide **3.91** was formed from alcohol **3.89** in an analogous fashion. Firstly iodination gave iodide **3.90** in 86 % yield. Then, using hydrobromic acid, this material was transformed to the bromide **3.91** in 86 % yield (Scheme 23).



3.89 **3.90** **3.91**

Scheme 23: Synthesis of bromide

To form benzyl bromide **3.94** we first reduced benzaldehyde **3.53** with sodium borohydride to give us alcohol **3.92** in 88 % yield. The alcohol **3.92** was treated with silver trifluoroacetate and iodine to give the iodide **3.93** in 82 % yield. From here we treated **3.93** with HBr to give the benzyl bromide **3.94** in 64 % yield (Scheme 24).

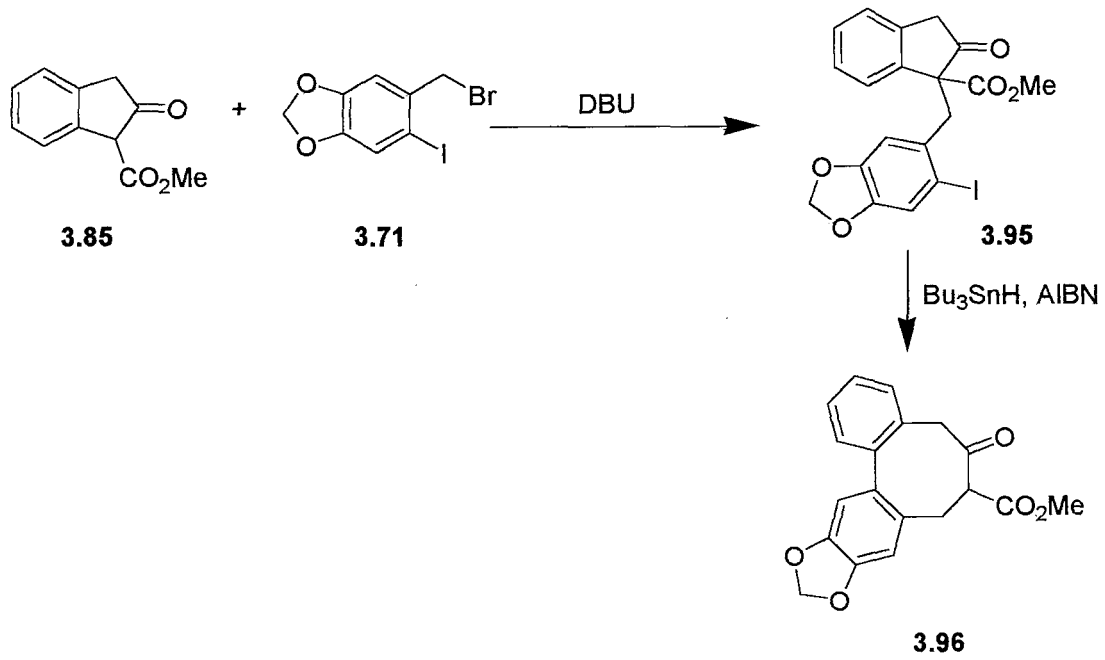


3.53 **3.92**

3.94 **3.93**

Scheme 24: Synthesis of bromide **3.94**

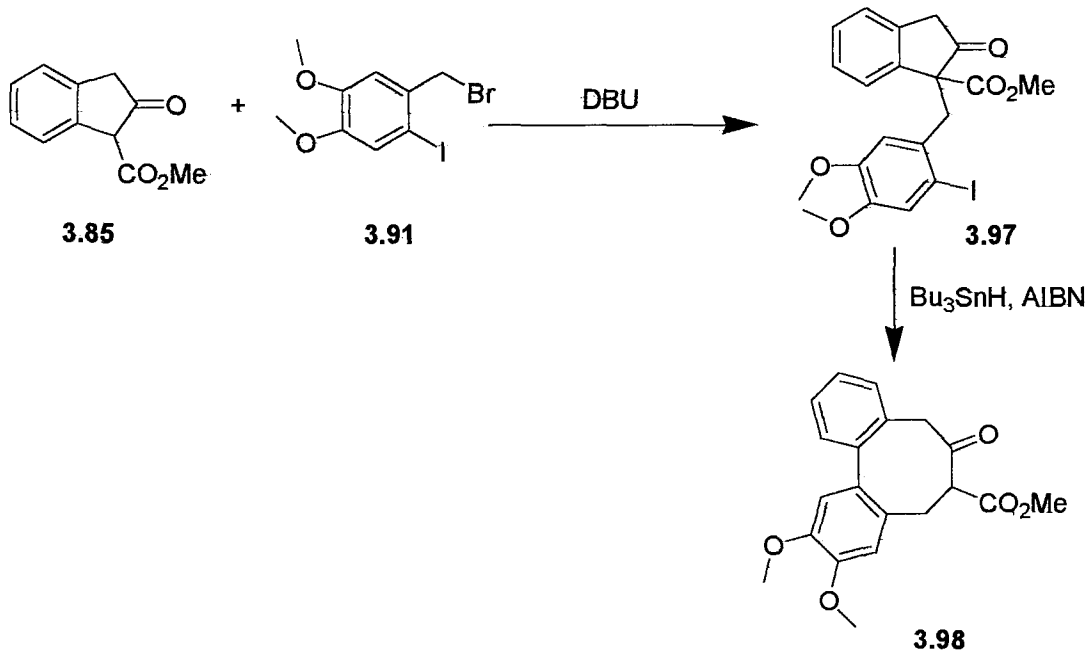
Now we had the requisite components to hand we set about synthesising our precursors. Treating indanone **3.85** with DBU and adding benzyl bromide **3.71** after 15 hours enabled us to form indanone **3.95** in 76 % yield. [66] We treated indanone **3.95** with tributyltin hydride and AIBN in toluene and were delighted to find that cyclooctene **3.96** was formed in 65 % yield (Scheme 25). This was very encouraging since the yield attained was almost double that achieved without the ester in place.



3.85 **3.71** **3.95** **3.96**

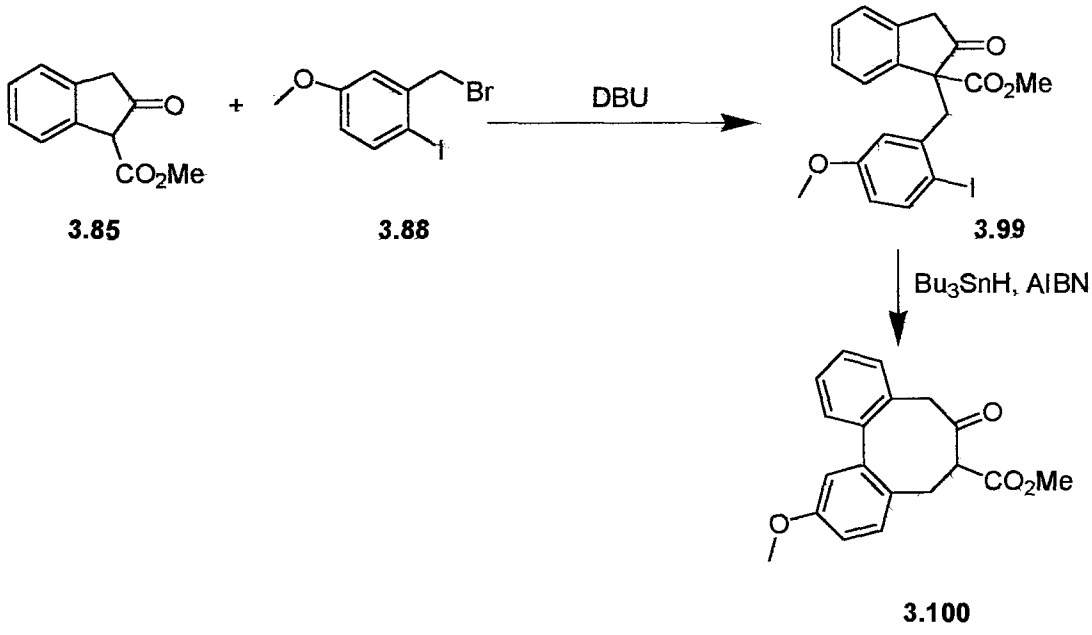
Scheme 25: Synthesis of dibenzocyclooctene **3.96**

Indanone **3.97** was formed in a similar fashion in 47 % yield. When treated with tributyltin hydride under standard radical forming conditions we were able to isolate cyclooctene **3.98** in 43 % yield.



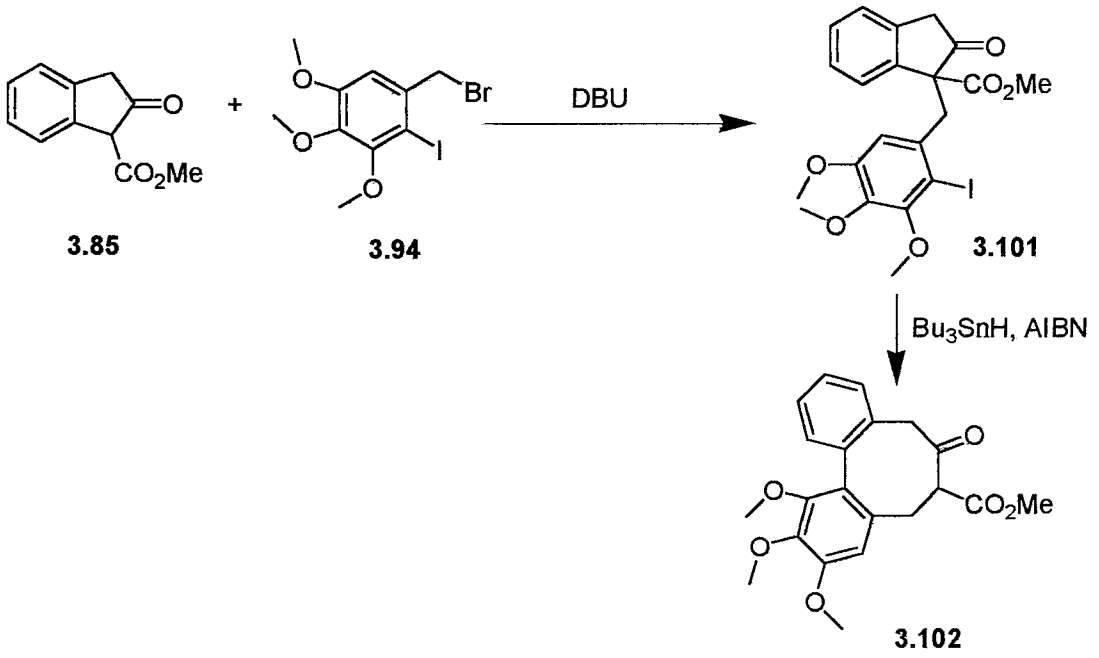
Scheme 26: Synthesis of dibenzocyclooctene **3.98**

Likewise indanone **3.99**, when treated with tributyltin hydride, gave the desired product **3.100** in 48 % yield (Scheme 27).



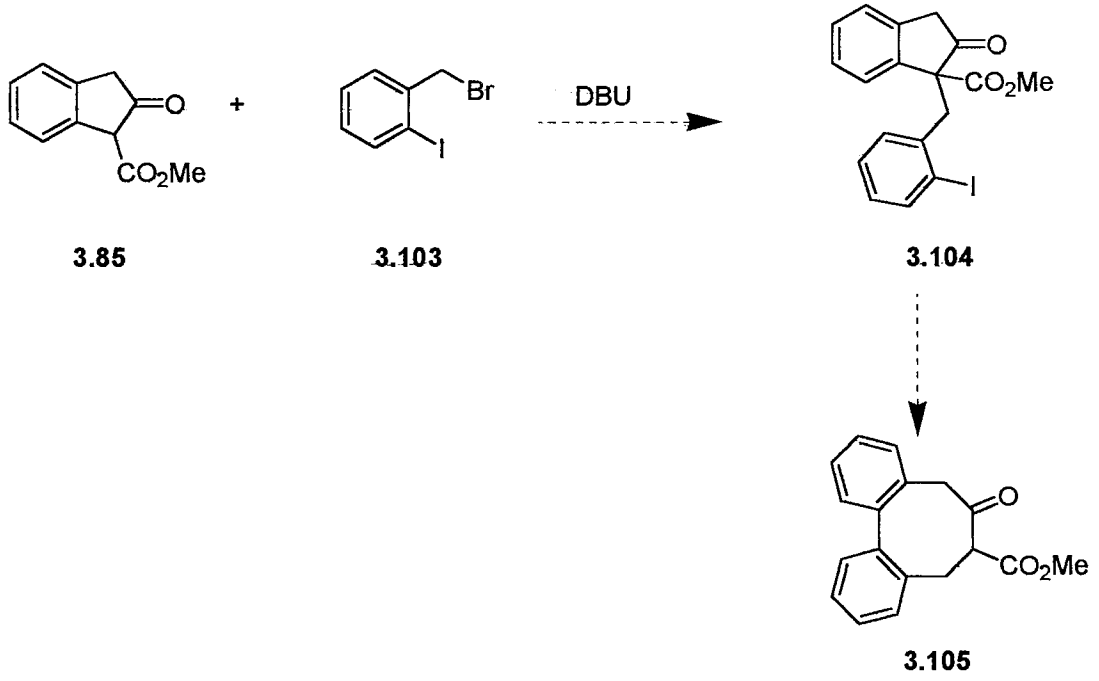
Scheme 27: Synthesis of dibenzocyclooctene **3.100**

A fourth example was achieved through alkylation of **3.85** with benzyl bromide **3.94**. Indanone **3.101**, formed in 39 % yield, when treated with tributyltin hydride gave the desired product **3.102** in 62 % yield (Scheme 28).



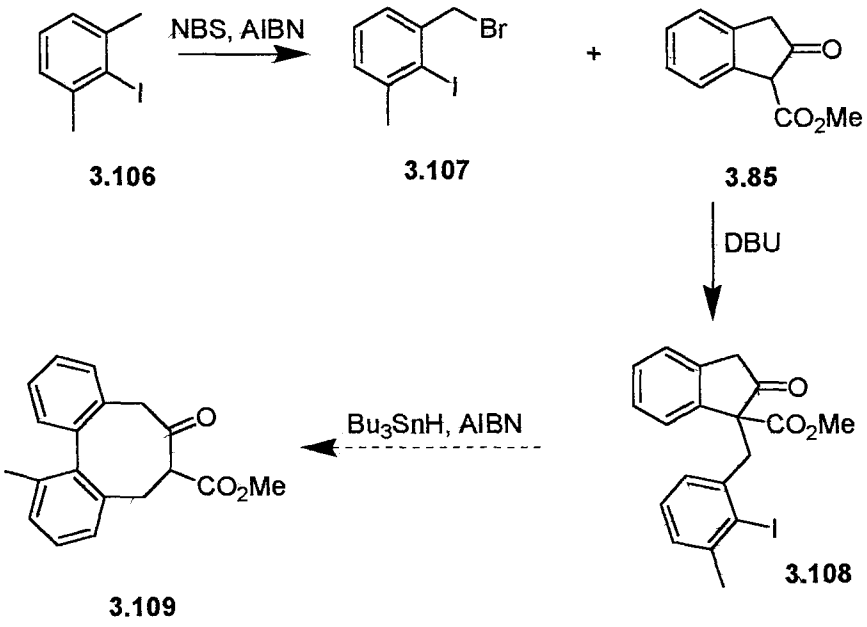
Scheme 28: Synthesis of dibenzocyclooctene **3.102**

These results were very pleasing. However we next experienced some disappointment. Alkylation of indanone **3.85** with 2-iodobenzyl bromide gave indanone **3.104** contaminated with unidentified material. When we attempted to transform this material into cyclooctene **3.105** we were unable to isolate any of the desired product Indeed recovered starting material was the only identifiable component in the product mixture (Scheme 29). Thus it appears that we needed an electron rich aryl iodide for this procedure to be effective.



Scheme 29: Synthesis of iodide **3.104**

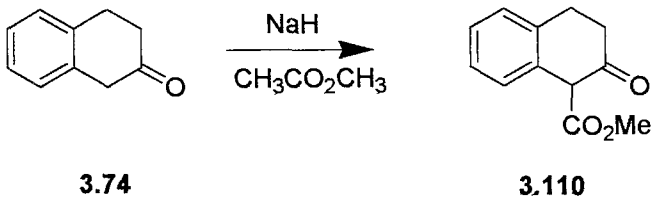
To investigate this effect further we brominated 2,6-dimethyl-1-iodobenzene **3.106** and coupled it to indanone **3.85** to give **3.108** in 32 % yield. We were unable to isolate the bromide due to its unstable nature. This indanone was then subjected to tributyltin hydride as before and we were unable to isolate our desired product **3.109** (Scheme 30). This suggests that electron rich aryl iodides are needed to achieve good yields in these reactions.



Scheme 30: Synthesis of dibenzocyclooctene

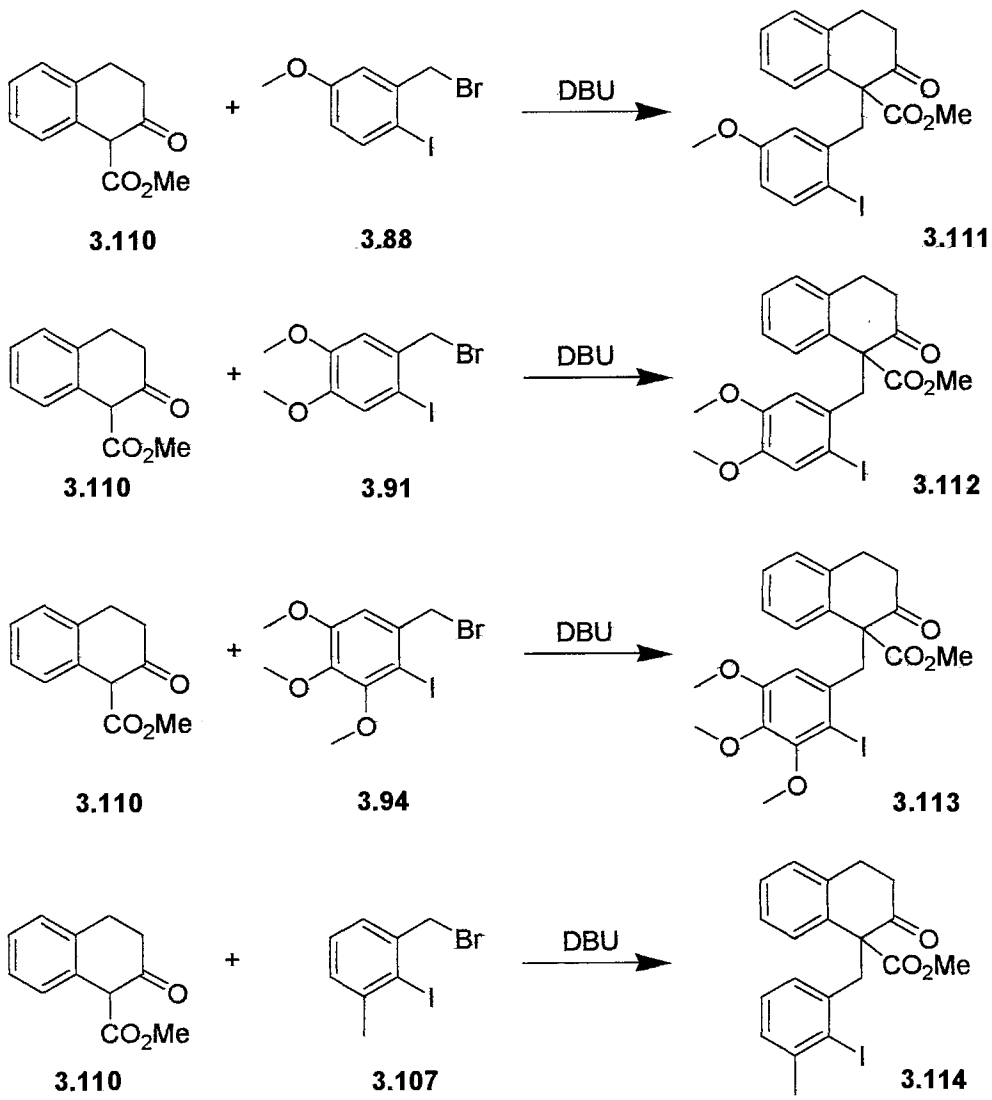
3.7 Tetralins

From these findings we hoped to extend the methodology to nine membered using tetralones as precursors. The tetralone **3.110** was prepared from **3.74** using sodium hydride and dimethylcarbonate, the desired product being isolated in 68 % yield (Scheme 31).



Scheme 31: Synthesis of tetralone **3.110**

We then alkylated tetralone **3.110** with a series of benzyl bromides using DBU to give the tetralones **3.111**, **3.112**, **3.113** and **3.114** in 29, 76, 57 and 19 % yield respectively.



3.110 3.88 3.111

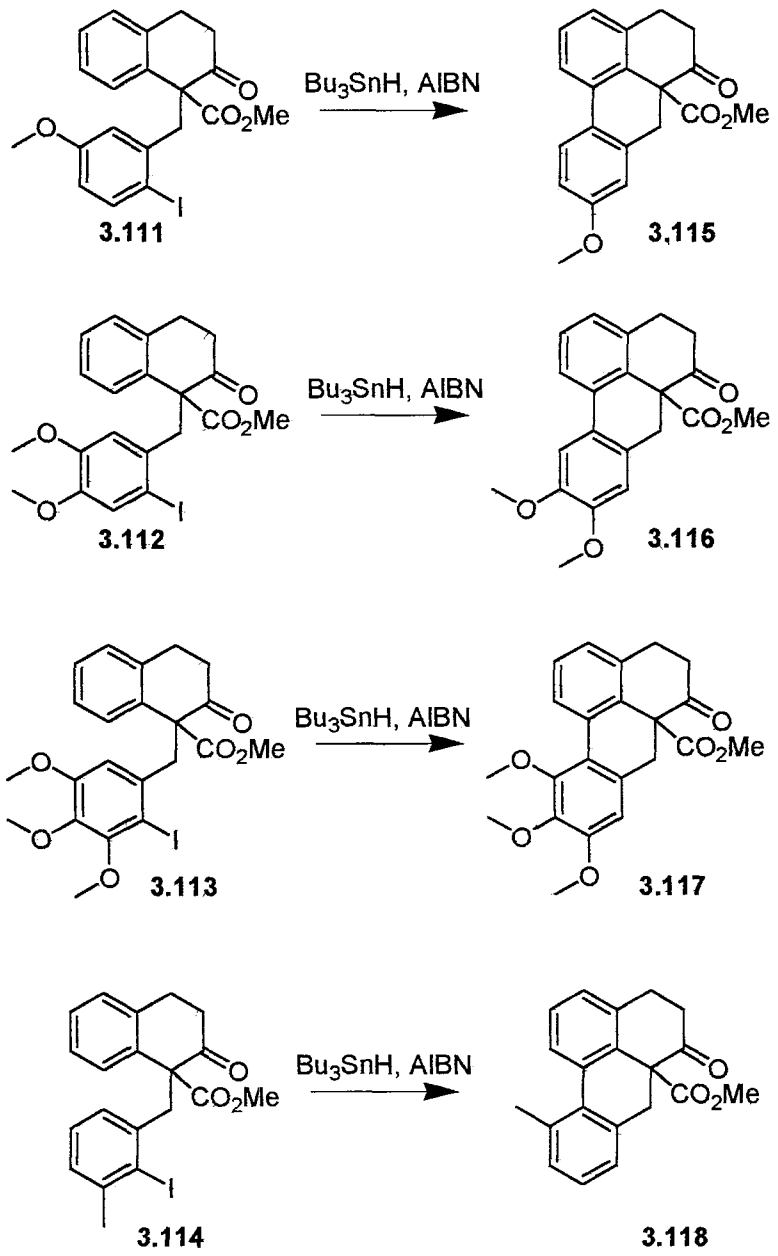
3.110 3.91 3.112

3.110 3.94 3.113

3.110 3.107 3.114

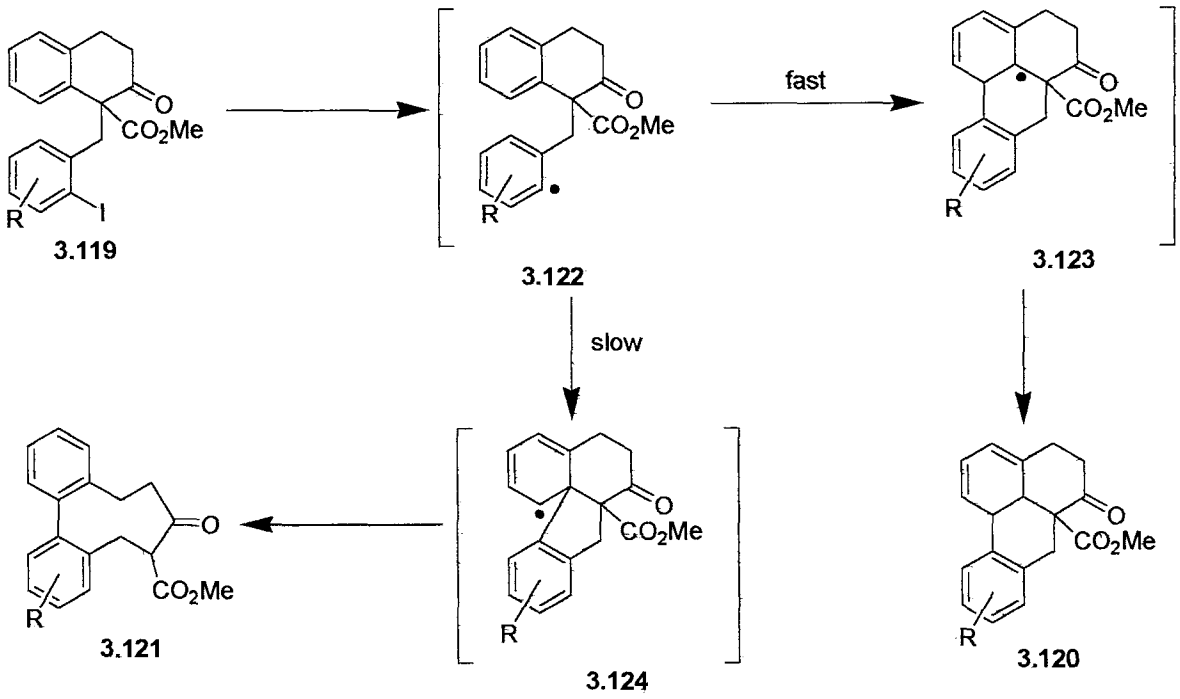
Scheme 32: Synthesis of iodides **3.111**, **3.112**, **3.113** and **3.114**

These substrates were each exposed to tributyltin hydride using our standard cyclisation conditions. Unexpectedly, we were unable to isolate the desired nine membered rings in any of the cases.



Scheme 33: Synthesis of tetralones **3.115**, **3.116**, **3.117** and **3.118**

Instead, the major products formed in these reactions are tetracyles **3.115**, **3.116**, **3.117** and **3.118** but these are contaminated with as yet unidentified products. We suspect that there are two diastereoisomers and reduced starting material (though not in all cases). Thus it seems that the larger saturated ring provides the radical intermediate an opportunity to add to the *ortho* carbon without building up strain within the system. As a consequence this becomes the favoured pathway (Scheme 34).

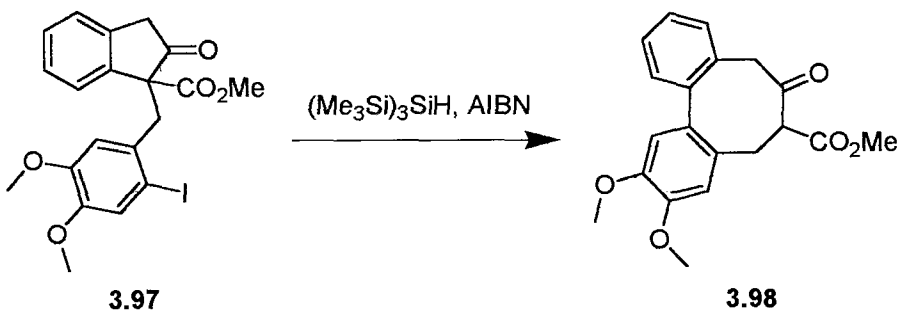


Scheme 34: Mechanism for formation of tetralones and nine-membered ring systems

The 6- *endo* cyclisation is a competing pathway to our *ipso* addition. In the case of the tetralones the 6-*endo* cyclisation is the preferred pathway since the addition of the radical to the arene is faster when forming **3.123** rather than **3.124**. This then leads to the formation of the tetracycle **3.120** and not the desired cyclononene **3.121**. If we could block this pathway we could access these the nine membered and possibly even larger ring systems.

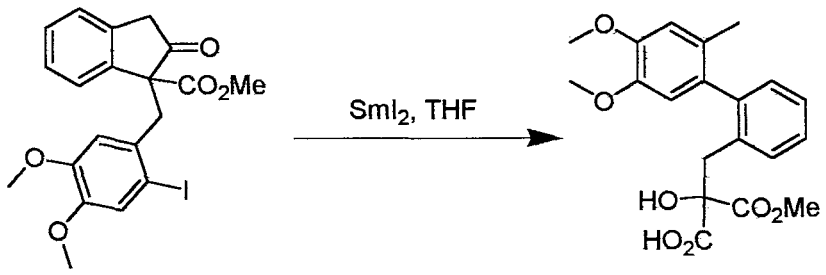
3.8 Alternative radical generating methods

We also investigated alternative methods for generating the radical intermediate. We substituted tris(trimethylsilyl)silane for tributyltin hydride and using the dimethoxy substrate **3.97**, we formed the cyclised product **3.98** in 56 % yield.



Scheme 35: Synthesis of dibenzocyclooctene **3.98**

When we attempted to use samarium diiodide with the same substrate we isolated a product that we were unable to assign with conviction. This product, which we tentatively propose to be **3.125**, was isolated in 32 % yield (Scheme 36). Further investigation is necessary to establish both the correctness of our assignment and the generality of this methodology.



3.97 **3.125**

Scheme 36: Product formed using samarium diiodide

3.9 Conclusions

In conclusion, we have developed a new approach to eight membered ring systems involving a radical induced fragmentation of indanones. This novel approach should allow us to target some biologically important natural products. There is also much scope for further study of the methodology in respect of substrates and method of radical generation.

3.10 Further Work

One of the aspects that needs to be addressed in any further work is the extent to which this procedure is effective. In particular, can nine - and ten - membered ring systems be prepared if the *ortho* carbon is blocked by a substituent? Can we replace the aryl iodide with an alkyl or vinyl iodide? The key step should allow access to a wide variety of targets and at present only the surface appears to have been touched.

Chapter 4

Experimental

4.0 Experimental

4.1 General

Reactions requiring anhydrous conditions were conducted in dried apparatus under a positive nitrogen atmosphere. Dry solvents were prepared by standard methods and where necessary commercial reagents were purified by distillation or recrystallisation prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium with benzophenone as an internal indicator immediately prior to use. Toluene was distilled from sodium prior to use. Chloroform and dichloromethane were distilled from calcium hydride immediately before use. Manganese(IV) oxide was activated by first suspending the solid in toluene and finally by removal of the solvent *in vacuo*. This procedure was repeated three times.

Organic extracts were concentrated using a Buchi-type rotary evaporator. All reactions mixtures were magnetically stirred and monitored by thin phase chromatography using Merck silica gel 60 F_{254} precoated aluminium sheets, phase thickness 0.25 mm. Compounds were visualised firstly by UV irradiation, then by heating plates exposed to solutions of phosphomolybdic acid in ethanol, 2,4-dinitrophenyl hydrazine in sulphuric acid or potassium permanganate in water. Column chromatography was performed on 230 – 400 mesh 60H silica gel (Fisher), slurry packed and run under low pressure. Petrol refers to petroleum ether b.p. 40-60°C and ether refers to diethyl ether.

Melting points were determined on a Griffin melting point apparatus and are uncorrected. UV spectra were recorded on a Pye Unicam (SP800) UV-vis spectrometer. Maxima are reported as λ_{max} (nm) followed by the extinction coefficient, ε ($dm^3mol^{-1}cm^{-1}$) in parentheses.

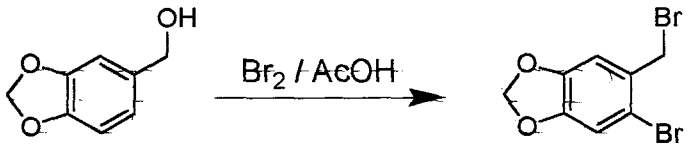
IR spectra were recorded on a Nicolet Impact 400 spectrophotometer (1 milliwatt helium neon laser at 633 nm). Details are reported as ν_{max} (cm^{-1}) followed by the relative intensities: s = strong, m = medium, w = weak and br = broad.

^{1}H spectra were recorded on a Bruker AC300 (300 MHz) spectrometer, Bruker AM300 (300 MHz) or a DPX 400 (400 MHz) spectrometer. Chemical shifts are quoted as δ values in ppm relative to residual $CHCl_3$ (δ_H = 7.27 p.p.m.), with the signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m =multiplet, br = broad and app = apparent.

^{13}C NMR were recorded on a Bruker AC300 (75.5 MHz) spectrometer or a DPX 400 (100 MHz) spectrometer. Chemical shifts are quoted as δ values (ppm) relative to residual $CHCl_3$ (δ_C = 77.2 ppm).

Mass spectra were under the supervision of Dr G. J. Langley at the University of Southampton using a variety of instruments. Signals are reported as values in atomic mass units followed in parentheses by the peak intensity relative to the base peak (100%).

4.2 6-Bromo-3,4-methylenedioxybenzyl bromide **2.6**



2.5 $C_8H_8O_3$ RMM 152

2.6 $C_8H_6O_2Br_2$ RMM 294

Dibromide **2.6** was prepared by the method of Padwa *et al.*[67] Piperonyl alcohol **2.5** (20.8 g, 137 mmol) was dissolved in acetic acid (50 mL) and cooled to 0 °C. A solution of bromine (8.5 mL, 166 mmol) in acetic acid (25 mL) was added dropwise over 20 minutes and the mixture was stirred for 3 h at room temperature. The resulting solid was collected by filtration and washed with water (2 x 30 mL). The organic solid was dissolved in DCM (50 mL) and washed with brine (30 mL) then dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The filtrate was extracted with DCM (3 x 30 mL) and the combined organic phases were dried ($MgSO_4$) and the solvent removed under vacuum. The combined solids were recrystallised from petrol to give the title compound **2.6** (38.0 g, 129 mmol, 94%) as a white crystalline solid.

Data are consistent with those reported in the literature.[67]

Melting point: 88-91 °C (petrol) Lit: 89-91 °C [67]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.02 (1H, s, ArH), 6.92 (1H, s, ArH), 6.00 (2H, s, OCH_2O), 4.57 (2H, s, CH_2Br)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 148.9 (C), 147.7 (C), 130.0 (C), 115.8 (CH), 113.3 (CH), 110.6 (CBr), 102.3 (OCH_2O), 34.3 (CH_2Br)

LRMS (APCI)

M/z: 296 ([M(^{81}Br, ^{81}Br)]$^+$, 51 %), 294 ([M(^{79}Br, ^{81}Br)]$^+$, 100 %), 292 ([M(^{79}Br, ^{79}Br)]$^+$, 54%) amu

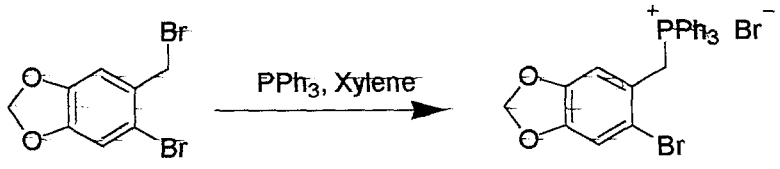
FT-IR (Neat)

ν_{max} 3050w, 1620w, 1480s, 1435w, 1409w, 1250s, 1212m, 1036m, 974w, 932m, 868s cm^{-1}

UV (Methanol)

λ_{max} (ε) 299 (4250), 261 (4800) nm

4.3 [(6-Bromo-1,3-benzodioxol-5-yl)methyl]triphenylphosphonium bromide **2.7**



2.6 $C_8H_6O_2Br_2$ RMM 294

2.7 $C_{26}H_{21}O_2Br_2P$ RMM 556

Bromide **2.6** (38.2 g, 129 mmol) was dissolved in xylene (60 mL) and triphenylphosphine (44.0 g, 47 mmol) was added. The mixture was stirred at 80 °C for 2 h and the resulting precipitate was collected by filtration and washed with cold xylene (2 x 40 mL) then petrol (3 x 30 mL) to give the title compound **2.7** (45.1 g, 81 mmol, 63%) as a white amorphous solid.

Data is consistent with the literature.[68]

Melting point: >250 °C (Ethanol) Lit: 278-280 °C (Ether / methanol)[68]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.79 (3H, m, 3 x ArH), 7.62 (12H, m, 12 x ArH), 7.00 (1H, d, J_{H-P} 1.8 Hz, ArH), 6.78 (1H, s, ArH), 5.92 (2H, s, OCH_2O), 5.53 (2H, d, J_{H-P} 13.2 Hz, CH_2P),

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 149.1 (CO), 148.1 (CO), 135.4 (d, J_{C-P} 2.0 Hz, 3 x CH), 134.5 (d, J_{C-P} 10.0 Hz, 6 x CH), 130.4 (d, J_{C-P} 12.5 Hz, 6 x CH), 120.1 (d, J_{C-P} 10.0 Hz, C), 118.4 (CBr), 117.5 (d, J_{C-P} 85.6 Hz, 3 x C), 112.7 (CH), 112.4 (d, J_{C-P} 4.0 Hz, CH), 102.4 (OCH_2O), 31.2 (d, J_{C-P} 48.0 Hz, CH_2P)

LRMS (APCI)

M/z 477 ([M(^{81}Br)-Br]$^+$, 100 %), 475 ([M(^{79}Br)-Br]$^+$, 83 %), 279 (25%), 263 (58%), 146 (34%) amu

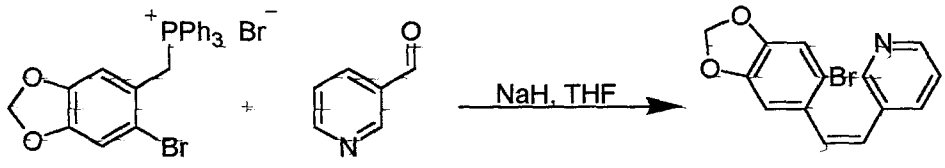
FT-IR ($CDCl_3$)

ν_{max} 3050m, 1620br s, 1503m, 1483s, 1437m, 1358w, 1264s, 1110m, 1037m, 931w, 895w, 866w cm^{-1}

UV (Methanol)

λ_{max} (ε) 298 (6000), 272 (7300) nm

4.4 *Z*-3-[2-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl]pyridine and *E*-3-[2-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl]pyridine **2.28**



2.7 **2.27** **2.28**

$C_{23}H_{21}O_2Br_2P$ RMM 556 C_6H_5ON RMM 107 $C_{14}H_{10}O_2BrN$ RMM 304

Sodium hydride (60% in mineral oil, 780 mg, 32.5 mmol) was washed with THF (10 mL) then further THF (50 mL) was added. After cooling to 0 °C, phosphonium bromide **2.7** (4.10 g, 7.40 mmol) was added and the mixture stirred at room temperature for 2 h then cooled to 0 °C. Aldehyde **2.27** (0.84 g, 7.90 mmol) was added as a solution in THF (10 mL) and the reaction mixture was stirred at room temperature for 2 h then filtered. The filtrate was concentrated *in vacuo* then diluted with DCM (50 mL) and filtered. Solvent was concentrated *in vacuo* and the crude material was separated by column chromatography (silica, 50% ether / petrol) to give the title compound **2.28** as the *Z* isomer (1.15 g, 3.80 mmol, 48%) and the *E* isomer (0.39 g, 1.30 mmol, 16%) both as white crystalline solids.

***Z*-3-[2-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl]pyridine**

Melting point: 85-87 °C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.41 (2H, m, ArH), 7.43 (1H, app dt, *J* 8.0, 2.0 Hz, ArH), 7.12 (1H, dd, *J* 8.0, 5.0 Hz, ArH), 7.06 (1H, s, ArH), 6.66 (1H, d, *J* 12.0 Hz, =CH), 6.57 (1H, d, *J* 12.0 Hz, =CH), 6.54 (1H, s, ArH), 5.92 (2H, s, OCH_2O)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 150.3 (C**H**), 148.4 (C**H**), 148.2 (**C**), 147.3 (**C**), 136.0 (C**H**), 132.3 (**C**), 132.0 (C**H**), 130.2 (**C**), 127.3 (C**H**), 123.3 (C**H**), 114.9 (**C**), 113.0 (C**H**), 110.0 (C**H**), 102.0 (O**C**H$_2$O)

LRMS (APCI)

M/z 306 ([MH(^{81}Br)]$^+$, 30 %), 304 ([MH(^{79}Br)]$^+$, 38 %), 224 ([M-^{79}Br]$^+$, 100 %) amu

HRMS (EI)

Calculated M$^+$: 302.9895; Found M$^+$: 302.9911

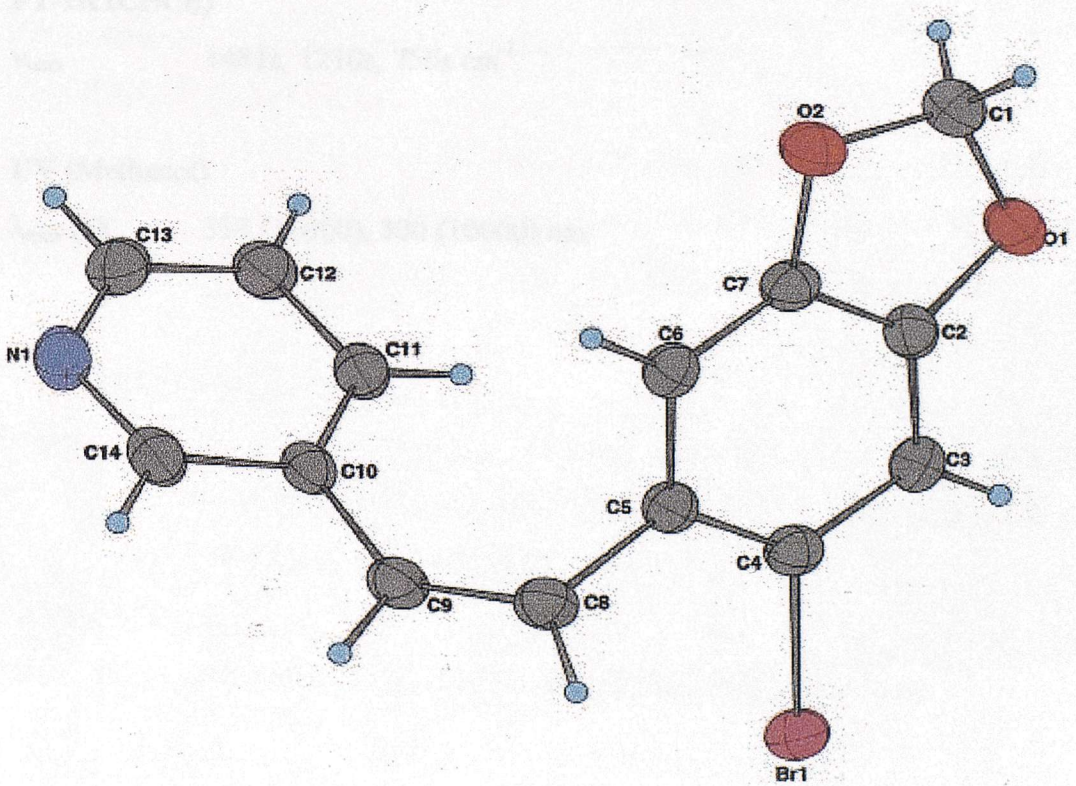
FT-IR (Neat)

ν_{max} 1486s, 1210s, 1037s, 756s cm^{-1}

UV (Methanol)

λ_{max} (ε) 294 (8200) nm

X-ray crystal structure was obtained on *Z* isomer and confirmed structure.



***E*-3-[2-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl]pyridine**

Melting point: 110-112 °C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.71 (1H, d, *J* 1.5 Hz, ArH), 8.50 (1H, dd, *J* 4.0, 2.0 Hz, ArH), 7.87 (1H, app dt, *J* 8.0, 2.0 Hz, ArH), 7.46 (1H, d, *J* 16.0 Hz, =CH), 7.31 (1H, dd, *J* 8.0, 4.0 Hz, ArH), 7.16 (1H, s, ArH), 7.06 (1H, s, ArH), 6.85 (1H, d, *J* 16 Hz, =CH), 6.02 (2H, s, OCH_2O)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 150.3 (C), 148.8 (CH), 148.6 (C), 148.0 (C), 132.9 (CH), 132.1 (CH), 130.0 (C), 129.5 (CH), 126.0 (CH), 123.7 (CH), 115.8 (C), 113.0 (CH), 106.0 (CH), 102.1 (OCH_2O)

LRMS (APCI)

M/z 306 ($[MH(^{81}Br)]^+$, 72 %), 304 ($[MH(^{79}Br)]^+$, 76 %), 226 (100%) amu

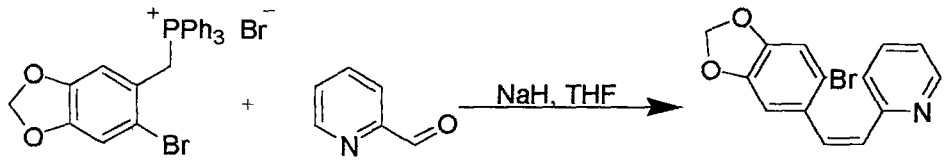
FT-IR ($CHCl_3$)

ν_{max} 1481s, 1210s, 756s cm^{-1}

UV (Methanol)

λ_{max} (ε) 337 (11000), 300 (10000) nm

4.5 2-[2-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl]pyridine **2.30**



2.7 **2.29** **2.30**

$C_{23}H_{21}O_2Br_2P$ RMM 556 C_6H_5ON RMM 107 $C_{14}H_{10}O_2BrN$ RMM 304

Sodium hydride (60% in mineral oil, 440 mg, 11.10 mmol) was washed with THF (10 mL) then further THF (50 mL) was added. After cooling to 0°C, phosphonium bromide **2.7** (5.4 g, 9.70 mmol) was added and the mixture stirred at room temperature for 2 h then cooled to 0 °C. Aldehyde **2.29** (1.84 g, 17.20 mmol) was added as a solution in THF (10 mL) and the reaction mixture was stirred at room temperature for 2 h then filtered. The filtrate was concentrated then diluted with DCM (50 mL) and filtered. The solvent was then removed *in vacuo* and the crude material was purified by column chromatography (silica, 50% ether / petrol) to give the title compound **2.30** (0.97 g, 3.20 mmol, 36%, *Z*:*E* ~ 8:1) as a yellow oil. The stereoisomers were separated during recrystallisation in ethanol. The *E*-isomer was not recovered from the recrystallisation liquor.

Melting Point: 105 – 106 °C (Ethanol)

***Z*-2-[2-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl]pyridine**

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.58 (1H, d, *J* 4.0 Hz, ArH), 7.48 (1H, app dt, *J* 7.0, 2.0 Hz, ArH), 7.11 – 7.07 (3H, m, ArH), 6.75 (1H, d, *J* 12.0 Hz, =CH), 6.74 (1H, d, *J* 12.0 Hz, =CH), 6.64 (1H, s, ArH), 5.94 (2H, s, OCH_2O)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 155.6 (CH), 149.6 (C), 148.2 (C), 147.2 (C), 136.0 (CH), 132.6 (CH), 131.2 (CH), 130.4 (C), 124.1 (CH), 122.1 (CH), 115.0 (C), 112.8 (CH), 110.3 (CH), 101.9 (OCH_2O)

LRMS (APCI)

M/z 306 ([MH(^{81}Br)]$^+$, 100 %), 304 ([MH(^{79}Br)]$^+$, 98 %) amu

FT-IR (Neat)

ν_{max} 1495m, 1476s, 1229s, 1105w, 1037s, 932m cm^{-1}

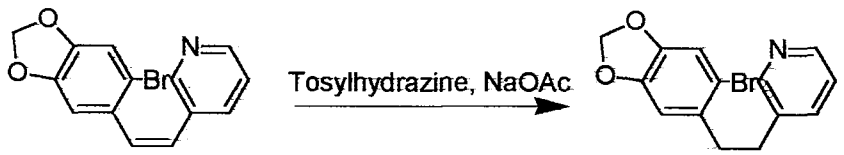
UV (Methanol)

λ_{max} (ε) 296 (6000) nm

CHN

Required: C 55.29%, H 3.31%, N 4.60%; Found: C 55.30%, H 3.33%, N 4.57%

4.6 3-[2-(6-Bromo-1,3-benzodioxol-5-yl)ethyl]pyridine **2.33**



2.28 $C_{14}H_{10}O_2BrN$ RMM 304

2.33 $C_{14}H_{12}O_2BrN$ RMM 306

Aryl bromide **2.28** (0.80 g, 2.60 mmol) was dissolved in 50% THF/water (30 mL). *p*-Tosylhydrazine (2.90 g, 16.00 mmol) and sodium acetate (1.30 g, 16.00 mmol) were added and the mixture was stirred at reflux for 72 h. Saturated K_2CO_3 solution (20 mL) was added and the organic phase was extracted with DCM (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) yielded the title compound **2.33** (0.60 g, 1.90 mmol, 74%) as a white solid.

Melting Point: 107 – 109 °C (DCM / Petrol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.45 (2H, m, 2 x ArH), 7.49 (1H, app d, *J* 7.0 Hz, ArH), 7.22 (1H, dd, *J* 7.0, 4.0 Hz, ArH), 6.99 (1H, s, ArH), 6.59 (1H, s, ArH), 5.94 (2H, s, OCH_2O), 2.96 – 2.82 (4H, m, 2 x CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 150.0 (CH), 147.6 (CH), 147.5 (C), 147.0 (C), 136.6 (C), 136.3 (CH), 133.1 (C), 123.5 (CH), 114.5 (C), 112.9 (CH), 110.2 (CH), 101.8 (OCH_2O), 38.0 (CH_2), 33.6 (CH_2)

LRMS (CI)

M/z 308 ([M(^{81}Br)H]$^+$, 96 %), 306 ([M(^{79}Br)H]$^+$, 100 %), 226 (52 %) amu

HRMS (EI)

Calculated M^+: 305.0051; Found M^+: 305.0042

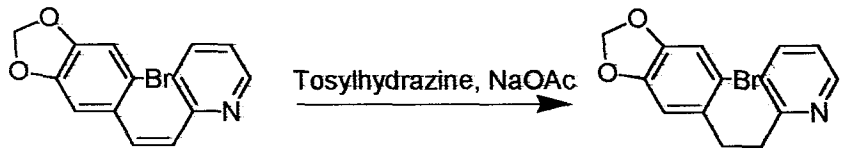
FT-IR (Neat)

ν_{max} 1479s, 1307w, 1234w, 1156s, 1043m, 929m, 815m cm^{-1}

UV (Methanol)

λ_{max} (ε) 298 (7500) nm

4.7 2-[2-(6-Bromo-1,3-benzodioxol-5-yl)ethyl]pyridine **2.38**



2.30 $C_{14}H_{10}O_2BrN$ RMM 304

2.38 $C_{14}H_{12}O_2BrN$ RMM 306

Aryl bromide **2.30** (0.75 g, 2.50 mmol) was dissolved in 50% THF/water (30 mL). *p*-Tosylhydrazine (2.20 g, 12.00 mmol) and sodium acetate (1.40 g, 17.00 mmol) were added and the mixture was stirred at reflux for 72 h. Saturated K_2CO_3 solution (20 mL) was added and the organic phase was extracted with DCM (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude material was purified by column chromatography (silica, 50% ether / petrol) to yield the title compound **2.38** (0.57 g, 1.90 mmol, 76 %) as a white solid.

Melting point: 93 – 94 °C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.56 (1H, d, *J* 4.0 Hz, ArH), 7.58 (1H, app td, *J* 8.0, 2.0 Hz, ArH), 7.15 – 7.10 (2H, m, 2 x ArH), 6.98 (1H, s, ArH), 6.64 (1H, s, ArH), 5.98 (2H, s, OCH_2O), 3.12 – 3.02 (4H, m, 2 x CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 160.9 (C), 149.4 (CH), 147.4 (C), 146.9 (C), 136.6 (CH), 133.9 (C), 123.2 (CH), 121.4 (CH), 114.5 (C), 112.8 (CH), 110.2 (CH), 101.7 (OCH_2O), 38.7 (CH_2), 36.4 (CH_2)

LRMS (CI)

M/z 308 ($[MH(^{81}Br)]^+$, 52 %), 306 ($[MH(^{79}Br)]^+$, 56 %), 228 ($[M-Br+2H]^+$, 62 %), 226 ($[M-Br]^+$, 100 %) amu

FT-IR (Neat)

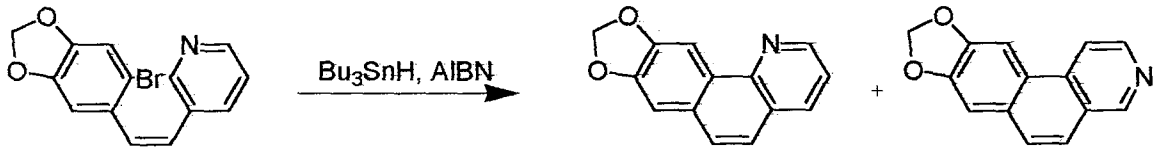
ν_{max} 1587w, 1500m, 1477s, 1433w, 1230s, 1115w, 1033s, 925m, 872w cm^{-1}

UV (Methanol)

λ_{max} (ε) 294 (7500), 231 (9700) nm

4.8 [1,3]Dioxolo[4',5':4, 5]benzo[*h*]quinoline **2.31** and

[1,3]Dioxolo[4',5':4, 5]benzo[*f*]isoquinoline **2.32**



2.28
$C_{14}H_{10}O_2BrN$ RMM 304

2.31
$C_{14}H_9O_2N$ RMM 223

2.32
$C_{14}H_9O_2N$ RMM 223

Aryl bromide **2.28** (0.85 g, 2.80 mmol) was dissolved in toluene (100 mL). AIBN (0.30 g, 1.81 mmol) and tributyltin hydride (1.5 mL, 1.40 g, 4.90 mmol) were added and the solution was stirred for 17 h at 80 °C. Saturated KF solution (30 mL) was added and the solution stirred for a further 24 h. The mixture was extracted with ether (3 x 20 mL) and the combined organic phases were washed with brine (20 mL) then dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was separated by column chromatography (silica, 50% ether / petrol) to give firstly **2.31** (0.30 g, 1.35 mmol, 48%) and then **2.32** (0.10 g, 0.45 mmol, 16%) as cream solids.

[1,3]Dioxolo[4',5':4, 5]benzo[*h*]quinoline

Melting point: 128-130 °C (Chloroform)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.82 (1H, dd, *J* 7.0, 2.0 Hz, ArH), 8.58 (1H, s, ArH), 8.06 (1H, dd, *J* 9.0, 2.0 Hz, ArH), 7.60 (1H, d, *J* 12.0 Hz, ArH), 7.48 (1H, d, *J* 12.0 Hz, ArH), 7.38 (1H, dd, *J* 9.0, 7.0 Hz, ArH), 7.12 (1H, s, ArH), 6.03 (2H, s, OCH_2O)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 149.1 (C), 148.7 (CH), 148.7 (C), 146.2 (C), 136.0 (CH), 130.5 (C), 127.2 (CH), 125.8 (C), 125.5 (C), 123.9 (CH), 121.2 (CH), 105.1 (CH), 102.5 (CH), 101.6 (OCH_2O)

LRMS (CI)

M/z 224 (MH^+, 100 %), 164 (18 %), 137 (12 %) amu

HRMS (EI)

Calculated M^+: 223.0633; Found M^+: 223.0629

FT-IR (Neat)

ν_{max} 1497m, 1461s, 1249s, 1214w, 1036s, 943m, 878s, 802w cm^{-1}

UV (Methanol)

λ_{max} (ε) 281 (15000), 252 (11000), 231 (17000) nm

CHN

Required: C 75.33%, H 4.06%, N 6.27%; Found: C 75.27%, H 4.06%, N 6.22%

[1,3]Dioxolo[4',5':4, 5]benzo[*f*]isoquinoline

Melting point: 185-188 °C decomp. (Chloroform)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 9.20 (1H, s, ArH), 8.64 (1H, d, *J* 7.0 Hz, ArH), 8.17 (1H, d, *J* 7.0 Hz, ArH), 7.94 (1H, s, ArH), 7.71 (2H, s, ArH), 7.24 (1H, s, ArH), 6.15 (2H, s, OCH_2O)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 152.0 (CH), 149.4 (C), 148.7 (C), 144.6 (CH), 130.6 (C), 127.9 (CH), 126.0 (C), 124.7 (C), 123.4 (CH), 115.9 (CH), 113.0 (C), 106.0 (CH), 101.9 (OCH_2O), 101.2 (CH)

LRMS (CI)

M/z 224 (MH^+, 100 %), 164 (20 %), 137 (10 %) amu

FT-IR (Neat)

ν_{max} 1602w, 1480s, 1272w, 1238s, 1196m, 1031s, 935s, 850s, 825m cm^{-1}

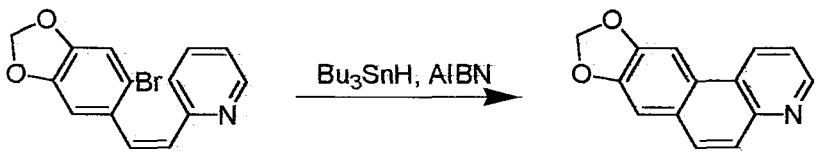
UV (Methanol)

λ_{max} (ε) 260 (9700) nm

CHN

Required: C 75.33%, H 4.06%, N 6.27%; Found: C 75.05%, H 4.23%, N 6.13%

4.9 [1,3]Dioxolo[4',5':4, 5]benzo[*f*]quinoline **2.37**



2.30
$C_{14}H_{10}O_2BrN$ RMM 304

2.37
$C_{14}H_9O_2N$ RMM 223

To a refluxing THF (40 mL) solution of aryl bromide **2.30** (0.15 g, 0.49 mmol) were added AIBN (15 mg, 0.09 mmol) and tributyltin hydride (0.16 mL, 0.15 g, 0.52 mmol). Further AIBN (2 x 50 mg, 2 x 0.30 mmol) was added after 2 h and 15 h respectively. After 24 h the reaction was cooled to room temperature, saturated KF solution (20 mL) was added and the mixture was stirred for a further 24 h. The aqueous phase was separated and extracted with ether (3 x 30 mL). The combined organic phases were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) yielded firstly **2.37** (0.04 g, 0.18 mmol, 36 %) as a brown solid then recovered starting material (0.05 g, 0.16 mmol, 33 %).

Melting point: 196-197 °C (Chloroform)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.82 (1H, d, *J* 4.0 Hz, ArH), 8.64 (1H, d, *J* 8.0 Hz, ArH), 7.85 (1H, s, ArH), 7.84 (1H, d, *J* 9.0 Hz, CH=CH), 7.78 (1H, d, *J* 9.0 Hz, CH=CH), 7.41 (1H, dd, *J* 8.0, 4.0 Hz, ArH), 7.19 (1H, s, ArH), 6.07 (2H, s, OCH_2O)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 149.2 (CH), 148.8 (C), 148.3 (C), 147.6 (C), 130.7 (CH), 130.4 (CH), 128.4 (C), 126.5 (CH), 126.0 (C), 125.3 (C), 121.1 (CH), 106.0 (CH), 101.8 (CH_2), 100.8 (CH)

LRMS (CI)

M/z 223 (M^+, 100 %), 164 (24 %), 138 (17 %) amu

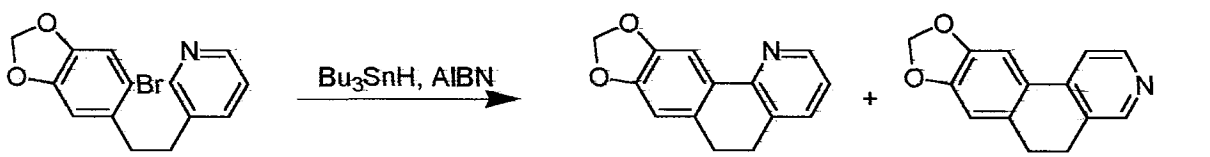
FT-IR (Neat)

ν_{max} 1497m, 1477s, 1257s, 1195m, 1031s, 935s, 909m, 853s, 806s, 733s cm^{-1}

UV (Methanol)

λ_{max} (ε) 285 (12000), 254 (8800), 232 (14000) nm

4.10 5,6-Dihydro[1,3]dioxolo[4',5':4, 5]benzo[*h*]quinoline **2.35** and 5,6-Dihydro[1,3]dioxolo[4',5':4, 5]benzo[*f*]isoquinoline **2.36**



2.33
$C_{14}H_{12}O_2BrN$ RMM 306

2.35
$C_{14}H_{11}O_2N$ RMM 225

2.36
$C_{14}H_{11}O_2N$ RMM 225

Aryl bromide **2.33** (0.59 g, 1.9 mmol) was dissolved in toluene (40 mL). AIBN (50 mg, 0.30 mmol) and tributyltin hydride (0.6 mL, 0.65 g, 2.3 mmol) was added and the solution was stirred for 17 h at 80 °C. Saturated KF solution (20 mL) was added and the solution was stirred for a further 24 h. The mixture was extracted with ether (3 x 30 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) gave cyclised product **2.35** (68 mg, 0.30 mmol, 15 %) as a brown solid then recovered starting material (0.23 g, 0.75 mmol, 39 %) and finally **2.36** (42 mg, 0.18 mmol, 10 %).

5,6-Dihydro[1,3]dioxolo[4',5':4, 5]benzo[*h*]quinoline

Melting point: 64-66 °C (Chloroform)

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 8.39 (1H, d, *J* 4.0 Hz, ArH), 7.75 (1H, s, ArH), 7.38 (1H, d, *J* 7.0 Hz, ArH), 6.99 (1H, dd, *J* 7.0, 4.0 Hz, ArH), 6.62 (1H, s, ArH), 5.90 (2H, s, OCH_2O), 2.92 – 2.68 (4H, m, 2 x CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 152.7 (C), 148.4 (C), 147.7 (CH), 147.3 (C), 135.5 (CH), 133.0 (C), 131.1 (C), 128.9 (C), 121.7 (CH), 108.2 (CH), 105.5 (CH), 101.2 (OCH_2O), 28.4 (CH_2), 28.3 (CH_2)

LRMS (CI)

M/z 225 (M^+, 100 %), 166 (28 %), 139 (24 %) amu

FT-IR (Neat)

ν_{max} 1483m, 1452s, 1414m, 1268m, 1228s, 1038s, 787m cm^{-1}

UV (Methanol)

λ_{max} (ε) 328 (10000), 285 (5400), 214 (13000) nm

CHN

Required: C 74.65%, H 4.92%, N 6.22%; Found: C 74.55%, H 4.86%, N 6.18%

5,6-Dihydro[1,3]dioxolo[4',5':4, 5]benzo[*f*]isoquinoline

Melting Point: 127 – 129 °C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.56 – 8.35 (2H, m, ArH), 7.51 (1H, d, *J* 8.0 Hz, ArH), 7.25 (1H, s, ArH), 6.61 (1H, s, ArH), 5.96 (2H, s, OCH_2O), 2.91 – 2.80 (4H, m, 2 x CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 150.1 (CH), 147.9 (CH), 147.8 (C), 147.4 (C), 136.9 (C), 136.5 (CH), 133.4 (C), 121.7 (C), 114.8 (C), 113.2 (CH), 110.4 (CH), 102.0 (OCH_2O), 38.0 (CH_2), 33.6 (CH_2)

LRMS (CI)

M/z 226 (MH^+, 100 %), 166 (36 %), 139 (26 %) amu

HRMS (EI)

Calculated M^+: 225.0790; Found M^+: 225.0781

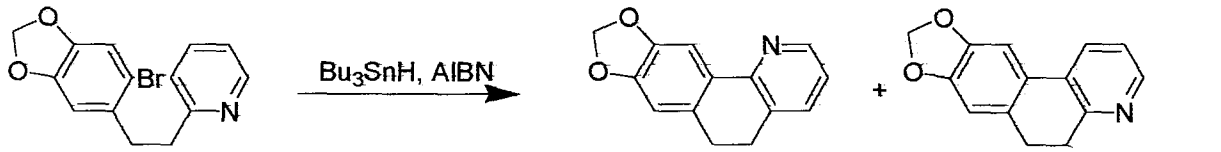
FT-IR (Neat)

ν_{max} 1476s, 1232m, 1037s, 932w, 714m cm^{-1}

UV (Methanol)

λ_{max} (ε) 325 (3500), 290 (5200), 234 (8600) nm

4.11 5,6-Dihydro[1,3]dioxolo[4',5':4, 5]benzo[*h*]quinoline **2.39** and 5,6-Dihydro[1,3]dioxolo[4',5':4, 5]benzo[*f*]quinoline **2.40**



2.38
$C_{14}H_{12}O_2BrN$ RMM 306

2.39
$C_{14}H_{11}O_2N$ RMM 225

2.40
$C_{14}H_{11}O_2N$ RMM 225

Aryl bromide **2.38** (0.40 g, 1.30 mmol) was dissolved in toluene (40 mL). AIBN (50 mg, 0.30 mmol) and tributyltin hydride (0.42 mL, 0.45 g, 1.60 mmol) were added and the solution was stirred for 17 h at 80 °C. Saturated KF solution (20 mL) was added and the mixture was stirred for a further 24 h. The mixture was extracted with ether (3 x 20 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) gave firstly **2.39** (48 mg, 0.21 mmol, 16 %) as a brown solid then recovered starting material (0.19g, 0.62 mmol, 41%) and finally **2.40** (106 mg, 0.46 mmol, 28 %) as a white solid.

5,6-Dihydro[1,3]dioxolo[4',5':4, 5]benzo[*h*]quinoline

Melting point: 64-66 °C (Chloroform)
The data was consistent with those reported previously.

5,6-Dihydro[1,3]dioxolo[4',5':4, 5]benzo[*f*]quinoline

Melting Point: 142-144 °C (Chloroform)

^{1}**H-NMR** (400 MHz, $CDCl_3$)

δ/ppm 8.41 (1H, d, *J* 4.0 Hz, ArH), 7.75 (1H, d, *J* 7.0 Hz, ArH), 7.08 (1H, dd, *J* 7.0, 4.0 Hz, ArH), 7.00 (1H, s, ArH), 6.61 (1H, s, ArH), 5.87 (2H, s, OCH_2O), 2.95 (2H, app t, *J* 7.0 Hz, CH_2), 2.78 (2H, app t, *J* 7.0 Hz, CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 157.2 (C), 147.7 (C), 147.3 (C), 147.1 (C), 131.4 (C), 130.0 (CH), 129.9 (CH), 126.6 (C), 122.4 (CH), 108.8 (CH), 104.3 (CH), 101.3 (CH_2), 31.9 (CH_2), 28.8 (CH_2)

LRMS (CI)

M/z 225 (M^+, 100 %), 166 (30 %), 139 (22 %) amu

FT-IR (Neat)

ν_{max} 1499w, 1478s, 1258m, 1195s, 1033s, 935s, 853m, 806m cm^{-1}

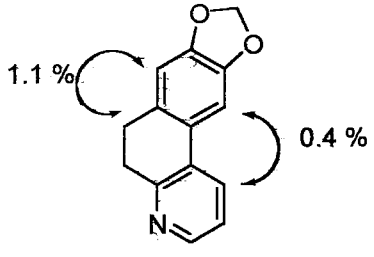
UV (Methanol)

λ_{max} (ε) 326 (6100), 282 (4700) nm

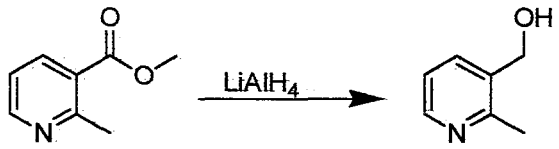
CHN

Required: C 74.65%, H 4.92%, N 6.22%; Found: C 74.13%, H 4.85%, N 6.09%

GOESY experiment confirmed structure of product.



4.12 (2-Methyl-3-pyridyl)methanol **2.47**



2.46 $C_8H_9O_2N$ RMM 151

2.47 C_7H_9ON RMM 123

Alcohol **2.47** was prepared by modifications of the procedure Ueyana *et al.*.[69] Lithium aluminium hydride (0.59 g, 15.0 mmol) was dissolved in THF (40 mL) then cooled to –78 °C. Methyl 2-methylnicotinate **2.46** (2.00 g, 13.0 mmol) was added as a solution in THF (10 mL) and the mixture was stirred for a further 1h whilst warming to ambient temperature. Saturated ammonium chloride (2 mL) was then added and the mixture was filtered. The filtrate was extracted with ether (3 x 20 mL) then dried ($MgSO_4$) and was concentrated *in vacuo* to give the title compound **2.47** (1.38 g, 11.2 mmol, 86%) as a pale yellow oil that was used directly in the next step.

Data are consistent with those reported in the literature. [69]

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 8.21 (1H, d, *J* 4.0 Hz, ArH), 7.71 (1H, d, *J* 8.0 Hz, ArH), 7.07 (1H, dd, *J* 8.0, 4.0 Hz, ArH), 5.24 (1H, br s, OH), 4.64 (2H, s, CH_2OH), 2.41 (3H, s, CH_3)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 155.8 (C), 147.0 (CH), 135.2 (C), 134.9 (CH), 121.6 (CH), 61.4 (CH_2), 21.3 (CH_3)

LRMS (CI)

M/z 124 (MH^+, 100 %), 108 (12 %) amu

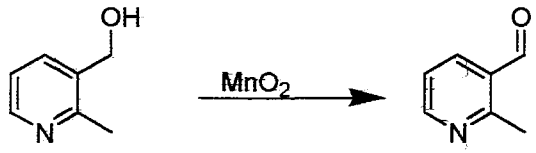
FT-IR (Neat)

ν_{max} 3197br w, 1582m, 1438s, 1050s, 727s cm^{-1}

UV (Methanol)

λ_{max} (ε) 262 (12000), 209 (16000) nm

4.13 (2-Methyl-3-pyridyl)aldehyde **2.48**



2.47 $C_7H_9O_2N$ RMM 123

2.48 C_7H_7ON RMM 121

Aldehyde **2.48** was prepared by the method of Kao *et al.*.[70] The alcohol **2.47** (1.38 g, 11.2 mmol) was dissolved in DCM (40 mL) and stirred at ambient temperature with activated manganese(IV) oxide (14.0 g, 16.00 mmol) for 40 h then filtered through a plug of Celite. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silica, ethyl acetate) to yield the title compound **2.48** (1.16 g, 9.6 mmol, 74% over 2 steps) as a yellow oil.

Data are consistent with those reported in the literature.[70]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 10.24 (1H, s, C<u>H</u>O), 8.58 (1H, dd, *J* 4.0, 2.0 Hz, Ar<u>H</u>), 8.00 (1H, dd, *J* 7.0, 2.0 Hz, Ar<u>H</u>), 7.23 (1H, dd, *J* 7.0, 4.0 Hz, Ar<u>H</u>), 2.79 (3H, s, C<u>H</u>$_3$)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 191.5 (<u>C</u>HO), 160.4 (<u>C</u>), 153.3 (<u>C</u>H), 138.3 (<u>C</u>H), 129.5 (<u>C</u>), 121.8 (<u>C</u>H), 22.5 (<u>C</u>H$_3$)

LRMS (CI)

M/z 122 (MH^+, 100 %), 93 (38 %) amu

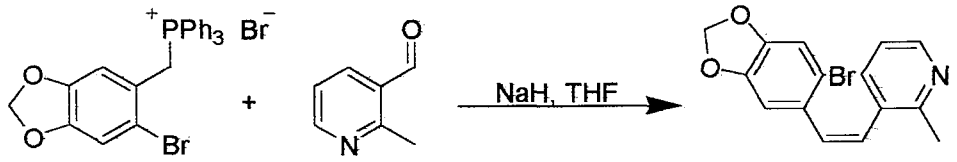
FT-IR (Neat)

ν_{max} 1702s, 1584m, 1439w, 1277w, 1222w, 880m, 790m, 725s cm^{-1}

UV (Methanol)

λ_{max} (ε) 264 (3200) nm

4.14 3-[2-(6-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl]-2-methylpyridine **2.49**



2.7 **2.48** **2.49**

$C_{23}H_{21}O_2Br_2P$ RMM 556 C_7H_8ON RMM 121 $C_{15}H_{12}O_2BrN$ RMM 318

Sodium hydride (60% in mineral oil, 560 mg, 14.0 mmol) was washed with THF (10 mL) then further THF (40 mL) was added. After cooling to 0 °C, phosphonium bromide **2.7** (2.10g, 3.80 mmol) was added and the mixture stirred at room temperature for 2 h then cooled to 0 °C. Aldehyde **2.48** (0.78 g, 6.40 mmol) was added as a solution in THF (10 mL) then the reaction mixture was warmed to room temperature over 10 min, stirred for a further 2 h and filtered. The filtrate was concentrated *in vacuo* then diluted with DCM (50 mL) and filtered. The solvent was then removed *in vacuo* and the residue was purified by column chromatography (silica, ether) to give the title compound **2.49** (1.69 g, 5.30 mmol, 83%, *Z*:*E* ~ 3:1) as an inseparable mixture of stereoisomers. The mixture of isomers was recrystallised to afford the *Z*-3-[2-(6-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl]-2-methylpyridine as a white solid. *E*-3-[2-(6-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl]-2-methylpyridine could not be isolated from the mother liquor.

***Z*-3-[2-(6-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl]-2-methylpyridine**

(Major Stereoisomer)

Melting Point: 112 – 114 °C (DCM / Petrol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.41 (1H, d, *J* 5.0 Hz, ArH), 7.44 (1H, d, *J* 8.0 Hz, ArH), 7.13 (1H, s, ArH), 7.05 (1H, dd, *J* 8.0, 5.0 Hz, ArH), 6.66 (1H, d, *J* 12.0 Hz, =CH), 6.56 (1H, d, *J* 12.0 Hz, =CH), 6.54 (1H, s, ArH), 5.92 (2H, s, OCH_2O), 2.52 (3H, s, CH_3)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 156.8 (C), 148.3 (CH), 147.4 (C), 137.3 (CH), 132.0 (CH), 131.5 (C), 130.2 (C), 128.1 (CH), 121.3 (CH), 115.9 (C), 115.5 (C), 113.1 (CH), 110.3 (CH), 102.4 (OCH_2O), 23.2 (CH_3)

LRMS (APCI)

M/z 320 (MH^+(^{81}Br), 98 %), 318 (MH^+(^{79}Br), 100 %), 130 (12 %), 127 (26 %) amu

HRMS (EI)

Calculated M^+: 317.0051 Found M^+: 317.0058

FT-IR (Neat)

ν_{max} 1498m, 1475s, 1437m, 1234m, 1037s, 931s, 758m cm^{-1}

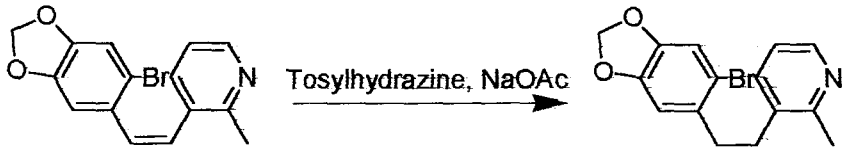
UV (Methanol)

λ_{max} (ε) 288 (10000) nm

CHN

Required: C 56.60%, H 3.77%, N 4.40%; Found: C 56.59%, H 3.50%, N 4.31%

4.15 3-[2-(6-Bromo-1,3-benzodioxol-5-yl)ethyl]-2-methylpyridine **2.50**



2.49 $C_{15}H_{12}O_2BrN$ RMM 318

2.50 $C_{15}H_{14}O_2BrN$ RMM 320

Aryl bromide **2.49** (1.00 g, 3.10 mmol) was dissolved in 50% THF/water (60 mL). Tosylhydrazine (3.00 g, 18.00 mmol) and sodium acetate (1.56 g, 18.00 mmol) were added and the mixture was stirred at reflux for 72 h. Saturated K_2CO_3 solution (20 mL) was added and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) yielded the title compound **2.50** (0.60 g, 2.00 mmol, 60 %) as a white crystalline solid.

Melting Point: 107 – 109 °C (DCM / Petrol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.35 (1H, dd, *J* 4.0, 2.0 Hz, ArH), 7.37 (1H, dd, *J* 8.0, 2.0 Hz, ArH), 7.05 (1H, dd, *J* 8.0, 4.0 Hz, ArH), 7.00 (1H, s, ArH), 6.60 (1H, s, ArH), 5.94 (2H, s, OCH_2O), 2.91 – 2.82 (4H, m, 2 x CH_2), 2.55 (3H, s, CH_3)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 156.8 (C), 147.5 (C), 147.1 (CH), 136.8 (CH), 134.5 (C), 133.4 (C), 121.5 (CH), 121.0 (C), 114.4 (C), 112.9 (CH), 110.1 (CH), 101.8 (CH_2), 36.7 (CH_2), 33.4 (CH_2), 22.4 (CH_3)

LRMS (CI)

M/z 320 (MH^+(^{81}Br), 98 %), 318 (MH^+(^{79}Br), 100 %), 242 ($[M+2H-Br]^+$, 84 %) amu

HRMS (EI)

Calculated M^+: 319.0208; Found M^+: 319.0208

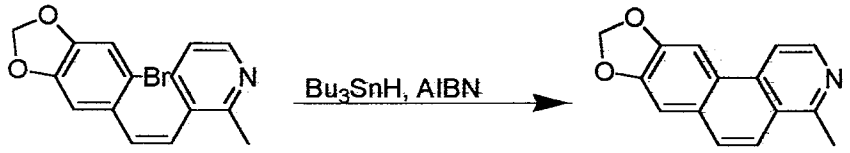
FT-IR (Neat)

ν_{max} 1477s, 1229s, 1037s, 928m cm^{-1}

UV (Methanol)

λ_{max} (ε) 288 (7700) nm

4.16 4-Methyl[1,3]dioxolo[4',5':4, 5]benzo[*f*]isoquinoline **2.51**



2.49
$C_{15}H_{12}O_2BrN$ RMM 318

2.51
$C_{15}H_{11}O_2N$ RMM 237

To a refluxing THF (40 mL) solution of aryl bromide **2.49** (0.2 g, 0.62 mmol) were added AIBN (50 mg, 0.30 mmol) and tributyltin hydride (0.2 mL, 0.18 g, 0.62 mmol). Further portions of AIBN (2 x 50 mg, 2 x 0.30 mmol) were added after 2 h and 15 h respectively. After 24 h the reaction was cooled, saturated KF solution (30 mL) was added and the mixture stirred for a further 24 h. The aqueous phase was separated and extracted with ether (3 x 20 mL). The combined organic phases were then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) yielded compound **2.51** (0.14 g, 0.59 mmol, 94%) as a white crystalline solid.

Melting Point: 210 – 212 °C decomp. (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.52 (1H, d, *J* 6.0 Hz, ArH), 8.04 (1H, d, *J* 6.0 Hz, ArH), 7.94 (1H, s, ArH), 7.86 (1H, d, *J* 9.0 Hz, ArH), 7.68 (1H, d, *J* 9.0 Hz, ArH), 7.22 (1H, s, ArH), 6.13 (2H, s, OCH_2O), 2.99 (3H, s, CH_3)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 158.2 (C), 149.2 (C), 148.7 (C), 143.2 (CH), 134.3 (C), 130.2 (C), 127.5 (CH), 125.2 (C), 125.1 (C), 121.5 (CH), 114.5 (CH), 105.8 (CH), 101.8 (OCH_2O), 101.4 (CH), 23.0 (CH_3)

LRMS (CI)

M/z 238 (MH^+, 100%), 178 (6 %), 151 (6 %) amu

HRMS (EI)

Calculated M^+: 237.0790; Found M^+: 237.0787

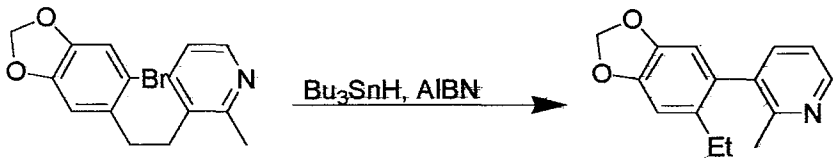
FT-IR (Neat)

ν_{max} 1479s, 1262s, 1198m, 1032s, 936s, 859m cm^{-1}

UV (Methanol)

λ_{max} (ε) 261 (15000) nm

4.17 3-(6-Ethyl-1,3-benzodioxol-5-yl)-2-methylpyridine **2.52**



2.50 $C_{15}H_{14}O_2BrN$ RMM 320

2.52 $C_{15}H_{15}O_2N$ RMM 241

Aryl bromide **2.50** (0.40 g, 1.30 mmol) was dissolved in toluene (40 mL). AIBN (50 mg, 0.30 mmol) and tributyltin hydride (0.34 mL, 0.31 g, 1.10 mmol) was added and the solution was stirred for 17 h at 80 °C. Saturated KF solution (20 mL) was added and the solution was stirred for a further 24 h. The mixture was extracted with ether (3 x 20 mL), then the organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) gave product **2.52** (22 mg, 0.09 mmol, 7 %) as a brown oil and then recovered starting material (0.25 g, 0.78 mmol, 67 %).

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.50 (1H, app d, *J* 3.0 Hz, ArH), 7.42 (1H, dd, *J* 7.0, 1.5 Hz, ArH) 7.15 (1H, dd, *J* 7.0, 4.0 Hz, ArH), 6.81 (1H, s, ArH), 6.55 (1H, s, ArH), 5.98 (2H, s, OCH_2O), 2.32 (3H, s, CH_3), 2.27 – 2.24 (2H, m, CH_2), 1.01 (3H, t, *J* 3.0 Hz, CH_3)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 156.8 (C), 147.9 (CH), 147.4 (C), 145.5 (C), 137.7 (CH), 135.5 (C), 131.5 (C), 127.9 (C), 120.8 (CH), 109.4 (CH), 108.6 (CH), 101.0 (OCH_2O), 25.9 (CH_2), 22.9 (CH_3), 15.4 (CH_3)

LRMS (CI)

M/z 241 (M^+, 100 %), 226 (58 %), 168 (24 %) amu

HRMS (EI)

Calculated M^+: 241.1103; Found M^+: 241.1112

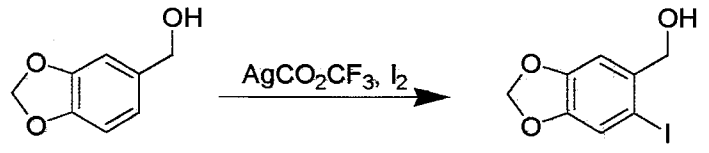
FT-IR (Neat)

ν_{max} 1502w, 1485s, 1458w, 1225s,1036s, 931m, 867w, 843w, 742m cm^{-1}

UV (Methanol)

λ_{max} (ε) 294 (6000), 260 (5700) nm

4.18 6-Iodo-3,4-methylenedioxybenzyl alcohol **2.57**



2.5 $C_8H_8O_3$ RMM 152

2.57 $C_8H_7O_3I$ RMM 278

Iodide **2.57** was synthesised by the method of Cossy *et al.*[20] Piperonyl alcohol (6.41 g, 42.20 mmol) and silver trifluoroacetate (9.48 g, 43.10 mmol) were dissolved in dry chloroform (80 mL). The mixture was cooled to 0 °C and iodine (10.90 g, 43.10 mmol) was added in one portion. The mixture was stirred for 30 mins and filtered. The filtrate was washed with sodium thiosulfate (30 mL) and the solvent removed *in vacuo*. The solid was recrystallised with $CHCl_3$ to give **2.57** (10.95 g, 39.4 mmol, 93%) as a white crystalline solid.

Melting point: 107-109 °C (Chloroform) Lit: 108 – 109 °C (Chloroform)[20]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.24 (1H, s, ArH), 7.00 (1H, s, ArH), 5.99 (2H, s, OCH_2O), 4.59 (2H, s, CH_2OH), 1.82 (1H, s, OH)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 148.6 (C), 147.9 (C), 136.2 (C), 118.5 (CH), 109.1 (CH), 101.7 (OCH_2O), 88.4 (C), 69.2 (CH_2OH)

LRMS (APCI)

M/z 278 (M^+, 14 %), 261 ($[M\text{-}OH]^+$, 22 %), 135 ($[MH\text{-}I\text{-}OH]^+$, 100 %) amu

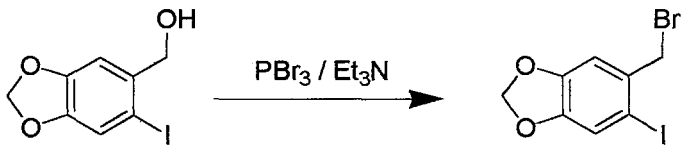
FT-IR ($CHCl_3$)

ν_{max} 3238br m, 1498m, 1475s, 1449m, 1237s, 1100s, 1038s, 927s, 857s cm^{-1}

UV (Methanol)

λ_{max} (ε) 294 (1200) nm

4.19 6-Iodo-3,4-methylenedioxybenzyl bromide **2.58**



2.57 $C_8H_7O_3I$ RMM 278

2.58 $C_8H_6O_2BrI$ RMM 341

Bromide **2.58** was synthesised by the method of Cossy *et al.*[20] To a cooled (0 °C) solution of alcohol **2.57** (2.63 g, 9.50 mmol) in DCM / THF (45 mL, 1:1) were added triethylamine (1.32 mL, 0.96 g, 9.50 mmol) and phosphorus tribromide (0.9 mL, 2.59 g, 9.50 mmol) successively. The mixture was stirred at 40 °C for 1 h and then cooled to rt. After cooling to room temperature the solution was poured over ice and then pH adjusted to 7 with a saturated solution of K_2CO_3 (10 mL) solution. The aqueous phase was extracted with DCM and the combined organic phases were dried and solvent removed *in vacuo*. The resulting solid was recrystallised with ethanol to give **2.58** (1.44 g, 4.2 mmol, 45%) as a yellow solid.

Melting Point: 83 – 85 °C (Chloroform) Lit: 72 °C[71]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.21 (1H, s, ArH), 6.98 (1H, s, ArH), 5.98 (2H, s, OCH_2O), 4.55 (2H, s, CH_2Br)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 149.0 (C), 133.8 (C), 109.0 (C), 108.1 (C), 119.2 (CH), 110.2 (CH), 102.2 (CH_2), 39.7 (CH_2)

LRMS (CI)

M/z 262 ($[MH-Br]^+$, 28 %), 136 ($[M-Br-I+2H]^+$, 100 %) amu

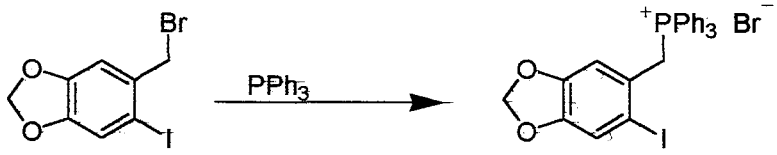
FT-IR (Neat)

ν_{max} 1499m, 1477s, 1249s, 1234s, 1209m, 1120m, 1035s, 931s, 866s cm^{-1}

UV (Methanol)

λ_{max} (ε) 300 (4400), 262 (6000), 220 (20000) nm

4.20 [(6-Iodo-1,3-benzodioxol-5-yl)methyl]triphenylphosphonium bromide **2.59**



2.58 $C_8H_6O_2BrI$ RMM 341

2.59 $C_{26}H_{21}O_2BrIP$ RMM 603

Bromide **2.58** (5.31 g, 15.60 mmol) and triphenylphosphine (6.00 g, 22.90 mmol) were dissolved in xylene (60 mL) and the mixture was stirred at 75 °C for 14 h. The precipitate was collected by filtration, washed with petrol (2 x 30 mL) and dried to give **2.59** (7.71 g, 12.80 mmol, 82%) as a white amorphous solid.

Melting Point: >250 °C (Ethanol) Lit: 268 – 272 °C (Ethanol) [71]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.30 (3H, m, ArH), 7.62 (12H, m, ArH), 7.05 (1H, s, ArH), 7.00 (1H, m, ArH), 5.92 (2H, s, OCH_2O), 5.59 (2H, d, *J* 15.0 Hz, CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 149.2 (2 x C), 135.4 (3 x CH), 134.6 (d, J_{C-P} 10 Hz, 6 x CH), 130.4 (d, J_{C-P} 13 Hz, 6 x CH), 118.7 (4 x C), 118.1 (CH), 112.9 (CH), 102.4 (OCH_2O), 93.8 (CI), 35.8 (d, J_{C-P} 28 Hz, CH_2P)

LRMS (ES+)

M/z 523 ($[M-Br]^+$, 85 %), 102 (100 %) amu

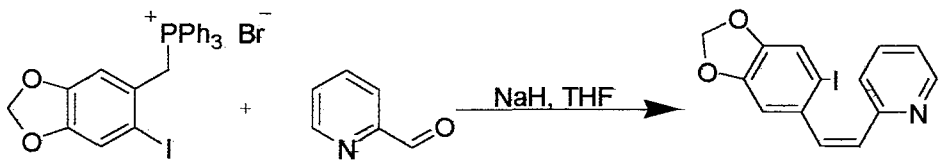
FT-IR (Neat)

ν_{max} 1477s, 1470s, 1235s, 1109s, 1035s, 846s, 754s, 745s cm^{-1}

UV (Methanol)

λ_{max} (ε) 303 (3000) nm

4.21 2-[2-Iodo-1,3-benzodioxol-5-yl)-1-ethenyl]pyridine **2.60**



2.59 **2.29** **2.60**

$C_{26}H_{21}O_2BrIP$ RMM 603 C_6H_5ON RMM 107 $C_{14}H_{10}O_2IN$ RMM 351

Sodium hydride (60% in mineral oil, 250 mg, 6.20 mmol) was washed with THF (10 mL) then further THF (30 mL) was added. After cooling to 0 °C, phosphonium bromide **2.59** (3.62 g, 6.00 mmol) was added and the mixture stirred at room temperature for 2 h then cooled to 0 °C. The aldehyde **2.29** (0.64 g, 5.98 mmol) was added as a solution in THF (10 mL) then the reaction mixture was warmed to room temperature, stirred for a further 2 h and the solid was removed by filtration. The filtrate was concentrated *in* vacuo then diluted with DCM (50 mL) and filtered. The solvent was the removed *in vacuo* and the residue was purified by column chromatography (silica, 50% ether / petrol) to give the title compound **2.60** (1.26 g, 3.59 mmol, 60%) as a white crystalline solid.

Melting Point: 90 – 93 °C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.57 (1H, d, *J* 5.0 Hz, ArH), 7.46 (1H, ddd, *J* 8.0, 7.0, 2.0 Hz, ArH), 7.32 (1H, s, ArH), 7.08 (1H, ddd, *J* 7.0, 5.0, 2.0 Hz, ArH), 7.01 (1H, d, *J* 8.0 Hz, ArH), 6.66 – 6.63 (2H, m, CH=CH), 6.64 (1H, s, ArH), 5.94 (2H, s, OCH_2O)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 155.5 (C), 149.7 (CH), 148.3 (C), 148.1 (C), 136.5 (CH), 135.9 (CH), 134.4 (C), 131.1 (CH), 124.1 (CH), 122.0 (CH), 118.5 (CH), 110.1 (CH), 101.8 (OCH_2O), 88.1 (C)

LRMS (CI)

M/z 352 (MH^+, 16 %), 226 ($[M+2H-I]^+$, 100 %) amu

HRMS (EI)

Calculated M^+: 350.9756; Found M^+: 350.9766

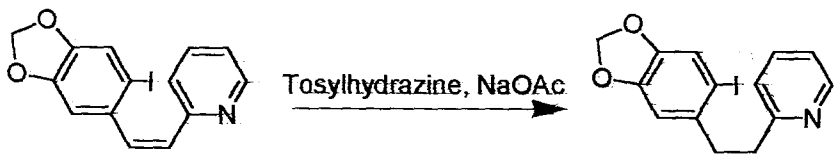
FT-IR (Neat)

ν_{max} 1474s, 1462w, 1231m, 1036s, 932m, 806m, 821s cm^{-1}

UV (Methanol)

λ_{max} (ε) 296 (6000) nm

4.22 2-[2-(6-Iodo-1,3-benzodioxol-5-yl)ethyl]pyridine **2.61**



2.60
$C_{14}H_{10}O_2IN$ RMM 351

2.61
$C_{14}H_{12}O_2IN$ RMM 353

Aryl bromide **2.60** (0.75 g, 2.50 mmol) was dissolved in 50% THF/water (30 mL). Tosylhydrazine (2.20 g, 12.00 mmol) and sodium acetate (1.40 g, 17.00 mmol) were added and the mixture was stirred at reflux for 72h. Saturated K_2CO_3 solution (20 mL) was added and the organic phase was extracted with DCM (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated. The crude material was purified by column chromatography (silica, 50% ether / petrol) to yield the title compound **2.61** and recovered starting material (0.57 g, 1.90 mmol, 70 % from NMR) as a white crystalline solid.

Melting Point: 102 – 103 °C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.58 (1H, br s, ArH), 7.60 (1H, app t, *J* 5.0 Hz, ArH), 7.28 (1H, s, ArH), 7.18 – 7.05 (2H, m, ArH), 6.70 (1H, s, ArH), 5.96 (2H, s, OCH_2O), 3.10 – 2.98 (4H, m, 2 x CH_2)

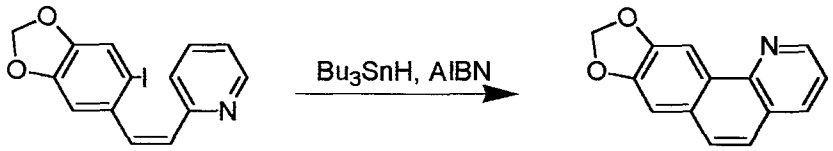
^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 160.8 (C), 149.5 (CH), 148.5 (C), 146.9 (C), 137.4 (C), 136.6 (CH), 123.3 (CH), 121.5 (CH), 118.7 (CH), 109.6 (CH), 101.6 (OCH_2O), 87.9 (C), 41.0 (CH_2), 39.1 (CH_2)

LRMS (CI)

M/z 354 (MH^+, 86 %), 228 ($[M+2H-I]^+$, 100 %) amu

4.23 [1,3]Dioxolo[4',5':4, 5]benzo[*f*]quinoline **2.37**



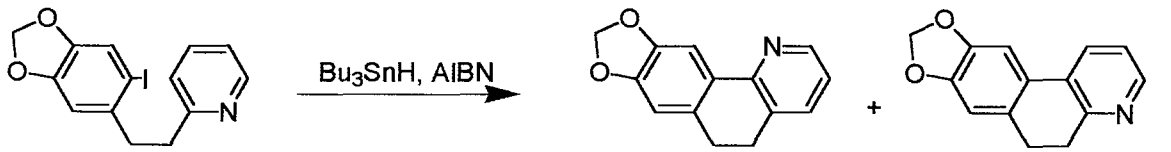
2.60
$C_{14}H_{10}O_2IN$ RMM 351

2.37
$C_{14}H_9O_2N$ RMM 223

Aryl iodide **2.60** (0.28 g, 0.80 mmol) was dissolved in toluene (40 mL). AIBN (15 mg, 0.10 mmol) and tributyltin hydride (0.3 mL, 0.33 g, 1.10 mmol) were added and the solution was stirred for 16 h at 80 °C. After cooling to room temperature saturated KF solution (20 mL) was added and the solution stirred for a further 24 h. The mixture was extracted with ether (3 x 20 mL) and the organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether/petrol) gave tetracycle **2.37** (63 mg, 0.28 mmol, 35 %) as a cream solid and finally recovered starting material (26 mg, 0.07 mmol, 10%).

The data are consistent with those reported previously.

4.24 5,6-Dihydro[1,3]dioxolo[4',5':4, 5]benzo[*h*]quinoline **2.39** and
5,6-Dihydro[1,3]dioxolo[4',5':4, 5]benzo[*f*]quinoline **2.40**



2.61
$C_{14}H_{12}O_2IN$ RMM 353

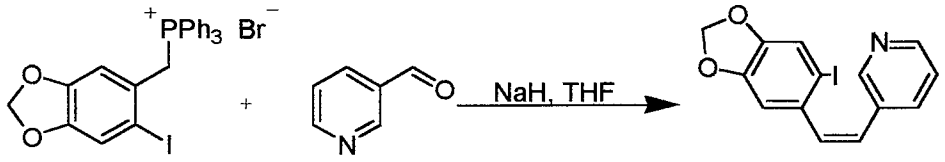
2.39
$C_{14}H_{11}O_2N$ RMM 225

2.40
$C_{14}H_{11}O_2N$ RMM 225

Aryl iodide **2.61** (0.10 g, 0.28 mmol) was dissolved in toluene (20 mL). AIBN (15 mg, 0.10 mmol) and tributyltin hydride (0.1 mL, 0.11 g, 0.37 mmol) were added and the solution was stirred for 14 h at 80 °C. After cooling to room temperature saturated KF solution (20 mL) was added and the solution stirred for a further 24 h. The mixture was extracted with ether (3 x 20 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) gave tetracycle **2.39** (22 mg, 0.10 mmol, 34 %) and finally tetracycle **2.40** (41 mg, 0.18 mmol, 64 %).

The data are consistent with those reported previously.

4.25 3-[2-Iodo-1,3-benzodioxol-5-yl)-1-ethenyl]pyridine **2.62**



2.59 **2.27** **2.62**

$C_{26}H_{21}O_2BrIP$ RMM 603 C_6H_5ON RMM 107 $C_{14}H_{10}O_2IN$ RMM 351

Sodium hydride (60% in mineral oil, 400 mg, 11.0 mmol) was washed with THF (10 mL) then further THF (40 mL) was added. After cooling to 0 °C, phosphonium bromide **2.59** (3.50 g, 5.80 mmol) was added and the mixture stirred at room temperature for 2 h then cooled to 0 °C. Aldehyde **2.27** (0.66 g, 6.20 mmol) was added as a solution in THF (10 mL) then the reaction mixture was warmed to room temperature, stirred for a further 2 h then the solid was removed by filtration. The filtrate was concentrated *in vacuo* then diluted with DCM (50 mL) and filtered. The solvent was the removed *in vacuo* and the residue was purified by column chromatography (silica, 50% ether / petrol) to give firstly the *Z* isomer (0.93 g, 2.60 mmol, 45%) as a white solid and then the *E* isomer (0.49 g, 1.40 mmol, 24%) as a white solid.

***Z*-3-[2-Iodo-1,3-benzodioxol-5-yl)-1-ethenyl]pyridine**

Melting Point: 125 – 127 °C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.39 (2H, m, ArH), 7.41 (1H, d, *J* 8.0 Hz, ArH), 7.28 (1H, s, ArH), 7.12 (1H, dd, *J* 8.0, 5.0 Hz, ArH), 6.56 (1H, d, *J* 11.7 Hz, =CH), 6.54 (1H, s, ArH), 6.50 (1H, d, *J* 11.7 Hz, =CH), 5.94 (2H, s, OCH_2O)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 150.3 (CH), 148.5 (C), 148.3 (CH), 148.2 (C), 136.0 (CH), 135.9 (CH), 134.2 (C), 132.2 (C), 127.0 (CH), 123.3 (CH), 118.6 (CH), 109.8 (CH), 101.9 (OCH_2O), 88.1 (C)

LRMS (CI)

M/z 352 (MH^+, 94 %), 224 ($[MH-I]^+$, 100 %), 166 (26 %), 139 (10 %) amu

HRMS (ES+)

Calculated MH^+: 351.9829; Found MH^+: 351.9833

FT-IR ($CHCl_3$)

ν_{max} 1496w, 1473s, 1432w, 1229s, 1037s, 935m, 875w, 809w cm^{-1}

UV (Methanol)

λ_{max} (ε) 292 (3300) nm

***E*-3-[2-Iodo-1,3-benzodioxol-5-yl)-1-ethenyl]pyridine**

Melting Point: 195 – 198 °C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.70 (1H, br s, ArH), 8.48 (1H, br s, ArH), 7.84 (1H, d, *J* 5.0 Hz, ArH), 7.30 (1H, d, *J* 14.0 Hz, =CH), 7.35 – 7.28 (1H, m, ArH), 7.29 (1H, s, ArH), 7.13 (1H, s, ArH), 6.78 (1H, d, *J* 14.0 Hz, =CH), 6.00 (2H, s, OCH_2O)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 149.1 (C), 148.8 (CH), 148.7 (C), 134.5 (CH), 133.5 (CH), 133.3 (C), 133.0 (CH), 126.3 (CH), 123.8 (CH), 123.2 (C), 118.9 (CH), 106.0 (CH), 102.1 (CH_2), 89.7 (C)

LRMS (CI)

M/z 352 (MH^+, 76 %), 224 ($[MH-I]^+$, 100 %), 166 (28 %), 139 (14 %) amu

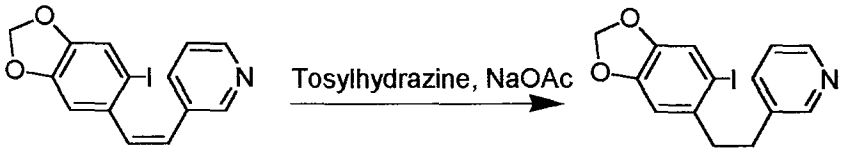
FT-IR ($CHCl_3$)

ν_{max} 1500w, 1474s, 1246m, 1040m, 961m, 931m, 843w cm^{-1}

UV (Methanol)

λ_{max} (ε) 339 (3700), 298 (3800) nm

4.26 3-[2-(6-Iodo-1,3-benzodioxol-5-yl)ethyl]pyridine **2.63**



2.62
$C_{14}H_{10}O_2IN$ RMM 351

2.63
$C_{14}H_{12}O_2IN$ RMM 353

Aryl bromide **2.62** (0.17 g, 0.48 mmol) was dissolved in 50% THF/water (40 mL). *p*-Tosylhydrazine (0.56 g, 3.50 mmol) and sodium acetate (0.27 g, 3.50 mmol) were added and the mixture was stirred at reflux for 72 h. Saturated K_2CO_3 solution (20 mL) was added and the aqueous phase was extracted with DCM (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) yielded the title compound **2.63** (0.14 g, 0.40 mmol, 83%) as a white crystalline solid.

Melting Point: 238 °C decomp. (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.46 (2H, m, ArH), 7.80 (1H, d, *J* 8.0 Hz, ArH), 7.53 (1H, d, *J* 8.0 Hz, ArH), 7.24 (1H, s, ArH), 6.65 (1H, s, ArH), 5.94 (2H, s, OCH_2O), 2.95 – 2.79 (4H, m, 2 x CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 150.1 (CH), 148.6 (C), 147.7 (CH), 147.1 (C), 136.7 (C), 136.5 (C), 136.2 (CH), 123.5 (CH), 118.8 (CH), 109.5 (CH), 101.7 (CH_2), 87.9 (C), 42.5 (CH_2), 33.9 (CH_2)

LRMS (CI)

M/z 354 (MH^+, 25 %), 228 ($[M+2H-I]^+$, 100 %), 135 (26 %) amu

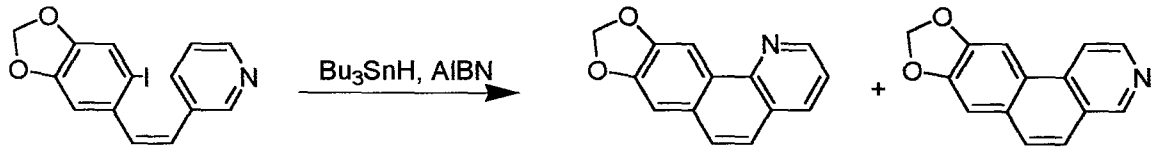
HRMS (ES+)

Calculated MH^+: 353.9985; Found MH^+: 353.9994

FT-IR ($CHCl_3$)

ν_{max} 3054w, 1422w, 1265s, 896w, 739s cm^{-1}

4.27 [1,3]Dioxolo[4',5':4, 5]benzo[*h*]quinoline **2.31** and
[1,3]Dioxolo[4',5':4, 5]benzo[*f*]isoquinoline **2.32**



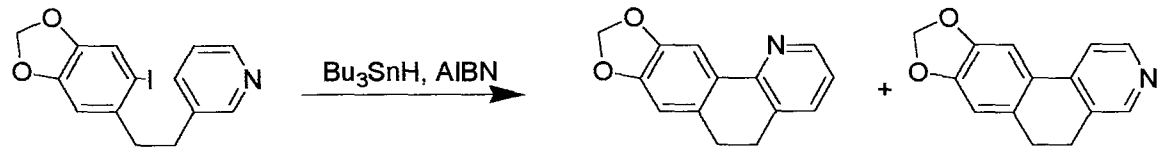
2.62
$C_{14}H_{10}O_2IN$ RMM 351

2.31
$C_{14}H_9O_2N$ RMM 223

2.32
$C_{14}H_9O_2N$ RMM 223

Aryl iodide **2.62** (0.31 g, 2.80 mmol) was dissolved in toluene (40 mL). AIBN (15 mg, 0.10 mmol) and tributyltin hydride (0.34 mL, 0.37 g, 1.30 mmol) were added and the solution was stirred for 18 h at 80 °C. After cooling to room temperature saturated KF solution (20 mL) was added and the solution stirred for a further 24 h. The mixture was extracted with ether (3 x 20 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) gave firstly the tetracycle **2.31** (58 mg, 0.26 mmol, 29%) as a white solid and then **2.32** (97 mg, 0.43 mmol, 49%) as a white solid.
The data are consistent with those reported previously.

4.28 5,6-Dihydro[1,3]dioxolo[4',5':4, 5]benzo[*h*]quinoline **2.35** and
5,6-Dihydro[1,3]dioxolo[4',5':4, 5]benzo[*f*]isoquinoline **2.36**



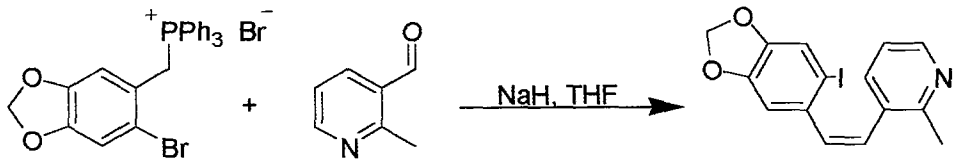
2.63
$C_{14}H_{12}O_2IN$ RMM 353

2.35
$C_{14}H_{11}O_2N$ RMM 225

2.36
$C_{14}H_{11}O_2N$ RMM 225

Aryl iodide **2.63** (0.23 g, 0.65 mmol) was dissolved in toluene (20 mL). AIBN (15 mg, 0.10 mmol) and tributyltin hydride (0.26 mL, 0.28 g, 0.97 mmol) was added and the solution was stirred for 17 h at 80 °C. After cooling to room temperature saturated KF solution (20 mL) was added and the solution stirred for a further 24 h. The mixture was extracted with ether (3 x 30 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether/petrol) gave firstly tetracycle **2.35** (44 mg, 0.20 mmol, 30 %) as a white solid then **2.36** (31 mg, 0.14 mmol, 21 %) as w white solid.
The data are consistent with those reported previously.

4.29 3-[2-(6-Iodo-1,3-benzodioxol-5-yl)-1-ethenyl]-2-methylpyridine **2.64**



2.59 **2.48** **2.64**

$C_{23}H_{21}O_2BrIP$ RMM 603 C_7H_8ON RMM 121 $C_{15}H_{12}O_2IN$ RMM 365

Sodium hydride (60% in mineral oil, 510 mg, 13.00 mmol) was washed with THF (10 mL) then further THF (40 mL) was added. After cooling to 0 °C, phosphonium bromide **2.59** (2.71 g, 4.50 mmol) was added and the mixture was stirred at room temperature for 2 h then cooled to 0 °C. Aldehyde **2.48** (0.55 g, 4.50 mmol) was added as a solution in THF (10 mL) then the reaction mixture was warmed to room temperature over 10 min, stirred for a further 2 h and the solid removed by filtration. The filtrate was concentrated *in vacuo* then diluted with DCM (50 mL) and filtered. The solvent was then removed *in vacuo* and the residue was purified by column chromatography (silica, ether) to give the title compound **2.64** as a mixture of *Z* and *E* isomers (0.87 g, 2.40 mmol, 52%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.36 (1H, d, *J* 5.0 Hz, ArH), 7.15 (1H, d, *J* 8.0 Hz, ArH), 6.98 (1H, dd, *J* 8.0, 5.0 Hz, ArH), 6.61 (2H, s, CH=CH), 6.37 (1H, s, ArH), 6.02 (1H, s, ArH), 5.91 (2H, s, OCH_2O), 2.53 (3H, s, CH_3)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 156.6 (C), 149.6 (C), 148.6 (C), 147.9 (CH), 137.0 (CH), 135.9 (CH), 133.8 (C), 131.1 (C), 127.6 (CH), 121.1 (CH), 118.9 (CH), 110.0 (CH), 101.8 (CH_2), 88.5 (C), 25.5 (CH_3)

LRMS (CI)

M/z 366 (MH^+, 22 %), 240 ($[M-I+2H]^+$, 100 %) amu

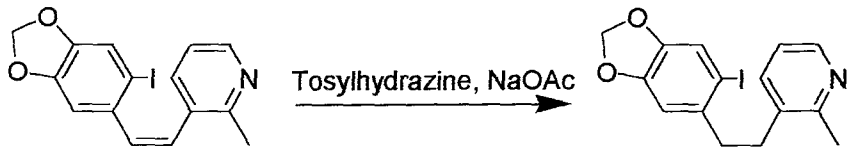
HRMS (CI)

Calculated M^+: 364.9913; Found M^+: 364.9909

FT-IR (Neat)

ν_{max} 1501w, 1472s, 1436m, 1228s, 1037s, 932w, 821w, 730w cm^{-1}

4.30 3-[2-(6-Iodo-1,3-benzodioxol-5-yl)ethyl]-2-methylpyridine **2.65**



2.64 $C_{15}H_{12}O_2IN$ RMM 365

2.65 $C_{15}H_{14}O_2IN$ RMM 367

Aryl bromide **2.64** (0.51 g, 1.4 mmol) was dissolved in 50% THF/water (40 mL). *p*-Tosylhydrazine (1.54 g, 9.7 mmol) and sodium acetate (0.7 g, 9.7 mmol) were added and the mixture was stirred at reflux for 72 h. Saturated K_2CO_3 solution (20 mL) was added and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) yielded the title compound **2.65** (0.42 g, 1.1 mmol, 72 %) as a white crystalline solid.

Melting Point: 91 – 94 °C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.34 (1H, m, ArH), 7.38 (1H, m, ArH), 7.24 (1H, s, ArH), 7.05 (1H, dd, *J* 7.0, 5.0 Hz, ArH), 6.62 (1H, s, ArH), 5.92 (2H, s, OCH_2O), 2.87 – 2.80 (4H, m, 2 x CH_2), 2.55 (3H, s, CH_3)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 148.7 (C), 147.1 (CH), 137.0 (C), 136.8 (CH), 134.6 (C), 130.1 (C), 128.4 (C), 121.5 (CH), 118.8 (CH), 109.5 (CH), 101.7 (CH_2), 88.9 (C), 41.2 (CH_2), 33.7 (CH_2), 22.5 (CH_3)

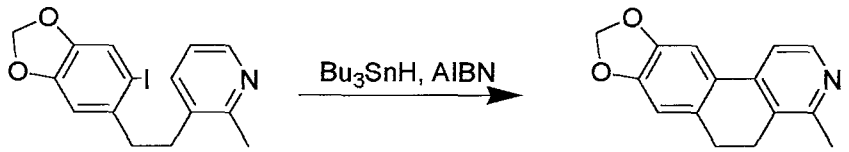
LRMS (CI)

M/z 368 (MH^+, 20 %), 242 ($[M-I+2H]^+$, 100 %), 135 (40 %) amu

FT-IR (Neat)

ν_{max} 1501w, 1476s, 1228s, 1039s, 930m, 883w cm^{-1}

4.31 5,6-Dihydro-4-methyl[1,3]dioxolo[4',5':4,5]benzo[*f*]isoquinoline **2.66**



2.65
$C_{15}H_{14}O_2IN$ RMM 367

2.66
$C_{15}H_{13}O_2N$ RMM 240

Aryl iodide **2.65** (0.10 g, 0.27 mmol) was dissolved in toluene (40 mL). AIBN (15 mg, 0.10 mmol) and tributyltin hydride (0.2 mL, 0.21 g, 0.75 mmol) was added and the solution was stirred for 17 h at 80 °C. Saturated KF solution (20 mL) was added and the solution was stirred for a further 24 h. The mixture was extracted with ether (3 x 20 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) gave product **2.66** (24 mg, 0.10 mmol, 37 %) as a white crystalline solid and recovered starting material (27 mg, 0.07 mmol, 27 %)

Melting Point: 152 – 153 °C (Ethanol)

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 8.29 (1H, d, *J* 5.0 Hz, ArH), 7.22 (1H, d, *J* 5.0 Hz, ArH), 7.15 (1H, s, ArH), 6.66 (1H, s, ArH), 5.91 (1H, s, OCH_2O), 2.73 (4H, s, 2 x CH_2), 2.50 (3H, s, CH_3)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 155.8 (C), 148.4 (C), 147.2 (CH + C), 142.2 (C), 132.7 (C), 129.1 (C), 126.2 (C), 115.6 (CH), 108.6 (CH), 104.9 (CH), 101.4 (CH_2), 28.5 (CH_2), 24.2 (CH_2), 22.7 (CH_3)

LRMS (CI)

M/z 240 (MH^+, 100 %) amu

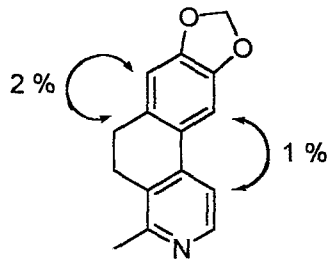
HRMS (ES+)

Calculated M^+: 240.1019; Found M^+: 240.1019

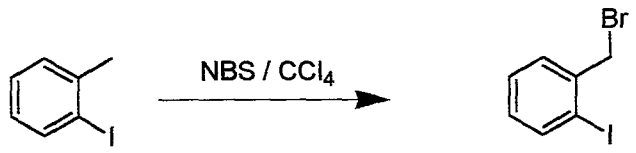
FT-IR (Neat)

ν_{max} 1583w, 1499m, 1474m, 1440w, 1260w, 1238s, 1033s, 928m, 845m cm^{-1}

GOSEY experiment confirmed structure



4.32 2-Iodobenzyl bromide **2.73**



2.72
C_7H_7I RMM 218

2.73
C_7H_6BrI RMM 297

Bromide **2.73** was prepared by the method of Bacon *et al.* [72] Iodotoluene **2.72** (20.0 g, 90.0 mmol) and NBS (16.3 g, 90.0 mmol) was dissolved in carbon tetrachloride (80 mL) and benzoyl peroxide (50 mg, 0.21 mmol) were added. The mixture was stirred for 3 h at reflux. The solution was filtered and the solvent removed *in vacuo*. The solid was obtained by using a small quantity of ethanol (10 mL) to induce crystallisation to give the product **2.73** (11.9 g, 0.04 mol, 44%) as a white crystalline solid.

Data are consistent with those reported in the literature.

Melting Point: 46 – 47 °C (Ethanol) Lit:48 – 50 °C (Methanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.87 (1H, d, *J* 7.0 Hz, ArH), 7.49 (1H, d, *J* 7.0 Hz, ArH), 7.36 (1H, t, *J* 7.0 Hz, ArH), 7.01 (1H, t, *J* 7.0 Hz, ArH), 4.62 (2H, s, CH_2Br)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 140.3 (C), 140.2 (CH), 130.7 (CH), 130.3 (CH), 129.1 (CH), 100.3 (C), 39.1 (CH_2)

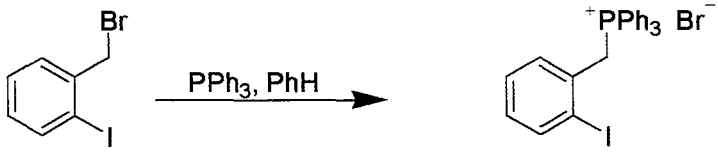
LRMS (CI)

M/z 218 ($[MH-Br]^+$, 100 %), 108 (12 %), 91 (86 %) amu

FT-IR (Neat)

ν_{max} 1437m, 1218s, 1013s, 758s, 719s cm^{-1}

4.33 (2-Iodo-benzyl)-triphenylphosphonium bromide **2.74**



2.73 C_7H_6BrI RMM 297

2.74 $C_{25}H_{21}BrI$ RMM 559

Experimental conducted using a modified literature procedure. [73] Iodobenzyl bromide **2.73** (10.8 g, 36.0 mmol) was dissolved in benzene (40 mL) and triphenylphosphine (13.0 g, 49.0 mmol) was added. The mixture was stirred for 4 h at reflux. The solution was cooled to rt, filtered and washed with petrol (3 x 30 mL) to give product **2.74** (18.8 g, 33.0 mmol, 93 %) as a white amorphous solid.

Data are consistent with those reported in the literature.

Melting Point: >250°C (Ethanol) Lit: 265 – 266 °C (Methanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.73 – 7.63 (3H, m, 3 x ArH), 7.59 – 7.50 (13H, m, 13 x ArH), 7.40 (1H, app dd, *J* 7.0, 2.0 Hz, ArH), 7.12 (1H, t, *J* 7.0 Hz, ArH), 6.88 (1H, app tt, *J* 7.0, 2.0 Hz, ArH), 5.52 (2H, d, *J* 18.0 Hz, CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 139.9 (CH), 134.6 (d, $J_{C\text{-}P}$ 13 Hz, 6 x CH), 132.4 (CH), 130.4 (d, $J_{C\text{-}P}$ 17 Hz, 6 x CH), 129.5 (CH), 128.5 (3 x CH), 117.4 (d, $J_{C\text{-}P}$ 85 Hz, 3 x C) 35.8 (d, $J_{C\text{-}P}$ 64 Hz, CH_2) Two quarternary carbons not observed

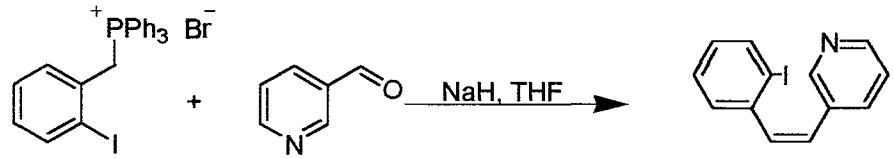
LRMS (ES+)

M/z 479 ($[M\text{-}Br]^+$, 100 %) amu

FT-IR (Neat)

ν_{max} 1436m, 1010s, 783m, 754s cm^{-1}

4.34 3-[2-(6-Iodo-benz-5-yl)ethenyl]pyridine **2.75**



2.74 **2.27** **2.75**

$C_{25}H_{21}BrIP$ RMM 559 C_6H_5ON RMM 107 $C_{13}H_{10}IN$ RMM 307

Sodium hydride (60% in mineral oil, 410 mg, 11.0 mmol) was washed with THF (10 mL) then further THF (40 mL) was added. After cooling to 0 °C, phosphonium bromide **2.74** (2.30 g, 4.10 mmol) was added and the mixture stirred at room temperature for 2 h then cooled to 0 °C. Aldehyde **2.27** (0.47 g, 4.40 mmol) was added as a solution in THF (10 mL) then the reaction mixture was warmed to room temperature over 10 min, stirred for a further 2 h and the solid was removed by filtration. The filtrate was concentrated then diluted with DCM (50 mL) and filtered. The solvent was the removed *in vacuo* and the residue was purified by column chromatography (silica, 50% ether / petrol) to give the title compound **2.75** (1.00 g, 9.30 mmol, 74%) as the *Z* isomer and a mixture of the *Z*:*E* isomers in a 1:1 ratio.

***Z*-3-[2-(6-Iodo-benz-5-yl)ethenyl]pyridine**

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.38 (2H, br s, ArH), 7.89 (1H, d, *J* 7.0 Hz, ArH), 7.32 (1H, d, *J* 7.0 Hz, ArH), 7.14 (1H, t, *J* 7.0 Hz, ArH), 7.08 (2H, m, ArH), 6.91 (1H, td, *J* 7.0, 1.5 Hz, ArH), 6.66 (1H, d, *J* 12.0 Hz, CH=CH), 6.57 (1H, d, *J* 12.0 Hz, CH=CH)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 150.4 (CH), 148.4 (CH), 141.2 (C), 139.5 (CH), 136.2 (CH), 135.9 (CH), 133.1 (CH), 130.6 (C), 129.7 (CH), 128.4 (CH), 127.5 (CH), 123.2 (CH), 99.6 (C)

LRMS (CI)

M/z 180 ($[M-I]^+$, 100 %) amu

HRMS (CI)

Calculated M^+: 306.9858; Found M^+: 306.9859

FT-IR (Neat)

ν_{max} 1461w, 1418m, 1024m, 1013s, 809m, 708s cm^{-1}

UV (Methanol)

λ_{max} (ε) 274 (8600) nm

***E*-3-[2-(6-Iodo-benz-5-yl)ethenyl]pyridine**

Melting Point: 55 – 56 °C (Ethanol) Lit: 54 – 56 °C

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 8.62 (1H, s, ArH), 8.41 (1H, d, *J* 4.0 Hz, ArH), 7.80 – 7.68 (2H, m, ArH), 7.03 – 6.87 (4H, m, ArH), 6.53 (1H, d, *J* 12.0 Hz, CH=CH), 6.42 (1H, d, *J* 12.0 Hz, CH=CH)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 149.1 (CH), 149.0 (CH), 141.2 (C), 139.4 (CH), 134.5 (CH), 133.3 (CH), 129.6 (CH), 130.6 (C), 128.4 (CH), 127.8 (CH), 126.6 (CH), 123.7 (CH), 99.7 (C)

LRMS (CI)

M/z 307 (M^+, 34 %), 180 ($[M-I]^+$, 100 %) amu

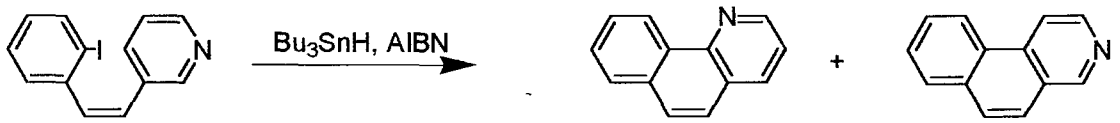
HRMS (CI)

Calculated M^+: 306.9858; Found M^+: 306.9868

FT-IR (Neat)

ν_{max} 1461w, 1432w, 1414w, 1011s, 959s, 796m, 796s, 749s, 710s cm^{-1}

4.35 Benzo[*h*]quinoline **2.76** and Benzo[*f*]isoquinoline **2.77**



2.75
$C_{13}H_{10}IN$ RMM 307

2.76
$C_{13}H_9N$ RMM 179

2.77
$C_{13}H_9N$ RMM 179

Aryl iodide **2.75** (0.49 g, 1.60 mmol) was dissolved in toluene (40 mL). AIBN (15 mg, 0.1 mmol) and tributyltin hydride (0.5 mL, 0.55 g, 1.80 mmol) was added and the solution was stirred for 17 h at 80 °C. Saturated KF solution (20 mL) was added and the solution stirred for a further 24 h. The mixture was extracted with ether (3 x 20 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 50% ether / petrol) gave product **2.76** [74] (0.12 g, 0.67 mmol, 41 %) as a yellow oil and product **2.77** (0.14 g, 0.78 mmol, 49 %) as a yellow oil but both were contaminated with residual tributyltin hydride.

Benzo[*h*]quinoline [75]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 9.37 (1H, d, *J* 7.0 Hz, ArH), 8.99 (1H, d, *J* 4.0 Hz, ArH), 8.07 (1H, dd, *J* 7.0, 4.0 Hz, ArH), 7.89 (1H, d, *J* 8.0 Hz, ArH), 7.74 (1H, m, ArH), 7.71 (2H, m, ArH), 7.60 (1H, d, *J* 8.0 Hz, ArH), 7.42 (1H, dd, *J* 4.0, 4.0 Hz, ArH)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 148.9 (CH), 146.7 (C), 135.9 (CH), 133.8 (C), 131.7 (C), 128.4 (CH), 128.0 (CH), 127.9 (CH), 127.2 (C), 126.5 (CH), 125.5 (CH), 124.5 (CH), 121.9 (CH)

LRMS (CI)

M/z 180 (MH^+, 100 %) amu

HRMS (CI)

Calculated M^+: 179.0735; Found M^+: 179.0741

FT-IR (Neat)

ν_{max} 1444m, 1403m, 833s, 805m, 746s, 721s cm^{-1}

Benzo[*f*]isoquinoline [76]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 9.25 (1H, s, ArH), 8.69 (1H, d, *J* 6.0 Hz, ArH), 8.58 (1H, t, *J* 5.0 Hz, ArH), 8.33 (1H, d, *J* 6.0 Hz, ArH), 7.87 (1H, t, *J* 5.0 Hz, ArH), 7.56 (2H, q, *J* 7.0 Hz, ArH), 7.64 (2H, m, ArH)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 151.8 (CH), 145.2 (CH), 135.0 (C), 133.6 (C), 129.0 (2 x CH), 128.6 (CH), 127.3 (CH), 127.1 (2 x C), 124.8 (CH), 123.3 (CH), 116.2 (CH)

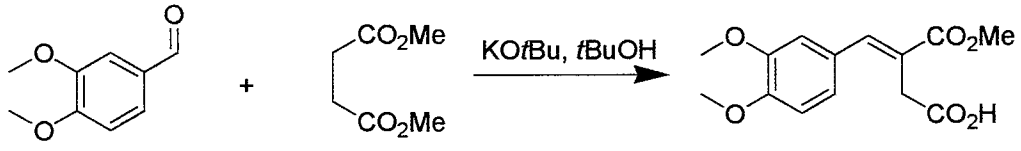
LRMS (CI)

M/z 180 (MH^+, 100 %) amu

FT-IR (Neat)

ν_{max} 1583w, 1474w, 1428w, 1037m, 1014m, 878w, 835s, 814s, 748s, 717s cm^{-1}

4.36 4-(3,4-Dimethoxyphenyl)-3-methoxycarbonylbut-3-enoic acid **3.13**



3.11 $C_9H_{10}O_3$ RMM 166 **3.12** $C_6H_{10}O_4$ RMM 146 **3.13** $C_{14}H_{16}O_6$ RMM 280

Acid **3.13** was prepared by the method of Ward *et al.* [54] To a solution of potassium *tert*-butoxide (11.2 g, 99.8 mmol) in *tert*-butanol (100 mL) was added 3,4-dimethoxybenzaldehyde (16.0 g, 96.3 mmol) and dimethyl succinate (14.5 g, 99.3 mmol) below 40 °C. The mixture was stirred at 40°C for 1 h and water (100 mL) was added. The solution was extracted with diethyl ether (3 x 50 mL) and the aqueous phase was acidified with c. HCl (20 mL). The aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with water (2 x 50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was recrystallised from ethanol to give a yellow solid (18.7 g, 66.8 mmol, 70%).

Data are consistent with those reported in the literature.

Melting point: 149-150 °C (Ethanol) lit: 149-150 °C[77]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 9.42 – 8.88 (1H, br s, CO_2H), 7.88 (1H, s, C<u>H</u>), 7.00 (1H, d, *J* 8.0 Hz, Ar<u>H</u>), 6.99 (1H, d, *J* 2.0 Hz, Ar<u>H</u>), 6.90 (1H, d, *J* 8.0 Hz, Ar<u>H</u>), 3.92 (3H, s, $CO_2C\underline{H}_3$), 3.90 (3H, s, $OC\underline{H}_3$), 3.86 (3H, s, $OC\underline{H}_3$), 3.63 (2H, s, $C\underline{H}_2$)

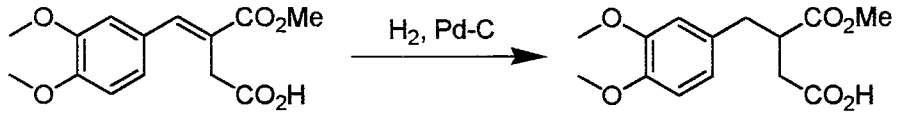
^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 176.8 (<u>C</u>O_2H), 168.6 (<u>C</u>), 150.2 (<u>C</u>), 149.0 (<u>C</u>), 142.9 (<u>C</u>H), 127.4 (<u>C</u>), 123.1 (<u>C</u>), 122.9 (<u>C</u>H), 112.4 (<u>C</u>H), 111.2 (<u>C</u>H), 56.0 (2 x O<u>C</u>H_3), 52.6 (O<u>C</u>H_3), 34.0 (<u>C</u>H_2)

FT-IR (Neat)

ν_{max} 1698s, 1516m, 1337m, 1243s, 1213w, 1145s, 1101w, 1027m, 848w, 818w cm^{-1}

4.37 4-(3,4-Dimethoxyphenyl)-3-methoxycarbonylbutanoic acid **3.14**



3.13
$C_{14}H_{16}O_6$ RMM 280

3.14
$C_{14}H_{18}O_6$ RMM 282

Acid **3.14** was prepared by the method of Robin *et al.* [48] Acid **3.13** (8.20 g, 29.0 mmol) was dissolved in methanol (50 mL) and 5% palladium on carbon (0.50 g, 10 mol%) was added. The reaction mixture was stirred under hydrogen at atmospheric pressure for 24 h. The mixture was filtered through Celite and concentrated *in vacuo* to give the title compound as a white solid (5.40 g, 19.0 mmol, 66%).

Melting Point: 107 – 109 °C (Ethanol) lit: 108 – 109 °C[77]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 6.79 (1H, d, *J* 8.0 Hz, ArH), 6.69 (1H, d, *J* 8.0 Hz, ArH), 6.67 (1H, s, ArH), 4.76 – 4.14 (1H, s, CO_2H), 3.86 (6H, s, 2 x OCH_3), 3.67 (3H, s, OCH_3), 3.04 (2H, m, CH_2CO_2H), 2.72 (2H, m, $ArCH_2$), 2.45 (1H, dd, *J* 17.0, 4.0 Hz, CH)

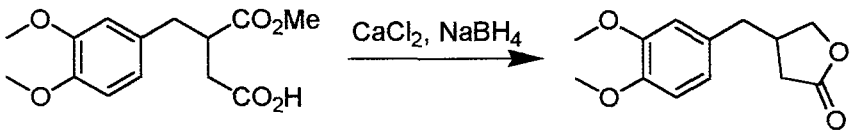
^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 174.8 (C), 173.8 (C), 149.1 (C), 148.0 (C), 130.6 (C), 121.3 (CH), 112.1 (CH), 111.4 (CH), 56.0 (CH_3), 55.9 (CH_3), 52.2 (CH_3), 37.4 (CH_2), 34.8 (CH_2), 18.4 (CH)

FT-IR (Neat)

ν_{max} 1698s, 1516m, 1337m, 1243s, 1145s, 1101m, 1027m, 850w, 818w cm^{-1}

4.38 β-(3,4-Dimethoxybenzyl)-γ-butyrolactone **3.15**



3.14
$C_{14}H_{18}O_6$ RMM 282

3.15
$C_{13}H_{16}O_4$ RMM 236

Lactone **3.15** was prepared by the method of Ganeshpure *et al.* [77] Calcium chloride (12.0 g, 0.10 mol) was dissolved in ethanol (50 mL) and cooled to –10 °C. A solution of sodium borohydride (8.20 g, 0.22 mol) in ethanol (100 mL) was added dropwise to the calcium chloride over 1h. Acid **3.14** (8.47 g, 30 mmol) was dissolved in ethanol (50 mL) and was added to a solution of potassium *tert*-butoxide (3.36 g, 30 mmol) in ethanol (50 mL). This solution was added dropwise to the solution of calcium borohydride over 1 h at –78 °C. The mixture was stirred overnight at room temperature and then concentrated *in vacuo*. The residue was partitioned between water (100 mL) and chloroform (100 mL). The mixture was acidified with c. HCl (20 mL) and refluxed for 1 h. The solution was separated and the organic phase was washed with water (2 x 50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. This afforded the title compound as a yellow oil (6.75 g, 28.0 mmol, 95%).

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 6.78 (1H, d, *J* 8.0 Hz, ArH), 6.66 (1H, d, *J* 8.0 Hz, ArH), 6.64 (1H, s, ArH), 4.29 (1H, dd, *J* 9.0, 7.0 Hz, OCHH), 4.00 (1H, dd, *J* 9.0, 7.0 Hz, OCHH), 3.84 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 2.79 (2H, m, CH_2), 2.68 (1H, m, CH), 2.57 (1H, d, *J* 17.0, 8.0 Hz, ArCHH), 2.24 (1H, d, *J* 17.0, 8.0 Hz, ArCHH)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 177.1 (C), 149.2 (C), 148.0 (C), 131.0 (C), 120.8 (CH), 112.0 (CH), 111.6 (CH), 72.8 (CH_2), 56.0 (2 x OCH_3), 38.7 (CH_2), 37.4 (CH), 34.3 (CH_2)

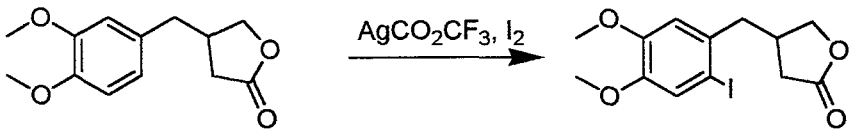
LRMS (CI)

M/z: 254 ($[M+H_2O]^+$, 54 %), 236 (M^+, 72 %), 151 (100%) amu

FT-IR (Neat)

ν_{max} 1777s, 1516s, 1263s, 1237s, 1157s, 1026m, 753w cm^{-1}

4.39 β-(3,4-Dimethoxy-6-iodobenzyl)-γ-butyrolactone **3.51**



3.15
$C_{13}H_{16}O_4$ RMM 236

3.51
$C_{13}H_{15}O_4I$ RMM 362

Lactone **3.51** was prepared by a modified method of Brown *et al.* [78] Lactone **3.15** (6.70 g, 28.0 mmol) was dissolved in dry chloroform (40 mL) and silver trifluoroacetate (6.30 g, 28.0 mmol) was added. The solution was cooled to 0 °C and iodine (7.27 g, 28.0 mmol) added in one portion. The reaction mixture was stirred for 1h and filtered. The filtrate was washed with sodium thiosulfate solution (2 x 20 mL) and the organic phase was dried ($MgSO_4$). The solvent was evaporated to afford a red-brown oil (9.93 g, 27.4 mmol, 98%).

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.18 (1H, s, ArH), 6.62 (1H, s, ArH), 4.30 (1H, app t, *J* 7.0 Hz, OCHH), 4.08 (1H, dd, *J* 9.0, 7.0 Hz, OCHH), 3.82 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 2.90 (1H, m, CH), 2.85 – 2.65 (2H, m, CH_2), 2.58 (1H, dd, *J* 17.0, 7.0 Hz, CHH), 2.31 (1H, dd, *J* 17.0, 7.0 Hz, CHH)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 177.0 (C), 149.6 (C), 148.6 (C), 133.5 (C), 122.0 (CH), 112.8 (CH), 88.3 (C), 72.5 (CH_2), 56.3 (CH_3), 56.2 (CH_3), 42.8 (CH_2), 36.4 (CH), 34.2 (CH_2)

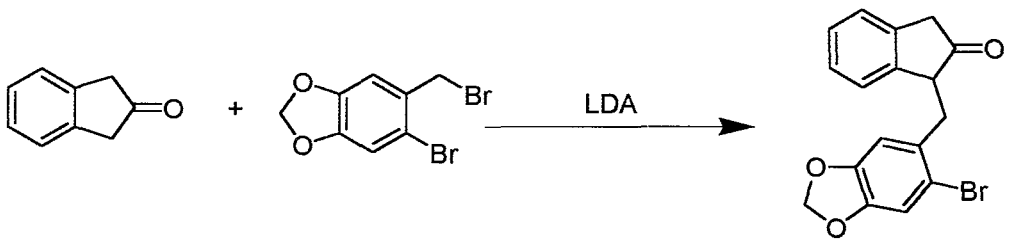
LRMS (CI)

M/z: 380 ($[M+H_2O]^+$, 54 %), 362 (M^+, 100 %), 277 (92%), 236 (74%) amu

FT-IR (Neat)

ν_{max} 1772s, 1503s, 1256m, 1216s, 1162s, 1017m, 792w cm^{-1}

4.40 1-(6-Iodo-benzo[1,3]dioxol-5-ylmethyl)-indan-2-one **3.72**



3.70 C_9H_8O RMM 132

2.6 $C_8H_8O_2Br_2$ RMM 294

3.72 $C_{17}H_{12}O_3Br$ RMM 345

Diisopropylamine (2.4 mL, 1.70 g, 16.0 mmol) was dissolved in THF (40 mL) and cooled to 0 °C. *n*-Buthyllithium (9.2 mL, 16.0 mmol) was added and the mixture was stirred for 1 h. The reaction was cooled to –78 °C and 2-indanone **3.70** (2.00 g, 15.0 mmol) was added and the reaction was stirred for 1 h. The aryl iodide (5.00 g, 15.0 mmol) was added and the reaction was warmed to rt over ½ h. Water (20 mL) was added and the mixture was extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (silica, 20% ether / petrol) yielded the title compound **3.72** as a white crystalline solid (2.80 g, 7.00 mmol, 47%).

Melting point: 114-116 °C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.30 – 7.21 (3H, m, ArH), 7.12 – 7.06 (2H, m, ArH), 6.70 (1H, s, ArH), 5.98 (2H, m, OCH_2O), 3.82 (1H, t, *J* 6.0 Hz, CH), 3.58 (2H, s, CH_2), 3.25 (1H, dd, *J* 14.0, 6.0 Hz, CHH), 2.97 (1H, dd, *J* 14.0, 6.0 Hz, CHH)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 148.0 (C), 147.7 (C), 141.7 (C), 137.0 (C), 131.0 (C), 128.0 (CH), 127.8 (CH), 125.7 (CH), 125.2 (CH), 115.5 (C), 113.0 (CH), 112.3 (CH), 102.2 (CH_2), 53.0 (CH), 43.4 (CH_2), 38.7 (CH_2), C=O not observed

LRMS (CI)

M/z: 261 ($[M\text{-}Br\text{-}CH_2\text{+}NH_4]^+$, 100 %), 189 (28 %), 135 (50 %), 76 (56 %) amu

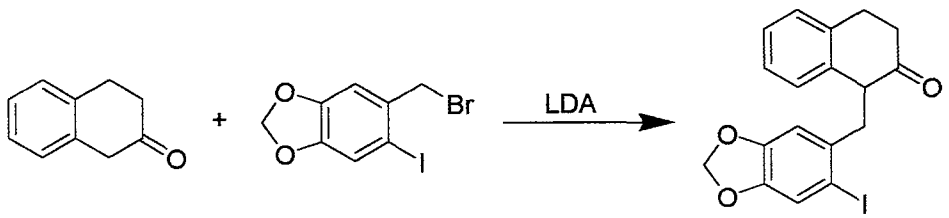
FT-IR (Neat)

ν_{max} 1740s, 1499m, 1474s, 1229s, 1038s, 751s cm^{-1}

UV (Methanol)

λ_{max} (ε) 248 (1800), 294 (1000) nm

4.41 1-(6-Iodo-benzo[1,3]dioxol-5-ylmethyl)-3,4-dihydro-*1H*-naphthalen-2-one **3.75**



3.74 $C_{10}H_{10}O$ RMM 146

3.71 $C_8H_6O_2BrI$ RMM 341

3.75 $C_{18}H_{15}O_3I$ RMM 406

Diisopropylamine (2.00 mL, 1.40 g, 14.0 mmol) was dissolved in THF (40 mL) and cooled to 0 °C. *N*-Butyllithium (7.5 mL, 14.0 mmol) was added and the mixture was stirred for 1 h. The reaction was cooled to –78 °C and β-tetralone **3.74** (2.00 g, 13.0 mmol) was added and the reaction was stirred for 1 h. The aryl iodide (5.20 g, 15.0 mmol) was added and the reaction was warmed to rt over ½ h. Water (20 mL) was added and the mixture was extracted with diethyl ether (3 x 20 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (silica, 20% ether / petrol) yielded the title compound **3.75** as a white crystalline solid (1.35 g, 3.00 mmol, 23%).

Melting point: 119-120 °C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.23 – 7.13 (4H, m, ArH), 6.83 (1H, d, *J* 7.0 Hz, ArH), 6.57 (1H, s, ArH), 5.94 (2H, s, OCH_2O), 3.73 (1H, app t, *J* 7.0 Hz, CH), 3.34 – 3.20 (2H, m, CH_2), 3.11 – 3.01 (2H, m, CH_2), 2.81 – 2.71 (2H, m, CH_2), 2.60 – 2.49 (2H, m, CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 212.8 (C=O), 146.9 (C), 146.8 (C), 137.9 (C), 136.6 (C), 129.5 (C), 128.6 (CH), 128.0 (CH), 127.3 (CH), 126.9 (CH), 118.7 (CH), 110.6 (CH), 101.8 (CH_2), 89.0 (C), 54.9 (CH), 42.6 (CH_2), 37.8 (CH_2), 27.9 (CH_2)

LRMS (CI)

M/z: 279 ($[M-I]^+$, 18 %), 261 ($[M-I-OH_2]^+$, 100 %), 207 (38 %), 76 (40 %) amu

FT-IR (Neat)

ν_{max} 2985s, 1742s, 1447s, 1374s, 1241s, 1048s cm^{-1}

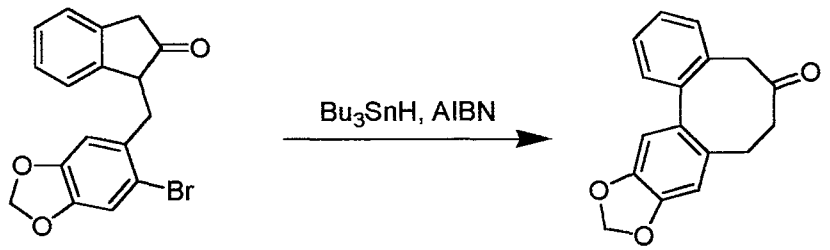
UV (Methanol)

λ_{max} (ε) 241 (3900), 295 (2300) nm

CHN

Required: C 53.22%, H 3.72%; Found: C 52.94%, H 3.71%

4.42 3,4-Methylenedioxy-7,8-dihydro-*5H*-dibenzo[*a,c*]cycloocten-6-one **3.73**



3.72
$C_{17}H_{13}O_3Br$ RMM 345

3.73
$C_{17}H_{14}O_3$ RMM 266

Aryl iodide **3.72** (1.00 g, 2.50 mmol) was dissolved in toluene (40 mL) and AIBN (15 mg, 0.10 mmol) was added. The mixture was warmed to 80 °C and tributyltin hydride (0.80 mL, 0.90 g, 2.90 mmol) was added. The reaction was stirred for 15 h and cooled to rt. Saturated KF solution (40 mL) was added and the mixture was stirred for 8 h. The reaction was extracted with diethyl ether (3 x 20 mL) and washed with brine (20 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (silica, 10% - 50% ether / petrol) gave recovered starting material (0.20 g, 23%, 0.60 mmol) and the title compound **3.73** (0.30 g, 1.00 mmol, 38%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.40 – 7.25 (4H, m, ArH), 6.84 (1H, s, ArH), 6.78 (1H, s, ArH), 6.02 (2H, s, OCH_2O), 3.65 (1H, d, *J* 11.0 Hz, CHH), 3.33 (1H, d, *J* 11.0 Hz, CHH), 2.70 – 2.42 (4H, m, 2 x CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 208.1 (C=O), 147.8 (C), 146.8 (C), 141.4 (C), 133.9 (C), 133.4 (C), 132.9 (C), 129.7 (CH), 129.4 (CH), 128.1 (CH), 127.7 (CH), 109.3 (2 x CH), 101.4 (CH_2), 48.1 (CH_2), 43.3 (CH_2), 29.6 (CH_2)

LRMS (CI)

M/z: 266 (M^+, 100 %), 249 (28 %), 223 (30 %), 165 (50 %) amu

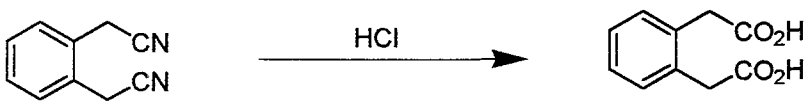
FT-IR (Neat)

ν_{max} 1703s, 1504m, 1480s, 1252m, 1218s, 1038s, 770s cm^{-1}

UV (Methanol)

λ_{max} (ε) 260 (3000), 294 (2600) nm

4.43 *o*-Phenylenediacetic acid **3.83**



3.82
$C_{10}H_8N_2$ RMM 194

3.83
$C_{10}H_{10}O_4$ RMM 194

Diacid **3.83** was prepared by the method of Moore *et al.* [79] *o*-Phenylenediacetonitrile (13.6 g, 87.1 mmol) was dissolved in c. HCl (60 mL) and the solution was heated at reflux for 4 h. The reaction was cooled to rt and the solid filtered and washed with water (3 x 50 mL). The solid was dried ($MgSO_4$) and the title compound **3.83** was isolated as a white crystalline solid (16.6 g, 85.6 mmol, 98%)

Melting point: 148 – 150 °C (H_2O) Lit: 149 – 150 °C [80]

^{1}H-NMR (300 MHz, CD_3COCD_3)

δ/ppm 7.32 – 7.20 (4H, m, Ar<u>H</u>), 3.74 (4H, s, 2 x CH_2)

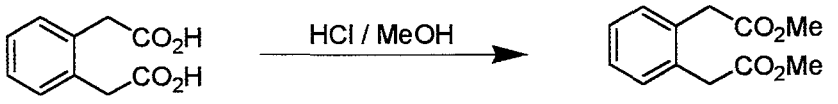
^{13}C-NMR (75.5 MHz, CD_3COCD_3)

δ/ppm 206.2 (2 x <u>C</u>), 134.8 (2 x <u>C</u>), 131.4 (2 x <u>C</u>H), 127.8 (2 x <u>C</u>H), 38.7 (2 x <u>C</u>H_2)

FT-IR (Neat)

ν_{max} 3054m, 2987m, 1422m, 1265s, 896m, 749s cm^{-1}

4.44 (2-Methoxycarbonylmethylphenyl)-acetic acid methyl ester **3.84**



3.83

$C_{10}H_{10}O_4$ RMM 194

3.84

$C_{12}H_{14}O_4$ RMM 222

Diester **3.84** was prepared by the method of Ali *et al.* [81] *o*-Phenylenediacetic acid (16.5 g, 85.1 mmol) was dissolved in MeOH (100 mL) and c. HCl (10 mL) was added. The mixture was heated at reflux for 4 h and cooled to rt. The solvent was concentrated *in vacuo* and the residue was extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried ($MgSO_4$) and solvent concentrated *in vacuo* to give the title compound **3.84** as a yellow oil (14.7 g, 66.2 mmol, 78%).

^{1}H-NMR (300 MHz, CD_3COCD_3)

δ/ppm 7.22 (4H, app s, Ar<u>H</u>), 3.71 (4H, s, 2 x C<u>H</u>$_2$), 3.64 (6H, s, 2 x $CO_2C\underline{H}_3$)

^{13}C-NMR (75.5 MHz, CD_3COCD_3)

δ/ppm 171.9 (2 x <u>C</u>O_2Me), 133.3 (2 x <u>C</u>), 131.2 (2 x <u>C</u>H), 127.9 (2 x <u>C</u>H), 52.3 (2 x <u>C</u>H_3), 38.9 (2 x <u>C</u>H_2)

LRMS (CI)

M/z: 223 (25%, $[MH]^+$), 190 (54%), 162 (100%) amu

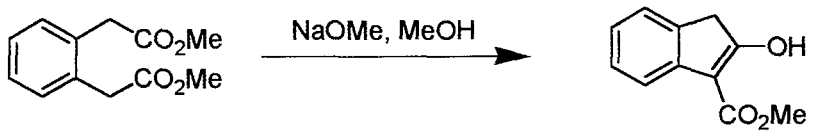
FT-IR (Neat)

ν_{max} 2953s, 1732s, 1497s, 1259s, 1010s, cm^{-1}

UV (Methanol)

λ_{max} (ε) 249 (1900) nm

4.45 2-Oxo-indan-1-carboxylic acid methyl ester **3.85**



3.84 $C_{12}H_{14}O_4$ RMM 222

3.85 $C_{11}H_{10}O_3$ RMM 190

Diester **3.84** (4.60 g, 20.7 mmol) was added to a solution of freshly prepared NaOMe (1.00 g, 43.5 mmol of Na dissolved in 40 mL of MeOH). The reaction was heated at reflux for 3 h and then cooled to rt. HCl (2M, 50 mL) was added and extracted with ethyl acetate (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was concentrated *in vacuo*. Purification by recrystallisation gave the title compound **3.85** as a brown crystalline solid (3.80 g, 19.8 mmol, 96%).

Melting point: 59-61°C (Ethanol) [82]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 11.03 (1H, br s, OH), 7.60 (1H, d, *J* 8.0 Hz, ArH), 7.29 (2H, m, ArH), 7.12 (1H, t, *J* 8.0 Hz, ArH), 3.97 (3H, s, CH_3), 3.59 (2H, s, CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 181.0 (C), 169.5 (CO_2Me), 139.6 (C), 133.3 (C), 127.2 (CH), 123.9 (CH), 123.8 (CH), 120.3 (CH), 105.3 (C), 51.7 (CH_3), 37.8 (CH_2)

LRMS (CI)

M/z: 132 ($[M-CO_2Me]^+$, 39 %), 104 (100%) amu

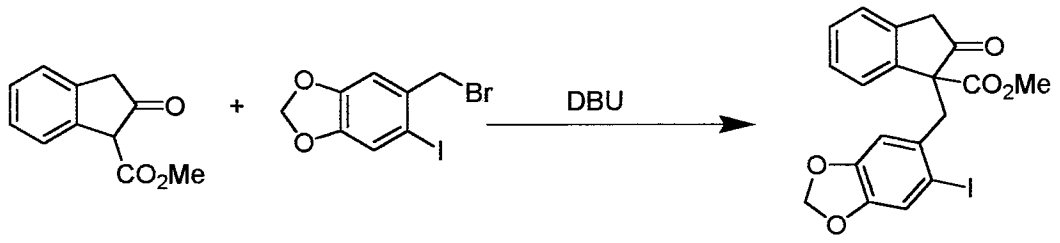
FT-IR (Neat)

ν_{max} 3054m, 1658m, 1593m, 1265s cm^{-1}

UV (Methanol)

λ_{max} (ε) 231 (5300), 260 (3600) nm

4.46 1-(6-Iodo-benzo[1,3]dioxol-5-ylmethyl)-2-oxo-indan-1-carboxylic acid methyl ester **3.95**



3.85 $C_{11}H_{10}O_3$ RMM 190

3.71 $C_8H_8O_2BrI$ RMM 341

3.95 $C_{19}H_{15}O_5I$ RMM 450

A modified procedure of Harmata et al. was used to prepare indanone **3.95**. [66] Indanone **3.85** (1.40 g, 7.40 mmol) was dissolved in CH_2Cl_2 (40 mL) and DBU (1.20 mL, 1.20 g, 8.00 mmol) was added. The mixture was stirred for 15 h at rt and the iodide **3.71** (2.1 g, 6.20 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was stirred for 1 h and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (2 x 30 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the residue was purified by column chromatography (silica, 10% ethyl acetate / petrol) to give the title compound **3.95** as a yellow crystalline solid (2.10 g, 4.80 mmol, 76%).

Melting point: 120 - 122°C (Ethanol)

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.38 – 7.26 (3H, m, ArH), 7.17 (1H, s, ArH), 7.11 (1H, d, *J* 7.0 Hz, ArH), 6.70 (1H, s, ArH), 5.98 (2H, d, *J* 7.0 Hz, OCH_2O), 3.62 (3H, s, OCH_3), 3.76 – 3.48 (4H, m, 2 x CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 211.3 (C=O), 170.8 (C=O), 148.6 (C), 147.7 (C), 140.2 (C), 137.6 (C), 132.3 (C), 129.2 (CH), 127.9 (CH), 125.9 (CH), 125.2 (CH), 119.0 (CH), 110.2 (CH), 102.0 (CH_2), 92.0 (C), 66.6 (C), 53.4 (CH_3), 44.3 (CH_2), 43.6 (CH_2)

LRMS (CI)

M/z: 307 (36 %, $[M-I-O]^+$), 261 (100 %), 135 (18 %) amu

FT-IR (Neat)

ν_{max} 3054s, 2986s, 1762w, 1422s, 1265s, 739s cm^{-1}

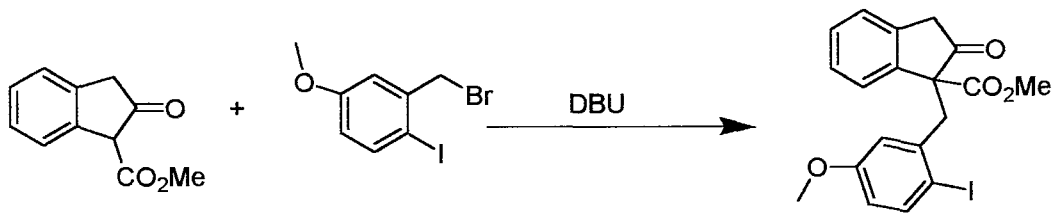
UV (Methanol)

λ_{max} (ε) 228 (1900), 289 (1000) nm

CHN (Ethanol)

Required: C 50.69%, H 3.36%; Found: C 50.81%, H 3.37%

4.47 1-(2-Iodo-5-methoxy-benzyl)-2-oxo-indan-1-carboxylic acid methyl ester **3.99**



3.85 $C_{11}H_{10}O_3$ RMM 190

3.88 C_9H_8OBrI RMM 327

3.99 $C_{19}H_{17}O_4I$ RMM 436

Indanone **3.85** (0.82 g, 4.32 mmol) was dissolved in CH_2Cl_2 (40 mL) and DBU (0.65 mL, 0.66 g, 4.35 mmol) was added. The mixture was stirred for 15 h at rt and the iodide **3.88** (1.42 g, 4.33 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was stirred for 1 h and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (2 x 30 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material was purified by column chromatography (silica, 10% ethyl acetate / petrol) to give the title compound **3.99** as a yellow crystalline solid (0.98 g, 2.25 mmol, 52%).

Melting point: 144 - 146°C (Ethanol)

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.44 (1H, d, *J* 7.0 Hz, ArH), 7.27 – 7.15 (3H, m, ArH), 7.09 (1H, d, *J* 6.0 Hz, ArH), 6.46 (1H, d, *J* 2.0 Hz, ArH), 6.37 (1H, dd, *J* 7.0, 2.0 Hz, ArH), 3.68 – 3.57 (2H, m, CH_2), 3.64 (3H, s, OCH_3), 3.56 (1H, d, *J* 18.0 Hz, CHH), 3.48 (3H, s, OCH_3), 3.22 (1H, d, *J* 18.0 Hz, CHH)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 211.1 (C=O), 170.8 (C=O), 159.8 (C), 140.4 (CH), 140.0 (C), 137.9 (C), 129.2 (CH), 128.1 (CH), 125.9 (CH), 125.3 (CH), 116.0 (CH), 115.6 (CH), 92.4 (C), 66.6 (C), 55.5 (CH_3), 53.4 (CH_3), 44.3 (CH_2), 43.6 (CH_2) One carbon (C) not observed

LRMS (CI)

M/z: 419 ($[M-CH_3]^+$, 100 %), 309 (84 %), 293 (76 %) amu

HRMS (ES+)

Calculated M^+: 450.0328; Found M^+: 450.0330

FT-IR (Neat)

ν_{max} 3054s, 1761s, 1467m, 1265s, 739s cm^{-1}

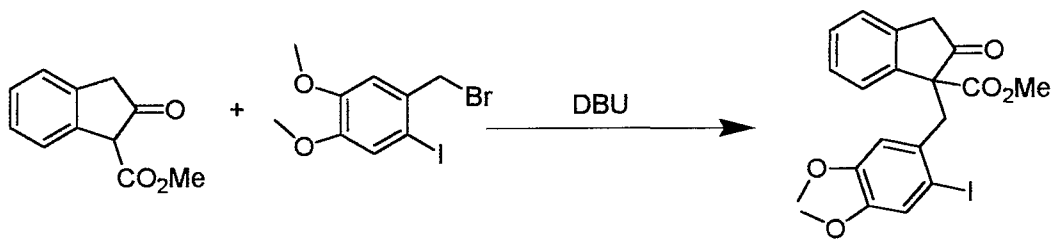
UV (Methanol)

λ_{max} (ε) 260 (12000) nm

CHN (Ethanol)

Required: C 52.31%, H 3.93%; Found: C 52.77%, H 3.97%

4.48 1-(2-Iodo-4,5-dimethoxy-benzyl)-2-oxo-indan-1-carboxylic acid methyl ester **3.97**



3.85 $C_{11}H_{10}O_3$ RMM 190

3.91 $C_{10}H_{10}O_2BrI$ RMM 357

3.97 $C_{20}H_{19}O_6I$ RMM 466

Indanone **3.85** (1.40 g, 7.40 mmol) was dissolved in CH_2Cl_2 (40 mL) and DBU (1.10 mL, 1.10 g, 7.20 mmol) was added. The mixture was stirred for 18 h at rt and the iodide **3.91** (2.80 g, 7.80 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was stirred for 1 h and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (2 x 30 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material was purified by column chromatography (silica, 10% ethyl acetate / petrol) to give the title compound **3.97** as a yellow crystalline solid (2.40 g, 5.20 mmol, 70%).

Melting point: 130 - 132°C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.41 – 7.27 (4H, m, ArH), 7.16 (1H, s, ArH), 6.39 (1H, s, ArH), 3.80 (3H, s, OCH_3), 3.78 – 3.60 (2H, m, CH_2), 3.72 (3H, s, OCH_3), 3.53 (3H, s, OCH_3), 3.24 (2H, d, *J* 18.0 Hz, CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 211.1 (C=O), 170.9 (C=O), 149.0 (C), 148.6 (C), 140.6 (C), 138.1 (C), 131.1 (C), 129.2 (CH), 128.2 (CH), 125.6 (CH), 125.3 (CH), 122.0 (CH), 112.8 (CH), 91.5 (C), 66.7 (C), 56.6 (CH_3), 55.8 (CH_3), 53.4 (CH_3), 44.0 (CH_2), 43.6 (CH_2)

LRMS (CI)

M/z: 277 ($[M\text{-}I\text{-}(OMe)_2]^+$, 100 %), 251 (26 %), 183 (18 %) amu

FT-IR (Neat)

ν_{max} 3054s, 1761w, 1422w, 1265s, 742s cm^{-1}

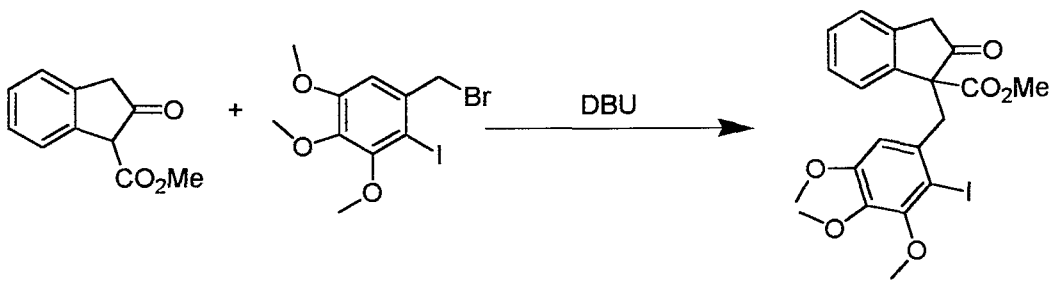
UV (Methanol)

λ_{max} (ε) 228 (2500), 268 (780) nm

CHN (Ethanol)

Required: C 51.52%, H 4.11%; Found: C 51.42%, H 4.17%

4.49 1-(2-Iodo-3,4,5-trimethoxy-benzyl)-2-oxo-indan-1-carboxylic acid methyl ester **3.101**



3.85 $C_{11}H_{10}O_3$ RMM 190

3.94 $C_{10}H_{12}O_3BrI$ RMM 387

3.101 $C_{21}H_{21}O_6I$ RMM 496

Indanone **3.85** (0.80 g, 4.20 mmol) was dissolved in CH_2Cl_2 (40 mL) and DBU (0.70 mL, 0.70 g, 4.60 mmol) was added. The mixture was stirred for 15 h at rt and the iodide **3.94** (1.70 g, 4.40 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was stirred for 1 h and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (2 x 30 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the residue was purified by column chromatography (silica, 10% ethyl acetate / petrol) to give the title compound **3.101** as a yellow crystalline solid (0.80 g, 1.60 mmol, 39%).

Melting point: 140 - 141°C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.21 – 7.10 (3H, m, ArH), 6.98 (1H, d, *J* 6.0 Hz, ArH), 6.35 (1H, s, ArH), 3.71 – 3.50 (3H, m, CH_2 + CHH), 3.70 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.52 (3H, s, OCH_3), 3.48 (3H, s, OCH_3), 3.25 (1H, d, *J* 18.0 Hz, CHH)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 211.0 (C=O), 170.9 (C=O), 153.3 (C), 141.3 (C), 140.4 (C), 137.9 (C), 134.7 (C), 129.2 (CH), 128.0 (CH), 125.9 (CH), 125.2 (CH), 109.8 (CH), 92.2 (C), 66.7 (C), 61.4 (CH_3), 61.0 (CH_3), 56.1 (CH_3), 53.4 (CH_3), 44.2 (CH_2), 43.6 (CH_2)

LRMS (CI)

M/z: 370 ($[MH-I]^+$, 72 %), 307 (100 %) amu

FT-IR (Neat)

ν_{max} 3054w, 1761w, 1423w, 1265s, 735s cm^{-1}

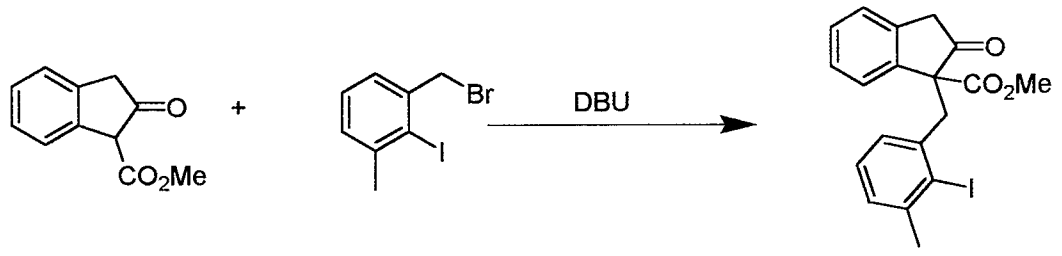
UV (Methanol)

λ_{max} (ε) 220 (5700), 265 (1100) nm

CHN (Ethanol)

Required: C 50.82%, H 4.26%; Found: C 50.28%, H 4.30%

4.50 1-(2-Iodo-3-methyl-benzyl)-2-oxo-indan-1-carboxylic acid methyl ester **3.108**



3.85 $C_{11}H_{10}O_3$ RMM 190

3.107 C_8H_8BrI RMM 311

3.108 $C_{19}H_{17}O_3I$ RMM 420

Iodide **3.107** was prepared by the method of Bacon *et al.* [72] 2,6-Dimethyl-1-iodobenzene (1.38 g, 5.96 mmol) was dissolved in carbon tetrachloride (20 mL) and NBS (1.38 g, 7.75 mmol) was added. The reaction was slowly heated to reflux and AIBN (0.2 g, 0.13 mmol) was added. The reaction was stirred for 4 h at reflux and then cooled. Upon cooling the solid was removed by filtration and the solvent concentrated *in vacuo*. The resulting yellow oil (1.08 g, 3.46 mmol, 58 %) was used directly without isolation. Indanone **3.85** (0.65 g, 3.42 mmol) was dissolved in CH_2Cl_2 (40 mL) and DBU (0.51 mL, 0.52 g, 3.44 mmol) was added. The mixture was stirred for 15 h at rt and the iodide **3.107** (1.08 g, 3.46 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was stirred for 1 h and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (2 x 30 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material was purified by column chromatography (silica, 10% ethyl acetate / petrol) to give the title compound as 2 diastereoisomers **3.108** as a yellow oil (0.46 g, 1.10 mmol, 32%).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.38 – 7.31 (2H, m, ArH), 7.25 (1H, t, *J* 8.0 Hz, ArH), 7.11 – 7.00 (3H, m, ArH), 6.92 (1H, d, *J* 7.0 Hz, ArH), 3.93 (2H, s, $ArCH_2$), 3.72 (3H, s, OCH_3), 3.62 (1H, d, *J* 23.0 Hz, CHH), 3.46 (1H, d, *J* 23.0 Hz, CHH), 2.45 (3H, s, CH_3)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 211.4 (C=O), 170.9 (C=O), 142.9 (C), 140.4 (C), 139.9 (C), 137.7 (C), 129.8 (CH), 128.6 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 126.0

(CH), 124.1 (CH), 111.6 (C), 66.6 (C), 53.4 (CH_3), 45.4 (CH_2), 43.7 (CH_2), 31.1 (CH_3)

LRMS (CI)

M/z: 293 ($[M-I]^+$, 57 %), 231 (100 %), 205 (45 %), 189 (37 %) amu

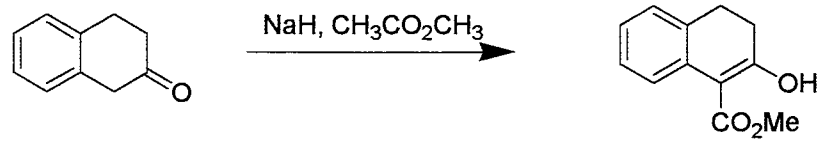
HRMS (ES+)

Calculated $M+Na^+$: 443.0114; Found $M+Na^+$: 443.0119

FT-IR (Neat)

ν_{max} 1760s, 1736s, 1478w, 1461w, 1434w, 1234s, 1139w, 1007w, 731s cm^{-1}

4.51 2-Oxo-1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid methyl ester **3.110**



3.74
$C_{10}H_{10}O$ RMM 146

3.110
$C_{12}H_{12}O_3$ RMM 204

The title compound was prepared by the literature method of Fuchs *et al.* [83] Hexane washed NaH (6.7 g, 167 mmol) was suspended in THF (80 mL) and β-tetralone (10 mL, 11.1 g, 75.7 mmol) in THF (20 mL) was added dropwise. The mixture was stirred for ½ h and dimethyl carbonate (38 mL, 40.7 g, 451 mmol) was added dropwise. The mixture was heated at reflux for 4 h and cooled to rt. The mixture was acidified to pH 4 with acetic acid. The solution was extracted with diethyl ether (3 x 50 mL), washed with $NaHCO_3$ (5 x 50 mL), brine (50 mL), dried ($MgSO_4$) and solvent concentrated *in vacuo* to give the title compound **3.110** as a purple oil (10.5 g, 51.5 mmol, 68%).

^{1}H-NMR (400 MHz, $CDCl_3$) [84]

δ/ppm 7.82 (1H, d, *J* 7.0 Hz, ArH), 7.31 (1H, t, *J* 7.0 Hz, ArH), 7.23 – 7.17 (2H, m, ArH), 4.00 (3H, s, OCH_3), 2.92 (2H, app t, *J* 6.0 Hz, CH_2), 2.63 (2H, app t, *J* 6.0 Hz, CH_2), 1.41 (1H, s, OH)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 178.9 (C=O), 172.9 (C), 133.6 (C), 131.8 (C), 127.9 (CH), 127.2 (CH), 126.7 (CH), 125.7 (CH), 100.4 (C), 52.1 (CH_3), 29.9 (CH_2), 28.4 (CH_2)

LRMS (CI)

M/z: 146 ($[MH-CO_2Me]^+$, 100 %), 131 (51 %), 115 (90 %), 89 (77 %) amu

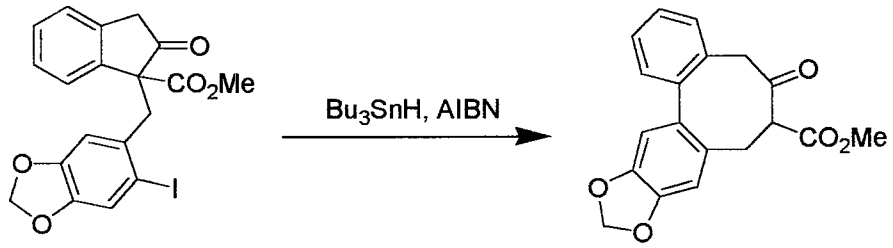
FT-IR (Neat)

ν_{max} 2955m, 1634s, 1600s, 1489s, 1442s, 1315s, 1227s, 908s cm^{-1}

UV (Methanol)

λ_{max} (ε) 234 (2000), 273 (1000) nm

4.52 1,2-Methylenedioxy-7-oxo-5,6,7,8-tetrahydro-dibenzo[*a,c*]cyclooctene-6-carboxylic acid methyl ester **3.96**



3.95

$C_{19}H_{15}O_5I$ RMM 450

3.96

$C_{19}H_{16}O_5$ RMM 324

Indanone **3.95** (0.55 g, 1.22 mmol) was dissolved in toluene (40 mL) and Bu_3SnH (0.48 mL, 0.52 g, 1.81 mmol) and AIBN (15 mg, 0.1 mmol) were added. The mixture was heated at 80°C for 15 h and cooled to rt. KF solution (20 mL) was added and the mixture was stirred for 8 h. The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (2 x 20 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material purified by column chromatography (silica, 20 % ether / petrol) to give the title compound **3.96** as a white crystalline solid (0.25 g, 0.77 mmol, 65%).

Melting point: 162 - 164°C (Ethanol)

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.28 – 7.07 (4H, m, ArH), 6.75 (1H, s, ArH), 6.68 (1H, t, *J* 7.0 Hz, ArH), 5.93 (2H, m, OCH_2O), 3.65 (3H, s, OCH_3), 3.54 – 3.52 (2H, m, CH_2), 3.32 (1H, app d, *J* 11.0 Hz, CH), 2.82 – 2.65 (2H, m, CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 203.5 (C=O), 171.2 (C=O), 148.2 (C), 147.5 (C), 141.1 (C), 134.4 (C), 132.9 (C), 131.2 (C), 130.2 (CH), 129.9 (CH), 129.4 (CH), 128.6 (CH), 128.3 (CH), 109.8 (CH), 101.8 (CH_2), 59.8 (CH), 52.6 (CH_3), 48.4 (CH_2), 32.7 (CH_2)

LRMS (CI)

M/z: 266 ($[MH-CO_2Me]^+$, 67 %), 165 (64 %), 44 (100 %) amu

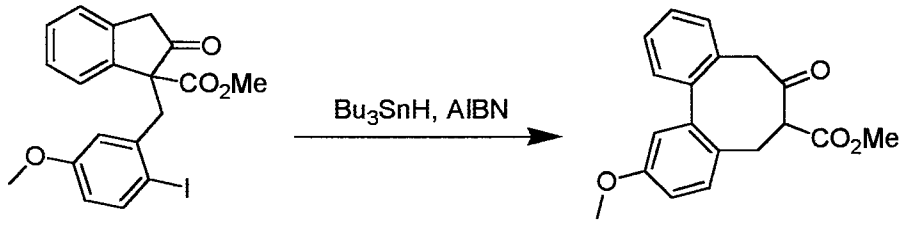
HRMS (ES+)

Calculated $M+Na^+$: 347.0890; Found $M+Na^+$: 347.0888

FT-IR (Neat)

ν_{max} 3054s, 1744w, 1482w, 1265s, 896m cm^{-1}

4.53 1-Methoxy-7-oxo-5,6,7,8-tetrahydro-dibenzo[*a,c*]cyclooctene-6-carboxylic acid methyl ester **3.100**



3.99
$C_{19}H_{17}O_4I$ RMM 436

3.100
$C_{19}H_{18}O_4$ RMM 310

Indanone **3.99** (0.52 g, 1.19 mmol) was dissolved in toluene (40 mL) and Bu_3SnH (0.47 mL, 0.52 g, 1.79 mmol) and AIBN (15 mg, 0.10 mmol) were added. The mixture was heated at 80°C for 15 h and cooled to rt. KF solution (20 mL) was added and the mixture was stirred for 8 h. The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (2 x 20 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material purified by column chromatography (silica, 20 % ether / petrol) to give the title compound **3.99** and reduced starting material as a yellow oil (0.18 g, 0.57 mmol, 48%).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.23 – 7.07 (7H, m, Ar<u>H</u>), 3.78 (3H, s, OC<u>H</u>$_3$), 3.68 (3H, s, OC<u>H</u>$_3$), 2.91 – 2.22 (5H, m, 2 x C<u>H</u>$_2$ + C<u>H</u>)

LRMS (CI)

M/z: 252 ([M-CH_3-CO_2Me]$^+$, 89 %), 209 (80 %), 165 (100 %) amu

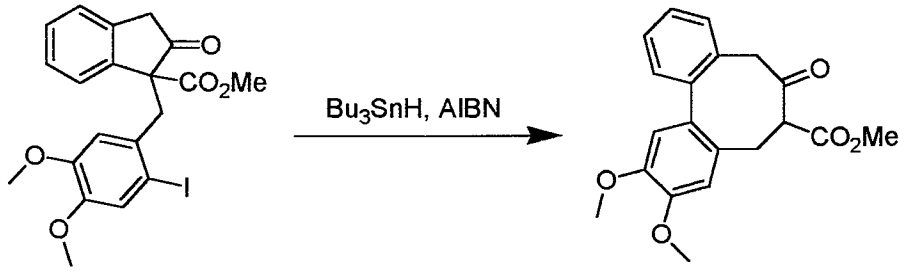
HRMS (ES+)

Calculated M+Na^+: 333.1097; Found M+Na^+: 333.1093

FT-IR (Neat)

ν_{max} 2938w, 1741s, 1608w, 1438w, 1276w, 1048w cm^{-1}

4.54 1,2-Dimethoxy-7-oxo-5,6,7,8-tetrahydro-dibenzo[*a,c*]cyclooctene-6-carboxylic acid methyl ester **3.98**



3.97
$C_{20}H_{19}O_5I$ RMM 466

3.98
$C_{20}H_{20}O_5$ RMM 340

Indanone **3.97** (0.12 g, 0.26 mmol) was dissolved in toluene (40 mL) and Bu_3SnH (0.1 mL, 0.09 g, 0.32 mmol) and AIBN (15 mg, 0.1 mmol) were added. The mixture was heated at 80°C for 15 h and cooled to rt. KF solution (20 mL) was added and the mixture was stirred for 8 h. The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (2 x 20 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material purified by column chromatography (silica, 20 % ether / petrol) to give the title compound as 2 diastereoisomers **3.98** and reduced starting material (52.9 mg, 0.16 mmol, 62%).
Melting point: 161 - 163°C (Ethanol)

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.42 (1H, d, *J* 5.0 Hz, ArH), 7.32 – 7.10 (3H, m, ArH), 6.71 (1H, d, *J* 5.0 Hz, ArH), 6.67 (1H, d, *J* 7.0 Hz, ArH), 3.82 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.68 – 3.35 (2H, m, CH_2), 3.29 (1H, t, *J* 8.0 Hz, CH), 2.82 – 2.59 (2H, m, CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$) *All signals quoted*

δ/ppm 209.3 (C=O), 204.5 (C=O), 203.7 (C=O), 171.3 (C), 170.5 (C), 149.9 (C), 149.5 (C), 148.9 (C), 148.8 (C), 148.7 (C), 141.7 (C), 136.5 (C), 136.4 (C), 134.0 (C), 133.6 (C), 133.3 (C), 133.0 (C), 132.9 (C), 130.2 (CH), 130.1 (CH), 129.9 (CH), 129.8 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 127.2 (C), 125.5 (CH), 123.5 (CH), 121.4 (CH), 114.1 (CH), 113.1 (CH), 112.7 (CH), 107.3 (CH), 60.8 (CH_3),

59.8 ($\underline{C}H_3$), 56.8 ($\underline{C}H_3$), 56.5 (2 x $\underline{C}H_3$), 56.4 ($\underline{C}H_3$), 52.7 ($\underline{C}H$), 48.3 ($\underline{C}H_2$), 44.8 ($\underline{C}H_2$), 32.5 ($\underline{C}H_2$), 32.4 ($\underline{C}H_2$)

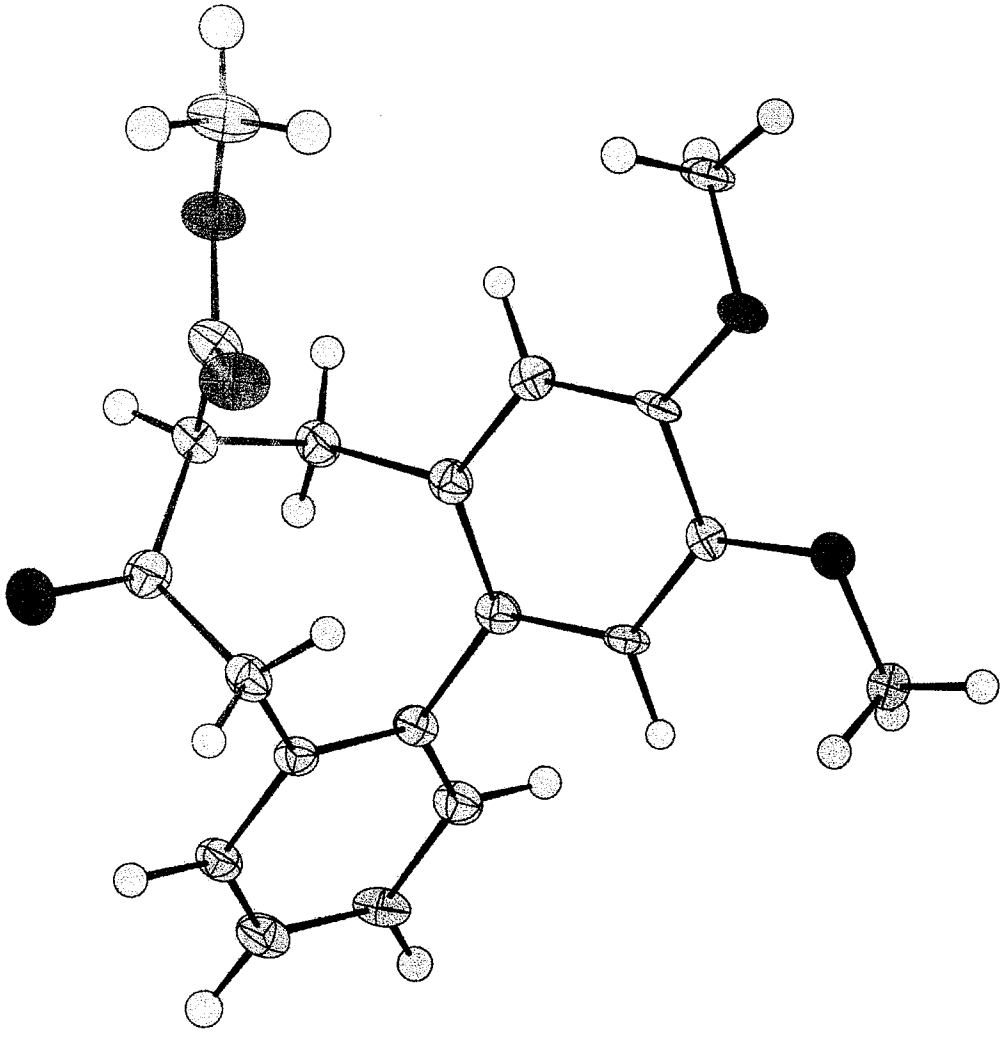
LRMS (CI)

M/z: 282 ($[MH-CO_2Me]^+$, 100 %), 165 (65 %) amu

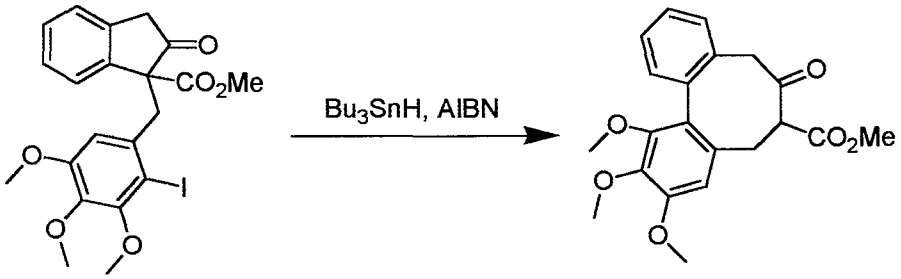
FT-IR (Neat)

ν_{max} 3054s, 1736s, 1516s, 1441s, 1265s, 1026s, 896s cm^{-1}

X-ray crystal structure obtained



4.55 1,2,3-Trimethoxy-7-oxo-5,6,7,8-tetrahydro-dibenzo[*a,c*]cyclooctene-6-carboxylic acid methyl ester **3.102**



3.101
$C_{21}H_{21}O_6I$ RMM 496

3.102
$C_{21}H_{21}O_6I$ RMM 370

Indanone **3.101** (0.80 g, 1.60 mmol) was dissolved in toluene (40 mL) and Bu_3SnH (0.8 mL, 0.90 g, 3.00 mmol) and AIBN (15 mg, 0.10 mmol) were added. The mixture was heated at 80°C for 15 h and cooled to rt. KF solution (20 mL) was added and the mixture was stirred for 8 h. The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (2 x 20 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material purified by column chromatography (silica, 20 % ether / petrol) to give the title compound as 2 diastereoisomers **3.102** as a yellow oil (0.20 g, 0.50 mmol, 33%).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.48 – 7.28 (4H, m, Ar<u>H</u>), 6.68 (1H, s, Ar<u>H</u>), 3.91 (6H, s, 2 x OC<u>H</u>$_3$), 3.89 - 3.42 (3H, m, C<u>H</u>$_2$ + C<u>H</u>), 3.77 (3H, s, OC<u>H</u>$_3$), 3.65 (3H, s, OC<u>H</u>$_3$), 2.96 – 2.62 (2H, m, C<u>H</u>$_2$)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 203.4 (<u>C</u>=O), 171.1 (<u>C</u>=O), 153.9 (<u>C</u>), 151.4 (<u>C</u>), 142.2 (<u>C</u>), 136.6 (<u>C</u>), 134.0 (<u>C</u>), 132.9 (<u>C</u>), 131.9 (<u>C</u>), 131.3 (<u>C</u>H), 129.9 (<u>C</u>H), 128.3 (<u>C</u>H), 127.6 (<u>C</u>H), 108.8 (<u>C</u>H), 61.2 (<u>C</u>H$_3$), 60.2 (<u>C</u>H$_3$), 56.4 (<u>C</u>H$_3$), 56.3 (<u>C</u>H$_3$), 48.7 (<u>C</u>H), 44.8 (<u>C</u>H$_2$), 36.2 (<u>C</u>H$_2$)

LRMS (CI)

M/z: 312 ([MH-CO_2Me]$^+$, 100 %), 256 (33 %), 165 (28 %) amu

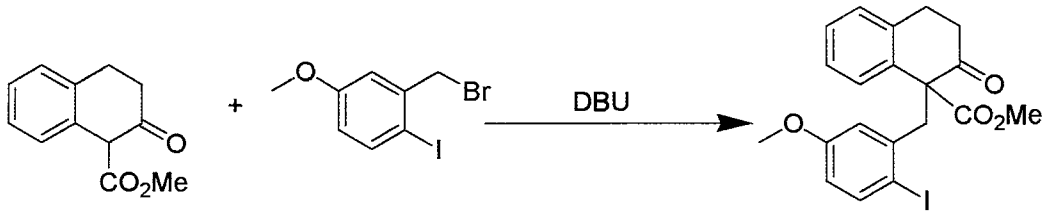
HRMS (ES+)

Calculated $M+Na^+$: 393.1308; Found $M+Na^+$: 393.1312

FT-IR (Neat)

ν_{max} 2940w, 1739s, 1455m, 1337m, 1236m, 1147m cm^{-1}

4.56 1-(2-Iodo-3-methoxy-benzyl)-2-oxo-1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid methyl ester **3.111**



3.110 $C_{12}H_{12}O_3$ RMM 204

3.88 C_8H_8OBrI RMM 327

3.111 $C_{20}H_{19}O_4I$ RMM 450

Tetralone **3.110** (1.00 g, 4.90 mmol) was dissolved in CH_2Cl_2 (40 mL) and DBU (0.80 mL, 0.80 g, 5.20 mmol) was added. The mixture was stirred for 15 h at rt and the iodide (1.60 g, 4.90 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was stirred for 1 h and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (2 x 30 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material was separated by column chromatography (silica, 10% ethyl acetate / petrol) to give 2 diastereoisomers **3.111** and recovered starting material as a yellow oil (0.30 g, 15 %, 0.70 mmol) and recovered starting material (0.80 g, 2.40 mmol, 29%)

.

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.54 (1H, d, *J* 8.0 Hz, ArH), 7.38 – 6.95 (4H, m, ArH), 6.41 (1H, dd, *J* 8.0, 2.0 Hz, ArH), 6.32 (1H, d, *J* 2.0 Hz, ArH), 4.00 – 3.82 (2H, m, CH_2), 3.72 (3H, s, OCH_3), 3.50 (3H, s, OCH_3), 2.91 – 2.28 (4H, m, 2 x CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 206.2 (C=O), 176.3 (C=O), 157.0 (C), 140.6 (CH), 137.8 (C), 134.6 (C), 133.3 (C), 128.9 (CH), 128.8 (CH), 128.2 (CH), 127.7 (CH), 116.4 (CH), 116.1 (CH), 88.9 (C), 62.1 (C), 55.9 (CH_3), 53.8 (CH_3), 48.9 (CH_2), 37.5 (CH_2), 23.1 (CH_2)

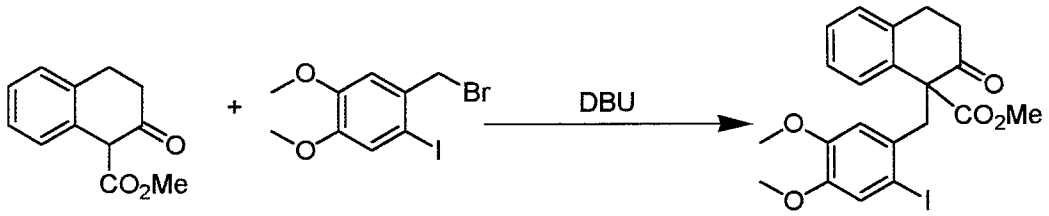
LRMS (CI)

M/z: 323 ($[M-I]^+$, 43 %), 263 (95 %), 247 (100 %) amu

FT-IR (Neat)

ν_{max} 2952s, 1743s, 1589s, 1465s, 1236s, 1172s, 910s, 731s cm^{-1}

4.57 1-(2-Iodo-3,4-dimethoxy-benzyl)-2-oxo-1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid methyl ester **3.112**



3.110 $C_{12}H_{12}O_3$ RMM 204

3.91 $C_9H_{10}O_2BrI$ RMM 357

3.112 $C_{21}H_{21}O_5I$ RMM 480

Tetralone **3.110** (1.00 g, 5.20 mmol) was dissolved in CH_2Cl_2 (40 mL) and DBU (0.80 mL, 0.80 g, 5.30 mmol) was added. The mixture was stirred for 15 h at rt and the iodide (2.30 g, 6.40 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was stirred for 1 h and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (2 x 30 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material was purified by column chromatography (silica, 10% ethyl acetate / petrol) to give the title compound **3.112** and recovered starting material as a yellow oil (1.80 g, 3.80 mmol, 76%).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.30 – 7.08 (4H, m, ArH), 7.06 (1H, s, ArH), 6.20 (1H, s, ArH), 3.98 – 3.82 (2H, m, CH_2), 3.76 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.50 (3H, s, OCH_3), 2.96 – 2.29 (4H, m, 2 x CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 208.6 (C=O), 172.1 (C=O), 148.8 (C), 148.6 (C), 137.2 (C), 136.0 (C), 131.4 (C), 128.9 (CH), 128.7 (CH), 128.2 (CH), 127.7 (CH), 122.3 (CH), 113.8 (CH), 90.4 (C), 64.6 (C), 56.5 (CH_3), 55.8 (CH_3), 52.2 (CH_3), 46.6 (CH_2), 39.5 (CH_2), 28.7 (CH_2)

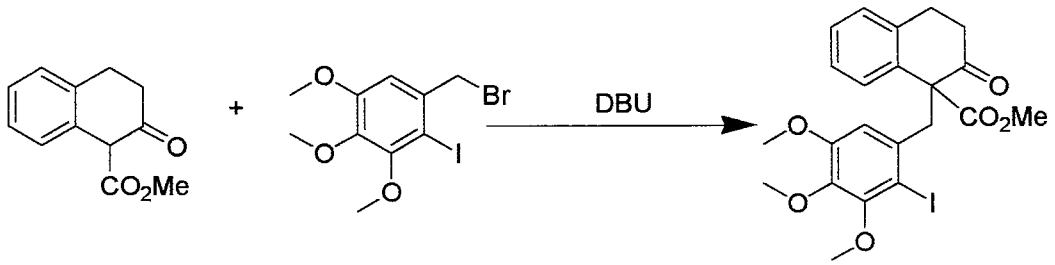
LRMS (CI)

M/z: 277 ($[M\text{-}I\text{-}CO_2Me\text{-}OH]^+$, 100 %), 189 (47 %) amu

FT-IR (Neat)

ν_{max} 2952m, 1743s, 1504s, 1215s, 1162s, 911s, 731s cm^{-1}

4.58 1-(2-Iodo-3,4,5-trimethoxy-benzyl)-2-oxo-1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid methyl ester **3.113**



3.110 $C_{12}H_{12}O_3$ RMM 204

3.94 $C_{10}H_{12}O_3BrI$ RMM 411

3.113 $C_{22}H_{23}O_6I$ RMM 510

Tetralone **3.110** (0.90 g, 4.60 mmol) was dissolved in CH_2Cl_2 (40 mL) and DBU (0.70 mL, 0.70 g, 4.60 mmol) was added. The mixture was stirred for 15 h at rt and the iodide (1.90 g, 4.80 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was stirred for 1 h and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (2 x 30 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material was purified by column chromatography (silica, 10% ethyl acetate / petrol) to give the title compound **3.113** as a yellow crystalline solid (1.30 g, 2.60 mmol, 57%).

Melting point: 110 - 112°C (Ethanol)

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.31 – 7.26 (2H, m, ArH), 7.20 (1H, dd, *J* 7.0, 2.0 Hz, ArH), 7.13 (1H, dd, *J* 7.0, 2.0, ArH) 6.26 (1H, s, ArH), 4.03 (1H, d, *J* 14.0 Hz, CHH), 3.82 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.67 (1H, d, *J* 14.0 Hz, CHH), 3.59 (3H, s, OCH_3), 2.85 (1H, m, CHH), 2.68 (1H, m, CHH), 2.50 – 2.35 (2H, m, CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 208.6 (C=O), 172.1 (C=O), 153.3 (C), 153.0 (C), 141.4 (C), 137.1 (C), 135.8 (C), 134.9 (C), 128.9 (CH), 128.8 (CH), 128.2 (CH), 127.6 (CH),

110.8 (<u>C</u>H), 91.4 (<u>C</u>), 64.8 (<u>C</u>), 61.4 (<u>C</u>H_3), 61.0 (<u>C</u>H_3), 56.1 (<u>C</u>H_3), 53.4 (<u>C</u>H_3), 46.6 (<u>C</u>H_2), 39.5 (<u>C</u>H_2), 27.6 (<u>C</u>H_2)

LRMS (CI)

M/z: 307 ([M-I-CO_2Me-OH]$^+$, 100 %), 293 (30 %), 178 (34 %) amu

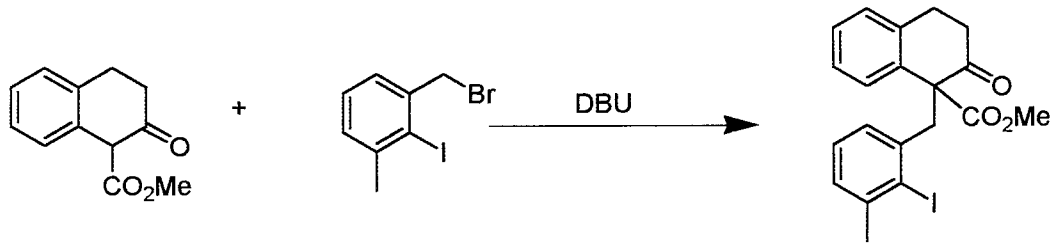
FT-IR (Neat)

ν_{max} 3054m, 1743s, 1266s, 738s cm^{-1}

CHN

Required: C 51.78%, H 4.54%; Found: C 51.66%, H 4.67%

4.59 1-(2-Iodo-3-methyl-benzyl)-2-oxo-1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid methyl ester **3.114**



3.110 $C_{12}H_{12}O_3$ RMM 204

3.107 C_8H_8BrI RMM 311

3.114 $C_{20}H_{19}O_3I$ RMM 434

The bromide used in this procedure was synthesised as in the synthesis of indanone **3.108** (Procedure 4.51). Tetralone **3.110** (1.00 g, 4.90 mmol) was dissolved in CH_2Cl_2 (40 mL) and DBU (1.0 mL, 1.00 g, 6.50 mmol) was added. The mixture was stirred for 15 h at rt and the iodide (1.90 g, 6.10 mmol) in CH_2Cl_2 (10 mL) was added. The reaction was stirred for 1 h and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (2 x 30 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material was purified by column chromatography (silica, 10% ethyl acetate / petrol) to give the title compound **3.114** as a colourless oil (0.40 g, 0.90 mmol, 19%).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.61 – 7.09 (4H, m, ArH), 7.05 (1H, d, *J* 7.0 Hz, ArH), 6.97 (1H, t, *J* 7.0 Hz, ArH), 6.70 (1H, d, *J* 7.0 Hz, ArH), 4.15 (1H, d, *J* 14.0 Hz, CHH), 3.86 (1H, d, *J* 14.0 Hz, CHH), 3.72 (3H, s, OCH_3), 2.85 (1H, m, CHH), 2.73 (1H, m, CHH), 2.54 (1H, m, CHH), 2.41 (3H, s, CH_3), 2.38 (1H, m, CHH)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 208.9 (C=O), 172.1 (C=O), 143.0 (C), 140.1 (C), 137.0 (C), 135.7 (C), 129.7 (CH), 129.5 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 103.9 (C), 64.8 (C), 53.3 (CH_3), 47.5 (CH_2), 39.4 (CH_2), 31.3 (CH_3), 28.2 (CH_2)

LRMS (CI)

M/z: 307 ($[M-I]^+$, 24 %), 247 (72 %), 231 (100 %) amu

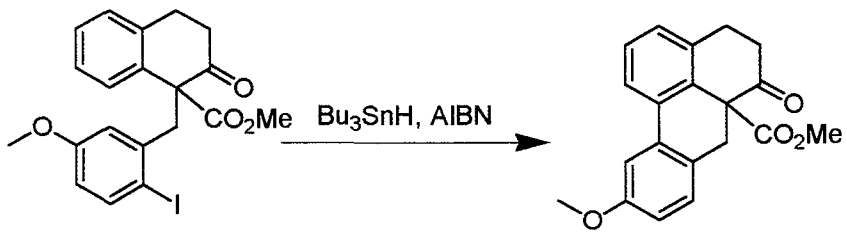
HRMS (ES+)

Calculated $M+Na^+$: 457.0271; Found $M+Na^+$: 457.0277

FT-IR (Neat)

ν_{max} 3019s, 1742s, 1216s, 755s cm^{-1}

4.60 9-Methoxy-6-oxo-5,6-dihydro-4*H*,7*H*-benzo[*de*]anthracene-6a-carboxylic acid methyl ester **3.115**



3.111
$C_{20}H_{19}O_4I$ RMM 450

3.115
$C_{20}H_{18}O_4$ RMM 322

Tetralone **3.111** (0.27 g, 0.60 mmol) was dissolved in toluene (20 mL) and Bu_3SnH (0.32 mL, 0.35 g, 1.20 mmol) and AIBN (15 mg, 0.1 mmol) were added. The mixture was heated at 100 °C for 24 h and cooled to rt. KF solution (20 mL) was added and the mixture was stirred for 8 h. The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (2 x 20 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material purified by column chromatography (silica, 20 % ether / petrol) to give the title compound **3.115** as an impure mixture of compounds with reduced starting material and 2 diastereoisomers of title compound (63.4 mg, 0.20 mmol, 33%).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.69 (1H, dd, *J* 8.0, 6.0 Hz, ArH), 7.42 – 6.84 (5H, m, ArH), 3.92 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.79 (1H, CHH), 3.57 (1H, CHH), 3.28 – 2.90 (2H, m, CH_2), 2.77 – 2.54 (2H, m, CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 205.0, 204.9 (C=O), 168.2, 167.6 (C=O), 157.9, 157.7 (C), 137.5 (C), 133.5, 132.9 (C), 128.9, 128.7 (CH), 126.8, 126.7 (CH), 126.2, 125.9 (CH), 125.2, 125.0 (CH), 123.9, 123.4 (CH), 120.3, 120.2 (CH), 111.4, 111.1 (CH), 110.8, 110.5 (CH), 102.1 (C), 59.0, 56.5 (C), 54.5, 54.3 (CH_3), 53.5, 53.4 (CH_3), 43.9, 41.5 (CH_2), 37.7, 35.8 (CH_2), 29.3, 28.6 (CH_2)

LRMS (CI)

M/z: 322 (M^+, 25 %), 263 (78 %), 221 (100 %) amu

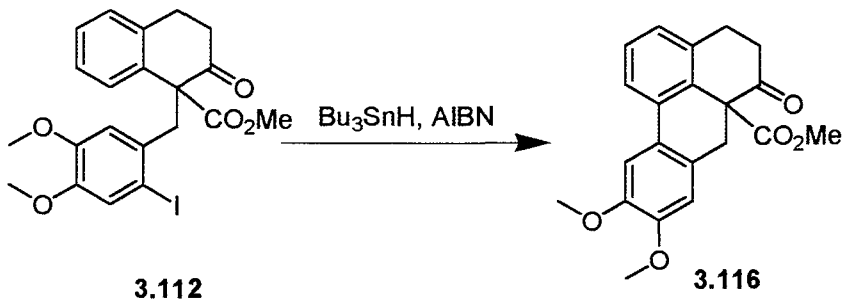
HRMS (ES+)

Calculated M+Na^+: 345.1097; Found M+Na^+: 345.1099

FT-IR (Neat)

ν_{max} 2951m, 1745s, 1608m, 1464m, 1230s, 1158m, 1037w cm^{-1}

4.61 9,10-Dimethoxy-6-oxo-5,6-dihydro-4*H*,7*H*-benzo[*de*]anthracene-6a-carboxylic acid methyl ester **3.116**



3.112

$C_{21}H_{21}O_5I$ RMM 480

3.116

$C_{21}H_{20}O_5$ RMM 352

Tetralone **3.112** (140 mg, 0.29 mmol) was dissolved in toluene (20 mL) and Bu_3SnH (0.16 mL, 0.17 g, 0.60 mmol) and AIBN (15 mg, 0.1 mmol) were added. The mixture was heated at 100 °C for 24 h and cooled to rt. KF solution (20 mL) was added and the mixture was stirred for 8 h. The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (2 x 20 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material purified by column chromatography (silica, 20 % ether / petrol) to give the title compound **3.116** as a white crystalline solid (54.8 mg, 0.15 mmol, 53%).

Melting point: 151 – 152 °C (Ethanol)

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.64 (1H, d, *J* 7.0 Hz, ArH), 7.40 (1H, t, *J* 7.0 Hz, ArH), 7.28 (1H, s, ArH), 7.21 (1H, d, *J* 7.0 Hz), 6.82 (1H, s, ArH), 3.95 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.62 – 3.33 (2H, m, CH_2), 3.54 (3H, s, OCH_3), 3.12 – 3.04 (3H, m, CH_2 + CHH), 2.96 – 2.58 (1H, m, CHH)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 207.1 (C=O), 169.8 (C=O), 149.7 (C), 148.8 (C), 137.0 (C), 135.2 (C), 131.1 (C), 128.8 (CH), 127.3 (CH), 126.9 (C), 125.7 (C), 122.4 (CH), 112.0 (CH), 107.7 (CH), 58.8 (C), 56.5 (CH_3), 56.3 (CH_3), 53.4 (CH_3), 37.7 (CH_2), 35.1 (CH_2), 28.7 (CH_2)

LRMS (CI)

M/z: 293 ($[M-CO_2Me]^+$, 28 %), 251 (30 %), 207 (46 %), 44 (100 %) amu

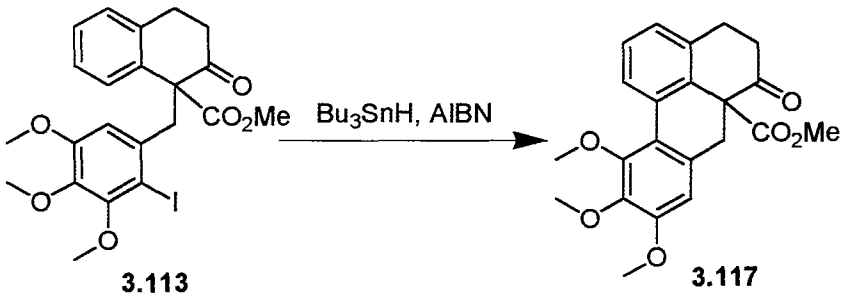
HRMS (ES+)

Calculated M^+: 352.1311; Found M^+: 352.1311

FT-IR (Neat)

ν_{max} 2956w, 1745m, 1517m, 1466m, 1212m, 910s cm^{-1}

4.62 9,10,11-Trimethoxy-6-oxo-5,6-dihydro-4*H*,7*H*-benzo[*de*]anthracene-6a-carboxylic acid methyl ester **3.117**



3.113 $C_{22}H_{23}O_6I$ RMM 510

3.117 $C_{22}H_{22}O_6$ RMM 382

Tetralone **3.113** (0.43 g, 0.84 mmol) was dissolved in toluene (40 mL) and Bu_3SnH (0.45 mL, 0.49 g, 1.69 mmol) and AIBN (15 mg, 0.1 mmol) were added. The mixture was heated at 80 °C for 15 h and cooled to rt. KF solution (20 mL) was added and the mixture was stirred for 8 h. The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (2 x 20 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material purified by column chromatography (silica, 20 % ether / petrol) to give the title compound **3.117** as an impure mixture of compounds with reduced starting material and 2 diastereoisomers of title compound (0.12 g, 0.32 mmol, 37%).

^{1}H-NMR (400 MHz, $CDCl_3$)

The NMR shows characteristic peaks at:

δ/ppm 7.36 – 6.95 (3H, m, Ar<u>H</u>), 5.76 (1H, s, Ar<u>H</u>), 3.92 – 3.50 (14H, m, 4 x O<u>CH</u>$_3$, <u>CH</u>$_2$), 3.42 – 2.28 (4H, m, 2 x <u>CH</u>$_2$)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 209.1, 206.7 (C=O), 191.4 (C), 171.8 (C), 169.7 (C), 153.4, 152.8 (C), 146.0 (C), 142.3 (C), 137.8 (C), 135.5 (C), 133.4 (C), 128.8, 128.7 (CH), 128.5, 128.4 (CH), 127.6, 127.5 (CH), 107.8, 107.7 (CH), 61.5, 61.3 (C), 61.2, 61.1 (CH_3), 56.6, 56.5 (CH_3), 56.4, 56.3 (CH_3), 53.4, 53.3 (CH_3), 47.3, 46.6 (CH_2), 39.8, 39.4 (CH_2), 29.5 (CH_3)

LRMS (CI)

M/z: 382 (M^+, 26 %), 323 (82 %), 281 (45 %), 207 (28 %) amu

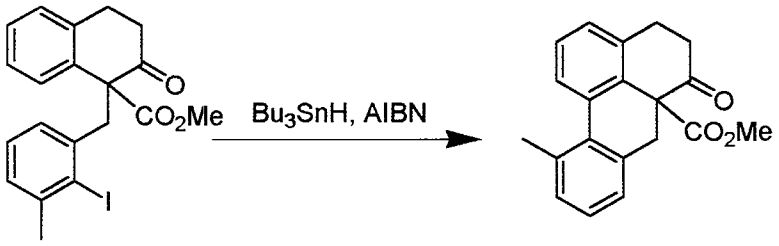
HRMS (ES+)

Calculated M^+: 382.1416; Found M^+: 382.1416

FT-IR (Neat)

ν_{max} 2938m, 1744s, 1463s, 1340s, 1235s, 1126s, 912s cm^{-1}

4.63 11-Methyl-6-oxo-5,6-dihydro-4*H*,7*H*-benzo[*de*]anthracene-6a-carboxylic acid methyl ester **3.118**



3.114
$C_{20}H_{19}O_3I$ RMM 434

3.118
$C_{20}H_{18}O_3$ RMM 306

Tetralone **3.114** (320 mg, 0.70 mmol) was dissolved in toluene (20 mL) and Bu_3SnH (0.4 mL, 0.4 g, 1.50 mmol) and AIBN (15 mg, 0.10 mmol) were added. The mixture was heated at 100 °C for 24 h and cooled to rt. KF solution (20 mL) was added and the mixture was stirred for 8 h. The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (2 x 20 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material purified by column chromatography (silica, 10 % ether / petrol) to give the title compound **3.118** as a colourless oil with reduced staring material and 2 diastereoisomers of **3.118** (71.4 mg, 0.20 mmol, 31%).

^{1}H-NMR (400 MHz, $CDCl_3$)

The NMR shows characteristic peaks at:

δ/ppm 7.39 – 6.88 (6H, m, Ar<u>H</u>), 3.92 – 3.34 (9H, m, O<u>CH</u>$_3$, 3 x <u>CH</u>$_2$), 1.45 (3H, s, <u>CH</u>$_3$)

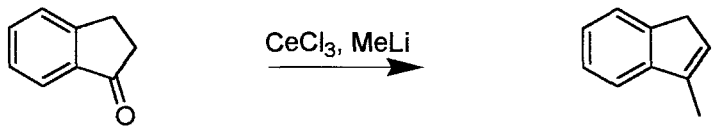
LRMS (CI)

M/z: 306 (M^+, 26 %), 247 (100 %) amu

FT-IR (Neat)

ν_{max} 3020s, 1741w, 1216s, 909s cm^{-1}

4.64 1-Methylindan-1-ene **3.67**



3.65
C_9H_8O RMM 132

3.67
$C_{10}H_{10}$ RMM 130

Dry $CeCl_3$ (24.3 g, 65.2 mmol) was dissolved in THF (40 mL) and was cooled to –78 °C. 1-indanone **3.65** (3.10 g, 23.5 mmol) was added and the mixture was stirred for 5 minutes. Methyllithium (15 mL) was added and the reaction was stirred for 2 h. The reaction was warmed to rt and brine (50 mL) was added. The mixture was extracted with diethyl ether (3 x 50 mL) and the combined organic phases were dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (50 mL) and PPTS (0.20 g, mmol) was added. The reaction was stirred for 4 h and water (20 mL) was added. The mixture was extracted with diethyl ether (3 x 20 mL), dried ($MgSO_4$) and solvent concentrated *in vacuo*. The title compound **3.67** was isolated as a colourless oil (1.30 g, 9.80 mmol, 42%).

Data is consistent with the literature. [85]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.56 – 7.19 (4H, m, ArH), 6.22 (1H, d, *J* 2.0 Hz, CH), 3.34 (2H, s, $ArCH_2$), 2.20 (3H, s, CH_3)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 146.3 (C), 144.5 (C), 140.1 (C), 128.9 (CH), 126.2 (CH), 124.6 (CH), 123.8 (CH), 119.0 (CH), 37.8 (CH_2), 13.2 (CH_3)

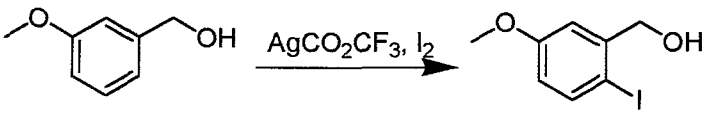
LRMS (CI)

M/z: 130 (M^+, 80 %), 115 (100 %), 102 (64 %), 65 (59 %) amu

FT-IR (Neat)

ν_{max} 3041s, 2912s, 1683s, 1462s, 1381s cm^{-1}

4.65 (2-Iodo-5-methoxy-phenyl)-methanol **3.87**



3.86 $C_8H_{10}O_2$ RMM 138

3.87 $C_8H_9O_2I$ RMM 264

Iodide **3.87** was prepared by the method of Horne *et al.*[86]The alcohol **3.86** (4.80 g, 34.8 mmol) and silver trifluoroacetate (7.81 g, 35.4 mmol) were dissolved in dry chloroform (80 mL). The mixture was cooled to 0 °C and iodine (9.40 g, 37.0 mmol) was added in one portion. The mixture was stirred for 30 mins and filtered. The filtrate was washed with sodium thiosulfate (30 mL) and solvent removed *in vacuo*. The solid was recrystallised with $CHCl_3$ to give the title compound **3.87** (7.90 g, 29.9 mmol, 86 %) as a white crystalline solid.

Data is consistent with the literature. [87]

Melting point: 88 – 90 °C (Chloroform) Lit: 66 – 67 °C (Ether / Petrol) [87]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.80 (1H, d, *J* 8.5 Hz, ArH), 7.11 (1H, d, *J* 2.0 Hz, ArH), 6.78 (1H, dd, *J* 8.5, 2.0 Hz, ArH), 4.71 (2H, s, CH_2), 3.93 (3H, s, OCH_3), 2.32 (1H, s, OH)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 160.6 (C), 141.4 (C), 141.0 (CH), 116.8 (CH), 116.4 (CH), 88.7 (C), 55.9 (CH_3), 39.1 (CH_2)

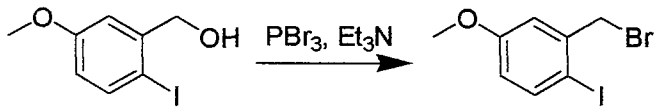
LRMS (CI)

M/z: 264 (M^+, 100 %) amu

FT-IR (Neat)

ν_{max} 3054s, 1589m, 1467s, 1265s, 1050m, 896m, 746s cm^{-1}

4.66 2-Bromomethyl-1-iodo-4-methoxy-benzene **3.88**



3.87
$C_8H_9O_2I$ RMM 264

3.88
C_8H_8OBrI RMM 344

To a cooled (0 °C) solution of alcohol **3.87** (4.80 g, 16.3 mmol) in DCM / THF (45 mL, 1:1) were added triethylamine (2.3 mL, 1.60 g, 16.3 mmol) and phosphorus tribromide (1.6 mL, 4.50 g, 16.5 mmol) successively. The mixture was stirred at 40 °C for 1 h then cooled to rt. Upon cooling to room temperature the solution was poured over ice and then pH adjusted to 7 with a saturated solution of K_2CO_3 (10 mL). The aqueous phase was extracted with DCM and the combined organic phases were dried ($MgSO_4$) and solvent removed *in vacuo*. The resulting solid was recrystallised from ethanol to give the title compound **3.88** and recovered starting material as a white crystalline solid (4.80 g, 13.9 mmol, 80 %).

Data is consistent with the literature.[88]

Melting Point: 147 – 148 °C (Ethanol)

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 7.10 (1H, d, *J* 8.5 Hz, ArH), 7.03 (1H, d, *J* 4.0 Hz, ArH), 6.61 (1H, dd, *J* 8.5, 4.0 Hz, ArH), 4.57 (2H, s, CH_2), 3.87 (3H, s, OCH_3)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 160.4 (C), 144.2 (C), 120.1 (CH), 119.9 (CH), 117.1 (CH), 81.0 (C), 59.1 (CH_3), 42.3 (CH_2)

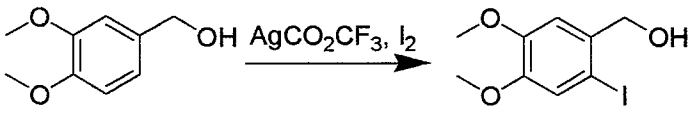
LRMS (CI)

M/z: 328 (MH^+, 17 %), 247 ($[M-Br]^+$, 100 %), 120 (33 %), 77 (46 %) amu

FT-IR (Neat)

ν_{max} 3054w, 1422m, 1265s, 896w, 742s cm^{-1}

4.67 (2-Iodo-4,5-dimethoxy-phenyl)-methanol **3.90**



3.89
$C_9H_{12}O_3$ RMM 168

3.90
$C_9H_{11}O_3I$ RMM 294

Iodide **3.90** was prepared by the method of Olivera *et al.* [89] The alcohol **3.89** (4.30 g, 25.6 mmol) and silver trifluoroacetate (5.60 g, 25.4 mmol) were dissolved in dry chloroform (40 mL). The mixture was cooled to 0 °C and iodine (6.50 g, 25.6 mmol) was added in one portion. The mixture was stirred for 30 mins and filtered. The filtrate was washed with sodium thiosulfate (30 mL) and solvent removed *in vacuo*. The solid was recrystallised with $CHCl_3$ to give the title compound **3.90** (6.50 g, 22.10 mmol, 86 %) as a white crystalline solid.

Data is consistent with the literature. [90]

Melting point: 112 – 114 °C (Chloroform) Lit: 103 - 104 °C (DCM / Petrol) [90]

^{1}H-NMR (300 MHz, $CDCl_3$) [47]

δ/ppm 7.18 (1H, s, Ar<u>H</u>), 6.98 (1H, s, Ar<u>H</u>), 4.67 (2H, s, C<u>H</u>$_2$), 3.62 (6H, s, 2 x OC<u>H</u>$_3$), 1.98 (1H, s, O<u>H</u>)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 149.6 (<u>C</u>), 149.0 (<u>C</u>), 135.4 (<u>C</u>), 121.6 (<u>C</u>H), 111.7 (<u>C</u>H), 85.4 (<u>C</u>I), 69.1 (<u>C</u>H$_2$), 56.4 (<u>C</u>H$_3$), 56.1 (<u>C</u>H$_3$)

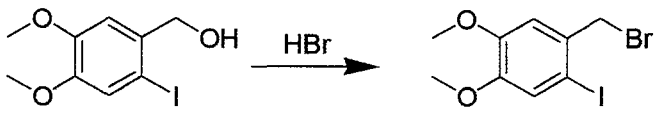
LRMS (CI)

M/z: 294 (M^+, 100 %), 139 (41 %) amu

FT-IR (Neat)

ν_{max} 3054s, 1501s, 1262s, 1157s, 749s cm^{-1}

4.68 1-Bromomethyl-2-iodo-4,5-dimethoxy-benzene **3.91**



3.90
$C_9H_{11}O_3I$ RMM 294

3.91
$C_9H_{10}O_2BrI$ RMM 374

Alcohol **3.90** (2.10 g, 7.10 mmol) was dissolved in HBr (40 mL) and the mixture was stirred for 1 h at rt. DCM (20 mL) was added and the phases were separated. The aqueous phase was extracted with DCM, dried and solvent removed *in vacuo* to give the title compound **3.91** as a red - brown solid (2.30 g, 6.10 mmol, 86 %).

Data is consistent with the literature. [89]

Melting point: 88 – 89 °C (Ether) Lit: 89 – 90 °C (Ether) [89]

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 7.27 (1H, s, ArH), 7.05 (1H, s, ArH), 4.66 (2H, s, CH_2), 3.92 (3H, s, OCH_3), 3.91 (3H, s, OCH_3),

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 148.8 (C), 148.7 (C), 131.6 (C), 121.0 (CH), 112.0 (CH), 87.7 (C), 55.3 (CH_3), 55.1 (CH_3), 38.6 (CH_2)

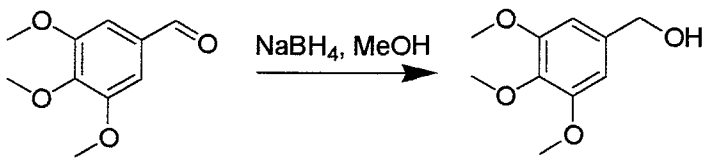
LRMS (CI)

M/z: 278 ($[MH-Br]^+$, 99 %), 277 ($[M-Br]^+$, 100 %), 139 (39 %), 108 (91 %) amu

FT-IR (Neat)

ν_{max} 2955w, 1593m, 1502s, 1375s, 1257s, 1221s, 1164m cm^{-1}

4.69 (3,4,5-Trimethoxy-phenyl)-methanol **3.92**



3.53
$C_{10}H_{12}O_4$ RMM 196

3.92
$C_{10}H_{14}O_4$ RMM 198

Aldehyde **3.53** (15.80 g, 80.6 mmol) was dissolved in methanol (80 mL) and cooled to 0 °C. Sodium borohydride (3.2 g, 84.2 mmol) was added and the mixture was stirred for 1 h. The solvent was concentrated *in vacuo* and the residue dissolved in DCM (30 mL). The mixture was washed with water (30 mL), dried ($MgSO_4$) and the solvent evaporated to give the title compound **3.92** as a yellow oil (14.10 g, 71.2 mmol, 88%). Data is consistent with the literature. [96]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 6.58 (2H, s, Ar<u>H</u>), 4.61 (2H, s, C<u>H</u>$_2$), 3.84 (9H, s, 3 x OC<u>H</u>$_3$), 3.20 – 2.80 (1H, br s, O<u>H</u>)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 153.1 (2 x <u>C</u>), 137.3 (<u>C</u>), 136.7 (<u>C</u>), 103.6 (2 x <u>C</u>H), 64.8 (<u>C</u>H$_2$), 60.8 (<u>C</u>H$_3$), 55.9 (2 x <u>C</u>H$_3$)

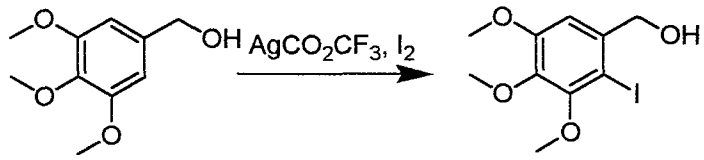
LRMS (CI)

M/z: 198 (M^+, 100 %), 183 (63 %), 155 (61 %), 127 (52 %) amu

FT-IR (Neat)

ν_{max} 3464br, 2940s, 1593s, 1460s, 1331s, 1237s, 1007s, 829s cm^{-1}

4.70 (2-Iodo-3,4,5-trimethoxy-phenyl)-methanol **3.93**



3.92 **3.93**

$C_{10}H_{14}O_4$ RMM 198 $C_{10}H_{13}O_4I$ RMM 324

Bromide **3.93** was prepared by the method of Larson *et al.* [91] Alcohol **3.92** (4.60 g, 23.2 mmol) and silver trifluoroacetate (5.20 g, 23.5 mmol) were dissolved in dry chloroform (80 mL). The mixture was cooled to 0 °C and iodine (6.30 g, 24.8 mmol) was added in one portion. The mixture was stirred for 30 mins and filtered. The filtrate was washed with sodium thiosulfate (30 mL) and solvent removed *in vacuo*. The solid was recrystallised with $CHCl_3$ to give the title compound **3.93** (6.20 g, 19.1 mmol, 82 %) as a white crystalline solid.

Data is consistent with the literature. [92]

Melting point: 55 – 56 °C (Chloroform) Lit: 56.5 – 57.5 °C [92]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 6.91 (1H, s, Ar<u>H</u>), 4.63 (2H, s, C<u>H</u>$_2$), 3.87 (3H, s, OC<u>H</u>$_3$), 3.86 (3H, s, OC<u>H</u>$_3$), 3.85 (3H, s, OC<u>H</u>$_3$), 2.65 (1H, s, O<u>H</u>)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 154.0 (<u>C</u>), 153.0 (<u>C</u>), 141.4 (<u>C</u>), 138.6 (<u>C</u>), 108.0 (<u>C</u>H), 84.5 (<u>C</u>), 69.4 (<u>C</u>H$_2$), 61.2 (<u>C</u>H$_3$), 61.0 (<u>C</u>H$_3$), 56.3 (<u>C</u>H$_3$)

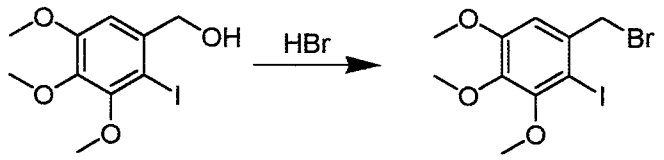
LRMS (CI)

M/z: 324 (M^+, 100 %), 198 (73 %), 154 (72 %), 139 (59 %) amu

FT-IR (Neat)

ν_{max} 3426br, 2936s, 1563s, 1392s, 1160s, 844s cm^{-1}

4.71 1-Bromomethyl-2-iodo-3,4,5-trimethoxy-benzene **3.94**



3.93

$C_{10}H_{13}O_4I$ RMM 324

3.94

$C_{10}H_{12}O_3BrI$ RMM 404

Alcohol **3.93** (2.00 g, 6.20 mmol) was dissolved in HBr (40 mL) and the mixture was stirred for 1 h at rt. DCM (20 mL) was added and the phases were separated. The aqueous phase was extracted with DCM, dried and solvent removed *in vacuo* to give the title compound **3.94** as a brown oil (1.60 g, 4.00 mmol, 64 %). Due to the instability of this compound it was used immediately upon formation.

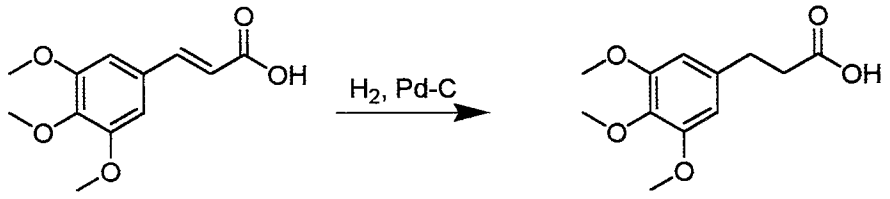
LRMS (CI)

M/z: 307 ($[M-Br]^+$, 100 %), 293 (25 %), 165 (23 %) amu

FT-IR (Neat)

ν_{max} 2953s, 1590s, 1479s, 1334s, 1242s, 1101s, 1003s, 928s cm^{-1}

4.72 3-(3,4,5-Trimethoxy-phenyl)-propionic acid **3.63**



3.62
$C_{12}H_{14}O_5$ RMM 238

3.63
$C_{12}H_{16}O_5$ RMM 240

Acid **3.63** was prepared by a modified method of Rapoport *et al.* [93] Cinnamic acid **3.62** (6.80 g, 28.6 mmol) was dissolved in MeOH (80 mL) and palladium on carbon (5 %, 0.50 g, 0.20 mmol) was added. The mixture was stirred under an atmosphere of hydrogen for 15 h at rt. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The solid was recrystallised with MeOH to give the title compound **3.63** as a white crystalline solid (6.60 g, 27.5 mmol, 96%).

Data is consistent with the literature. [94]

Melting point: 107 – 108 °C (Ethanol) Lit: 104 °C [94]

^{1}H-NMR (300 MHz, $CDCl_3$)

δ/ppm 6.42 (2H, s, ArH), 3.86 (6H, s, 2 x OCH_3), 3.82 (3H, s, OCH_3), 3.70 (1H, s, OH), 2.92 (2H, app t, *J* 8.0 Hz, CH_2), 2.60 (2H, app t, *J* 8.0 Hz, CH_2)

^{13}C-NMR (75.5 MHz, $CDCl_3$)

δ/ppm 178.9 (C=O), 153.3 (2 x C), 136.5 (C), 136.0 (C), 105.3 (2 x CH), 61.0 (CH_3), 56.2 (2 x CH_3), 35.9 (CH_2), 31.1 (CH_2)

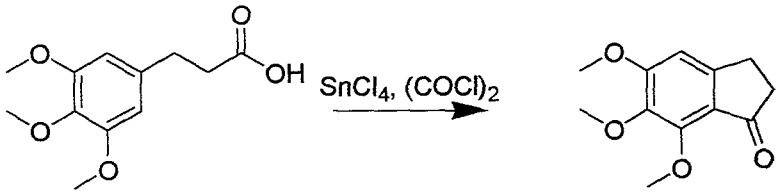
LRMS (CI)

M/z: 254 (93 %), 239 ($[M-H]^+$, 21 %), 181 (100 %) amu

FT-IR (Neat)

ν_{max} 2942s, 1732s, 1712s, 1591s, 1509s, 1456s, 1423s, 1127s cm^{-1}

4.73 5,6,7-Trimethoxy-indan-1-one **3.61**



3.63
$C_{12}H_{16}O_5$ RMM 240

3.61
$C_{12}H_{14}O_4$ RMM 222

Indanone **3.61** was prepared by a modified method of Koo *et al.* [95] Acid **3.63** (6.10 g, 25.4 mmol) was dissolved in DCM (40 mL) and cooled to 0 °C. Oxalyl chloride (2.4 mL, 3.49 g, 27.5 mmol) was added and the mixture was stirred for 1 h. Tin tetrachloride (3.0 mL, 9.39 g, 36.0 mmol) was added and the reaction was stirred for 2 h. Water (20 mL) was added and the phases were separated. The aqueous phase was extracted with DCM (3 x 20 mL) and the combined organic phases were washed with brine (2 x 50 mL). The organic phase was dried and the solvent removed *in vacuo*. The solid was recrystallised using EtOH to give the title compound as a white crystalline solid (4.70 g, 21.7 mmol, 83%).

Data is consistent with the literature. [95]

Melting point: 110 – 112 °C (Ethanol) Lit: 111.5 – 113.5 °C [95]

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 6.65 (1H, s, ArH), 4.02 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 2.99 (2H, app t, *J* 6.0 Hz, CH_2), 2.63 (2H, app t, *J* 6.0 Hz, CH_2)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 203.4 (C=O), 159.8 (C), 153.4 (C), 151.7 (C), 140.8 (C), 122.9 (C), 103.9 (CH), 62.1 (CH_3), 61.5 (CH_3), 56.4 (CH_3), 37.3 (CH_2), 25.8 (CH_2)

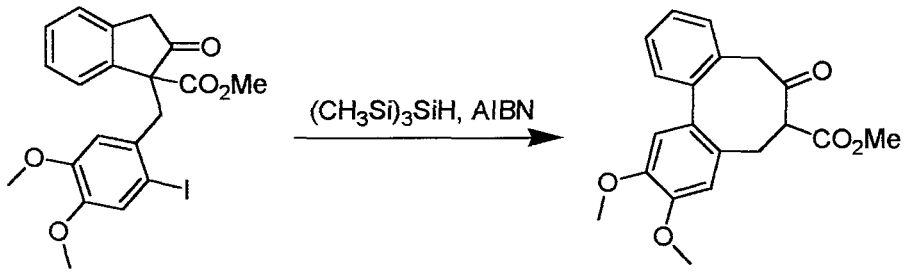
LRMS (CI)

M/z: 222 (M^+, 94 %), 207 (100 %) amu

FT-IR (Neat)

ν_{max} 3055s, 1698s, 1593s, 1483s, 1325s, 1265s, 1146s cm^{-1}

4.74 1,2-Dimethoxy-7-oxo-5,6,7,8-tetrahydro-dibenzo[*a,c*]cyclooctene-6-carboxylic acid methyl ester **3.98**



3.97

$C_{20}H_{19}O_5I$ RMM 466

3.98

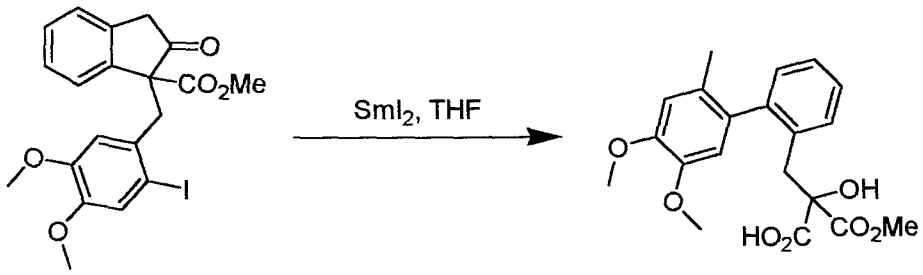
$C_{20}H_{20}O_5$ RMM 340

Indanone **3.97** (0.24 g, 0.52 mmol) was dissolved in toluene (40 mL) and tris(trimethylsilyl)silane (0.16 mL, 0.13 g, 0.52 mmol) and AIBN (15 mg, 0.1 mmol) was added. The mixture was heated at 80 °C for 15 h and cooled to rt. KF solution (20 mL) was added and the mixture was stirred for 8 h. The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (2 x 20 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the crude material purified by column chromatography (silica, 5 % ethyl acetate / toluene) to give the title compound as a red crystalline solid **3.98** (99.0 mg, 0.29 mmol, 56%).

The data are consistent with those reported previously.

4.75 3,4-Dimethoxy-6-methyl-2'-(2-hydroxy malonic acid monomethyl ester)-biphenyl

3.125



3.97

$C_{20}H_{19}O_5I$ RMM 466

3.125

$C_{20}H_{22}O_7$ RMM 374

To a solution of freshly prepared SmI_2 under a positive argon atmosphere (formed from 0.5 g, 3.30 mmol Sm powder and 0.52 g, 1.80 mmol 1,2-diiodoethane *via* a modified method of Kilburn *et al.*) [97, 98] in THF (40 mL) cooled to –78 °C was added indanone **3.97** (0.29 g, 0.60 mmol). The reaction was stirred for 24 h and warmed to room temperature. Water (20 mL) was added and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with water (3 x 20 mL), brine (2 x 20 mL) and dried ($MgSO_4$). The solvent was concentrated *in vacuo* and the residue purified by column chromatography (silica, 5 % ethyl acetate / toluene) to yield the title compound as a green oil (0.05 g, 0.19 mmol, 32%).

^{1}H-NMR (400 MHz, $CDCl_3$)

δ/ppm 10.92 (1H, s, O<u>H</u>), 7.48 (1H, d, *J* 6.0 Hz, Ar<u>H</u>), 7.19 (1H, dd, *J* 6.0, 6.0 Hz, Ar<u>H</u>), 7.17 (1H, d, *J* 6.0Hz, Ar<u>H</u>), 7.10 (1H, s, Ar<u>H</u>), 7.00 (1H, dd, *J* 6.0, 6.0 Hz, Ar<u>H</u>), 6.68 (1H, s, Ar<u>H</u>), 3.87 (3H, s, $CO_2C\underline{H}_3$), 3.74 (6H, s, 2 x $OC\underline{H}_3$), 3.45 (2H, s, $C\underline{H}_2$), 2.28 (3H, s, $C\underline{H}_3$), 1.45 (1H, s, O<u>H</u>)

^{13}C-NMR (100 MHz, $CDCl_3$)

δ/ppm 181.2 (<u>C</u>), 169.7 (<u>C</u>), 149.6 (<u>C</u>), 148.0 (<u>C</u>), 139.9 (<u>C</u>), 134.0 (<u>C</u>), 133.5 (<u>C</u>), 127.5 (<u>C</u>H), 124.2 (<u>C</u>H), 124.0 (<u>C</u>H), 121.9 (<u>C</u>H), 113.2 (<u>C</u>H), 111.7 (<u>C</u>H), 105.6 (<u>C</u>), 88.8 (<u>C</u>), 56.6 ($\underline{C}H_3$), 56.2 ($\underline{C}H_3$), 51.9 ($\underline{C}H_3$), 38.1 ($\underline{C}H_2$), 27.9 ($\underline{C}H_3$)

LRMS (CI)

M/z: 278 ($[MH\text{-}CO_2Me\text{-}OH\text{-}OMe]^+$, 100 %), 263 (29 %), 108 (60 %) amu

Chapter 5

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6.0 Bibliography

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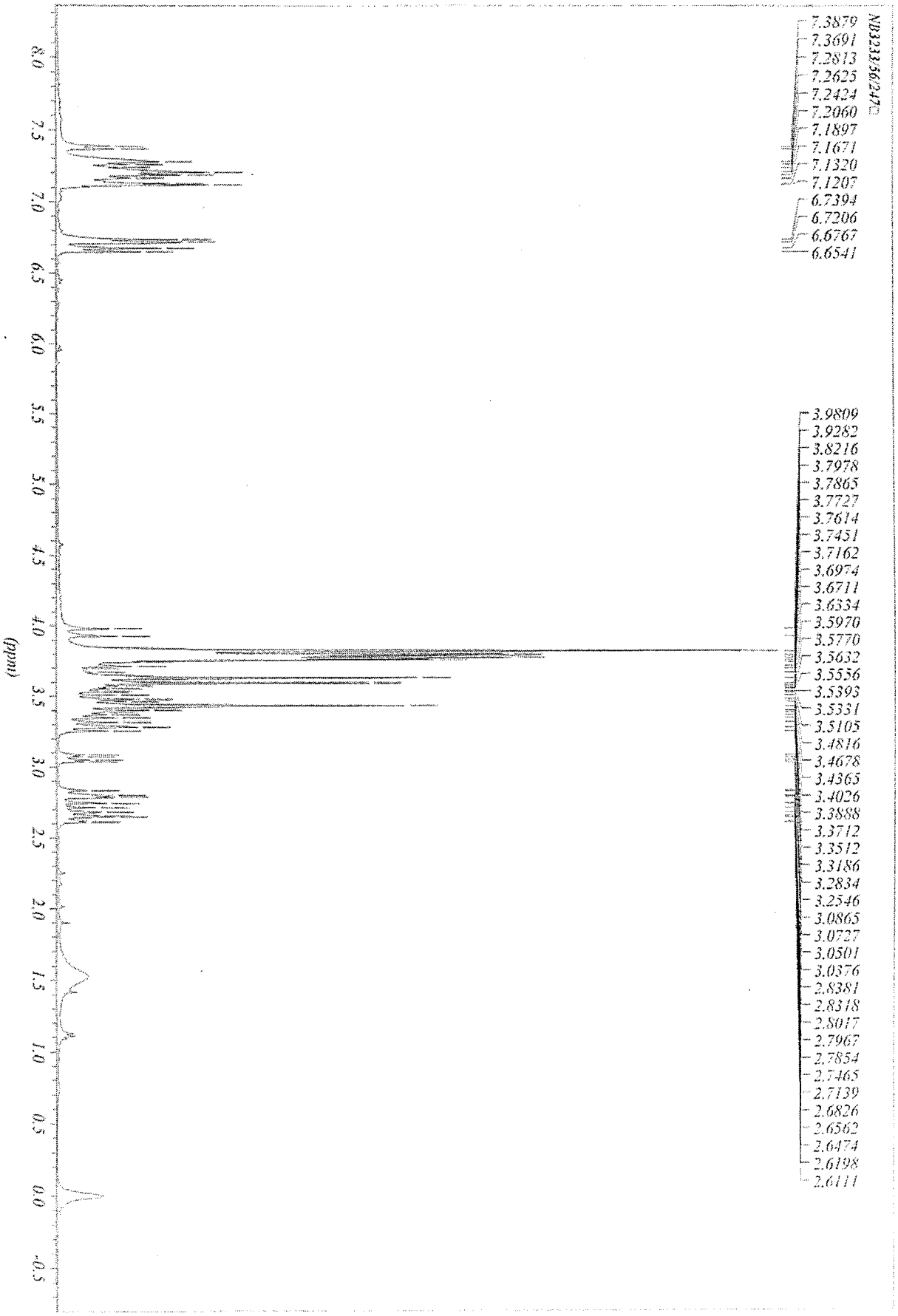
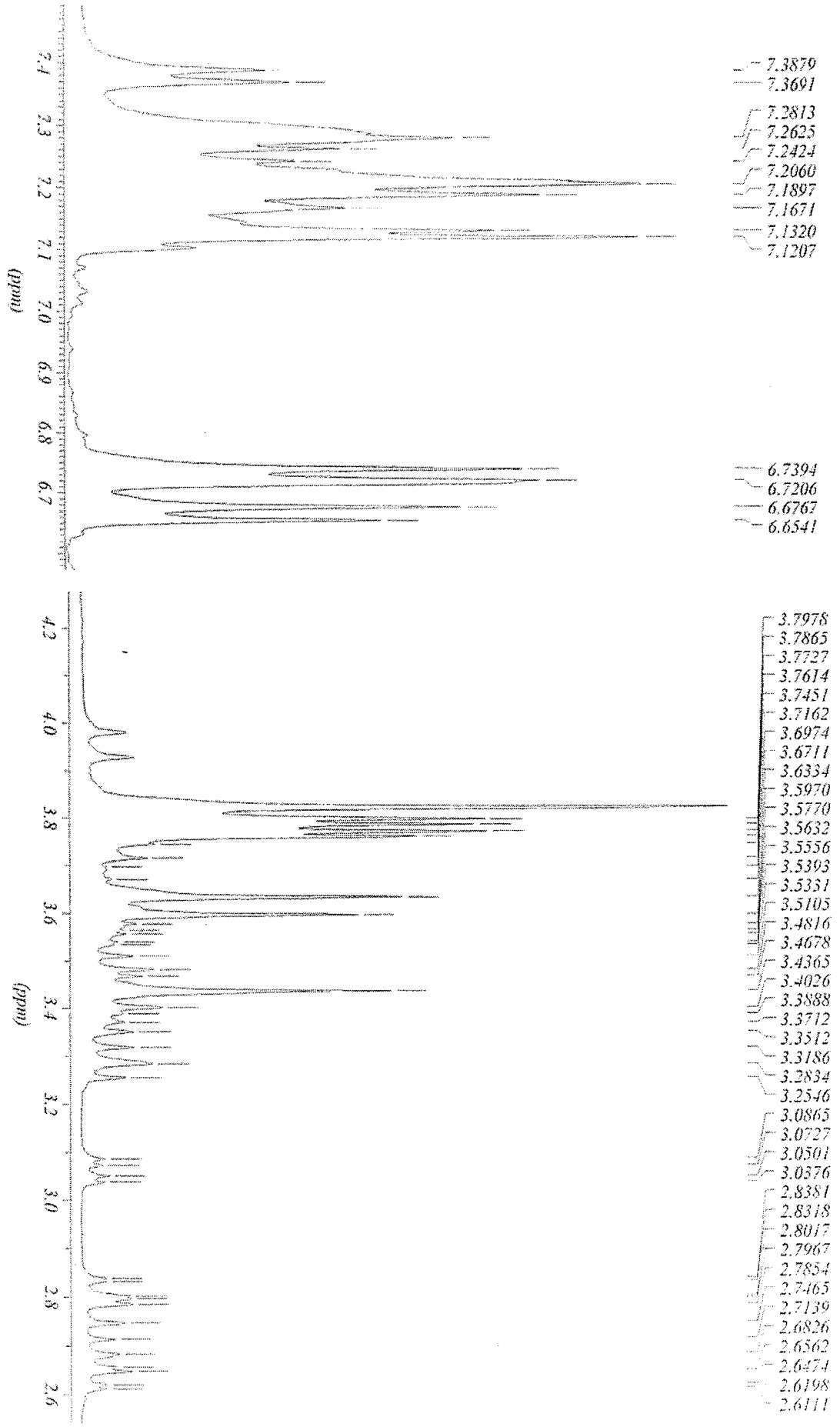
Appendix

Appendix data for 1,2-Dimethoxy-7-oxo-5,6,7,8-tetrahydro-dibenzo[*a,c*]cyclooctene-6-carboxylic acid methyl ester **3.98**

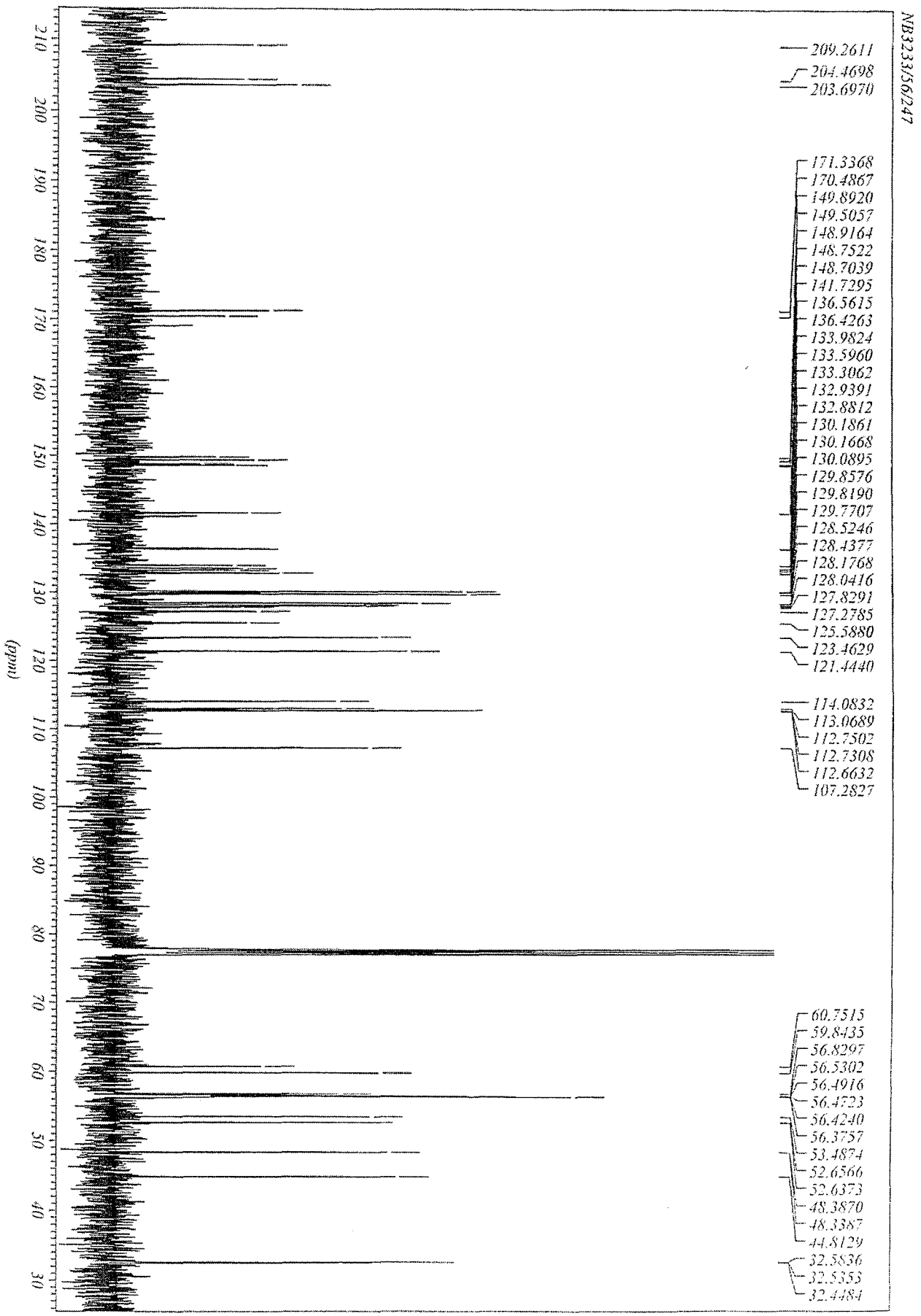
A1: ^{1} H NMR



A2: ^{1}H Expansions



A3: ^{13}C NMR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132.9391
132.8812
130.1861
130.1668
130.0895
129.8576
129.8190
129.7707
128.5246
128.4377
128.1768
128.0416
127.8291
127.2785
125.5880
123.4629
121.4440
114.0832
113.0689
112.7502
112.7308
112.6632
107.2827
60.7515
59.8435
56.8297
56.5302
56.4916
56.4723
56.4240
56.3757
53.4874
52.6566
52.6373
48.3870
48.3387
44.8129
32.5836
32.5353
32.4484
(ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30

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Data Collection Summary

Summary report for Directory: diska/02srf007

Report generated Jul 18, 2002; 16:29:31

Unit cell

18947 reflections with 2.91°<theta<27.48° (resolution between 7.00A and 0.77A) were used for unit cell refinement

Symmetry used in scalepack	p1
a (Angstrom)	8.6267 +/- 0.0004
b (Angstrom)	9.7387 +/- 0.0004
c (Angstrom)	11.8218 +/- 0.0006
alpha (°)	66.830 +/- 0.002
beta (°)	86.7147 +/- 0.0018
gamma (°)	68.002 +/- 0.003
Volume (A3)**	841.86 +/- 0.07
Mosaicity (°)	1.175 +/- 0.004

Data collection

Summary

Total number of images collected	245
Total exposure time	81.9 minutes
Data collection exposure time	79.9 minutes
Data collection wall-clock time	111.5 minutes

Experimental Conditions

Wavelength	0.71073 A
Generator setting	50kV 90mA
Crystal to detector distance	30.00 mm

Scans

Type	Name	# images	Total Rotation	Per frame Rotation	Exposure per frame	Used in scaling
data collection	s01f	181	362.0° phi	2.000°	20 seconds	Yes
data collection	s02f	23	46.0° omega	2.000°	20 seconds	Yes
data collection	s03f	33	66.0° omega	2.000°	20 seconds	Yes
Phi/Chi	i01f - i08f	8			15 seconds	

Scalepack Scaling

Deleted observations

Zero sigma or profile test	1
Overload or incomplete profile	503
Sigma cutoff	93
High resolution limit	87

Final Data Set

Scale factor	10.00
Number of 'full' reflections	1735
Number of 'partial' reflections	26618
Total number of integrated reflections	13400
Total number of unique reflections	3792
Data completeness	98.4%
Resolution range	7.00-0.77 A
Theta range	2.91°-27.48°
Average Intensity	40.0
Average Sigma(I)	2.3
Overall R-merge (linear)	0.077

Crystal Information

Collection Temperature	120 K
Crystal Size	x x
Crystal Colour	
Crystal Shape	

SORTAV Absorption correction

Max Transmission Factor	1.00637
Min Transmission Factor	0.86759

N.B. The scaling summary is redundant as outliers are treated during the absorption correction using SORTAV. The quoted data completeness is for the stated resolution ranges, and the Overall R-merge is that before the absorption correction. The SORTAV transmission factors are based on a crude approximation and the expected formula (not always correct!). For more information visit the service web site at: http://www.soton.ac.uk/~xservice/

O(1)	- C(8)	1.370(5)
O(1)	- C(24)	1.427(5)
O(2)	- C(3)	1.365(5)
O(2)	- C(17)	1.433(5)
C(3)	- C(8)	1.402(6)
C(3)	- C(9)	1.388(6)
O(4)	- C(21)	1.344(6)
O(4)	- C(25)	1.450(6)
C(5)	- C(6)	1.409(6)
C(5)	- C(8)	1.378(6)
C(6)	- C(7)	1.492(6)
C(6)	- C(11)	1.386(6)
C(7)	- C(13)	1.401(6)
C(7)	- C(20)	1.399(6)
C(9)	- C(11)	1.414(6)
O(10)	- C(21)	1.208(6)
C(11)	- C(22)	1.519(6)
O(12)	- C(15)	1.202(6)
C(13)	- C(14)	1.398(6)
C(13)	- C(19)	1.531(6)
C(14)	- C(16)	1.394(7)
C(15)	- C(19)	1.517(7)
C(15)	- C(23)	1.526(6)
C(16)	- C(18)	1.379(7)
C(18)	- C(20)	1.387(6)
C(21)	- C(23)	1.504(7)
C(22)	- C(23)	1.550(6)

C(8)	- O(1)	- C(24)	117.0(3)
C(3)	- O(2)	- C(17)	117.1(3)
O(2)	- C(3)	- C(8)	115.6(4)
O(2)	- C(3)	- C(9)	124.6(4)
C(8)	- C(3)	- C(9)	119.8(4)
C(21)	- O(4)	- C(25)	115.9(4)
C(6)	- C(5)	- C(8)	121.0(4)
C(5)	- C(6)	- C(7)	118.5(4)
C(5)	- C(6)	- C(11)	119.9(4)
C(7)	- C(6)	- C(11)	121.6(4)
C(6)	- C(7)	- C(13)	120.2(4)
C(6)	- C(7)	- C(20)	120.4(4)
C(13)	- C(7)	- C(20)	119.4(4)
O(1)	- C(8)	- C(3)	115.5(4)
O(1)	- C(8)	- C(5)	124.9(4)
C(3)	- C(8)	- C(5)	119.5(4)
C(3)	- C(9)	- C(11)	120.9(4)
C(6)	- C(11)	- C(9)	118.9(4)
C(6)	- C(11)	- C(22)	122.4(4)
C(9)	- C(11)	- C(22)	118.6(4)
C(7)	- C(13)	- C(14)	119.5(4)
C(7)	- C(13)	- C(19)	121.2(4)
C(14)	- C(13)	- C(19)	119.3(4)
C(13)	- C(14)	- C(16)	120.4(4)
O(12)	- C(15)	- C(19)	121.6(4)
O(12)	- C(15)	- C(23)	118.5(4)
C(19)	- C(15)	- C(23)	119.8(4)

C(14) - C(16) - C(18)	119.9(4)
C(16) - C(18) - C(20)	120.4(4)
C(13) - C(19) - C(15)	108.3(4)
C(7) - C(20) - C(18)	120.4(4)
O(4) - C(21) - O(10)	124.1(5)
O(4) - C(21) - C(23)	112.1(4)
O(10) - C(21) - C(23)	123.8(4)
C(11) - C(22) - C(23)	118.8(4)
C(15) - C(23) - C(21)	108.1(4)
C(15) - C(23) - C(22)	117.0(4)
C(21) - C(23) - C(22)	111.0(4)

Atom	u(11) U(iso)	u(22) Size	u(33) D/100	u(23) A/100	u(13)	u(12)
O(1)	0.0228(17)	0.0291(17)	0.0218(17)	-0.0059(14)	0.0031(13)	- 0.0121(14)
O(2)	0.0169(15)	0.0370(19)	0.0233(17)	-0.0115(15)	0.0058(13)	- 0.0124(14)
C(3)	0.0095(19)	0.023(2)	0.028(2)	-0.0119(19)	0.0062(17)	- 0.0086(17)
O(4)	0.0227(17)	0.041(2)	0.037(2)	-0.0224(17)	0.0059(15)	- 0.0101(15)
C(5)	0.0096(19)	0.021(2)	0.028(2)	-0.0075(19)	0.0003(17)	- 0.0067(17)
C(6)	0.019(2)	0.018(2)	0.024(2)	-0.0104(18)	0.0025(17)	- 0.0086(18)
C(7)	0.018(2)	0.022(2)	0.024(2)	-0.0084(18)	0.0031(17)	- 0.0086(18)
C(8)	0.021(2)	0.025(2)	0.019(2)	-0.0057(19)	0.0044(18)	- 0.0104(19)
C(9)	0.021(2)	0.018(2)	0.024(2)	-0.0090(18)	0.0001(18)	- 0.0072(18)
O(10)	0.034(2)	0.041(2)	0.049(2)	-0.0285(19)	0.0047(17)	- 0.0125(17)
C(11)	0.021(2)	0.019(2)	0.024(2)	-0.0092(18)	0.0031(18)	- 0.0091(18)
O(12)	0.033(2)	0.033(2)	0.036(2)	-0.0033(17)	0.0039(16)	- 0.0154(17)
C(13)	0.017(2)	0.019(2)	0.022(2)	-0.0089(18)	0.0007(17)	- 0.0077(18)
C(14)	0.022(2)	0.029(2)	0.023(2)	-0.0102(19)	0.0036(18)	- 0.015(2)
C(15)	0.023(2)	0.020(2)	0.030(3)	-0.008(2)	0.0012(19)	- 0.0064(19)
C(16)	0.023(2)	0.039(3)	0.025(2)	-0.018(2)	0.0073(19)	- 0.016(2)
C(17)	0.012(2)	0.040(3)	0.031(3)	-0.014(2)	0.0047(18)	- 0.012(2)
C(18)	0.017(2)	0.029(2)	0.037(3)	-0.019(2)	0.0043(19)	- 0.0090(19)
C(19)	0.024(2)	0.020(2)	0.031(3)	-0.0109(19)	0.0062(19)	- 0.0116(19)
C(20)	0.021(2)	0.023(2)	0.029(3)	-0.0114(19)	0.0027(19)	- 0.0097(19)

C(21)	0.028(3)	0.032(3)	0.034(3)	-0.016(2)	0.007(2)	-
0.017(2)						
C(22)	0.025(2)	0.028(2)	0.022(2)	-0.0083(19)	0.0026(18)	-
0.014(2)						
C(23)	0.022(2)	0.027(2)	0.026(2)	-0.0079(19)	0.0051(19)	-
0.012(2)						
C(24)	0.024(2)	0.026(2)	0.022(2)	-0.0029(19)	0.0000(19)	-
0.010(2)						
C(25)	0.023(3)	0.050(3)	0.053(4)	-0.031(3)	0.010(2)	-
0.011(2)						

Atom	x/a	y/b	z/c	U(iso)	Occ
O(1)	0.0849(4)	0.8934(4)	0.8294(3)	0.0254	
O(2)	0.3834(4)	0.7316(4)	0.9462(3)	0.0255	
C(3)	0.2548(5)	0.7197(5)	1.0173(4)	0.0188	
O(4)	0.4865(4)	0.2434(4)	1.4047(3)	0.0319	
C(5)	-0.0446(5)	0.8011(5)	1.0185(4)	0.0201	
C(6)	-0.0246(5)	0.7089(5)	1.1471(4)	0.0192	
C(7)	-0.1779(5)	0.7056(5)	1.2115(4)	0.0215	
C(8)	0.0926(5)	0.8073(5)	0.9541(4)	0.0223	
C(9)	0.2754(5)	0.6301(5)	1.1442(4)	0.0206	
O(10)	0.3264(5)	0.2014(5)	1.2873(4)	0.0384	
C(11)	0.1349(5)	0.6240(5)	1.2107(4)	0.0208	
O(12)	0.0145(5)	0.2097(4)	1.4813(3)	0.0369	
C(13)	-0.1994(5)	0.5592(5)	1.2728(4)	0.0189	
C(14)	-0.3422(6)	0.5577(6)	1.3346(4)	0.0232	
C(15)	0.0429(6)	0.3104(5)	1.3938(4)	0.0257	
C(16)	-0.4654(6)	0.7015(6)	1.3318(4)	0.0262	
C(17)	0.5467(5)	0.6725(6)	1.0099(5)	0.0272	
C(18)	-0.4453(5)	0.8458(6)	1.2692(5)	0.0260	
C(19)	-0.0700(6)	0.4005(5)	1.2725(4)	0.0237	
C(20)	-0.3023(6)	0.8487(5)	1.2099(4)	0.0235	
C(21)	0.3394(6)	0.2566(6)	1.3600(5)	0.0291	
C(22)	0.1640(6)	0.5344(6)	1.3506(4)	0.0242	
C(23)	0.1920(6)	0.3527(6)	1.4082(4)	0.0253	
C(24)	-0.0784(6)	0.9934(6)	0.7637(4)	0.0260	
C(25)	0.6364(6)	0.1441(7)	1.3692(6)	0.0397	

Atom	x/a	y/b	z/c	U(iso)	Occ
H(51)	-0.1614	0.8630	0.9729	0.0217	
H(91)	0.3922	0.5704	1.1892	0.0248	
H(141)	-0.3561	0.4510	1.3813	0.0294	
H(161)	-0.5677	0.6979	1.3800	0.0356	
H(171)	0.6310	0.6852	0.9494	0.0334	
H(172)	0.5438	0.7330	1.0621	0.0334	
H(173)	0.5817	0.5538	1.0658	0.0334	
H(181)	-0.5372	0.9516	1.2651	0.0313	
H(191)	-0.1301	0.3349	1.2618	0.0295	
H(192)	-0.0026	0.4263	1.1998	0.0295	
H(201)	-0.2887	0.9544	1.1641	0.0272	
H(221)	0.2645	0.5435	1.3789	0.0280	
H(222)	0.0625	0.5903	1.3849	0.0280	
H(231)	0.2147	0.3192	1.5003	0.0306	

H(241)	-0.0687	1.0523	0.6736	0.0287
H(242)	-0.1385	1.0768	0.7985	0.0287
H(243)	-0.1456	0.9272	0.7712	0.0287
H(251)	0.7394	0.1408	1.4056	0.0510
H(252)	0.6402	0.0302	1.3984	0.0510
H(253)	0.6340	0.1886	1.2760	0.0510

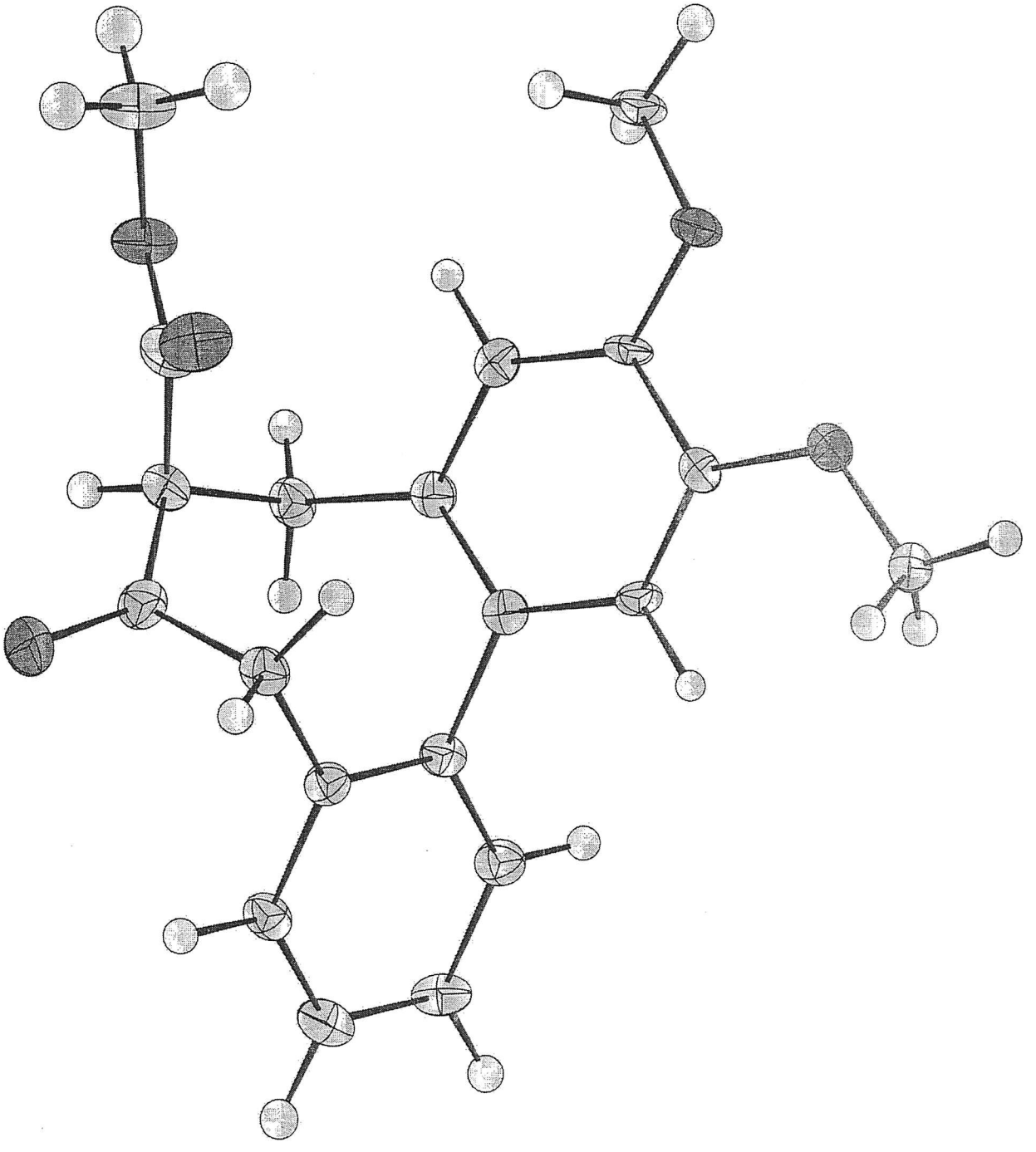
Scale	Du(iso)	Ou(iso)	Polarity	Flack	Extinction
0.552(2)	0.050	0.050	1.000	0.000	0.000

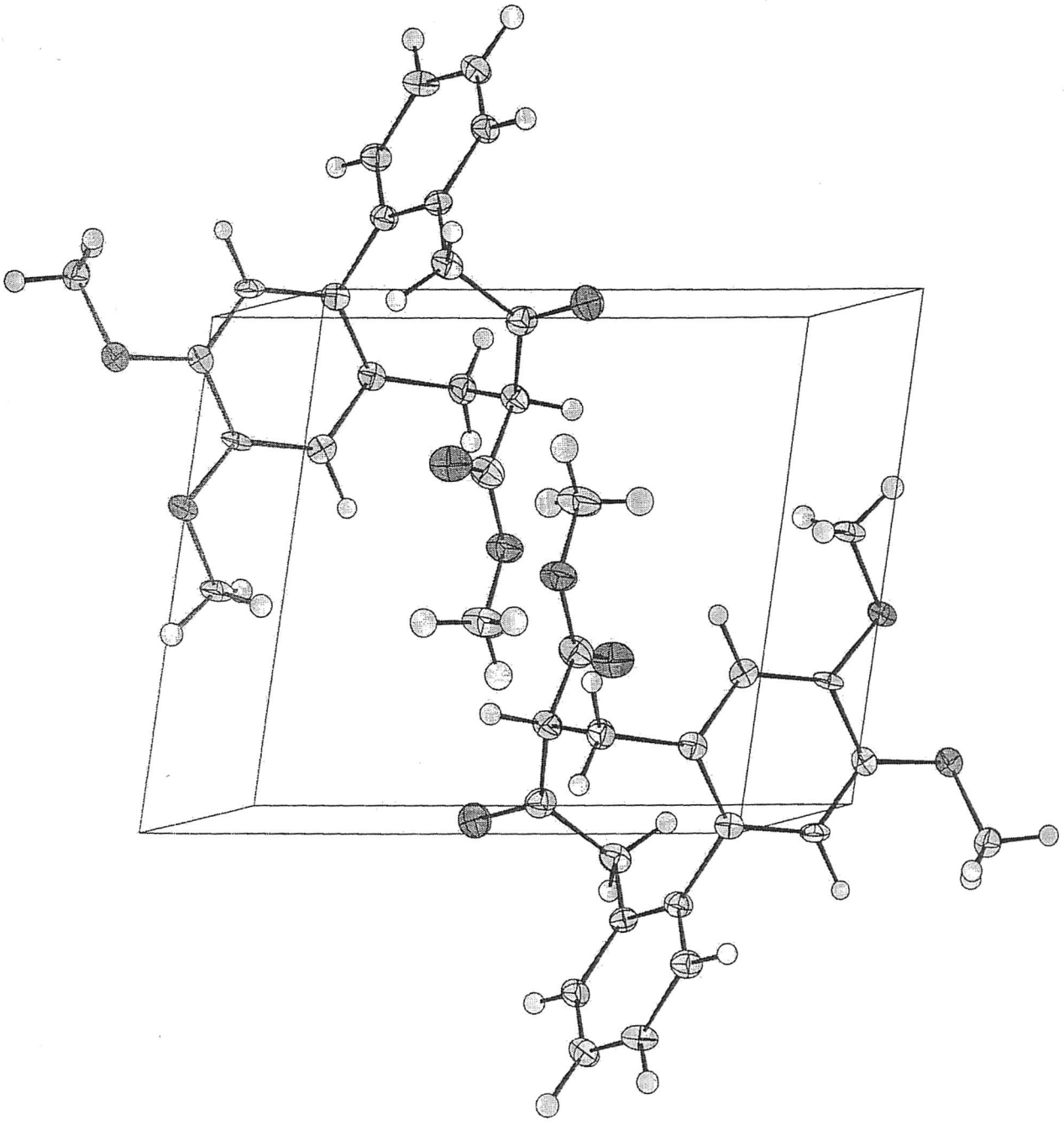
7181823 Compound X 02-19-07

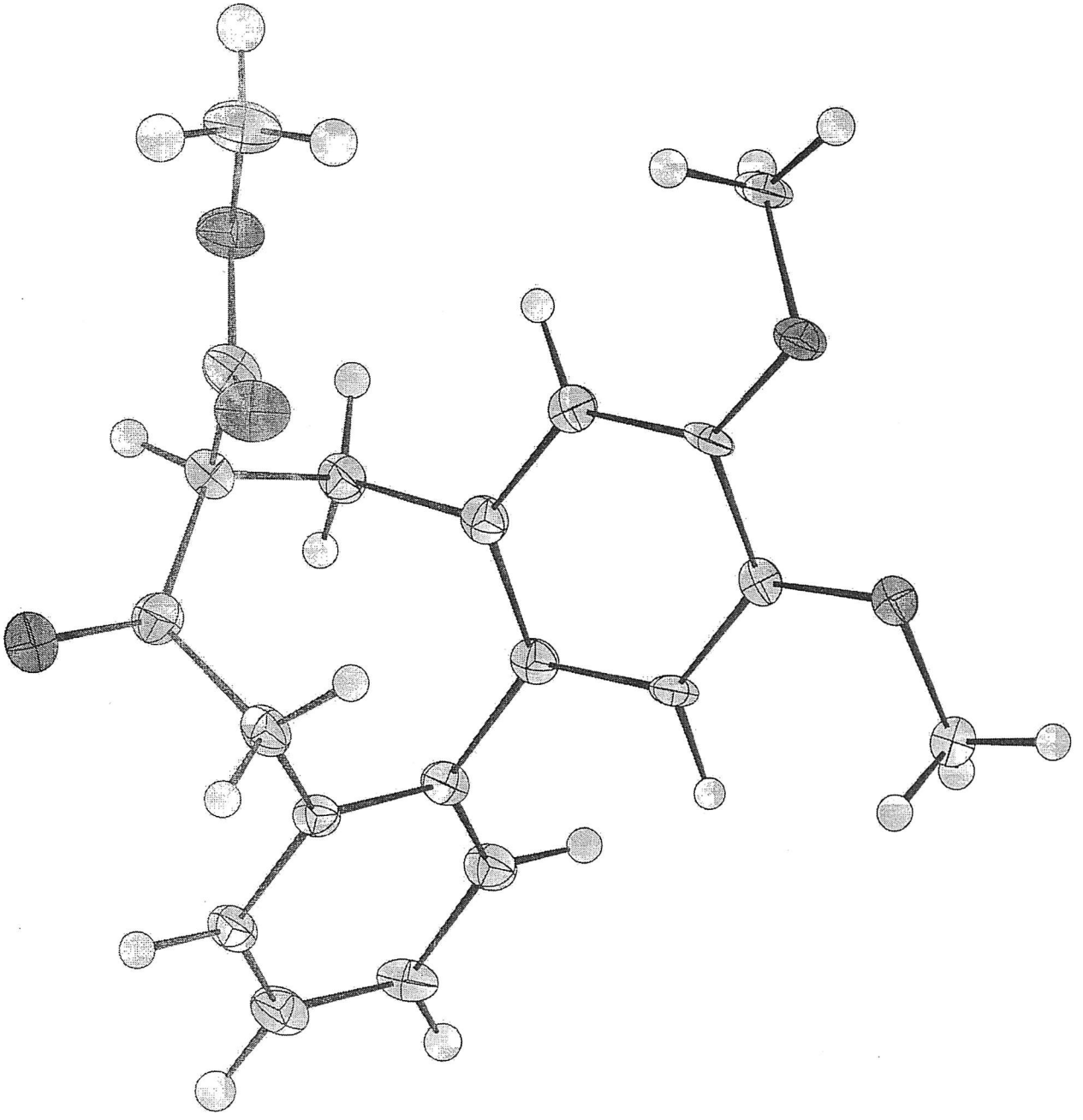
Formula	C20 H20 O5		
Crystal Class	Triclinic	Space Group	P -1
a	8.6263(4)	alpha	66.8318(19)
b	9.7380(4)	beta	86.7176(17)
c	11.8207(6)	gamma	68.004(3)
Volume	841.70(7)	Z	2
Radiation type	Mo K\a	Wavelength	0.710730
Dx	1.34	Mr	340.38
Mu	0.096	Temperature (K)	120
Size	0.01x 0.20x 0.20		
Colour	colourless	Shape	plate
Cell from	3406 Reflections	Theta Range	3 to 27
Standard Interval	0	Standard Count	0
Diffractometer type	KAPPACCD	Scan type	OMEGA
Absorption type	multi-scan	Transmissionrange	0.98 1.00
Reflections measured	7055	Independent reflections	3778
Rint	0.0002	Theta max	27.43
Hmin, Hmax	-11 11		
Kmin, Kmax	-12 12		
Lmin, Lmax	-15 15		

Refinement on Fsqd

R-factor	0.074	Weighted R-factor	0.172
		Max shift/su	0.0001
Delta Rho min	-0.39	Delta Rho max	0.46
Reflections used	2148	sigma(I) limit	3.00
Number of parameters	226	Goodness of fit	1.027







Appendix B: X-ray data for *Z*-3-[2-Bromo-1,3-benzodioxol-5-yl)-1-ethenyl]pyridine **2.28**

University of Southampton · Department of Chemistry

EPSRC National Crystallography Service

Table 1. Crystal data and structure refinement.

Identification code	**00sot052**	
Empirical formula	$C_{14}H_{10}BrNO_2$	
Formula weight	304.14	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	$a = 6.7354(13)$ Å	$\alpha = 90°$
	$b = 21.279(4)$ Å	$\beta = 91.40(3)°$
	$c = 8.2990(17)$ Å	$\gamma = 90°$
Volume	1189.1(4) Å^3	
Z	4	
Density (calculated)	1.699 Mg / m^3	
Absorption coefficient	3.449 mm^{-1}	
F(000)	608	
Crystal	Colourless; block	
Crystal size	0.20 × 0.08 × 0.08 mm^3	
θ range for data collection	3.03 – 27.48°	
Index ranges	$-8 \le h \le 8$, $-26 \le k \le 27$, $-9 \le l \le 10$	
Reflections collected	10187	
Independent reflections	2702 [R_{int} = 0.0444]	
Completeness to $\theta = 27.48°$	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7820 and 0.5455	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2702 / 0 / 164	
Goodness-of-fit on F^2	1.021	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0331$, $wR2 = 0.0752$	
R indices (all data)	$R1 = 0.0600$, $wR2 = 0.0868$	
Extinction coefficient	0.0084(11)	
Largest diff. peak and hole	0.540 and −0.505 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement:** *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction:** *SORTAV* (R. H. Blessing, Acta Cryst. A51 (1995) 33–37; R. H. Blessing, J. Appl. Cryst. 30 (1997) 421–426). **Program used to solve structure:** *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A46 467–473). **Program used to refine structure:** *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: *http://www.soton.ac.uk/~xservice/strat.htm*

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Br1	472(1)	4007(1)	4187(1)	51(1)	1
O1	6613(3)	5360(1)	2414(3)	60(1)	1
O2	7894(3)	4608(1)	714(2)	56(1)	1
N1	7347(4)	1380(1)	1968(3)	61(1)	1
C1	8209(4)	5220(1)	1378(4)	55(1)	1
C2	5424(4)	4838(1)	2396(3)	43(1)	1
C3	3714(4)	4744(1)	3215(3)	45(1)	1
C4	2797(4)	4162(1)	2990(3)	41(1)	1
C5	3527(4)	3697(1)	1979(3)	41(1)	1
C6	5277(4)	3827(1)	1141(3)	44(1)	1
C7	6189(4)	4391(1)	1384(3)	42(1)	1
C8	2457(4)	3102(1)	1700(3)	49(1)	1
C9	3171(4)	2519(1)	1691(3)	49(1)	1
C10	5139(4)	2274(1)	2130(3)	41(1)	1
C11	6559(4)	2585(1)	3064(3)	45(1)	1
C12	8338(4)	2293(2)	3425(4)	53(1)	1
C13	8674(5)	1700(2)	2854(4)	59(1)	1
C14	5631(5)	1664(1)	1653(4)	52(1)	1

Table 3. Bond lengths [Å] and angles [°].

Br1–C4	1.904(3)
O1–C2	1.368(3)
O1–C1	1.424(4)
O2–C7	1.369(3)
O2–C1	1.427(4)
N1–C14	1.324(4)
N1–C13	1.330(4)
C2–C3	1.366(4)
C2–C7	1.378(4)
C3–C4	1.394(4)
C4–C5	1.395(4)
C5–C6	1.410(4)
C5–C8	1.473(4)
C6–C7	1.362(4)
C8–C9	1.331(4)
C9–C10	1.462(4)
C10–C11	1.385(4)
C10–C14	1.399(4)
C11–C12	1.375(4)
C12–C13	1.369(4)
C2–O1–C1	105.9(2)
C7–O2–C1	105.6(2)
C14–N1–C13	116.5(3)
O1–C1–O2	108.5(2)
C3–C2–O1	127.9(3)
C3–C2–C7	122.3(3)
O1–C2–C7	109.8(2)
C2–C3–C4	116.1(3)
C3–C4–C5	123.3(3)
C3–C4–Br1	116.9(2)
C5–C4–Br1	119.8(2)
C4–C5–C6	118.0(2)
C4–C5–C8	121.7(2)
C6–C5–C8	120.2(3)
C7–C6–C5	118.6(3)
C6–C7–O2	128.1(3)
C6–C7–C2	121.7(3)
O2–C7–C2	110.2(2)
C9–C8–C5	128.8(2)
C8–C9–C10	131.1(3)
C11–C10–C14	115.9(3)
C11–C10–C9	125.3(3)
C14–C10–C9	118.7(2)
C12–C11–C10	119.5(3)
C13–C12–C11	119.4(3)
N1–C13–C12	123.3(3)
N1–C14–C10	125.4(3)

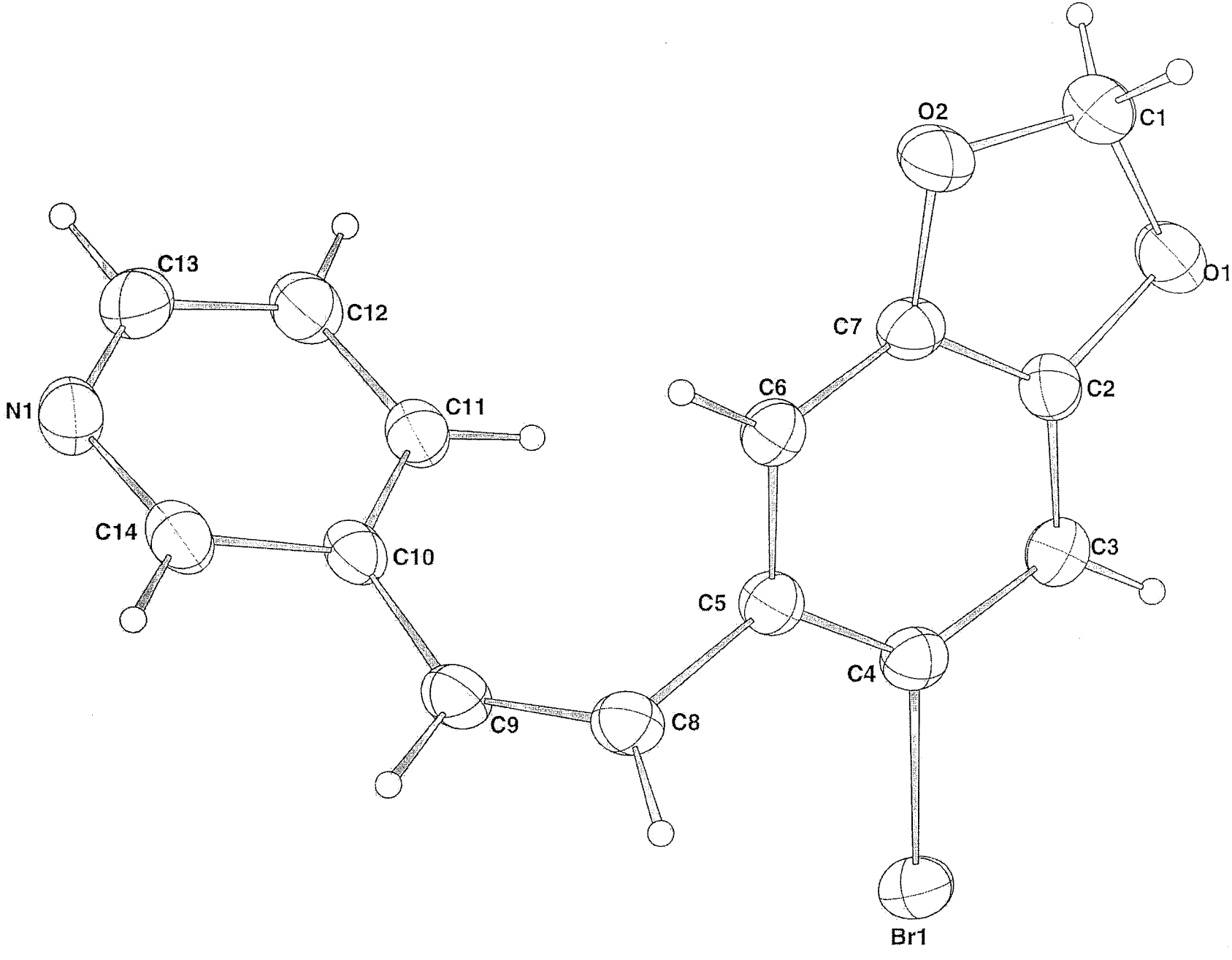
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br1	40(1)	54(1)	58(1)	3(1)	9(1)	2(1)
O1	58(1)	44(1)	80(2)	−9(1)	17(1)	−11(1)
O2	53(1)	53(1)	62(1)	0(1)	18(1)	−9(1)
N1	68(2)	41(2)	76(2)	−1(1)	19(1)	2(1)
C1	51(2)	49(2)	65(2)	8(2)	6(1)	−4(1)
C2	43(1)	37(2)	49(2)	3(1)	−2(1)	0(1)
C3	45(2)	42(2)	47(2)	−4(1)	4(1)	4(1)
C4	37(1)	45(2)	41(1)	4(1)	0(1)	2(1)
C5	39(1)	41(2)	42(1)	3(1)	−1(1)	0(1)
C6	46(2)	42(2)	45(2)	−4(1)	5(1)	3(1)
C7	39(1)	45(2)	42(1)	6(1)	5(1)	2(1)
C8	40(1)	51(2)	55(2)	−5(1)	−1(1)	−6(1)
C9	44(2)	44(2)	58(2)	−10(1)	3(1)	−11(1)
C10	48(2)	35(1)	41(1)	0(1)	11(1)	−7(1)
C11	52(2)	37(2)	46(2)	−1(1)	7(1)	−3(1)
C12	52(2)	49(2)	58(2)	5(1)	1(1)	−6(1)
C13	51(2)	53(2)	73(2)	14(2)	15(2)	6(2)
C14	62(2)	39(2)	55(2)	−3(1)	12(1)	−10(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	x	y	z	U_{eq}	*S.o.f.*
H1A	9460	5232	1980	66	1
H1B	8259	5529	520	66	1
H3	3193	5050	3884	54	1
H6	5797	3533	437	53	1
H8	1096	3139	1502	59	1
H9	2263	2216	1347	58	1
H11	6312	2987	3445	54	1
H12	9304	2497	4050	64	1
H13	9889	1511	3099	71	1
H14	4675	1439	1067	62	1


O2
C1
O1
C13
C12
C7
C6
C2
N1
C11
C14
C10
C3
C5
C4
C9
C8
Br1

Appendix C:3,4-Dimethoxy-6-methyl-2'-(2-hydroxy malonic acid monomethyl ester)-biphenyl **3.125**

C1: LRMS

chem soton

Mass Spectrometry
Department of Chemistry
University of Southampton
www.soton.ac.uk/~msweb

Sample Name:		**Sample ID:**	NB3233/57 /257	Operator:	
Acquisition Date:	29/07/02	Run Time (min):	12.45	Scans:	1495
Acquisition Time:	12:06:27	Dil Factor:	0.00	Revision:	1.2
Low Mass (m/z):	34.60	High Mass (m/z):	560.40	Vial:	44
Samp Vol:	0.00	Samp Wt:	0.00	Inj Vol (uL):	1.00
Comments:	HARROWVEN				
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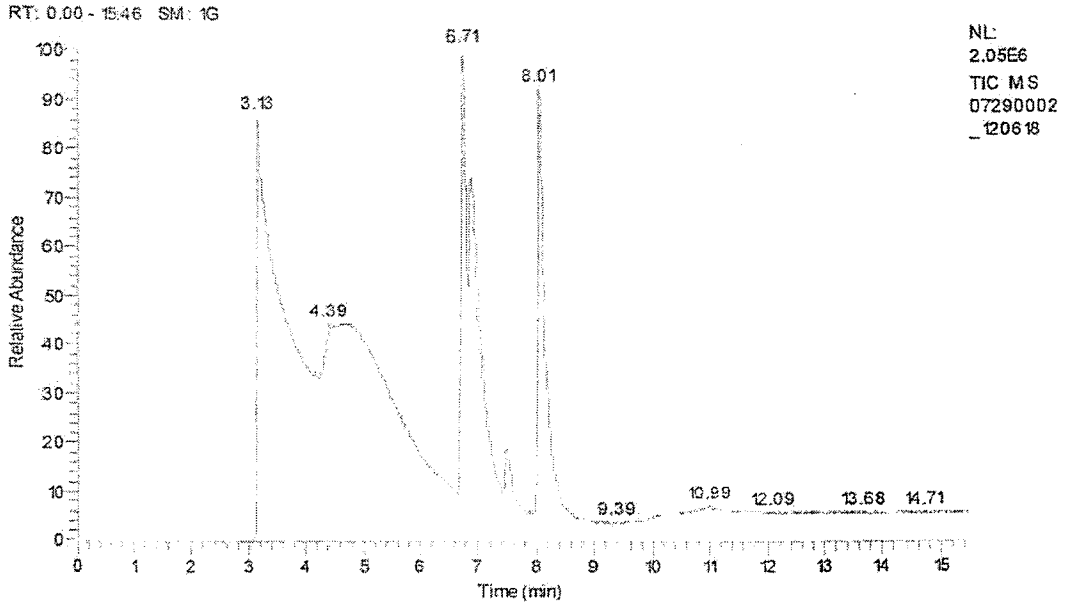
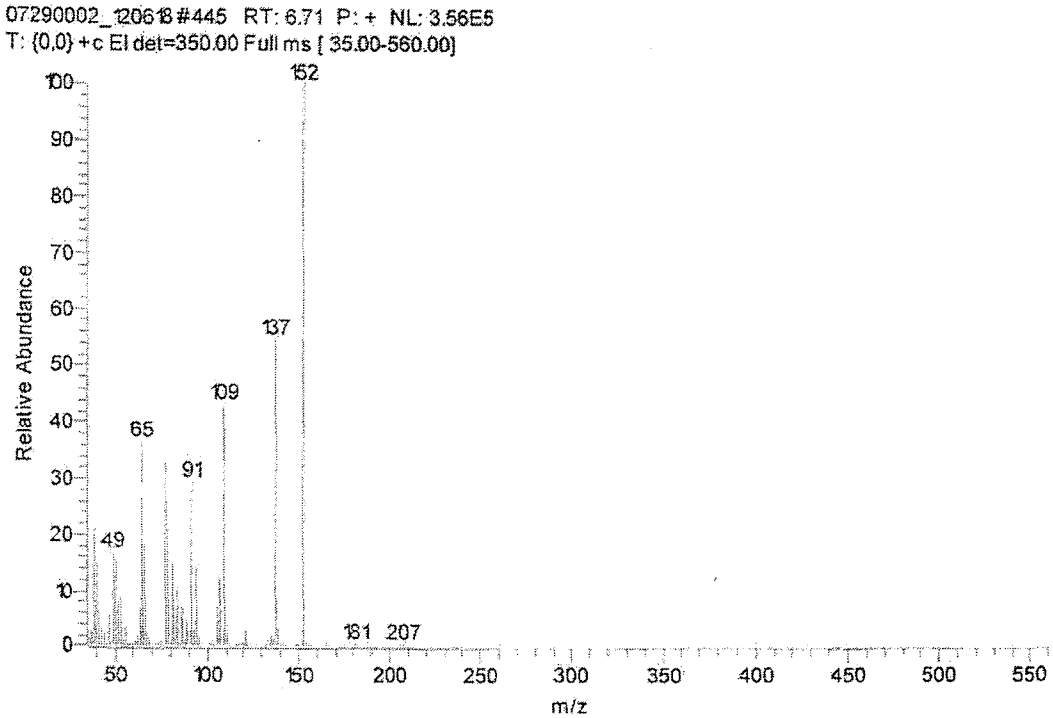
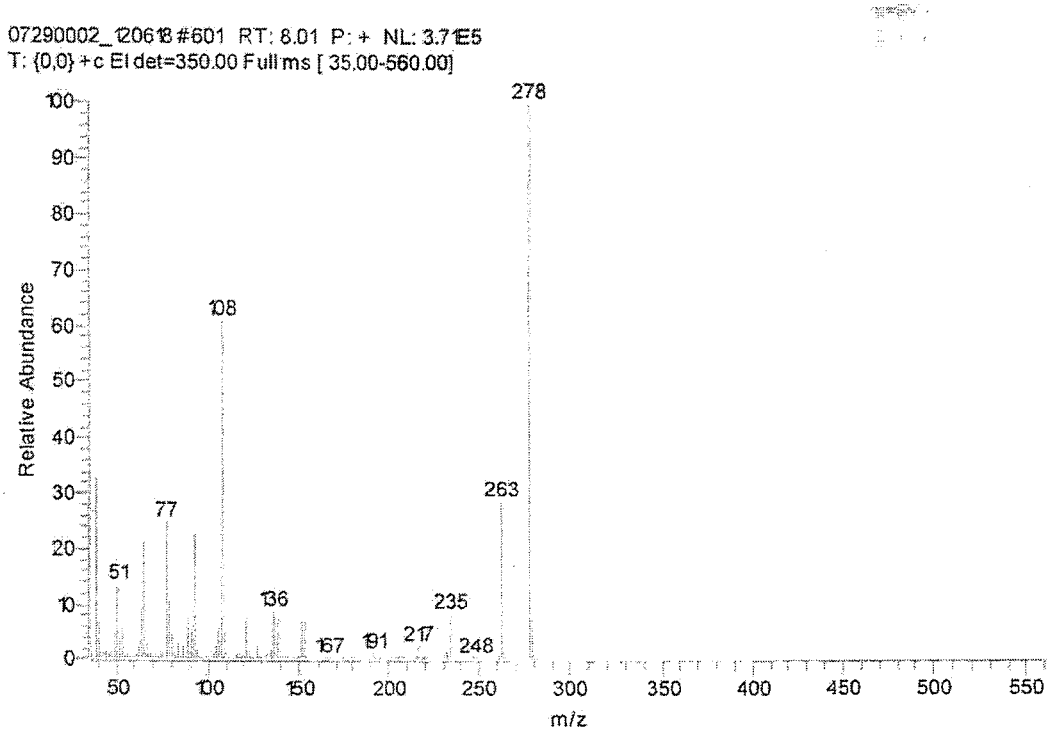
Proc Method:	C:\Xcalibur\methods\EIMS				
Data Path:	D:\D-data\				



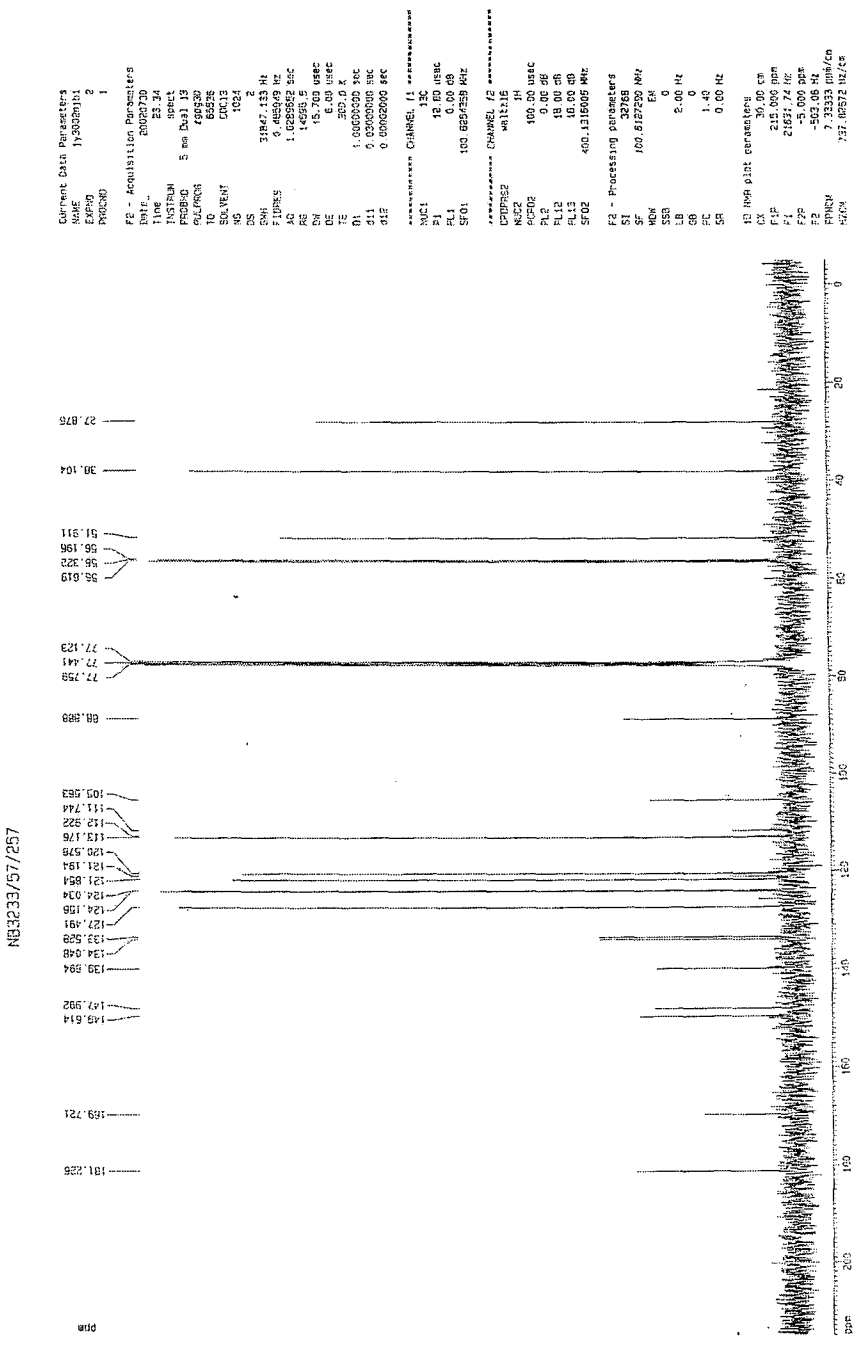


m/z	Intensity	Relative
39.14	73744.0	20.70
40.15	52880.0	14.84
49.04	58496.0	16.42
51.08	55072.0	15.46
52.13	27456.0	7.71
53.12	30476.0	8.56
65.04	128880.0	36.18
66.16	64176.0	18.02
76.99	115520.0	32.43
78.15	40272.0	11.31
79.10	73376.0	20.60
81.06	51824.0	14.55
83.95	37200.0	10.44
91.01	103312.0	29.00
94.01	50192.0	14.09
105.06	24732.0	6.94
106.95	43632.0	12.25
109.03	154048.0	43.24
137.02	193344.0	54.28
152.06	356224.0	100.00



m/z	Intensity	Relative
39.07	120848.0	32.54
40.15	24576.0	6.62
51.10	49744.0	13.40
63.07	33392.0	8.99
64.06	27888.0	7.51
65.08	77312.0	20.82
76.97	91824.0	24.73
78.18	39056.0	10.52
79.17	27292.0	7.35
89.06	26932.0	7.25
92.85	81680.0	22.00
107.96	224704.0	60.51
120.98	26952.0	7.26
136.04	32020.0	8.62
138.95	26132.0	7.04
151.12	27776.0	7.48
152.17	25576.0	6.89
234.95	30044.0	8.09
262.90	105968.0	28.54
277.96	371328.0	100.00

C2: ^{13}C NMR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51.911
56.196
56.322
56.619
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77.441
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111.744
112.922
113.176
120.578
121.194
121.854
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PROCNO 1
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TE 300.0 K
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SR 0.00 Hz
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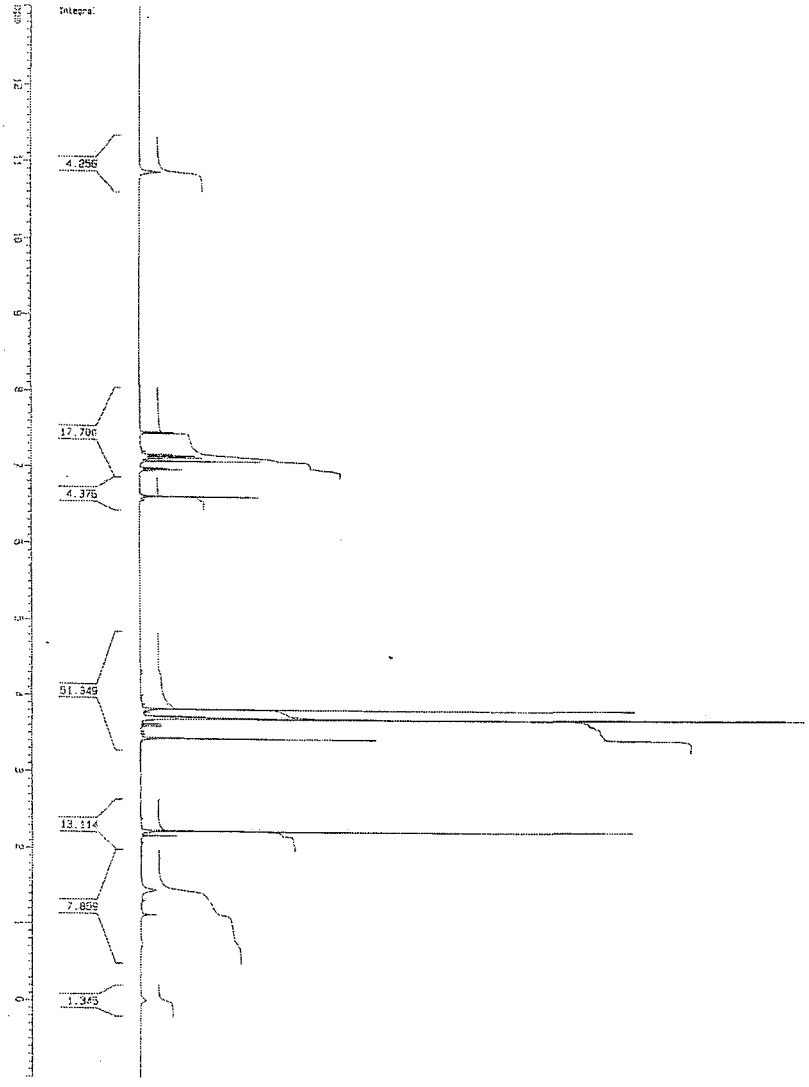
F2P -5.000 ppm
F2 -503.06 Hz
PPMCM 7.33333 ppm/cm
HZCM 737.86572 Hz/cm

C3: ^{1}H NMR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4.375
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1.345
NB3233/57/257
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D1
F2 - Processing parameters
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SF
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SSB
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1D NMR plot parameters
CX
F1P
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F2P
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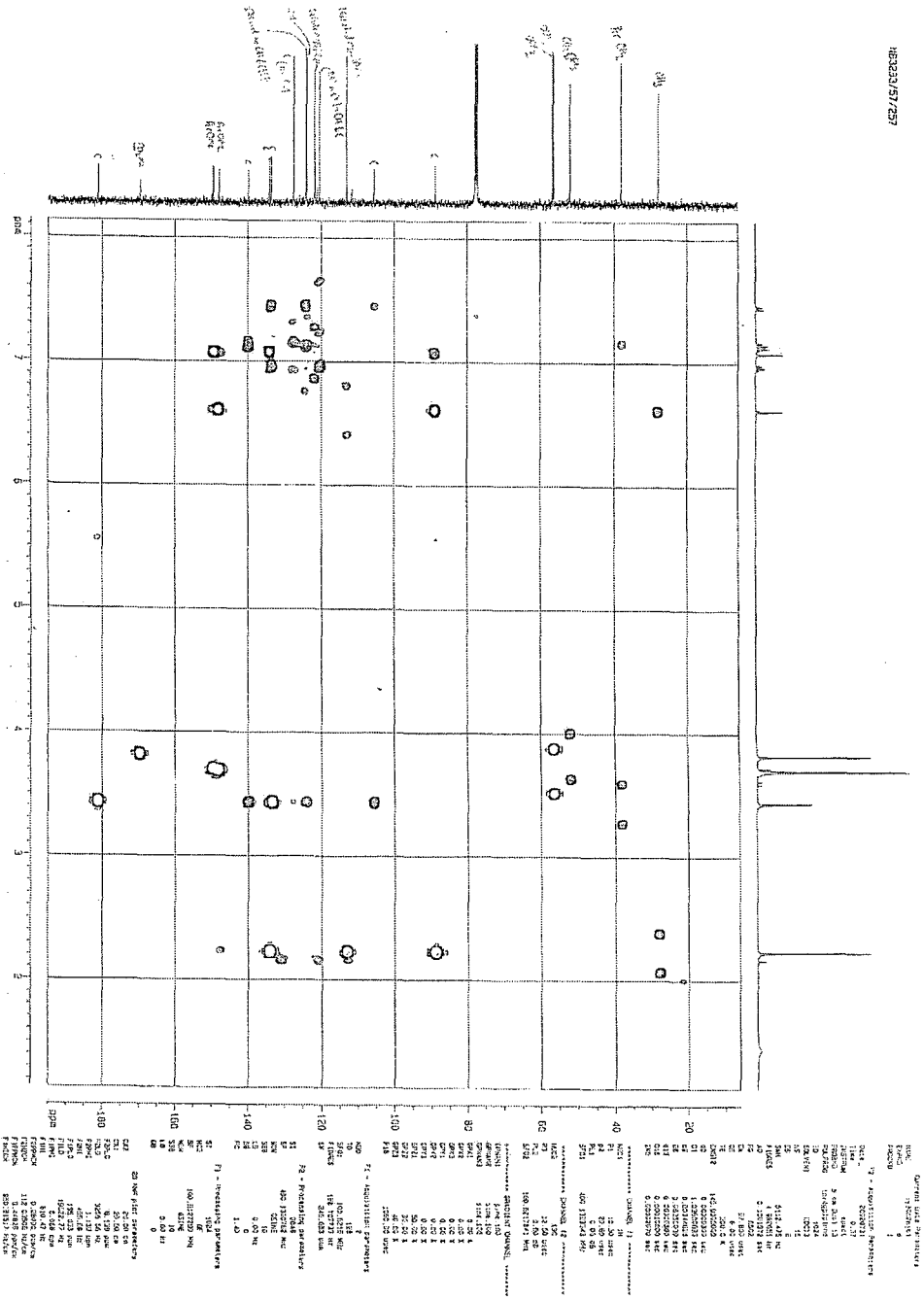
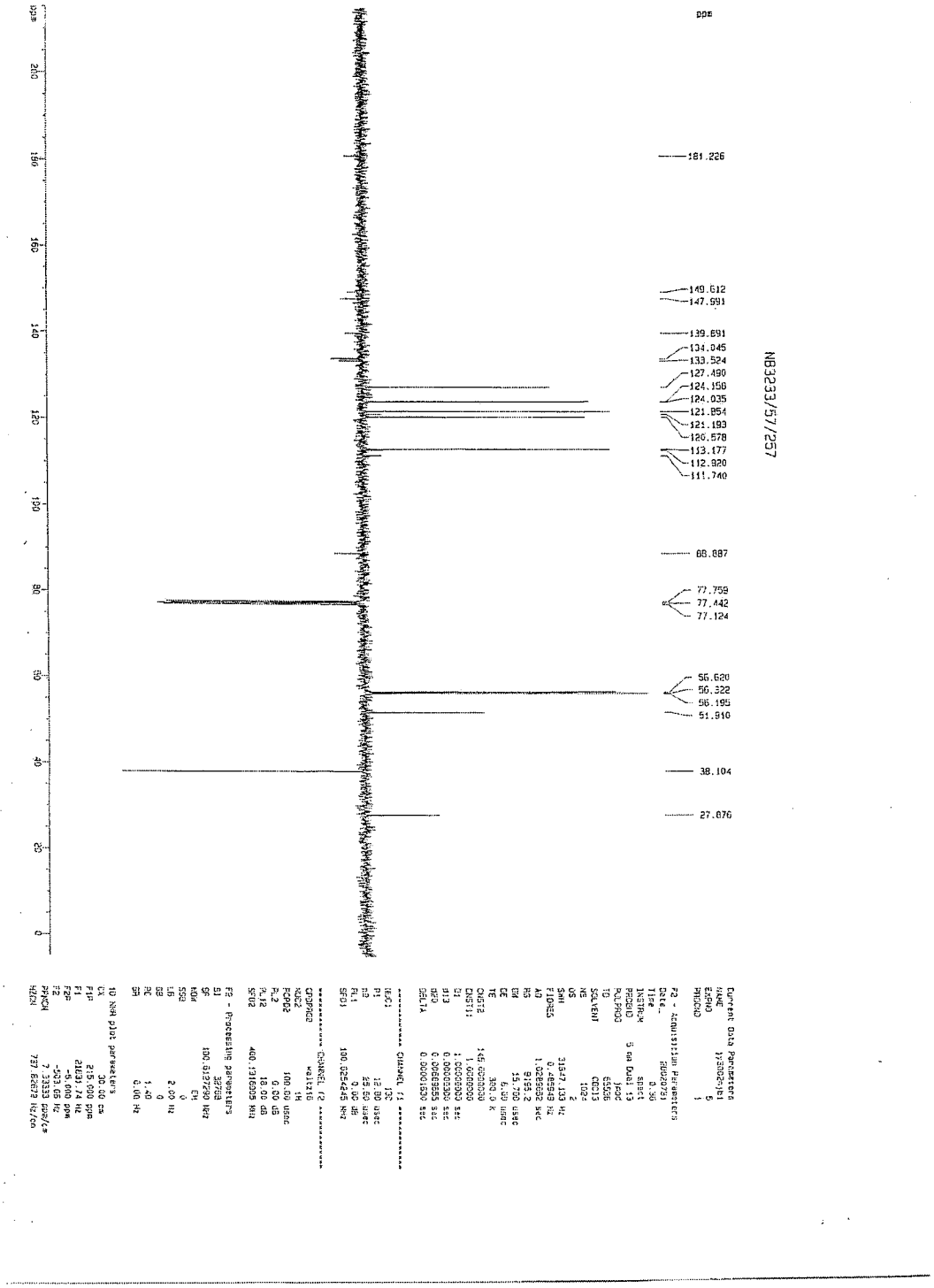
C4: HMQC C-H Correlation



C5: DEPT 145 NMR



C6: COSY H-H Correlation