UNIVERSITY OF SOUTHAMPTON

The Total Synthesis of Cavicularin & Riccardin C

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A Thesis Submitted for the Degree of Doctor of Philosophy

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ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

SCHOOL OF CHEMISTRY

Doctor of Philosophy

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by Timothy Woodcock

This thesis is concerned with the total synthesis of three natural products, the biarylheptanoid acerogenin E and the bis(bibenzyl) macrocycles cavicularin and riccardin C. The most interesting of these from a structural perspective is cavicularin, as its macrocyclic core imparts such strain on the system that it causes one of the arenes within it to adopt a boat conformation. It was first identified as a constituent of the liverwort *Cavicularia densa* within the last decade, and herein we describe the first total synthesis of this demanding natural product. Key features of our synthesis are a McMurry macrocyclisation to form an 18 membered ring, and a radical induced transannular ring contraction to generate the strained 14-membered macrocyclic core.

Our convergent approach also allowed us to complete a short synthesis of the related bis(bibenzyl) macrocycle riccardin C. First isolated from *Reboulia hemispherica*, it has since been found in a number of natural sources and has been the subject of two total syntheses. Work directed towards acerogenin E, a natural product from the *Betula* species, is also described.

An overview of these and related bis(bibenzyls) and biarylheptanoids macrocyclic natural products, including their isolation, biological activity and previous synthetic work, is presented in Chapter I. Experimental procedures and characterisation data are provided in Chapter III.

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 2001 and October 2004. No part of this thesis has previously been submitted for a degree.

Acknowledgements

Contemporaneously a big thanks to a super boss David (dereg gubnee breve nevi) Harrowven and industrial supervisor Peter Howes for their support, guidance, and many pub lunches!

Thanks to those who made my time in Southampton enjoyable; Stanley, for the weekends of football – I enjoyed playing as Thierry with Owen alongside and Keane centre mid – you're a great bunch!! Richard Brown and the team for great games of 5 and 6-aside! Hian and Pete for always being up for a whipping at squash! The drinking team – best not to mention names here, but I would mainly blame it on Heather, Ian and Alex – I should've been more like Pete! Thanks to Heather for what seemed to be lifelong membership of Margaritas - Tuesdays will never be the same again! Stu, you are the 131st wonder of the world and a wonderful singer! Many thanks to the old boys Mike, Ben, Matt (for taking abuse), Willow (for taking abuse, even now!), and the lovely Mel (for taking abuse, and giving it back!). The moody cow in the Staff Club also needs a mention for serving us beer!

Accommodation-wise, I should thank Brian for a great first pad in Southampton and for letting me live in sin, even if you didn't realise (sorry!). And Helen and Rog for the penthouse flat where life was simple!

Cheers to David, Heather, Dave, Ian and Peter for the proof reading – it's been a massive help!

Thanks to the services at Southampton, Joan and Neil for the NMR; John and Julie for the MS; and the X-ray people for rushing my samples through! Thanks to the EPSRC and GSK for their financial support – it was nice while it lasted!

Cheers to my bro for giving me a country retreat and restful weekends, albeit on an uncomfortable couch!
Finally, many thanks to my folks for their support and continual harassment – I appreciate the nagging now!

List of abbreviations

Ac	acetyl
AIBN	α,α-azo-*iso*-butyronitrile
amu	atomic mass units
aq.	aqueous
Ar	aryl
9-BBN	9-borabicyclo[3.3.1]-nonane
Bn	benzyl
Bu	butyl
Bt	benzothiazole
BTEA	benzyltriethylammonium
BTMA	benzyltrimethylammonium
CAN	ammonium cerium(IV) nitrate
cat.	catalytic
CHN	combustion analysis
CI	chemical ionisation
conc.	concentrated
d	days
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DIAD	di-*iso*-propyl azodicarboxylate
DIBAL-H	di-*iso*-butylaluminium hydride
DHP	dihydropyran
DMAP	4-dimethylaminopyridine
DMA	dimethylacetamide
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide

DNA	deoxyribonucleic acid
dppf	1,1-bis(diphenylphosphino)ferrocene
EI	electron impact
eq.	Equivalents
Equ.	Equation
ES	electrospray
Et	ethyl
ether	diethyl ether
FG	functional group
FT	fourier transform
GC	gas chromatography
h	hours
Het	heteroaryl
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HMTA	hexamethylenetetramine
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
Im	imidazole
IR	infrared
LDA	lithium di-*iso*-propylamide
lit.	literature
LRMS	low resolution mass spectroscopy
M	molar
m-CPBA	*meta*-choloroperoxybenzoic acid
Me	methyl
min	minutes
MOM	methoxymethyl
MP	melting point
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectroscopy

PCC	pyridinium chlorochromate
Ph	phenyl
Piv	pivalate
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl
i-Pr	*iso*propyl
PPTS	pyridinium *para*-toluenesulfonate
PTC	phase transfer catalyst
py	pyridine
p-TsOH	*para*-toluenesulfonic acid
RCM	ring closing metathesis
RCAM	ring closing alkyne metathesis
RSM	recovered starting material
RT	room temperature
sat.	saturated
SM	starting material
TBAB	tetrabutylammonium bromide
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	toluyl
Tris	tri-*iso*-propylsulfonyl
Ts	*para*-toluenesulfonyl
TTMSS	*tris*-(trimethylsilyl)silane
UV	ultraviolet
VAZO®	1,1'-azobis(cyclohexanecarbonitrile)
Δ	heat

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CHAPTER I. Background

I.1 Biarylheptanoids

Biarylheptanoids are a family of natural plant metabolites consisting of two hydroxylated aromatics linked by a linear seven-carbon tether. They have typically been extracted from the stem bark of deciduous trees indigenous to Japan such as the *Acer*, *Alnus*, *Betula* and *Myrica* genus.[1-7]

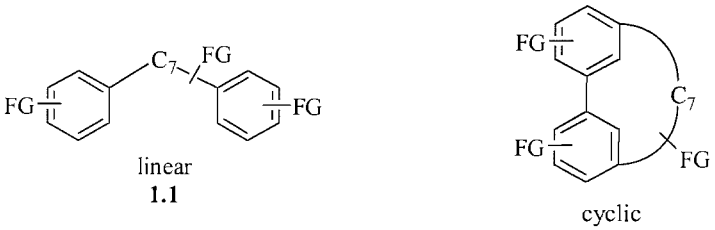
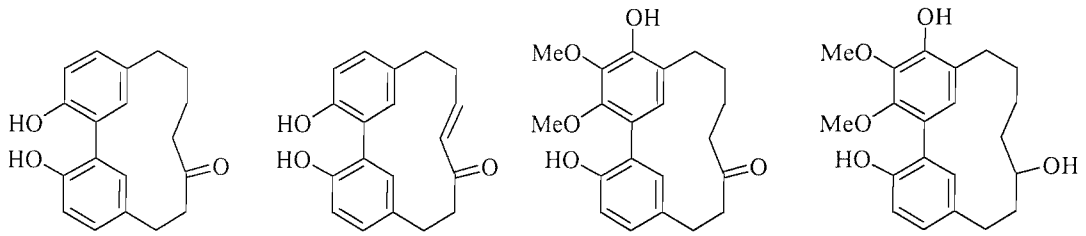
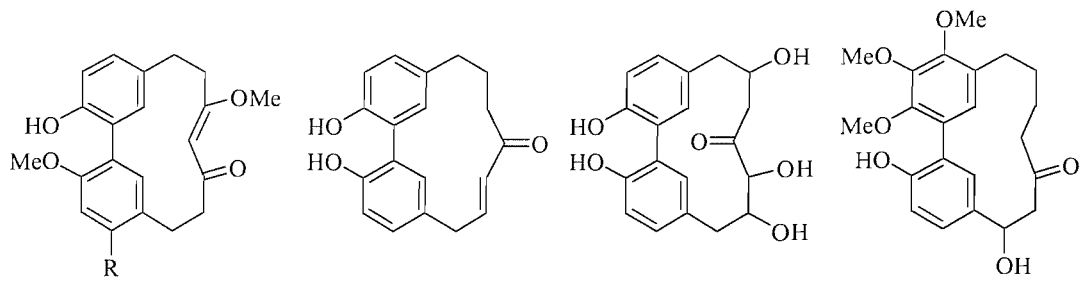


Figure 1

They are present in two forms, linear **1.1** and cyclic **1.2** (Figure 1). Traditionally, the bark of these trees has been used in Japanese folk medicine to treat asthma and remedy hepatic disorders and eye diseases.[1] More specifically, myricanol **1.6** has found use as an insect repellent (Figure 2).[8]



1.3 Acerogenin E **1.4** Alnusone **1.5** Myricanone **1.6** Myricanol



1.7 R = OMe Garuganin II **1.8** R = H Garuganin V **1.9** Trideoxyasadaninene **1.10** Asadanin **1.11** Porson

Figure 2

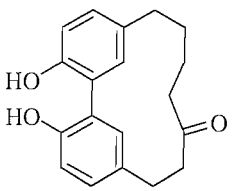
Studies directed towards determining the bioactive constituents of the stem bark have led to reports that biarylheptanoids show inhibitory activity on nitric oxide (NO) production in lipopolysaccaride (LPS) activated macrophages.[1] Nitric oxide is produced by the oxidation of L-arginine catalysed by NO synthase. The NO free radical has been suggested to cause physiological and pathological processes such as vasodilation, and chronic or acute inflammation.[9] The linear biarylheptanoids **1.1** have also been shown to exhibit a wider range of biological activities including anti-inflammatory, antihepatoxic, antifungal, and antibacterial properties.[10]

The co-occurrence of linear **1.1** and cyclic **1.2** biarylheptanoids suggests that the former **1.1** are biosynthetic precursors of the latter **1.2**, and that biaryl macrocyclisation is a natural process.[2,3,11-13]

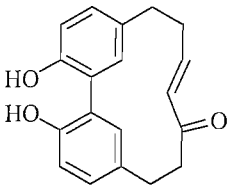
The total synthesis of macrocyclic biarylheptanoids has attracted synthetic chemists for decades. Their structure is fairly simple; however, the real synthetic challenge lies in overcoming the strain associated with closure of the 13-membered biaryl-containing macrocycle. Previously, Semmelhack and Whiting have developed a zero-valent nickel mediated biaryl coupling reaction for the synthesis of alnusone **1.4** (Scheme 1), myricanone **1.5** and myricanol **1.6** (Scheme 6).[14-16] The literature also documents previous attempts to effect macrocyclisation where dimerisation was the only process observed (Scheme 7).[17-19] These syntheses and attempted syntheses are described in more detail in the following sections.

a) Alnusone and acerogenin E

The acerogenins and alnusones form part of the family of macrocyclic biarylheptanoids containing a common *meta* substituted biphenol. Acerogenin E **1.3** (the only biaryl-containing acerogenin) has been isolated as a constituent of the inner bark of the *Betula* and *Acer* species.[3,5,20] Alnusone **1.4** has been isolated from the wood of *Alnus Japonica*.[3,5] As part of studies to characterise the bioactive components of natural medicines, Morikawa *et al.* have reported that acerogenin E **1.3** shows inhibitory activity without cytotoxic effects in an assay for NO production from LPS-activated macrophages.[1]



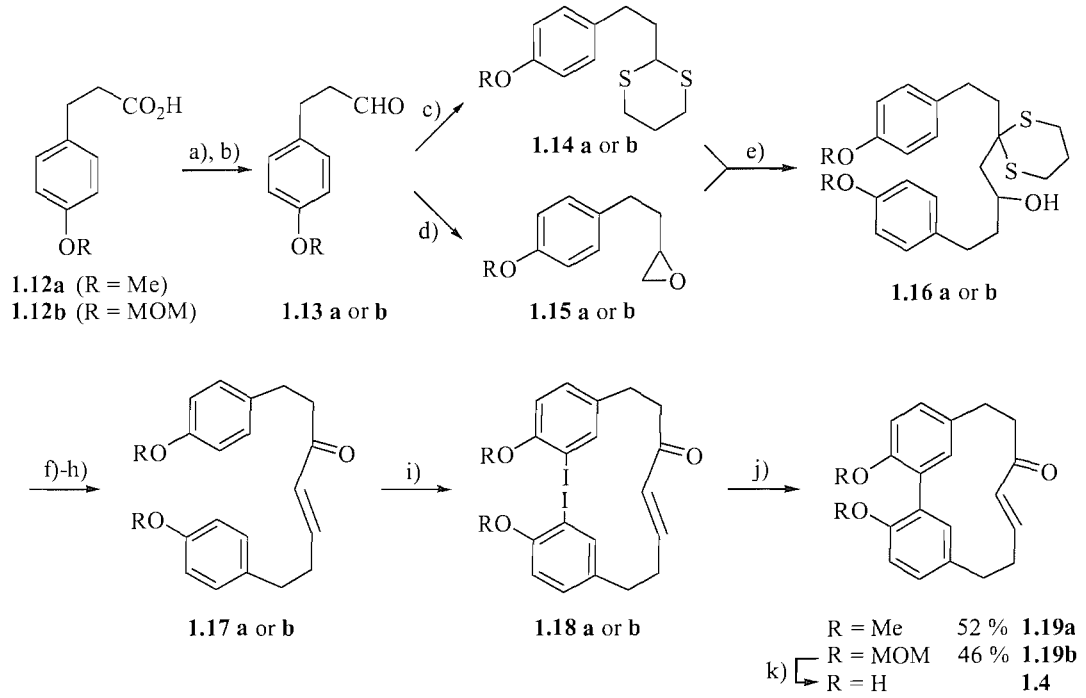
1.3 Acerogenin E



1.4 Alnusone

Figure 3

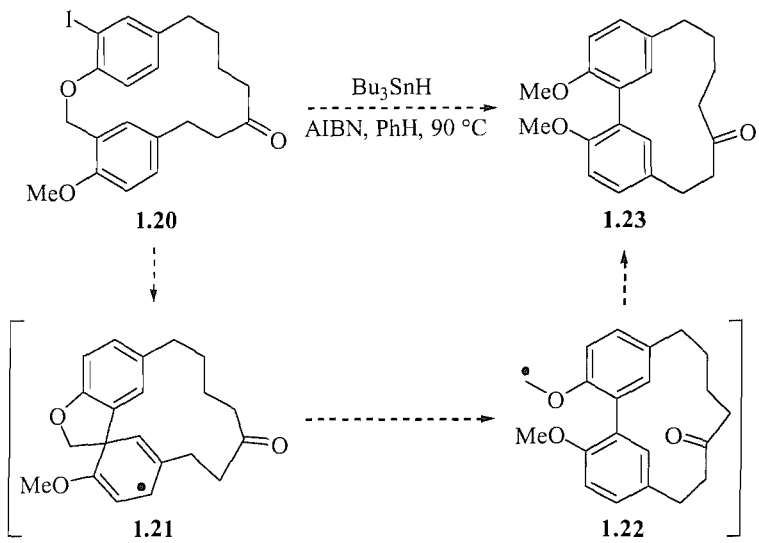
The first synthesis of alnusone dimethyl ether **1.19a** was published in 1975 by Semmelhack, and six years later the first total synthesis of alnusone **1.4** was detailed.[14,15] The key step employed a Ni^0 mediated intramolecular biaryl coupling to form the strained 13-membered macrocycle. Bifurcation of aldehyde **1.13** yields thioacetal **1.14** and epoxide **1.15** (Scheme 1). Combining the dithiane anion with the epoxide **1.15** provides linear biarylheptanoid **1.16** which, by a simple sequence of functional group conversions, yields heptenone **1.17**. Iodination *ortho* to the two methoxy groups was achieved using iodine and silver salts, and subsequent nickel(0) mediated coupling gave alnusone dimethyl ether **1.19a**. Deprotection of the methoxy groups of **1.19a** could not be achieved therefore the route was repeated with methoxymethyl groups (*viz* **1.12b** → **1.19b**). The key nickel(0) mediated biaryl coupling proceeded in similar yield, and required a stoichiometric amount of the reagent. The reaction has received considerable attention over the years and has been adapted to be performed with catalytic nickel and a stoichiometric quantity of zinc.[21,22]



a) $LiAlH_4$, 98 %; b) CrO_3, py, 83 %; c) $HS(CH_2)_3SH$, 94 %; d) NaH, DMSO, Me_3SI, 86 %; e) *n*-BuLi; f) MeOH, HgO, $HgCl_2$, 99 %; g) Ac_2O, 99 %; h) diazabicyclononane, 81 %; i) I_2, $AgCO_2CF_3$, 75 %; j) $Ni(PPh_3)_4$, 52 %; k) aq. $AcOH/H_2SO_4$, 72 %.

Scheme 1

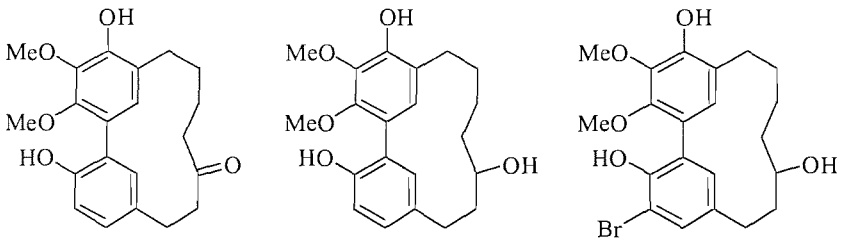
In our group, Nunn attempted to form acerogenin E **1.3** *via* a ring contraction strategy whereby a radical induced *ipso*-substitution reaction was envisioned as a means to form the key aryl-aryl bond (Scheme 2).[23] Although he succeeded in forming the macrocyclic ether **1.20** subsequent transannular ring contraction to acerogenin E dimethyl ether **1.23** failed. None of the products of the reaction could be identified. Nunn had previously shown that related starting materials undergo the reaction readily.[24]



Scheme 2

b) Myricanone and myricanol

Myricanone **1.5** and myricanol **1.6** were isolated in 1970 by Crombie *et al.* while seeking to isolate rotenoids from the stem bark of *Myrica nagi*.[6,25] Detailed spectral analysis, comparison with similar compounds and X-ray analysis of a brominated derivative, 16-bromomyricanol **1.24** helped identify the natural products.[12]

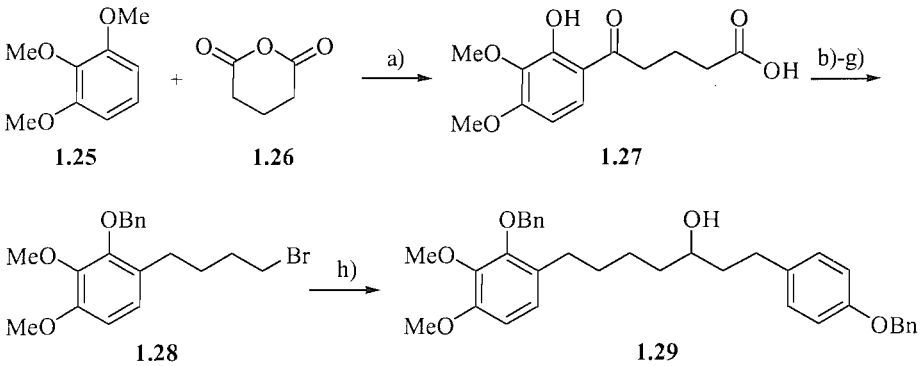


1.5 Myricanone **1.6** Myricanol **1.24** 16-Bromomyricanol

Figure 4

In 1978 Whiting tested a variety of aryl-aryl cyclisation methods in a program to effect the synthesis of myricanone **1.5** and myricanol **1.6**, and some related unnatural biarylheptanoids.[8,16,26] The linear biarylheptanoid **1.29** was synthesised in 8 steps from 1,2,3-trimethoxybenzene **1.25** and glutaric anhydride **1.26** (Scheme 3). A series of

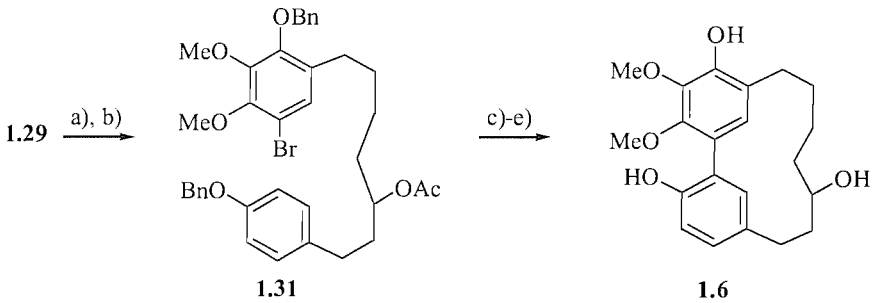
functional group manipulations transformed ketoacid **1.27** into bromide **1.28** which was treated with magnesium to form the corresponding alkyl Grignard reagent. Subsequent reaction with *p*-benzyloxydihydrocinnamaldehyde **1.30** gave linear biarylheptanoid **1.29**.



a) $AlCl_3$; b) Me_2SO_4, ^-OH; c) Pd, H^+; d) BnCl; e) $LiAlH_4$; f) TsCl; g) NaBr; h) i) Mg; ii) *p*-benzyloxydihydrocinnamaldehyde **1.30**.

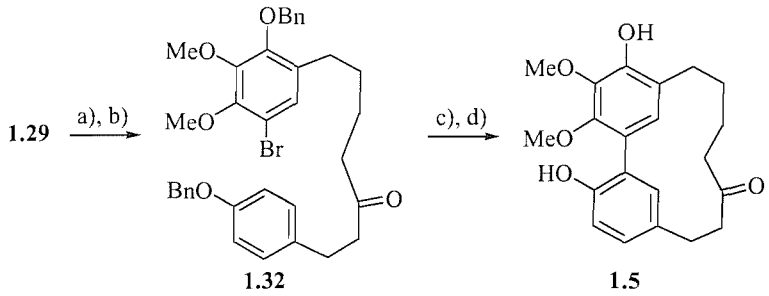
Scheme 3

Bromination of **1.29** and subsequent protection of the secondary alcohol gave aryl bromide **1.31**, which cyclised in low yield on irradiation at 254 nm (Scheme 4). A similar outcome was observed when ketone **1.32** was treated analogously giving myricanone **1.5** after deprotection (Scheme 5).



a) Br_2, AcOH, 41 %; b) Ac_2O, 78 %; c) hυ (254 nm), 10 %; d) Pd/C, H_2; e) KOH.

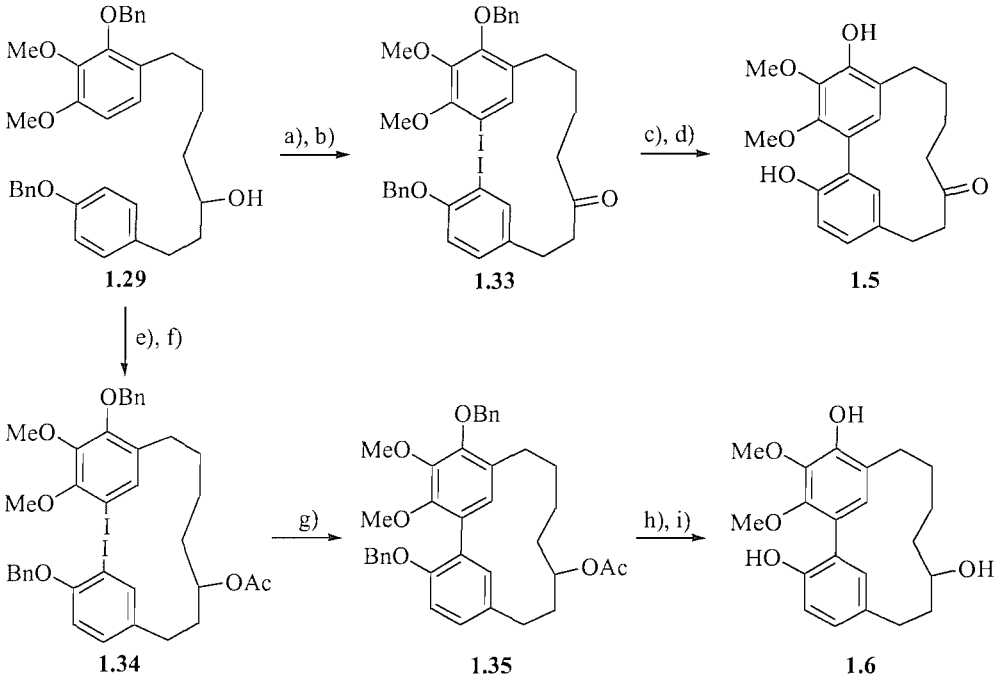
Scheme 4



a) Br_2, AcOH, 41 %; b) PCC, 90 %; c) hυ (254 nm), 10 %; d) Pd/C, H_2, 75 %.

Scheme 5

The diiodobiarylheptanoids **1.33** and **1.34** were each prepared from **1.29** by silver salt mediated iodination (Scheme 6). Treatment with a stoichiometric amount of nickel(0) led to macrocyclisation giving myricanone **1.5** and myricanol **1.6** respectively in low yield following benzyl deprotection.

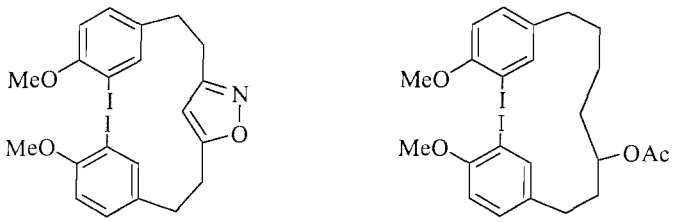


a) I_2, $AgCO_2CF_3$, 44 %; b) PCC, 82 %; c) $Ni(PPh_3)_2Cl_2$, Zn, 10 %; d) Pd/C, H_2; e) Ac_2O; f) I_2, $AgCO_2CF_3$, 41 %; g) $Ni(PPh_3)_2Cl_2$, Zn, 7 %; h) Pd/C, H_2; i) KOH.

Scheme 6

Whiting attributed the poor yields attained in the Ni(0) cyclisation, compared to those achieved in the alnusone synthesis to the fact that alnusone **1.4** contains three sp^2 carbons in the heptane chain, reducing both angle strain and transannular H-H steric interactions.[16]

However, 10 years later, Whiting successfully cyclises alkyl acetate **1.37** in 49 % (Figure 5), which was higher than that realised with isooxazole **1.36** (31 %).

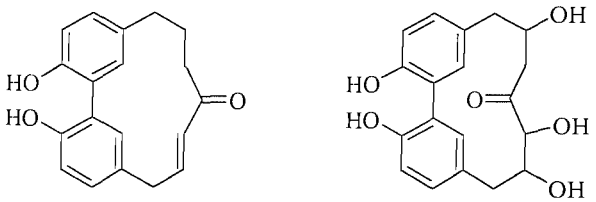


1.36 **1.37**

Figure 5

c) Trideoxyasadaninene

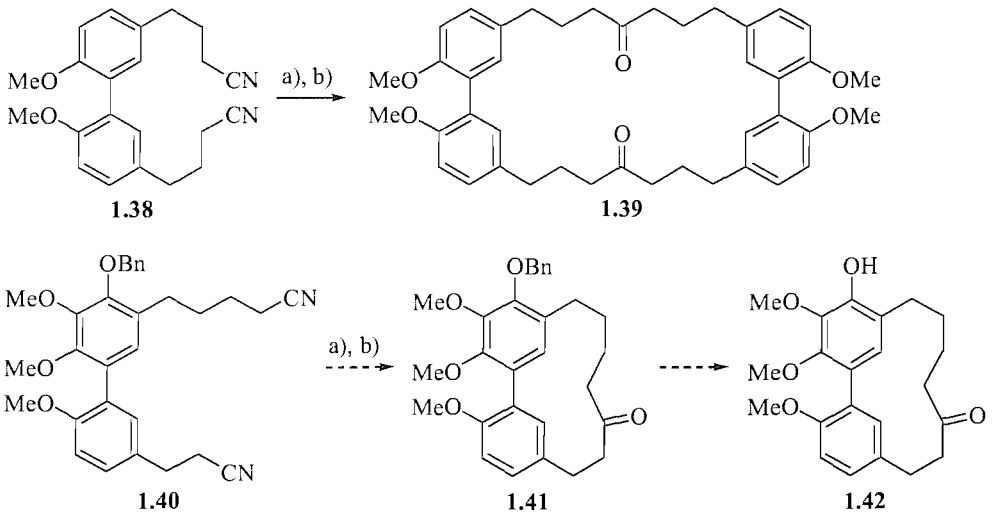
Trideoxyasadaninene **1.9** is part of the family of asadanins which share the common biarylheptanoid skeleton and have been isolated from the wood of *Ostrya japonica*.[27] Trideoxyasadaninene **1.9** is a structural isomer of alnusone **1.4**, and varies from the other asadanins only in oxidation level.



1.9 Trideoxyasadaninene **1.10** Asadanin

Figure 6

The asadanins have received little synthetic interest since their isolation in the 1960's, however Brown has attempted to synthesise trideoxyasadaninene **1.9** beginning with formation of the biaryl bond *via* an Ullmann coupling.[19] Further manipulations led to bis-nitrile **1.38**, which was envisioned as a precursor to the natural products. However, the attempted intramolecular Thorpe-Ziegler condensation of **1.38** to effect closure of the macrocycle led instead to dimer **1.39** (Scheme 7). The same group also targeted *O*-methylmyricanone **1.42** through cyclisation of **1.40**, the biaryl bond having been preformed by means of a Suzuki reaction. However no identifiable products were isolated from their attempted cyclisation of **1.40**.



a) $NaNC_6H_5Me$, 28 %; b) 12 M HCl, 70 %.

Scheme 7

I.2 Macrocyclic biphenyls

The macrocyclic bisbibenzyls are a class of compounds found in bryophytes (liverworts). They are each derived from similar building blocks that link to form 14, 16, 18 and 20-membered rings. Bryophytes can be subdivided into 3 classes; mosses, liverworts and hornworts.[28] Liverworts grow on rock and soil, and are traditionally used in Japanese folk medicine as diuretics, antitumoural, antibacterial and antifungal agents.[28,29] Some macrocyclic bisbibenzyls have been found to exhibit cytotoxic activity against KB cells and P388 lympholytic leukemia.[30]

The biosynthesis of macrocyclic bisbibenzyls is believed to begin with lunularic acid **1.43a** or lunularin **1.43b** (also very common to liverworts).[30-32] Various oxidative phenolic couplings and cyclisations transform these into a multitude of macrocyclic bisbibenzyls (Figure 7). Perrottetin E **1.44** has been suggested as the early open chain precursor in the biosynthesis of riccardins A **1.46a** and C **1.46c** and the plagiochins **1.47a-d**. Even though the isoplagiochins **1.48a-f** lack a C-O bond, lunularin **1.43** is also a possible building block for these natural products *via* C-C bond formation. The bazzanins **1.49** are essentially chlorinated isoplagiochins **1.48**, however it is unclear at what stage the chlorine atoms are introduced in nature.

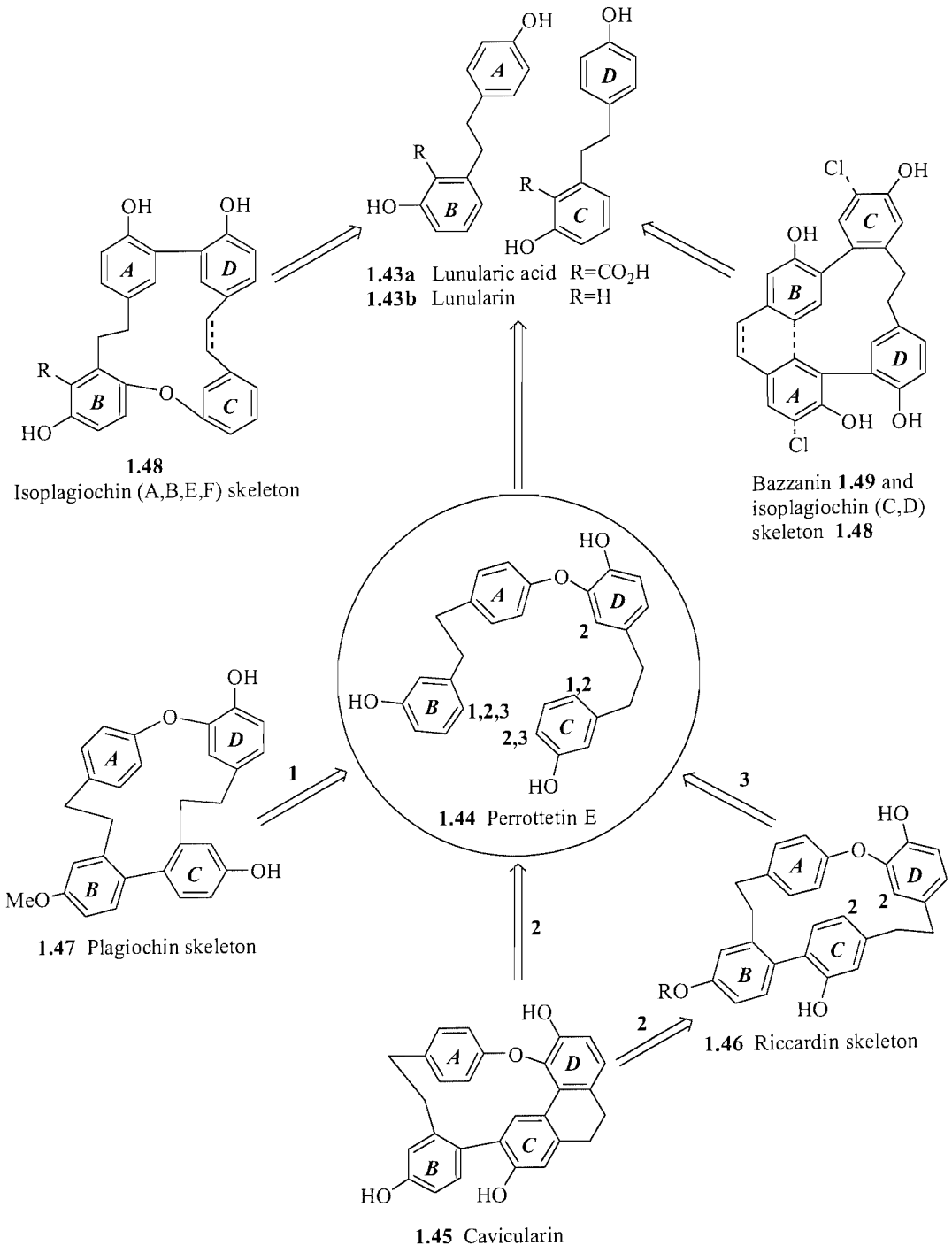
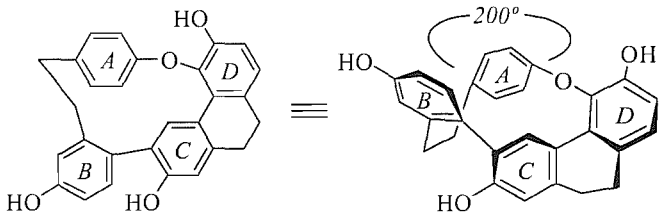


Figure 7. Biosynthesis of macrocyclic bis(bibenzyls) from lunularin 1.43b

a) Cavicularin

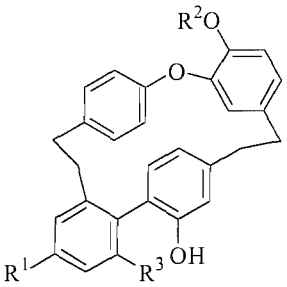


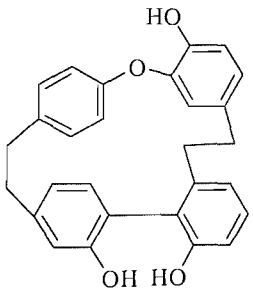
1.45

Figure 8

Cavicularin **1.45** was first isolated in 1996 from the methanolic extract of the liverwort *Cavicularia densa*, collected from Mount Ishizuchi, Ehime, Japan in 1995.[33] It is a novel phenolic secondary metabolite, and extensive 2D-NMR (600 MHz) and X-ray analysis have confirmed its structure. Cavicularin **1.45** is a highly strained 14-membered macrocyclic bibenzyl-dihydrophenanthrene derivative which makes it very interesting from a synthetic viewpoint. In the solid state arene *A* adopts a boat like confirmation, making it unique. Even though it does not contain any chiral carbon centres, it displays optical activity due to planar and axial chirality.

b) Riccardins





1.46a Riccardin A R^1=OMe R^2=H R^3=H
1.46c Riccardin C R^1=OH R^2=H R^3=H
1.46d Riccardin D R^1=H R^2=H R^3=OH
1.46e Riccardin E R^1=H R^2=H R^3=OMe
1.46f Riccardin F R^1=OH R^2=Me R^3=H

1.50 Isoriccardin C

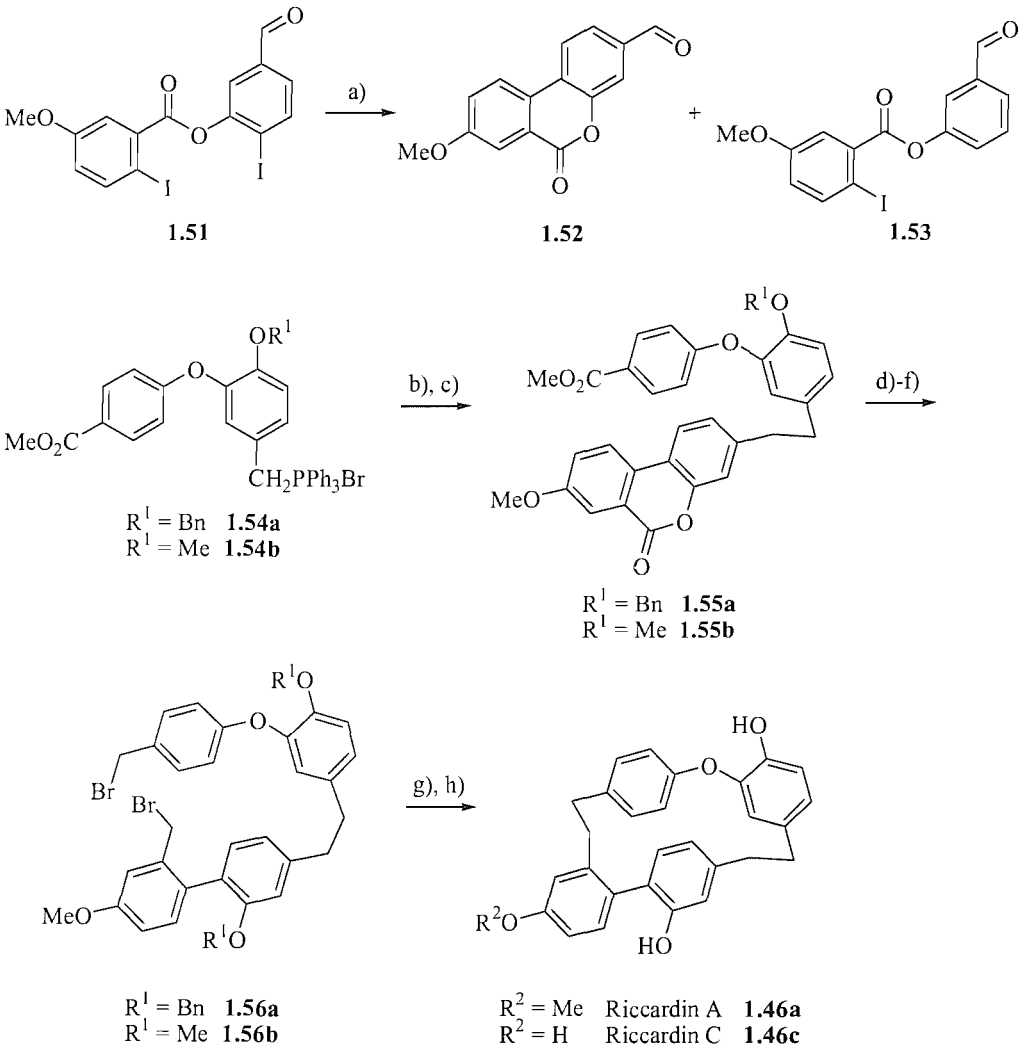
Figure 9

Riccardin C **1.46c** has been isolated from a variety of liverworts and was first identified in *Reboulia hemispherica* by Asakawa in 1982.[31,34] It displays *in vitro* cytotoxicity against nasal epidermoid carcinoma cells and weak inhibitory activity against

HIV-1 reverse transcriptase.[35] Riccardin A **1.46a** displays cytotoxic activity against KB cells, and it has also been found to stimulate the growth of nerve endings in the central nervous system.[29,30] X-ray analysis of the diacetate of riccardin A **1.46a** was used to certify the structure.[30]

i) Nógrádi synthesis of riccardin A and C

Riccardin C **1.46c** was first synthesised by Nógrádi (Scheme 8).[36,37]



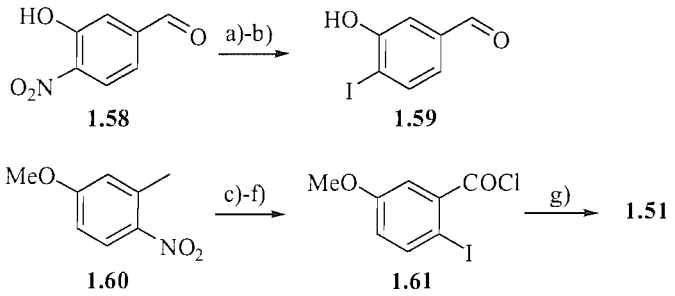
a) $Ni(PPh_3)_4$, 17 %;
Riccardin A: b) (**1.54a**), **1.52**, NaOMe, 64 %; c) Pd/C, H_2, 100 %; d) $LiAlH_4$, 80 %; e) BnBr, 91 %; f) PBr_3, 100 %; g) Na, 15 %.
Riccardin C: b) (**1.54b**), **1.52**, NaOMe; c) Pd/C, H_2, 55 %; d) $LiAlH_4$; e) CH_2N_2, 30 %; f) PBr_3, 100 %; g) Na, 30 %; h) BBr_3, 37 %.

Scheme 8

The first reaction of note in the synthesis was a Ni(0) assisted intramolecular aryl-aryl bond formation that transformed diiodide **1.51** into lactone **1.52** in 17 % yield, giving **1.53** as a significant by-product.[37] A Wittig reaction between **1.54b** and **1.52** followed to give bibenzyl **1.55b** after hydrogenation. Sequential reduction of both the lactone and ester functions, methylation of the phenol, and bromination of the resulting diol gave **1.56b**. Treatment with sodium then induced a Wurtz coupling to close the macrocycle giving riccardin A dimethyl ether **1.57**. Deprotection with boron tribromide gave riccardin C **1.46c** in 14 steps and an overall yield of 0.04 % from **1.59**.

Riccardin A **1.46a** was also synthesised by making use of a different protecting group strategy. Thus, the benzyl protected phosphonium salt **1.54a** was used in place of **1.54b** and taken through a similar sequence. Notably, the Wurtz macrocyclisation of **1.56a** also induced partial debenzylation of the product. Debenzylation of the crude product mixture gave riccardin A **1.46a** in low yield.

Though interesting, the Ni(0) cyclisation of **1.51** to **1.52** is an obvious deficiency with the synthesis. It is troublesome and low yielding, and the synthesis of the diiodo precursor **1.51** requires additional steps that are low yielding (Scheme 9).[37-39]



1.58 **1.59** **1.60** **1.61** **1.51**

a) $SnCl_2.2H_2O$, HCl; b) $NaNO_2$, NaI, 20 % (2 steps); c) Pd/C, H_2; d) $NaNO_2$, KI, 60 %; e) $KMnO_4$, 54 %; f) $SOCl_2$; g) **1.59**, 63 %.

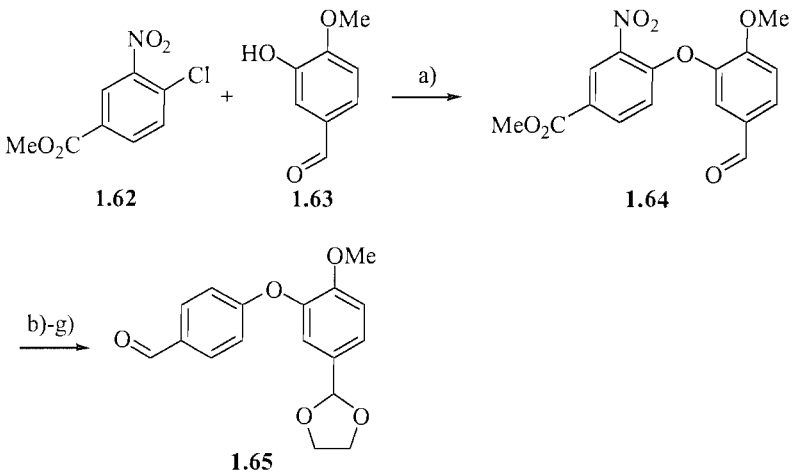
Scheme 9

ii) Eicher synthesis of riccardin C

In 1998 Eicher published a synthesis of riccardin C **1.46c** in which a Wittig macrocyclisation featured as a key step.[40] First, aryl ether **1.65** was formed by a lengthy sequence beginning with an Ullmann coupling between phenol **1.63** and aryl chloride **1.62**

(Scheme 10). Phosphonium salt **1.71** was also prepared in a sequence featuring a Suzuki reaction between aryl triflate **1.69** and boronic acid **1.67** (Scheme 11). The resulting biaryl **1.70** was then subjected to radical bromination and treatment with triphenylphosphine to furnish the functionalised biaryl **1.71**.

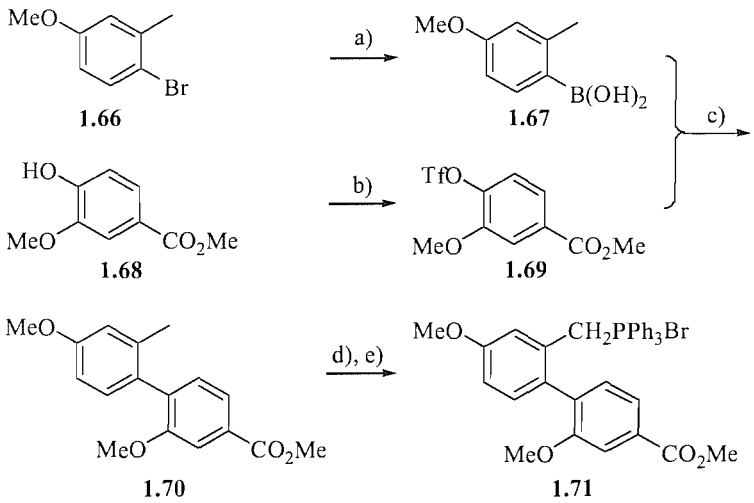
The Wittig reaction to conjoin **1.65** and **1.71** proceeded in good yield to give **1.72** (Scheme 12). Further functional group manipulations then gave substrate **1.75**, primed for an intramolecular Wittig reaction which was achieved in good yield. Reduction of the resulting alkene and removal of methyl ethers gave riccardin C **1.46c** in 12 % overall yield, the longest linear sequence being 15 steps.



1.62 **1.63** **1.64** **1.65**

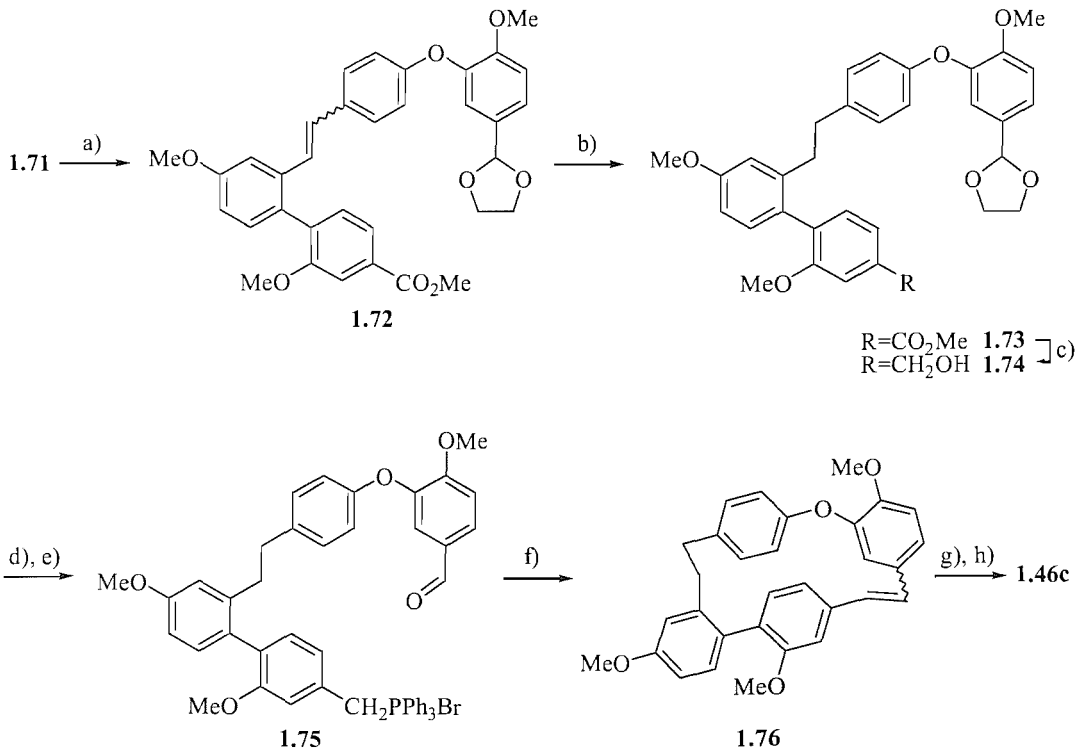
a) NaH, 88 %; b), Ac_2O, H_2SO_4, 86 %; c) Pd/C, H_2; d) $NaNO_2$, H_3PO_2, 74 % (two steps); e) Al_2O_3, $HO(CH_2)_2OH$, 85 %; f) $LiAlH_4$, 84 %; g) PCC, Al_2O_3, 95 %.

Scheme 10



a) i) Mg; ii) $B(On\text{-}C_4H_9)_3$; iii) HCl, 75 %; b) Tf_2O, 95 %; c) $Pd(PPh_3)_4$, K_3PO_4, 93 %; d) NBS; e) PPh_3, 68 %.

Scheme 11



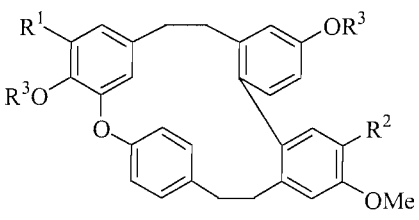
a) **1.65**, K_2CO_3, 18-crown-6, 85 %; b) Pd/C, H_2, 93 %; c) $LiAlH_4$, 88 %; d) HBr; e) PPh_3, 77 % (two steps); f) NaOMe, 80 %; g) Pd/C, H_2, 92 %; h) BBr_3, 88 %.

Scheme 12

Eicher's route makes use of very reliable chemistry. However, in the formation of aryl ether **1.65** they used the nitro group in **1.62** to facilitate the S_NAr displacement of chlorine. Consequently it took seven steps to prepare the biaryl ether **1.65** in an overall yield of 34 %. Although the route to biaryl **1.71** is short and proceeds in high yield, the route is rather expensive. For example, methyl 4-hydroxy-3-methoxybenzoate **1.77** is £2.58 per gram, and triflic anhydride is £3.92 per gram.

c) Plagiochins

The plagiochins **1.47a-d** were first reported in 1987 having been isolated from the liverwort *Plagiochila acanthophylla* by Asakawa *et al.*[41] Extensive NMR studies, and formation of acetate and methoxy derivatives, allowed the structures of **1.47a** to **1.47d** to be elucidated. Plagiochin A **1.47a** exhibits an interesting neurotrophic activity in the culture of fetal rat's cerebral hemisphere.[42] The main challenge presented by their synthesis is the bis-*ortho* substituted biaryl in the plagiochin skeleton.



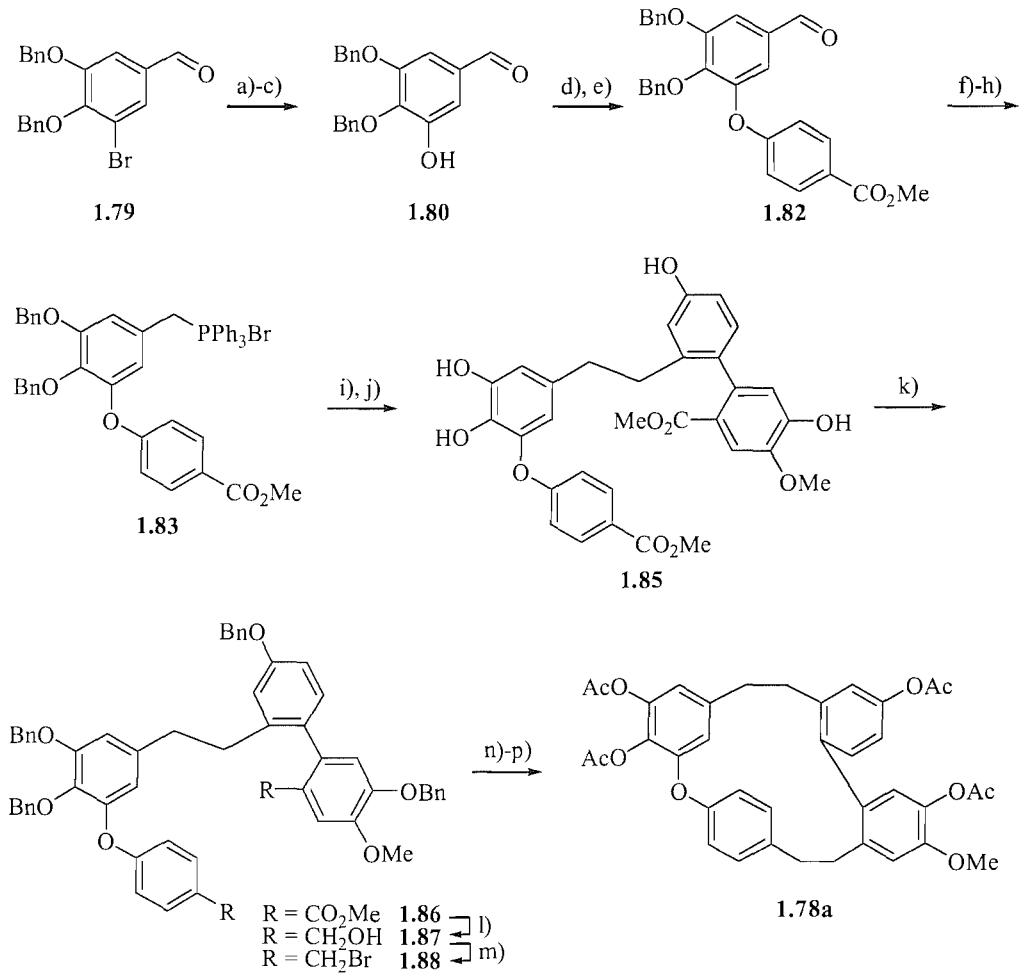
1.47a	Plagiochin A	R^1=OH	R^2=OH	R^3=H
1.78a	Plagiochin A tetraacetate	R^1=OAc	R^2=OAc	R^3=Ac
1.47b	Plagiochin B	R^1=OH	R^2=H	R^3=H
1.78b	Plagiochin B triacetate	R^1=OAc	R^2=H	R^3=Ac
1.47c	Plagiochin C	R^1=H	R^2=OH	R^3=H
1.78c	Plagiochin C triacetate	R^1=H	R^2=OAc	R^3=Ac
1.47d	Plagiochin D	R^1=H	R^2=H	R^3=H

Figure 10

i) Nógrádi synthesis of plagiochin A and B

A modified Wurtz coupling of bis(benzylbromide) **1.88** and **1.92** features as the key ring closure in the synthesis of plagiochins A **1.47a** and B **1.47b** by Nógrádi *et al.*[43] Biphenyl **1.84** was formed *via* a Suzuki coupling reaction, as described in Scheme 16, while aryl ether **1.82** was synthesised using a traditional copper mediated Ullman reaction between phenol **1.80** (derived from vanillin **1.89** in 6 steps) and methyl 4-bromobenzaoate **1.81** (Scheme 13).[44,45] Coupling of the biaryl **1.84** and aryl ether **1.83** was achieved by means of a Wittig reaction. A lengthy sequence of hydrogenation, reprotection, and bromination transformed the material into the bisbromide **1.88** in good yield. Ring closure

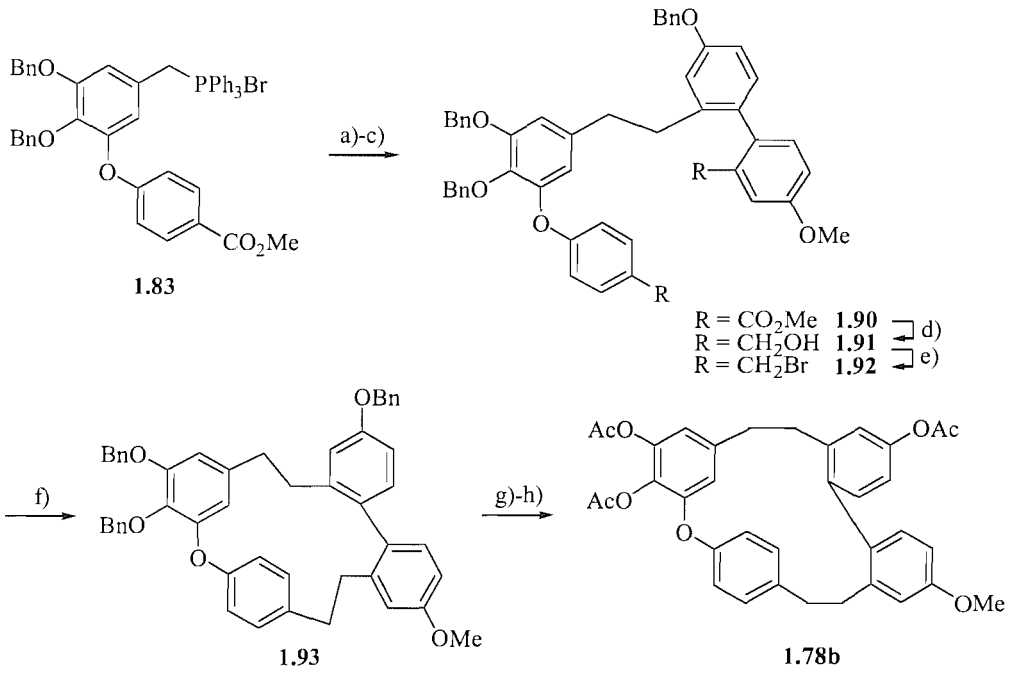
was then effected by a modified Wurtz reaction, which gave many unwanted side reactions. Indeed, plagiochin A tetracetate **1.78a** was isolated in a mere 8 % yield.



a) NH_4Cl, $(MeO)_3CH$, 96 %; b) i) BuLi; ii) $B(OBu)_3$; iii) HCl, 74 %; c) H_2O_2, 86 %; d) NH_4Cl, $(MeO)_3CH$, 95 %; e) methyl 4-bromobenzoate **1.81**, CuO, 60 %; f) $NaBH_4$, 92%; g) PBr_3, 91 %; h) PPh_3, 75 %; i) NaOMe, **1.84**, 83 %; j) H_2, Pd/C, 94 %; k) BnBr, 95 %; l) $LiAlH_4$, 80 %; m) PBr_3, 90 %; n) Na, $(Ph_2C)_2$, 8 %; o) H_2, Pd/C; p) Ac_2O, 74 %.

Scheme 13

Plagiochin B **1.47b** was synthesised from biaryl **1.89** (synthesis described in Scheme 15) and Wittig salt **1.83** using the same strategy (Scheme 14). Again, macrocyclisation of **1.92** was effected by a Wurtz coupling reaction and proceeded in very low yield. Exchanging the benzyl groups for acetates completed a synthesis of plagiochin B triacetate **1.78b**. The disadvantages in Nógrádi's route is that it is rather long and the key Wurtz macrocyclisation proceeds in very low yield (4 %).



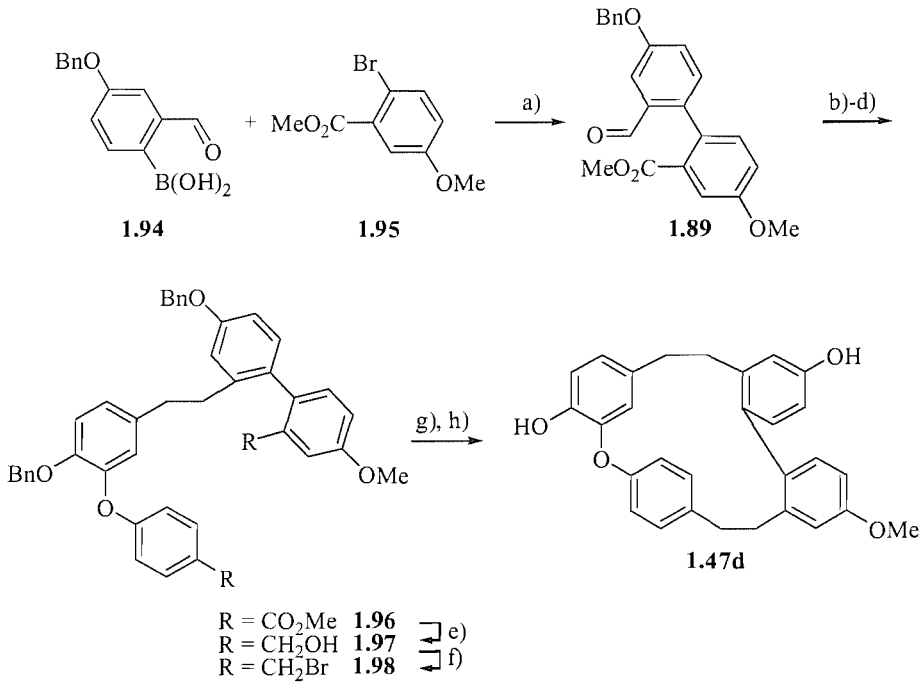
a) **1.89**, NaOMe, 92 %; b) H_2, Pd/C, 92 %; c) BnBr, 97 %; d) $LiAlH_4$, 90 %; e) PBr_3, 90 %; f) Na, $(Ph_2C)_2$, 4 %; g) H_2, Pd/C; h) Ac_2O, 64 %.

Scheme 14

ii) Nógrádi synthesis of plagiochin C and D

Plagiochins C **1.47c** and D **1.47d** provide an interesting synthetic challenge as they contain an *ortho-ortho* substituted biaryl. Nógrádi has also targeted these two natural products and again employed an intramolecular Wurtz coupling to effect the macrocyclisation reaction.[46]

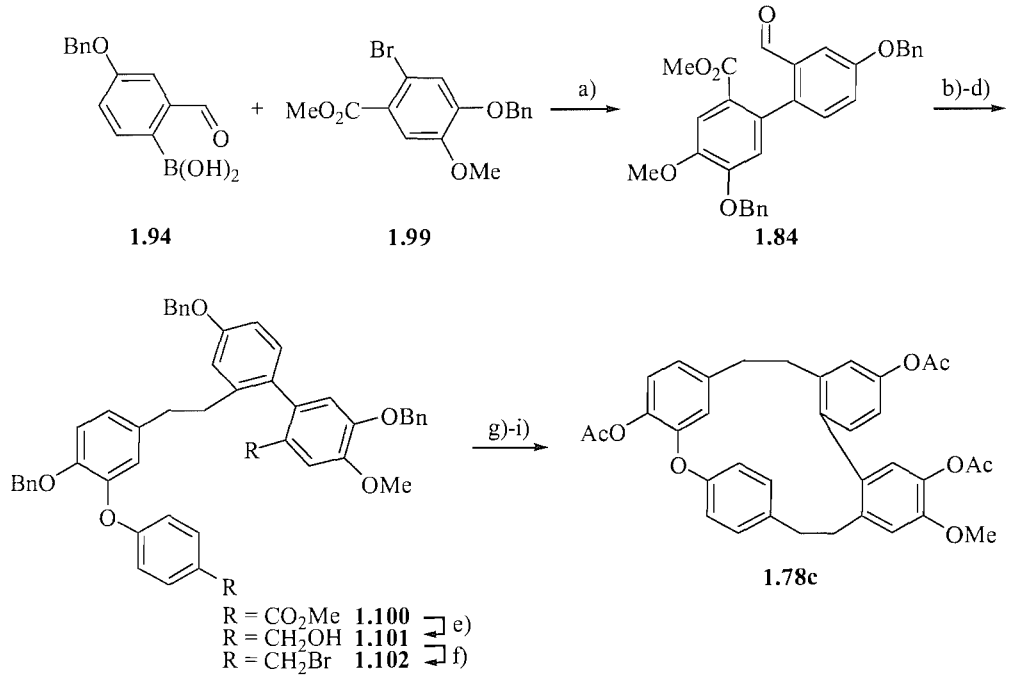
The synthesis began with the preparation of biphenyl **1.89** *via* a Suzuki coupling reaction between boronic acid **1.94** and aryl bromide **1.95** (Scheme 15). Aryl ether **1.54a** was synthesised *via* the usual copper mediated Ullman reaction analogous to the formation of **1.83** (Scheme 13). These subunits were then coupled by a Wittig reaction. A lengthy but high yielding sequence advanced this material to bis-bromide **1.98** allowing ring closure by a tetraphenylethene assisted Wurtz reaction. Final hydrogenation of the product mixture yielded plagiochin D **1.47d** in 15 % yield from **1.98**.



a) $Pd(PPh_3)_4$, DME, aq. $NaHCO_3$, Δ, 35 %; b) **1.54a**, NaOMe, MeOH, 85 %; c) H_2, Pd/C, EtOH/EtOAc; d) BnCl, K_2CO_3, 83 % (two steps); e)$LiAlH_4$, Et_2O, 70 %; f) PBr_3, 90 %; g) Na; h) H_2, Pd/C, 17 %.

Scheme 15

Plagiochin C triacetate **1.78c** was synthesised using the same strategy (Scheme 16), beginning with aryl bromide **1.99** (prepared in seven steps from vanillin **1.89**). Interestingly the Wurtz macrocyclisation reaction of **1.102** proceeded in 34 % yield, substantially higher than had been achieved in each of the aforementioned syntheses.



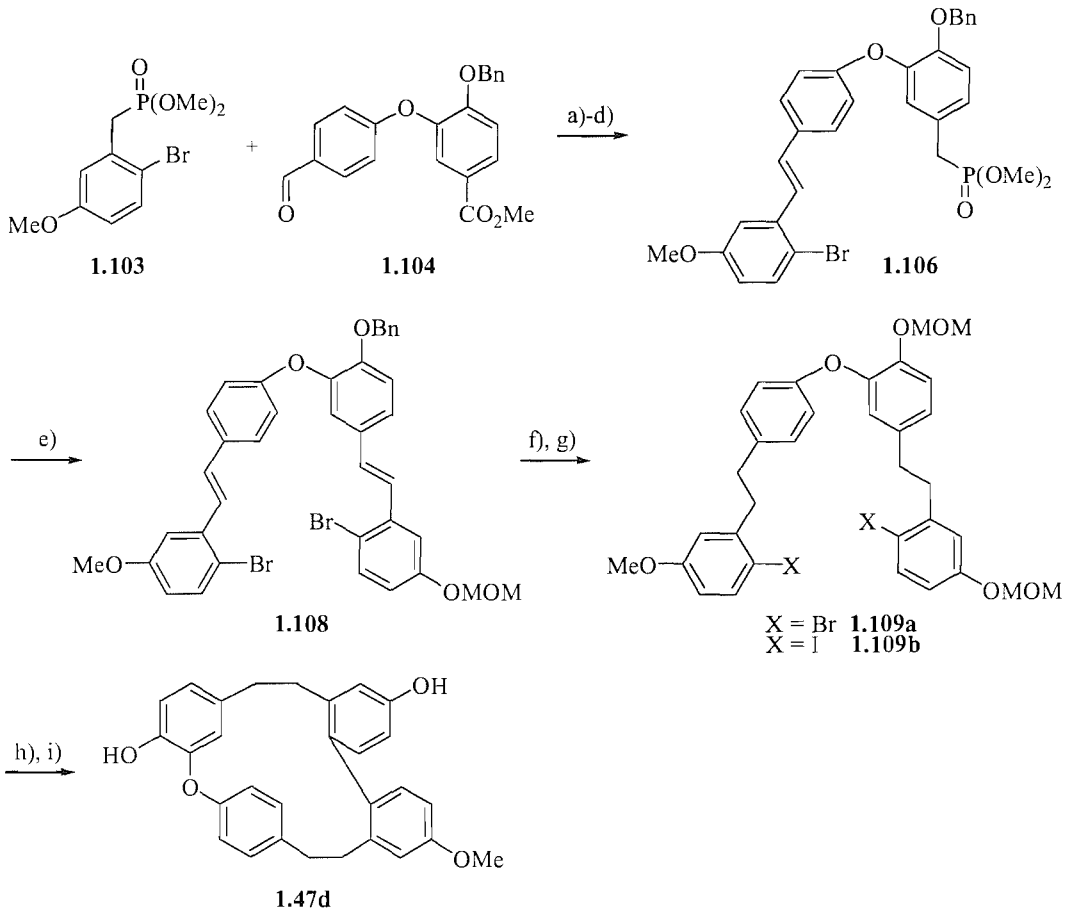
a) $Pd(PPh_3)_4$, DME, aq. $NaHCO_3$, Δ, 60 %; b) **1.54a**, NaOMe, MeOH, 83 %; c) H_2, Pd/C, EtOH/EtOAc, 94 %; d) BnBr, 84 %; e) $LiAlH_4$, Et_2O, 72 %; f) PBr_3; g) Na, 34 %; h) H_2, Pd/C; i) Ac_2O, 78%

Scheme 16

iii) Fukuyama synthesis of plagiochin D

A more linear approach was used by Fukuyama *et al.* in their synthesis of plagiochin D **1.47d** (Scheme 17).[42] Aryl ether **1.104** was combined with phosphonate **1.103** (readily derived from *m*-anisaldehyde **1.105**) in a Wadsworth-Emmons reaction. A further Wadsworth-Emmons reaction between **1.106** and bromo-benzaldehyde **1.107** then gave tetraaryl **1.108**. Catalytic hydrogenation of the resulting diene **1.110** was performed cleanly using PtO_2. Complications were encountered when using palladium on carbon catalyst as oxidative addition to the aryl-bromine bond and subsequent reduction competed with alkene hydrogenation forming **1.110**. Intramolecular ring closure of **1.109** to the 16-membered ring was then attempted using a variety of conditions, including Ni(0) mediated coupling and Suzuki-Miyaura Pd(0) catalysed cross-coupling with bis(pinacolato)diboron, both of which failed. By contrast, Stille-Kelly intramolecular cyclisation of **1.109a** proceeded, albeit in a very modest 17 % yield. Stille cyclisation of the intermediate bromo-stannane

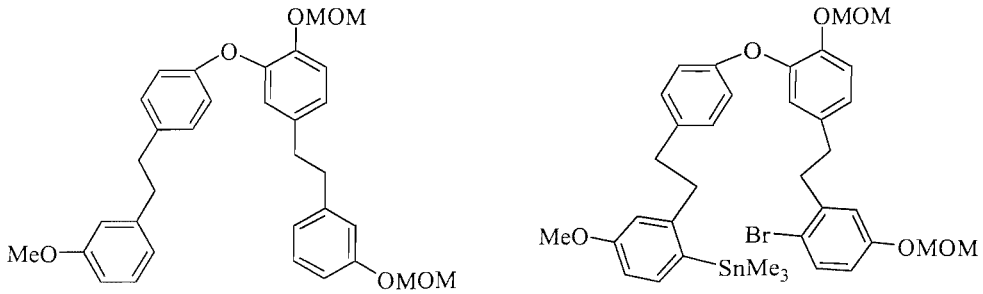
1.111 (where Br and $SnMe_3$ groups are interchangeable) gave a similar outcome, dimers accounting for 15 % of the mass balance.



a) NaH, 94 %; b) $LiAlH_4$; c) CBr_4, PPh_3; d) $P(OMe)_3$, 81 %; e) **1.107**, NaH, 89 %; f) H_2, PtO_2; g) NaH, MOMCl, 73 % (two steps); h) $(Me_3Sn)_2$, $Pd(PPh_3)_4$, 17 %; i) HBr, 87 %.

Scheme 17

As with the Nógrádi synthesis, the route falls foul of the lability of benzyl protecting groups under conditions employed for catalytic hydrogenation. The Stille-Kelly reaction proceeds in low yield due to competing side reactions and poor conversion (recovered starting material **1.109a** accounting for 45 % of the mass balance). Notably, use of the bis-iodide **1.109b** did not improve the yield of the macrocyclisation reaction.

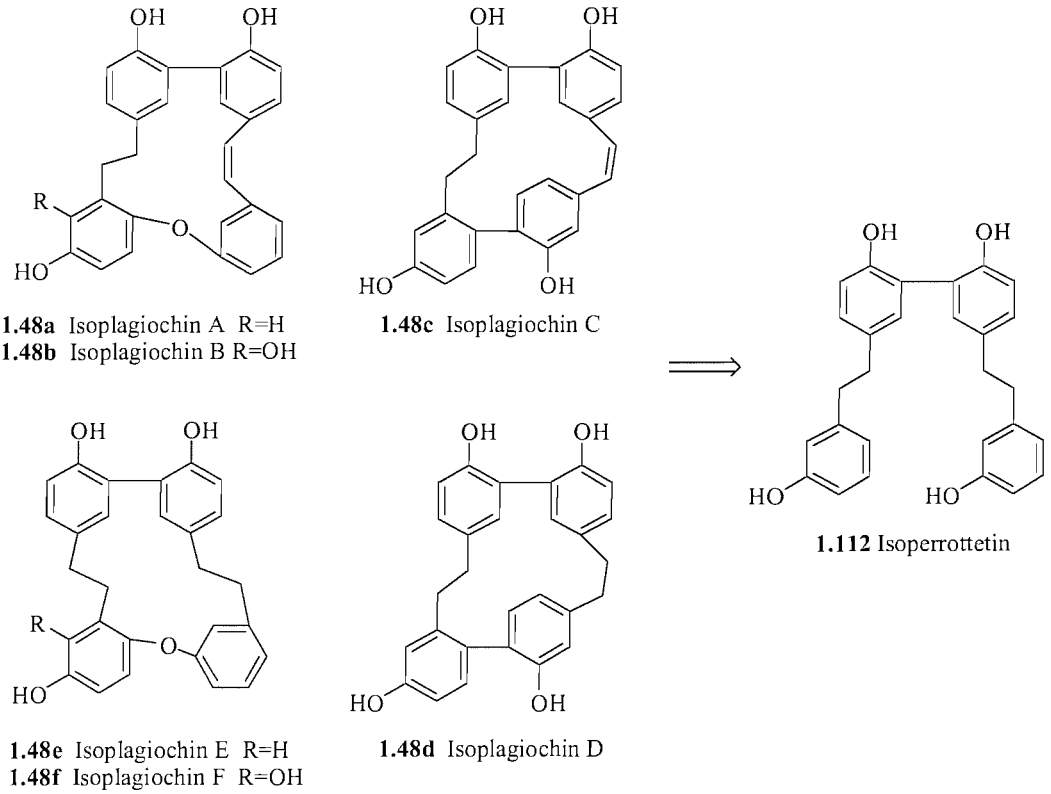


1.110 **1.111**

Figure 11

d) Isoplagiochins

Isoplagiochins A-D **1.48a-d** have been isolated from the methanolic extract of the liverwort *Plagiochila fruticosa* by Asakawa *et al.*[47,48] Subsequently, Anton *et al.* isolated isoplagiochins E **1.48e** and F **1.48f** from an unidentified *Plagiochila* species in Costa Rica.[49] The biosynthesis is suggested to be derived from a dimerisation of lunularin **1.43** with a possible intermediate being isoperrottetin **1.112** (Scheme 18).[47] Interestingly, optical rotation for isoplagiochins C **1.48c** and D **1.48d** have been reported in the literature, but depend on the plant source and isolation procedure.[47,50-52] To date, studies on the activity of compounds in the class has been limited with a single report indicating that isoplagiochin D **1.48d** displays antifungal activity.[53]



1.48a Isoplagiochin A R=H
1.48b Isoplagiochin B R=OH

1.48c Isoplagiochin C

1.112 Isoperrottetin

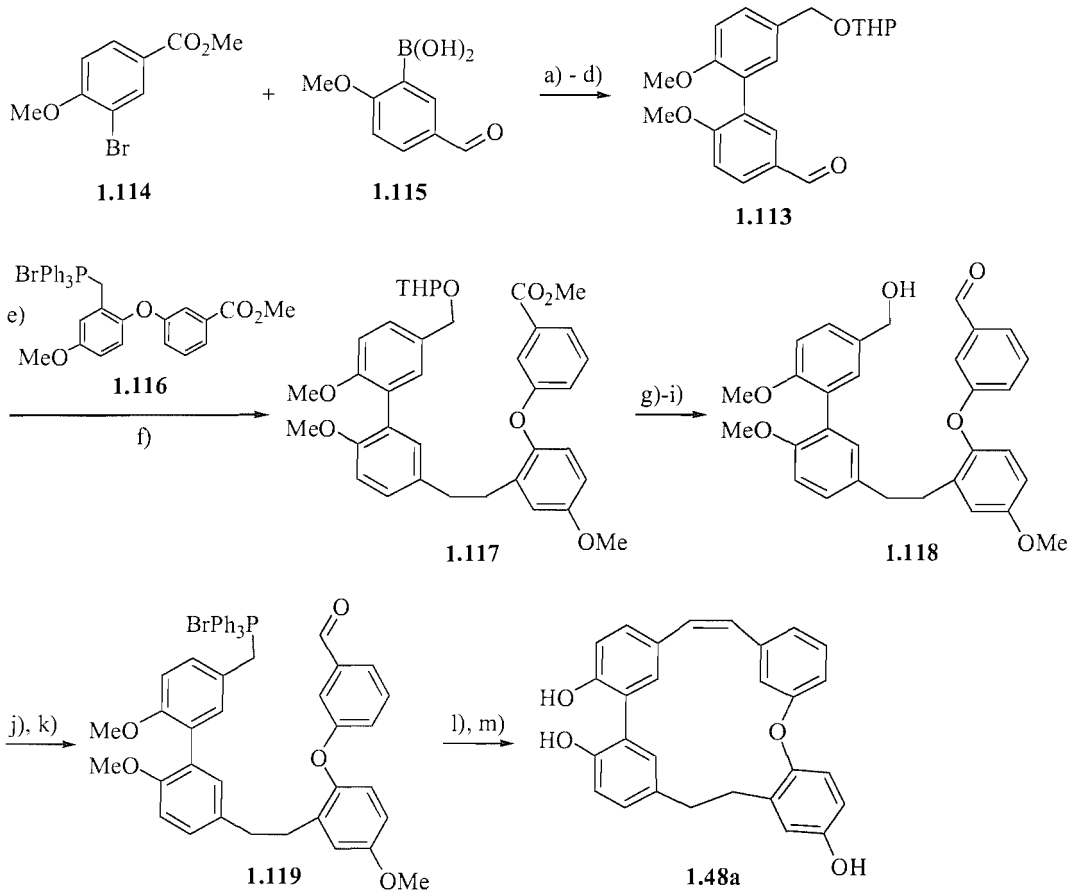
1.48e Isoplagiochin E R=H
1.48f Isoplagiochin F R=OH

1.48d Isoplagiochin D

Scheme 18

i) Nógrádi synthesis of isoplagiochin A

Nógrádi *et al.* have also addressed the synthesis of isoplagiochin A **1.48a**.[54] They began with the formation of biphenyl **1.113** by a Pd(0) catalysed Suzuki cross coupling reaction between methyl 3-bromo-4-methoxybenzoate **1.114** and 3-borono-4-methoxybenzaldehyde **1.115**. The aldehyde functionality was transiently masked whilst the ester group was converted to the protected benzyl alcohol **1.113** in two steps (Scheme 19).



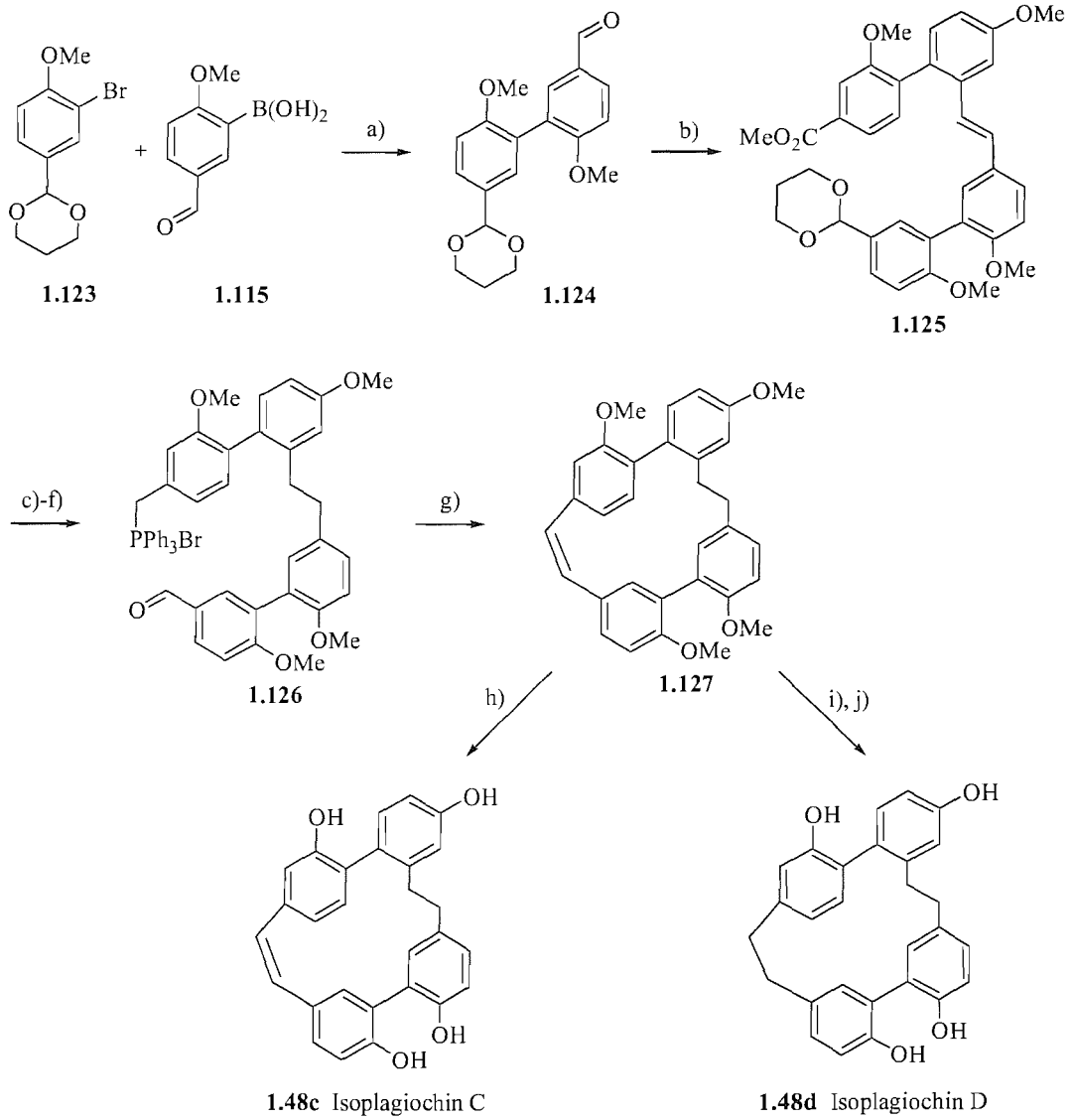
a) $Pd(PPh_3)_4$, $NaHCO_3$, 37 %; b) NH_4NO_3, $HC(OEt)_3$, 100 %; c) i) $LiAlH_4$; ii) H_2SO_4, 77 %; d) DHP, 100 %; e) NaOMe, MeOH, 37 %; f) H_2, Pd/C, EtOH, 89 %; g) $LiAlH_4$, 92 %; h) PCC, NaOAc, 51 %; i) Amberlite IR 120, 36 %; j) dibromotriphenylphosphorane; k) PPh_3, 94 %; l) KO^tBu, DMF, 32 %; m) BBr_3, 10 %.

Scheme 19

Aryl ether **1.116** was formed in 20 % yield using the Ullmann ether synthesis to unite 2-bromo-5-methoxybenzaldehyde **1.120** and methyl 3-hydroxybenzoate **1.121**. Conversion of the resulting aldehyde **1.122** to the phosphonium salt **1.116** was achieved in 3 steps. The Wittig reaction between **1.113** and **1.116** proceeded in low yield and many functional group manipulations were needed to access the Wittig salt **1.119**. Intramolecular cyclisation proceeded in modest yield (32 %) doubtless reflecting the high strain within the macrocycle. Isoplagiochin A **1.48a** was finally given on deprotection of the aryl methyl ethers with boron tribromide which proceeded in very low yield (10 %).

ii) Eicher synthesis of isoplagiochin C and D

Eicher employed a similar strategy in the synthesis of isoplagiochins C **1.48c** and D **1.48d** (Scheme 20).[40] Biaryl **1.124** was synthesised in high yield using the ubiquitous Suzuki reaction, and its Wittig reaction with biaryl **1.71** gave tetra aryl **1.125**.



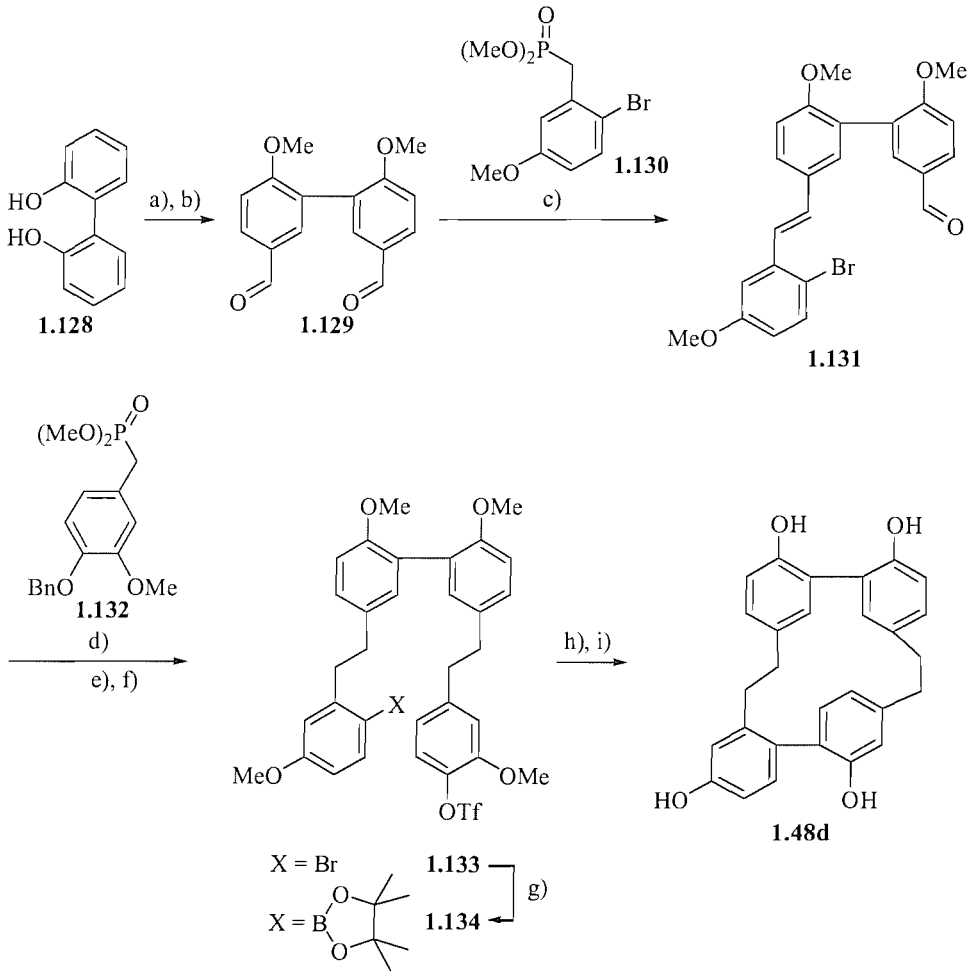
a) $Pd(PPh_3)_4$, EtOH, Na_2CO_3, 86 %; b) **1.71**, K_2CO_3, 88 %; c) H_2, Pd/C, 93 %; d) $LiAlH_4$, e) AcOH, 93 % (two steps); f) PBr_3, PPh_3, 60 %; g) NaOMe, 74 %; h) BBr_3, 86 %; i) H_2, Pd/C, 91 %; j) BBr_3, 82 %.

Scheme 20

Further reactions transformed this material into **1.126** facilitating the key intramolecular Wittig reaction to macrocycle **1.127**. From this common intermediate both isoplagiochins C **1.48c** and D **1.48d** could be accessed.

iii) Fukuyama synthesis of isoplagiochin D

The Fukuyama synthesis of isoplagiochin D **1.48d** is more linear (Scheme 21).[55] Beginning with biphenol **1.128**, protection and regioselective electrophilic substitution gave bisaldehyde **1.129** in good yield.



a) MeI, K_2CO_3; b) HMTA, TFA, 72 % over 2 steps; c) NaH, 73 %; d) NaH, 75 %; e) H_2, PtO_2; f) Tf_2O, 97 % over 2 steps; g) $PdCl_2(dppf)$, pinacolato borane, 76 %; h) $Pd(PPh_3)_4$, K_3PO_4, 41 %; i) BBr_3, 89 %.

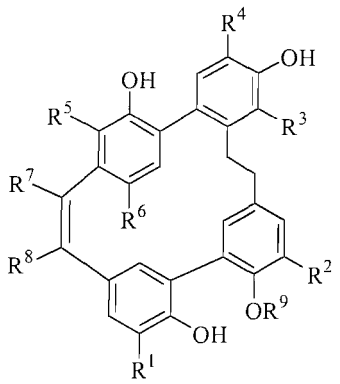
Scheme 21

Sequential Horner-Wadsworth-Emmons reactions and functional group interconversions then gave tetra-arene **1.133**, primed for an intramolecular Suzuki-Miyaura reaction. Careful treatment of bromide **1.133** with a palladium catalyst and pinacolato borane gave an intermediate boronate compound **1.134**, which underwent an intramolecular cross coupling reaction in the presence of catalytic palladium(0) and base. Deprotection of the aryl methyl ethers then gave isoplagiochin D **1.48d** in 9 steps from **1.128** in 10.6 % overall yield.

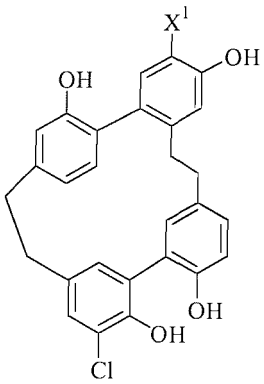
This synthesis makes good use of the benzyl protecting group, allowing the selective unmasking of one phenol upon hydrogenation. Conversion of this to the corresponding triflate **1.133** facilitated the key cyclisation strategy. Hydrogenation conditions were carefully chosen to prevent reduction of the aryl-bromine bond. The macrocyclisation proceeded in good yield.

e) Bazzanins

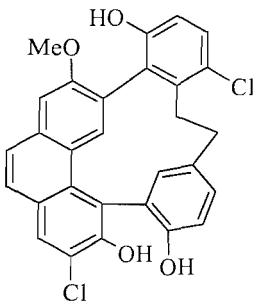
The series also contains a limited number of halogen containing compounds. These were found in bryophytes and were given the trivial name bazzanins after the liverwort they were isolated from, *Bazzania*.[50,53,56,57] These liverworts are mainly distributed in the tropics and sub-tropics, though there are four known European species that grow in dense, widespread pads on forest ground, boggy soil and tree trunks. Results have shown that the bazzanins are genuine natural products and not artefacts of any external factors outside the liverwort.[58] With the exception of bazzanin K **1.49k**, all are based on the isoplagiochin ring system **1.47c** and **1.47d** differing only in the number and position of chlorine substituents (Figure 12). Eight chlorines are found in bazzanin R **1.49r** while only one is present in bazzanin A **1.49a**. Bazzanins J **1.49j** and S **1.49s** are saturated variants, while bazzanin K **1.49k** has an additional bond linking two of the arenes. The bazzanin series also exhibits optical activity, however they are not isolated enantiopure from nature.[51] Bazzanins B **1.49b** and S **1.49s** have been found to exhibit antifungal activity.[53]



1.49a-i Bazzanin A-I
1.49l-r Bazzanin L-R



1.49j X^1 = Cl Bazzanin J
1.49s X^1 = H Bazzanin S



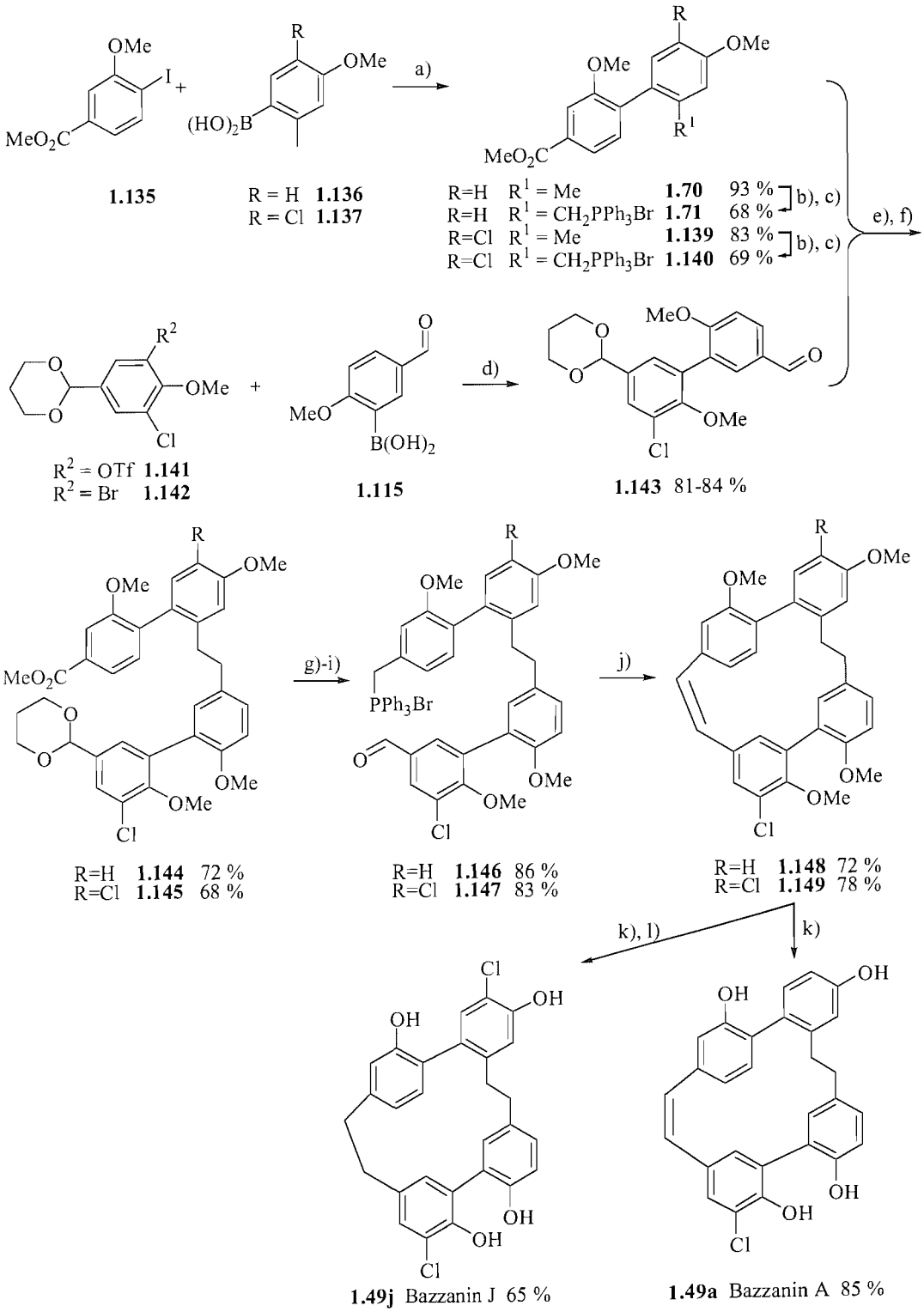
1.49k Bazzanin K

		R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9
1.49a	bazzanin A	Cl	H	H	H	H	H	H	H	H
1.49b	bazzanin B	Cl	H	H	H	H	H	Cl	H	H
1.49c	bazzanin C	Cl	H	H	Cl	H	H	Cl	H	H
1.49d	bazzanin D	Cl	H	H	H	Cl	H	Cl	H	H
1.49e	bazzanin E	Cl	H	H	Cl	Cl	H	Cl	H	H
1.49f	bazzanin F	Cl	H	Cl	H	H	Cl	Cl	H	H
1.49g	bazzanin G	Cl	Cl	Cl	H	Cl	H	Cl	H	H
1.49h	bazzanin H	Cl	H	Cl	H	Cl	Cl	Cl	H	H
1.49i	bazzanin I	Cl	Cl	H	Cl	Cl	Cl	Cl	H	H
1.49l	bazzanin L	H	H	Cl	Cl	Cl	H	H	H	Me
1.49m	bazzanin M	H	H	Cl	Cl	Cl	H	H	H	H
1.49n	bazzanin N	H	Cl	Cl	Cl	Cl	H	H	H	H
1.49o	bazzanin O	Cl	H	Cl	Cl	Cl	Cl	H	H	Me
1.49p	bazzanin P	Cl	Cl	Cl	Cl	Cl	H	H	H	H
1.49q	bazzanin Q	Cl	Cl	Cl	Cl	Cl	Cl	H	H	H
1.49r	bazzanin R	Cl	Cl	Cl	Cl	Cl	Cl	Cl	Cl	H

Figure 12

i) Speicher synthesis of bazzanin A and J

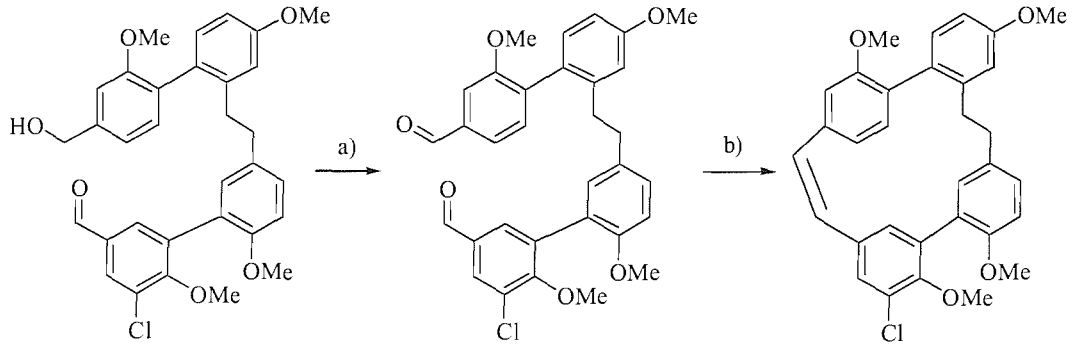
Speicher *et al.* have reported the synthesis of bazzanins A **1.49a** and J **1.49j** by a common strategy (Scheme 22).[59] The synthesis of bazzanin J **1.49j** began with boronic acid **1.137** which was derived from commercially available 2-chloro-5-methylphenol **1.138** in 3 steps in 44 % yield. Suzuki coupling between **1.137** and aryl iodide **1.135** gave the chlorinated biaryl **1.139** in good yield. Radical bromination and treatment with triphenylphosphine gave Wittig salt **1.140** in good yield.



a) $Pd(PPh_3)_4$, K_3PO_4; b) NBS, AIBN; c) PPh_3; d) $Pd(PPh_3)_4$, K_3PO_4; e) K_2CO_3, 18-c-6; f) H_2, Pd/C; g) $LiAlH_4$; h) HOAc; i) Ph_3P-HBr; j) NaOMe; k) BBr_3; l) H_2, Pd/C, 88 %.

Scheme 22

Formation of the second biaryl fragment **1.143**, common to both bazzanin A **1.49a** and J **1.49j**, was achieved through coupling of either aryl bromide **1.142** or aryl triflate **1.141** (prepared from isovanillin **1.63** in four and five steps respectively in yields of 28 % and 48 %) with boronic acid **1.117**. The resulting biaryl **1.143** was then conjoined with **1.71** and **1.140** by Wittig reaction to yield tetra aryls **1.144** and **1.145** respectively. Standard functional group manipulations were then used to advance these to **1.146** and **1.147**, which underwent a Wittig macrocyclisation to the respective *cis* 16-membered carbocycles **1.148** and **1.149**. Stereoselective *cis* cyclisation could also be achieved in good yield using a McMurry macrocyclisation of the bis-aldehyde derivative **1.151**, to yield bazzanin A tetramethyl ether **1.148** (Scheme 23).



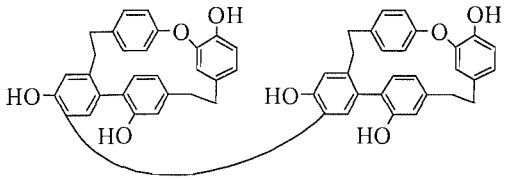
1.150 **1.151** **1.148**

a) PCC, 85 %; b) $TiCl_3(DME)_2$, Zn-Cu, 70 %.

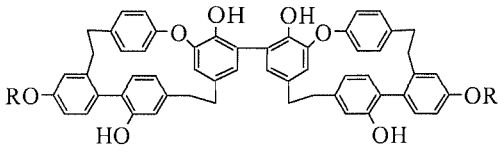
Scheme 23

f) Pusilatins

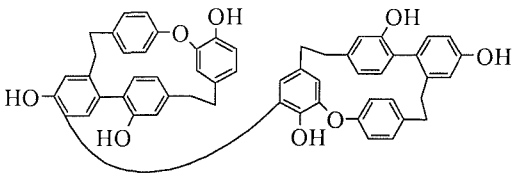
Isolated from the liverwort *Blasia pusilla* in 1992, pusilatin A **1.152a** to E **1.152e** are the first examples of macrocyclic bis(bibenzyl) dimers to be found in Nature (Figure 13).[48,60] The structure of pusilatin A **1.152a** has been confirmed by 2D NMR and X-ray analysis of the hexaacetate derivatives. They are dimers of riccardin C **1.46c**, with variation in the C-C or C-O linkage (Figure 13). Pusilatins B **1.152b** and C **1.152c** have been shown to exhibit selective DNA polymerase β inhibitory activity and moderate cytotoxicity.[35]



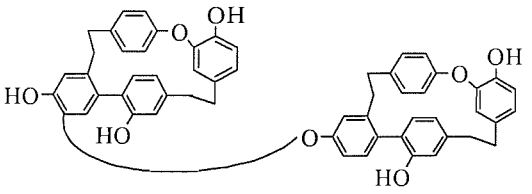
1.152a Pusilatin A



1.152b Pusilatin B R=H
1.152e Pusilatin E R=Me



1.152c Pusilatin C

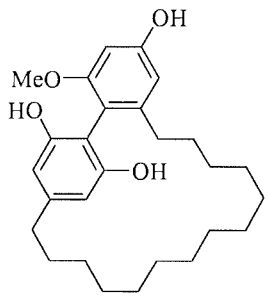


1.152d Pusilatin D

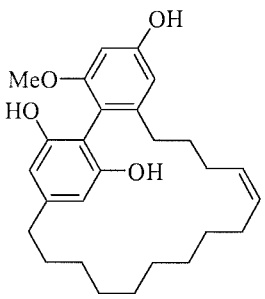
Figure 13

g) Turrianes

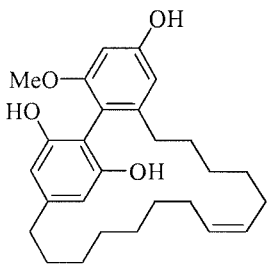
The turrianes **1.153** are a group of macrocyclic biaryls isolated from the stem wood of the Australian tree *Grevillea striata* R. Br.[61,62] Currently there are no reports on the biological activity of the turrianes **1.153**, however related 5-alkylresorcinol derivatives **1.154** have been found to exhibit inhibitory effects on a number of enzymes and cytotoxicity against various tumour cell lines.[63] Longer chain alkyl resorcinol derivatives have also been shown to cleave DNA under oxidative conditions. The length of the alkyl tether appears to correlate to the biological response, giving impetus for the synthesis of these macrocycles.



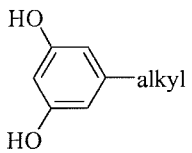
1.153a



1.153b



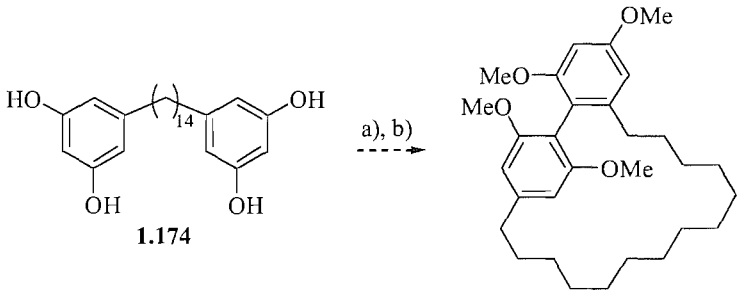
1.153c



1.154

Figure 14

In an unsuccessful attempt to isolate the phenolic components of an extract from *Grevillea striata* R. Br., Ridley *et al.* based their structural assignments on decomposition studies and chemical reactions.[61] Utilising the presumed biosynthetic precursor striatol **1.174**, Ridley attempted cyclisation under oxidative conditions (Scheme 24). However, the results from this were inconclusive.



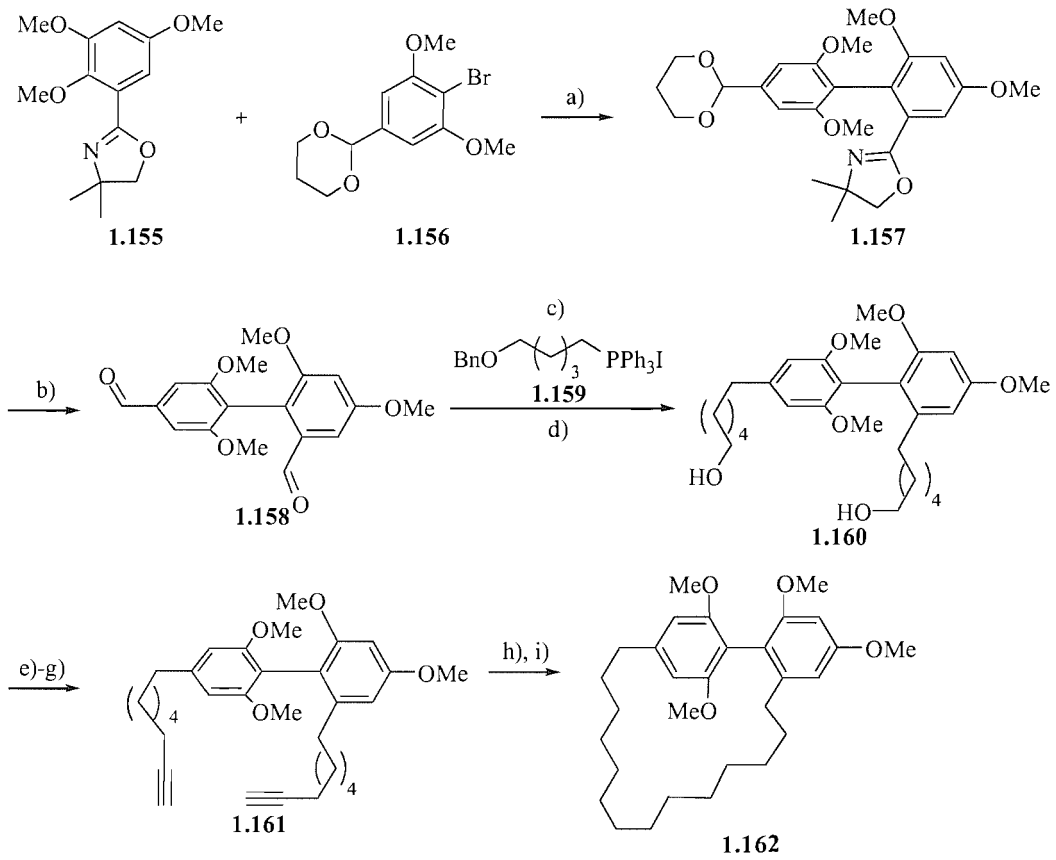
1.174 **1.153a**

a) acetylacetonatomanganese(III); b) Me_2SO_4, K_2CO_3.

Scheme 24

i) Sargent synthesis of tetramethoxyturriane

Mindful of the problems encountered by Ridley *et al.*, Sargent first constructed the biaryl bond by addition of the Grignard reagent derived from **1.156** and dihydro-oxazole **1.155** (formed by a sequence of Lossen rearrangement and Sandmeyer reaction).[64,65] A tandem Wittig reaction of bis-aldehyde **1.158** with two equivalents of **1.159** followed by catalytic hydrogenation gave **1.160** (Scheme 25). Oxidation of **1.160** was followed by a dual Corey-Fuchs reaction with tetrabromomethane to form a bis(dibromovinyl) species which was treated with BuLi to install the acetylene groups of **1.161**. Macrocyclisation was effected by oxidative Glaser coupling of the diyne moieties of **1.161** using copper(II). Hydrogenation then secured tetramethoxyturraine **1.162** in 16 % overall yield.

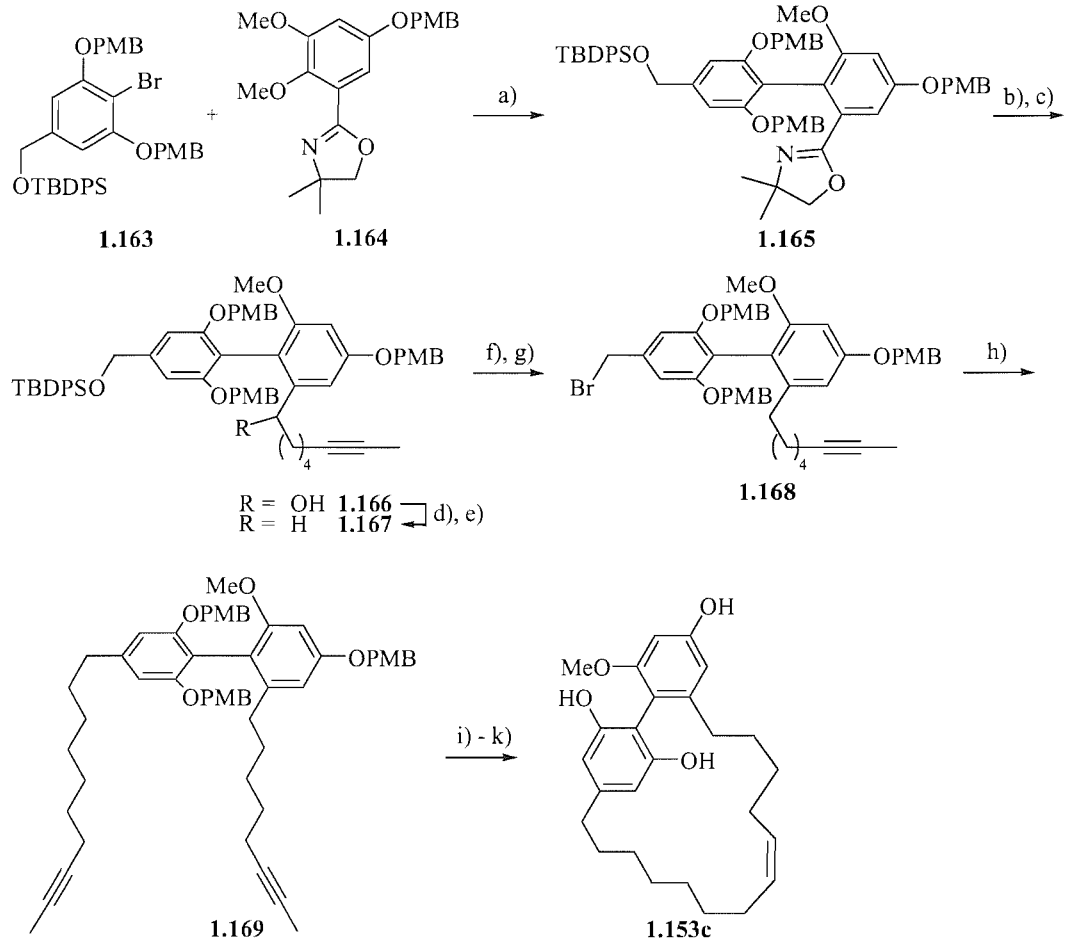


a) Mg, 84 %; b) i) MeI, $MeNO_2$; ii) $NaBH_4$; iii) HCl, 85 %; c) BuLi; d) Pd/C, H_2, 54 %; e) PCC, 93 %; f) PPh_3, CBr_4; g) BuLi, 58 %; h) $Cu(OAc)_2$, 78 %; i) Pd/C, H_2, 96 %.

Scheme 25

ii) Fürstner synthesis of turrianes

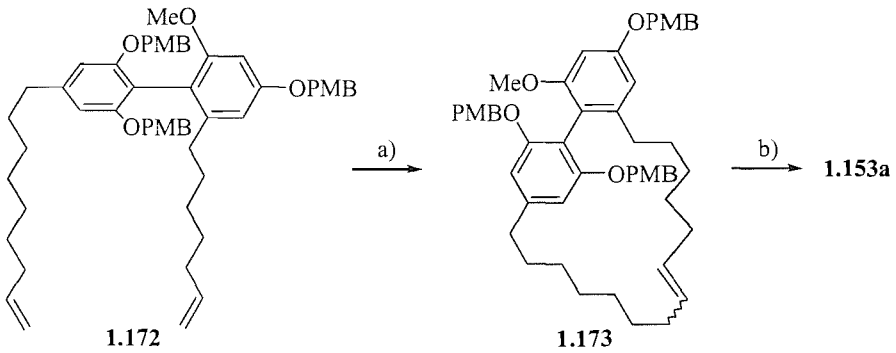
In addition to the saturated turrianes **1.153a**, Fürstner *et al.* also targeted the alkene derivatives **1.153b** and **1.153c**.[62] Once again, the initial biaryl **1.165** was formed using Meyers oxazoline chemistry between oxazoline **1.164** and the aryl Grignard derived from bromide **1.163** (Scheme 26). Conversion of the oxazoline **1.165** to the benzaldehyde followed by treatment with alkyne Grignard **1.170** installed the first alkyl chain. A similar procedure was used for installation of the second alkyl chain (*viz.* **1.168** → **1.169**) using Grignard reagent **1.171**. Macrocyclisation of **1.169** was performed using RCAM (ring closing alkyne metathesis) followed by hydrogenation using Lindlar's catalyst to selectively give *cis* product **1.153c** after PMB deprotection.



a) Mg, 84 %; b) i) F_3CSO_3Me; ii) $NaBH_4$; iii) oxalic acid, 70 %; c) 5-heptynylmagnesium bromide **1.170**, 66 %; d) PhOC(S)Cl, 90 %; e) Bu_3SnH, AIBN, 76 %; f) $Bu_4NF.3H_20$, 96 %; g) i) $(MeSO_2)_2O$; ii) LiBr, 81 %; h) 7-nonynylmagnesium bromide **1.171**, 73 %; i) $[Mo(CO)_6]$, F_3CPhOH, 76 %; j) Lindlar catalyst, H_2, 97 %; k) $BF_3.Et_2O$, 54 %.

Scheme 26

In parallel studies, a RCM reaction of diene **1.172** gave a mixture of *E*/*Z* isomers **1.173**. The approach was only suitable for the synthesis of the saturated turriane **1.153a** which was readily accomplished by hydrogenation of the alkene **1.173** (Scheme 27).



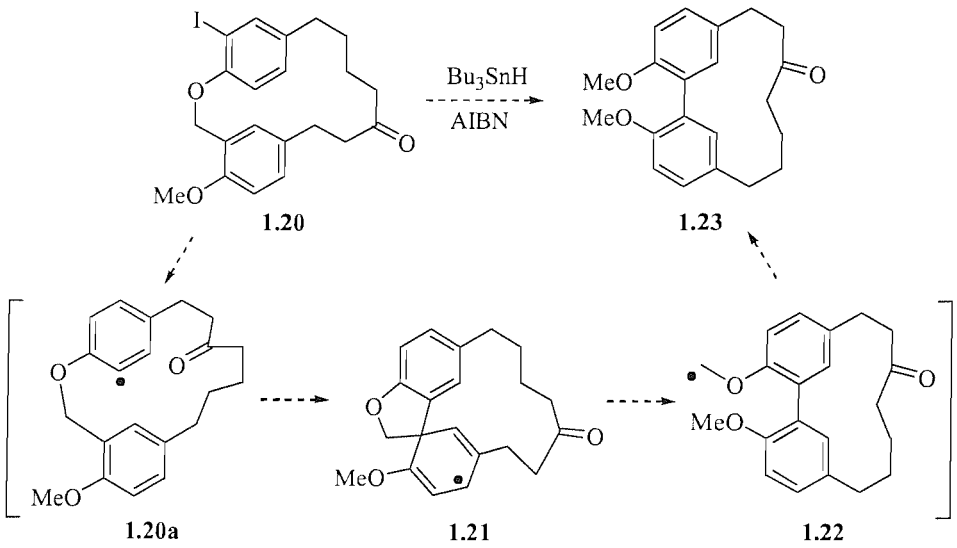
a) $[Mo(CO)_6]$,F_3CPhOH, 77 %, *ca* 1:1 *E*/*Z*; b) Pd/C, H_2, 87 %.

Scheme 27

CHAPTER II – Acerogenin E

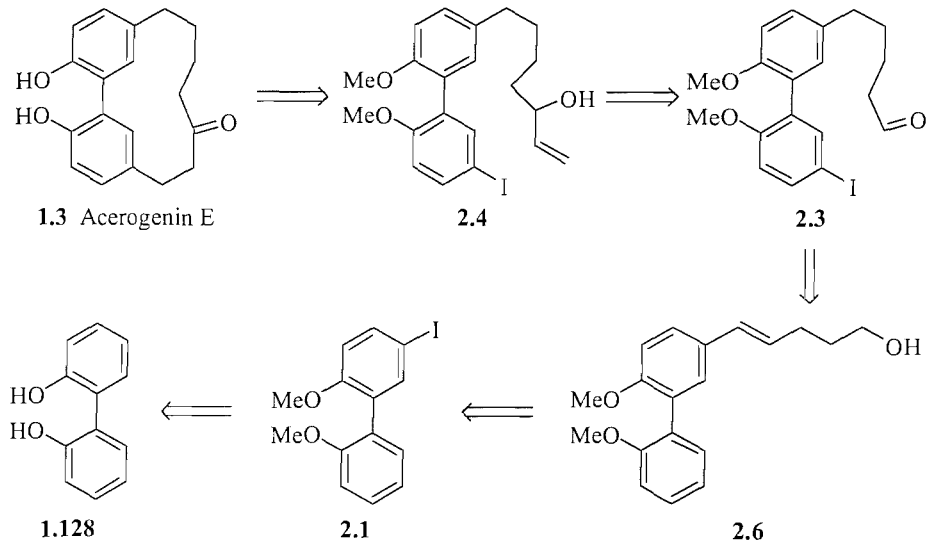
II.1 Retrosynthesis

The synthetic challenge presented by the biarylheptanoids lies in the formation of a highly strained 13-membered macrocycle containing a *meta*-substituted biaryl unit. Previous work in our group had sought to address the synthesis using a radical induced ring contraction strategy (*viz* **1.20** → **1.23**, Scheme 28). However, while the synthesis of the precursor iodide **1.20** was readily achieved, all attempts at the key step were met with failure.[23]



Scheme 28

The new route envisioned was to use an intramolecular Heck reaction to effect the critical macrocyclisation step (Scheme 29). First, a palladium mediated cross-coupling of aryl iodide **2.1** and 4-penten-ol **2.2** would be used to install a 5-carbon chain. Hydrogenation of the alkene in **2.6** followed by iodination and oxidation of the alcohol to aldehyde **2.3** would then facilitate introduction of the final two carbons by means of a Grignard reaction. Treatment of **2.4** with a palladium(0) catalyst, using Heck type conditions, ought then to facilitate cyclisation to dimethoxy-acerogenin E **2.5**, which could be deprotected to yield acerogenin E **1.3**.



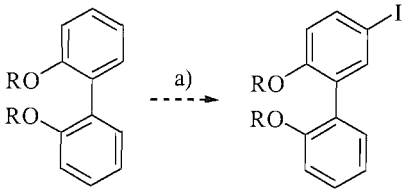
1.3 Acerogenin E **2.4** **2.3** **2.6** **1.128** **2.1**

Scheme 29

II.2 Towards acerogenin E

a) To allylic alcohol 2.4

Our approach to acerogenin E **1.3** began with biphenol **1.128** and immediately hit upon a complication when attempts to effect its monoiodination to **2.7** led only to complex product mixtures (Scheme 30). Similar results were attained with the corresponding dimethyl ether **2.8**, prompting us to explore a different avenue (Scheme 31).



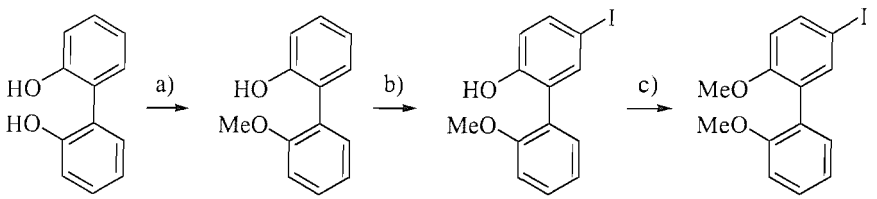
R=H **1.128**
R=Me **2.8**

R=H **2.7**
R=Me **2.1**

a) iodination

Scheme 30

To that end, desymmetrisation of biphenol **1.128** by monomethylation was readily accomplished using methyl iodide and potassium carbonate to provide biaryl **2.9** in 95% yield. Selective iodination of the phenol could then be accomplished using sodium iodide and sodium hypochlorite in basified methanol. Protection as its methyl ether then proceeded in excellent yield to give aryl iodide **2.1** (Scheme 31).[66]



2.7 **2.9** **2.10** **2.1**

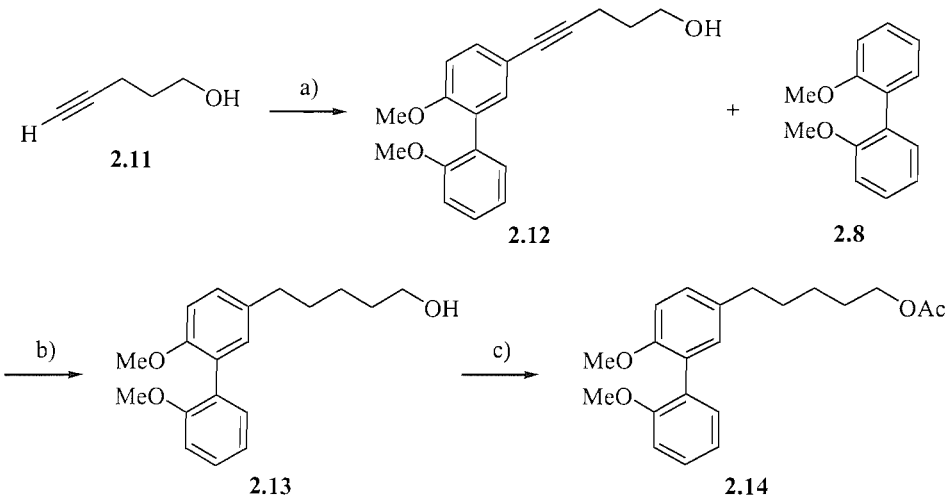
a) MeI, K_2CO_3, acetone, RT, 24 h, 95 %; b) NaOH, NaI, NaOCl, MeOH, 0 °C, 77 %; c) MeI, NaH, THF, 0 °C - RT, 20 h, 97 %.

Scheme 31

i) Sonogashira Coupling

Several options were now available to install the alkyl side chain. A Sonogashira reaction between biaryl **2.1** and 4-pentynol **2.11** gave the desired alkyne **2.12** though the low

yield limited the method's appeal (Scheme 32). Reduction of biphenyl **2.1** to **2.8** was noted as the main side reaction and our attempts to eliminate this pathway proved intractable.[67,68] This was clearly disappointing given that alkyne **2.12** could be readily hydrogenated to **2.13** using Pd/C and its alcohol protected as an acetate **2.14** using acetic anhydride.

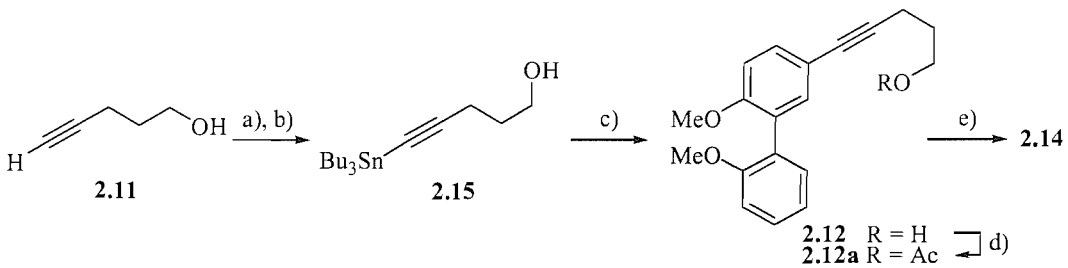


a) $PdCl_2$, PPh_3, CuI, DMF, Et_3N, Δ, 15 h, 27 % of **2.12**, 27 % of **2.8**; b) Pd/C, H_2, EtOAc, RT, 2 h, 90 %; c) Ac_2O, py, DMAP, CH_2Cl_2, RT, 10 min, 88 %.

Scheme 32

ii) Stille Coupling

The palladium mediated cross-coupling between iodide **2.1** and stannane **2.15** proved to be more efficient giving **2.12** in 39 - 60 % yield. The product could then be protected as the acetate **2.12a** and reduced to **2.14**. Best results were obtained when using the $Pd_2(dba)_3$ - $AsPh_3$ catalyst-ligand system (Scheme 33).[69]

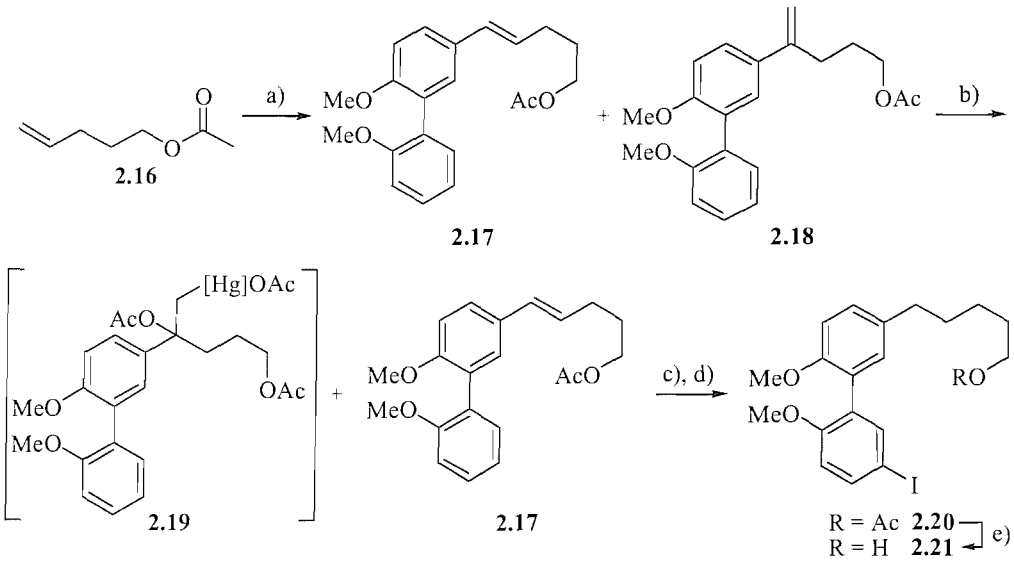


a) 2 eq. ^{n}BuLi, -78 °C, 40 min; b) i) $^n Bu_3SnCl$, -78 °C, 2 h; ii) H_2O, 47 %; c) **2.1**, $Pd_2(dba)_3$, NMP, $AsPh_3$, RT, 65 h, 59 %; d) Ac_2O, py, DMAP, CH_2Cl_2, RT, 10 min, 90 %; e) H_2, Pd/C, EtOAc, RT, 2 h, 90 %.

Scheme 33

iii) Heck Coupling

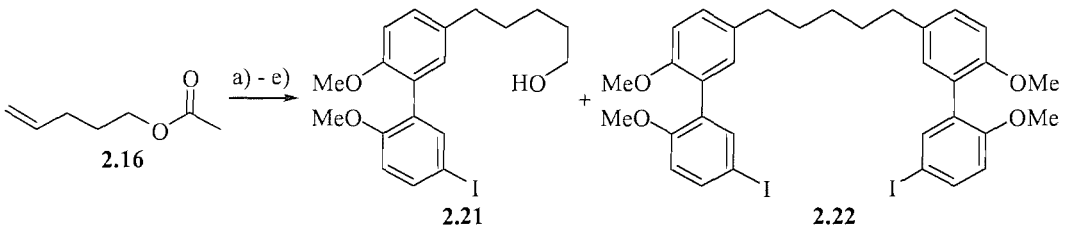
A Heck reaction between 4-pentenol **2.2** and iodide **2.1** was examined next and found to give a complex mixture of products. However, the corresponding Heck coupling between acetate **2.16** and iodide **2.1** provided a 4:1 mixture of the regioisomeric alkenes **2.17** and **2.18** in good yield (67 %) (Scheme 34). The ratio of external to internal alkenes **2.18**:**2.17** was worse than anticipated and their separation could not be achieved by column chromatography. Indeed it was necessary to react the mixture with mercuric(II) trifluoroacetate (1.1 equivalents with respect to the external alkene **2.18**) to remove all the unwanted isomer **2.18** - subsequent chromatographic purification giving **2.17** as a single product.



a) **2.1**, $Pd(OAc)_2$, DMF, H_2O, K_2CO_3, Bu_4NBr, 85 °C, 67 %, 4:1 **2.17**:**2.18** respectively; b) $Hg(CF_3CO_2)_2$, THF, RT, 0.5 h, 80 %; c) H_2, Pd/C, EtOAc, 97 %; d) $BTEA.ICl_2$, $ZnCl_2$, AcOH, RT, 99 %; e) NaOMe, MeOH, RT, 0.5 h, 98 %.

Scheme 34

Interestingly, our attempts to optimise the Heck reaction for **2.17** uncovered an unusual side reaction. When the base was changed from potassium carbonate to triethylamine the product mixture comprised acetates **2.17** and **2.18** and a further unknown product of similar polarity. Sequential treatment with mercuric(II) trifluoroacetate, hydrogenation, iodination and saponification provided alcohol **2.21** and dimer **2.22**, implyng **2.23b** as a by-product in the original Heck reaction (Scheme 35).

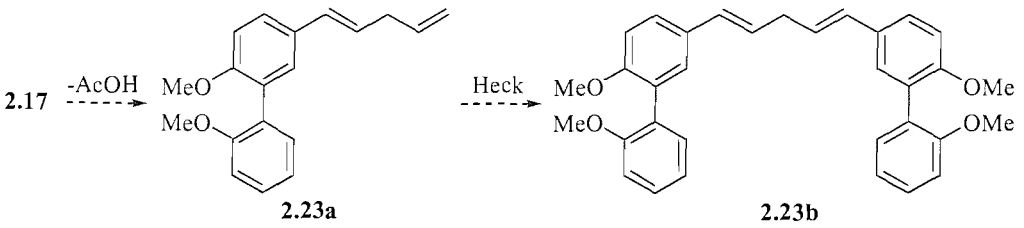


2.16 **2.21** **2.22**

a) **2.1**, $Pd(OAc)_2$, DMF, H_2O, NEt_3, Bu_4NBr, 80 °C, (53 % **2.17**); b) $Hg(CF_3CO_2)_2$, THF, RT, 0.5 h; c) H_2, Pd/C, EtOAc; d) $BTEA.ICl_2$, $ZnCl_2$, AcOH, RT; e) NaOMe, MeOH, RT, 0.5 h, overall 16 % **2.21**, 3 % **2.22**.

Scheme 35

Indeed, under the reaction conditions it is plausible that acetic acid is eliminated from **2.17** to yield a terminal alkene **2.23a**. This reacts with further starting material **2.1** furnishing diene **2.23b** (Scheme 36).



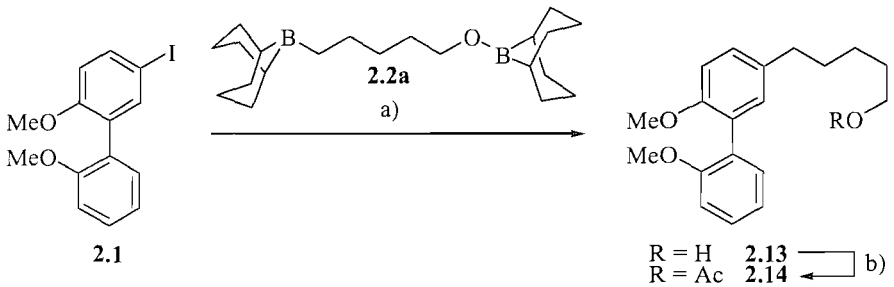
2.23a **2.23b**

Scheme 36

iv) Suzuki Coupling

These frustrations prompted us to explore the use of a *B*-alkyl Suzuki reaction. We felt that this would be more desirable as it removed the need to use toxic tin and mercury reagents, shortened the synthetic sequence and would allow us to control the regiochemical course of the reaction. To that end, biaryl **2.1** was coupled with the organoborane derived

from *in situ* treatment of 4-pentenol **2.2** with 2 equivalents of 9-BBN. Using $Pd(PPh_3)_4$ and K_2CO_3 in DMF at 50 °C, alcohol **2.13** was furnished in 66 % yield (Scheme 37).[70,71]

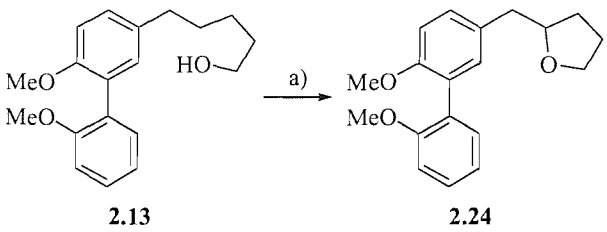


a) i) 9-BBN, THF, RT, 6 h; ii) $Pd(PPh_3)_4$, K_2CO_3, DMF, 50 °C, 2.5 h, 66 %; b) Ac_2O, py, DMAP, CH_2Cl_2, RT, 0.5 h, 88 %.

Scheme 37

Similarly, reaction of pent-4-enyl acetate **2.16** with 9-BBN, followed by Suzuki coupling with **2.1** also gave the desired product **2.14** but in moderate yield. In this case however, isolation of **2.14** from the 9-BBN derived by-products could not be achieved to a satisfactory standard for further manipulations.

The direct iodination of alcohol **2.13** proved troublesome. Many literature methods were examined but to no avail. One side reaction worthy of note was the formation of tetrahydrofuran **2.24** when **2.13** was heated in acetonitrile with *N*-iodosuccinimide (Scheme 38). This indicated a need to protect the alcohol function.

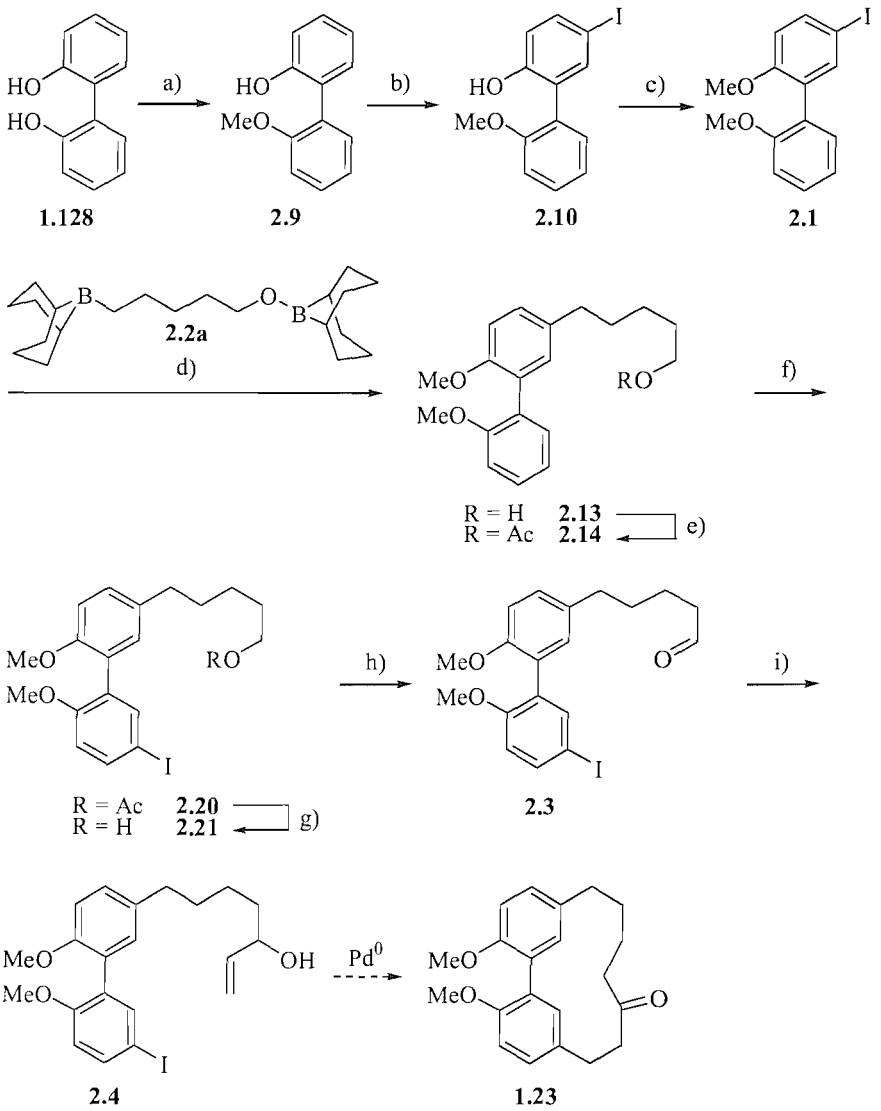


a) NIS, MeCN, Δ, 15 h, 10 %.

Scheme 38

Pleasingly, iodination of the protected alcohol **2.14** with $BTEA.ICl_2$ proceeded smoothly and in near quantitative yield to give acetate **2.20**.[72] Saponification of the acetate **2.20** and Dess-Martin periodinane oxidation of the resulting alcohol **2.21** then gave

aldehyde **2.3**, which was transformed into allylic alcohol **2.4** on exposure to vinylmagnesium chloride (Scheme 39).



a) MeI, K_2CO_3, acetone, RT, 24 h, 95 %; b) NaOH, NaI, NaOCl, MeOH, 0 °C, 77 %; c) MeI, NaH, THF, 0 °C - RT, 20 h, 97 %; d) i) 9-BBN, THF, RT, 6 h; ii) $Pd(PPh_3)_4$, K_2CO_3, DMF, 50 °C, 2.5 h, 66 %; e) Ac_2O, py, DMAP, CH_2Cl_2, RT, 0.5 h, 88 %; f) $BTEA.ICl_2$, AcOH, $ZnCl_2$, RT, 99 %; g) NaOMe, MeOH, RT, 1.5 h, 98 %; h) DMP, CH_2Cl_2, 0 °C, 0.5 h, 98 %; i) VinylMgCl, THF, 0 °C, 0.5 h, 89 %.

Scheme 39

b) Macrocyclisation

The key Heck macrocyclisation step (Scheme 39) was initially attempted with allylic alcohol **2.4** using the conditions detailed in Table 1. Each experiment led to a myriad of polar products and/or recovered starting material **2.4**.

Table 1. Macrocyclisation conditions with allylic alcohol 2.4.

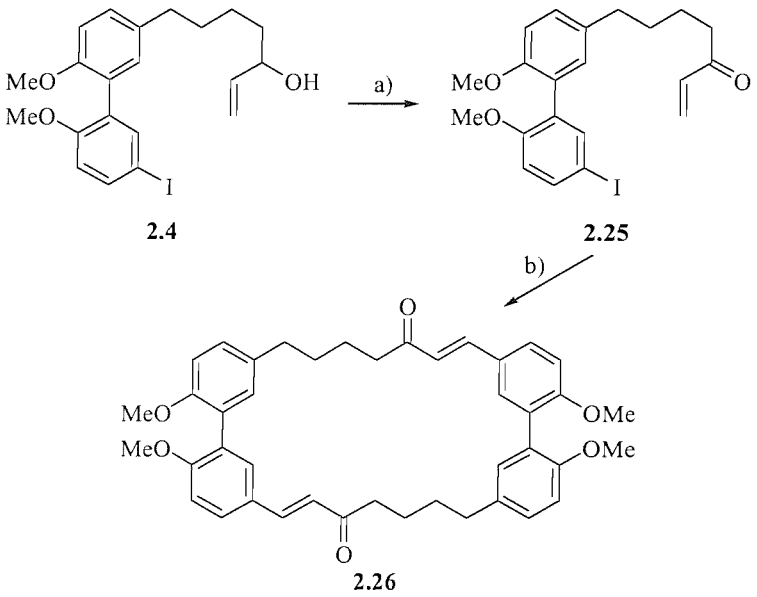
Entry	Catalyst	mol %	Solvent	Base	PTC	Temp °C	[mM]
1	$Pd(OAc)_2$	20	wet DMF	$NaHCO_3$	✓	90	1
2	$Pd(PPh_3)_4$	10	MeCN	K_2CO_3	×	Δ	40
3	$Pd(OAc)_2$	10	THF	Ag_2CO_3	×	Δ	17 [a]
4	$Pd(PPh_3)_4$	10	MeCN	K_2CO_3	×	Δ	17
5	$Pd(PPh_3)_4$	18	MeCN	K_2CO_3	×	Δ	11
6	$Pd(PPh_3)_4$	10	MeCN	Et_3N	×	Δ	37
7	$Pd(OAc)_2$	15	DMF	Et_3N	×	80	9 [b]
8	$Pd_2(dba)_3$	6	wet DMF	Et_3N	✓	80	22
9	$Pd(PPh_3)_4$	100	wet DMF	Et_3N	×	80	13.5
10	$Pd(OAc)_2$	100	wet DMF	$NaHCO_3$	✓	80	13.5
11	$Pd(dppf)_2Cl_2$	10	wet DMF	K_2CO_3	✓	80	13.5
12	$Pd(PhCN)_2Cl_2$	10	MeCN	Et_3N	×	Δ	13.5
13	$Pd_2(dba)_3$	10	MeCN	$NaHCO_3$	✓	Δ	13.5
14	$Pd(dppf)_2Cl_2$	10	wet DMF	K_2CO_3	✓	110	3

[a] PPh_3 ligand added. [b] n-Bu_3P ligand added. PTC indicates that TBAB was included in the reaction mixture.

With the exception of entries 3 and 14, crude ^1H NMR analysis indicated the formation of products from the Heck reaction, though none of these were the anticipated cyclised product. In the case of entries 3 and 14, only recovered starting material was isolated. High dilution conditions (entries 1, 7 and 14) were examined in the hope of minimising competitive intermolecular reactions, yet these too provided only polymeric material. In the same vein, use of a stoichiometric amount of catalyst (Entries 9 & 10) failed to promote the desired outcome.

In the hope of promoting macrocyclisation, alcohol **2.4** was oxidised to the corresponding enone **2.25** with the Dess-Martin periodinane reagent (treatment with barium

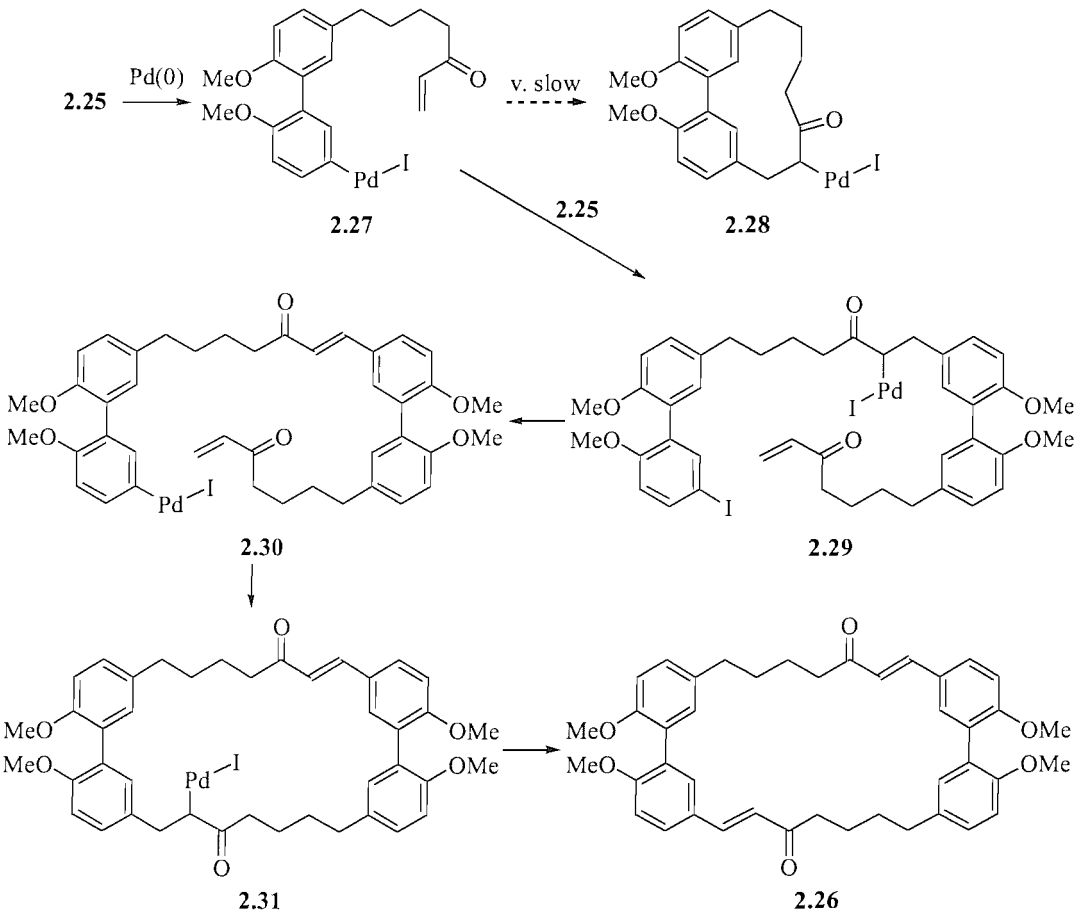
manganate had proven ineffectual). The alkene in an enone is electron deficient compared to its allylic alcohol counterpart, and is consequently more susceptible to Heck coupling. Indeed, when **2.25** was treated under standard Heck conditions, using high dilution and tetrabutylammonium bromide as an accelerant, the *trans,trans* dimer **2.26** was given in good yield (54 %) rather than the anticipated acerogenin E precursor (Scheme 40).



a) DMP, CH_2Cl_2, 0 °C, 0.5 h, 88 %; b) $Pd(OAc)_2$, K_2CO_3, DMF, Bu_4NBr, 100 °C, 23 h, 54 %.

Scheme 40

The result proved that the intermolecular addition of the first formed organopalladium intermediate **2.27** outpaced macrocyclisation to **2.28** (Scheme 41) indicating that strain in the macrocycle becomes an important factor in determining the reaction outcome. Once dimerisation has occurred, strain presents no longer a significant barrier to macrocyclisation so the intramolecular Heck reaction becomes the more favourable process. The resulting 26-membered carbocycle **2.31** finally undergoes dehydropalladation to give **2.26**.[17]

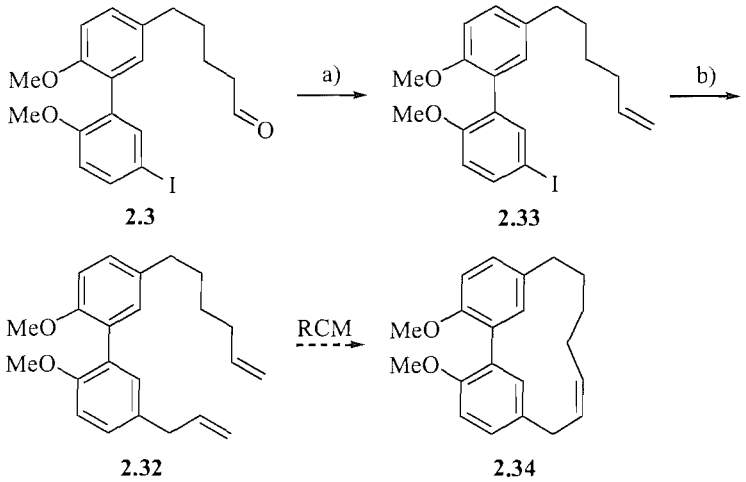


Scheme 41

c) RCM Strategy

At this juncture it seemed appropriate to explore an alternative route to acerogenin E **1.3** based on a ring closing metathesis strategy. To that end, diene **2.32** was prepared from

aldehyde **2.3** by sequential methylenation and alkylation (Scheme 42). Exposure of this diene **2.32** to Grubbs' 2nd generation catalyst gave a multitude of products, none of which could be isolated in sufficient quantity and purity to allow proper characterisation. Those data attained suggested the formation of much polymeric material.

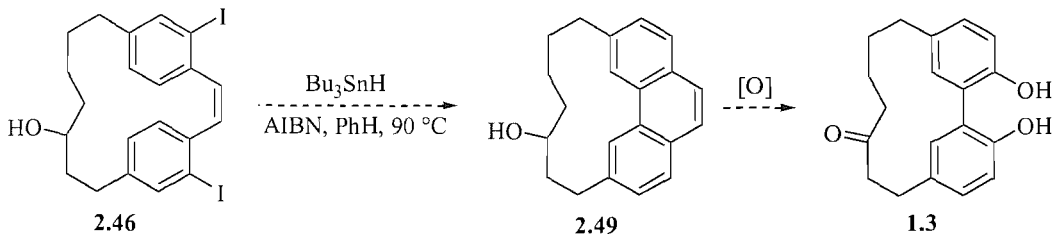


a) H_3CPPh_3Br, KO^{t}Bu, THF, 24 %; b) i) *n*-BuLi, THF, - 78 °C; ii) CuCN, 40 min; iii) allyl bromide, 19 h, - 78 °C - RT, 94 %.

Scheme 42

d) Towards a Radical Ring Contraction

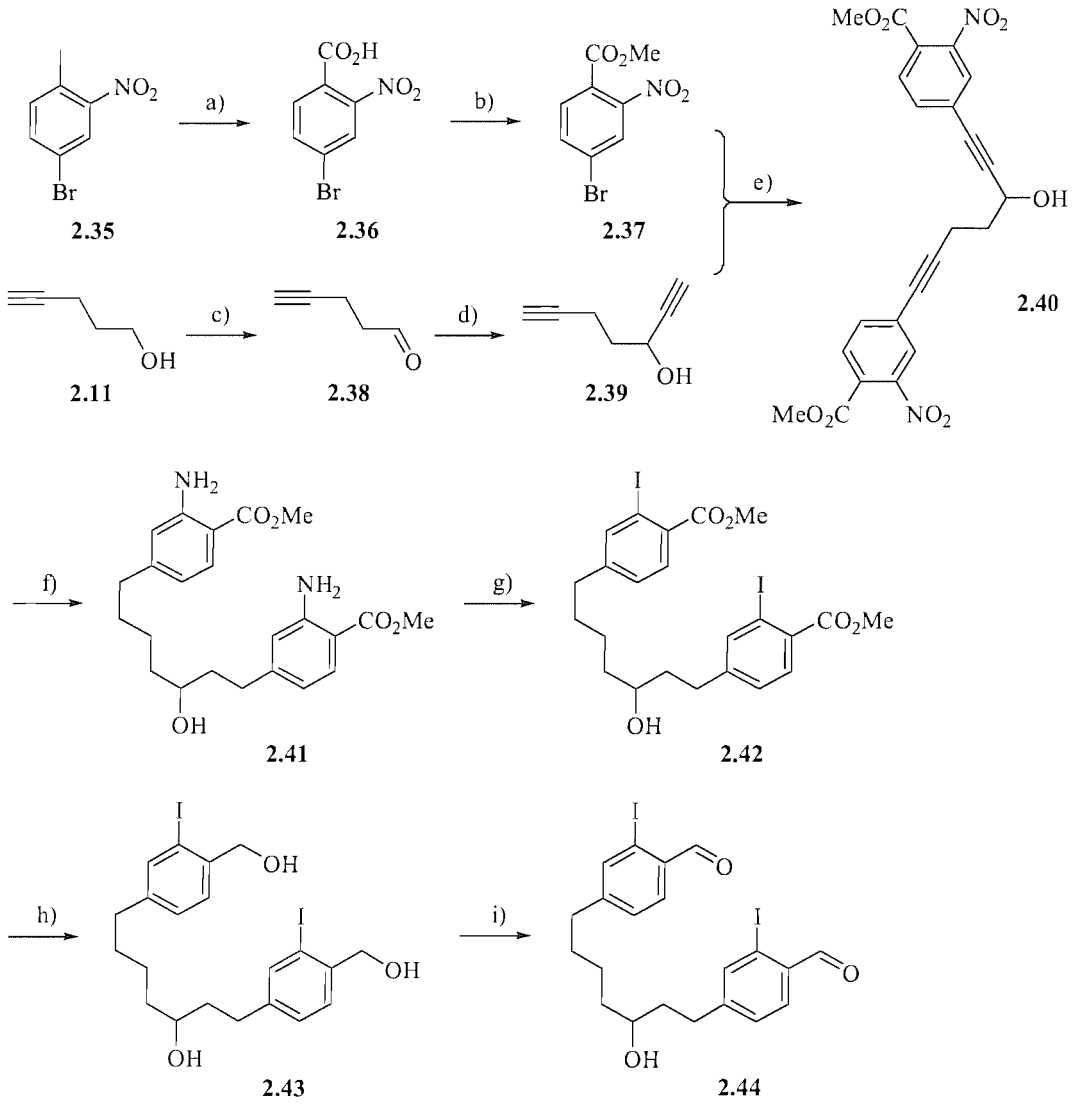
At this stage, it seemed appropriate to revisit a radical ring contraction strategy towards acerogenin E **1.3**, this time utilising a macrocyclic stilbene derivative **2.46**. It was thought that this type of precursor would be appropriately orientated for biaryl bond formation (Scheme 43).



Scheme 43

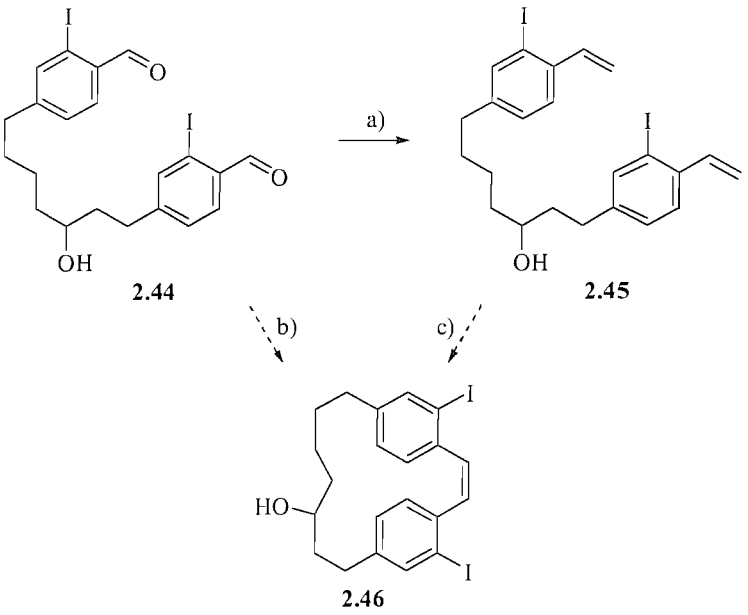
The initial stages of our new approach required oxidation of 4-bromo-2-nitrotoluene **2.35** to benzoic acid **2.36** (Scheme 44). Esterification with acidic methanol then gave **2.37** in good yield. Simultaneous preparation of bis-alkyne **2.39** from 4-pentynol **2.11** proved more problematic due to the volatility of the intermediate aldehyde **2.38**. Nonetheless, sufficient material was obtained from the subsequent Grignard reaction to proceed with our synthesis. A tandem Sonogashira coupling between aryl bromide **2.37** and bis-alkyne **2.39** proceeded slowly but efficiently at 60 °C to give diyne **2.40** in 63 % yield. Simultaneous reduction of the alkyne and nitro groups of **2.40** was then achieved using catalytic hydrogenation in acetic acid giving bis-aniline **2.41** in 74 % yield. When ethanol was used as the solvent, the reaction was slow and inefficient giving many partially reduced products even after prolonged reaction times.

A Sandmeyer reaction was next employed to transform the bis-aniline **2.41** to bis-iodide **2.42**.[73] Partial reduction of the methyl ester function of **2.42** to bisbenzaldehyde **2.44** with DIBAL-H was low yielding so reduction to the bis-benzyl alcohol **2.43** was effected. Oxidation with barium manganate then gave the desired bis-aldehyde **2.44** in 80 % yield over two steps.[74] At this juncture we attempted to effect macrocyclisation to the acerogenin E precursor **2.46** using McMurry coupling conditions (Scheme 45).[75,76] Alas, this gave a myriad of products with complete consumption of the starting material **2.44**. Consequently a double Wittig reaction was performed on **2.44** to give diene **2.45**. Ring closing metathesis was then attempted using both generations of Grubbs' catalyst. Disappointingly none of the desired product **2.46** was observed.[77]



a) $KMnO_4$, H_20, py, Δ, 68 %; b) MeOH, $SOCl_2$, Δ, 81 %; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 78 %; d) ethynyl grignard, THF, 0 °C, 17 %; e) $Pd(PPh_3)_4$, Et_3N, CuI, 60 °C, 16 h, 63 %; f) AcOH, H_2, 29 h, 74 %; g) i) H_2SO_4, acetone, $NaNO_2$, H_2O, urea; ii) KI, H_2O, 70 %; h) DIBAL-H, CH_2Cl_2, -78 °C - RT, 18 h, 98 %; i) $BaMnO_4$, RT, 20 h, 82 %.

Scheme 44



a) $MePPh_3$, KO^tBu, THF, RT, 1.5 h, 75 %; b) $TiCl_4$, Zn; c) Grubbs' catalyst.

Scheme 45

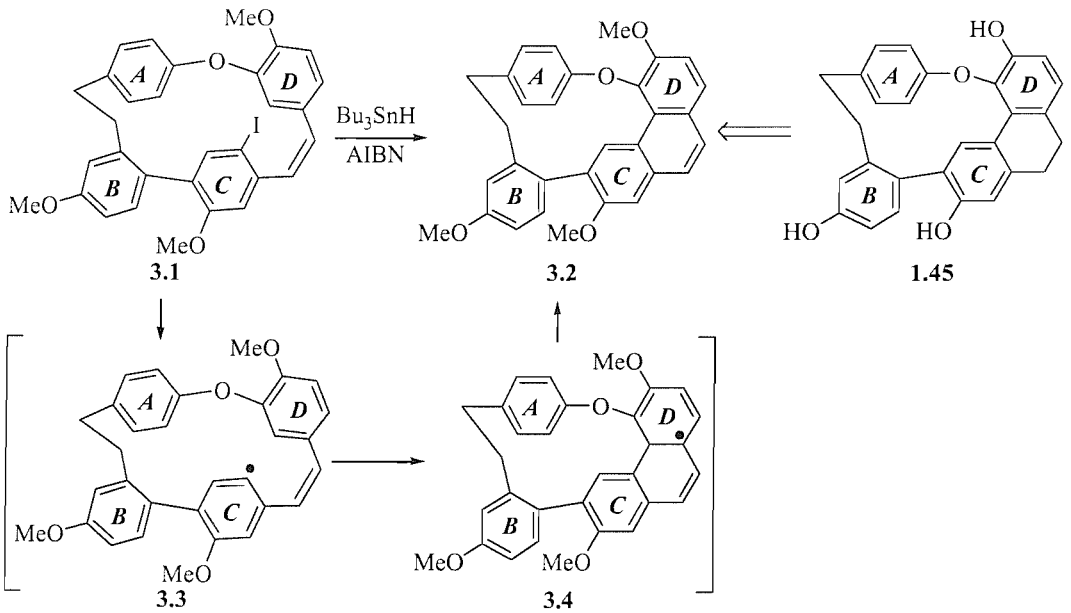
II.3 Conclusion and further work

All our attempts to form the strained *meta*-bridged biaryl of the biarylheptanoid skeleton were unfortunately met with resistance. These failures prompted us to abandon our efforts towards acerogenin E. Further work could involve a synthesis whereby an intramolecular Wittig reaction is used to form the stilbene-macrocycle **2.46**. This type of strategy has proved successful in the synthesis of riccardin C **1.46c**.[40]

CHAPTER III. The Total Synthesis of Cavicularin and Riccardin C

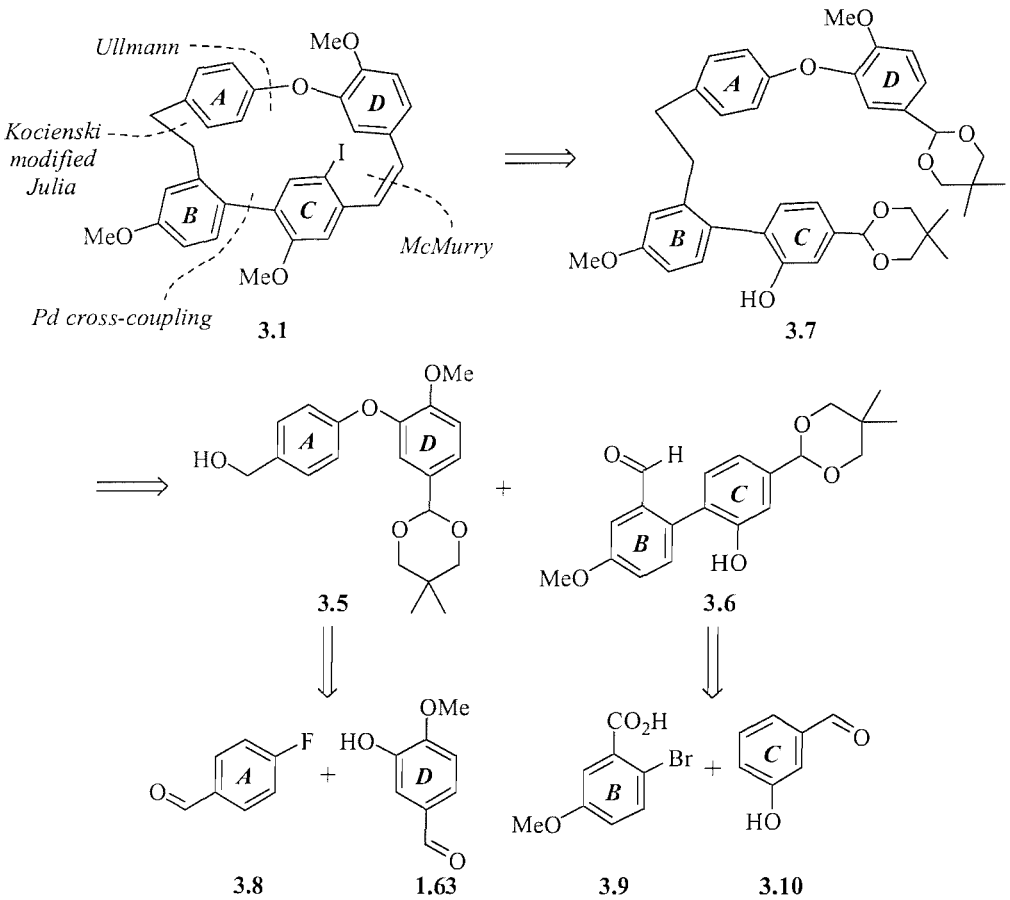
III.1 Retrosynthesis

Our proposed route to cavicularin **1.45** was based on a radical induced ring contraction strategy to construct the key aryl-aryl bond (Scheme 46).[78] It relies upon the formation of a larger 18-membered macrocycle **3.1** (from which riccardin C **1.46c** is easily derived), and subsequent transannular radical cyclisation to an adjacent arene to access dihydro-cavicularin trimethyl ether **3.2**. In this way we hoped to overcome the inherent difficulty associated with the synthesis of an arene that adopts a highly strained 'boat' conformation. As radical additions to arenes are irreversible and have an early transition state we postulated that the close proximity of the radical donor and arene acceptor, coupled to the early transition state associated with most radical reactions, would help facilitate the cyclisation reaction. Moreover, this could be achieved without significant distortion of arene *A*. Indeed, that would only occur on rearomatisation of **3.4** to **3.2**, where the energy required for bending the arene would be more than compensated for by the aromatisation of ring *D*.[79,80]



Scheme 46

Formation of the precursor **3.1** was envisioned using a McMurry reaction to effect the crucial macrocyclisation step (Scheme 47). We hoped that a modified Kocienski-Julia coupling would bring together the two biaryls *AD* **3.5** and *BC* **3.6**, procuring a phenol **3.7** that would be selectively iodinated in the *para*-position. In turn the biaryl ether **3.5** could be accessed in two steps from commercially available and cheap starting materials 4-fluorobenzaldehyde **3.8** and isovanillin **1.63**. The biaryl **3.6** would be synthesised by an intramolecular palladium mediated coupling reaction of the ester derived from acid **3.9** and phenol **3.10**.



Scheme 47

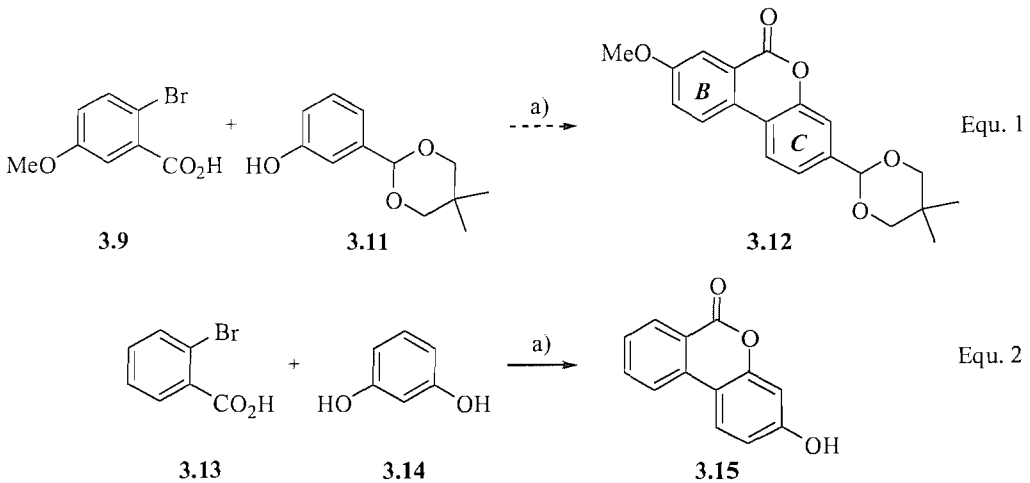
III.2 The Total Synthesis of Cavicularin and Riccardin C

a) Biaryl fragment BC

Traditionally the syntheses of macrocyclic bis(bibenzyls) have relied upon an intermolecular Suzuki cross coupling reaction to form the biaryl bond (See section I.2). The exception is the Nógrádi synthesis of riccardin C **1.46c** which utilises an intramolecular nickel mediated coupling leading to the formation of lactone **1.52** in low yield (Scheme 8).[36,37] Discussed below is an alternative method for the formation of a similar lactone **3.12**. Trial and error led to a sequence which presents considerable advantages with respect to prior syntheses.

i) Intermolecular Copper Strategy

All attempts to effect a copper mediated intermolecular coupling reaction between bromobenzoic acid **3.9** and phenol **3.11** (Scheme 48, Equ. 1) failed to give lactone **3.12** under a wide variety of conditions. Literature precedent utilised resorcinol **3.14** and its derivatives in combination with bromo acid **3.13** to give biaryl **3.15** in modest yield (Scheme 48, Equ. 2).[81-83] Resorcinol **3.14** is however, a special substrate as the site of biaryl bond formation is doubly activated by the presence of *ortho* and *para* hydroxy groups. It seems that phenol **3.11** is not sufficiently activated to undergo a similar reaction.



a) aq. NaOH, $CuSO_4$, 52 %.

Scheme 48

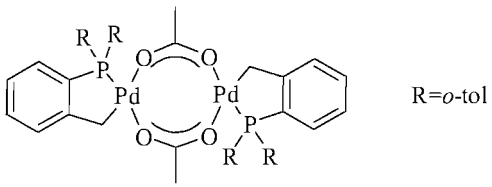
ii) Intramolecular Palladium Mediated Cyclisation Strategy

Turning to an intramolecular metal mediated strategy to form the biaryl bond required the prior formation of esters **3.16-3.22** (cf. Scheme 49, Scheme 51, Scheme 52). These were synthesised from the corresponding acid and phenol *via* a DCC mediated coupling reaction in excellent yield to give a substrate primed for palladium catalysed biaryl formation.[84] Table 2 lists the attempts made at lactone formation from a variety of substrates (Scheme 49). Entries 1-4 show that at temperatures lower than 130 °C no cyclisation was observed with any catalyst/ligand system. However at reaction temperatures greater than 130 °C (entries 5-8) cyclisation occured in useful yield only when using Herrmann's catalyst **3.23** (Figure 15).

Table 2. Attempts of palladium catalysed biaryl formation.

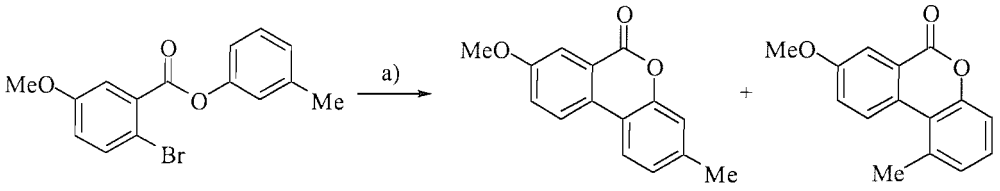
Entry	SM	Catalyst	Ligand	Solvent	Temp (°C)	Yield of lactone (%)
1	**3.16**	$Pd(PPh_3)_2Cl_2$	PPh_3	DMA	120	0
2	**3.16**	$Pd(OAc)_2$	P(*o*-tol)$_3$	DMA	120	0
3	**3.16**	$Pd(PPh_3)_4$	-	DMF	110	0
4	**3.16**	**3.23**	-	DMF	110	0
5	**3.17**	$Pd(PPh_3)_4$	-	DMF	140	< 10
6	**3.18**	$Pd(OAc)_2$	PPh_3	DMF	140	< 10
7	**3.18**	**3.23**	-	DMF	130	53
8	**3.16**	**3.23**	-	DMF	140	38

Herrmann's catalyst **3.23** (Figure 15) is stable up to temperatures of 250 °C, around 100 °C more than conventional palladium catalysts such as $Pd(PPh_3)_2(OAc)_2$, and therefore does not deposit palladium during high temperature reactions.[85] It has been reported to be more active than catalysts formed *in-situ* from equimolar amounts of $Pd(OAc)_2$ and P(*o*-tol)$_3$, and can be readily prepared from $Pd(OAc)_2$ and tri-*o*-tolylphosphine by brief heating in toluene followed by cooling to RT and isolation of the resulting yellow solid.[85]



3.23

Figure 15. Herrmann's catalyst 3.23

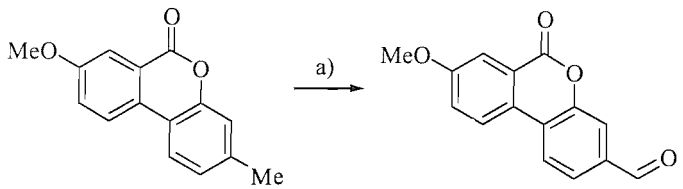


3.18 **3.24** **3.25**

a) See Table 2.

Scheme 49

The best yield was achieved using methyl substituted ester **3.18** (Table 2, Entry 7). However, there was evidence for the formation of regioisomer **3.25**, though this was not isolated (Scheme 49). Following the procedure of Falk *et al.*,[86] lactone **3.24** underwent benzylic oxidation with NBS to successfully yield aldehyde **1.52** after further oxidation with silver nitrate (Scheme 50). Attempts to effect the oxidation with ammonium cerium(IV) nitrate (CAN) failed in spite of good literature precedence.

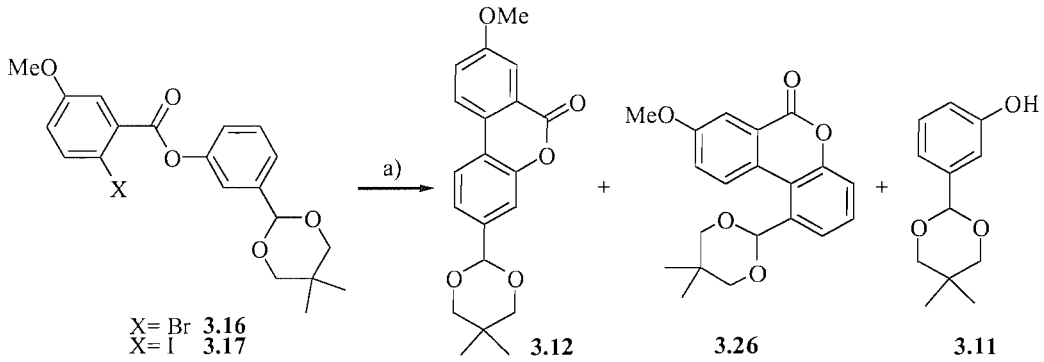


3.24 **1.52**

a) i) NBS, AIBN, CCl_4, Δ, 17 h; ii) $AgNO_3$, 80 °C, 15 min, 67 %.

Scheme 50

Acetal **3.16** also underwent cyclisation to **3.12** in useful yield but surprisingly gave significant quantities of phenol **3.11** and the more strained regioisomer **3.26** as by-products (Scheme 51).



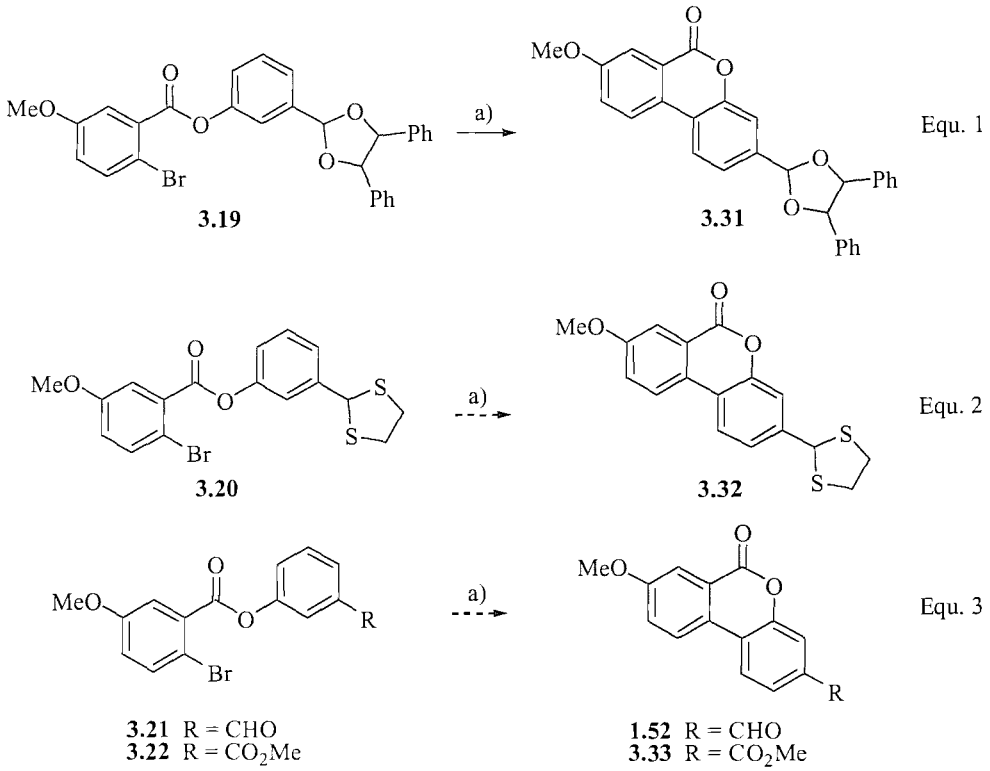
a) See Table 2.

Scheme 51

In an attempt to reduce this side reaction, various *meta* substituted phenols **3.27-3.30** were coupled with bromobenzoic acid **3.9** and tested in the palladium mediated insertion reaction (Entries 1-4, Table 3, Scheme 52). Increasing the steric bulk of the acetal group caused cyclisation of **3.19** to occur in low yield (Entry 1, Table 3) with no observed formation of the regioisomeric product. Esters **3.20**, **3.21** and **3.22** each gave a reaction but this led to baseline material rather than the desired lactone (Entries 2-4, Table 3, Scheme 52, Equ. 2 & 3).

Table 3. Attempts of palladium catalysed biaryl formation.

Entry	SM	Catalyst	Solvent	Temp (°C)	Yield of lactone (%)
1	**3.19**	**3.23**	DMF	135	19
2	**3.20**	**3.23**	DMF	135	×
3	**3.21**	**3.23**	DMF	135	×
4	**3.22**	**3.23**	DMF	135	×



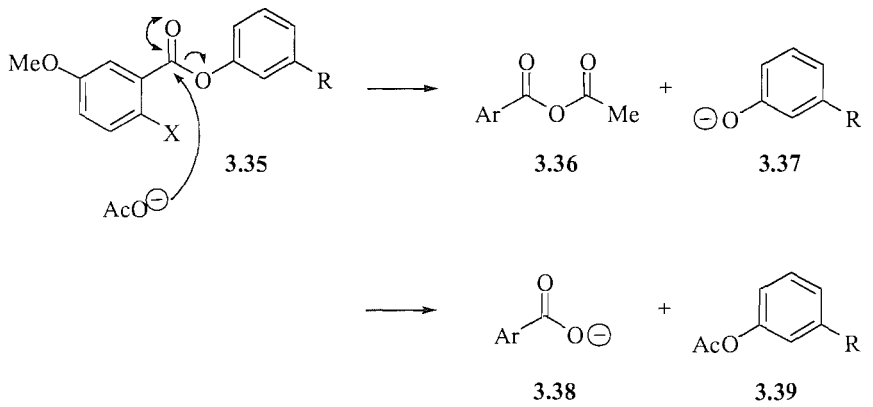
a) See Table 3.

Scheme 52

Comparing the electron deficient (Entries 3 and 4, Table 3) and the electron rich (Entries 7 and 8, Table 2) arene acceptors we can hypothesise that the former undergo intramolecular Heck reactions more efficiently because the arene bonds are more electrophilic. For electron rich arenes, these arene bonds are much less reactive towards the organopalladium intermediate and this gives side reactions greater opportunity to occur.

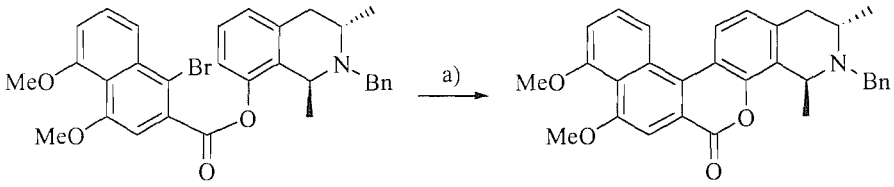
Hydrolysis of the ester **3.35** was observed as a major side reaction under the reaction conditions leading to isolation of the starting phenol **3.37** and/or its acetate derivative **3.39**. This problem has also been reported by Suzuki *et al.*[87] At the high temperatures employed in these coupling reactions it is possible for the base to attack the ester **3.35** to form anhydride **3.36**. The ejected phenol **3.37** then attacks the anhydride **3.36** to form benzoate **3.38** and acetate **3.39**. It was hoped that a more hindered base might reduce this side reaction. However, the use of sodium pivalate or DBU showed no improvement in the

overall yield. Similarly, extensive drying of the solvents had little impact on the course of the reaction.



Scheme 53

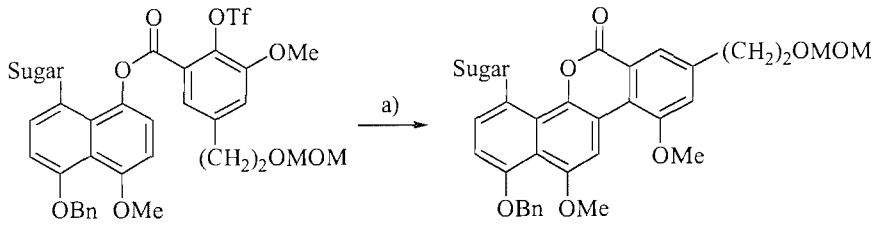
The general lack of reactivity of esters **3.16** to **3.22** towards intramolecular coupling may be attributed to the preferred S-*trans* configuration of the ester. This ensures that the aryl groups are distanced from one another. The reaction has nonetheless proven to be useful in the synthesis of dioncophylline **3.41** for example (Scheme 54).[88]



a) $Pd(PPh_3)_2Cl_2$, NaOAc, DMA, 130 °C, 75 %.

Scheme 54

Likewise, in work directed towards gilvocarin **3.42**, Suzuki achieved the key cyclisation of triflate **3.43** to lactone **3.44** in 65 % yield (Scheme 55).[87]

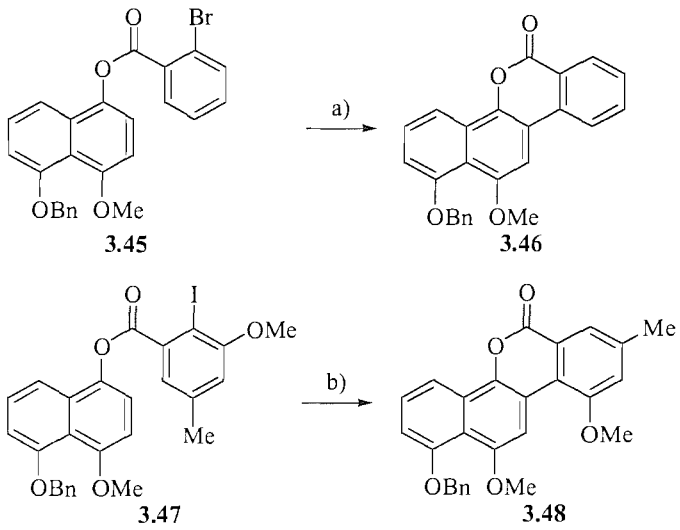


3.43 **3.44**

a) $Pd(PPh_3)_2Cl_2$, NaOPiv, DMA, 80 °C, 65 %

Scheme 55

Martin *et al.* reports yields of 40 and 75 % for related cyclisations of bromide **3.45** and iodide **3.47** respectively, when heated with $Pd(PPh_3)_2Cl_2$ (Scheme 56).[89]



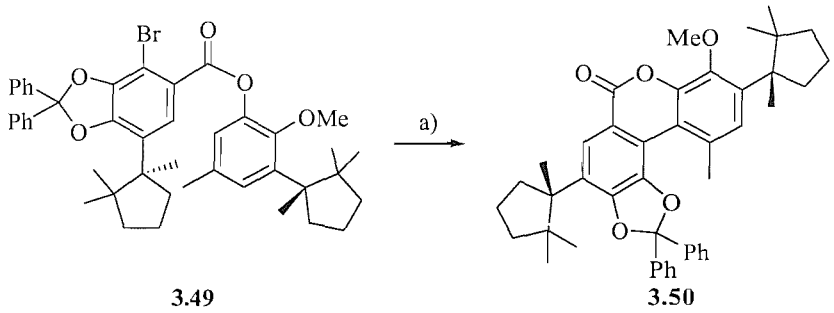
3.45 **3.46**

3.47 **3.48**

a) $Pd(PPh_3)_2Cl_2$, NaOAc, DMA, 130 °C, 40 %;
b) $Pd(PPh_3)_2Cl_2$, NaOAc, DMA, 130 °C, 76 %.

Scheme 56

Literature precedence is not confined to naphthalene derivatives. Bringmann *et al.* cyclised bromide **3.49** in high yield using an *in-situ* generated palladium catalyst (Scheme 57). Indeed, more recent examples involving aryl bromides have given comparable or improved yields using Hermann's catalyst **3.23**.[52,84,88,90]



3.49 **3.50**

a) $Pd(PPh_3)_2Cl_2$, PPh_3, NaOAc, DMA, 130 °C, 86 %.

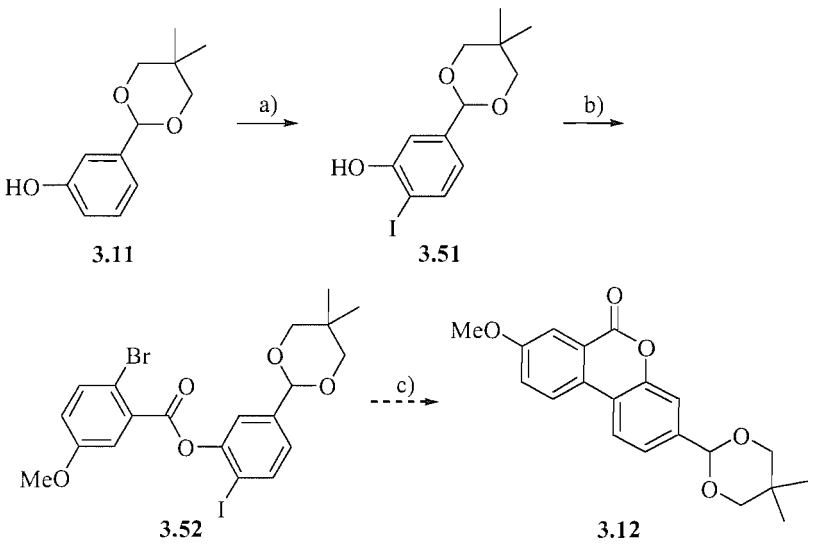
Scheme 57

All of the examples from the literature have one aspect in common – they all have a single mode of cyclisation through which the palladium intermediate can undergo the Heck reaction. In our example, both *ortho* carbons of the acceptor arene were unsubstituted, providing two possible cyclisation modes. This was certainly a factor contributing to the reduced yield observed with our synthesis.

These literature reports, together with our own results attained with esters **3.16-3.22**, show that choice of catalyst is crucial for a favourable outcome. Steric hindrance plays an important role in determining the course of such reactions. Moverover, high temperatures are needed in order to overcome the preferred S-*trans* configuration of the ester and promote cyclisation. Electron withdrawing substituents on the phenol ring are helpful as they improve the reactivity of the arene ring towards a Heck coupling.

iii) Bis-halo Cross Coupling Strategy

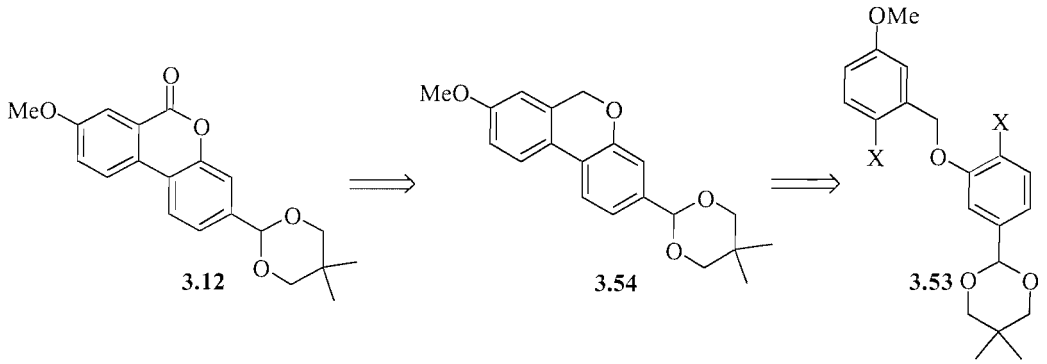
Iodophenol **3.51** was procured from a silver salt mediated *ortho* iodination of phenol **3.11** in moderate yield. Coupling with bromobenzoic acid **3.9** then gave ester **3.52** which we hoped would undergo regioselective intramolecular cross coupling to lactone **3.12** (Scheme 58). Attempts to perform a zero-valent nickel mediated coupling, in a similar fashion to Nógrádi, gave no indication of biaryl bond formation.[37]



a) I_2, $AgCO_2CF_3$, $CHCl_3$, 3 h, 65 %; b) DCC, DMAP, DMF, CH_2Cl_2, 73 %; c) $Ni(PPh_3)_2Cl_2$, Zn, PPh_3, DMF, 55 °C.

Scheme 58

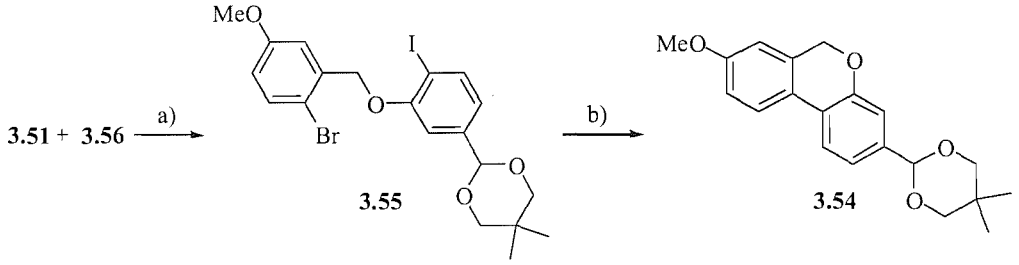
Believing that the S-*trans* orientation of the ester group might have contributed to this failure, we decided to use a simple aryl ether tether **3.53** to conjoin the two arenes. Oxidation of the resulting ether **3.54** with PCC would then give lactone **3.12** (Scheme 59).[91]



Scheme 59

Aryl ether **3.55** was readily synthesised from iodophenol **3.51** and 2-bromo-5-methoxybenzyl bromide **3.56** (Scheme 60). Pleasingly, halogen-metal exchange with *n*-butyllithium, followed by treatment with copper cyanide, transformed **3.55** into the desired biaryl **3.54**, albeit in low yield. In an attempt to increase the yield, copper cyanide was

replaced with silver nitrate. However the increased reactivity reported for such systems did not equate to an improvement in yield.



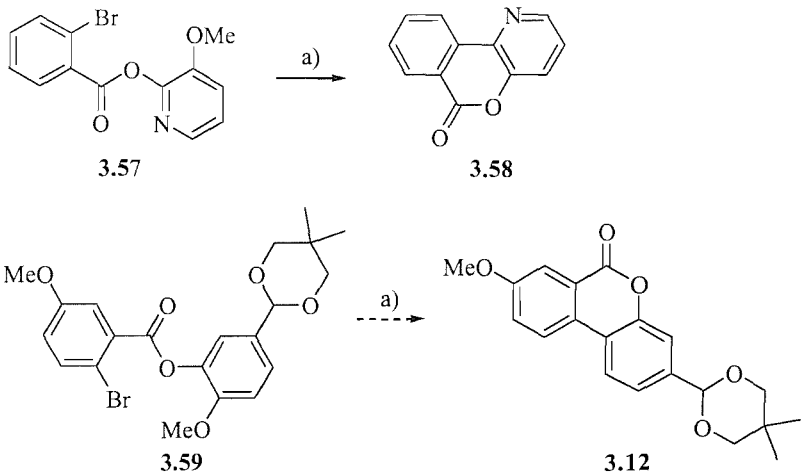
a) K_2CO_3, acetone, 94 %, b) i) *n*-BuLi, THF, -78 °C, 30 min; ii) CuCN, -78 °C - RT, 18 h, 34 %.

Scheme 60

Aryl ether **3.55** was also subjected to the Stille-Kelly conditions using hexamethylditin and a palladium catalyst.[92] Disappointingly, no cyclisation was observed.

iv) Radical Strategy

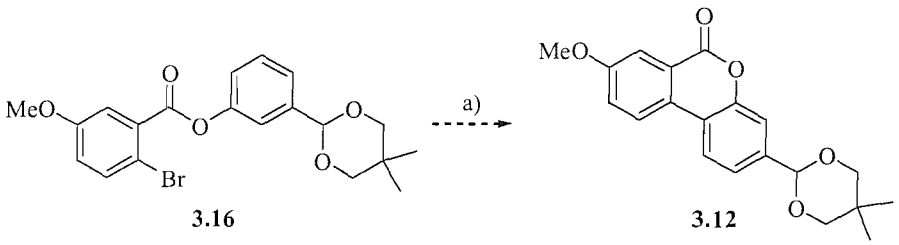
Having explored several metal mediated cross coupling approaches, we next turned our attention to a radical based strategy. The literature provides good precedent for such a reaction; the high yielding radical induced *ipso* substitution of aryl ester **3.57** giving us the impetus to try a similar reaction with ester **3.59** (Scheme 61).[93] Disappointingly, subjecting our substrate **3.59** to standard radical forming conditions gave none of the desired lactone **3.12**.



a) $(Me_3Si)_3SiH$, AIBN, PhH, 80 °C, 75 %.

Scheme 61

To further explore the radical cyclisation strategy, aryl bromide **3.16** was subjected to radical forming conditions using microwave irradiation (Scheme 62). Again no products of cyclisation were observed, suggesting that we had been unable to overcome the barrier presented by the S-*trans* orientation of the ester group.

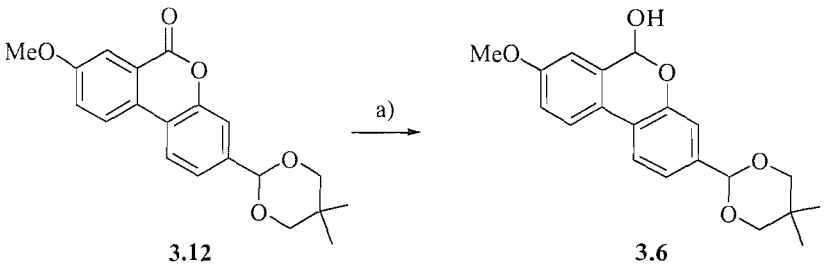


3.16 **3.12**

a) Bu_3SnH, VAZO, PhH, microwave irradiation, 140 °C

Scheme 62

Thus we decided to accept the low yielding palladium route to **3.12** with grace in order to move our synthesis forward. To that end, lactone **3.12** was reduced to lactol **3.6** using DIBAL-H (Scheme 63). The modest yield achieved was not improved when the quenching solvent was rigorously de-gassed before use. In all cases, recovered starting material accounted for most of the outstanding mass balance.



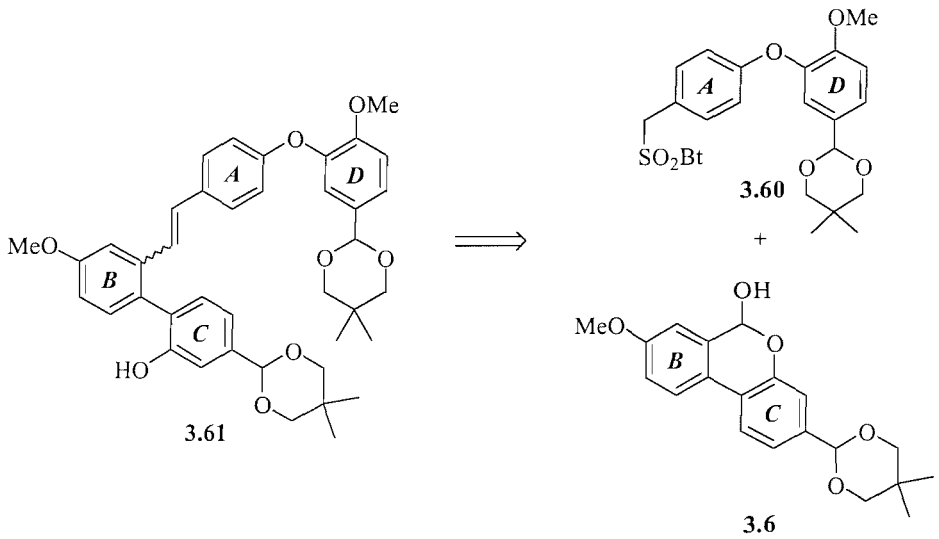
3.12 **3.6**

a) DIBAL-H, PhH, -78 °C, 1 h, 60 % (+ 20 % RSM **3.12**).

Scheme 63

b) Biaryl ether AD

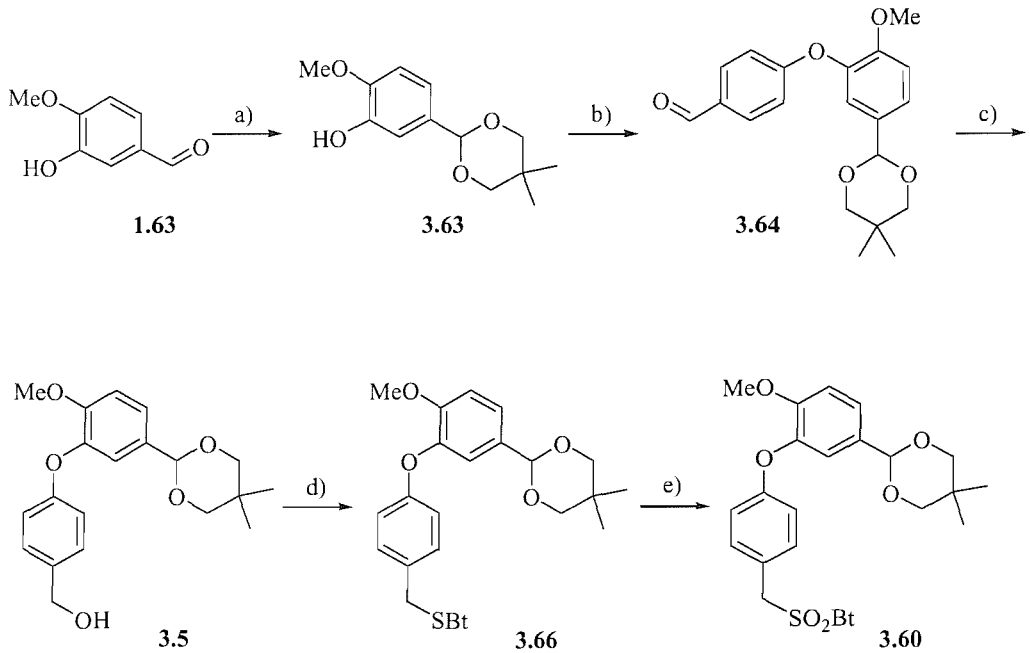
With biaryl **3.6** secured, our next challenge was to synthesise aryl ether **3.60** corresponding to the *AD* ring system of cavicularin **1.45**. These fragments could then be combined in an olefination reaction (Scheme 64). The approach to aryl ether **3.60** is described in the following section together with several alternative substrates considered.



Scheme 64

i) Kocieński-Julia Strategy

Initially our approach envisioned the use of a Kocieński-Julia olefination reaction to effect union of sulfone **3.60** and lactol **3.6** (Scheme 64).[94,95] To that end, protection of isovanillin **1.63** with neopentyl glycol **3.62** gave acetal **3.63** in high yield.[96] Subsequent nucleophilic aromatic substitution of 4-fluorobenzaldehyde **3.8** with phenol **3.63** gave aryl ether **3.64** in excellent yield.[97] Reduction of **3.64** with sodium borohydride to benzyl alcohol **3.5** followed by a Mitsunobu reaction with 2-mercaptobenzothiazole **3.65** gave sulfide **3.66** in excellent yield.

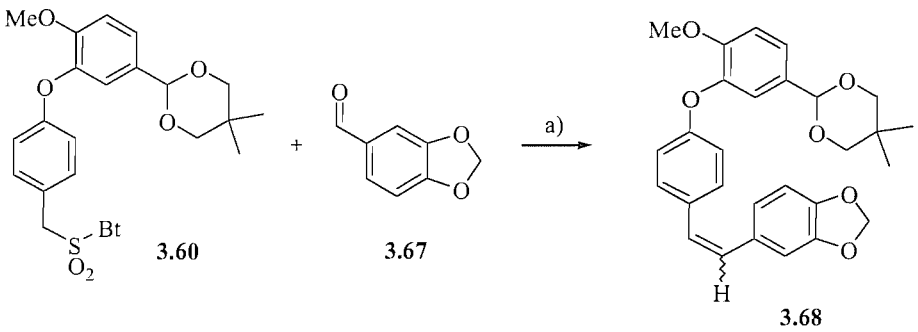


a) **3.62**, PPTS, PhH, 3 h, Δ, 88 %; b) **3.8**, DMF, K_2CO_3, 140 °C, 2.5 h, 94 %; c) $NaBH_4$, MeOH, 0 °C, 2 h, 95 %; d) **3.65**, PPh_3, DIAD, THF, 0 °C - RT, 18 h, 72 %; e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 30 min, 85 %.

Scheme 65

Oxidation of sulfide **3.66** with either ammonium molybdate or *m*-CPBA concomitantly caused partial removal of the acetal group giving rise to complex product mixtures. However, several trials with *m*-CPBA showed that the oxidation of **3.66** to **3.60** benefited from the use of a 10-fold excess of the base allowing the product **3.60** to be isolated in 85 % yield. Even so, under these modified conditions the deacetalization side reaction was not completely suppressed, presumably due to the electron rich character of the arene and its extreme sensitivity towards acids.

Use of sulfone **3.60** in a Kocieński-Julia reaction was successful in a test reaction with piperonal **3.67** giving stilbene **3.68** in 85 % yield as a mixture of (*E*)- and (*Z*)-isomers. However no reaction was observed with lactol **3.6** under a variety of reaction conditions. Consequently, the approach was abandoned in favour of some more conventional olefination procedures.



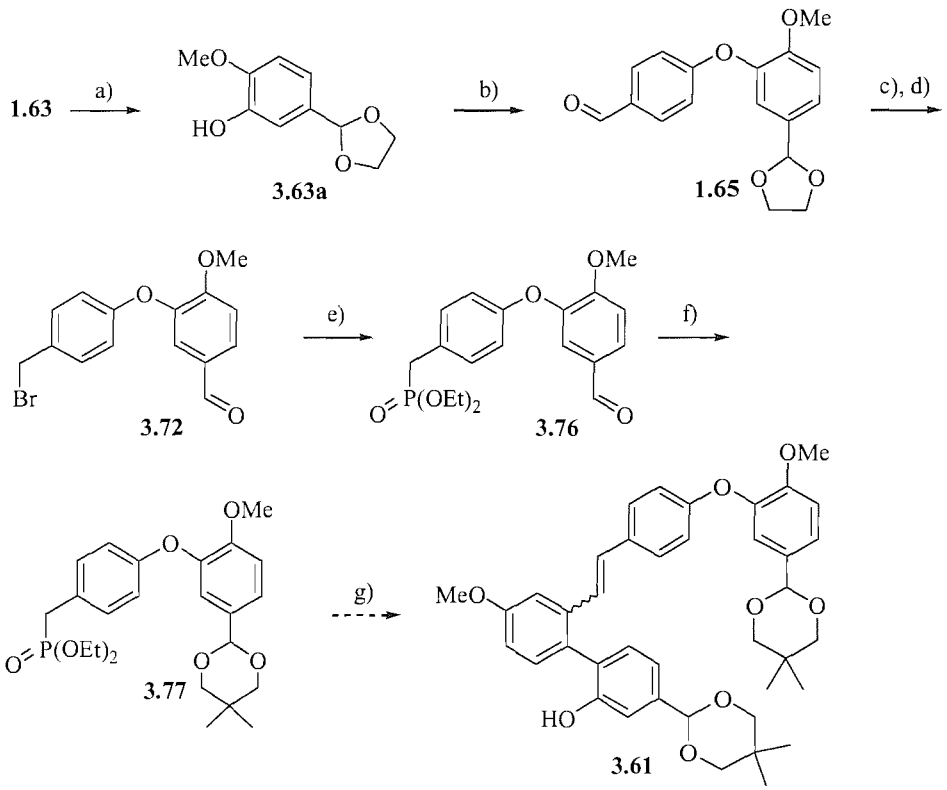
a) NaHMDS, -78 °C, 3 h, 85 %.

Scheme 66

ii) Wadsworth-Emmons Strategy

The sensitivity of the neopentyl glycol acetal **3.5** towards acid prompted us to switch our attention to the ethylene glycol derived acetal **1.65** (Scheme 67). Aryl ether **1.65** was synthesised by the aforementioned S_NAr reaction between phenol **3.63a** and 4-fluorobenzaldehyde **3.8** in very good yield, eclipsing the 7 step synthesis of **1.65** reported by Eicher *et al.* (Scheme 10).[40]

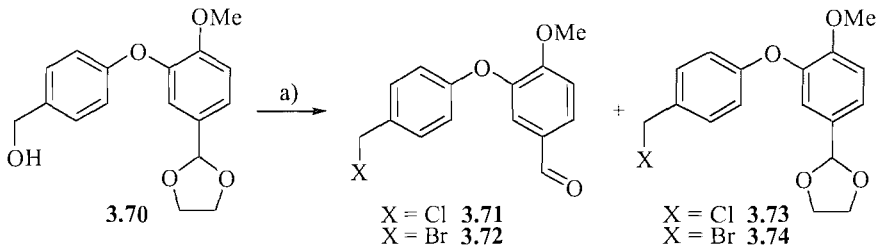
However, forming a benzyl halide **3.73-3.75** from either benzyl alcohol **3.5** or **3.70** proved troublesome due to the sensitivity of the acetal group (Scheme 68, Scheme 69). Various reaction conditions were screened, and in all but one case partial deprotection of the acetal was observed.



a) **3.69**, PPTS, PhH, 3 h, Δ, 84 %; b) **3.8**, K_2CO_3, DMF, 155 °C, 19 h, 90 %; c) $NaBH_4$, MeOH, 0 °C, 1 h, 92 %; d) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 0.5 h, 87 %; e) $P(OEt)_3$, 90 °C, 20 h, 95 %; f) **3.62**, PPTS, PhH, 2 h, Δ, 99 %; g) KO^{t}Bu.

Scheme 67

At this point, we decided to accept an inelegant re-protection of the aldehyde **3.72** in order to move our synthesis forward (Scheme 67, *viz* **3.76** → **3.77**). Quantitative conversion of **3.70** to benzyl bromide **3.72** was achieved with simultaneous deprotection of the acetal moiety, using carbon tetrabromide and triphenylphosphine. Subsequent treatment with triethyl phosphite followed by reacetalization gave phosphonate **3.77** in near quantitative yield. [Notably, the corresponding benzyl chloride **3.71** was unreactive towards triethyl phosphite]. Use of **3.77** in a Wadsworth-Emmons reaction was then attempted using conditions reported by Kodama *et al.*[98] However, treatment of phophonate **3.77** with potassium *tert*-butoxide and lactol **3.6** gave no useful reaction.

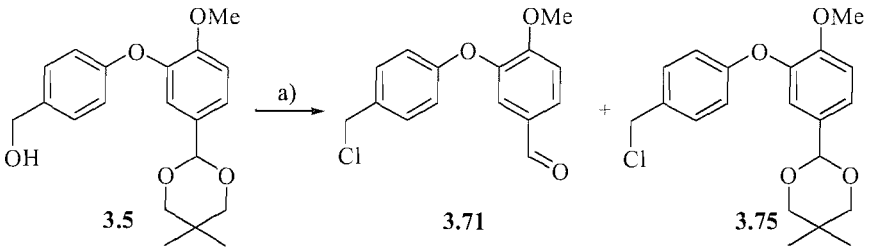


3.70 X = Cl **3.71** X = Br **3.72** X = Cl **3.73** X = Br **3.74**

a)

p-TsCl, Et_3N, DMAP, then MeOH	**3.71**:**3.73** 4:1
p-TsCl, LiCl, Et_3N	**3.71**:**3.73** 1:1
NCS, Me_2S	**3.71**:**3.73** 1:1
CBr_4, PPh_3	**3.72**:**3.74** 1:0

Scheme 68



3.5 **3.71** **3.75**

a)

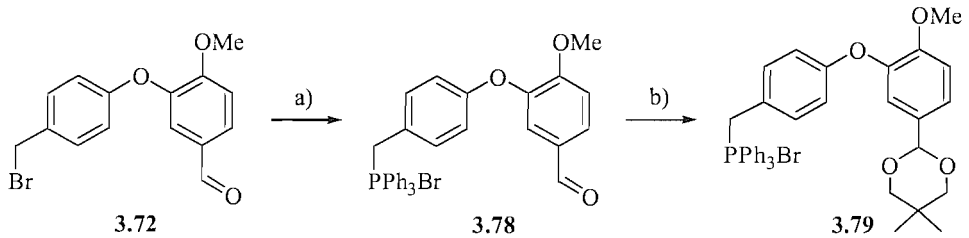
p-TsCl, Et_3N, DMAP, then MeOH	**3.71**:**3.75** 4:1
p-TsCl, LiCl, Et_3N	**3.71**:**3.75** 1:1
p-TsCl, LiCl, 2,6-lutidine	**3.71**:**3.75** 4:1

Scheme 69

iii) Wittig Strategy

An alternative strategy was to utilise a Wittig reaction between phosphonium salt **3.79** and lactol **3.6**. Benzyl bromide **3.72** was treated with triphenylphosphine followed by

neopentyl glycol **3.62** in the presence of catalytic PPTS to give the acetal protected phosphonium salt **3.79** in excellent yield (Scheme 70).



3.72 **3.78** **3.79**

a) PPh_3, PhH, Δ, 23 h, 86 %; b) **3.62**, PPTS, PhH, Δ, 18 h, 97 %.

Scheme 70

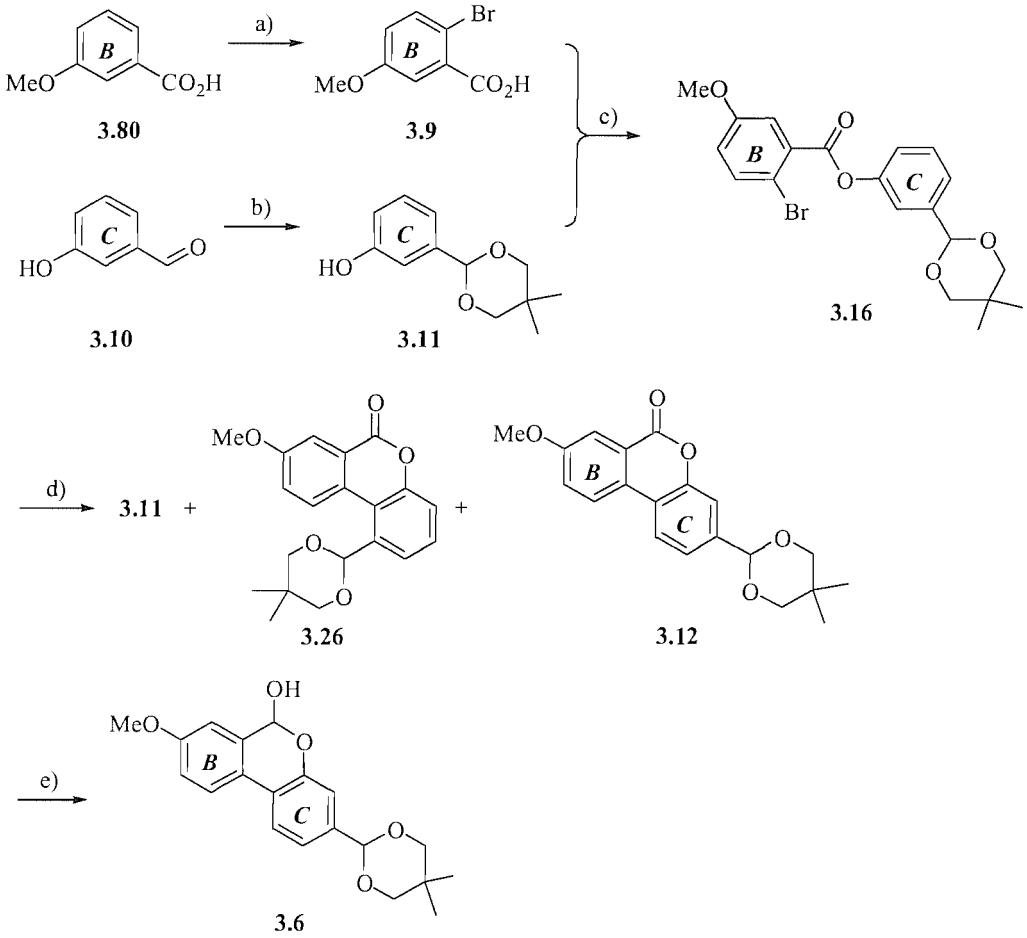
It is worth noting that standard Wittig reactions between **3.79** and lactol **3.6** failed. However, treatment of Wittig salt **3.79** with potassium carbonate, lactol **3.6** and 18-crown-6 led to coupling of these fragments giving tetraaryl **3.61** in 66 % yield (Scheme 73).

In hindsight the Kocieński-Julia and Wadsworth-Emmons olefination reactions may have been successful had a crown ether been included and an appropriate base identified. These couplings were not investigated further as the Wittig route involves the same number of steps, and was very reliable and clean.

c) Conclusion

Summarised below are the routes developed to prepare the two key fragments for the *BC* **3.6** and *AD* **3.79** ring systems.

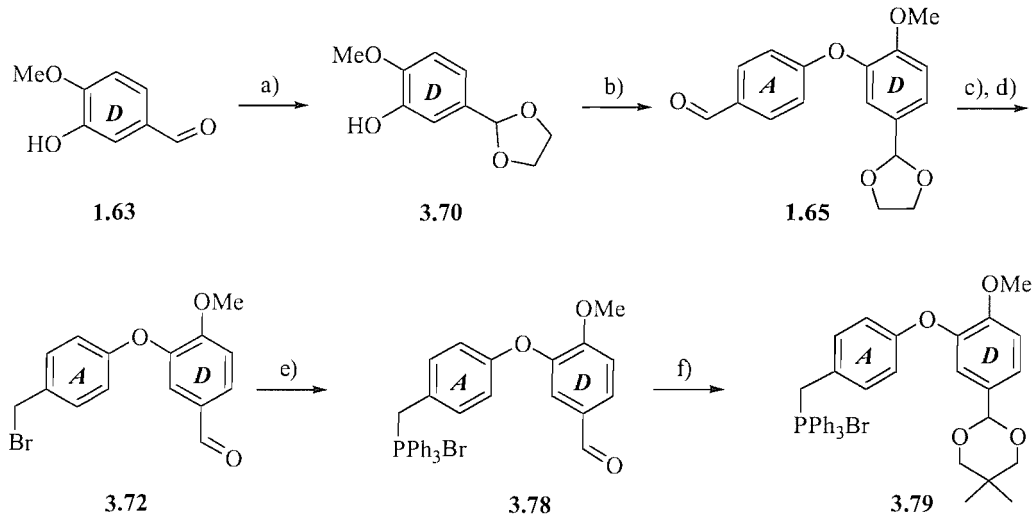
The route developed for the formation of biaryl **3.6** (Scheme 71) was reliable on a small scale, but scaling up the palladium cyclisation of **3.16** → **3.12** gave lower yields, with the reaction proving to be somewhat capricious. Despite the low yield, the strategy developed improves on the Nógrádi synthesis of a similar biaryl **1.52** *via* an intramolecular nickel coupling. Fewer steps are required and the difficult synthesis of two aryl iodides is avoided.



a) Br_2, AcOH, 6 h, RT, 77 %; b) **3.62**, PPTS, Δ, 3 h, 84 %; c) DCC, DMAP, DMF, CH_2Cl_2, 2 h, 0 °C, 92 %; d) HC **3.23**, DMF, NaOAc, 140 °C, 18 h, 38 % (3:1, **3.12**:**3.26**); e) DIBAL-H, PhH, -78 °C, 1 h, 45 %.

Scheme 71

Aryl ether **3.79** was synthesised in six steps from isovanillin **1.63** (Scheme 72). The coupling of **3.70** and 4-fluorobenzaldehyde **3.8** by nucleophilic aromatic substitution proceeded in excellent yield. However, subsequent conversion to the benzyl bromide **3.72** provoked deacetalization. This was a minor inconvenience as after formation of the Wittig salt **3.78**, reprotection was required before the Wittig reaction could be undertaken (Scheme 73).

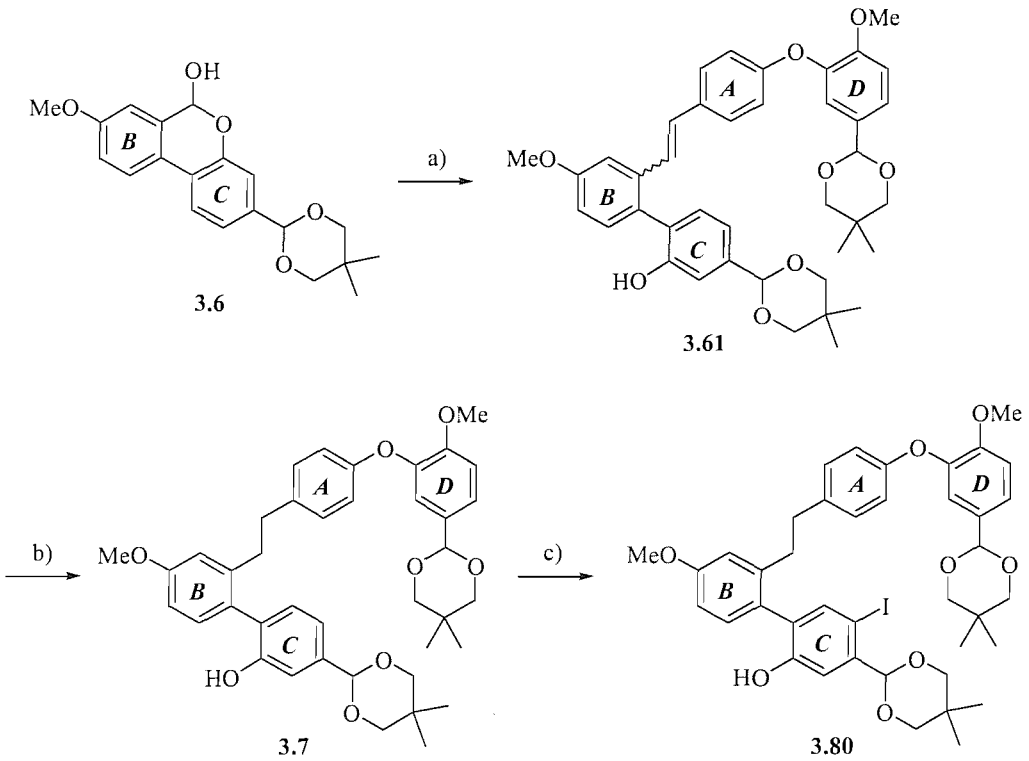


a) **3.69**, PPTS, PhH, 3 h, Δ, 84 %; b) **3.8**, K_2CO_3, DMF, 155 °C, 19 h, 90 %; c) $NaBH_4$, MeOH, 0 °C, 1 h, 92 %; d) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 0.5 h, 87 %; e) PPh_3, PhH, Δ, 23 h, 86 %; b) **3.62**, PPTS, PhH, Δ, 18 h, 97%.

Scheme 72

d) Tetraaryls

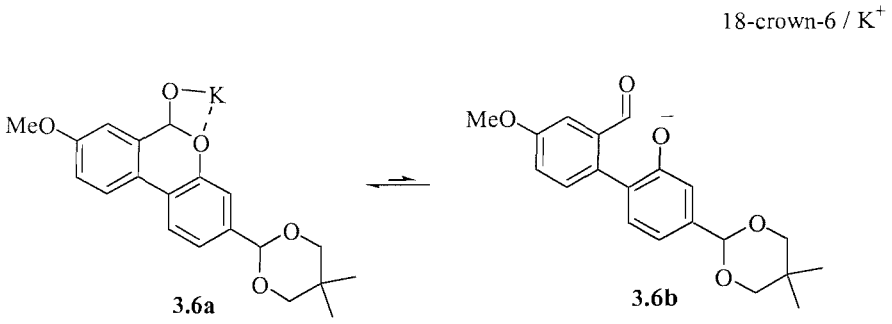
With the two fragments in hand, we were now in a position to carry out the key olefination reaction to the tetraaryl species. Wittig reaction between lactol **3.6** and phosphonium salt **3.79** occurred in good yield to give phenol **3.61** when using catalytic 18-crown-6 (Scheme 73).



a) **3.79**, K_2CO_3, 18-crown-6, CH_2Cl_2, Δ, 18 h, 66 %; b) PtO_2, H_2, Et_3N, EtOH, 18 h, 89 %; c) NaI, NaOCl, NaOH, MeOH, H_2O, 0 °C, 3 h, 73 %.

Scheme 73

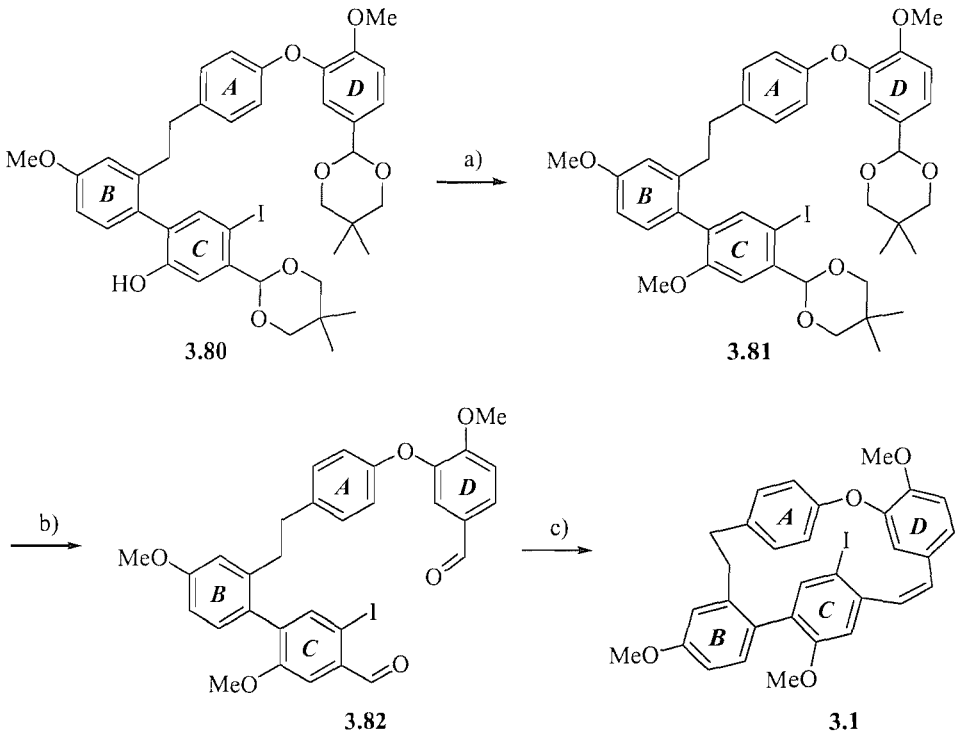
Without addition of the crown ether, no reaction was observed. This was thought to be due to the crown ether destabilising the deprotonated lactol **3.6a**, shifting the equilibrium between lactol **3.6a** and the free aldehyde/phenol **3.6b** further to the right.



Scheme 74

Hydrogenation of the *E*/*Z* mixture **3.61** was ineffectual using diimide or H_2, Pd/C when conducted in either ethyl acetate or ethanol. However, the reaction proceeded smoothly using Adams' catalyst (PtO_2) in ethanol to yield alkane **3.7**. (10 equivalents of triethylamine were added to help prevent hydrogenolysis of benzyl acetal functions).[40] Selective iodination of **3.7** *para* to the phenol of arene *C* was successful using the basic conditions described by Edgar *et al.*[17,66] Having served its purpose, the phenol was next protected with methyl iodide to give **3.81**. Subsequent deprotection of both acetals with aqueous acid then gave the bisaldehyde derivative **3.82** in good yield (Scheme 75).

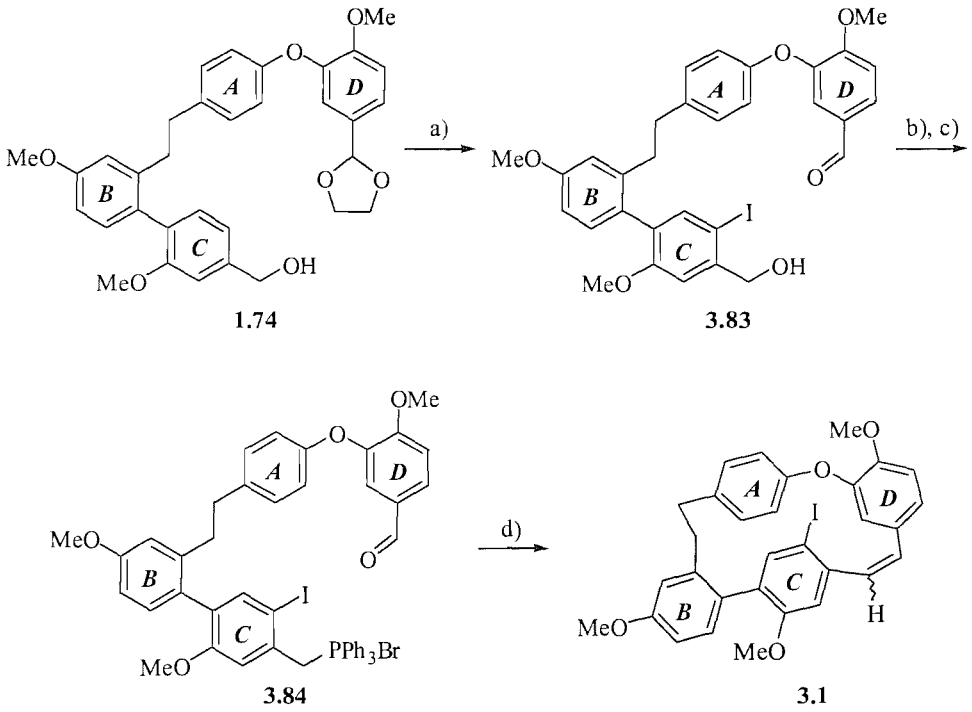
Our strategy now relied upon a McMurry macrocyclisation. Employing a low valent titanium species, formed by reduction of titanium tetrachloride with magnesium turnings, macrocyclisation was successfully achieved in 35 % yield by slow addition of the bisaldehyde **3.82** to the slurry at –78 °C over 5 h. Heating the mixture at reflux for 11 h then gave macrocycle **3.1** exclusively as the (*Z*)-stereoisomer.



a) MeI, K_2CO_3, acetone, RT, 18 h, 88 %; b) PPTS, H_2O, acetone, Δ, 18 h, 83 %; c) i) $TiCl_4$, Mg, THF, -78 °C, 5 h; ii) Δ, 11 h, 35 %.

Scheme 75

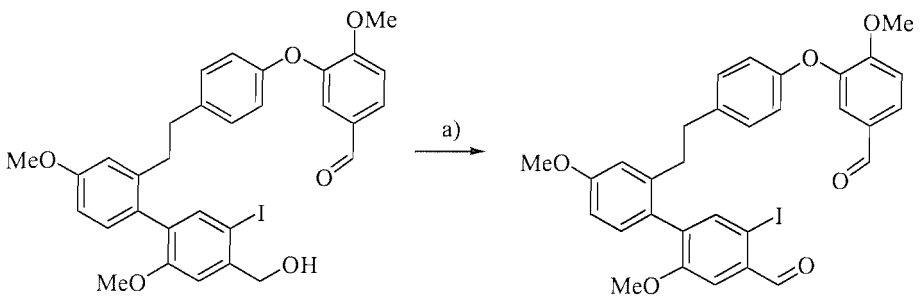
Concurrently we made use of a late intermediate in the total synthesis of riccardin C **1.46c** by Eicher *et al.* to address the synthesis of the same macrocycle.[40] Thus, benzyl alcohol **1.74** was prepared as reported (Scheme 11), in yields comparable to those reported.[40] Arene ***C*** was selectively iodinated *ortho* to the benzyl alcohol using a silver salt directed iodination. Fortuitously the acetal group was also hydrolysed under the reaction conditions leading to aldehyde **3.83**. The alcohol was now transformed into the corresponding bromide **3.83a**, which was readily displaced with triphenylphospine to give phosphonium salt **3.84**. When this was added dropwise to a solution of sodium methoxide in dichloromethane macrocycle **3.1** was formed in excellent yield. Interestingly, a 3:1 ratio of *Z*/*E* isomers was obtained when the reaction was maintained at ambient temperature, which was improved to 13:2 when the reaction was heated to reflux for 1 hour.



a) I_2, $AgCO_2CF_3$, CH_2Cl_2, 0 °C, 3 h, 70 %; b) PBr_3, PhH, 0 °C, 9 h; c) PPh_3, PhH, Δ, 40 h, 72 %; d) NaOMe, CH_2Cl_2, RT, 17 h then Δ, 1 h, 93 % (13:2, *Z*/*E*).

Scheme 76

Benzyl alcohol **3.83** could also be oxidised with barium manganate to give bisaldehyde **3.82**, providing an alternative route to the McMurry precursor (Scheme 77).



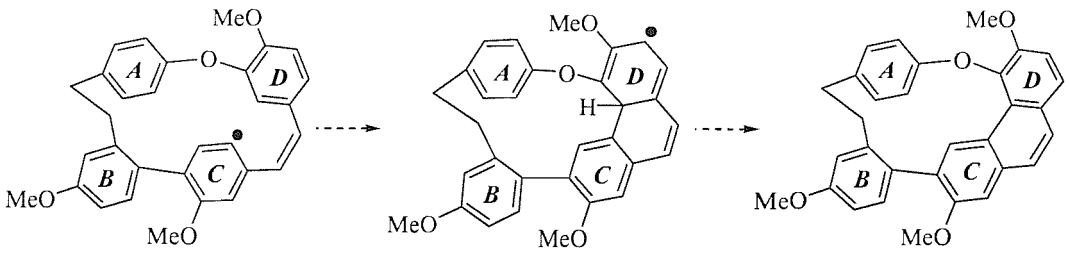
3.83 **3.82**

a) $BaMnO_4$, CH_2Cl_2, 18 h, RT, 88 %

Scheme 77

e) Transannular Radical Ring Contraction

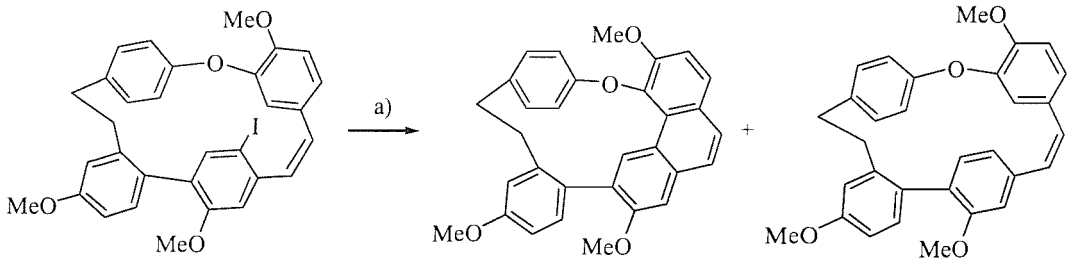
With iodide **3.1** in hand, we were now in a position to carry out the key transannular ring contraction reaction. Two main issues were anticipated in the transannular radical ring contraction; a) the kinetics of the radical ring contraction reaction leading to the 14-membered ring, and b) the thermodynamic barrier towards bending of arene *A*. We reasoned that the early transition state associated with radical cyclisation reactions would help to overcome the kinetic hurdle, with the *cis*-alkene tether helping to promote the 6-*endo/exo* trig *ortho*-cyclisation.[78] The thermodynamic barrier presented by the need to bend arene *A* would then transfer to the second phase of the reaction where the re-aromatisation of arene *D* would provide a significant driving force.[79,80]



3.3 **3.4** **3.2**

Scheme 78

Using standard radical forming conditions, with 2 eq. tributyltin hydride, 0.2 eq. AIBN, PhH, 90 °C resulted in an inseparable mixture of the macrocycles **3.2** and **1.76** (Scheme 79).

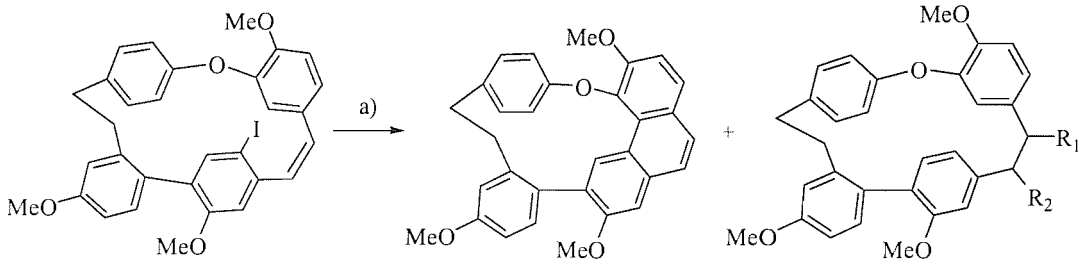


3.1 **3.2** **1.76**

a) Bu_3SnH, AIBN, PhH, 90 °C, 2.5 h. inseparable

Scheme 79

Increasing the quantity of AIBN also promoted the formation of two products of similar polarity. Fortunately, these could be separated by HPLC (Scheme 80). Analysis showed the major fraction to be an adduct **3.85** resulting from the addition of *iso*butyronitrile radical across the alkene as indicated by a large peak at δ_H 1.5 ppm in the ^1H NMR and at δ_C 24.1 ppm in the ^{13}C NMR. The exact structure however, remains unknown as we were unable to determine the regiochemistry of the adduct **3.85**. More importantly, the second product was the expected phenanthrene **3.2**, isolated in 24 % yield.

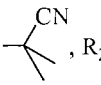


3.1 **3.2** **3.85**

a) Bu_3SnH, AIBN, PhH, 90 °C, 2.5 h, 24 % of **3.2**.

separable

R_1=H, R_2= 

or R_1=  , R_2=H

Scheme 80

X-ray analysis of the ring contraction product **3.2** is shown below (Figure 16). Points of interest include the bent aromatic, arene *A*, and the variation in bond lengths within the arene. It is also apparent that the phenanthrene moiety is distorted from planarity to a significant extent.

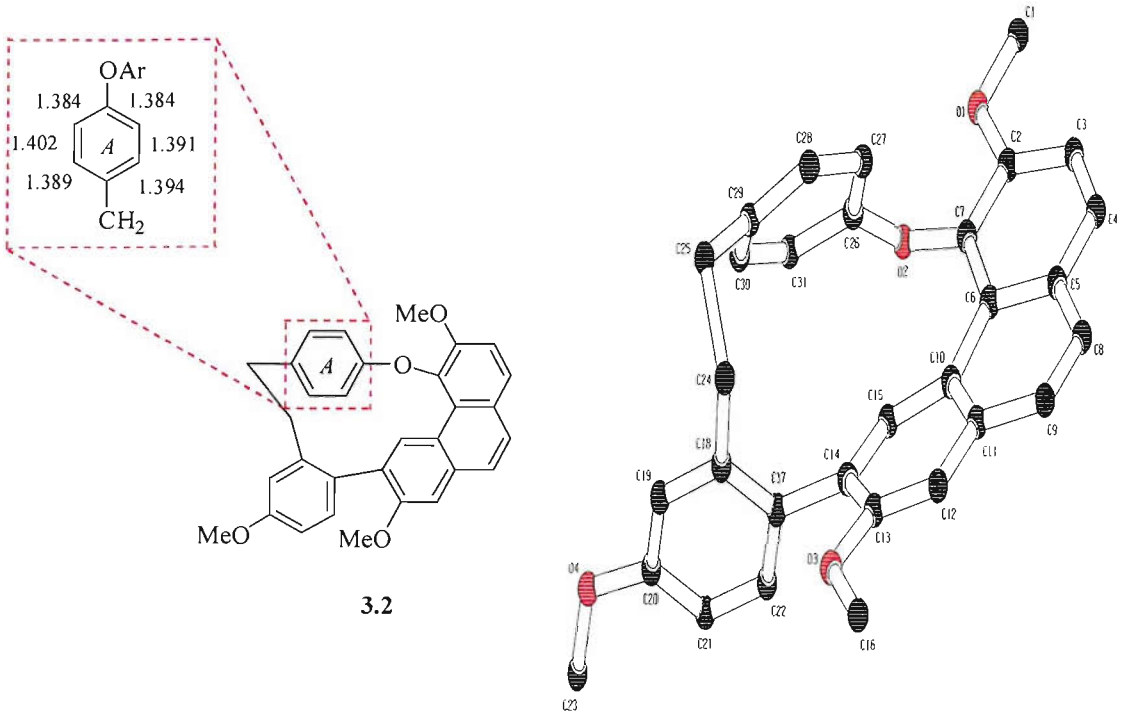
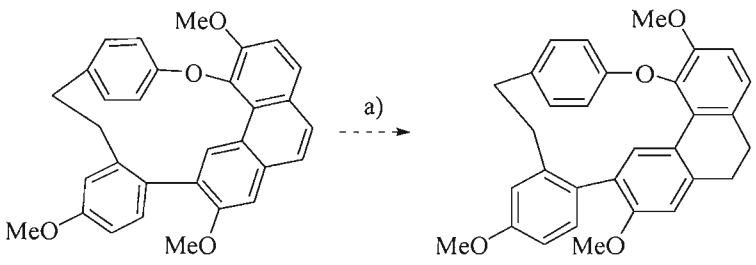


Figure 16

With the key carbon skeleton constructed, we now needed to effect the partial hydrogenation of the phenanthrene moiety *viz* **3.2** → **3.87**. Various conditions were investigated, including diimide reduction and catalytic hydrogenation with a variety of catalysts. Disappointingly, over reduction of the arenes was observed on each occasion.

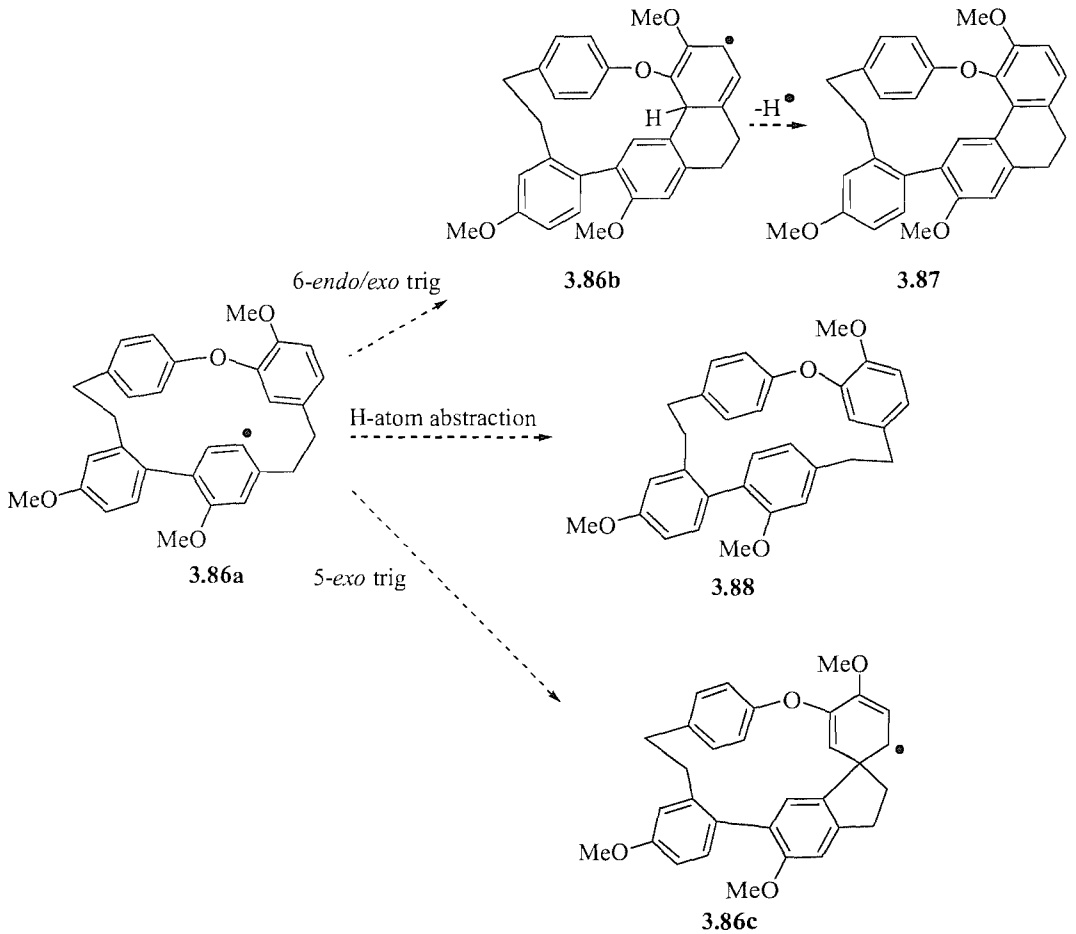


3.2 **3.87**

a) hydrogenation

Scheme 81

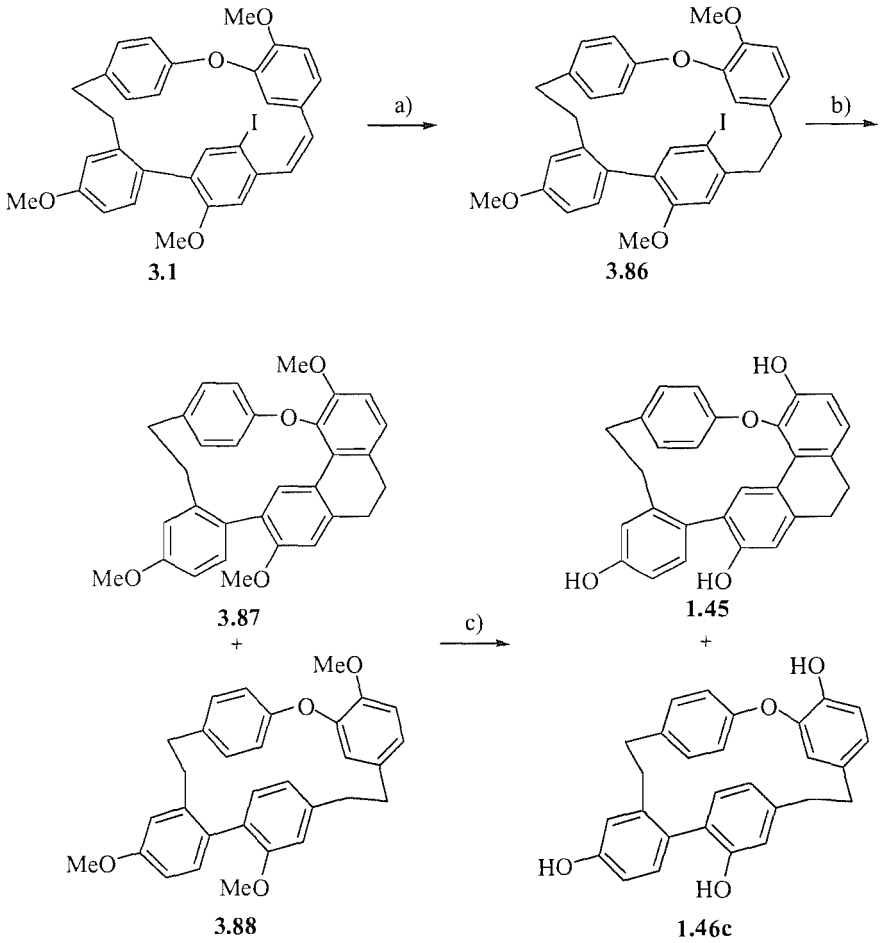
Given these frustrations, and the side reaction with AIBN experienced in the previous step, we considered altering the sequence of reactions to perform the hydrogenation before the transannular radical ring contraction. While this change was likely to remedy both problems, it was anticipated that we would see a reduction in the efficiency of the key transannular radical cyclisation (Scheme 82).[23] These are known to be less efficient when a saturated tether is employed in substrates as the extra flexibility means that the 6-*exo*/*endo* cyclisation competes on a more even basis with 5-*exo* cyclisation and H-atom abstraction pathways.[78] We hoped that the macrocycle **3.86a** would be sufficiently constrained to favour 6-*endo*/*exo* trig cyclisation over the possible 5-*exo* trig pathway since the spirocycle **3.86c** thus generated would incur considerable ring strain, disfavouring its formation.



Scheme 82

Hydrogenation in the presence of aryl halides, especially iodides, can be troublesome.[18] However, the use of diimide, formed *in-situ* from *para*-tosylhydrazine and

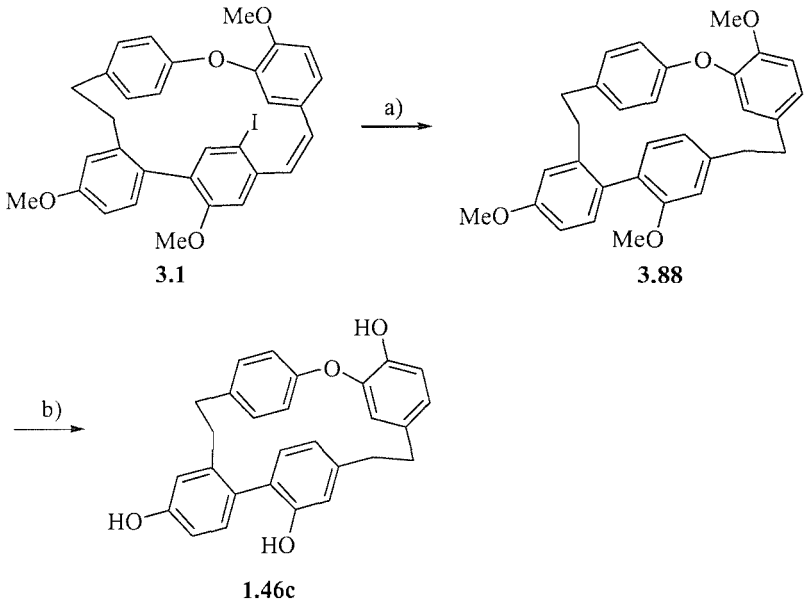
sodium acetate (Scheme 83), provides a useful alternative.[99] For macrocycle **3.1** the reaction proved to be very slow, taking seven days and a large excess of the aforementioned reagents to go to completion giving **3.86** in high yield. Pleasingly, treating the resulting iodinated macrocycle **3.86** with TTMSS and AIBN, we were able to effect the radical ring contraction to cavicularin trimethyl ether **3.87**. However, accompanying this product was riccardin C trimethyl ether **3.88**, resulting from simple reduction of the Ar-I bond. These could not be separated at this stage. Separation was accomplished following deprotection of the crude material with boron tribromide, which allowed both cavicularin **1.45** and riccardin C **1.46c** to be isolated in a combined 95 % yield (ratio 1:2 respectively) over the two steps, completing the first total synthesis of cavicularin **1.45**.



a) *p*-$TsNHNH_2$, NaOAc, THF/H_2O, 90 °C, 7 d, 91 %; b) TTMSS, AIBN, PhH, 90 °C, 4 h; c) BBr_3, CH_2Cl_2, 0 °C, 1/2, 95 % (over two steps)

Scheme 83

A total synthesis of riccardin C **1.46c** was also achieved from macrocycle **3.1** by simultaneous hydrogenation of the alkene and hydrogenolysis of aryl iodide using H_2, Pd/C. Deprotection of the methyl ethers of **3.88** with boron tribromide then gave riccardin C **1.46c** (Scheme 84), which displayed physical and spectroscopic characteristics identical to those reported in the literature.[34,35]



3.1 **3.88** **1.46c**

a) Pd/C, H_2, EtOH, 2 h, 84 %; b) BBr_3, CH_2Cl_2, 0 °C, 18 h, 86 %.

Scheme 84

Initially our analysis of riccardin C **1.46c** by ^1H NMR revealed several discrepancies with the published data. For example, Eicher *et al.* reported a phenolic proton at δ_H 8.48 ppm when the spectra were recorded in $CDCl_3$/DMSO.[40] By contrast our sample of riccardin C **1.46c** displayed 3 phenolic protons at δ_H 9.25, 8.99, and 8.85 ppm when its ^1H NMR was recorded in either $CDCl_3$ with an aliquot of d^6 DMSO, or d^6 DMSO with an aliquot of $CDCl_3$ (Figure 17, B). The sample also showed discrepancies in the ^{13}C NMR spectrum casting doubt on the authenticity of our sample.[35,40] This prompted us to methylate our sample of 'riccardin C'. Pleasingly the resulting sample displayed spectral characteristics identical to those obtained by us and others for riccardin C trimethyl ether

3.88.[30,31,40] Simultaneously, the ^{1}H NMR spectra of our synthetic sample of riccardin C **1.46c** was recorded in pure $CDCl_3$ (Figure 17, A). These data were identical to those reported by Asakawa *et al.* and others confirming that we had indeed achieved the total synthesis.[34,35]

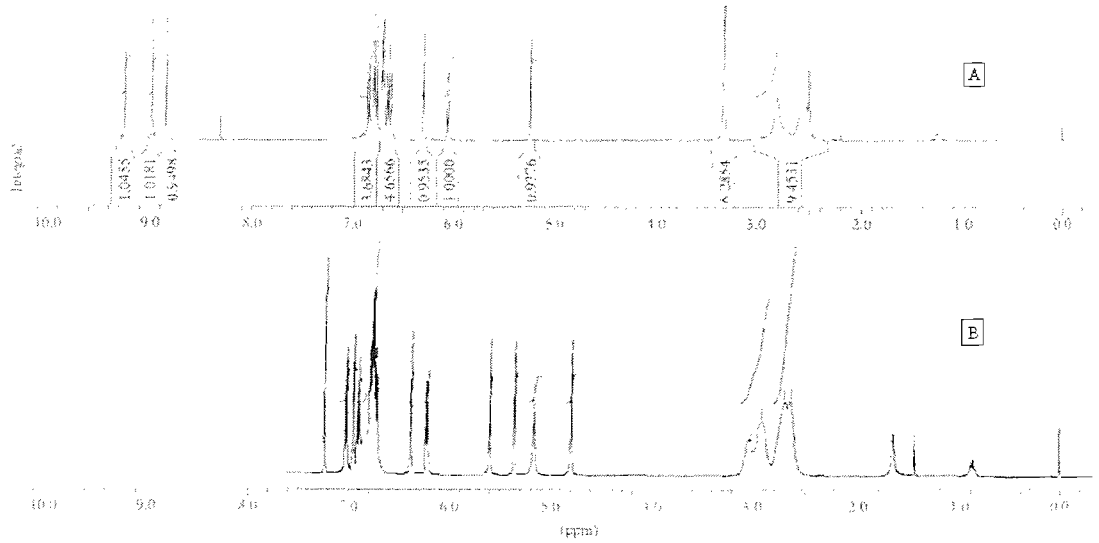
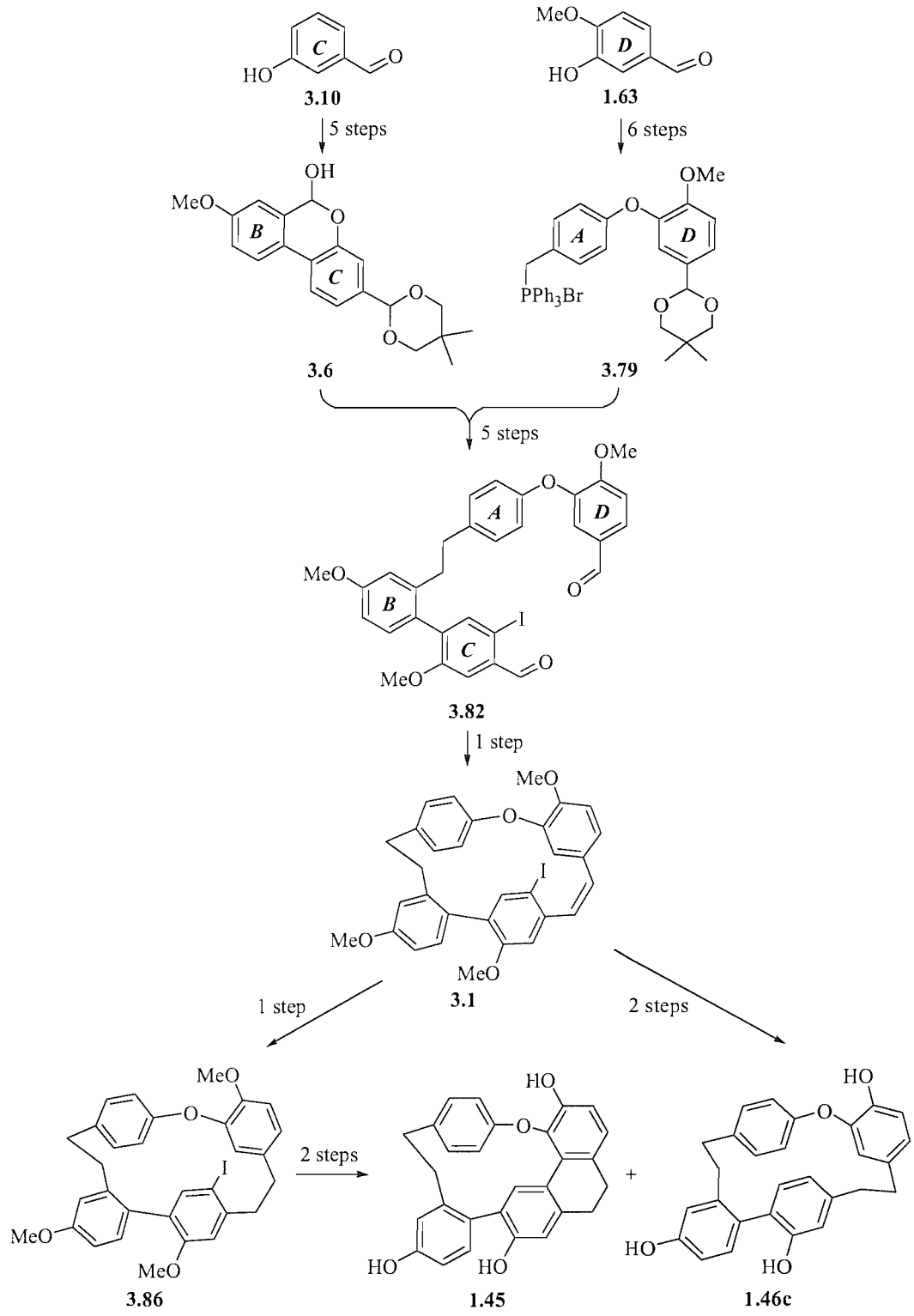


Figure 17

III.3 - Conclusion and further work

In summary, we have secured the first total synthesis of cavicularin **1.45** in 14 steps and 0.24 % overall yield from **3.10** (Scheme 85). Particularly noteworthy are the use of a McMurry macrocyclisation and a transannular radical induced ring contraction to construct the highly strained macrocyclic skeleton. We have also achieved a total synthesis of riccardin C **1.46** in the shortest route reported to date (Scheme 85).


3.10
5 steps
1.63
6 steps
3.6
3.79
5 steps
3.82
1 step
3.1
1 step
2 steps
3.86
2 steps
1.45
1.46c

Scheme 85

There are two reactions in the total synthesis of cavicaulrin **1.45** that are low yielding, namely the palladium mediated lactone formation **3.16** → **3.12** (Scheme 71) and the transannular radical induced ring contraction **3.86** → **3.87** (Scheme 83). The main issues with the palladium reaction are the low yield resulting from the formation of the undesired regioisomer **3.26** and hydrolysis of the ester precursor **3.16**. An alternative strategy making use of an intermolecular Suzuki or related reaction could be beneficial, though it would require further functional group manipulation to yield the desired lactone.

The problems associated with both the synthesis and hydrogenation of phenatherene **3.2** made it necessary to perform the transannular ring contraction reaction with a saturated tether *viz* **3.86**. As anticipated, the yield of the ring contraction product was reduced in favour of simple Ar-I bond reduction. This reaction could benefit from further optimisation. In particular, using mediators such as Co(I)salophen, where H-atom abstraction does not occur, could prove beneficial. Applying different reaction conditions for example, the use of microwave irradiation or even higher dilution might also help to slow the intermolecular (second order) reactions – biasing the reaction in favour of the intramolecular (first order) cyclisation.

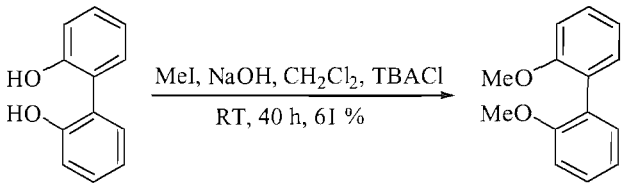
CHAPTER IV – Experimental

IV.1 - General remarks

All air and/or moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried glassware. Reactions were monitored by TLC using glass-backed plates coated with silica gel 60 containing a fluorescence indicator active at 254 nm; the chromatograms were visualised under UV light (254 nm) and by staining with, most commonly, 20 % phosphomolybdic acid in ethanol or 10% aqueous $KMnO_4$. Where flash chromatography was undertaken, Apollo silica gel (0.040-0.063 mm, 230-400 mesh) was used, slurry packed and run at low pressure. HPLC was performed using a Kontron Instruments pump with a 10 mm × 250 mm Biosyl D 90/10 column eluting at 3 mL/min. Infrared (IR) spectroscopy was performed using a Bio-Rad FT-IR Goldengate spectrometer or Thermo Mattson Satellite FT-IR spectrometer. Positions of absorption maxima are quoted in cm^{-1}. Letters after give an indication of the relative strength of the peak (w = weak, m = moderate, s = strong, br. = broad). ^{1}H and ^{13}C spectroscopy was performed on a Bruker AC/AM300 or DPX400 spectrometer at operating frequencies indicated in the text. Chemical shifts are quoted as δ-values in ppm and multiplicities are reported using the following notation: s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, m = multiplet, app. = apparent, br. = broad, obs. = obscured. Chemical ionisation (CI) and electron ionisation (EI) mass spectroscopy was performed on a Thermoquest Trace GCMS spectrometer. Electrospray (ES) mass spectroscopy was performed on a Micromass Platform (MP) spectrometer. High resolution EIMS was performed on a VG Analytical 70-250-SE spectrometer and high resolution ESMS was performed on a Bruker Apex III spectrometer. Combustion analysis was performed by Butterworth Laboratories. Melting points were carried out using a Griffin melting point apparatus and are uncorrected. UV spectroscopy was performed using a Pye Unicam SP8-400 spectrometer or Agilent 8453 spectrometer using either methanol or dichloromethane as the solvent. Positions of absorption maxima are quoted in nm and shoulders are designated sh. Benzene, toluene, 1,4-dioxane, ether and THF were distilled from sodium immediately before use. Except in the case of toluene, benzophenone was used as an intemal indicator of water content. Chloroform and dichloromethane were distilled from calcium hydride immediately prior to use. Where appropriate, all other solvents and reagents were purified according to standard methods.[100]

IV.2 – Experimental Procedures for Chapter II

2,2'-Dimethoxybiphenyl **2.8**



1.128

$C_{12}H_{10}O_2$
Mol. Wt.: 186

2.8

$C_{14}H_{14}O_2$
Mol. Wt.: 214

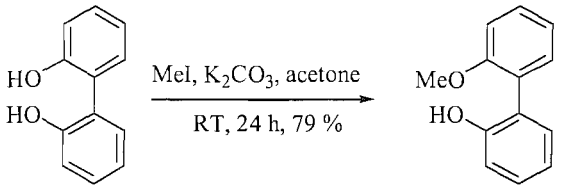
Iodomethane (3.70 mL, 59.40 mmol) was added to a solution of **1.128** (2.14 g, 11.50 mmol) in dichloromethane (50 mL). Aq. NaOH (0.57 M, 50 mL) and *N*-tetrabutylammonium chloride (0.26 g, 0.94 mmol) were added, and the reaction mixture was stirred for 40 h at RT. The organic layer was separated, and the aqueous layer extracted with dichloromethane (3 × 20 mL). The organic fractions were combined and the solvent removed *in vacuo*. Water (50 mL) was added and the reaction was extracted with ether (3 × 30 mL). The organic fractions were washed with 2M NaOH (3 × 20 mL), brine (3 × 20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the crude solid was recrystallised from ethanol to yield 2,2'-dimethoxybiphenyl **2.8** (1.50 g, 7.00 mmol, 61 %) as colourless crystals.

The spectroscopic and physical data attained compares well with literature values, except for the melting point, reported as 154-155 °C.[101,102]

MP	160-161 °C (ethanol) [Lit. 154-155 °C (ethanol)][101,102]
ν_{max}/cm^{-1} (neat)	1512 (w), 1479 (w), 1455 (w).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	276 (6980), 235 (7620).
δ_H (300 MHz, $CDCl_3$)	7.34 (2H, ddd, *J* 8.2, 7.4, 1.7 Hz, Ar*H*), 7.25 (2H, dd, *J* 7.4, 1.7 Hz, Ar*H*), 7.02 (2H, td, *J* 7.4, 1.2 Hz, Ar*H*), 6.99 (2H, dd, *J* 8.2, 1.2 Hz, Ar*H*), 3.78 (6H, s, 2 × OCH_3) ppm.

δ_C (75 MHz, $CDCl_3$)	157.2 (2 × *C*), 131.6 (2 × *C*H), 128.8 (2 × *C*H), 127.9 (2 × *C*), 120.5 (2 × *C*H), 111.2 (2 × *C*H), 55.9 (2 × *C*H_3) ppm.
LRMS (EI)	214 (M^+, 100 %), 199 ($[M-CH_3]^+$, 18 %), 184 ($[M-C_2H_6]^+$, 31 %) amu.

2'-Methoxybiphenyl-2-ol **2.9**



1.128

$C_{12}H_{10}O_2$
Mol. Wt.: 186

2.9

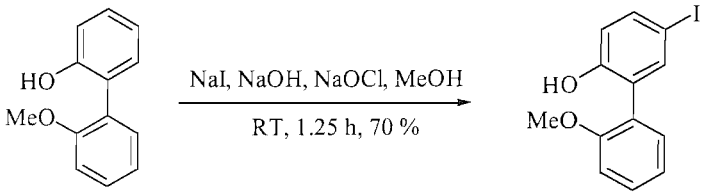
$C_{13}H_{12}O_2$
Mol. Wt.: 200

Iodomethane (1.08 mL, 17.30 mmol) was added to a mixture of potassium carbonate (2.36 g, 17.00 mmol) and **1.128** (3.15 g, 17.00 mmol) in acetone (30 mL). The reaction mixture was stirred for 24 h at RT, filtered, and solvent removed *in vacuo*. The crude reaction mixture was partitioned between dichloromethane (60 mL) and 2M HCl (50 mL). The aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic phases concentrated *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/9) gave **2.9** (2.69 g, 13.50 mmol, 79 %) as a white crystalline solid. The spectroscopic and physical data attained compares well with literature values.[19]

MP	77-78 °C (heptane) [Lit. 78 °C (heptane)][19]
ν_{max}/cm^{-1} (neat)	3385 (br), 2931w, 1498 (m), 1479 (m), 1455 (m), 1430 (m), 1228 (m).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	276 (10400).
δ_H (300 MHz, $CDCl_3$)	7.42 (1H, td, *J* 8.5, 1.8 Hz, Ar*H*), 7.37 (1H, dd, *J* 7.9, 1.8 Hz, Ar*H*), 7.35-7.30 (1H, m, Ar*H*),

	7.28 (1H, dd, *J* 7.3, 1.8 Hz, Ar*H*),
	7.15 (1H, td, *J* 7.3, 1.2 Hz, Ar*H*),
	7.07-7.04 (3H, m, 3 × Ar*H*),
	6.28 (1H, br. s, O*H*),
	3.92 (3H, s, OCH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	155.6 (*C*), 153.9 (*C*), 132.7 (*C*H), 131.5 (*C*H), 129.5 (*C*H), 129.4 (*C*H), 127.2 (*C*), 126.4 (*C*), 122.3 (*C*H), 121.2 (*C*H), 117.6 (*C*H), 111.7 (*C*H), 56.3 (CH_3) ppm.
LRMS (CI)	218 ($[M+NH_4]^+$, 78 %), 200 (M^+, 100 %) amu.

5-Iodo-2'-methoxybiphenyl-2-ol **2.10**



2.9

$C_{13}H_{12}O_2$
Mol. Wt.: 200

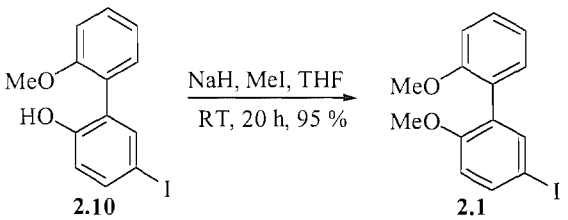
2.10

$C_{13}H_{11}IO_2$
Mol. Wt.: 326

Following the procedure for iodination of phenols by Edgar *et al.*[66], to a solution of **2.9** (6.30 g, 31.50 mmol) in methanol (50 mL), was added sodium iodide (4.78 g, 31.88 mmol) and NaOH (1.28 g, 32.0 mmol). Aqueous NaOCl (650 mM, 48.2 mL) was added dropwise over 75 min at 0 °C, and the reaction mixture was stirred for a further 1 h at 0 °C, followed by treatment with aq. sodium thiosulfate (10 % w/v, 20 mL). The mixture was adjusted to pH 7 using 2M aq. HCl, and extracted with ether (3 × 30 mL). The organic fractions were combined, dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/9) gave **2.10** (7.16 g, 21.96 mmol, 70 %) as an oil.

ν_{max}/cm^{-1} (neat)	1495 (m), 1479 (m), 1259 (m), 1230 (s).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	273 (4920).
δ_H (300 MHz, $CDCl_3$)	7.59-7.54 (2H, m, Ar*H*), 7.42 (1H, td, *J* 7.5, 1.6 Hz, Ar*H*), 7.32 (1H, dd, *J* 7.5, 1.6 Hz, Ar*H*), 7.14 (1H, td, *J* 7.4, 0.7 Hz, Ar*H*), 7.07-7.04 (1H, m, Ar*H*), 6.82 (1H, d, *J* 8.9 Hz, Ar*H*), 6.28 (1H, s, ArO*H*), 3.93 (3H, s, O*CH*$_3$) ppm.
δ_C (75 MHz, $CDCl_3$)	155.5 (*C*), 153.9 (*C*), 139.7 (*C*H), 138.0 (*C*H), 132.5 (*C*H), 130.1 (*C*H), 129.0 (*C*), 125.6 (*C*), 122.5 (*C*H), 119.9 (*C*H), 111.7 (*C*H), 83.1 (*C*), 56.4 (*C*H$_3$) ppm.
LRMS (EI)	326 (M^+, 100 %), 200 ($[MH-I]^+$, 20 %), 184 ($[M-ICH_3]^+$, 20 %) amu.
HRMS (EI)	Found M^+: 325.9803. $C_{13}H_{11}IO_2$ requires 325.9804.

5-Iodo-2,2'-dimethoxybiphenyl **2.1**



2.10
$C_{13}H_{11}IO_2$
Mol. Wt.: 326

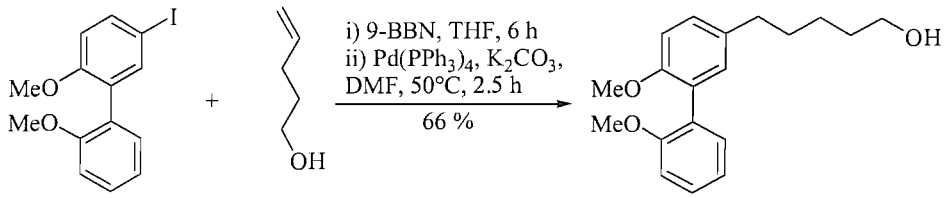
2.1
$C_{14}H_{13}IO_2$
Mol. Wt.: 340

NaH (60 % in mineral oil, 0.21 g, 8.75 mmol) was added to **2.10** (1.32 g, 4.05 mmol) in THF (10 mL) at 0 °C. Iodomethane (0.53 mL, 8.51 mmol) was added and the resulting mixture was warmed to RT and stirred under nitrogen for 20 h. The reaction mixture was partitioned between ether (20 mL) and water (20 mL). The phases were separated and the aqueous phase was extracted with chloroform (3 × 10 mL), organic fractions combined and

solvent removed *in vacuo*. Ether (10 mL) was added, and the solution was washed with brine (3 × 10 mL), dried ($MgSO_4$), and solvent removed under reduced pressure. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/5) gave **2.1** as a colourless oil (1.31 g, 3.85 mmol, 95 %).

ν_{max}/cm^{-1} (neat)	1579 (w), 1501 (m), 1480 (m), 1241 (s), 1028 (s).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	274 (11400).
δ_H (400 MHz, $CDCl_3$)	7.61 (1H, dd, *J* 8.5, 2.3 Hz, Ar*H*), 7.54 (1H, d, *J* 2.3 Hz, Ar*H*), 7.37-7.31 (1H, m, Ar*H*), 7.20 (1H, dd, *J* 7.3, 1.8 Hz, Ar*H*), 7.04-6.95 (2H, m, 2 × Ar*H*), 6.74 (1H, d, *J* 8.8 Hz, Ar*H*), 3.79 (3H, s, OC*H*$_3$), 3.76 (3H, s, OC*H*$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	157.5 (*C*), 157.3 (*C*), 140.2 (*C*H), 137.6 (*C*H), 131.6 (*C*H), 130.7 (*C*), 129.5 (*C*H), 126.7 (*C*), 120.8 (*C*H), 113.8 (*C*H), 111.5 (*C*H), 83.0 (*C*), 56.2 (*C*H$_3$), 56.1 (*C*H$_3$) ppm.
LRMS (CI)	358 ([M + NH_4]$^+$, 12 %), 341 (MH^+, 34 %), 215 ([MH_2-I]$^+$, 100 %) amu.
HRMS (EI)	Found M^+: 339.9962. $C_{14}H_{13}IO_2$ requires 339.9960.

5-(6,2'-Dimethoxybiphenyl-3-yl)pentan-1-ol **2.13**



2.1 $C_{14}H_{13}IO_2$ Mol. Wt.: 340

2.2 $C_6H_{12}O$ Mol. Wt.: 100

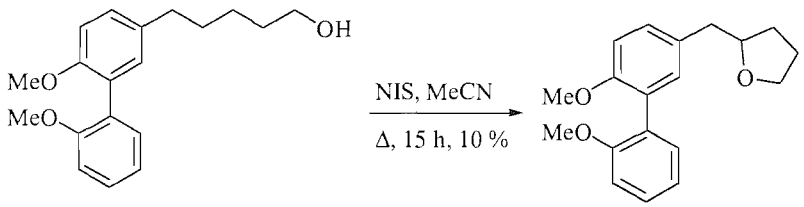
2.13 $C_{19}H_{24}O_3$ Mol. Wt.: 300

Following the procedure of Iglesias *et al.*[103], **2.2** (0.31 mL, 3.00 mmol) was dissolved in THF (20 mL) and 9-BBN (16.00 mL, 8.00 mmol) was slowly added at 0 °C over 10 min. After 6 h at RT, the solution was added to a solution of **2.1** (1.10 g, 3.26 mmol), $Pd(PPh_3)_4$ (300 mg, 0.26 mmol), and K_2CO_3 (1.79 g, 13.00 mmol) in DMF (30 mL). The mixture was heated at 50 °C for 2.5 h, then partitioned between ethyl acetate (60 mL) and water (40 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic fractions were washed with brine (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/1) gave **2.13** (590 mg, 1.97 mmol, 66 %) as a viscous oil.

ν_{max}/cm^{-1} (neat)	3153 (br, m), 2951 (m), 1470 (s), 1377 (s), 1095 (s).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	280 (4070).
δ_H (300 MHz, $CDCl_3$)	7.33 (1H, app. td, *J* 7.8, 1.8 Hz, Ar*H*), 7.26 (1H, dd, *J* 7.5, 1.8 Hz, Ar*H*), 7.13 (1H, dd, *J* 8.3, 2.3 Hz, Ar*H*), 7.07 (1H, d, *J* 2.3 Hz, Ar*H*), 7.05 (1H, app. td, *J* 7.3, 1.0 Hz, Ar*H*), 6.99 (1H, dd, *J* 8.0, 1.0 Hz, Ar*H*), 6.91 (1H, d, 8.3 Hz, Ar*H*), 3.79 (3H, s, OC*H*$_3$), 3.76 (3H, s, OC*H*$_3$), 3.65 (2H, t, *J* 6.5 Hz, OC*H*$_2$),

	2.61 (2H, t, *J* 5.8 Hz, ArCH_2),
	1.71-1.58 (4H, m, 2 × CH_2),
	1.47-1.39 (3H, m, CH_2 + O*H*) ppm.
δ_C (100 MHz, $CDCl_3$)	157.5 (*C*), 155.6 (*C*), 134.6 (*C*), 131.9 (2 × *C*H), 128.9 (*C*H), 128.6 (*C*H), 128.5 (*C*), 128.0 (*C*), 120.8 (*C*H), 111.6 (*C*H), 111.5 (*C*H), 63.4 (CH_2), 56.3 (CH_3), 56.1 (CH_3), 35.4 (CH_2), 33.1 (CH_2), 31.7 (CH_2), 25.8 (CH_2) ppm.
LRMS (CI)	318 ($[M + NH_4]^+$, 40 %), 301 (MH^+, 100 %) amu.
HRMS (EI)	Found M^+: 300.1731. $C_{19}H_{24}O_3$ requires 300.1725.

2-(6,2'-Dimethoxybiphenyl-3-ylmethyl)tetrahydrofuran **2.24**



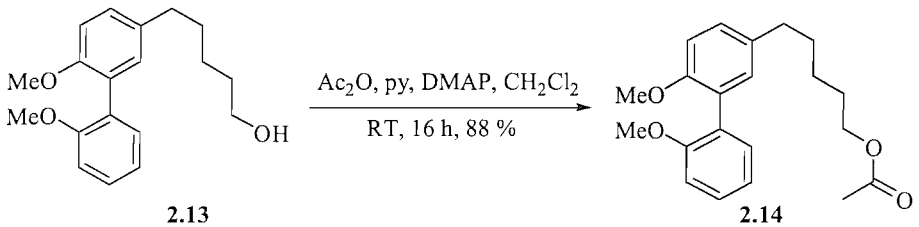
2.13
$C_{19}H_{24}O_3$
Mol. Wt.: 300

2.24
$C_{19}H_{22}O_3$
Mol. Wt.: 298

5-(6,2'-Dimethoxybiphenyl-3-yl)-pentan-1-ol **2.13** (83 mg, 0.28 mmol) was dissolved in acetonitrile (50 mL), and *N*-iodosuccinimide (68 mg, 0.30 mmol) was added. The mixture was heated at reflux for 4 h, then cooled to RT, concentrated *in vacuo* and purified by column chromatography (SiO_2, ether/petroleum ether, 3/1), to yield 2-(6,2'-dimethoxybiphenyl-3-ylmethyl)tetrahydrofuran **2.24** (8 mg, 27 μmol, 10 %).

ν_{max}/cm^{-1} (neat)	2931 (s), 1593 (m), 1505 (s), 1488 (s), 1242 (s), 1032 (s).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	279 (7000), 241 (4000).
δ_H (400 MHz, $CDCl_3$)	7.33 (1H, td, *J* 7.5, 1.8 Hz, Ar*H*), 7.25 (1H, dd, *J* 7.5, 1.8 Hz, Ar*H*), 7.19 (1H, dd, *J* 8.3 , 2.3 Hz, Ar*H*), 7.11 (1H, d, *J* 2.3 Hz, Ar*H*), 7.03-6.97 (2H, m, Ar*H*), 6.91 (1H, d, *J* 8.3 Hz, Ar*H*), 4.07 (1H, quin., *J* 6.6 Hz, OC*H*), 3.95-3.73 (2H, obs. m, OCH_2), 3.78 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 2.91 (1H, dd, *J* 13.7, 6.5 Hz, ArCH*H*), 2.71 (1H, dd, *J* 13.7, 6.5 Hz, ArCH*H*), 1.99-1.82 (2H, m, 2 × C*H*H), 1.62-1.57 (2H, m, 2 × C*H*H) ppm.
δ_C (100 MHz, $CDCl_3$)	157.3 (*C*), 155.9 (*C*), 132.5 (*C*H), 131.7 (*C*H), 130.8 (*C*), 129.4 (*C*H), 128.7 (*C*H), 128.1 (*C*), 127.9 (*C*), 120.5 (*C*H), 111.4 (*C*H), 111.3 (*C*H), 80.4 (*C*H), 68.1 (*C*H_2), 56.0 (*C*H_3), 55.9 (*C*H_3), 41.3 (*C*H_2), 31.1 (*C*H_2), 25.8 (*C*H_2) ppm.
LRMS (EI)	298 (M^+, 26 %), 227 ($[M-C_4H_7O]^+$, 55 %), 71 ($[C_4H_7O]^+$, 100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 321.1460. $C_{19}H_{22}O_3Na$ requires 321.1461.

5-(6,2'-dimethoxy-biphenyl-3-yl)pentyl acetate **2.14**



2.13
$C_{19}H_{24}O_3$
Mol. Wt.: 300

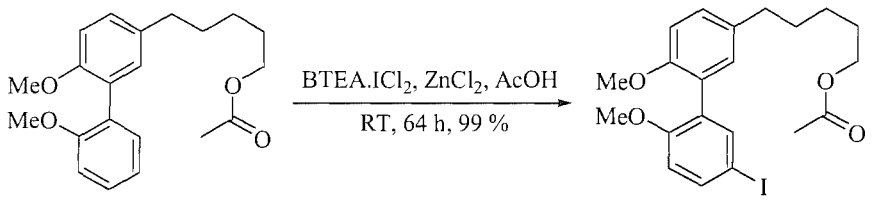
2.14
$C_{21}H_{26}O_4$
Mol. Wt.: 342

To a dichloromethane solution (10 mL) of **2.13** (350 mg, 1.17 mmol) were added acetic anhydride (0.13 mL, 1.40 mmol), pyridine (1 mL) and DMAP (80 mg, 0.65 mmol). The solution was stirred for 16 h then washed with 2M aq. HCl (20 mL), sat. sodium bicarbonate solution (3 × 20 mL) and brine (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield **2.14** (352 mg, 1.03 mmol, 88 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	1739 (s), 1508 (s), 1453 (s), 1263 (m), 1240 (m), 1032 (m).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	270 (4790).
δ_H (300 MHz, $CDCl_3$)	7.34 (1H, td, *J* 7.4, 1.8 Hz, Ar*H*), 7.26 (1H, dd, *J* 7.7, 1.5 Hz, Ar*H*), 7.14 (1H, dd, *J* 8.2, 2.2 Hz, Ar*H*), 7.07 (1H, d, *J* 2.2 Hz, Ar*H*), 7.02 (1H, td, *J* 7.4, 1.0 Hz, Ar*H*), 6.99 (1H, dd, *J* 8.2, 1.0 Hz, Ar*H*), 6.91 (1H, d, *J* 8.2 Hz, Ar*H*), 4.07 (2H, t, *J* 6.7 Hz, OCH_2), 3.79 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 2.61 (2H, t, *J* 7.4 Hz, ArCH_2), 2.05 (3H, s, COCH_3), 1.72-1.63 (4H, m, 2 × CH_2), 1.46-1.40 (2H, m, CH_2) ppm.

δ_C (75 MHz, $CDCl_3$)	171.4 (*C*), 157.2 (*C*), 155.3 (*C*), 134.2 (*C*), 131.7 (*C*H), 131.6 (*C*H), 128.7 (*C*H), 128.4 (*C*H), 128.1 (*C*), 127.7 (*C*), 120.5 (*C*H), 111.2 (*C*H), 111.2 (*C*H), 64.7 (CH_2), 56.0 (CH_3), 55.9 (CH_3), 35.0 (CH_2), 31.4 (CH_2), 28.6 (CH_2), 25.7 (CH_2), 21.2 (CH_3) ppm.
LRMS (EI)	342 (M^+, 28 %), 282 ($[MH-CH_3CO_2]^+$, 23 %), 227 ($[M-CH_3CO_2(CH_2)_4]^+$, 100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 365.1720. $C_{21}H_{26}O_4Na$ requires 365.1723.

5-(5'-Iodo-6,2'-dimethoxybiphenyl-3-yl)pentyl acetate **2.20**



2.14
$C_{21}H_{26}O_4$
Mol. Wt.: 342

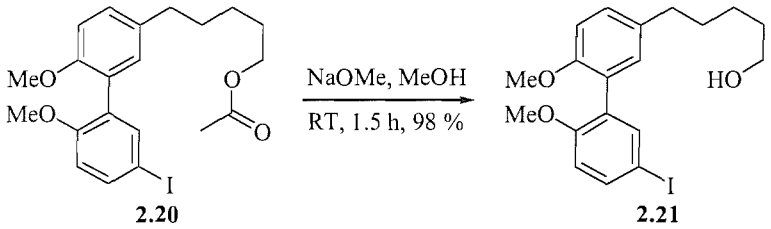
2.20
$C_{21}H_{25}IO_4$
Mol. Wt.: 468

$ZnCl_2$ (1 M in ether, 0.60 mL) and $BTEA.ICl_2$ (216 mg, 0.55 mmol) was added to **2.14** (145 mg, 0.42 mmol) in acetic acid (5 mL) and stirred at RT for 64 h. The reaction mixture was partitioned between ether (20 mL) and sat. $NaHCO_3$ (50 mL) and stirred for 2 h. The aqueous phase was extracted with ether (3 × 20 mL), organic fractions combined and washed with sat. $NaHCO_3$ (4 × 30 mL), sat. sodium thiosulfate (3 × 10 mL), and brine (3 × 10 mL) dried ($MgSO_4$) and concentrated *in vacuo* to yield **2.20** (197 mg, 0.42 mmol, 99 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	2931 (s), 2855 (m), 1734 (s), 1503 (m), 1479 (s), 1460 (m), 1384 (w), 1237 (s), 1034 (m).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	282 (15000).

δ_H (300 MHz, $CDCl_3$)	7.60 (1H, dd, *J* 8.5, 2.1 Hz, Ar*H*), 7.53 (1H, d, *J* 2.3 Hz, Ar*H*), 7.14 (1H, dd, *J* 8.5, 2.3 Hz, Ar*H*), 7.01 (1H, d, *J* 2.1 Hz, Ar*H*), 6.89 (1H, d, *J* 8.2 Hz, Ar*H*), 6.74 (1H, d, *J* 8.7 Hz, Ar*H*), 4.07 (2H, t, *J* 6.8 Hz, OCH_2), 3.77 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 2.60 (2H, t, *J* 7.5 Hz, ArCH_2), 2.05 (3H, s, COCH_3), 1.72-1.61 (4H, m, 2 × CH_2), 1.47-1.37 (2H, m, CH_2) ppm.
δ_C (75 MHz, $CDCl_3$)	171.4 (*C*), 157.2 (*C*), 155.2 (*C*), 139.9 (*C*H), 137.3 (*C*H), 134.4 (*C*), 131.3 (*C*H), 130.7 (*C*), 128.9 (*C*H), 126.2 (*C*), 113.5 (*C*H), 111.1 (*C*H), 82.8 (*C*), 64.7 (*C*H_2), 56.0 (2 × *C*H_3), 35.0 (*C*H_2), 31.4 (*C*H_2), 28.6 (*C*H_2), 25.8 (*C*H_2), 21.2 (*C*H_3) ppm.
LRMS (CI)	468 (M^+, 40 %), 342 ($[MH\text{-}I]^+$, 75 %), 282 ($[M\text{-}I\text{-}CH_3CO_2]^+$, 22 %), 227 ($[MH\text{-}I\text{-}CH_3CO_2(CH_2)_4]^+$, 100 %) amu.
HRMS (ES+)	Found $[2M+Na]^+$: 959.1484. $C_{42}H_{50}O_8I_2Na$ requires 959.1487.

5-(5'-Iodo-6,2'-dimethoxybiphenyl-3-yl)pentan-1-ol **2.21**



2.20

$C_{21}H_{25}IO_4$
Mol. Wt.: 468

2.21

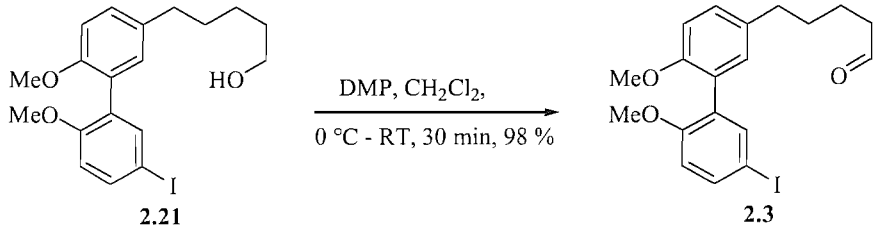
$C_{19}H_{23}IO_3$
Mol. Wt.: 426

Sodium metal (22 mg, 0.96 mmol) was added portionwise to methanol (20 mL). **2.20** (190 mg, 0.41 mmol) was added and the mixture was stirred for 1.5 h at RT. The solution was acidified to pH 1 with 2M aq. HCl, and concentrated *in vacuo*. The crude reaction mixture was extracted with CH_2Cl_2 (4 × 10 mL), organic fractions combined and washed with brine (3 × 10 mL), dried ($MgSO_4$) and the solvent removed under vacuum to yield **2.21** (172 mg, 0.40 mmol, 98 %) as a clear oil.

ν_{max}/cm^{-1} (neat)	3368 (br, m), 2926 (s), 2846 (m), 1502 (s), 1484 (s), 1461 (s), 1262 (s), 1242 (s).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	283 (5000).
δ_H (300 MHz, $CDCl_3$)	7.60 (1H, dd, *J* 8.5, 2.4 Hz, Ar*H*), 7.53 (1H, d, *J* 2.4 Hz, Ar*H*), 7.15 (1H, dd, *J* 8.2, 2.4 Hz, Ar*H*), 7.02 (1H, d, *J* 2.4 Hz, Ar*H*), 6.89 (1H, d, *J* 8.5 Hz, Ar*H*), 6.74 (1H, d, *J* 8.7 Hz, Ar*H*), 3.76 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.65 (2H, t, *J* 6.6 Hz, CH_2OH), 2.60 (2H, t, *J* 7.5 Hz, ArCH_2), 1.71-1.56 (4H, m, 2 × CH_2), 1.49-1.39 (3H, m, CH_2 + O*H*) ppm.
δ_C (75 MHz, $CDCl_3$)	157.2 (*C*), 155.1 (*C*), 139.9 (*C*H), 137.3 (*C*H), 134.5 (*C*),

	131.6 (*C*), 131.3 (*C*H), 128.9 (*C*H), 126.1 (*C*), 113.5 (*C*H), 111.1 (*C*H), 82.8 (*C*), 63.1 (*C*H_2), 56.0 (2 × *C*H_3), 35.1 (*C*H_2), 32.8 (*C*H_2), 31.5 (*C*H_2), 25.6 (*C*H_2) ppm.
LRMS (CI)	427 (MH^+, 100 %) amu.
HRMS (ES+)	Found $[2M+Na]^+$: 875.1284. $C_{38}H_{46}O_6I_2Na$ requires 875.1276.

5-(5'-Iodo-6,2'-dimethoxybiphenyl-3-yl)pentanal **2.3**



2.21

$C_{19}H_{23}IO_3$
Mol. Wt.: 426

2.3

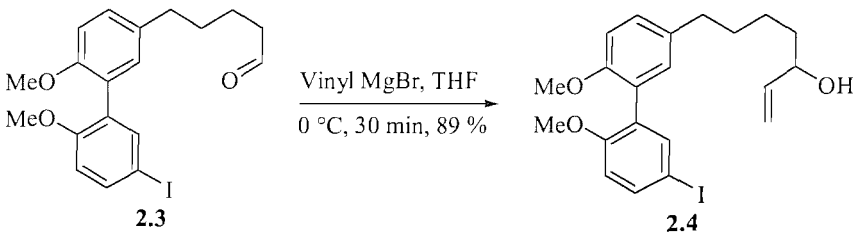
$C_{19}H_{21}IO_3$
Mol. Wt.: 424

Dess-Martin periodinane (210 mg, 0.50 mmol) was added to **2.21** (170 mg, 0.40 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was warmed to RT, stirred for 30 min, followed by addition of 1M aq. NaOH (10 mL) and Et_2O (20 mL) and stirred for a further 20 min. The organic phase was washed with 1M NaOH (3 × 10 mL), water (3 × 10 mL) and brine (3 × 10 mL), dried ($MgSO_4$) and the solvent removed under vacuum to yield **2.3** (165 mg, 0.39 mmol, 98 %) as a clear oil.

ν_{max}/cm^{-1} (neat)	2921 (s), 2851 (m), 1720 (s), 1498 (s), 1479 (s), 1460 (s), 1238 (s), 1020 (m).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	281 (12200).
δ_H (300 MHz, $CDCl_3$)	9.77 (1H, t, *J* 1.7 Hz, C*H*O) 7.60 (1H, dd, *J* 8.7, 2.4 Hz, Ar*H*), 7.52 (1H, d, *J* 2.1 Hz, Ar*H*), 7.14 (1H, dd, *J* 8.2, 2.1 Hz, Ar*H*),

	7.01 (1H, d, *J* 1.9 Hz, Ar*H*),
	6.88 (1H, d, *J* 8.5 Hz, Ar*H*),
	6.74 (1H, d, *J* 8.7 Hz, Ar*H*),
	3.76 (3H, s, OCH_3),
	3.75 (3H, s, OCH_3),
	2.61 (2H, t, *J* 7.1 Hz, ArCH_2),
	2.47 (2H, td, *J* 6.8, 1.7 Hz, C(O)CH_2),
	1.71-1.66 (4H, m, 2 × CH_2) ppm.
δ_C (75 MHz, $CDCl_3$)	202.8 (*C*H), 157.2 (*C*), 155.3 (*C*), 139.9 (*C*H), 137.3 (*C*H), 133.9 (*C*), 131.3 (*C*H), 130.7 (*C*), 128.9 (*C*H), 126.2 (*C*), 113.5 (*C*H), 111.2 (*C*H), 82.8 (*C*), 56.0 (2 × *C*H_3), 44.0 (*C*H_2), 34.9 (*C*H_2), 31.2 (*C*H_2), 21.9 (*C*H_2) ppm.
LRMS (EI)	424 (M^+, 100 %), 353 ([M-HC(O)$(CH_2)_3$]$^+$, 42 %) amu.
HRMS (EI)	Found M^+: 424.0530. $C_{19}H_{21}O_3I$ requires 424.0524.

7-(5'-Iodo-6,2'-dimethoxybiphenyl-3-yl)hept-1-en-3-ol **2.4**



2.3

$C_{19}H_{21}IO_3$
Mol. Wt.: 424

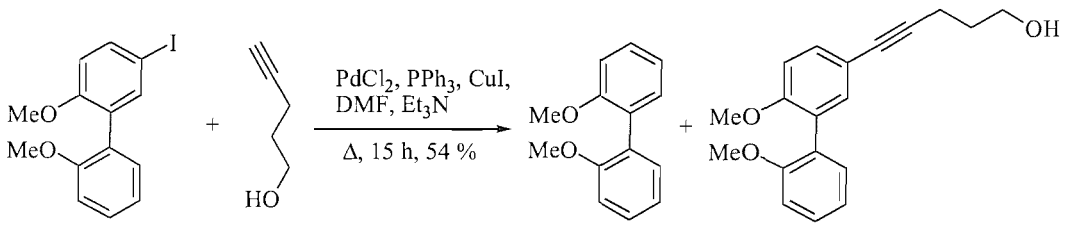
2.4

$C_{21}H_{25}IO_3$
Mol. Wt.: 452

To a cooled (0 °C) solution of **2.3** (150 mg, 0.35 mmol) in THF (5 mL) was added vinylmagnesium bromide (1M in THF, 0.41 mL, 0.41 mmol). After 30 min, sat. ammonium chloride (10 mL) was added. Following extraction with ether (3 × 10 mL), the organic fractions were combined, washed with brine (3 × 10 mL), dried ($MgSO_4$) and the solvent removed under vacuum to yield **2.4** (140 mg, 0.31 mmol, 89 %).

ν_{max}/cm^{-1} (neat)	3400 (br, m), 2926 (s), 2851 (m), 1479 (s), 1243 (s), 1033 (m), 993 (w), 914 (m).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	281 (6660).
δ_H (300 MHz, $CDCl_3$)	7.60 (1H, dd, *J* 8.7, 2.4 Hz, Ar*H*), 7.53 (1H, d, *J* 2.1 Hz, Ar*H*), 7.14 (1H, dd, *J* 8.5, 2.4 Hz, Ar*H*), 7.01 (1H, d, *J* 2.1 Hz, Ar*H*), 6.88 (1H, d, *J* 8.2 Hz, Ar*H*), 6.74 (1H, d, *J* 8.7 Hz, Ar*H*), 5.88 (1H, ddd, *J* 17.1, 10.3, 6.3 Hz, C*H*=CH_2) 5.23 (1H, dt, *J* 17.1, 1.2 Hz, HC=CH*H*), 5.11 (1H, dt, *J* 10.3, 1.2 Hz, HC=C*H*H), 4.11 (1H, td, *J* 6.3, 6.1 Hz, C*H*OH) 3.76 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 2.59 (2H, t, *J* 7.6 Hz, ArCH_2), 1.70-1.39 (7H, m, 3 × CH_2 + O*H*) ppm.
δ_C (75 MHz, $CDCl_3$)	157.2 (*C*), 155.1 (*C*), 141.4 (*C*H), 139.9 (*C*H), 137.3 (*C*H), 134.6 (*C*), 131.3 (*C*H), 130.8 (*C*), 128.9 (*C*H), 126.2 (*C*), 114.9 (*C*H_2), 113.5 (*C*H), 111.1 (*C*H), 82.8 (*C*), 73.4 (*C*H), 56.0 (2 × *C*H_3), 37.0 (*C*H_2), 35.1 (*C*H_2), 31.7 (*C*H_2), 25.2 (*C*H_2) ppm.
LRMS (EI)	452 (M^+, 76 %), 353 ([M-$C_6H_{11}O$]$^+$, 100 %), 307 (5 %), 227 (14 %), 211 (10 %) amu.
HRMS (EI)	Found M^+: 452.0860. $C_{21}H_{25}O_3I$ requires 452.0849.

5-(6,2'-Dimethoxybiphenyl-3-yl)pent-4-yn-1-ol **2.12**



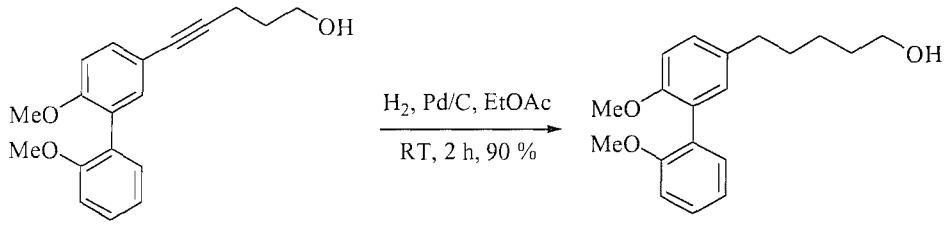
2.1 $C_{14}H_{13}IO_2$ Mol. Wt.: 340 | **2.11** C_5H_8O Mol. Wt.: 84 | **2.8** 27 % $C_{14}H_{14}O_2$ Mol. Wt.: 214 | **2.12** 27 % $C_{19}H_{20}O_3$ Mol. Wt.: 296

Following the general procedure of Sonogashira coupling reported by Tsukayama *et al.*,[67] 5-iodo-2,2'-dimethoxybiphenyl **2.1** (0.50 g, 1.5 mmol) was dissolved in a solution of DMF (15 mL) and Et_3N (15 mL). $PdCl_2$ (8 mg, 0.045 mmol) and PPh_3 (23.6 mg, 0.09 mmol) were added, followed by addition of CuI (5.7 mg, 0.045 mmol) and 4-pentyn-1-ol **2.11** (0.41 mL, 4.40 mmol). The mixture was heated under reflux for 15 h then cooled to RT and concentrated *in vacuo*. The crude reaction mixture was partitioned between ether (30 mL) and water (30 mL). The aqueous phase was extracted with ether (4 × 30 mL) and the combined organic fractions were washed with water (3 × 20 mL) and brine (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield a crude product (573 mg). Purification by column chromatography (SiO_2, ether/petroleum ether, 3/1) firstly yielded 2,2'dimethoxybiphenyl **2.8** (83 mg, 0.39 mmol, 27 %), and finally 5-(6,2'-dimethoxybiphenyl-3-yl)pent-4-yn-1-ol **2.12** (117 mg, 0.40 mmol, 27 %).

ν_{max}/cm^{-1} (neat)	3385 (br, m), 2941 (m), 2241 (w), 1593 (m), 1479 (s), 1238 (s), 1020 (s).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	274 (9150), 251 (32500), 238 (37300).
δ_H (400 MHz, $CDCl_3$)	7.37 (1H, dd, *J* 8.5, 1.8 Hz, Ar*H*), 7.34 (1H, app. td, *J* 7.5, 1.8 Hz, Ar*H*), 7.30 (1H, d, *J* 2.3 Hz, Ar*H*), 7.22 (1H, dd, *J* 7.5, 1.8 Hz, Ar*H*), 7.00 (1H, app. td, *J* 7.5, 1.0 Hz, Ar*H*), 6.97 (1H, dd, *J* 8.5, 1.0 Hz, Ar*H*),

	6.88 (1H, d, *J* 8.5 Hz, Ar*H*),
	3.82 (2H, t, *J* 6.3 Hz, OCH_2),
	3.78 (3H, s, OCH_3),
	3.77 (3H, s, OCH_3),
	2.53 (2H, t, *J* 5.3 Hz, CCH_2),
	1.85 (2H, app. quin, *J* 6.3 Hz, $CH_2CH_2CH_2$),
	1.45 (1H, s, O*H*) ppm.
δ_C (100 MHz, $CDCl_3$)	157.5 (*C*), 157.2 (*C*), 135.1 (*C*H), 132.3 (*C*H), 131.7 (*C*H), 129.2 (*C*H), 128.4 (*C*), 127.5 (*C*), 120.8 (*C*H), 116.0 (*C*), 111.5 (*C*H), 111.3 (*C*H), 88.0 (*C*), 81.5 (*C*), 62.4 (CH_2), 56.2 (OCH_3), 56.1 (OCH_3), 31.9 (CH_2), 16.5 (CH_2) ppm.
LRMS (CI)	297 (MH^+, 100 %) amu.
HRMS (EI)	Found M^+: 296.1408. $C_{19}H_{20}O_3$ requires 296.1412.

5-(6,2'-Dimethoxybiphenyl-3-yl)pentan-1-ol **2.13**



2.12

$C_{19}H_{20}O_3$
Mol. Wt.: 296

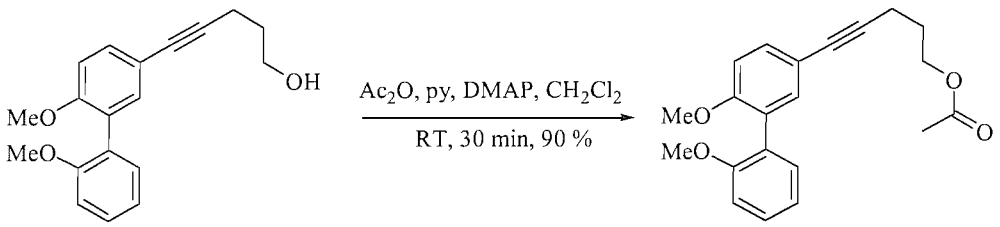
2.13

$C_{19}H_{24}O_3$
Mol. Wt.: 300

5-(6,2'-Dimethoxy-biphenyl-3-yl)pent-4-yn-1-ol **2.12** (102 mg, 0.035 mmol) was dissolved in EtOAc (50 mL) and the Pd/C catalyst (5 % w/w, 40 mg, 0.38 g.atom) was added. The reaction was vigorously stirred under a hydrogen atmosphere for 2 h, then filtered through Celite and concentrated *in vacuo* to yield 5-(6,2'-dimethoxybiphenyl-3-yl)pentan-1-ol **2.13** (93 mg, 0.31 mmol, 90 %) as a clear oil.

Spectral data was identical to that reported above.

5-(6,2'-Dimethoxybiphenyl-3-yl)pent-4-ynyl acetate **2.12a**



2.12

$C_{19}H_{20}O_3$
Mol. Wt.: 296

2.12a

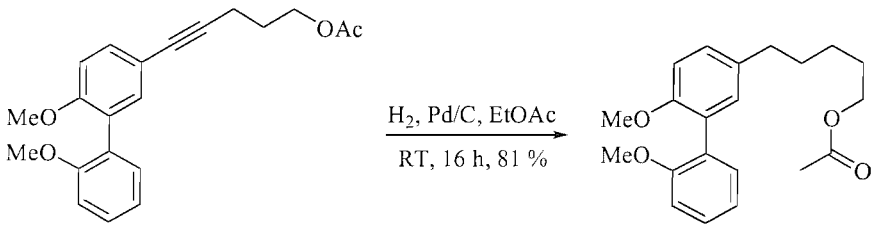
$C_{21}H_{22}O_4$
Mol. Wt.: 338

To a dichloromethane solution (20 mL) of **2.12** (268 mg, 0.91 mmol) were added acetic anhydride (0.1 mL, 1.06 mmol), pyridine (1 mL) and DMAP (50 mg, 0.42 mmol). The solution was stirred for 30 min, and then washed with 2M HCl (3 × 10 mL), water (3 × 10 mL), sat. sodium bicarbonate (3 × 10 mL), brine (3 × 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield **2.12a** (276 mg, 0.817 mmol, 90 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	1739 (m), 1504 (m), 1485 (m), 1240 (s), 1045 (s).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	277 (11800), 254 (35800), 236 (41200)
δ_H (300 MHz, $CDCl_3$)	7.38 (1H, dd, *J* 8.7, 2.2 Hz, Ar*H*), 7.35 (1H, obs. app. td, *J* 7.5, 1.7 Hz, Ar*H*), 7.30 (1H, d, *J* 2.2 Hz, Ar*H*), 7.22 (1H, dd, *J* 7.5, 1.7 Hz, Ar*H*), 7.01-6.97 (2H, m, 2 × Ar*H*), 6.89 (1H, d, *J* 8.7 Hz, Ar*H*), 4.23 (2H, t, *J* 6.2 Hz, OCH_2), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 2.51 (2H, t, *J* 7.0 Hz, C≡CCH_2), 2.08 (3H, s, COCH_3), 1.93 (2H, app. quint., *J* 6.7 Hz, CH_2) ppm.

δ_C (75 MHz, $CDCl_3$)	171.2 (*C*), 157.1 (*C*), 156.9 (*C*), 134.8 (*C*H), 132.1 (*C*H), 131.5 (*C*H), 129.0 (*C*H), 128.1 (*C*), 127.2 (*C*), 120.5 (*C*H), 115.6 (*C*), 111.2 (*C*H), 111.0 (*C*H), 87.0 (*C*), 81.2 (*C*), 63.4 (CH_2), 55.9 (CH_3), 55.8 (CH_3), 28.1 (CH_2), 21.2 (CH_3), 16.4 (CH_2) ppm.
LRMS (EI)	338 (M^+, 74 %), 295 ($[M-CH_3CO]^+$, 47 %), 278 ($[M-CH_3CO_2H]^+$, 100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 361.1410. $C_{21}H_{22}O_4Na$ requires 361.1410.

5-(6,2'-Dimethoxybiphenyl-3-yl)pentyl acetate **2.14**



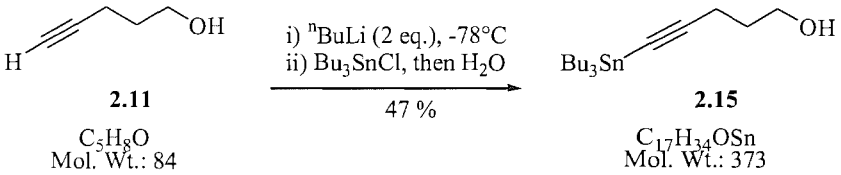
2.12a
$C_{21}H_{22}O_4$
Mol. Wt.: 338

2.14
$C_{21}H_{26}O_4$
Mol. Wt.: 342

2.12a (250 mg, 0.74 mmol) was dissolved in EtOAc (100 mL) and the Pd/C catalyst (5 % w/w, 101 mg, 0.96 g.atom) was added. The reaction was stirred vigorously under a hydrogen atmosphere for 16 h, then filtered through Celite and concentrated *in vacuo* to yield **2.14** (205 mg, 0.60 mmol, 81 %) as a colourless oil.

Spectral data was identical to that reported above.

5-Tributylstannanyl-pent-4-yn-1-ol **2.15**



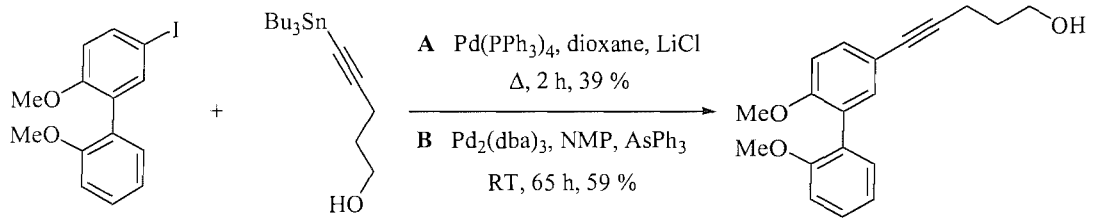
2.11
C_5H_8O
Mol. Wt.: 84

2.15
$C_{17}H_{34}OSn$
Mol. Wt.: 373

n-Butyl lithium (5.5 mL, 11.70 mmol) was added to **2.11** (0.5 mL, 5.37 mmol) in THF (5 mL) at –78 °C and stirred for 40 mins. Tributyltin chloride (3 mL, 11.00 mmol) was slowly added at –78 °C and stirred for a further 2 h. The reaction mixture was warmed to RT and partitioned between ether (20 mL) water (20 mL). The aqueous layer was extracted with ether (3 × 20 mL), organic fractions combined and washed with brine (3 × 20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/4) gave **2.15** (0.93 g, 2.50 mmol, 47 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	3319 (br, m), 2956 (s), 2926 (s), 2872 (s), 2853 (s), 2142 (m), 1464 (m), 1071 (m).
δ_H (300 MHz, $CDCl_3$)	3.78 (2H, app. q, *J* 6.0 Hz, CH_2O), 2.39 (2H, t, *J* 6.7 Hz, CH_2), 1.78 (2H, app. quint, *J* 6.7 Hz, CH_2), 1.60-1.50 (6H, m, 3 × CH_2), 1.40-1.26 (6H, m, 3 × CH_2), 1.00-0.84 (15H, m, 3 × CH_2 + 3 × CH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	111.1 (*C*), 62.5 (CH_2), 31.7 (CH_2), 29.0 (3 × CH_2), 27.1 (3 × CH_2), 22.8 (*C*), 17.2 (CH_2), 13.8 (3 × CH_3), 11.1 (3 × CH_2) ppm.
LRMS	Did not fly by GCMS

5-(6,2'-Dimethoxybiphenyl-3-yl)pent-4-yn-1-ol **2.12**



2.1 $C_{14}H_{13}IO_2$ Mol. Wt.: 340

2.15 $C_{17}H_{34}OSn$ Mol. Wt.: 373

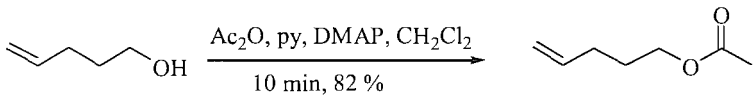
2.12 $C_{19}H_{20}O_3$ Mol. Wt.: 296

Method **A**: Following the general procedure for Stille coupling reported by Cummins *et al.*[104], **2.15** (0.93 g, 2.50 mmol) was combined with **2.1** (0.85 g, 2.51 mmol), $Pd(PPh_3)_4$ (139 mg, 0.12 mmol) and LiCl (0.66 g. 15.53 mmol) in dioxane (15 mL). The mixture was heated under reflux for 2 h, cooled to RT, and 10 % aq. NH_3 (10 mL) added. The mixture was extracted with ether (3 × 10 mL), organic fractions combined, and washed with brine (3 × 20 mL), dried ($MgSO_4$), and solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/1), gave **2.12** (288 mg, 0.97 mmol, 39 %) as a viscous green oil.

Method **B**: Following the general procedure for Stille coupling reported by Dominguez *et al.*[69], **2.1** (0.81 g, 2.39 mmol) in NMP (2 mL) was added to $Pd_2(dba)_3$ (88 mg, 0.10 mmol), and $AsPh_3$ (271 mg, 0.88 mmol) in NMP (20 mL). The mixture was stirred for 10 min before addition of **2.15** (2.09 g, 5.61 mmol) in NMP (5 mL), and subsequently stirred for 65 h at RT. 10 % aq. KF solution (10 mL) was added and stirred for 30 mins. The mixture was extracted with ether (3 × 10 mL), organic fractions combined, and washed with water (3 × 20 mL), 10 % aq. KF solution (3 × 20 mL), brine (3 × 20 mL), dried ($MgSO_4$), and solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/1), gave **2.12** (420 mg, 1.42 mmol, 59 %) as an oil.

Spectral data was identical to that reported above.

4-Pentenyl acetate **2.16**



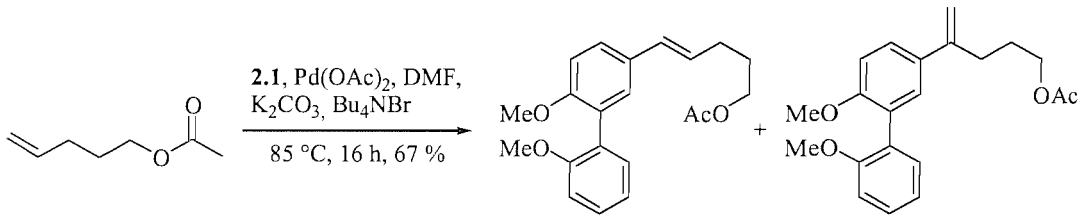
2.2
$C_5H_{10}O$
Mol. Wt.: 86

2.16
$C_7H_{12}O_2$
Mol. Wt.: 128

A dichloromethane solution (20 mL) of 4-penten-1-ol **2.2** (3.6 mL, 35.00 mmol) was treated with acetic anhydride (3.5 mL, 37 mmol), pyridine (3.5 mL) and DMAP (18 mg, 0.15 mmol). The solution was stirred for 10 min then washed with 2M HCl (3 × 20 mL), sat. sodium bicarbonate solution (3 × 30 mL) and brine (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield **2.16** (3.69 g, 28.83 mmol, 82 %) as a colourless oil.
The yield and spectroscopic data compares well with literature values.[105]

ν_{max}/cm^{-1} (neat)	1739 (s), 1508 (s), 1453 (s), 1263 (m), 1240 (m), 1032 (m).
δ_H (300 MHz, $CDCl_3$)	5.80 (1H, ddt, *J* 17.0, 10.1, 6.8 Hz, C*H*=CH_2), 5.07-4.96 (2H, m, CH=CH_2), 4.07 (2H, t, *J* 6.6 Hz, CH_2O), 2.16-2.08 (2H, m, CH_2CH), 2.04 (3H, s, CH_3), 1.72 (2H, app. quint., *J* 6.6 Hz, CH_2) ppm.
δ_C (75 MHz, $CDCl_3$)	171.3 (*C*), 137.6 (*C*H), 115.4 (*C*H_2), 64.0 (*C*H_2), 30.2 (*C*H_2), 27.9 (*C*H_2), 21.1 (*C*H_3) ppm.
LRMS (EI)	129 (MH^+, 32 %), 69 ($[M\text{-}CH_3CO_2]^+$, 75 %), 67 ($[M\text{-}C_2H_5O_2]^+$, 100 %) amu.

5-(6,2'-Dimethoxy-biphenyl-3-yl)-pent-4-enyl acetate **2.17** and 4-(6,2'-dimethoxy-biphenyl-3-yl)-pent-4-enyl acetate **2.18**

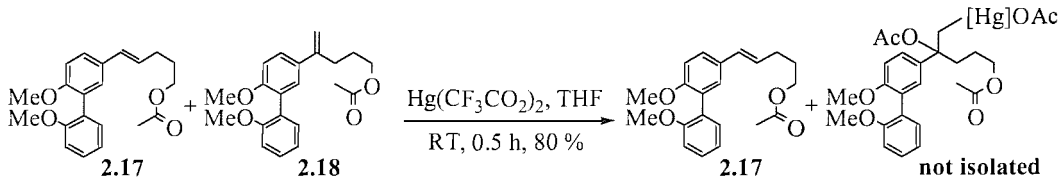


2.16 $C_7H_{12}O_2$ Mol. Wt.: 128

2.17 $C_{21}H_{24}O_4$ Mol. Wt.: 340 4:1 **2.18** $C_{21}H_{24}O_4$ Mol. Wt.: 340

To a solution of **2.1** (3.03 g, 8.91 mmol) in DMF (30 mL) was added $Pd(OAc)_2$ (126 mg, 0.56 mmol), K_2CO_3 (4.93 g, 35.72 mmol), Bu_4NBr (2.88 g, 8.93 mmol), and **2.16** (1.16 g, 9.06 mmol). The mixture was heated at 85 °C for 16 h then cooled, and partitioned between EtOAc (50 mL) and water (80 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL), and the combined organic fractions were washed with water (3 × 30 mL) and brine (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/7) gave firstly reduced starting material **2.8** (350 mg, 1.64 mmol, 18 %), then a 4:1 inseparable mixture of **2.17** and **2.18** (1.99 g, 5.85 mmol, 67 %) as a colourless oil. The isomers were subjected to mercuration thus allowing separation and purification of **2.17** as described below.

5-(6,2'-Dimethoxy-biphenyl-3-yl)-pent-4-enyl acetate **2.17**



2.17 **2.18** **2.17** **not isolated**

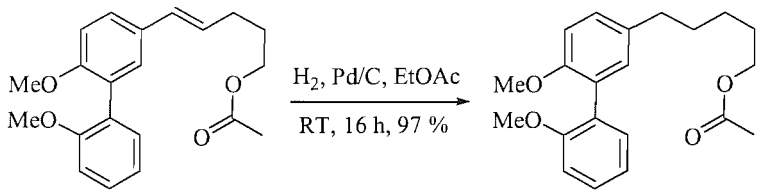
$C_{21}H_{24}O_4$ Mol. Wt.: 340 $C_{21}H_{24}O_4$ Mol. Wt.: 340 $C_{21}H_{24}O_4$ Mol. Wt.: 340

To a stirred solution of alkenes **2.17** and **2.18** (~ 4:1 respectively, 1.68 g, 4.94 mmol) in THF (30 mL), was added mercuric(II) trifluoroacetate (425 mg, 1.00 mmol).[67] The mixture was stirred at RT for 0.5 h, silica (1 g) was added and the solvent removed under reduced pressure. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/4), gave **2.17** (1.34 g, 3.93 mmol, 80 %) as a colourless oil.

ν_{max}/cm^{-1} (neat)	1740 (s), 1595 (m), 1500 (s), 1483 (s), 1240 (s), 1038 (m).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	262 (8500), 241 (8300).
δ_H (300 MHz, $CDCl_3$)	7.38-7.23 (4H, m, 4 × Ar*H*), 7.05-6.98 (2H, m, 2 × Ar*H*), 6.92 (1H, d, *J* 8.2 Hz, Ar*H*), 6.39 (1H, d, *J* 16.0 Hz, ArC*H*=CH), 6.07 (1H, dt, *J* 16.0, 7.0 Hz, ArCH=C*H*), 4.12 (2H, t, *J* 6.6 Hz, OCH_2), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 2.27 (2H, app. q, 7.0 Hz, CHCH_2), 2.07 (3H, s, COCH_3), 1.80 (2H, app. quin, *J* 6.8 Hz, CH_2) ppm.
δ_C (75 MHz, $CDCl_3$)	171.4 (*C*), 157.2 (*C*), 156.5 (*C*), 131.5 (*C*H), 130.3 (*C*H), 130.2 (*C*), 129.1 (*C*H), 128.9 (*C*H), 128.1 (*C*), 127.9 (*C*), 127.3 (*C*H), 126.5 (*C*H), 120.5 (*C*H), 111.3 (*C*H), 111.2

	(*C*H), 64.2 (*C*H_2), 56.0 (*C*H_3), 55.9 (*C*H_3), 29.5 (*C*H_2), 28.6 (*C*H_2), 21.2 (*C*H_3) ppm.
LRMS (CI)	341 (MH^+, 100 %), 281 ($[M\text{-}CH_3CO_2]^+$, 42 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 363.1568. $C_{21}H_{24}O_4Na$ requires 363.1567.

5-(6,2'-Dimethoxybiphenyl-3-yl pentyl acetate **2.14**



2.17

$C_{21}H_{24}O_4$
Mol. Wt.: 340

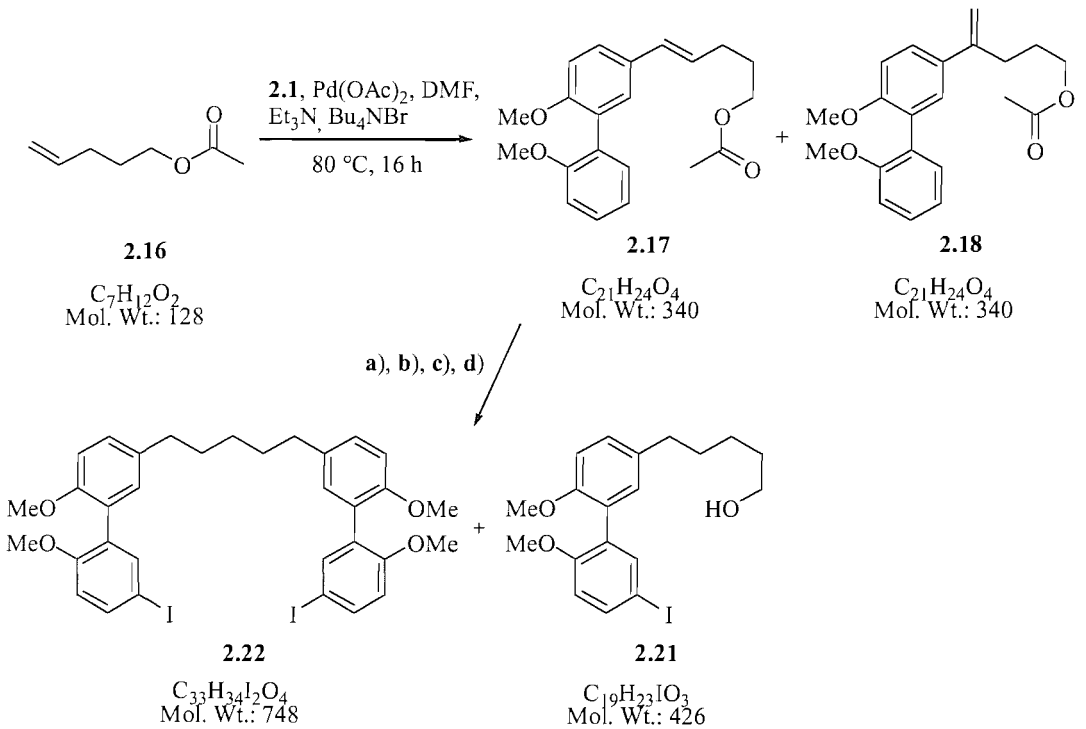
2.14

$C_{21}H_{26}O_4$
Mol. Wt.: 342

Pd/C catalyst (5 % w/w, 101 mg, 0.96 g.atom) was added to **2.17** (1.34 g, 3.93 mmol) in EtOAc (100 mL). The reaction was stirred vigorously under a hydrogen atmosphere for 16 h, then filtered through Celite and concentrated *in vacuo* to yield **2.14** (1.29 g, 3.77 mmol, 96 %) as a colourless oil.

Spectral data was identical to that reported above.

1,5(Bis-(5'-iodo-6,2'-dimethoxybiphenyl-3-yl)pentane **2.22** and 5-(5'-iodo-6,2'-dimethoxybiphenyl-3-yl)pentan-1-ol **2.21**



2.16
$C_7H_{12}O_2$
Mol. Wt.: 128

2.17
$C_{21}H_{24}O_4$
Mol. Wt.: 340

2.18
$C_{21}H_{24}O_4$
Mol. Wt.: 340

a), b), c), d)

2.22
$C_{33}H_{34}I_2O_4$
Mol. Wt.: 748

2.21
$C_{19}H_{23}IO_3$
Mol. Wt.: 426

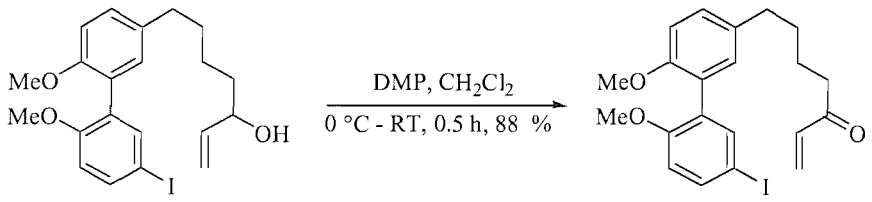
To a solution of **2.1** (6.27 g, 18.44 mmol) in DMF (50 mL) was added $Pd(OAc)_2$ (210 mg, 0.94 mmol), triethylamine (10.3 mL, 74.0 mmol), Bu_4NBr (6.10 g, 18.90 mmol), and **2.16** (2.48 g, 19.38 mmol). The mixture was heated at 80-90 °C for 16 h then cooled, and partitioned between EtOAc (50 mL) and water (80 mL). The aqueous phase was extracted with EtOAc (3 × 30 mL), and the combined organic fractions were washed with water (3 × 30 mL) and brine (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/7) gave firstly reduced starting material **2.8** (2.10 g, 9.81 mmol, 53 %), then an inseparable mixture of **2.17**, **2.18** and an unknown compound (2.79 g) as a clear oil. Removal of **2.18** was achieved by treatment of the mixture with $Hg(CF_3CO_2)_2$ (**a**) followed by column chromatography (*viz* **2.17** + **2.18** → **2.17**). Hydrogenation (**b**) of the alkene (*viz* **2.17** → **2.14**), iodination (**c**) (*viz* **2.14** → **2.20**) and saponification (**d**) of the ester (*viz* **2.20** → **2.21**) then gave after column chromatography

(SiO_2, ether/petroleum ether, 1/7) **2.22** (428 mg, 0.57 mmol) as a white solid and **2.21** (1.42 g, 3.03 mmol) as a colourless oil.

Data for **2.22**

MP	111-113 °C (acetonitrile)
ν_{max}/cm^{-1} (neat)	1501 (m), 1483 (m), 1459 (m), 1262 (m), 1242 (s), 1031 (m).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	279 (10400).
δ_H (300 MHz, $CDCl_3$)	7.60 (2H, dd, *J* 8.7, 2.4 Hz, 2 × Ar*H*), 7.54 (2H, d, *J* 2.4 Hz, 2 × Ar*H*), 7.14 (2H, dd, *J* 8.5, 2.4 Hz, 2 × Ar*H*), 7.02 (2H, d, *J* 2.4 Hz, 2 × Ar*H*), 6.88 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 6.74 (2H, d, *J* 8.7 Hz, 2 × Ar*H*), 3.76 (12H, s, 4 × OC*H*$_3$), 2.60 (4H, t, *J* 7.8 Hz, 2 × ArC*H*$_2$CH$_2$), 1.70-1.58 (4H, m, 2 × C*H*$_2$), 1.48-1.40 (2H, m, C*H*$_2$) ppm.
δ_C (75 MHz, $CDCl_3$)	157.2 (2 × *C*), 155.1 (2 × *C*), 139.9 (2 × *C*H), 137.3 (2 × *C*H), 134.8 (2 × *C*), 131.3 (2 × *C*H), 130.8 (2 × *C*), 128.9 (2 × *C*H), 126.1 (2 × *C*), 113.5 (2 × *C*H), 111.1 (2 × *C*H), 82.8 (2 × *C*), 56.0 (4 × *C*H$_3$), 35.1 (2 × *C*H$_2$), 31.7 (2 × *C*H$_2$), 29.2 (*C*H$_2$) ppm.
HRMS (ES+)	Found $[M+Na]^+$: 771.0459. $C_{33}H_{34}O_4I_2Na$ requires 771.0439.

7-(5'-Iodo-6,2'-dimethoxy-biphenyl-3-yl)-hept-1-en-3-one **2.25**



2.4

$C_{21}H_{25}IO_3$
Mol. Wt.: 452

2.25

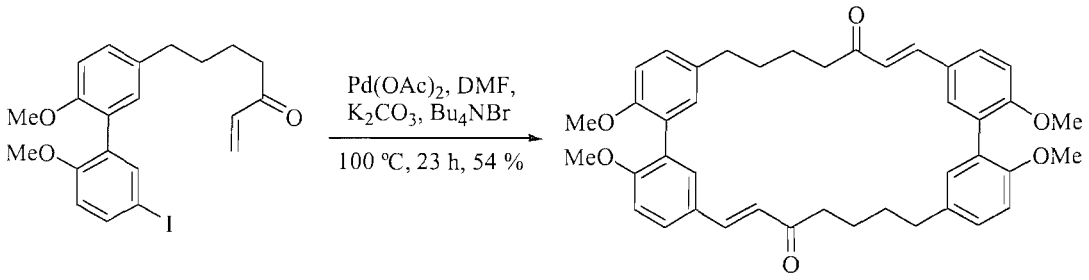
$C_{21}H_{23}IO_3$
Mol. Wt.: 450

Dess-Martin periodinane (810 mg, 1.91 mmol) was added to **2.4** (540 mg, 1.19 mmol) in dichloromethane (5 mL) at 0 °C. The reaction mixture was warmed to RT, stirred for 0.5 h, then 1M NaOH (8 mL) and ether (20 mL) added. After 20 min, the organic phase was washed with 1M NaOH (3 × 10 mL), water (3 × 10 mL) and brine (3 × 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield **2.25** (471 mg, 1.05 mmol, 88 %) as a clear oil.

ν_{max}/cm^{-1} (neat)	1679 (m), 1502 (s), 1484 (s), 1461 (s), 1243 (s), 1031 (m).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	278 (8700).
δ_H (300 MHz, $CDCl_3$)	7.59 (1H, dd, *J* 8.7, 2.4 Hz, Ar*H*), 7.52 (1H, d, *J* 2.4 Hz, Ar*H*), 7.14 (1H, dd, *J* 8.5, 2.4 Hz, Ar*H*), 7.01 (1H, d, *J* 2.4 Hz, Ar*H*), 6.88 (1H, d, *J* 8.5 Hz, Ar*H*), 6.74 (1H, d, *J* 8.7 Hz, Ar*H*), 6.36 (1H, dd, *J* 17.6, 10.3 Hz, C*H*=CH_2), 6.21 (1H, dd, *J* 17.6, 1.4 Hz, HC=C*H*H), 5.82 (1H, dd, *J* 10.3, 1.4 Hz, HC=CH*H*), 3.76 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 2.64-2.58 (4H, m, 2 × CH_2),

	1.69-1.60 (4H, m, 2 × CH_2) ppm.
δ_C (75 MHz, $CDCl_3$)	201.1 (*C*), 157.2 (*C*), 155.2 (*C*), 139.8 (*C*H), 137.3 (*C*H), 136.7 (*C*H), 134.2 (*C*), 131.3 (*C*H), 130.7 (*C*), 128.9 (*C*H), 128.1 (CH_2), 126.2 (*C*), 113.5 (*C*H), 111.2 (*C*H), 82.8 (*C*), 56.0 (2 × CH_3), 39.6 (CH_2), 35.0 (CH_2) 31.3 (CH_2), 23.8 (CH_2), ppm.
LRMS (CI)	468 ($[M+NH_4]^+$, 22 %), 451 (MH^+, 35 %), 327 ($[MH-ICH_3+NH_4]^+$, 100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 473.0579. $C_{21}H_{23}O_3INa$ requires 473.0584.

26-membered macrocycle **2.26**



2.25

$C_{21}H_{23}IO_3$
Mol. Wt.: 450

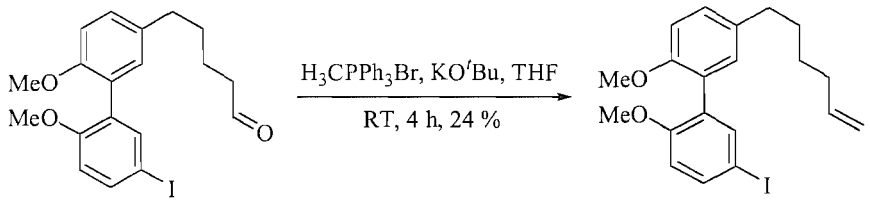
2.26

$C_{42}H_{44}O_6$
Mol. Wt.: 645

$Pd(OAc)_2$ (6.6 mg, 0.03 mmol), K_2CO_3 (150 mg, 1.09 mmol), and Bu_4NBr (343 mg, 1.07 mmol) in DMF (50 mL) was heated to 100 °C, then enone **2.25** (120 mg, 0.27 mmol) in DMF (100 mL) was added over a period of 5 h. After a further 18 h the reaction was cooled to RT, and partitioned between ether (50 mL) and water (200 mL). The aqueous phase was extracted with ether (3 × 50 mL), and the combined organic fractions were washed with water (3 × 30 mL) and brine (3 × 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 3/1, then chloroform) gave macrocycle **2.26** (93 mg, 0.15 mmol, 54 %) as a viscous oil.

ν_{max}/cm^{-1} (neat)	2930 (w), 1658 (m), 1598 (s), 1501 (s), 1268 (s), 1245 (s).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	308 (37400).
δ_H (300 MHz, $CDCl_3$)	7.56 (2H, d, *J* 16.2 Hz, 2 × C*H*), 7.54 (2H, dd, *J* 8.5, 2.4 Hz, 2 × Ar*H*), 7.48 (2H, d, *J* 2.4 Hz, 2 × Ar*H*), 7.14 (2H, dd, *J* 8.2, 2.4 Hz, 2 × Ar*H*), 7.03 (2H, d, *J* 2.1 Hz, 2 × Ar*H*), 6.97 (2H, d, *J* 8.7 Hz, 2 × Ar*H*), 6.87 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 6.67 (2H, d, *J* 16.2 Hz, 2 × C*H*), 3.83 (6H, s, 2 × OCH_3), 3.76 (6H, s, 2 × OCH_3), 2.70 (4H, t, *J* 6.6 Hz, 2 × C(O)CH_2), 2.60 (4H, m, 2 × ArCH_2), 1.77-1.63 (8H, m, 4 × CH_2) ppm.
δ_C (75 MHz, $CDCl_3$)	201.3 (2 × *C*), 159.6 (2 × *C*), 155.6 (2 × *C*), 143.1 (2 × *C*H), 134.7 (2 × *C*), 131.9 (2 × *C*H), 131.2 (2 × *C*H), 129.4 (2 × *C*H), 129.3 (2 × *C*), 129.2 (2 × *C*H), 127.4 (2 × *C*), 127.2 (2 × *C*), 125.0 (2 × *C*H), 111.4 (2 × *C*H), 111.1 (2 × *C*H), 56.1 (4 × *C*H_3), 40.1 (2 × *C*H_2), 35.1 (2 × *C*H_2), 32.0 (2 × *C*H_2), 24.8 (2 × *C*H_2) ppm.
HRMS (ES+)	Found $[M+Na]^+$: 667.3027. $C_{42}H_{44}O_6Na$ requires 667.3030. Found MH^+: 667.3244. $C_{42}H_{45}O_6$ requires 645.3210. Found $[2M+Na]^+$: 1311.6161. $C_{84}H_{88}O_{12}Na$ requires 1311.6162.

5-Hex-5-enyl-5'-iodo-2,2'-dimethoxybiphenyl **2.33**



2.3

$C_{19}H_{21}IO_3$
Mol. Wt.: 424

2.33

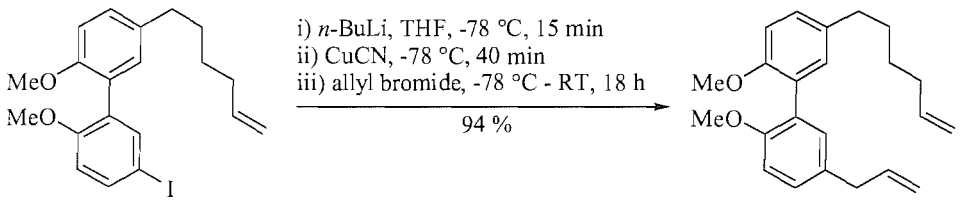
$C_{20}H_{23}IO_2$
Mol. Wt.: 422

Potassium *tert*-butoxide (47 mg, 0.42 mmol) was added to methyltriphenylphosphonium bromide (150 mg, 0.42 mmol) in THF (10 mL) and the resulting bright yellow solution was stirred for 1 h at RT. Aldehyde **2.3** (140 mg, 0.33 mmol) was added as a solution in THF (5 mL) and stirred for a further 3 h at RT. The crude reaction mixture was partitioned between dichloromethane (20 mL) and sat. aq. ammonium chloride solution (10 mL). The aqueous layer was extracted with further portions of dichloromethane (3 × 10 mL), organic fractions combined, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/10) gave alkene **2.33** (33 mg, 0.08 mmol, 24 %) as an oil.

ν_{max}/cm^{-1} (neat)	2924 (w), 2904 (w), 1680 (m), 1484 (s), 1420 (s), 1242 (s), 1029 (m).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	270 (6400).
δ_H (400 MHz, $CDCl_3$)	7.60 (1H, dd, *J* 8.5, 2.5 Hz, Ar*H*), 7.54 (1H, d, *J* 2.3 Hz, Ar*H*), 7.14 (1H, dd, *J* 8.3, 2.3 Hz, Ar*H*), 7.02 (1H, d, *J* 2.3 Hz, Ar*H*), 6.89 (1H, d, *J* 8.3 Hz, Ar*H*), 6.74 (1H, d, *J* 8.5 Hz, Ar*H*), 5.89-5.77 (1H, m, C*H*), 5.04-4.94 (2H, m, CH_2), 3.76 (3H, s, OCH_3), 3.76 (3H, s, OCH_3),

	2.60 (2H, t, *J* 6.3 Hz, ArCH_2), 2.11-2.06 (2H, m, CH_2), 1.70-1.60 (2H, m, CH_2), 1.52-1.43 (2H, m, CH_2) ppm.
δ_C (100 MHz, $CDCl_3$)	157.3 (*C*), 155.2 (*C*), 139.9 (*C*H), 139.1 (*C*H), 137.3 (*C*H), 134.7 (*C*), 131.4 (*C*H), 130.9 (*C*), 128.9 (*C*H), 126.2 (*C*), 114.5 (*C*H_2), 113.6 (*C*H), 111.1 (*C*H), 82.8 (*C*), 56.0 (2 × *C*H_3), 35.0 (*C*H_2), 33.8 (*C*H_2), 31.2 (*C*H_2), 28.8 (*C*H_2) ppm.
LRMS (EI)	423 (MH^+, 97 %), 353 ([M-$(CH_2)_3CHCH_2$]$^+$, 100 %), 252 (65 %) amu.
HRMS (ES+)	Found [M+Na]$^+$: 445.0611. $C_{20}H_{23}IO_2Na$ requires 445.0635.

5'-Allyl 5-hex-5-enyl 2,2'-dimethoxybiphenyl **2.32**



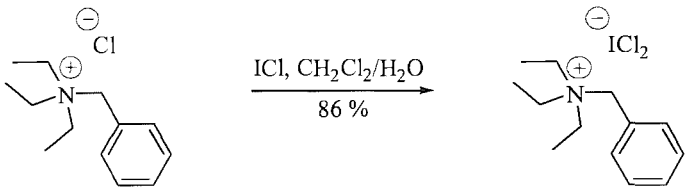
2.33
$C_{20}H_{23}IO_2$
Mol. Wt.: 422

2.32
$C_{23}H_{28}O_2$
Mol. Wt.: 336

n-Butyl lithium (2.49 M in hexanes, 0.05 mL, 124.5 μmol) was added to iodide **2.33** (16 mg, 37.9 μmol) in THF (5 mL) at –78 °C and stirred for 15 min. Copper(I) cyanide (20 mg, 223.3 μmol) was added and the solution slowly turned yellow over 40 min. Allyl bromide (11 μL, 127.1 μmol) was added to the reaction mixture at –78 °C and stirring continued for 1 h, before warming to RT and stirring for a further 18 h. The mixture was partitioned between ether (5 mL) and sat. aq. ammonium chloride solution (3 mL). The aqueous layer was extracted with ether (3 × 5 mL), organic fractions combined and washed with brine (3 × 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Et_2O/petroleum ether, 2 %) gave diene **2.32** (12 mg, 35.7 mmol, 94 %) as an oil.

ν_{max}/cm^{-1} (neat)	2956 (s), 2916 (m), 2872 (m), 1483 (m), 1432 (s), 1243 (s), 1232 (s), 1157 (s).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	268 (7100), 239 (5400).
δ_H (400 MHz, $CDCl_3$)	7.04 (1H, dd, *J* 8.3, 2.2 Hz, Ar*H*), 7.03 (1H, d, *J* 2.2 Hz, Ar*H*), 6.97 (1H, dd, *J* 8.2, 2.2 Hz, Ar*H*), 6.96 (1H, d, *J* 2.2 Hz, Ar*H*), 6.83 (1H, d, *J* 8.2 Hz, Ar*H*), 6.81 (1H, d, *J* 8.3 Hz, Ar*H*), 6.02 (1H, ddt, *J* 17.2, 10.5, 6.8 Hz, C*H*=CH_2), 5.84 (1H, ddt, *J* 17.2, 10.3, 6.7 Hz, C*H*=CH_2), 5.18-4.95 (4H, m, 2 × =CH_2), 3.80 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.40 (2H, d, *J* 6.9 Hz, ArCH_2), 2.59 (2H, t, *J* 7.6 Hz, ArCH_2), 2.12 (2H, dt, *J* 7.4, 6.9 Hz, CH_2), 1.68 (2H, app. quint., *J* 7.6 Hz, CH_2), 1.50 (2H, app. quint., *J* 7.6 Hz, CH_2) ppm.
δ_C (100 MHz, $CDCl_3$)	155.7 (*C*), 155.4 (*C*), 139.2 (*C*H), 138.1 (*C*H), 134.6 (*C*), 132.0 (*C*), 131.9 (*C*H), 131.7 (*C*H), 128.9 (*C*H), 128.4 (*C*H), 128.2 (*C*), 127.8 (*C*), 115.6 (*C*H_2), 114.5 (*C*H_2), 111.4 (*C*H), 111.3 (*C*H), 56.0 (*C*H_3), 55.9 (*C*H_3), 39.6 (*C*H_2), 35.1 (*C*H_2), 33.9 (*C*H_2), 31.2 (*C*H_2), 28.8 (*C*H_2) ppm.
LRMS (EI)	336 (M^+, 77 %), 267 ([M-C_5H_9,]$^+$, 100 %) amu.
HRMS (ES+)	Found [M+Na]$^+$: 359.1995. $C_{23}H_{28}O_2Na$ requires 359.1981.

Benzyltriethylammonium dichloroiodate (BTEA.ICl_2) **2.48**



2.47
$C_{13}H_{22}ClN$
Mol. Wt.: 228

2.48
$C_{13}H_{22}Cl_2IN$
Mol. Wt.: 390

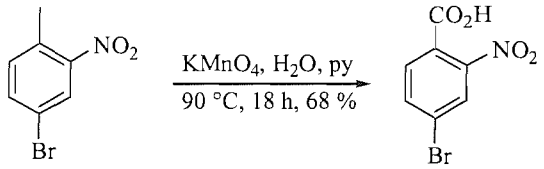
Following the procedure for the preparation of BTMA.ICl_2 by Kajigaeshi *et al.*,[106] benzyltriethylammonium chloride **2.47** (11.39 g, 49.96 mmol) in water (200 mL) was added dropwise to ICl (8.12 g, 49.97 mmol) in dichloromethane (400 mL). After 1 h of vigorous stirring the organic layer was separated, dried ($MgSO_4$), and solvent removed *in vacuo* to give the residue, which was recrystallised from CH_2Cl_2/ether (3/1) to yield **2.48** (16.77 g, 43.00 mmol, 86 %) as bright yellow crystals.

The yield compares well with literature data for BTMA.ICl_2.[106]

Spectroscopic data attained compares well with literature values, except for ^{1}H NMR.[107]

MP	76-78 °C (CH_2Cl_2/ether) [Lit. 84-86 °C][107]
ν_{max}/cm^{-1} (film)	2356 (s), 2319 (s), 1481 (s), 1449 (s), 1156 (m), 908 (s).
δ_H (300 MHz, $CDCl_3$)	7.55-7.47 (5H, m, 5 × Ar*H*), 4.45 (2H, s, ArCH_2), 3.32 (6H, q, *J* 7.2 Hz, 3 × CH_2), 1.52 (9H, t, *J* 7.2 Hz, 3 × CH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	132.5 (2 × *C*H), 131.5 (*C*H), 130.1 (2 × *C*H), 126.2 (*C*), 61.4 (CH_2), 53.3 (3 × CH_2), 8.6 (3 × CH_3) ppm.
LRMS (ES+)	193 ($[MH-ICl_2]^+$, 18 %), 192 ($[M-ICl_2]^+$, 100 %) amu.

4-Bromo-2-nitrobenzoic acid **2.36**



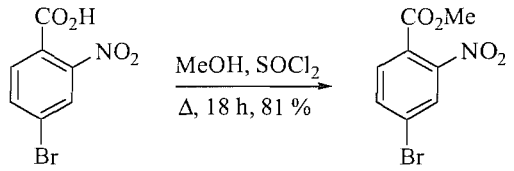
2.35
$C_7H_6BrNO_2$
Mol. Wt.: 216

2.36
$C_7H_4BrNO_4$
Mol. Wt.: 246

Following the procedure of Qian *et al.*,[108] potassium permanganate (52.32 g, 286.84 mol) was added portionwise to 4-bromo-2-nitrotoluene **2.35** (9.98 g, 46.20 mmol) in pyridine (51 mL) and water (120 mL). The reaction mixture was heated at 90 °C for 18 h, then cooled and filtered through Celite and acidified to pH 4 using 6M HCl. Cooling in an ice bath precipitated acid **2.36** (7.69 g, 31.26 mmol, 68 %) as a pale yellow crystalline solid.
The spectroscopic and physical data attained compares well with literature values.[108]

MP	161-163 °C [160-164 °C][108]
ν_{max}/cm^{-1} (film)	2879 (br. w), 1705 (s), 1596 (m), 1541 (s), 1412 (m), 1357 (m), 1275 (m).
δ_H (400 MHz, CD_3OD)	8.07 (1H, d, *J* 1.8 Hz, Ar*H*), 7.90 (1H, dd, *J* 8.3, 1.8 Hz, Ar*H*), 7.78 (1H, dd, *J* 8.3 Hz, Ar*H*) ppm. O*H* not observed.
δ_C (100 MHz, CD_3OD)	165.5 (*C*), 149.6 (*C*), 135.3 (*C*H), 131.5 (*C*H), 126.4 (*C*H), 125.9 (*C*), 125.2 (*C*) ppm.
LRMS (ES-)	494 (2M{^{81}Br}$^-$, 8 %), 493 ([2M{^{81}Br}{^{79}Br}+H]$^-$, 50 %), 491 ([2M{^{79}Br}+H]$^-$, 100 %), 489 ([2M{^{79}Br}]$^-$, 48 %) amu.

Methyl 4-bromo-2-nitrobenzoate **2.37**



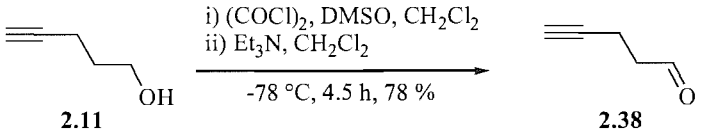
2.36
$C_7H_4BrNO_4$
Mol. Wt.: 246

2.37
$C_8H_6BrNO_4$
Mol. Wt.: 260

Thionyl chloride (8.3 mL, 113.76 mmol) was added to a solution of 4-bromo-2-nitrobenzoic acid **2.36** (7.16 g, 29.11 mmol) in methanol (100 mL) and heated under reflux for 18 h. The reaction was cooled and solvent (50 mL) removed *in vacuo*. Further cooling in an ice bath gave ester **2.37** (6.15 g, 23.65 mmol, 81 %) as a pale yellow solid which was collected by filtration.

MP	44-46 °C [Lit. 41-43 °C][109]
ν_{max}/cm^{-1} (film)	3099 (w), 3037 (w), 1717 (s), 1587 (m), 1525 (s), 1431 (m), 1351 (s), 1292 (s), 1246 (s), 1122 (s), 1037 (m).
δ_H (400 MHz, $CDCl_3$)	8.02 (1H, d, *J* 1.8 Hz, Ar*H*), 7.81 (1H, dd, *J* 8.0, 1.8 Hz, Ar*H*), 7.66 (1H, d, *J* 8.0 Hz, Ar*H*), 3.92 (3H, s, OCH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	165.1 (*C*), 148.8 (*C*), 136.0 (*C*H), 131.5 (*C*H), 127.2 (*C*H), 126.0 (*C*), 124.9 (*C*) 53.7 (CH_3) ppm.
LRMS (EI)	261 (M{^{81}Br}$^+$, 65 %), 259 (M{^{79}Br}$^+$, 67 %), 230 ([M{^{81}Br}-MeO]$^+$, 92 %), 228 ([M{^{79}Br}-MeO]$^+$, 100 %) amu.

4-Pentynal **2.38**



2.11
C_5H_8O
Mol. Wt.: 84

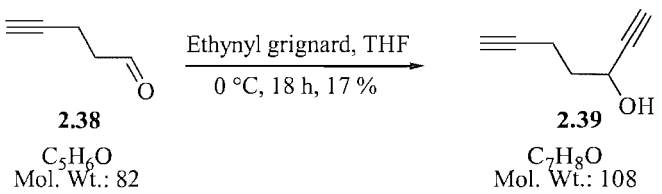
2.38
C_5H_6O
Mol. Wt.: 82

Following the procedure of Adams *et al.*,[110] to a solution of oxalyl chloride (9.12 mL, 104.54 mmol) in dichloromethane (200 mL) at –78 °C was added DMSO (14.8 mL, 208.56 mmol) in dichloromethane (30 mL) over 20 mins, and stirred for an additional 0.5 h. 4-pentynol **2.11** (8.85 mL, 95.24 mmol) in dichloromethane (70 mL) was added *via* cannula over 10 mins, and stirred for a further 70 mins at –78 °C. Triethylamine (66.20 mL, 475.5 mmol) was added at –78 °C and the reaction mixture stirred for an additional 1 h before warming to RT over 1.5 h. The reaction mixture was partitioned over water (200 mL), and acidified with 1 % HCl (in sat. NaCl, 180 mL). The aqueous phase was extracted with dichloromethane (3 × 100 mL), organic fractions combined and washed with 1 % HCl (in sat. NaCl, 6 × 100 mL), sat. sodium bicarbonate (2 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$) and solvent removed carefully under reduced pressure (~100 mbar, 30 °C) to yield aldehyde **2.38** (8.15 g, 99.39 mmol, 78 %) as an orange oil.

The spectroscopic and physical data attained compares well with literature values.[110]

ν_{max}/cm^{-1} (neat)	3296 (w), 2935 (m), 2874 (m), 1739 (s), 1241 (s), 1138 (s).
δ_H (400 MHz, $CDCl_3$)	9.81 (1H, s, C*H*O), 2.71 (2H, t, *J* 7.0 Hz, CH_2), 2.51 (2H, dt, *J* 7.0, 2.5 Hz, CH_2), 1.99 (1H, t, *J* 2.8 Hz, C≡C*H*) ppm.
δ_C (100 MHz, $CDCl_3$)	200.1 (*C*), 82.3 (*C*), 69.3 (*C*H), 42.4 (*C*H_2), 11.6 (*C*H_2) ppm.
LRMS	Did not fly by GCMS.

Heptdyn-3-ol **2.39**



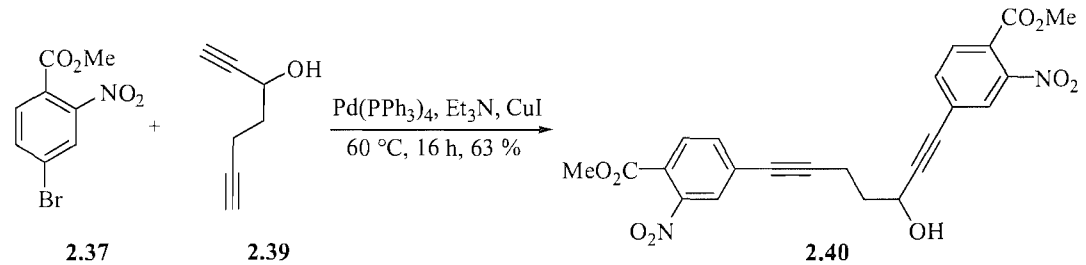
2.38
C_5H_6O
Mol. Wt.: 82

2.39
C_7H_8O
Mol. Wt.: 108

To a solution of aldehyde **2.38** (3.52 g, 42.93 mmol) in THF (20 mL) was added ethynylmagnesium chloride (0.5 M, 100 mL, 50.00 mmol) at 0 °C. The mixture was stirred for 18 h at RT and quenched with sat. ammonium chloride (10 mL). The aqueous phase was extracted with ether (3 × 50 mL), organic phases combined and washed with 1 % HCl (in sat. NaCl, 6 × 100 mL), sat. sodium bicarbonate (2 × 50 mL), and brine (2 × 50 mL), dried ($MgSO_4$) and solvent removed carefully under reduced pressure (~100 mbar, 30 °C) to yield alcohol **2.39** (0.78 g, 7.22 mmol, 17 %) as an orange oil.

ν_{max}/cm^{-1} (neat)	3294 (s), 2928 (m), 2198 (w), 1061 (m).
δ_H (400 MHz, $CDCl_3$)	4.57 (1H, app. qd, *J* 6.1, 2.3 Hz, C*H*OH),
	2.51 (1H, d, *J* 2.3 Hz, C≡C*H*),
	2.48-2.33 (2H, m, CH_2),
	2.13-2.07 (1H, m, O*H*),
	2.00 (1H, t, *J* 2.8 Hz, C≡C*H*),
	1.95 (2H, app. q, *J* 6.8 Hz, CH_2) ppm.
δ_C (75 MHz, $CDCl_3$)	83.3 (*C*), 73.7 (*C*H), 72.9 (*C*), 69.4 (*C*H), 61.2 (*C*H), 36.1 (CH_2), 14.6 (CH_2) ppm.
LRMS	Did not fly by GCMS or LCMS.

Dimethyl 4,4'-(3-hydroxy-1,6-heptadiyne-1,7-diyl)bis(2-nitrobenzoate) **2.40**



2.37 $C_8H_6BrNO_4$ Mol. Wt.: 260

2.39 C_7H_8O Mol. Wt.: 108

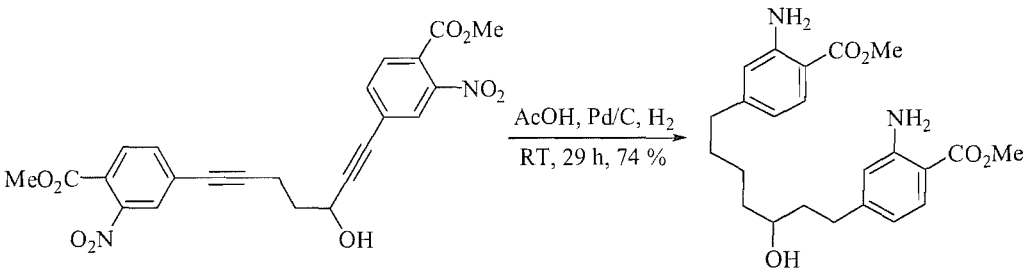
2.40 $C_{23}H_{18}N_2O_9$ Mol. Wt.: 466

To a solution of bis-alkyne **2.39** (755 mg, 6.99 mmol) and aryl bromide **2.37** (3.80 g, 14.62 mmol) in triethylamine (25 mL) was added tetrakis(triphenylphosphine) palladium(0) (163 mg, 0.14 mmol) and copper(I) iodide (47 mg, 0.25 mmol). The mixture was heated to 60 °C for 18 h, cooled to RT and acidified with 2M HCl (80 mL). The aqueous phase was extracted with EtOAc (4 × 50 mL), organic fractions combined and washed with brine (3 × 30 mL), dried ($MgSO_4$) and solvent removed under reduced pressure. Purification by column chromatography (SiO_2, EtOAc, cyclohexane, 1/2) gave biaryl **2.40** (2.06 g, 4.42 mmol, 63 %) as an oil.

λ_{max}/nm (ε_{max}, MeOH)	264 (32700), 245 (42000).
ν_{max}/cm^{-1} (neat)	3521 (br. m), 3021 (m), 2955 (m), 2231 (m), 1732 (s), 1614 (s), 1538 (s), 1356 (s), 1295 (s).
δ_H (400 MHz, $CDCl_3$)	7.88 (1H, d, *J* 1.3 Hz, Ar*H*), 7.83 (1H, d, *J* 1.3 Hz, Ar*H*), 7.72-7.59 (4H, m, 4 × Ar*H*), 4.83 (1H, app. q, *J* 6.1 Hz, C*H*OH), 3.91 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 2.75-2.67 (2H, m, CH_2), 2.56 (1H, d, *J* 5.3 Hz, O*H*), 2.15-2.10 (2H, m, CH_2) ppm.
δ_C (100 MHz, $CDCl_3$)	165.4 (*C*), 165.3 (*C*), 148.6 (*C*), 148.5 (*C*), 135.6 (*C*H), 135.4 (*C*H), 130.2 (*C*H), 130.1 (*C*H), 128.3 (*C*), 126.9

	(*C*), 126.9 (*C*H), 126.7 (*C*H), 126.7 (*C*), 125.8 (*C*), 92.6 (*C*), 92.4 (*C*), 80.5 (*C*), 77.1 (*C*), 59.6 (*C*H), 53.8 (CH_3), 53.7 (CH_3), 34.0 (CH_2), 13.8 (CH_2) ppm.
LRMS (ES+)	484 ($[M+NH_4]^+$, 100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 489.0900. $C_{23}H_{18}N_2O_9$ requires 489.0904.

Dimethyl 4,4'-(3-hydroxy-1,7-heptanediyl)bis(2-aminobenzoate) **2.41**



2.40
$C_{23}H_{18}N_2O_9$
Mol. Wt.: 466

2.41
$C_{23}H_{30}N_2O_5$
M. Wt.: 414

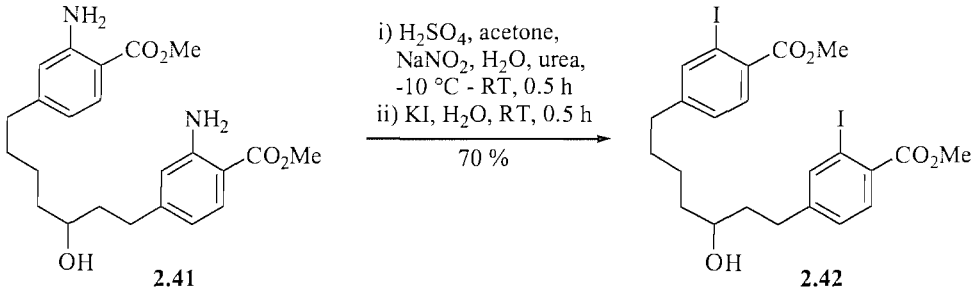
Nitro alkyne **2.40** (530 mg, 1.14 mmol) was dissolved in acetic acid (20 mL) and the Pd/C catalyst (5 % w/w, 20 mg, 0.19 g.atom) was added. The reaction was vigorously stirred under a hydrogen atmosphere for 29 h, then filtered through Celite followed by a pad of silica, and concentrated *in vacuo* to yield aniline **2.41** (348 mg, 0.84 mmol, 74 %) as a brown oil that was used with minimal characterisation.

ν_{max}/cm^{-1} (neat)	3477 (m), 3370 (m), 2936 (m), 1689 (s), 1619 (s), 1436 (m), 1300 (s), 1247 (s).
δ_H (400 MHz, CD_3OD)	7.67 (2H, dd, *J* 8.3, 2.5 Hz, 2 × Ar*H*), 6.55 (1H, d, *J* 2.5 Hz, Ar*H*), 6.54 (1H, d, *J* 2.5 Hz, Ar*H*), 6.40 (1H, d, *J* 8.3 Hz, Ar*H*),

6.39 (1H, d, *J* 8.3 Hz, Ar*H*),
3.80 (6H, s, 2 × OC*H*$_3$),
3.53-3.47 (1H, m, C*H*OH),
2.67-2.60 (1H, m, ArC*H*H),
2.53-2.46 (1H, m, ArC*H*H),
2.48 (2H, t, *J* 7.5 Hz, CH_2),
1.70-1.55 (4H, m, 2 × CH_2),
1.46-1.30 (4H, m, 2 × CH_2) ppm.
NH_2 and O*H* not observed.

LRMS (ES+) 415 (MH^+, 100 %) amu.

Dimethyl 4,4'-(3-hydroxy-1,7-heptanediyl)bis(2-iodobenzoate) **2.42**



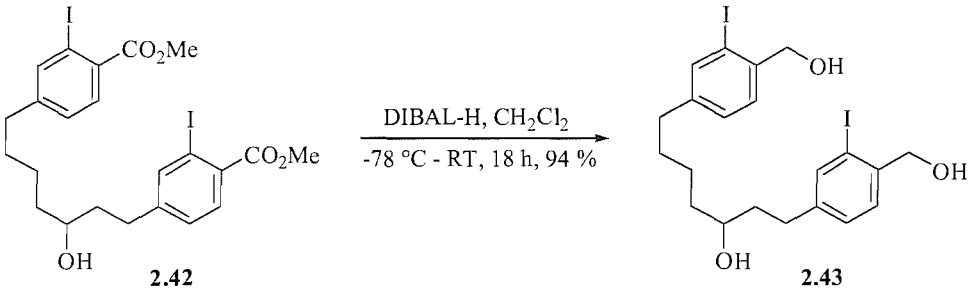
2.41
$C_{23}H_{30}N_2O_5$
Mol. Wt.: 414

2.42
$C_{23}H_{26}I_2O_5$
Mol. Wt.: 636

To a solution of bis-aniline **2.41** (390 mg, 0.94 mmol) in acetone (10 mL) and sulphuric acid (3M, 9 mL) at −10 °C was added sodium nitrate (200 mg, 2.90 mmol) in water (2 mL) dropwise, followed by urea (40 mg). Potassium iodide (546 mg, 3.29 mmol) in water (5 mL) was added, and the mixture was stirred at RT for 0.5 h. A second portion of KI (425 mg, 2.56 mmol) in water (3 mL) was added and the mixture allowed to stir for a further 0.5 h. The reaction was quenched with sat. sodium thiosulfate (50 mL) and extracted with EtOAc (3 × 20 mL), organic phases combined and washed with sat. sodium thiosulfate (20 mL), brine (3 × 10 mL), dried ($MgSO_4$), and solvent removed *in vacuo*. Purification by column chromatography (SiO_2, EtOAc/cyclohexane, 1/3) gave aryl iodide **2.42** (422 mg, 0.66 mmol, 70 %) as a colourless oil.

λ_{max}/nm (ε_{max}, MeOH)	204 (64600).
ν_{max}/cm^{-1} (neat)	3430 (w), 2928 (m), 2854 (m), 1727 (s), 1594 (m), 1433 (m), 1294 (s), 1258 (s).
δ_H (400 MHz, $CDCl_3$)	7.85 (1H, d, *J* 1.3 Hz, Ar*H*), 7.84 (1H, d, *J* 1.0 Hz, Ar*H*), 7.76 (1H, d, *J* 8.0 Hz, Ar*H*), 7.75 (1H, d, *J* 8.0 Hz, Ar*H*), 7.23 (1H, dd, *J* 8.0, 1.5 Hz, Ar*H*), 7.20 (1H, dd, *J* 8.0, 1.5 Hz, Ar*H*), 3.92 (6H, s, 2 × OC*H*$_3$), 3.63-3.56 (1H, br. s, C*H*OH), 2.82-2.74 (1H, m, ArC*H*H), 2.68-2.62 (1H, obs. m, ArC*H*H), 2.60 (2H, t, *J* 7.5 Hz, C*H*$_2$), 1.77-1.59 (4H, m, 2 × C*H*$_2$), 1.52-1.45 (2H, m, C*H*$_2$), 1.37-1.33 (2H, m, C*H*$_2$) ppm.
δ_C (100 MHz, $CDCl_3$)	166.9 (2 × *C*), 148.2 (*C*), 148.0 (*C*), 141.6 (2 × *C*H), 132.4 (*C*), 132.3 (*C*), 131.3 (2 × *C*H), 128.3 (*C*H), 128.2 (*C*H), 94.8 (*C*), 94.7 (*C*), 71.0 (*C*H), 52.6 (2 × *C*H$_3$), 38.7 (*C*H$_2$), 37.6 (*C*H$_2$), 35.3 (*C*H$_2$), 31.5 (*C*H$_2$), 31.0 (*C*H$_2$), 25.3 (*C*H$_2$) ppm.
LRMS (ES+)	654 ([M+NH$_4$]$^+$, 637 (MH$^+$, 15 %) amu.
HRMS (ES+)	Found [M+Na]$^+$: 658.9755. $C_{23}H_{26}O_5I_2Na$ requires 658.9762.

Dimethyl 4,4'-(3-hydroxy-1,7-heptanediyl)bis(2-iodobenzoate) **2.43**

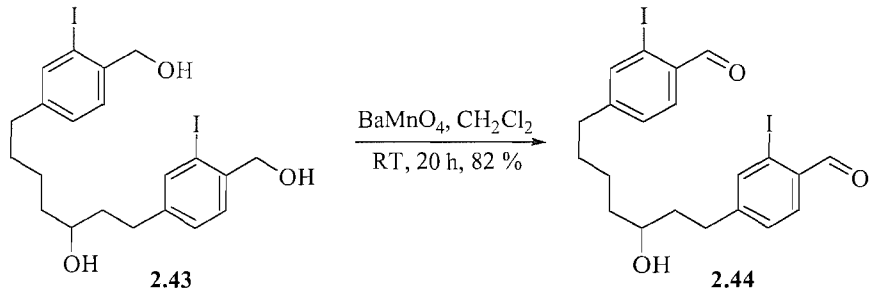


2.42
$C_{23}H_{26}I_2O_5$
Mol. Wt.: 636

2.43
$C_{21}H_{26}I_2O_3$
Mol. Wt.: 580

Diisobutylaluminium hydride (1M in CH_2Cl_2, 2.45 mL, 2.45 mmol) was added to bis-ester **2.42** (413 mg, 0.65 mmol) in dichloromethane (25 mL) at –78 °C and stirred for 2 h. The reaction was warmed to RT and stirred for a further 16 h. Hydrochloric acid (1M, 8 mL) was added slowly at 0 °C. The phases were separated and the aqueous layer extracted with dichloromethane (4 × 20 mL), organic fractions combined and solvent removed *in vacuo* to yield bis-benzyl alcohol **2.43** (356 mg, 0.61 mmol, 94 %) as a white crystalline solid which was used directly without further purification.

4,4'-(3-hydroxy-1,7-heptanediyl)bis(2-iodobenzaldehyde) **2.44**



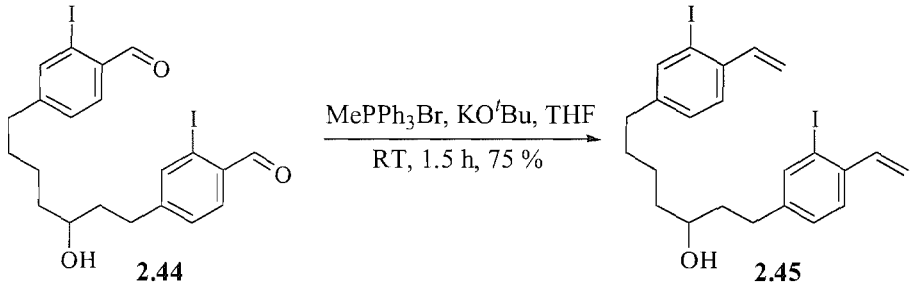
2.43
$C_{21}H_{26}I_2O_3$
Mol. Wt.: 580

2.44
$C_{21}H_{22}I_2O_3$
Mol. Wt.: 576

Barium manganate (925 mg, 3.61 mmol) was added to bis-benzyl alcohol **2.43** (348 mg, 0.60 mmol) in dichloromethane (25 mL) and stirred for 20 h at RT. The reaction was filtered through Celite and solvent removed *in vacuo* to yield bis-benzaldehyde **2.44** (281 mg, 0.49 mmol, 82 %) as a white solid.

MP	79-81 °C (ether/petroleum ether)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	230 sh. (8600), 207 (23700).
ν_{max}/cm^{-1} (neat)	2929 (w), 2854 (w), 1685 (s), 1588 (s), 1550 (w), 1385 (m), 1264 (m), 1208 (m), 1031 (m), 831 (m).
δ_H (400 MHz, $CDCl_3$)	10.01 (2H, s, 2 × C*H*O), 7.81-7.77 (4H, m, 4 × Ar*H*), 7.31-7.26 (2H, m, 2 × Ar*H*), 3.64-3.58 (1H, br. m, C*H*OH), 2.86-2.79 (1H, m, ArC*H*H), 2.73-2.62 (1H, obs. m, ArC*H*H), 2.63 (2H, t, *J* 7.6 Hz, CH_2), 1.83-1.60 (5H, m, 2 × CH_2 + O*H*), 1.55-1.35 (4H, m, 2 × CH_2) ppm.
δ_C (100 MHz, $CDCl_3$)	195.6 (2 × *C*H), 151.4 (*C*), 151.2 (*C*), 140.6 (2 × *C*H), 133.4 (*C*), 133.4 (*C*), 130.4 (2 × *C*H), 129.1 (2 × *C*H), 101.3 (2 × *C*), 71.0 (*C*H), 38.6 (*C*H_2), 37.6 (*C*H_2), 35.6 (*C*H_2), 31.8 (*C*H_2), 30.1 (*C*H_2), 25.4 (*C*H_2) ppm.
LRMS (ES+)	594 ($[M+NH_4]^+$, 80 %), 577 (MH^+, 100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 598.9534. $C_{21}H_{22}O_3I_2Na$ requires 598.9551.

1,7-bis(4-ethenyl-3-iodophenyl)-3-heptanol **2.45**



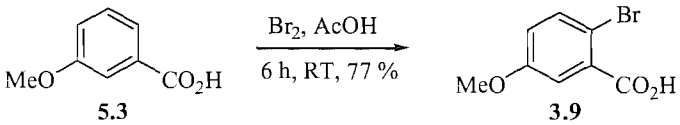
2.44
$C_{21}H_{22}I_2O_3$
Mol. Wt.: 576

2.45
$C_{23}H_{26}I_2O$
Mol. Wt.: 572

To a stirred suspension of methyltriphenylphosphonium bromide (431 mg, 1.21 mmol) in THF (10 mL) was added potassium *tert*-butoxide (1M in THF, 1.2 mL, 1.20 mmol), and the mixture stirred for 0.5 h. Bis-aldehyde **2.44** (170 mg, 0.30 mmol) in THF (10 mL) was added, and the reaction stirred for a further 1 h at RT. The mixture was diluted with Et_2O (30 mL) and partitioned over sat. ammonium chloride (20 mL). The aqueous phase was extracted with Et_2O (2 × 20 mL), organic fractions combined and washed with brine, dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by column chromatography (SiO_2, EtOAc/cyclohexane, 1/4) gave bis-styrene **2.45** (128 mg, 0.22 mmol, 75 %) as a gum.

ν_{max}/cm^{-1} (neat)	3375 (br. w), 2928 (s), 2854 (m), 1623 (w), 1595 (m), 1478 (s), 1385 (m), 1020 (s).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	235 (3000), 208 (6700).
δ_H (400 MHz, $CDCl_3$)	7.70 (1H, d, *J* 1.5 Hz, Ar*H*), 7.67 (1H, d, *J* 1.5 Hz, Ar*H*), 7.44 (1H, d, *J* 8.0 Hz, Ar*H*), 7.42 (1H, d, *J* 8.0 Hz, Ar*H*), 7.16 (1H, dd, *J* 8.0, 1.5 Hz, Ar*H*), 7.13 (1H, dd, *J* 8.0, 1.5 Hz, Ar*H*), 6.88 (2H, dd, *J* 17.3, 10.8 Hz, 2 × C*H*=), 5.60 (2H, d, *J* 17.3 Hz, 2 × =C*H*H), 5.28 (2H, d, *J* 10.8 Hz, 2 × =CH*H*), 3.65-3.56 (1H, br. m, C*H*OH), 2.77-2.70 (1H, m, ArC*H*H), 2.65-2.57 (1H, obs. m, ArC*H*H), 2.56 (2H, t, *J* 7.5 Hz, CH_2), 1.80-1.60 (5H, m, 2 × CH_2 + O*H*), 1.52-1.30 (4H, m, 2 × CH_2) ppm.
δ_C (100 MHz, $CDCl_3$)	144.2 (*C*), 143.9 (*C*), 140.5 (*C*H), 140.5 (*C*H), 139.4 (*C*H), 139.4 (*C*H), 138.5 (*C*), 138.4 (*C*), 128.8 (2 × *C*H), 116.3 (*C*H), 116.2 (*C*H), 115.1 (2 × *C*H_2), 100.0 (2 × *C*), 71.2 (*C*H), 39.1 (*C*H_2), 37.6 (*C*H_2), 35.1 (*C*H_2), 31.3 (2 × *C*H_2), 25.4 (*C*H_2) ppm.
LRMS (ES+)	617 ($[M+CO_2H]^-$, 100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 594.9968. $C_{23}H_{26}I_2Na$ requires 594.9966.

2-Bromo-5-methoxy-benzoic acid **3.9**



5.3
$C_8H_8O_3$
Mol. Wt.: 152

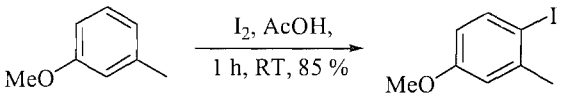
3.9
$C_8H_7BrO_3$
Mol. Wt.: 231

To a solution of 3-methoxybenzoic acid **5.3** (15.04 g, 98.95 mmol) in acetic acid (150 mL) was added bromine (5.10 mL, 99.53 mmol). After 6 h at RT, water (250 mL) was added and the solution cooled over ice causing precipitation of the title compound **3.9** (17.53 g, 75.89 mmol, 77 %) as white needles.

The spectroscopic and physical data attained compares well with literature values.[111]

MP	158-160 °C (ethanol/water) [Lit. 160-161 °C (methanol/water)][111]
ν_{max}/cm^{-1} (solid)	2888 (br. m), 2616 (br. m), 1694 (s), 1671 (s), 1564 (s), 1440 (s), 1264 (s), 1227 (s), 1049 (s), 899 (s), 817 (s).
δ_H (400 MHz, CD_3OD)	7.58 (1H, d, *J* 8.8 Hz, Ar*H*), 7.36 (1H, d, *J* 3.0 Hz, Ar*H*), 7.01 (1H, dd, *J* 8.8, 3.0 Hz, Ar*H*), 3.85 (3H, s, OC*H*$_3$) ppm. O*H* was not observed.
δ_C (100 MHz, CD_3OD)	181.7 (*C*), 161.1 (*C*), 136.9 (*C*H), 136.1 (*C*), 120.3 (*C*H), 118.2 (*C*H), 112.9 (*C*), 57.0 (*C*H$_3$) ppm.
LRMS (ES-)	464 ([2M{^{81}Br}]$^-$, 8 %), 463 ([2M{^{81}Br}-H]$^-$, 64 %), 461 ([2M{^{81}Br}{^{79}Br}-H]$^-$, 100 %) amu.

4-Iodo-3-methylanisole **5.5**



5.4
$C_8H_{10}O$
Mol. Wt.: 122

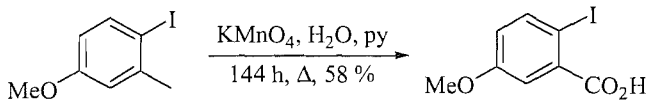
5.5
C_8H_9IO
Mol. Wt.: 248

$ZnCl_2$ (6.00 g, 44.03 mmol) and BTEA.ICl_2 (15.59 g, 39.97 mmol) was added to **5.4** (5 mL, 39.66 mmol) in acetic acid (40 mL) and stirred at RT for 1 h. The reaction mixture was partitioned between ether (50 mL) and sat. $NaHSO_3$ (50 mL). The organic phase was separated and washed with sat. $NaHSO_3$ (4 × 30 mL), aq. sodium hydroxide solution (2M, 30 mL), and brine (3 × 10 mL) dried over $MgSO_4$ and concentrated *in vacuo*. Recrystallisation from ethanol gave **5.5** (8.34 g, 33.63 mmol, 85 %) as a white crystalline solid.

The spectroscopic and physical data attained compares well with literature values.[39,112]

MP	43-44 °C (ethanol) [Lit. 44-45 °C (ethanol)][39]
λ_{max}/nm (ε_{max}, CH_2Cl_2)	281 (1300), 237 (14400)
ν_{max}/cm^{-1} (solid)	3000 (w), 2934 (w), 2836 (w), 1593 (m), 1566 (m), 1470 (s), 1402 (m), 1289 (s), 1238 (s), 1160 (s), 1129 (m), 1052 (s), 1010 (m), 913 (w), 859 (s), 780 (s).
δ_H (300 MHz, $CDCl_3$)	7.67 (1H, d, *J* 8.5 Hz, Ar*H*), 6.83 (1H, d, *J* 2.9 Hz, Ar*H*), 6.50 (1H, dd, *J* 8.5, 2.9 Hz, Ar*H*), 3.78 (3H, s, OCH_3), 2.41 (3H, s, Ar CH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	160.0 (*C*), 142.5 (*C*), 139.5 (*C*H), 116.0 (*C*H), 113.5 (*C*H), 89.8 (*C*), 55.5 (CH_3), 28.4 (CH_3) ppm.
LRMS (EI)	248 (M^+, 100 %), 233 ($[M-CH_3]^+$, 36 %) amu.

2-Iodo-5-methoxy-benzoic acid **5.6**



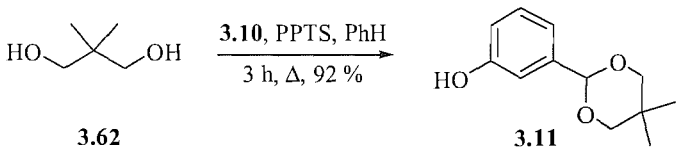
5.5
C_8H_9IO
Mol. Wt.: 248

5.6
$C_8H_7IO_3$
Mol. Wt.: 278

To solution of arene **5.5** (15.75 g, 63.51 mmol) in pyridine (120 mL) and water (40 mL) was added potassium permanganate (13.45 g, 85.13 mmol) portionwise. The reaction was refluxed for 144 h with further portions of potassium permanganate totalling (57.17, 361.84 mmol) being added at 24 h intervals. The mixture was cooled and manganese dioxide removed by filtration through Celite. The solution was acidified with 6M HCl, and resulting precipitate filtered to yield iodo acid **5.6** (10.21 g, 36.73 mmol, 58 %) as a white solid.
The spectroscopic and physical data attained compares well with literature values.[39, 113]

MP	138-140 °C (ethanol) [Lit. 135-138 °C ($CHCl_3$/hexane)][113]
λ_{max}/nm (ε_{max}, MeOH)	298 (4200), 215 (56500).
ν_{max}/cm^{-1} (solid)	3327 (br. m), 3046 (w), 2885 (w), 1609 (m), 1466 (s), 1455 (s), 1401 (m), 1292 (s), 1214 (s), 1104 (s), 1079 (s), 997 (s), 959 (s), 913 (m), 855 (m), 761 (s).
δ_H (400 MHz, CD_3OD)	7.88 (1H, d, *J* 8.8 Hz, Ar*H*), 7.39 (1H, d, *J* 3.1 Hz, Ar*H*), 6.87 (1H, dd, *J* 8.8, 3.1 Hz, Ar*H*), 3.85 (3H, s, OCH_3) ppm. O*H* not observed.
δ_C (100 MHz, CD_3OD)	182.1 (*C*), 170.7 (*C*), 143.8 (*C*H), 139.5 (*C*), 120.6 (*C*H), 118.2 (*C*H), 83.2 (*C*), 56.9 (CH_3) ppm.
LRMS (ES-)	556 ([2M$^+$, 100 %) amu.

3-(5,5-Dimethyl-[1,3]dioxan-2-yl)-phenol **3.11**



3.62
$C_5H_{12}O_2$
Mol. Wt.: 104

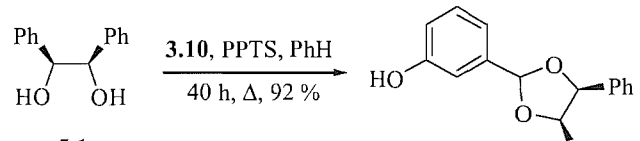
3.11
$C_{12}H_{16}O_3$
Mol. Wt.: 208

To a solution of 3-hydroxybenzaldehyde **3.10** (12.28 g, 100.56 mmol) and diol **3.62** (25.54 g, 245.22 mmol) in benzene (350 mL) was added pyridinium *p*-toluenesulfonate (1.00 g, 3.98 mmol). The mixture was heated at reflux under a Dean-Stark apparatus for 3 h then cooled to RT and diluted with ether (100 mL). The organic phase was washed with sat. sodium bicarbonate (3 × 50 mL) and brine (30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting solid was recrystallised from di*iso*propyl ether to give phenol **3.11** (19.18 g, 92.21 mmol, 92 %) as a white solid.

MP	144-146 °C (di*iso*propyl ether)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	280 (5400), 274 (5600).
ν_{max}/cm^{-1} (solid)	3290 (br. m), 2962 (w), 2873 (w), 1608 (m), 1463 (s), 1393 (m), 1292 (m), 1217 (m), 1098 (s), 996 (s), 973 (s), 909 (m), 795 (s).
δ_H (300 MHz, $CDCl_3$)	7.25 (1H, d, *J* 7.7 Hz, Ar*H*), 7.08-7.00 (2H, m, 2 × Ar*H*), 6.81 (1H, ddd, *J* 8.1, 2.6, 1.1 Hz, Ar*H*), 5.36 (1H, s, ArC*H*), 4.98 (1H, s, ArO*H*), 3.79 (2H, d, *J* 10.6 Hz, 2 × OC*H*H), 3.66 (2H, d, *J* 10.6 Hz, 2 × OC*H*H), 1.31 (3H, s, C*H*$_3$), 0.81 (3H, s, C*H*$_3$) ppm.
δ_C (75 MHz, $CDCl_3$)	155.8 (*C*), 140.1 (*C*), 129.8 (*C*H), 118.8 (*C*H), 116.2 (*C*H), 113.3 (*C*H), 101.7 (*C*H), 77.8 (2 × *C*H$_2$), 30.4 (*C*), 23.2 (*C*H$_3$), 22.0 (*C*H$_3$) ppm.

LRMS (EI)	208 (M^+, 42 %), 207 ($[M-H]^+$, 67 %), 121 ($[M-C_5H_{10}O]^+$, 100 %) amu.
CHN	Found C 69.36 %, H 7.71 %; $C_{12}H_{16}O_3$ requires C 69.21 %, H 7.74.

3-(4,5-Diphenyl-[1,3]dioxolan-2-yl)-phenol **3.27**



5.1
$C_{14}H_{14}O_2$
Mol. Wt.: 214

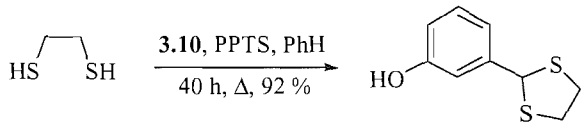
3.27
$C_{21}H_{18}O_3$
Mol. Wt.: 318

To a solution of 3-hydroxybenzaldehyde **3.10** (679 mg, 5.56 mmol) and diol **5.1** (3.57 g, 16.67 mmol) in benzene (65 mL) was added pyridinium *p*-toluenesulfonate (418 mg, 1.66 mmol). The mixture was heated at reflux under a Dean-Stark apparatus for 40 h then cooled to RT and diluted with dichloromethane (50 mL). The organic phase was washed with water (3 × 40 mL), sat. sodium bicarbonate (30 mL) and brine (3 × 30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude material was purified by column chromatography (SiO_2, ether/petroleum ether, 1/3) to give phenol **3.27** (1.62 g, 5.10 mmol, 92 %) as a white solid.

MP	169-171°C ($CHCl_3$)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	281 (1500), 275 (1700), 228 (1700).
ν_{max}/cm^{-1} (neat)	3390 (br. m), 3031 (w), 2891 (w), 1597 (m), 1496 (m), 1455 (s), 1284 (m), 1174 (s), 1098 (s), 1069 (s), 1000 (s).
δ_H (400 MHz, $CDCl_3$)	7.37-7.28 (11H, m, 11 × Ar*H*), 7.25-7.21 (1H, m, Ar*H*), 7.14-7.12 (1H, m, Ar*H*), 6.96 (1H, dd, *J* 8.0, 2.5 Hz, Ar*H*), 6.35 (1H, s, ArC*H*), 4.99 (1H, s, ArO*H*), 4.96 (1H, d, *J* 8.0 Hz, OC*H*Ph), 4.92 (1H, d, *J* 8.0 Hz, OC*H*Ph) ppm.

δ_C (100 MHz, $CDCl_3$)	155.9 (*C*), 140.2 (*C*), 138.1 (*C*), 136.6 (*C*), 130.0 (*C*H), 128.8 (5 × *C*H), 128.5 (*C*H), 127.1 (2 × *C*H), 126.6 (2 × *C*H), 119.3 (*C*H), 116.5 (*C*H), 113.6 (*C*H), 104.4 (*C*H), 87.3 (*C*H), 85.4 (*C*H) ppm.
LRMS (ES+)	659 ($[2M+Na]^+$, 28 %), 341 ($[M+Na]^+$, 100 %) amu.
CHN	Found C 79.25 %, H 5.65 %; $C_{21}H_{18}O_3$ requires C 79.22 %, H 5.70 %.

3-[1,3]Dithiolan-2-yl-phenol **3.28**



5.2
$C_2H_6S_2$
Mol. Wt.: 94

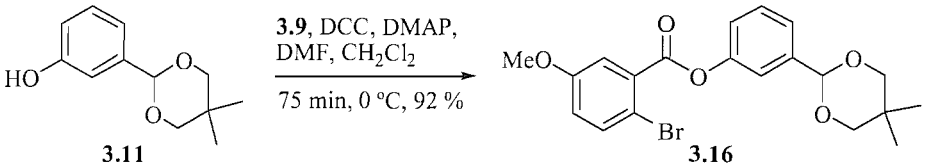
3.28
$C_9H_{10}OS_2$
Mol. Wt.: 198

To a solution of 3-hydroxybenzaldehyde **3.10** (1.22 g, 10.00 mmol) and thiol **5.2** (2.50 mL, 29.80 mmol) in benzene (65 mL) was added pyridinium *p*-toluenesulfonate (602 mg, 2.40 mmol). The mixture was heated at reflux under a Dean-Stark apparatus for 40 h then cooled to RT and diluted with dichloromethane (50 mL). The organic phase was washed with water (3 × 40 mL), sat. sodium bicarbonate (30 mL) and brine (3 × 30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude material was purified by column chromatography (SiO_2, ether/petroleum ether, 1/2) to give **3.28** (1.82 g, 9.19 mmol, 92 %) as a colourless oil. The spectroscopic and physical data attained compares well with literature values.[114]

λ_{max}/nm (ε_{max}, MeOH)	276 (6800), 203 (20500)
ν_{max}/cm^{-1} (neat)	3387 (br. s), 2923 (w), 1591 (s), 1487 (m), 1453 (s), 1339 (w), 1276 (s), 1216 (s), 1150 (m), 905 (s).
δ_H (400 MHz, $CDCl_3$)	7.18 (1H, app. t, *J* 7.8 Hz, Ar*H*), 7.09-7.03 (2H, m, 2 × Ar*H*), 6.74 (1H, dd, *J* 8.0, 2.5 Hz, Ar*H*), 5.60 (1H, s, ArC*H*), 4.90 (1H, s, ArO*H*),

	3.52-3.46 (2H, m, SCH_2),
	3.39-3.33 (2H, m, SCH_2) ppm.
δ_C (100 MHz, $CDCl_3$)	155.8 (*C*), 142.5 (*C*), 129.9 (*C*H), 120.6 (*C*H), 115.3 (*C*H), 114.9 (*C*H), 56.1 (*C*H), 40.3 (2 × *C*H_2) ppm.
LRMS (ES+)	237 ($[M+K]^+$, 100 %) amu.

2-Bromo-5-methoxy-benzoic acid 3-(5,5-dimethyl-[1,3]dioxan-2-yl)-phenyl ester **3.16**

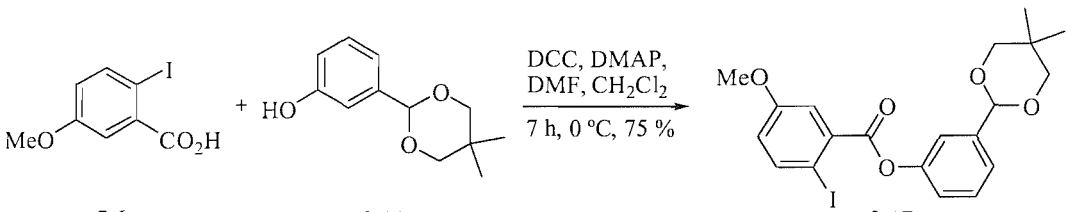


Following the general procedure of Bringmann *et al.*[84] To a solution of acid **3.9** (587 mg, 2.54 mmol) in DMF/CH_2Cl_2 (1/1, 2 mL) was added DMAP (28 mg, 0.23 mmol) and phenol **3.11** (479 mg, 2.30 mmol). The mixture was cooled to 0 °C and DCC (606 mg, 2.94 mmol) added. After 30 min, the reaction was warmed to RT, stirred for 45 min, filtered and the solvent removed under reduced pressure. The crude mixture was dissolved in dichloromethane (10 mL), washed with 0.5 M HCl (2 × 10 mL) and sat. sodium bicarbonate (2 × 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/4 - 1/2) gave **3.16** (886 mg, 2.11 mmol, 92 %) as a colourless oil.

λ_{max}/nm (ε_{max}, MeOH)	270 (7700), 201 (13200).
ν_{max}/cm^{-1} (neat)	2957 (w), 2847 (w), 1748 (m), 1593 (w), 1473 (m), 1393 (m), 1318 (m), 1287 (m), 1213 (s), 1149 (m), 1103 (s), 1039 (m), 1017 (m), 905 (w).
δ_H (400 MHz, $CDCl_3$)	7.59 (1H, d, *J* 8.8 Hz, Ar*H*),
	7.51 (1H, d, *J* 2.8 Hz, Ar*H*),
	7.45-7.40 (3H, m, 3 × Ar*H*),

	7.27-7.23 (1H, obs. m, Ar*H*), 6.95 (1H, dd, *J* 8.8, 2.8 Hz, Ar*H*), 5.43 (1H, s, ArC*H*), 3.84 (3H, s, OCH_3), 3.78 (2H, d, *J* 10.5 Hz, 2 × OC*H*H), 3.65 (2H, d, *J* 10.5 Hz, 2 × OC*H*H), 1.28 (3H, s, CH_3), 0.80 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	164.4 (*C*), 158.8 (*C*), 150.8 (*C*), 140.5 (*C*), 135.5 (*C*H), 132.1 (*C*), 129.5 (*C*H), 124.0 (*C*H), 122.1 (*C*H), 119.9 (*C*H), 119.6 (*C*H), 116.9 (*C*H), 112.8 (*C*), 101.0 (*C*H), 77.8 (2 × CH_2), 55.9 (CH_3), 30.4 (*C*), 23.3 (CH_3), 22.1 (CH_3) ppm.
LRMS (EI)	422 (M{^{81}Br}$^+$, 4 %), 420 (M{^{79}Br}$^+$, 4 %), 301 (20 %), 299 (21 %), 213 (100 %) amu.
HRMS (ES+)	Found [M+Na]$^+$: 443.0464. $C_{20}H_{21}O_5BrNa$ requires 443.0464.

2-Iodo-5-methoxy-benzoic acid 3-(5,5-dimethyl-[1,3]dioxan-2-yl)-phenyl ester **3.17**



5.6
$C_8H_7IO_3$
Mol. Wt.: 278

3.11
$C_{12}H_{16}O_3$
Mol. Wt.: 208

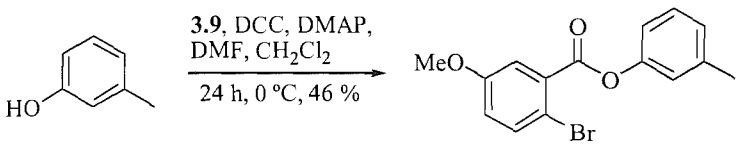
3.17
$C_{20}H_{21}IO_5$
Mol. Wt.: 468

Following the general procedure of Bringmann *et al.*[84] To a solution of acid **5.6** (4.12 g, 14.82 mmol) in DMF/CH_2Cl_2 (1/1, 10 mL) was added DMAP (43 mg, 0.35 mmol) and phenol **3.11** (2.52 g, 12.12 mmol). The mixture was cooled to 0 °C and DCC (3.68 g, 17.84 mmol) added. After 10 min, the reaction was warmed to RT, stirred for 7 h, filtered and the solvent removed under reduced pressure. The crude mixture was dissolved in

dichloromethane (50 mL), washed with 0.5 M HCl (2 × 20 mL) and sat. sodium bicarbonate (2 × 20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/3) gave **3.17** (4.23 g, 9.04 mmol, 75 %) as a colourless oil.

λ_{max}/nm (ε_{max}, MeOH)	241 (11400), 203 (31200).
ν_{max}/cm^{-1} (neat)	2956 (w), 2846 (w), 1742 (m), 1590 (w), 1565 (m), 1468 (m), 1392 (m), 1314 (m), 1285 (s), 1210 (s), 1101 (s), 1037 (s), 734 (m).
δ_H (300 MHz, $CDCl_3$)	7.91 (1H, d, *J* 8.7 Hz, Ar*H*), 7.57 (1H, d, *J* 3.2 Hz, Ar*H*), 7.46-7.42 (3H, m, 3 × Ar*H*), 7.30-7.26 (1H, obs. m, Ar*H*), 6.83 (1H, dd, *J* 8.7, 3.0 Hz, Ar*H*), 5.44 (1H, s, ArC*H*), 3.86 (3H, s, OCH_3), 3.79 (2H, d, *J* 11.3 Hz, 2 × OC*H*H), 3.66 (2H, d, *J* 11.3 Hz, 2 × OC*H*H), 1.29 (3H, s, CH_3), 0.82 (3H, s, CH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	164.6 (*C*), 159.8 (*C*), 150.8 (*C*), 142.4 (*C*H), 140.5 (*C*), 135.1 (*C*), 129.5 (*C*H), 124.0 (*C*H), 122.1 (*C*H), 120.2 (*C*H), 119.6 (*C*H), 117.1 (*C*H), 101.0 (*C*H), 83.2 (*C*), 77.8 (2 × CH_2), 55.8 (CH_3), 30.4 (*C*), 23.3 (CH_3), 22.1 (CH_3) ppm.
LRMS (EI)	468 (M^+, 10 %), 347 (80 %), 261 (100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 491.0316. $C_{20}H_{21}O_5INa$ requires 491.0326.

2-Bromo-5-methoxy-benzoic acid m-tolyl ester **3.18**



3.34
C_7H_8O
Mol. Wt.: 108

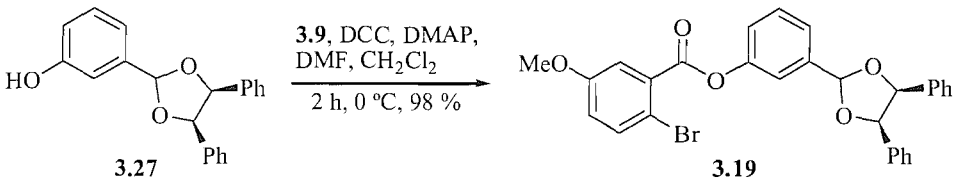
3.18
$C_{15}H_{13}BrO_3$
Mol. Wt.: 321

Following the general procedure of Bringmann *et al.*[84] To a solution of acid **3.9** (15.85 g, 68.61 mmol) in DMF/CH_2Cl_2 (1/1, 40 mL) was added DMAP (68 mg, 0.56 mmol) and phenol **3.34** (7.26 mL, 69.42 mmol). The mixture was cooled to 0 °C and DCC (17.24 g, 83.56 mmol) added. After 15 min, the reaction was warmed to RT, stirred for 24 h, filtered and the solvent removed under reduced pressure. The crude mixture was dissolved in dichloromethane (80 mL), washed with 0.5 M HCl (2 × 20 mL) and sat. sodium bicarbonate (2 × 20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/20) gave **3.18** (10.28 g, 32.03 mmol, 46 %) as a viscous oil that solidified on standing.

MP	29-30 °C (di*iso*propyl ether)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	303 (3300), 229 (13100).
ν_{max}/cm^{-1} (solid)	2936 (w), 1747 (s), 1592 (m), 1571 (m), 1475 (m), 1237 (s), 1213 (s), 1143 (s), 1044 (m), 819 (m).
δ_H (300 MHz, $CDCl_3$)	7.61 (1H, d, *J* 8.8 Hz, Ar*H*), 7.52 (1H, d, *J* 3.3 Hz, Ar*H*), 7.36-7.30 (1H, m, Ar*H*), 7.12-7.05 (3H, m, 3 × Ar*H*), 6.97 (1H, dd, *J* 8.8, 3.3 Hz, Ar*H*), 3.86 (3H, s, OCH_3), 2.41 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	181.3 (*C*), 164.7 (*C*), 158.9 (*C*), 150.8 (*C*), 139.9 (*C*), 135.5 (*C*H), 129.4 (*C*H), 127.1 (*C*H), 122.3 (*C*H), 119.7

	(*C*H), 118.7 (*C*H), 116.9 (*C*H), 112.6 (*C*), 55.9 (CH_3), 21.5 (CH_3) ppm.
LRMS (ES+)	345 ([M{^{81}Br}+Na]$^+$, 53 %), 343 ([M{^{79}Br}+Na]$^+$, 60 %), 267 (100 %) amu.
CHN	Found C 56.13 %, H 3.99 %, Br 24.74 %; $C_{15}H_{13}O_3Br$ requires C 56.10 %, H 4.08 %, Br 24.88 %.

2-Bromo-5-methoxy-benzoic acid 3-(4,5-dimethyl-[1,3]dioxolan-2-yl)-phenyl ester **3.19**

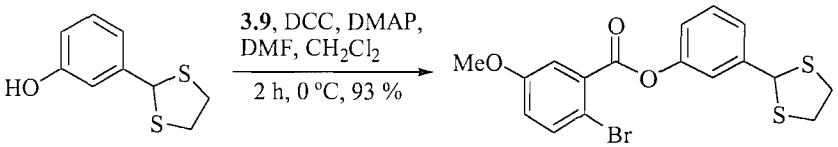


Following the general procedure of Bringmann *et al.*[84] To a solution of acid **3.9** (1.21 g, 5.24 mmol) in DMF/CH_2Cl_2 (1/1, 2 mL) was added DMAP (33 mg, 0.27 mmol) and phenol **3.27** (1.49 g, 4.69 mmol). The mixture was cooled to 0 °C and DCC (1.18 g, 5.72 mmol) added. After 30 min, the reaction was warmed to RT, stirred for 2 h, filtered and the solvent removed under reduced pressure. The crude mixture was dissolved in dichloromethane (10 mL), washed with 0.5 M HCl (2 × 10 mL) and sat. sodium bicarbonate (2 × 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/6) gave **3.19** (2.44 g, 4.60 mmol, 98 %) as a colourless oil.

λ_{max}/nm (ε_{max}, MeOH)	262 (3200), 240 (4100), 202 (18000).
ν_{max}/cm^{-1} (neat)	2901 (w), 1746 (m), 1593 (w), 1570 (w), 1475 (m), 1454 (m), 1399 (w), 1286 (m), 1209 (s), 1086 (s), 1015 (s), 909 (m), 760 (s).

δ_H (400 MHz, $CDCl_3$)	7.64-7.60 (3H, m, 3 × Ar*H*), 7.57-7.52 (2H, m, 2 × Ar*H*), 7.39-7.31 (11H, m, 11 × Ar*H*), 6.98 (1H, dd, *J* 8.8, 3.3 Hz, Ar*H*), 6.48 (1H, s, ArC*H*), 5.00 (1H, d, *J* 8.0 Hz, OC*H*), 4.95 (1H, d, *J* 8.0 Hz, OC*H*), 3.87 (3H, s, OCH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	164.5 (*C*), 158.9 (*C*), 151.0 (*C*), 140.6 (*C*), 137.9 (*C*), 136.5 (*C*), 135.5 (*C*H), 132.1 (*C*), 129.8 (*C*H), 128.8 (2 × *C*H), 128.8 (2 × *C*H), 128.8 (*C*H), 128.5 (*C*H), 127.1 (2 × *C*H), 126.6 (2 × *C*H), 124.4 (*C*H), 122.6 (*C*H), 119.9 (*C*H), 119.8 (*C*H), 116.9 (*C*H), 112.7 (*C*), 103.9 (*C*H), 87.4 (*C*H), 85.4 (*C*H), 55.9 (CH_3) ppm.
LRMS (ES+)	555 ($[M\{^{81}Br\}+Na]^+$, 100 %), 553 ($[M\{^{79}Br\}+Na]^+$, 87 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 553.0631. $C_{29}H_{23}BrO_5$ requires 553.0621.

2-Bromo-5-methoxy-benzoic acid 3-[1,3]dithiolan-2-yl-phenyl ester **3.20**

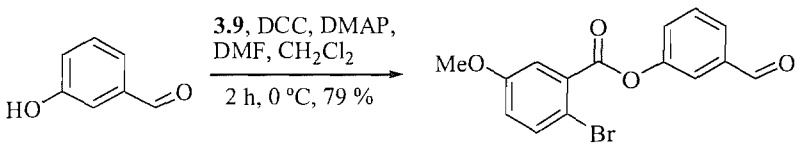


Following the general procedure of Bringmann *et al.*[84] To a solution of acid **3.9** (2.41 g, 10.43 mmol) in DMF/CH_2Cl_2 (1/1, 4 mL) was added DMAP (23 mg, 0.19 mmol) and phenol **3.28** (1.88 g, 9.47 mmol). The mixture was cooled to 0 °C and DCC (2.34 g, 11.34 mmol) added. After 30 min, the reaction was warmed to RT, stirred for 2 h, filtered and the solvent removed under reduced pressure. The crude mixture was dissolved in

dichloromethane (10 mL), washed with 0.5 M HCl (2 × 10 mL) and sat. sodium bicarbonate (2 × 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 3/1) gave **3.20** (3.61 g, 8.78 mmol, 93%) as a colourless oil.

λ_{max}/nm (ε_{max}, MeOH)	271 (11300).
ν_{max}/cm^{-1} (neat)	2928 (w), 1745 (m), 1590 (m), 1570 (m), 1475 (m), 1285 (m), 1205 (s), 1135 (m), 1040 (s), 1015 (s), 821 (m), 747 (m).
δ_H (400 MHz, $CDCl_3$)	7.60 (1H, d, *J* 8.8 Hz, Ar*H*), 7.53 (1H, d, *J* 3.0 Hz, Ar*H*), 7.46-7.43 (2H, m, 2 × Ar*H*), 7.38 (1H, dd, *J* 7.9, 7.9 Hz, Ar*H*), 7.20-7.16 (1H, m, Ar*H*), 6.97 (1H, dd, *J* 8.8, 3.0 Hz, Ar*H*), 5.66 (1H, s, ArC*H*), 3.86 (3H, s, OCH_3), 3.54-3.46 (2H, m, SCH_2), 3.40-3.33 (2H, m, SCH_2) ppm.
δ_C (100 MHz, $CDCl_3$)	164.4 (*C*), 158.8 (*C*), 150.8 (*C*), 142.8 (*C*), 135.5 (*C*H), 132.0 (*C*), 129.6 (*C*H), 125.9 (*C*H), 121.4 (*C*H), 121.2 (*C*H), 119.8 (*C*H), 117.0 (*C*H), 112.7 (*C*), 55.9 (CH_3), 55.8 (*C*H), 40.4 (2 × CH_2) ppm.
LRMS (ES+)	435 (([M{^{81}Br}+Na]$^+$, 100 %), 433 ([M{^{79}Br}+Na]$^+$, 90 %) amu.
HRMS (ES+)	Found [M+Na]$^+$: 432.9529. $C_{17}H_{15}BrO_3S_2$ requires 432.9538.

2-Bromo-5-methoxy-benzoic acid 3-formyl-phenyl ester **3.21**



3.29
$C_7H_6O_2$
Mol. Wt.: 122

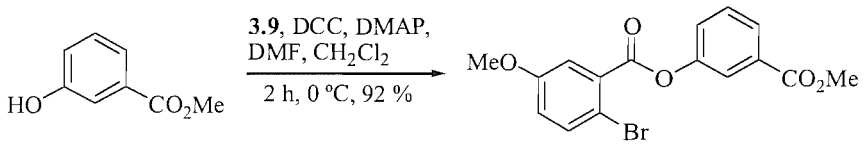
3.21
$C_{15}H_{11}BrO_4$
Mol. Wt.: 335

Following the general procedure of Bringmann *et al.*[84] To a solution of acid **3.9** (2.29 g, 9.91 mmol) in DMF/CH_2Cl_2 (1/1, 4 mL) was added DMAP (28 mg, 0.23 mmol) and phenol **3.29** (1.09 g, 8.93 mmol). The mixture was cooled to 0 °C and DCC (2.25 g, 10.90 mmol) added. After 10 min, the reaction was warmed to RT, stirred for 2 h, filtered and the solvent removed under reduced pressure. The crude mixture was dissolved in dichloromethane (10 mL), washed with 0.5 M HCl (2 × 10 mL) and sat. sodium bicarbonate (2 × 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/2) gave **3.21** (2.37 g, 7.08 mmol, 79 %) as a white solid.

MP	80-81 °C (aq. ethanol)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	289 (5000), 244 (21800), 229 (19500).
ν_{max}/cm^{-1} (solid)	2939 (w), 2839 (w), 1745 (s), 1694 (s), 1589 (m), 1472 (m), 1283 (s), 1201 (s), 1131 (s), 1037 (s), 937 (m), 881 (m), 812 (m).
δ_H (400 MHz, $CDCl_3$)	10.05 (1H, s, C*H*O), 7.84-7.79 (2H, m, 2 × Ar*H*), 7.63 (1H, d, *J* 8.0 Hz, Ar*H*), 7.62 (1H, d, *J* 8.8 Hz, Ar*H*), 7.57-7.53 (1H, obs. m, Ar*H*), 7.54 (1H, d, *J* 3.0 Hz, Ar*H*), 6.99 (1H, dd, *J* 8.8, 3.2 Hz, Ar*H*), 3.87 (3H, s, OCH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	191.2 (*C*H), 164.3 (*C*), 158.9 (*C*), 151.4 (*C*), 138.1 (*C*), 135.6 (*C*H), 131.5 (*C*), 130.4 (*C*H), 127.9 (*C*H), 127.8

	(*C*H), 122.5 (*C*H), 120.0 (*C*H), 117.1 (*C*H), 112.8 (*C*), 55.9 (CH_3) ppm.
LRMS (EI)	334 (M{^{79}Br}$^+$, 19 %), 254 ([M-Br]$^+$, 8 %), 213 ([M-$C_7H_5O_2$]$^+$, 100 %) amu.
CHN	Found C 53.73 %, H 3.34 %; $C_{15}H_{11}O_4Br$ requires C 53.76 %, H 3.31 %.

2-Bromo-5-methoxy-benzoic acid 3-methoxycarbonyl-phenyl ester **3.22**



3.30
$C_8H_8O_3$
Mol. Wt.: 152

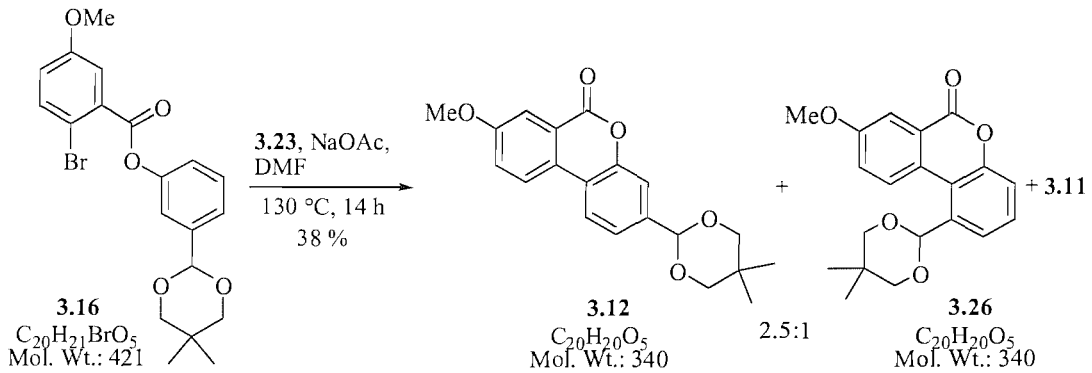
3.22
$C_{16}H_{13}BrO_5$
Mol. Wt.: 365

Following the general procedure of Bringmann *et al.*[84] To a solution of acid **3.9** (2.56 g, 11.06 mmol) in DMF/CH_2Cl_2 (1/1, 4 mL) was added DMAP (31 mg, 0.25 mmol) and phenol **3.30** (1.52 g, 10.00 mmol). The mixture was cooled to 0 °C and DCC (2.49 g, 12.07 mmol) added. After 10 min, the reaction was warmed to RT, stirred for 2 h, filtered and the solvent removed under reduced pressure. The crude mixture was dissolved in dichloromethane (10 mL), washed with 0.5 M HCl (2 × 10 mL) and sat. sodium bicarbonate (2 × 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, dichloromethane/petroleum ether, 1/1) gave **3.22** (3.35 g, 9.18 mmol, 92 %) as a white solid.

MP	71-73 °C (ethanol)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	306 (3200), 285 (3400), 230 (24700).
ν_{max}/cm^{-1} (film)	2935 (w), 1743 (s), 1716 (s), 1589 (m), 1478 (m), 1451 (s), 1392 (w), 1286 (s), 1223 (s), 1100 (s), 1013 (s), 858 (m), 821 (m), 744 (m).

δ_H (400 MHz, $CDCl_3$)	8.00-7.92 (2H, m, 2 × Ar*H*), 7.62 (1H, d, *J* 8.8 Hz, Ar*H*), 7.55-7.46 (3H, m, 3 × Ar*H*), 6.98 (1H, dd, *J* 8.8, 3.3 Hz, Ar*H*), 3.94 (3H, s, OC*H*$_3$), 3.87 (3H, s, OC*H*$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	166.3 (*C*), 164.3 (*C*), 158.9 (*C*), 150.8 (*C*), 135.6 (*C*H), 132.0 (*C*), 131.7 (*C*), 129.7 (*C*H), 127.5 (*C*H), 126.4 (*C*H), 123.0 (*C*H), 120.0 (*C*H), 117.0 (*C*H), 112.8 (*C*), 55.9 (*C*H$_3$), 52.5 (*C*H$_3$) ppm.
LRMS (EI)	364 ([M{^{79}Br}]$^+$, 5 %), 215 (100 %) amu.
CHN	Found C 52.68 %, H 3.49 %; $C_{16}H_{13}O_5Br$ requires C 52.62 %, H 3.59 %.

3-(5,5-Dimethyl-[1,3]dioxan-2-yl)-8-methoxy-benzo[c]chromen-6-one **3.12** and 1-(5,5-Dimethyl-[1,3]dioxan-2-yl)-8-methoxy-benzo[c]chromen-6-one **3.26**



Following the general procedure of Bringmann *et al.*[84] To a solution of ester **3.16** (1.22 g, 2.90 mmol) in DMF (30 mL) was added Herrmann's catalyst **3.23** (65 mg, 0.14 mmol) and sodium acetate (478 mg, 5.83 mmol). The reaction was heated at 130 °C for 14 h, cooled to RT and partitioned between EtOAc (70 mL) and 1 M HCl (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with 1 M HCl (4 × 50 mL) and brine (3 × 30 mL), dried

($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/3) then (SiO_2, CH_2Cl_2) gave **3.12** (265 mg, 0.78 mmol, 27 %) as a white solid followed by **3.26** (112 mg, 0.33 mmol, 11 %) as a white solid and finally phenol **3.11** (212 mg, 1.02 mmol, 35 %) as a white solid.

No improvement in yield was observed when the reaction was conducted with the corresponding aryl iodide **3.17**. Reaction employing sodium pivalate, very dry DMF or DMA as solvent were all investigated but showed no improvement. Other catalysts studied were ineffective.

Data for **3.12**

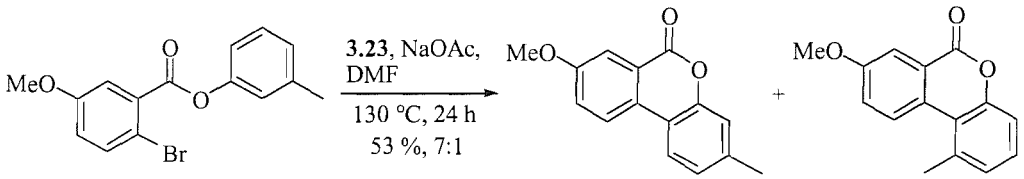
MP	172-173 °C (ether/petroleum ether)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	334 (5000), 305 (11300), 295 (9900), 282 (13800), 233 (23500).
ν_{max}/cm^{-1} (solid)	2954 (w), 2845 (w), 1735 (s), 1616 (m), 1441 (m), 1381 (m), 1288 (s), 1219 (s), 1097 (s), 1022 (s), 804 (m).
δ_H (400 MHz, $CDCl_3$)	8.06 (1H, d, *J* 8.8 Hz, Ar*H*), 7.99 (1H, d, *J* 8.3 Hz, Ar*H*), 7.82 (1H, d, *J* 2.8 Hz, Ar*H*), 7.51 (1H, d, *J* 1.3 Hz, Ar*H*), 7.48 (1H, dd, *J* 8.3, 1.3 Hz, Ar*H*), 7.40 (1H, dd, *J* 8.8, 2.8 Hz, Ar*H*), 5.47 (1H, s, ArC*H*), 3.95 (3H, s, OCH_3), 3.81 (2H, d, *J* 11.3 Hz, 2 × OC*H*H), 3.69 (2H, d, *J* 11.3 Hz, 2 × OC*H*H), 1.31 (3H, s, CH_3), 0.83 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	161.3 (*C*), 160.3 (*C*), 150.4 (*C*), 140.3 (*C*), 128.0 (*C*), 124.3 (*C*H), 123.7 (*C*H), 122.7 (*C*), 122.5 (*C*H), 122.3 (*C*H), 118.6 (*C*), 115.7 (*C*H), 111.4 (*C*H), 100.7 (*C*H), 77.8 (2 × CH_2), 55.9 (CH_3), 30.4 (*C*), 23.1 (CH_3), 22.0 (CH_3) ppm.

LRMS (EI)	340 (M^+, 55 %), 254 ([M-$C_5H_{10}O$]$^+$, 100 %) amu.
CHN	Found C 70.48 %, H 5.79 %; $C_{20}H_{20}O_5$ requires 70.57 %, H 5.92 %.

Data for **3.26**

MP	215-218 °C ($CDCl_3$)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	333 (10200), 302 (13000), 292 (12900), 281 (17200), 262 (14000), 234 (43900).
ν_{max}/cm^{-1} (solid)	2965 (w), 2857 (w), 1717 (s), 1612 (m), 1501 (m), 1473 (m), 1334 (s), 1286 (s), 1085 (s), 1012 (s), 981 (s), 807 (s).
δ_H (400 MHz, $CDCl_3$)	8.02 (1H, d, *J* 9.0 Hz, Ar*H*), 7.93 (1H, dd, *J* 7.8, 1.5 Hz, Ar*H*), 7.89 (1H, d, *J* 3.0 Hz, Ar*H*), 7.48 (1H, app. t, *J* 8.0 Hz, Ar*H*), 7.42-7.38 (2H, m, 2 × Ar*H*), 5.84 (1H, s, ArC*H*), 3.96 (3H, s, OC*H*$_3$), 3.88 (2H, d, *J* 11.0 Hz, 2 × OC*H*H), 3.76 (2H, d, *J* 11.0 Hz, 2 × OC*H*H), 1.42 (3H, s, C*H*$_3$), 0.89 (3H, s, C*H*$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	161.3 (*C*), 159.9 (*C*), 150.6 (*C*), 135.2 (*C*), 128.9 (*C*H), 128.8 (*C*H), 127.6 (*C*), 124.1 (*C*), 124.0 (*C*H), 123.3 (*C*H), 118.4 (*C*H), 117.3 (*C*), 112.0 (*C*H), 99.2 (*C*H), 77.8 (2 × *C*H$_2$), 55.9 (*C*H$_3$), 30.5 (*C*), 23.3 (*C*H$_3$), 22.0 (*C*H$_3$) ppm.
LRMS (EI)	340 (M^+, 92 %), 254 ([M-$C_5H_{10}O$]$^+$, 90 %), 253 ([M-$C_5H_{11}O$]$^+$, 100 %) amu.
CHN	Found C 70.48 %, H 5.79 %; $C_{20}H_{20}O_5$ requires 70.57 %, H 5.92 %.

8-Methoxy-3-methyl-benzo[c]chromen-6-one **3.24** and 8-methoxy-1-methyl-benzo[c]chromen-6-one **3.25**



3.18
$C_{15}H_{13}BrO_3$
Mol. Wt.: 321

3.24
$C_{15}H_{12}O_3$
Mol. Wt.: 240

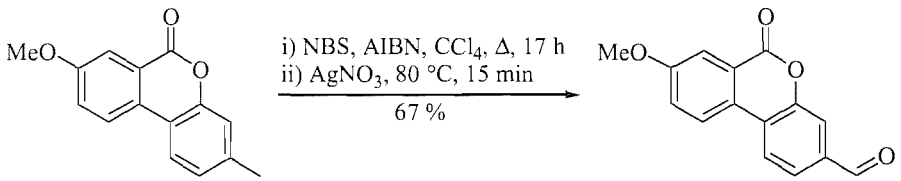
3.25
$C_{15}H_{12}O_3$
Mol. Wt.: 240

Following the general procedure of Bringmann *et al.*[84] To a solution of ester **3.18** (9.85 g, 30.69 mmol) in DMF (260 mL) was added Herrmann's catalyst **3.23** (183 mg, 0.39 mmol) and sodium acetate (5.04 g, 61.46 mmol). The reaction was heated at 130 °C for 24 h, cooled to RT and partitioned between EtOAc (150 mL) and 1 M HCl (150 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with 1 M HCl (4 × 50 mL) and brine (3 × 30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/6) gave **3.24** (2.44 g, 10.17 mmol, 33 %) as a white solid followed by an inseparable mixture of **3.24** and **3.25** (1.45 g, 6.04 mmol, 20 %, 2:1) as a white solid.

MP	207-208 °C (di*iso*propyl ether)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	339 (7800), 305 (15100), 294 (14000), 280 (21600), 272 (16700), 234 (37700).
ν_{max}/cm^{-1} (solid)	2930 (w), 2845 (w), 1713 (s), 1620 (m), 1467 (m), 1294 (s), 1070 (m), 1034 (s), 886 (m), 806 (s).
δ_H (400 MHz, $CDCl_3$)	8.01 (1H, d, *J* 8.8 Hz, Ar*H*), 7.86 (1H, d, *J* 8.8 Hz, Ar*H*), 7.81 (1H, d, *J* 1.8 Hz, Ar*H*), 7.39 (1H, dd, *J* 8.0, 1.8 Hz, Ar*H*), 7.17-7.12 (2H, m, 2 × Ar*H*), 3.94 (3H, s, OCH_3), 2.45 (3H, s, ArCH_3) ppm.

δ_C (100 MHz, $CDCl_3$)	161.7 (*C*), 159.9 (*C*), 150.7 (*C*), 140.2 (*C*), 128.6 (*C*), 125.8 (*C*H), 124.5 (*C*H), 123.4 (*C*H), 122.2 (*C*), 122.1 (*C*H), 117.9 (*C*H), 111.3 (*C*H), 102.8 (*C*), 56.0 (CH_3), 22.5 (CH_3) ppm.
LRMS (EI)	240 (M^+, 100 %), 225 ($[M-Me]^+$, 85 %) amu.
CHN	Found C 75.07 %, H 5.08 %. $C_{15}H_{12}O_3$ requires C 74.99 %, H 5.03 %.

8-Methoxy-6-oxo-6*H*-benzo[c]chromene-3-carbaldehyde **1.52**



3.24
$C_{15}H_{12}O_3$
Mol. Wt.: 240

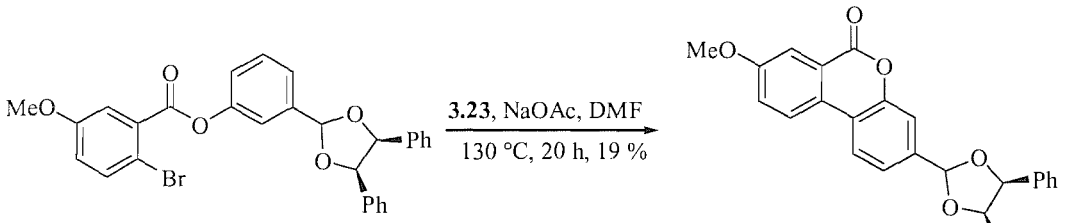
1.52
$C_{15}H_{10}O_4$
Mol. Wt.: 254

A solution of arene **3.24** (200 mg, 0.83 mmol) and *N*-bromosuccinimide (445 mg, 2.50 mmol) in carbon tetrachloride (8 mL) was heated to reflux, then AIBN (30 mg, 0.18 mmol) was added. After 17 h the reaction was cooled, and the resulting yellow solid filtered, and washed with carbon tetrachloride (2 mL) and hot water (5 mL).

A solution of the yellow solid in ethanol/ethyl acetate (1/1, 10 mL) was heated to 80 °C, then a solution of silver nitrate (1.86 g, 10.95 mol) in water (5 mL) was added dropwise over 10 min. After a further 5 min the reaction was cooled, filtered and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/1) gave aldehyde **1.52** (142 mg, 0.56 mmol, 67 %) as a white solid.
The spectroscopic and physical data attained were in accordance with literature values.[37]

MP	236-240 °C ($CHCl_3$) [Lit. 228-234 °C][37]
λ_{max}/nm (ε_{max}, CH_2Cl_2)	352 (11000), 337 (12400), 322 (11500), 242 (11600).
ν_{max}/cm^{-1} (film)	1732 (s), 1687 (s), 1609 (s), 1559 (m), 1521 (m), 1488 (m), 1448 (m), 1295 (s), 1278 (s), 1220 (m) 1074 (m), 1037 (m), 812 (s).
δ_H (300 MHz, $CDCl_3$)	10.07 (1H, s, C*H*O), 8.14 (1H, d, *J* 9.0 Hz, Ar*H*), 8.13 (1H, d, *J* 8.6 Hz, Ar*H*), 7.88-7.83 (3H, m, 3 × Ar*H*), 7.46 (1H, dd, *J* 9.0, 2.6 Hz, Ar*H*), 3.98 (3H, s, OCH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	190.8 (*C*H), 161.5 (*C*), 160.7 (*C*), 150.7 (*C*), 136.8 (*C*), 126.9 (*C*), 125.0 (*C*H), 124.6 (2 × *C*H), 123.7 (*C*), 123.5 (*C*), 123.2 (*C*H), 119.3 (*C*H), 111.9 (*C*H), 56.1 (*C*H_3) ppm.
LRMS (EI)	254 (M^+, 100 %) amu.

3-(4,5-Diphenyl-[1,3]dioxolan-2-yl)-8-methoxy-benzo[c]chromen-6-one **3.31**



3.19
$C_{29}H_{23}BrO_5$
Mol. Wt.: 531

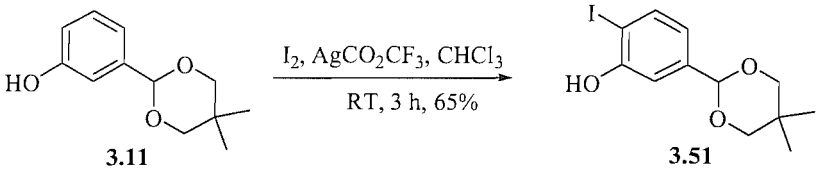
3.31
$C_{29}H_{22}O_5$
Mol. Wt.: 450

Following the general procedure of Bringmann *et al.*[84] To a solution of ester **3.19** (477 mg, 0.90 mmol) in DMF (20 mL) was added Herrmann's catalyst **3.23** (27.5 mg, 0.06 mmol) and sodium acetate (152 mg, 1.85 mmol). The reaction was heated at 130 °C for 20 h, cooled to RT and partitioned between EtOAc (50 mL) and 1 M HCl (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The

combined organic phases were washed with 1 M HCl (2 × 20 mL) and brine (3 × 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/9) gave **3.31** (77 mg, 0.17 mmol, 19 %) as a white solid

MP	113-115 °C (di*iso*propyl ether)
λ_{max}/nm (ε_{max}, MeOH)	334 (6300), 306 (12700), 295 (11300), 283 (14600), 234 (24500).
ν_{max}/cm^{-1} (solid)	1727 (s), 1614 (m), 1525 (m), 1487 (m), 1343 (s), 1277 (s), 1205 (m), 1070 (s), 1032 (s), 904 (m), 816 (m).
δ_H (300 MHz, $CDCl_3$)	8.07 (1H, d, *J* 8.8 Hz, Ar*H*), 8.04 (1H, d, *J* 8.2 Hz, Ar*H*), 7.83 (1H, d, *J* 2.7 Hz, Ar*H*), 7.70 (1H, d, *J* 1.7 Hz, Ar*H*), 7.62 (1H, dd, *J* 8.2, 1.7 Hz, Ar*H*), 7.43-7.32 (11H, m, 11 × Ar*H*), 6.48 (1H, s, ArC*H*), 5.02 (1H, d, *J* 8.1 Hz, OC*H*), 4.96 (1H, d, *J* 8.1 Hz, OC*H*), 3.95 (3H, s, OCH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	161.3 (*C*), 160.4 (*C*), 150.6 (*C*), 140.3 (*C*), 137.8 (*C*), 136.3 (*C*), 128.8 (5 × *C*H), 128.6 (*C*H), 127.9 (*C*), 127.0 (2 × *C*H), 126.7 (2 × *C*H), 124.4 (*C*H), 123.8 (*C*H), 123.0 (*C*H), 122.7 (*C*), 122.6 (*C*H), 119.1 (*C*), 116.0 (*C*H), 111.5 (*C*H), 103.8 (*C*H), 87.4 (*C*H), 85.5 (*C*H), 56.0 (CH_3) ppm.
LRMS (ES+)	1374 ($[3M+Na]^+$, 45 %), 923 ($[2M+Na]^+$, 100 %), 473 ($[M+Na]^+$, 15 %) amu.
CHN	Found C 77.20 %, H 4.89 %; $C_{29}H_{22}O_5$ requires C 77.32 %, H 4.92 %.

5-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2-iodo-phenol **3.51**



3.11
$C_{12}H_{16}O_3$
Mol. Wt.: 208

3.51
$C_{12}H_{15}IO_3$
Mol. Wt.: 334

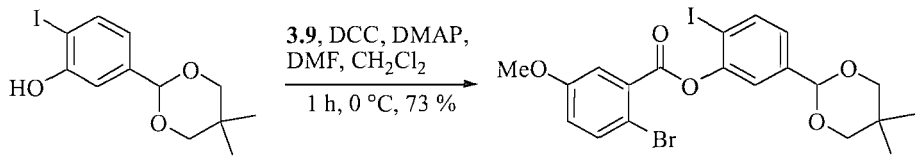
To a cooled (0 °C) solution of phenol **3.11** (671 mg, 3.23 mmol) and silver trifluoroacetate (855 mg, 3.87 mmol) in chloroform (20 mL) was added dropwise a solution of iodine (859 mg, 3.38 mmol) in chloroform (20 mL). The mixture was warmed to RT, stirred for 3 h and filtered through Celite. The organic phase was washed with sodium thiosulphate (3 × 40 mL), brine (3 × 30 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/2) gave **3.51** (700 mg, 2.10 mmol, 65 %) as a white solid.

MP	118-120 °C (di*iso*propyl ether)
λ_{max}/nm (ε_{max}, MeOH)	282 (7800), 235 (11000), 204 (32500).
ν_{max}/cm^{-1} (solid)	3324 (br. w), 2956 (m), 2852 (w), 1606 (w), 1394 (m), 1215 (m), 1099 (s), 1016 (m), 982 (m), 729 (w).
δ_H (400 MHz, $CDCl_3$)	7.66 (1H, d, *J* 8.3 Hz, Ar*H*), 7.15 (1H, d, *J* 2.0 Hz, Ar*H*), 6.84 (1H, dd, *J* 8.3, 2.0 Hz, Ar*H*), 5.36 (1H, s, ArC*H*), 5.33 (1H, s, ArO*H*), 3.77 (2H, d, *J* 10.0 Hz, 2 × OC*H*H), 3.64 (2H, d, *J* 10.0 Hz, 2 × OC*H*H), 1.28 (3H, s, CH_3), 0.81 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	155.0 (*C*), 141.3 (*C*), 138.4 (*C*H), 120.4 (*C*H), 113.2 (*C*H), 100.9 (*C*H), 86.0 (*C*), 77.8 (2 × *C*H_2), 30.4 (*C*), 23.2 (*C*H_3), 22.0 (*C*H_3) ppm.
LRMS (EI)	334 (M^+, 42 %), 333 ([M-H]$^+$, 50 %), 248 ([M-$C_5H_{10}O$]$^+$,

100 %) amu.

CHN Found C 43.41 %, H 4.44 %; $C_{12}H_{15}O_3I$ requires C 43.13 %, H 4.52 %.

2-Bromo-5-methoxy-benzoic acid 5-(5,5-dimethyl-[1,3]dioxan-2-yl)-2-iodo-phenyl ester **3.52**



3.51
$C_{12}H_{15}IO_3$
Mol. Wt.: 334

3.52
$C_{20}H_{20}BrIO_5$
Mol. Wt.: 547

Following the general procedure of Bringmann *et al.*[84] To a solution of acid **3.9** (769 mg, 3.33 mmol) in DMF/CH_2Cl_2 (1/4, 5 mL) was added DMAP (38 mg, 0.31 mmol) and phenol **3.51** (1.01 g, 3.02 mmol). The mixture was cooled to 0 °C and DCC (777 mg, 3.77 mmol) added. After 15 min, the reaction was warmed to RT, stirred for 1 h, filtered and the solvent removed under reduced pressure. The crude mixture was dissolved in dichloromethane (10 mL), washed with 0.5 M HCl (2 × 10 mL) and sat. sodium bicarbonate (2 × 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/3) gave **3.52** (1.20 g, 2.19 mmol, 73 %) as a colourless oil.

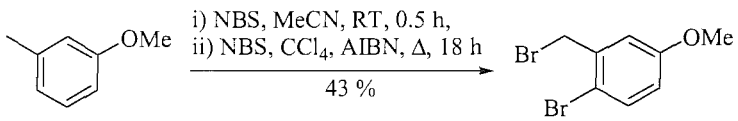
λ_{max}/nm (ε_{max}, MeOH) 288 (5800), 204 (59900).

ν_{max}/cm^{-1} (neat) 3016 (w), 2958 (w), 2854 (w), 1751 (m), 1594 (w), 1474 (m), 1285 (m), 1213 (s), 1101 (s), 1015 (s).

δ_H (300 MHz, $CDCl_3$) 7.88 (1H, d, *J* 8.1 Hz, Ar*H*),
7.78 (1H, d, *J* 2.9 Hz, Ar*H*),
7.63 (1H, d, *J* 8.8 Hz, Ar*H*),
7.45 (1H, d, *J* 1.8 Hz, Ar*H*),
7.20 (1H, dd, *J* 8.1, 1.8 Hz, Ar*H*),
7.00 (1H, dd, *J* 8.8, 2.9 Hz, Ar*H*),
5.40 (1H, s, ArC*H*),

	3.89 (3H, s, OCH_3),
	3.77 (2H, d, J 11.1 Hz, 2 × OCHH),
	3.66 (2H, d, J 11.1 Hz, 2 × OCHH),
	1.27 (3H, s, CH_3),
	0.81 (3H, s, CH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	163.1 (*C*), 158.8 (*C*), 151.1 (*C*), 140.9 (*C*), 139.5 (*C*H), 135.7 (*C*H), 131.1 (*C*), 125.8 (*C*H), 121.2 (*C*H), 120.2 (*C*H), 117.4 (*C*H), 113.3 (*C*), 100.2 (*C*H), 90.6 (*C*), 77.7 (2 × *C*H_2), 56.0 (*C*H_3), 30.4 (*C*), 23.2 (*C*H_3), 22.0 (*C*H_3) ppm.
LRMS (EI)	548 ([M{^{81}Br}]$^+$, 2 %), 546 ([M{^{79}Br}]$^+$, 2 %), 301 (10 %), 299 (11 %), 215 (100 %), 213 (99 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 568.9448. $C_{20}H_{20}O_5IBrNa$ requires 568.9438.

2-Bromo-5-methoxybenzyl bromide **3.56**



5.8
$C_8H_{10}O$
Mol. Wt.: 122

3.56
$C_8H_8Br_2O$
Mol. Wt.: 280

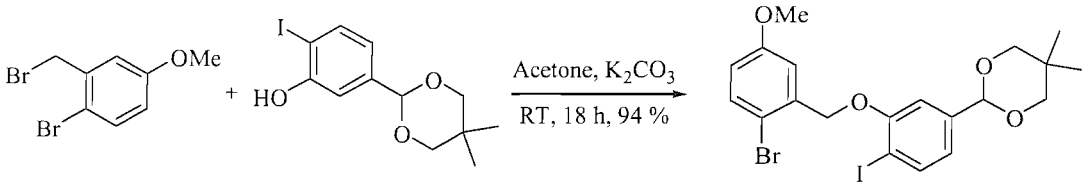
To a solution of aryl **5.8** (1.9 mL, 15.07 mmol) in acetonitrile (16 mL) was added NBS (2.95 g, 16.57 mmol) at RT and stirred for 30 min. The solvent was removed *in vacuo*, and crude product dissolved in carbon tetrachloride (5 mL). The solid was filtered, and washed with carbon tetrachloride, and solvent removed under reduced pressure to yield the crude bromo aryl **5.8a** (2.61 g, 12.97 mmol). The crude mixture was dissolved in carbon tetrachloride (10 mL), to which NBS (3.07 g, 17.25 mmol) and AIBN (170 mg, 1.04 mmol) were added and the mixture heated under reflux for 18 h. The solid was filtered, washed with carbon tetrachloride, and solvent removed under reduced pressure to yield the crude product which

was recrystallised from petroleum ether to yield benzyl bromide **3.56** (1.82 g, 6.50 mmol, 43 %) as a pale yellow solid.

The spectroscopic and physical data attained compares well with literature values.[115]

MP	88-90 °C (petroleum ether) [Lit. 85-87 °C (hexane)][115]
λ_{max}/nm (ε_{max}, CH_2Cl_2)	295 (3700), 238 (9100).
ν_{max}/cm^{-1} (solid)	2960 (w), 2834 (w), 1572 (m), 1478 (s), 1281 (s), 1243 (s), 1216 (m), 1168 (m), 1018 (m), 731 (m).
δ_H (400 MHz, $CDCl_3$)	7.46 (1H, d, *J* 8.8 Hz, Ar*H*), 7.00 (1H, d, *J* 3.0 Hz, Ar*H*), 6.75 (1H, dd, *J* 8.8, 3.0 Hz, Ar*H*), 4.56 (2H, s, ArCH_2Br), 3.81 (3H, s, OCH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	159.4 (*C*), 138.0 (*C*), 134.1 (*C*H), 116.7 (*C*H), 116.3 (*C*H), 114.9 (*C*), 55.7 (*C*H$_3$), 33.6 (*C*H$_2$) ppm.
LRMS (EI)	280 (M{^{81}Br^{79}Br}$^+$, 40 %), 278 (M{^{79}Br^{79}Br}$^+$, 22 %), 240 (82 %), 201 ([M{^{81}Br}-Br]$^+$, 40 %), 199 ([M{^{79}Br}-Br]$^+$, 100 %)amu.

2-[3-(2-Bromo-5-methoxy-benzyloxy)-4-iodo-phenyl]-5,5-dimethyl-[1,3]dioxane **3.55**



3.56
$C_8H_8Br_2O$
Mol. Wt.: 280

3.51
$C_{12}H_{15}IO_3$
Mol. Wt.: 334

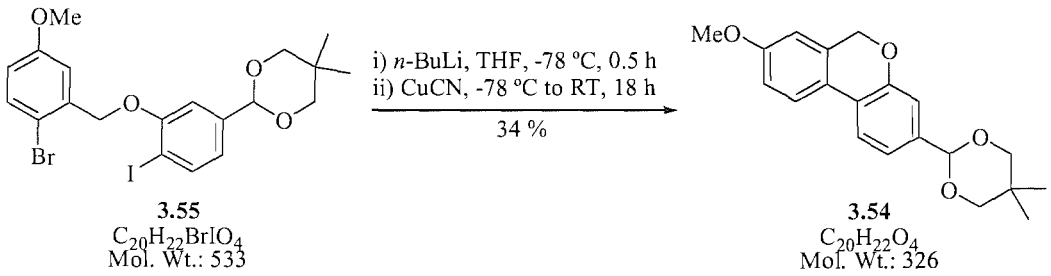
3.55
$C_{20}H_{22}BrIO_4$
Mol. Wt.: 533

To a solution of phenol **3.51** (602 mg, 1.80 mmol) in acetone (10 mL) was added potassium carbonate (252 mg, 1.82 mmol) followed by **3.56** (517 mg, 1.85 mmol). The mixture was stirred for 72 h, filtered and solvent removed *in vacuo*. Purification by column

chromatography (SiO_2, ether/petroleum ether, 10 %) gave **3.55** (904 mg, 1.70 mmol, 94 %) as a white crystalline solid.

MP	139-140 °C (petroleum ether)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	280 (26800), 232 (13000)
ν_{max}/cm^{-1} (solid)	2956 (m), 2867 (m), 1577 (m), 1473 (m), 1456 (m), 1415 (m), 1387 (s), 1269 (s), 1183 (m), 1102 (s), 1050 (s), 1017 (s), 984 (s), 805 (s).
δ_H (400 MHz, $CDCl_3$)	7.82 (1H, d, *J* 8.0 Hz, Ar*H*), 7.50 (1H, d, *J* 3.0 Hz, Ar*H*), 7.45 (1H, d, *J* 8.8 Hz, Ar*H*), 7.08 (1H, d, *J* 1.7 Hz, Ar*H*), 6.94 (1H, dd, *J* 8.0, 1.7 Hz, Ar*H*), 7.50 (1H, dd, *J* 8.8, 3.0 Hz, Ar*H*), 5.38 (1H, s, ArC*H*), 5.17 (2H, s, ArCH_2), 3.85 (3H, s, OCH_3), 3.79 (2H, d, *J* 11.1 Hz, 2 × OC*H*H), 3.66 (2H, d, *J* 11.1 Hz, 2 × OC*H*H), 1.30 (3H, s, CH_3), 0.82 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	159.5 (*C*), 156.9 (*C*), 140.8 (*C*), 139.5 (*C*H), 137.0 (*C*), 133.1 (*C*H), 121.1 (*C*H), 115.8 (*C*H), 114.0 (*C*H), 111.7 (*C*), 110.5 (*C*H), 101.0 (*C*H), 87.1 (*C*), 77.8 (2 × CH_2), 70.1 (CH_2), 55.8 (CH_3), 30.4 (*C*), 23.3 (CH_3), 22.1 (CH_3) ppm.
LRMS (EI)	453 ([M-Br]$^+$, 2 %), 326 ([M-Br-I]$^+$, 6 %), 201 (100 %) amu.
CHN	Found C 45.07 %, H 3.98 %, Br 14.64 %; $C_{20}H_{22}O_4BrI$ requires C 45.05 %, H 4.16 %, Br 14.99 %.

3-(5,5-Dimethyl-[1,3]dioxan-2-yl)-8-methoxy-6*H*-benzo[c]chromene **3.54**



3.55
$C_{20}H_{22}BrIO_4$
Mol. Wt.: 533

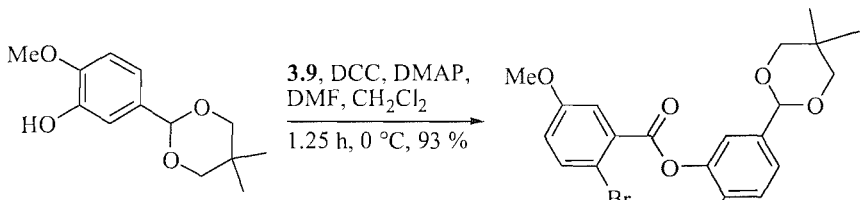
3.54
$C_{20}H_{22}O_4$
Mol. Wt.: 326

To a cooled (-78 °C) solution of bishalo-arene **3.55** (146 mg, 0.27 mmol) in THF (12 mL) was added *n*-butyl lithium (2.3 M in hexanes, 0.25 mL, 0.58 mmol), and the mixture stirred for 30 min. Copper(I) cyanide (61 mg, 0.68 mmol) was added in one portion at -78 °C, and stirred for a further 45 min before slowly warming to RT. The reaction was stirred for 17 h, SiO_2 (0.2 g) added, and solvent removed under reduced pressure. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/3-1/2) gave **3.54** (30 mg, 0.09 mmol, 34 %) as a white solid.

MP	146-148 °C (petroleum ether)
λ_{max}/nm (ε_{max}, MeOH)	313 (6300), 279 (8900).
ν_{max}/cm^{-1} (solid)	2955 (w), 2851 (w), 1618 (w), 1490 (m), 1383 (m), 1281 (s), 1247 (s), 1097 (s), 1018 (s), 981 (s), 883 (m), 812 (s), 768 (m).
δ_H (400 MHz, $CDCl_3$)	7.65 (1H, d, *J* 8.0 Hz, Ar*H*), 7.63 (1H, d, *J* 8.7 Hz, Ar*H*), 7.18 (1H, dd, *J* 8.0, 1.7 Hz, Ar*H*), 7.15 (1H, d, *J* 1.7 Hz, Ar*H*), 6.92 (1H, dd, *J* 8.7, 2.5 Hz, Ar*H*), 6.69 (1H, dd, *J* 2.5 Hz, Ar*H*), 5.37 (1H, s, ArC*H*), 5.08 (2H, s, ArCH_2), 3.84 (3H, s, OCH_3), 3.78 (2H, d, *J* 11.1 Hz, 2 × OC*H*H),

	3.66 (2H, d, *J* 11.1 Hz, 2 × OC*H*H),
	1.31 (3H, s, C*H*$_3$),
	0.81 (3H, s, C*H*$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	159.7 (*C*), 154.2 (*C*), 139.1 (*C*), 133.4 (*C*), 123.8 (*C*H), 123.7 (*C*), 123.0 (*C*), 122.8 (*C*H), 120.1 (*C*H), 115.4 (*C*H), 114.2 (*C*H), 110.3 (*C*H), 101.5 (*C*H), 77.8 (2 × *C*H$_2$), 68.7 (*C*H$_2$), 55.6 (*C*H$_3$), 30.4 (*C*), 23.2 (*C*H$_3$), 22.1 (*C*H$_3$) ppm.
LRMS (EI)	326 (M^+, 95 %), 240 ($[M-C_5H_{10}O]^+$, 100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 349.1402. $C_{20}H_{22}O_4Na$ requires 349.1416.

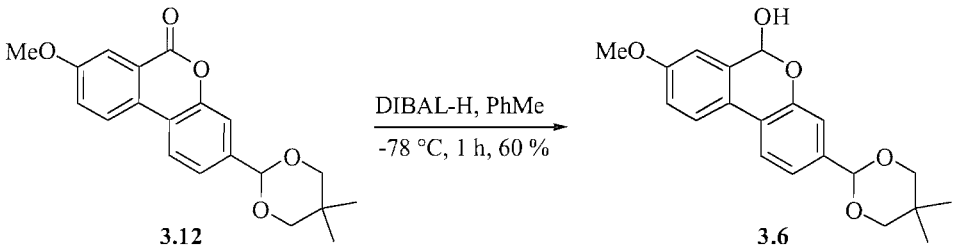
2-Bromo-5-methoxy-benzoic acid 5-(5,5-dimethyl-[1,3]dioxan-2-yl)-2-methoxy-phenyl ester **3.59**



Following the general procedure of Bringmann *et al.*[84] To a solution of acid **3.9** (1.17 g, 5.07 mmol) in DMF/CH_2Cl_2 (1/1, 5 mL) was added DMAP (29 mg, 0.24 mmol) and phenol **3.63** (1.09 g, 4.58 mmol). The mixture was cooled to 0 °C and DCC (1.14 g, 5.53 mmol) added. After 10 min, the reaction was warmed to RT, stirred for 75 min, filtered and the solvent removed under reduced pressure. The crude mixture was dissolved in dichloromethane (30 mL), washed with 0.5 M HCl (2 × 10 mL) and sat. sodium bicarbonate (2 × 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/3-1/2) gave **3.59** (1.91 g, 4.24 mmol, 93 %) as a white solid.

MP	90-91 °C (ether/petroleum ether)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	278 (9100), 229 (16900).
ν_{max}/cm^{-1} (solid)	2960 (w), 2851 (w), 1748 (m), 1592 (w), 1518 (m), 1471 (m), 1393 (m), 1321 (m), 1279 (s), 1206 (s), 1123 (s), 1095 (s), 1013 (s), 980 (m), 923 (m), 820 (m).
δ_H (400 MHz, $CDCl_3$)	7.61-7.58 (2H, m, 2 × Ar*H*), 7.42-7.37 (2H, m, 2 × Ar*H*), 7.01 (1H, d, *J* 8.3 Hz, Ar*H*), 6.96 (1H, dd, *J* 8.8, 3.0 Hz, Ar*H*), 5.38 (1H, s, ArC*H*), 3.86 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 3.77 (2H, d, *J* 11.1 Hz, 2 × OC*H*H), 3.65 (2H, d, *J* 11.1 Hz, 2 × OC*H*H), 1.29 (3H, s, C*H*$_3$), 0.80 (3H, s, C*H*$_3$) ppm.
δ_C (100 MHz, $CDCl_3$)	163.6 (*C*), 158.7 (*C*), 151.6 (*C*), 139.6 (*C*), 135.4 (*C*H), 131.8 (*C*), 131.8 (*C*), 125.0 (*C*H), 121.0 (*C*H), 119.8 (*C*H), 117.1 (*C*H), 113.0 (*C*), 112.3 (*C*H), 101.0 (*C*H), 77.5 (2 × *C*H$_2$), 56.3 (*C*H$_3$), 55.9 (*C*H$_3$), 30.4 (*C*), 23.3 (*C*H$_3$), 22.1 (*C*H$_3$) ppm.
LRMS (EI)	452 (M{^{81}Br}$^+$, 2 %), 450 (M{^{79}Br}$^+$, 2 %), 215 (97 %), 213 (100 %) amu.
CHN	Found C 55.92 %, H 5.18 %; $C_{21}H_{23}O_6Br$ requires C 55.89 %, H 5.14 %.

3-(5,5-Dimethyl-[1,3]dioxan-2-yl)-8-methoxy-6*H*-benzo[c]chromen-6-ol **3.6**



3.12
$C_{20}H_{20}O_5$
Mol. Wt.: 340

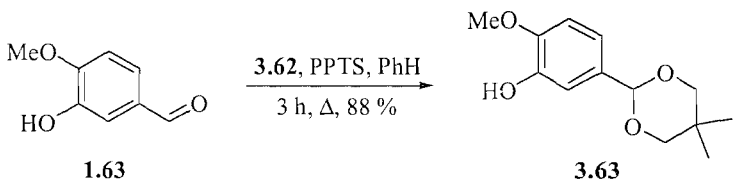
3.6
$C_{20}H_{22}O_5$
Mol. Wt.: 342

To a solution of lactone **3.12** (1.38 g, 4.06 mmol) in toluene (70 mL) at –78 °C was added DIBAL-H (5.00 mL, 5.00 mmol). The reaction was stirred for 1 h then warmed to RT and diluted with deoxygenated EtOAc (80 mL) and washed with water (3 × 50 mL). The aqueous phase was extracted with chloroform (3 × 20 mL) and the combined organic fractions washed with brine (3 × 30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/2-2/1) gave recovered lactone **3.12** (271 mg, 0.80 mmol, 20 %), and lactol **3.6** (825 mg, 2.41 mmol, 60 %) as a white solid.

MP	209-210 °C (ether/petroleum ether)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	303 (17200), 278 (23200), 229 (11700).
ν_{max}/cm^{-1} (solid)	3368 (br. m), 2949 (m), 2861 (w), 1623 (w), 1456 (m), 1423 (m), 1382 (m), 1275 (s), 1099 (s), 1013 (s), 978 (s), 884 (s), 812 (s).
δ_H (300 MHz, C_6D_6)	7.71 (1H, d, *J* 1.6 Hz, Ar*H*), 7.60 (1H, d, *J* 8.1 Hz, Ar*H*), 7.50 (1H, dd, *J* 8.1, 1.6 Hz, Ar*H*), 7.41 (1H, d, *J* 8.8 Hz, Ar*H*), 6.80 (1H, dd, *J* 8.8, 2.6 Hz, Ar*H*), 6.60 (1H, d, *J* 2.6 Hz, Ar*H*), 6.00 (1H, d, *J* 7.3 Hz, C*H*OH), 5.32 (1H, s, ArC*H*), 3.57 (2H, d, *J* 11.2 Hz, 2 × OC*H*H),

	3.30 (2H, d, *J* 11.2 Hz, 2 × OC*H*H),
	3.24 (3H, s, OCH_3),
	2.43 (1H, d, *J* 7.3 Hz, O*H*)
	1.55 (3H, s, CH_3),
	1.22 (3H, s, CH_3) ppm.
δ_C (100 MHz, DMSO)	160.0 (*C*), 150.8 (*C*), 139.8 (*C*), 134.7 (*C*), 124.6 (*C*H), 123.1 (*C*H), 122.5 (*C*), 121.6 (*C*), 120.6 (*C*H), 116.6 (*C*H), 116.2 (*C*H), 111.7 (*C*H), 101.3 (*C*H), 92.9 (*C*H), 77.4 (2 × *C*H_2), 56.2 (*C*H_3), 30.7 (*C*), 23.6 (*C*H_3), 22.3 (*C*H_3) ppm.
LRMS (CI)	360 ([M+NH_4]$^+$, 10 %), 343 (MH^+, 37 %), 326 (78 %), 240 ([M-$C_5H_{10}O_2$]$^+$, 100 %) amu.
CHN	Found C 69.96 %, H 6.52 %; $C_{20}H_{22}O_5$ requires C 70.16 %, H 6.48 %.

5-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2-methoxy-phenol **3.63**



1.63
$C_8H_8O_3$
Mol. Wt.: 152

3.63
$C_{13}H_{18}O_4$
Mol. Wt.: 238

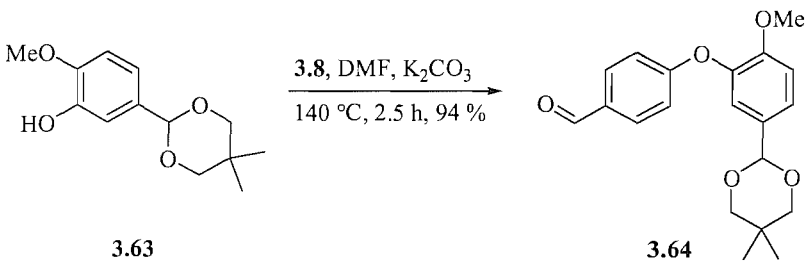
Following the procedure of Gangakhedkar, to a solution of isovanillin **1.63** (15.03 g, 98.56 mmol) and diol **3.62** (30.79 g, 295.63 mmol) in benzene (350 mL) was added pyridinium *p*-toluenesulfonate (1.00 g, 3.98 mmol).[96] The mixture was heated at reflux under a Dean-Stark apparatus for 3 h then cooled and diluted with dichloromethane (50 mL). The organic phase was washed with water (3 × 40 mL), sat. sodium bicarbonate (30 mL) and brine (3 × 30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting solid was

recrystallised from di*iso*propyl ether to give **3.63** (20.58 g, 86.49 mmol, 88 %) as a white crystalline solid.

The spectroscopic and physical data attained compares well with literature values.[96]

MP	122-123 °C (di*iso*propyl ether) [Lit. 118 °C][96]
λ_{max}/nm (ε_{max}, CH_2Cl_2)	278 (3200), 230 (6900).
ν_{max}/cm^{-1} (solid)	3421 (br. w), 2951 (m), 2856 (w), 1598 (w), 1521 (m), 1464 (m), 1391 (m), 1275 (s), 1162 (m), 1125 (s), 1100 (s), 1013 (s), 982 (s), 915 (m), 866 (m), 812 (s), 762 (m).
δ_H (300 MHz, $CDCl_3$)	7.11 (1H, d, *J* 2.2 Hz, Ar*H*), 7.01 (1H, dd, *J* 8.5, 2.2 Hz, Ar*H*), 6.84 (1H, d, *J* 8.5 Hz, Ar*H*), 5.64 (1H, s, ArO*H*), 5.32 (1H, s, ArC*H*), 3.88 (3H, s, OCH_3), 3.76 (2H, d, *J* 10.4 Hz, 2 × OC*H*H), 3.64 (2H, d, *J* 10.4 Hz, 2 × OC*H*H), 1.30 (3H, s, CH_3), 0.80 (3H, s, CH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	147.1 (*C*), 145.6 (*C*), 132.2 (*C*), 118.1 (*C*H), 112.8 (*C*H), 110.4 (*C*H), 101.7 (*C*H), 77.8 (2 × *C*H_2), 56.1 (*C*H_3), 30.3 (*C*), 23.2 (*C*H_3), 22.0 (*C*H_3) ppm.
LRMS (EI)	238 (M^+, 84 %), 237 ($[M-H]^+$, 91 %), 151 ($[M-C_5H_{10}O]^+$, 100 %) amu.

4-[5-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2-methoxy-phenoxy]-benzaldehyde **3.64**



3.63
$C_{13}H_{18}O_4$
Mol. Wt.: 238

3.64
$C_{20}H_{22}O_5$
Mol. Wt.: 342

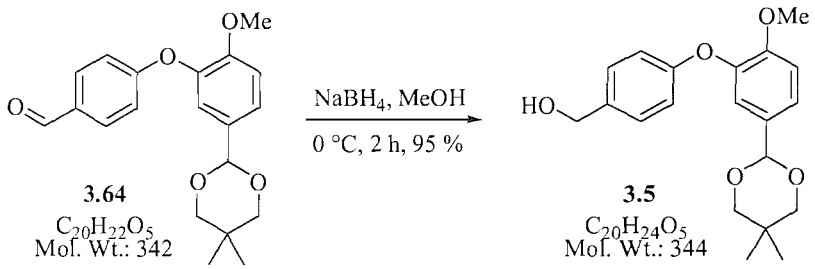
To a solution of phenol **3.63** (18.60 g, 78.15 mmol) and 4-fluorobenzaldehyde **3.8** (9.60 g, 77.38 mmol) in DMF (80 mL) was added potassium carbonate (9.62 g, 69.71 mmol). The mixture was heated to 150 °C for 2.5 h then cooled and poured into ice water (200 mL). The resulting solid was filtered and recrystallised from di*iso*propyl ether to give aryl ether **3.64** (24.77 g, 72.43 mmol, 94 %) as a white crystalline solid.

The spectroscopic and physical data attained compares well with literature values.[96]

MP	79-81 °C (di*iso*propyl ether) [Lit. 76 °C][96]
λ_{max}/nm (ε_{max}, CH_2Cl_2)	283 (21300), 229 (14500).
ν_{max}/cm^{-1} (solid)	2952 (w), 2867 (w), 1685 (m), 1586 (s), 1504 (m), 1435 (m), 1394 (m), 1273 (s), 1228 (s), 1216 (s), 1157 (s), 1124 (s), 1100 (s), 1012 (s), 983 (s), 814 (s).
δ_H (400 MHz, $CDCl_3$)	9.91 (1H, s, C*H*O), 7.81 (2H, d, *J* 8.6 Hz, 2 × Ar*H*), 7.39 (1H, dd, *J* 8.4, 2.0 Hz, Ar*H*), 7.29 (1H, d, *J* 2.0 Hz, Ar*H*), 7.03 (1H, d, *J* 8.4 Hz, Ar*H*), 6.99 (2H, d, *J* 8.6 Hz, 2 × Ar*H*), 5.36 (1H, s, ArC*H*), 3.79 (3H, s, OCH_3), 3.76 (2H, d, *J* 11.1 Hz, 2 × OC*H*H), 3.63 (2H, d, *J* 11.1 Hz, 2 × OC*H*H),

	1.28 (3H, s, CH_3),
	0.80 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	191.0 (*C*H), 163.7 (*C*), 152.2 (*C*), 142.8 (*C*), 132.4 (*C*),
	132.0 (2 × *C*H), 131.1 (*C*), 124.5 (*C*H), 120.9 (*C*H), 116.5
	(2 × *C*H), 112.9 (*C*H), 101.1 (*C*H), 77.8 (2 × CH_2), 56.2
	(CH_3), 30.6 (*C*), 23.2 (CH_3), 22.0 (CH_3) ppm.
LRMS (EI)	342 (M^+, 88 %), 256 ($[M-C_5H_{10}O]^+$, 100 %) amu.

{4-[5-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2-methoxy-phenoxy]-phenyl}-methanol **3.5**



3.64
$C_{20}H_{22}O_5$
Mol. Wt.: 342

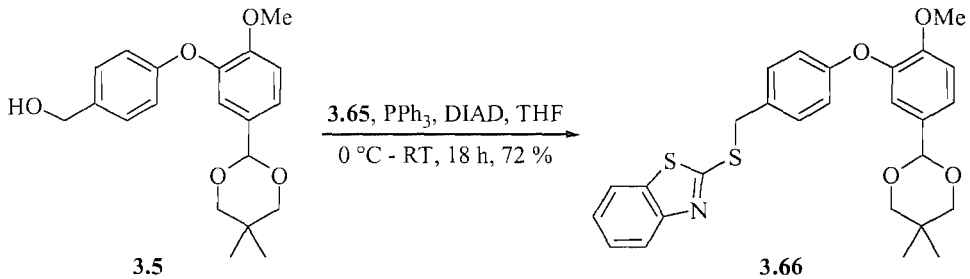
3.5
$C_{20}H_{24}O_5$
Mol. Wt.: 344

To a cooled (0 °C) solution of aldehyde **3.64** (29.09 g, 85.06 mmol) in methanol (500 mL) was added sodium borohydride (2.20 g, 58.15 mmol). After 2 h water (20 mL) was added cautiously. The solvent was removed *in vacuo* and the residue partitioned between ether (1 L) and water (250 mL). The organic phase was separated, washed with water (2 × 250 mL) and brine (3 × 50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Recrystallisation of the crude material from aq. ethanol gave benzyl alcohol **3.5** (26.47 g, 76.94 mmol, 90 %) as a white solid.

MP	120-121 °C (aq. ethanol)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	274 (3500), 230 (15300).
ν_{max}/cm^{-1} (solid)	3486 (m), 2950 (w), 2852 (w), 1609 (w), 1510 (s), 1379
	(m), 1274 (m), 1213 (s), 1125 (s), 1092 (s), 1018 (s), 983
	(s), 892 (m), 801 (m).

δ_H (400 MHz, $CDCl_3$)	7.32 (1H, dd, *J* 8.3, 2.0 Hz, Ar*H*),
	7.27 (2H, d, *J* 8.8 Hz, 2 × Ar*H*),
	7.16 (1H, d, *J* 2.0 Hz, Ar*H*),
	7.01 (1H, d, *J* 8.3 Hz, Ar*H*),
	6.93 (2H, d, *J* 8.8 Hz, 2 × Ar*H*),
	5.31 (1H, s, ArC*H*),
	4.63 (2H, d, *J* 5.6 Hz, ArCH_2),
	3.83 (3H, s, OCH_3),
	3.73 (2H, d, *J* 11.0 Hz, 2 × OC*H*H),
	3.61 (2H, d, *J* 11.0 Hz, 2 × OC*H*H),
	1.71 (1H, t, *J* 5.6 Hz, O*H*)
	1.26 (3H, s, CH_3),
	0.78 (3H, s, CH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	157.7 (*C*), 152.0 (*C*), 144.6 (*C*), 135.0 (*C*), 132.0 (*C*),
	128.7 (2 × *C*H), 122.9 (*C*H), 119.5 (*C*H), 117.3 (2 × *C*H),
	112.6 (*C*H), 101.3 (*C*H), 77.8 (2 × *C*H_2), 65.1 (*C*H_2), 56.2
	(*C*H_3), 30.3 (*C*), 23.2 (*C*H_3), 22.0 (*C*H_3) ppm.
LRMS (ES+)	367 ($[M+Na]^+$, 100 %) amu.
CHN	Found C 69.49 %, H 6.95 %; $C_{20}H_{24}O_5$ requires C 69.75
	%, H 7.02 %.

2-{4-[5-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2-methoxy-phenoxy]-benzylsulfanyl}-benzothiazole **3.66**



3.5
$C_{20}H_{24}O_5$
Mol. Wt.: 344

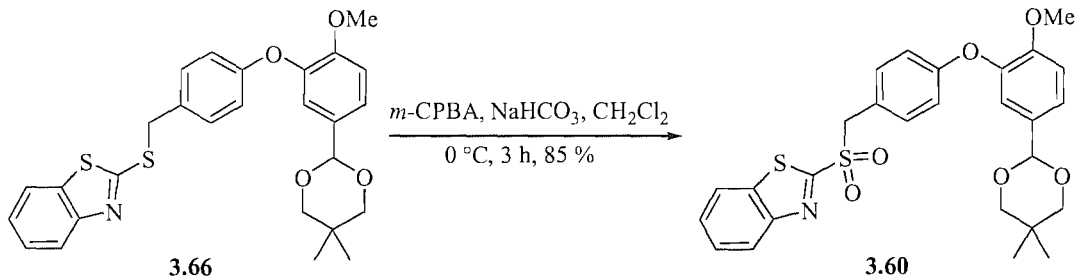
3.66
$C_{27}H_{27}NO_4S_2$
Mol. Wt.: 494

To a cooled (-10 °C) solution of 2-mercaptobenzathiazole **3.65** (8.26 g, 49.39 mmol), benzyl alcohol **3.5** (15.06 g, 43.78 mmol) and triphenylphosphine (11.49 g, 43.79 mmol) in THF (150 mL) was added DIAD (8.40 mL, 44.19 mmol). The mixture was warmed to RT, stirred for 18 h and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, CH_2Cl_2/petroleum ether, 1/1) and recrystallisation from ether/petroleum ether gave **3.66** (15.57 g, 31.52 mmol, 72 %) as a white solid.

MP	158-160 °C (ether/petroleum ether)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	302 (22300), 280 (34000), 235 (50800).
ν_{max}/cm^{-1} (solid)	2941 (w), 2842 (w), 1610 (m), 1505 (s), 1456 (m), 1424 (s), 1383 (m), 1268 (s), 1230 (s), 1125 (s), 1099 (s), 1014 (s), 971 (m), 893 (m), 807 (s), 763 (s).
δ_H (400 MHz, $CDCl_3$)	7.91 (1H, d, *J* 7.8 Hz, Ar*H*), 7.76 (1H, d, *J* 8.0 Hz, Ar*H*), 7.43 (1H, ddd, *J* 8.3, 7.3, 1.3 Hz, Ar*H*), 7.37 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.34-7.28 (2H, m, 2 × Ar*H*), 7.18 (1H, d, *J* 2.0 Hz, Ar*H*), 7.00 (1H, d, *J* 8.5 Hz, Ar*H*), 6.89 (2H, d, *J* 8.8 Hz, Ar*H*), 5.31 (1H, s, ArC*H*),

	4.58 (2H, s, ArCH_2),
	3.81 (3H, s, OCH_3),
	3.73 (2H, d, J 11.0 Hz, 2 × OCHH),
	3.61 (2H, d, J 11.0 Hz, 2 × OCHH),
	1.26 (3H, s, CH_3),
	0.78 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	166.7 (*C*), 157.9 (*C*), 153.3 (*C*), 152.2 (*C*), 144.3 (*C*), 135.5 (*C*), 132.1 (*C*), 130.5 (2 × *C*H), 129.9 (*C*), 126.2 (*C*H), 124.5 (*C*H), 123.2 (*C*H), 121.7 (*C*H), 121.2 (*C*H), 120.0 (*C*H), 117.1 (2 × *C*H), 112.7 (*C*H), 101.3 (*C*H), 77.8 (2 × *C*H_2), 56.3 (*C*H_3), 37.5 (*C*H_2), 30.3 (*C*), 23.2 (*C*H_3), 22.0 (*C*H_3) ppm.
LRMS (ES+)	516 ([M+Na]$^+$, 100 %) amu.
CHN	Found C 65.68 %, H 5.35 %, N 2.93 %, S 13.00 %; $C_{27}H_{27}NO_4S_2$ requires C 65.69 %, H 5.51 %, N 2.84 %, S 12.99 %.

2-{4-[5-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2-methoxy-phenoxy]-benzylsulfanyl}-benzothiazole **3.60**



3.66
$C_{27}H_{27}NO_4S_2$
Mol. Wt.: 494

3.60
$C_{27}H_{27}NO_6S_2$
Mol. Wt.: 526

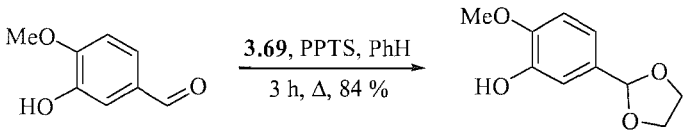
To a cooled (0 °C) solution of thioether **3.66** (457 mg, 0.93 mmol) and $NaHCO_3$ (805 mg, 9.82 mmol) in dichloromethane (10 mL) was added *m*-CPBA (1.17 g, 52.5 % aq., 3.54 mmol) in two portions. The mixture was stirred for 0.5 h and partitioned between

dichloromethane (50 mL) and sat. sodium thiosulphate (30 mL). The organic phase was separated and washed with sat. $NaHCO_3$ (2 × 30 mL) and brine (3 × 20 mL). The organic phase was dried ($MgSO_4$) and solvent removed *in vacuo*, to yield **3.60** (415 mg, 0.79 mmol, 85 %) as a gum, which was recrystallised from ether/petroleum ether.

MP	185-186 °C (ether/petroleum ether)
ν_{max}/cm^{-1} (solid)	2950 (w), 2852 (w), 1615 (w), 1506 (m), 1474 (m), 1386 (m), 1333 (s), 1274 (s), 1227 (s), 1151 (s), 1123 (s), 1102 (s), 1019 (s), 980 (m), 879 (m), 761 (s).
λ_{max}/nm (ε_{max}, CH_2Cl_2)	276 (41300), 230 (20500).
δ_H (300 MHz, $CDCl_3$)	8.26 (1H, app. d, *J* 7.8 Hz, Ar*H*), 7.97 (1H, app. d, *J* 7.8 Hz, Ar*H*), 7.65 (1H, app. td, *J* 8.3, 1.5 Hz, Ar*H*), 7.58 (1H, app. td, *J* 8.3, 1.3 Hz, Ar*H*), 7.32 (1H, dd, *J* 8.5, 2.1 Hz, Ar*H*), 7.16 (2H, d, *J* 8.7 Hz, 2 × Ar*H*), 7.16 (1H, d, *J* 2.1 Hz, Ar*H*), 6.98 (1H, d, *J* 8.5 Hz, Ar*H*), 6.81 (2H, d, *J* 8.7 Hz, 2 × Ar*H*), 5.31 (1H, s, ArC*H*), 4.71 (2H, s, ArCH_2), 3.77 (3H, s, OCH_3), 3.74 (2H, d, *J* 11.1 Hz, 2 × OC*H*H), 3.62 (2H, d, *J* 11.1 Hz, 2 × OC*H*H), 1.27 (3H, s, CH_3), 0.79 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	165.5 (*C*), 159.1 (*C*), 152.8 (*C*), 152.1 (*C*), 143.8 (*C*), 137.2 (*C*), 132.5 (2 × *C*H), 132.2 (*C*), 128.1 (*C*H), 127.8 (*C*H), 125.6 (*C*H), 123.5 (*C*H), 122.5 (*C*H), 120.1 (*C*H), 119.9 (*C*), 117.1 (2 × *C*H), 112.8 (*C*H), 101.2 (*C*H), 77.8 (2 × CH_2), 60.6 (CH_2), 56.2 (CH_3), 30.3 (*C*), 23.2 (CH_3), 22.0 (CH_3) ppm.

LRMS (ES+)	548 ($[M+Na]^+$, 100 %) amu.
CHN	Found C 61.34 %, H 5.15 %, N 2.85 %, S 11.94 %; $C_{27}H_{27}NO_6S_2$ requires C 61.69 %, H 5.18 %, N 2.66 %, S 12.20 %.

5-[1,3]Dioxolan-2-yl-2-methoxy-phenol **3.63a**



1.63
$C_8H_8O_3$
Mol. Wt.: 152

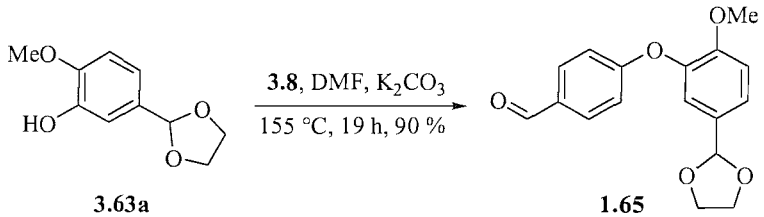
3.63a
$C_{10}H_{12}O_4$
Mol. Wt.: 196

To a solution of isovanillin **1.63** (15.20 g, 99.90 mmol) and diol **3.69** (16.70 mL, 299.45 mmol) in benzene (350 mL) was added pyridinium *p*-toluenesulfonate (1.00 g, 3.98 mmol). The mixture was heated at reflux under a Dean-Stark apparatus for 3 h then cooled and diluted with dichloromethane (50 mL). The organic phase was washed with water (3 × 40 mL), sat. sodium bicarbonate (30 mL) and brine (3 × 30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude material was purified by column chromatography (SiO_2, ether/petroleum ether, 1/1) to give **3.63a** (16.50 g, 84.18 mmol, 84 %) as a colourless oil.

λ_{max}/nm (ε_{max}, CH_2Cl_2)	307 (7750), 272 (11300), 231 (15000).
ν_{max}/cm^{-1} (neat)	3387 (br. m), 2890 (m), 1595 (m), 1513 (m), 1442 (m), 1403 (m), 1273 (s), 1166 (m), 1127 (m), 1077 (s), 1023 (s), 948 (m), 873 (m), 806 (m), 760 (m).
δ_H (300 MHz, $CDCl_3$)	7.08 (1H, d, *J* 2.0 Hz, Ar*H*), 7.00 (1H, dd, *J* 8.2, 2.0 Hz, Ar*H*), 6.87 (1H, d, *J* 8.2 Hz, Ar*H*), 5.76 (1H, s, ArO*H*), 5.71 (1H, s, ArC*H*),

	4.16-4.00 (4H, m, 2 × OCH_2),
	3.91 (3H, s, OCH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	147.5 (*C*), 145.8 (*C*), 131.4 (*C*), 118.6 (*C*H), 112.9 (*C*H),
	110.5 (*C*H), 103.8 (*C*H), 65.4 (2 × CH_2), 56.2 (CH_3) ppm.
LRMS (EI)	152 ($[M-C_2H_4O]^+$, 94 %), 151 ($[M-C_2H_5O]^+$, 100 %) amu.
CHN	Found C 61.56 %, H 6.29 %; $C_{10}H_{12}O_4$ requires C 61.22
	%, H 6.16 %.

4-(5-[1,3]Dioxolan-2-yl-2-methoxy-phenoxy])-benzaldehyde **1.65**



3.63a
$C_{10}H_{12}O_4$
Mol. Wt.: 196

1.65
$C_{17}H_{16}O_5$
Mol. Wt.: 300

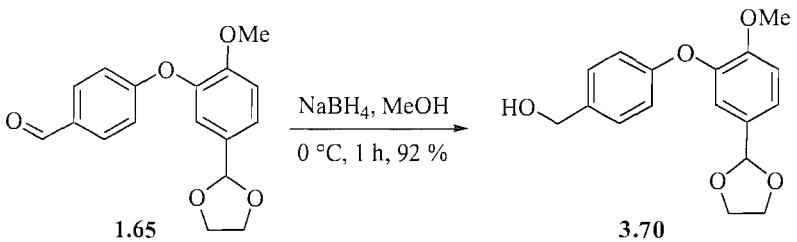
To a solution of phenol **3.63a** (16.09 g, 82.11 mmol) and 4-fluorobenzaldehyde **3.8** (8.90 mL, 82.97 mmol) in DMF (100 mL) was added potassium carbonate (10.20 g, 73.81 mmol). The mixture was heated to 155 °C for 19 h then cooled and poured into ice water (150 mL) and extracted with ether (3 × 200 mL). The organic fractions were combined, washed with brine (3 × 50 mL), dried ($MgSO_4$), and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 4/1) gave aryl ether **1.65** (22.42 g, 74.73 mmol, 90 %) as a clear oil.

The spectroscopic and physical data attained compares well with literature values.[40]

λ_{max}/nm (ε_{max}, CH_2Cl_2)	283 (18500), 229 (12300).
ν_{max}/cm^{-1} (neat)	2889 (w), 2842 (w), 1693 (s), 1600 (m), 1581 (m), 1503
	(m), 1432 (w), 1394 (w), 1274 (s), 1229 (s), 1155 (m),
	1126 (m), 1083 (m), 1025 (m), 833 (w).
δ_H (400 MHz, $CDCl_3$)	9.91 (1H, s, C*H*O),
	7.82 (2H, d, *J* 8.8 Hz, 2 × Ar*H*),

	7.36 (1H, dd, *J* 8.5, 2.0 Hz, Ar*H*),
	7.25 (1H, d, *J* 2.0 Hz, Ar*H*),
	7.04 (1H, d, *J* 8.5 Hz, Ar*H*),
	6.99 (2H, d, *J* 8.8 Hz, 2 × Ar*H*),
	5.75 (1H, s, ArC*H*),
	4.14-3.98 (4H, m, 2 × OCH_2),
	3.80 (3H, s, OCH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	190.9 (*C*H), 163.5 (*C*), 152.5 (*C*), 143.0 (*C*), 132.0 (2 × *C*H), 131.5 (*C*), 131.2 (*C*), 124.9 (*C*H), 120.9 (*C*H), 116.5 (2 × *C*H), 112.9 (*C*H), 103.2 (*C*H), 65.5 (2 × CH_2), 56.2 (CH_3) ppm.
LRMS (EI)	300 (M^+, 57 %), 255 ($[M-C_2H_5O]^+$, 44 %), 228 (100 %) amu.

[4-(5-[1,3]Dioxolan-2-yl-2-methoxy-phenoxy)-phenyl]-methanol **3.70**



1.65
$C_{17}H_{16}O_5$
Mol. Wt.: 300

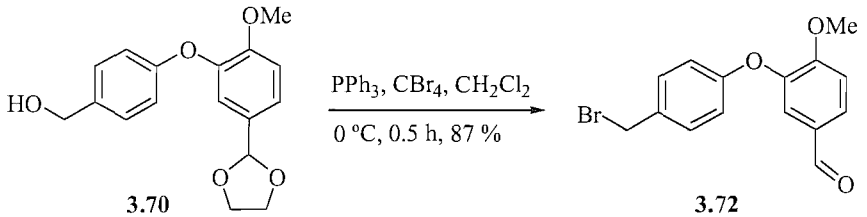
3.70
$C_{17}H_{18}O_5$
Mol. Wt.: 302

To a cooled (0 °C) solution of aldehyde **1.65** (22.45 g, 74.83 mmol) in methanol (250 mL) was added sodium borohydride (1.58 g, 41.77 mmol). After 1 h water (20 mL) was added cautiously. The solvent was removed *in vacuo* and the residue partitioned between ether (1.5 L) and water (250 mL). The organic phase was separated, washed with water (2 × 250 mL) and brine (3 × 50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Recrystallisation of the crude material from ethanol/water gave benzyl alcohol **3.70** (20.79 g, 68.84 mmol, 92 %) as a clear crystalline solid.

The spectroscopic and physical data attained compares well with literature values.[40]

MP	83-85 °C (aq. ethanol) [Lit. 80 °C (aq. ethanol)][40]
λ_{max}/nm (ε_{max}, CH_2Cl_2)	274 (8600), 231 (35900).
ν_{max}/cm^{-1} (solid)	3455 (w), 2971 (w), 2864 (w), 1619 (m), 1507 (s), 1439 (s), 1381 (s), 1266 (s), 1214 (s), 1126 (m), 1024 (s), 952 (m), 840 (m), 803 (s).
δ_H (400 MHz, $CDCl_3$)	7.26 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 7.24 (1H, dd, *J* 8.3, 2.0 Hz, Ar*H*), 7.10 (1H, d, *J* 2.0 Hz, Ar*H*), 6.99 (1H, d, *J* 8.3 Hz, Ar*H*), 6.91 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 5.68 (1H, s, ArC*H*), 4.59 (2H, d, *J* 5.3 Hz, ArCH_2), 4.08-4.02 (2H, m, OCH_2), 4.00-3.94 (2H, m, OCH_2), 3.82 (3H, s, OCH_3), 1.98 (1H, t, *J* 5.3 Hz, O*H*) ppm.
δ_C (100 MHz, $CDCl_3$)	157.4 (*C*), 152.3 (*C*), 145.0 (*C*), 135.3 (*C*), 131.0 (*C*), 128.7 (2 × *C*H), 123.3 (*C*H), 119.4 (*C*H), 117.4 (2 × *C*H), 112.7 (*C*H), 103.4 (*C*H), 65.3 (2 × CH_2), 65.0 (CH_2), 56.2 (CH_3) ppm.
LRMS (ES+)	325 ([M+Na]$^+$, 100 %) amu.

3-(4-Bromomethyl-phenoxy)-4-methoxy-benzaldehyde **3.72**



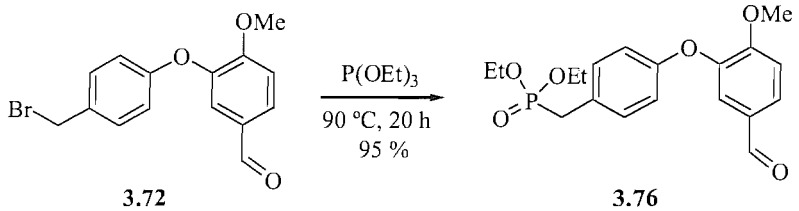
3.70
$C_{17}H_{18}O_5$
Mol. Wt.: 302

3.72
$C_{15}H_{13}BrO_3$
Mol. Wt.: 321

To a cooled (0 °C) solution of benzyl alcohol **3.70** (1.02 g, 3.38 mmol) and triphenylphosphine (1.36 g, 5.19 mmol) in dichloromethane (10 mL) was added carbon tetrabromide (1.73 g, 5.20 mmol) portionwise over 20 min. The reaction was allowed to warm to RT and after 30 min SiO_2 (2 g) was added and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/1-2/1) gave aldehyde **3.72** (947 mg, 2.95 mmol, 87 %) as a white solid.
The benzyl bromide was used crude in the literature procedure.[98]

MP	86-87 °C (ether/petroleum ether) [Lit. unreported][98]
λ_{max}/nm (ε_{max}, CH_2Cl_2)	269 (17300), 254 (17100).
ν_{max}/cm^{-1} (neat)	2841 (w), 1689 (s), 1599 (m), 1504 (s), 1433 (m), 1273 (s), 1222 (s), 1119 (s), 1019 (m), 815 (m), 750 (s).
δ_H (300 MHz, $CDCl_3$)	9.85 (1H, s, C*H*O), 7.71 (1H, dd, *J* 8.3, 2.0 Hz, Ar*H*), 7.51 (1H, d, *J* 2.0 Hz, Ar*H*), 7.36 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 7.13 (1H, d, *J* 8.3 Hz, Ar*H*), 6.92 (2H, d, *J* 8.8 Hz, 2 × Ar*H*), 4.51 (2H, s, ArCH_2Br), 3.94 (3H, s, OCH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	190.3 (*C*H), 157.4 (*C*), 156.7 (*C*), 145.7 (*C*), 132.8 (*C*), 130.8 (2 × *C*H), 130.5 (*C*), 128.6 (*C*H), 120.8 (*C*H), 117.9 (2 × *C*H), 112.4 (*C*H), 56.5 (*C*H$_3$), 33.4 (*C*H$_2$) ppm.
LRMS (EI)	241 ([M-Br]$^+$, 100 %), 207 (92 %) amu.

[4-(5-Formyl-2-methoxy-phenoxy)-benzyl]-phosphonic acid diethyl ester **3.76**



3.72
$C_{15}H_{13}BrO_3$
Mol. Wt.: 321

3.76
$C_{19}H_{23}O_6P$
Mol. Wt.: 378

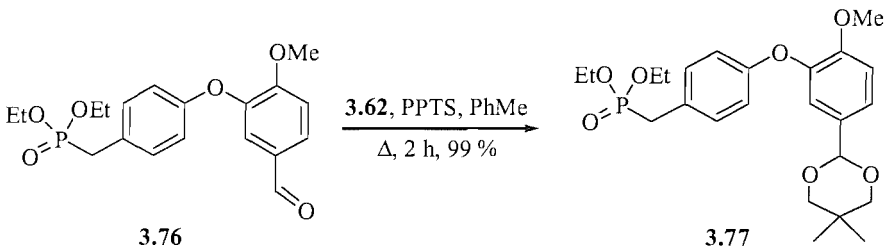
Following the procedure of Kodama *et al.*, benzyl bromide **3.72** (907 mg, 2.83 mmol) and triethyl phosphite (0.49 mL, 2.86 mmol) were heated to 90 °C for 20 h. [98] The reaction was directly purified by column chromatography (SiO_2, methanol/ether, 1-10%) to yield **3.76** (1.02 g, 2.70 mmol, 95 %) as a colourless oil.

The yield and spectroscopic data compares well with the literature.[98]

λ_{max}/nm (ε_{max}, CH_2Cl_2)	275 (13000), 231 (18600).
ν_{max}/cm^{-1} (neat)	2985 (w), 1690 (m), 1600 (w), 1580 (w), 1505 (s), 1433 (w), 1277 (s), 1217 (s), 1121 (w), 1024 (s), 963 (m), 907 (s), 753 (s), 729 (s).
δ_H (400 MHz, $CDCl_3$)	9.81 (1H, s, C*H*O), 7.67 (1H, dd, *J* 8.3, 2.0 Hz, Ar*H*), 7.44 (1H, d, *J* 2.0 Hz, Ar*H*), 7.26 (2H, dd, *J* 8.8, 2.7 Hz, 2 × Ar*H*), 7.10 (1H, d, *J* 8.3 Hz, Ar*H*), 6.92 (2H, d, *J* 8.6 Hz, 2 × Ar*H*), 4.10-3.99 (4H, m, 2 × POCH_2), 3.94 (3H, s, OCH_3), 3.16 (2H, d, *J* 21.3 Hz, CH_2), 1.26 (6H, t, *J* 7.0 Hz, 2 × CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	190.4 (*C*H), 156.4 (*C*), 156.0 (*C*), 146.5 (*C*), 131.4 (d, *J* 6.7 Hz, 2 × *C*H), 130.4 (*C*), 128.2 (*C*H), 126.9 (d, *J* 9.2

	Hz, *C*), 119.7 (*C*H), 118.4 (d, *J* 2.9 Hz, 2 × *C*H), 112.3 (*C*H), 62.3 (d, *J* 6.8 Hz, 2 × CH_2), 56.4 (CH_3), 33.2 (d, *J* 138.1 Hz, CH_2), 16.6 (d, *J* 5.8 Hz, 2 × CH_3) ppm.
LRMS (EI)	350 ($[M\text{-}CO]^+$, 7 %), 241 ($[M\text{-}PO(OEt)_2]^+$, 100 %) amu.

{4-[5-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2-methoxy-phenoxy]-benzyl}-phosphonic acid diethyl ester **3.77**



3.76
$C_{19}H_{23}O_6P$
Mol. Wt.: 378

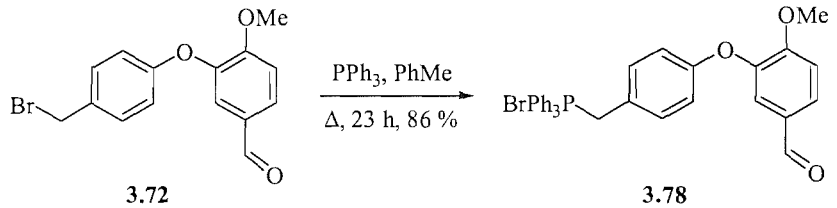
3.77
$C_{24}H_{33}O_7P$
Mol. Wt.: 464

To a solution of aldehyde **3.76** (1.00 g, 2.65 mmol) and neopentyl glycol **3.62** (833 mg, 8.00 mmol) in benzene (70 mL) was added pyridinium *p*-toluenesulfonate (87 mg, 0.35 mmol). The mixture was heated at reflux under a Dean-Stark apparatus for 2 h, cooled and partitioned between dichloromethane (100 mL) and sat. sodium bicarbonate (3 × 40 mL). The organic phase was separated and washed with brine (30 mL), dried ($MgSO_4$) and solvent removed *in vacuo*. Phosphate **3.77** (1.23 g, 2.64 mmol, 99 %) crystallised to a white solid on standing.

MP	118-120 °C (ethanol)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	275 (6000), 230 (27300).
ν_{max}/cm^{-1} (solid)	2984 (w), 2848 (w), 1610 (w), 1509 (m), 1427 (m), 1243 (s), 1174 (m), 1103 (m), 1021 (s), 972 (s), 783 (s).
δ_H (400 MHz, $CDCl_3$)	7.30 (1H, dd, *J* 8.3, 2.0 Hz, Ar*H*), 7.21 (2H, dd, *J* 8.5, 2.5 Hz, 2 × Ar*H*), 7.16 (1H, d, *J* 2.0 Hz, Ar*H*),

	6.99 (1H, d, *J* 8.3 Hz, Ar*H*),
	6.89 (2H, d, *J* 8.5 Hz, 2 × Ar*H*),
	5.30 (1H, s, ArC*H*),
	4.05-3.98 (4H, m, 2 × POCH_2),
	3.82 (3H, s, OCH_3),
	3.73 (2H, d, *J* 11.0 Hz, 2 × OC*H*H),
	3.60 (2H, d, *J* 11.0 Hz, 2 × OC*H*H),
	3.11 (2H, d, *J* 21.1 Hz, PCH_2),
	1.27-1.23 (6H, m, 2 × CH_2CH_3),
	1.25 (3H, s, CH_3),
	0.78 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	157.1 (*C*), 152.0 (*C*), 144.8 (*C*), 132.1 (*C*), 131.0 (d, *J* 6.8 Hz, 2 × *C*H), 125.6 (d, *J* 9.2 Hz, *C*), 122.9 (*C*H), 119.5 (*C*H), 117.4 (d, *J* 2.9 Hz, 2 × *C*H), 112.7 (*C*H), 101.3 (*C*H), 77.5 (2 × *C*H_2), 62.3 (d, *J* 6.8 Hz, 2 × *C*H_2), 56.3 (*C*H_3), 33.2 (d, *J* 138.1 Hz, *C*H_2), 30.3 (*C*), 23.2 (*C*H_3), 22.0 (*C*H_3), 16.5 (d, *J* 6.8 Hz, 2 × *C*H_3) ppm.
LRMS (ES+)	487 ($[M+Na]^+$, 100 %) amu.
CHN	Found C 61.85 %, H 7.05 %, P 6.30 %; $C_{24}H_{33}O_7P$ requires C 62.06 %, H 7.16 %, P 6.67 %.

[4-(5-Formyl-2-methoxy-phenoxy)-benzyl] triphenyl phosphonium bromide **3.78**



3.72
$C_{15}H_{13}BrO_3$
Mol. Wt.: 321

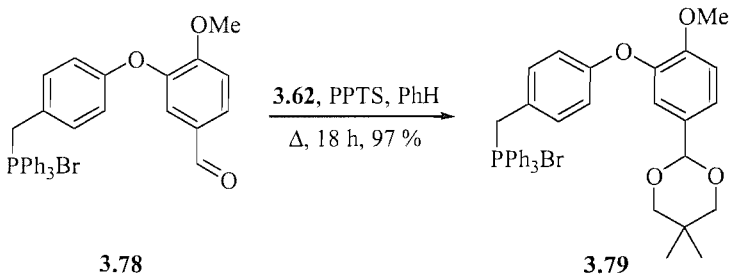
3.78
$C_{33}H_{28}BrO_3P$
Mol. Wt.: 583

A solution of benzyl bromide **3.72** (900 mg, 2.80 mmol) and triphenylphosphine (749 mg, 2.86 mmol) in toluene (40 mL) was heated at reflux for 23 h and then cooled to RT. The resulting white solid **3.78** (1.40 g, 2.40 mmol, 86 %) was collected by filtration.

MP	262-263 °C (toluene)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	270 (12600), 230 (29100).
ν_{max}/cm^{-1} (film)	2912 (w), 1686 (m), 1600 (m), 1580 (m), 1505 (s), 1437 (s), 1277 (s), 1227 (s), 1217 (s), 1112 (s), 1020 (m).
δ_H (300 MHz, $CDCl_3$)	9.79 (1H, s, C*H*O), 7.76-7.69 (9H, m, 9 × Ar*H*), 7.64-7.57 (7H, m, 7 × Ar*H*), 7.33 (1H, d, *J* 1.9 Hz, Ar*H*), 7.08 (2H, d, *J* 8.7 Hz, 2 × Ar*H*), 7.07 (1H, d, *J* 8.9 Hz, Ar*H*), 6.68 (2H, d, *J* 8.7 Hz, 2 × Ar*H*), 5.38 (2H, d, *J* 14.1 Hz, ArCH_2P), 3.87 (3H, s, OCH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	190.3 (*C*H), 157.2 (*C*), 157.1 (*C*), 156.4 (*C*), 145.8 (*C*), 135.1 (d, *J* 3.0 Hz, 3 × *C*H), 134.5 (d, *J* 9.4 Hz, 6 × *C*H), 133.1 (d, *J* 5.4 Hz, 2 × *C*H), 130.3 (d, *J* 12.3 Hz, 6 × *C*H), 129.1 (*C*H), 122.2 (d, *J* 3.9 Hz, *C*), 119.1 (*C*H), 118.3 (d, *J* 3.4 Hz, 2 × *C*H), 117.8 (d, *J* 82.5 Hz, 3 × *C*), 112.4

	(*C*H), 56.4 (*C*H$_3$), 30.2 (d, *J* 47.1 Hz, *C*H$_2$) ppm.
LRMS (ES+)	503 ([M-Br]$^+$, 100 %) amu.
CHN	Found C 67.94 %, H 4.77 %. $C_{33}H_{28}BrO_3P$ requires C 67.93 %, H 4.84 %.

{4-[5-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2-methoxy-phenoxy]-benzyl} triphenyl phosphonium bromide **3.79**



3.78
$C_{33}H_{28}BrO_3P$
Mol. Wt.: 583

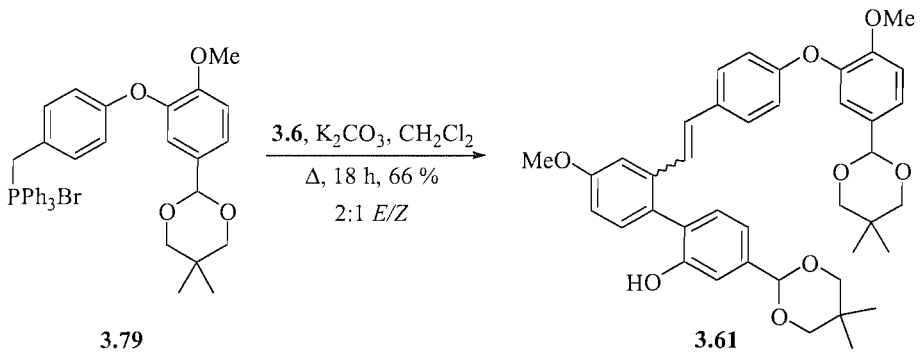
3.79
$C_{38}H_{38}BrO_4P$
Mol. Wt.: 670

To a suspension of benzaldehyde **3.78** (1.38 g, 2.37 mmol) in toluene (70 mL) was added neopentyl glycol (732 mg, 7.03 mmol) and pyridinium *p*-toluenesulfonate (97 mg, 0.39 mmol). The mixture was heated at reflux for 18 h under a Dean-Stark apparatus then cooled to RT and diluted with dichloromethane (150 mL). The organic phase was washed with sat. $NaHCO_3$ (4 × 10 mL) and brine (2 × 20 mL) and dried ($MgSO_4$). The solvent was removed in *vacuo* to yield **3.79** (1.54 g, 2.30 mmol, 97 %) as a viscous oil which crystallised on trituration with hot ethanol.

MP	160-162 °C (toluene/$CHCl_3$)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	276 (9700), 270 (9600), 230 (27100).
ν_{max}/cm^{-1} (solid)	2860 (w), 1610 (m), 1589 (m), 1506 (s), 1438 (s), 1274 (s), 1225 (s), 1097 (s), 1014 (m), 838 (m).
δ_H (400 MHz, $CDCl_3$)	7.74-7.67 (9H, m, 9 × Ar*H*),

	7.61-7.56 (6H, m, 6 × Ar*H*), 7.26 (1H, dd, *J* 8.3, 2.0 Hz, Ar*H*), 7.07 (1H, d, *J* 2.0 Hz, Ar*H*), 7.00-6.93 (3H, m, 3 × Ar*H*), 6.66 (2H, d, *J* 8.5 Hz, 2 × Ar*H*), 5.30 (2H, d, *J* 14.1 Hz, ArCH_2P), 5.29 (1H, s, ArC*H*), 3.77 (3H, s, OCH_3), 3.70 (2H, d, *J* 11.0 Hz, 2 × OC*H*H), 3.60 (2H, d, *J* 11.0 Hz, 2 × OC*H*H), 1.23 (3H, s, CH_3), 0.77 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	158.1 (*C*), 151.7 (*C*), 144.3 (*C*), 135.0 (d, *J* 3.4 Hz, 3 × *C*H), 134.5 (d, *J* 9.7 Hz, 6 × *C*H), 132.8 (d, *J* 5.9 Hz, 2 × *C*H), 132.1 (*C*), 130.3 (d, *J* 12.6 Hz, 6 × *C*H), 123.1 (*C*H), 120.9 (d, *J* 3.9 Hz, *C*), 119.1 (*C*H), 118.2 (d, *J* 88.0 Hz, 3 × *C*), 117.7 (d, *J* 3.4 Hz, 2 × *C*H), 112.6 (*C*H), 101.1 (*C*H), 77.7 (2 × CH_2), 56.2 (CH_3), 30.3 (d, *J* 46.9 Hz, CH_2), 30.3 (*C*), 23.2 (CH_3), 22.0 (CH_3) ppm.
LRMS (ES+)	589 (M^+, 100 %) amu.
CHN	Found C 68.31 %, H 5.79 %, P 4.80 %. $C_{38}H_{38}BrO_4P$ requires C 68.16 %, H 5.72 %, P 4.63 %.

4-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2'-(2-{4-[5-(5,5-dimethyl-[1,3]dioxan-2-yl)-2-methoxy-phenoxy]-phenyl}-vinyl)-4'-methoxy-biphenyl-2-ol **3.61**



3.79
$C_{38}H_{38}BrO_4P$
Mol. Wt.: 670

3.61
$C_{40}H_{44}O_8$
Mol. Wt.: 653

To a solution of lactol **3.6** (463 mg, 1.35 mmol) and phosphonium salt **3.79** (1.01 g, 1.51 mmol) in CH_2Cl_2 (80 mL) was added potassium carbonate (195 mg, 1.41 mmol) and 18-crown-6 (22 mg). The mixture was heated at reflux for 18 h then cooled to RT, filtered and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ethyl acetate/petroleum ether, 1/3-1/2) gave (*E*)-**3.61** (176 mg, 0.27 mmol, 18 %), followed by a mixture of (*E*)-**3.61** and (*Z*)-**3.61** (6:5 ratio, 475 mg, 0.73 mmol, 48 %) both as viscous oils.

Data given for (*E*)-**3.61**.

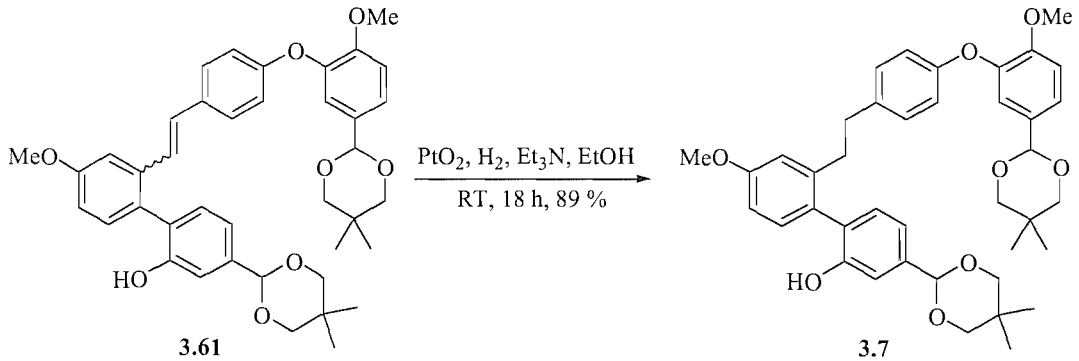
ν_{max}/cm^{-1} (film) 3405 (br. w), 2954 (w), 2946 (w), 1693 (w), 1601 (m), 1504 (m), 1467 (m), 1425 (m), 1392 (m), 1274 (s), 1216 (s), 1056 (m), 1098 (s), 1014 (s), 983 (m), 908 (m), 812 (m), 756 (s), 730 (s).

λ_{max}/nm (ε_{max}, CH_2Cl_2) 278 (22200), 229 (21300).

δ_H (400 MHz, $CDCl_3$) 7.44-7.35 (4H, m, 4 × Ar*H*),
7.30-7.21 (5H, m, 5 × Ar*H*),
7.16 (1H, d, *J* 16.1 Hz, C*H*),
7.11 (1H, d, *J* 8.5 Hz, Ar*H*),
7.02 (1H, dd, *J* 8.5, 2.5 Hz, Ar*H*),
6.96 (1H, d, *J* 8.5 Hz, Ar*H*),
6.92-6.85 (1H, m, Ar*H*)
6.91 (1H, obs. d, *J* 16.1 Hz, C*H*),

	5.53 (1H, s, ArC*H*), 5.42 (1H, s, ArC*H*), 5.06 (1H, s, ArO*H*), 4.01 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.90 (2H, d, *J* 11.0 Hz, 2 × OC*H*H), 3.84 (2H, d, *J* 11.0 Hz, 2 × OC*H*H), 3.79 (2H, d, *J* 11.0 Hz, 2 × OC*H*H), 3.71 (2H, d, *J* 11.0 Hz, 2 × OC*H*H), 1.44 (3H, s, CH_3), 1.36 (3H, s, CH_3), 0.93 (3H, s, CH_3), 0.89 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	160.1 (*C*), 158.1 (*C*), 153.3 (*C*), 152.1 (*C*), 144.5 (*C*), 139.9 (*C*), 138.1 (*C*), 132.5 (2 × *C*H), 132.1 (*C*), 131.6 (*C*), 131.5 (*C*H), 130.4 (*C*H), 128.2 (*C*H), 127.7 (*C*), 127.3 (*C*), 124.7 (*C*H), 123.0 (*C*H), 119.8 (*C*H), 118.4 (*C*H), 117.3 (2 × *C*H), 114.2 (*C*H), 113.7 (*C*H), 112.7 (*C*H), 110.5 (*C*H), 101.7 (*C*H), 101.3 (*C*H), 77.9 (2 × CH_2), 77.8 (2 × CH_2), 56.3 (CH_3), 55.6 (CH_3), 30.5 (*C*), 30.3 (*C*), 23.3 (CH_3), 23.2 (CH_3), 22.1 (CH_3), 22.0 (CH_3) ppm.
LRMS (ES+)	675 ($[M+Na]^+$, 100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 675.3076. $C_{40}H_{44}O_8Na$ requires 675.3081

4-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2'-(2-{4-[5-(5,5-dimethyl-[1,3]dioxan-2-yl)-2-methoxy-phenoxy]-phenyl}-ethyl)-4'-methoxy-biphenyl-2-ol **3.7**



3.61
$C_{40}H_{44}O_8$
Mol. Wt.: 653

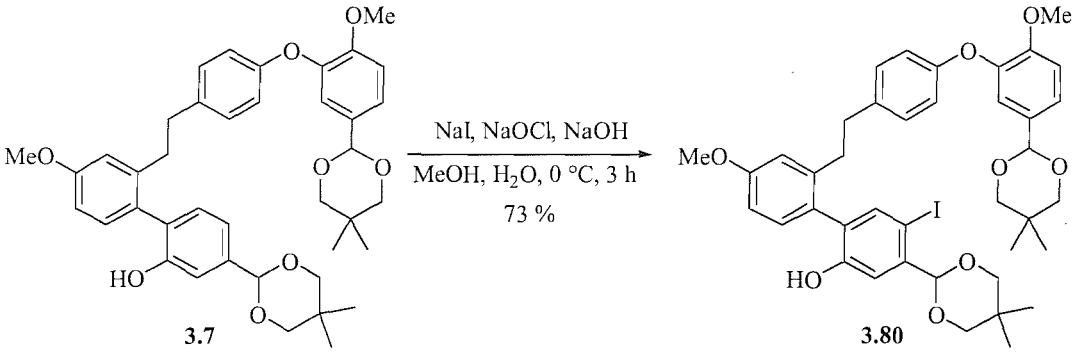
3.7
$C_{40}H_{46}O_8$
Mol. Wt.: 655

To a solution of alkene **3.61** (2:1 mixture of (*E*)- and (*Z*)- isomers, 190 mg, 0.29 mmol) in ethanol (40 mL) was added platinum oxide (23 mg, 0.10 mmol) and triethylamine (0.6 mL, 4.30 mmol). The mixture was stirred vigorously under an atmosphere of hydrogen at RT for 18 h, then filtered through Celite and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 2/1) gave **3.7** (169 mg, 0.26 mmol, 89 %) as a colourless oil.

λ_{max}/nm (ε_{max}, CH_2Cl_2)	277 (8600), 230 (20600).
ν_{max}/cm^{-1} (film)	3403 (br. w), 2955 (w), 2846 (w), 1607 (w), 1505 (m), 1393 (w), 1273 (m), 1229 (m), 1100 (s), 1016 (m), 983 (m), 905 (s).
δ_H (400 MHz, $CDCl_3$)	7.29 (1H, dd, *J* 8.5, 2.2 Hz, Ar*H*), 7.16 (1H, app. s, Ar*H*), 7.13-7.05 (4H, m, **4** × Ar*H*), 6.99 (1H, d, *J* 8.5 Hz, Ar*H*), 6.86-6.82 (4H, m, **4** × Ar*H*), 6.78 (2H, d, *J* 8.5 Hz, 2 × Ar*H*) 5.41 (1H, s, ArC*H*), 5.30 (1H, s, ArC*H*), 4.81 (1H, s, ArO*H*),

	3.83 (3H, s, OCH_3),
	3.82 (3H, s, OCH_3),
	3.80 (2H, d, J 10.8 Hz, 2 × OCHH),
	3.73 (2H, d, J 11.0 Hz, 2 × OCHH),
	3.68 (2H, d, J 11.0 Hz, 2 × OCHH),
	3.60 (2H, d, J 10.8 Hz, 2 × OCHH),
	2.69 (4H, br. s, 2 × CH_2),
	1.32 (3H, s, CH_3),
	1.26 (3H, s, CH_3),
	0.83 (3H, s, CH_3),
	0.78 (3H, s, CH_3) ppm.
δ_C (100 MHz, $CDCl_3$)	159.9 (*C*), 156.2 (*C*), 153.1 (*C*), 152.0 (*C*), 145.2 (*C*), 142.8 (*C*), 139.9 (*C*), 135.5 (*C*), 132.0 (*C*H), 132.0 (*C*), 131.0 (*C*H), 129.6 (2 × *C*H), 127.9 (*C*), 127.6 (*C*), 122.5 (*C*H), 119.4 (*C*H), 118.3 (*C*H), 117.2 (2 × *C*H), 115.6 (*C*H), 113.3 (*C*H), 112.7 (*C*H), 112.4 (*C*H), 101.6 (*C*H), 101.4 (*C*H), 77.9 (2 × *C*H_2), 77.8 (2 × *C*H_2), 56.3 (*C*H_3), 55.5 (*C*H_3), 36.5 (*C*H_2), 35.6 (*C*H_2), 30.4 (*C*), 30.3 (*C*), 23.3 (*C*H_3), 23.2 (*C*H_3), 22.1 (*C*H_3), 22.0 (*C*H_3) ppm.
LRMS (ES+)	677 ($[M+Na]^+$, 32 %), 142 (100 %) amu
HRMS (ES+)	Found $[M+Na]^+$: 677.3099. $C_{40}H_{46}O_8Na$ requires 677.3085.

4-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2'-(2-{4-[5-(5,5-dimethyl-[1,3]dioxan-2-yl)-2-methoxy-phenoxy]-phenyl}-ethyl)-5-iodo-4'-methoxy-biphenyl-2-ol **3.80**



3.7
$C_{40}H_{46}O_8$
Mol. Wt.: 655

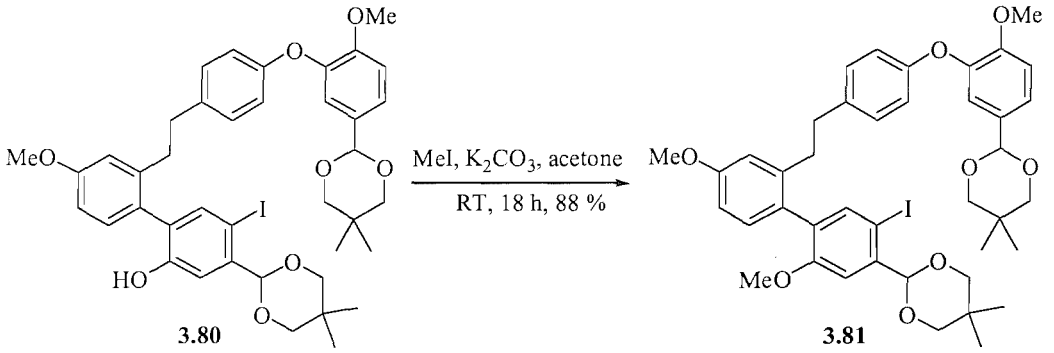
3.80
$C_{40}H_{45}IO_8$
Mol. Wt.: 781

To a solution of **3.7** (98 mg, 0.15 mmol) in methanol (5 mL), was added sodium iodide (24.5 mg, 0.16 mmol) and NaOH (7.3 mg, 0.18 mmol). Aq. NaOCl (650 mM, 0.24 mL, 0.16 mmol) was added dropwise over 1 h at 0 °C, and the reaction mixture stirred for a further 2 h at 0 °C, followed by treatment with aq. sodium thiosulfate (10 % w/v, 20 mL). The mixture was adjusted to pH 7 using 2M aq. HCl, and extracted with ether (3 × 30 mL). The organic fractions were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/1) gave **3.80** (85 mg, 0.11 mmol, 73 %) as an oil.

λ_{max}/nm (ε_{max}, CH_2Cl_2)	277 (7900), 231 (40700).
ν_{max}/cm^{-1} (film)	3405 (br. w), 2954 (w), 2847 (w), 1606 (w), 1505 (s), 1466 (m), 1393 (s), 1272 (s), 1225 (s), 1166 (m), 1127 (m), 1099 (s), 1014 (m), 985 (m), 904 (s).
δ_H (300 MHz, $CDCl_3$)	7.47 (1H, s, Ar*H*), 7.35 (1H, s, Ar*H*), 7.29 (1H, dd, *J* 8.5, 2.2 Hz, Ar*H*), 7.12 (1H, d, *J* 2.1 Hz, Ar*H*), 7.06 (1H, dd, *J* 8.8, 2.1 Hz, Ar*H*), 6.98 (1H, d, *J* 8.5 Hz, Ar*H*), 6.87 (1H, d, *J* 8.8 Hz, Ar*H*),

	6.84-6.78 (5H, m, 5 × Ar*H*)
	5.46 (1H, s, ArC*H*),
	5.29 (1H, s, ArC*H*),
	4.83 (1H, s, ArO*H*),
	3.82 (3H, s, OCH_3),
	3.81 (3H, s, OCH_3),
	3.79-3.70 (6H, m, 6 × OC*H*H),
	3.60 (2H, d, *J* 10.5 Hz, 2 × OC*H*H),
	2.71 (4H, br. s, 2 × CH_2),
	1.32 (3H, s, CH_3),
	1.26 (3H, s, CH_3),
	0.83 (3H, s, CH_3),
	0.78 (3H, s, CH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	160.1 (*C*), 156.2 (*C*), 153.8 (*C*), 152.0 (*C*), 145.1 (*C*), 142.5 (*C*), 140.9 (*C*), 140.7 (*C*H), 135.2 (*C*), 132.0 (*C*), 131.8 (*C*H), 130.5 (*C*), 129.7 (2 × *C*H), 126.2 (*C*), 122.5 (*C*H), 119.5 (*C*H), 117.2 (2 × *C*H), 115.6 (*C*H), 115.3 (*C*H), 112.7 (*C*H), 112.5 (*C*H), 104.6 (*C*H), 101.4 (*C*H), 85.1 (*C*), 77.0 (2 × CH_2), 77.8 (2 × CH_2), 56.3 (CH_3), 55.5 (CH_3), 36.5 (CH_2), 35.3 (CH_2), 30.4 (*C*), 30.3 (*C*), 23.3 (CH_3), 23.2 (CH_3), 22.0 (CH_3), 22.0 (CH_3) ppm.
LRMS (ES+)	803 ($[M+Na]^+$, 20 %), 393 (6 %), 249 (100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 803.2075. $C_{40}H_{45}IO_8Na$ requires 803.2051.

4-(5,5-Dimethyl-[1,3]dioxan-2-yl)-2'-(2-{4-[5-(5,5-dimethyl-[1,3]dioxan-2-yl)-2-methoxy-phenoxy]-phenyl}-ethyl)-5-iodo-2,4'-dimethoxybiphenyl **3.81**



3.80

$C_{40}H_{45}IO_8$
Mol. Wt.: 781

3.81

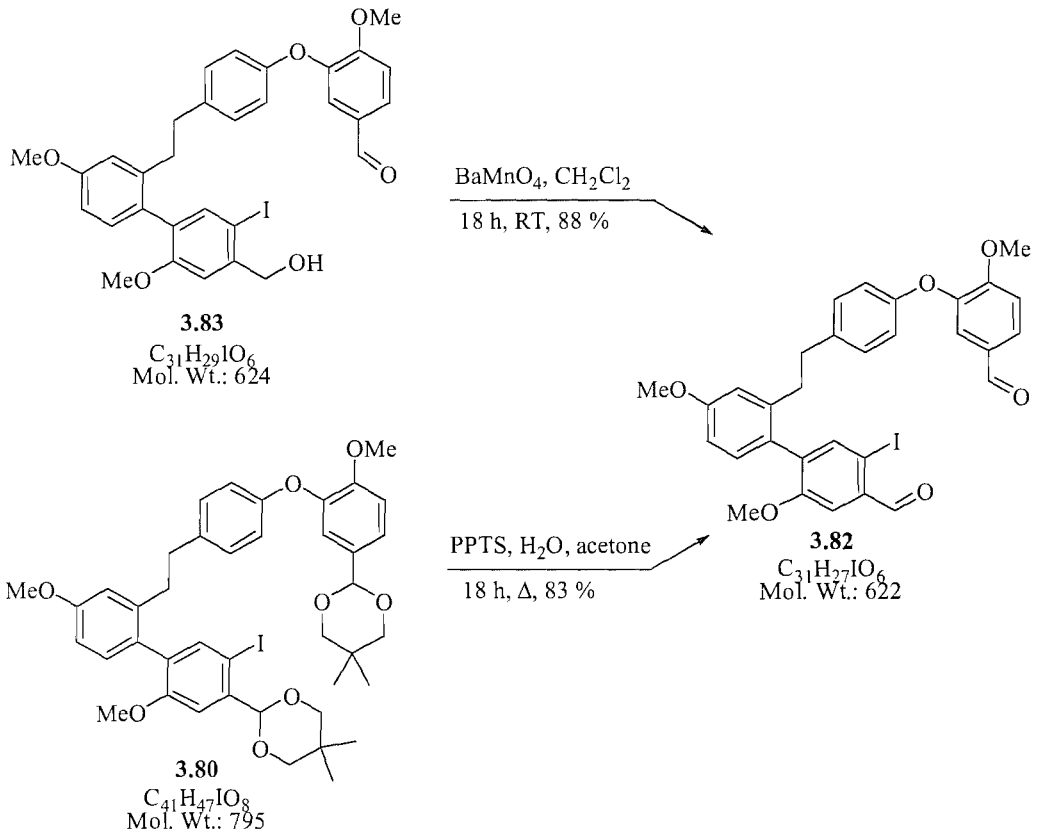
$C_{41}H_{47}IO_8$
Mol. Wt.: 795

Iodomethane (10 μL, 0.16 mmol) was added to a mixture of potassium carbonate (15 mg, 0.11 mmol) and **3.80** (30 mg, 0.04 mmol) in acetone (4 mL). The reaction mixture was stirred for 18 h at RT, filtered, and solvent removed *in vacuo* to yield **3.81** (27 mg, 0.03 mmol, 88 %) as an oil.

λ_{max}/nm (ε_{max}, CH_2Cl_2)	276 (2700), 230 (12900).
ν_{max}/cm^{-1} (film)	2954 (m), 2847 (w), 1607 (w), 1506 (s), 1464 (m), 1391 (s), 1265 (s), 1222 (s), 1102 (s), 1020 (m), 893 (w).
δ_H (300 MHz, $CDCl_3$)	7.54 (1H, s, Ar*H*), 7.32 (1H, s, Ar*H*), 7.29 (1H, dd, *J* 8.8, 2.0 Hz, Ar*H*), 7.12 (1H, d, *J* 2.1 Hz, Ar*H*), 7.04-6.97 (2H, m, 2 × Ar*H*), 6.91 (2H, d, *J* 8.9 Hz, 2 × Ar*H*), 6.81 (2H, d, *J* 8.9 Hz, 2 × Ar*H*), 6.78-6.76 (2H, m, 2 × Ar*H*), 5.50 (1H, s, ArC*H*), 5.30 (1H, s, ArC*H*), 3.83 (3H, s, OCH_3), 3.80 (3H, s, OCH_3),

	3.79 (3H, s, OCH_3),
	3.78-3.70 (6H, m, 6 × OC*H*H),
	3.60 (2H, d, *J* 10.6 Hz, 2 × OC*H*H),
	2.72 (4H, br. s, 2 × CH_2)
	1.35 (3H, s, CH_3),
	1.27 (3H, s, CH_3),
	0.85 (3H, s, CH_3),
	0.78 (3H, s, CH_3) ppm.
δ_C (75 MHz, $CDCl_3$)	159.3 (*C*), 157.6 (*C*), 156.1 (*C*), 152.0 (*C*), 145.1 (*C*), 141.8 (*C*), 141.5 (*C*H), 140.2 (*C*), 135.9 (*C*), 133.4 (*C*), 132.0 (*C*), 131.4 (*C*H), 129.6 (2 × *C*H), 129.2 (*C*), 122.5 (*C*H), 119.5 (*C*H), 117.2 (2 × *C*H), 114.6 (*C*H), 112.7 (*C*H), 111.4 (*C*H), 110.3 (*C*H), 105.0 (*C*H), 101.4 (*C*H), 85.8 (*C*), 77.8 (4 × CH_2), 56.3 (CH_3), 55.8 (CH_3), 55.4 (CH_3), 36.3 (CH_2), 35.6 (CH_2), 30.4 (*C*), 30.3 (*C*), 23.5 (CH_3), 23.2 (CH_3), 22.0 (CH_3), 22.0 (CH_3) ppm.
LRMS (ES+)	817 ($[M+Na]^+$, 100 %), 795 (MH^+, 14 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 817.2224. $C_{41}H_{47}IO_8Na$ requires 817.2208.

3-{4-[2-(4'-formyl-5'-iodo-4,2'-dimethoxy-biphenyl-2-yl)-ethyl]-phenoxy}-4-methoxy-benzaldehyde **3.82**



Oxidation:

To a solution of benzyl alcohol **3.83** (479 mg, 0.77 mmol) in dichloromethane (40 mL) was added barium manganate (531 mg, 2.07 mmol). The mixture was stirred at RT for 18 h then filtered through Celite and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 2/1) gave **3.82** (420 mg, 0.68 mmol, 88 %) as an unstable oil.

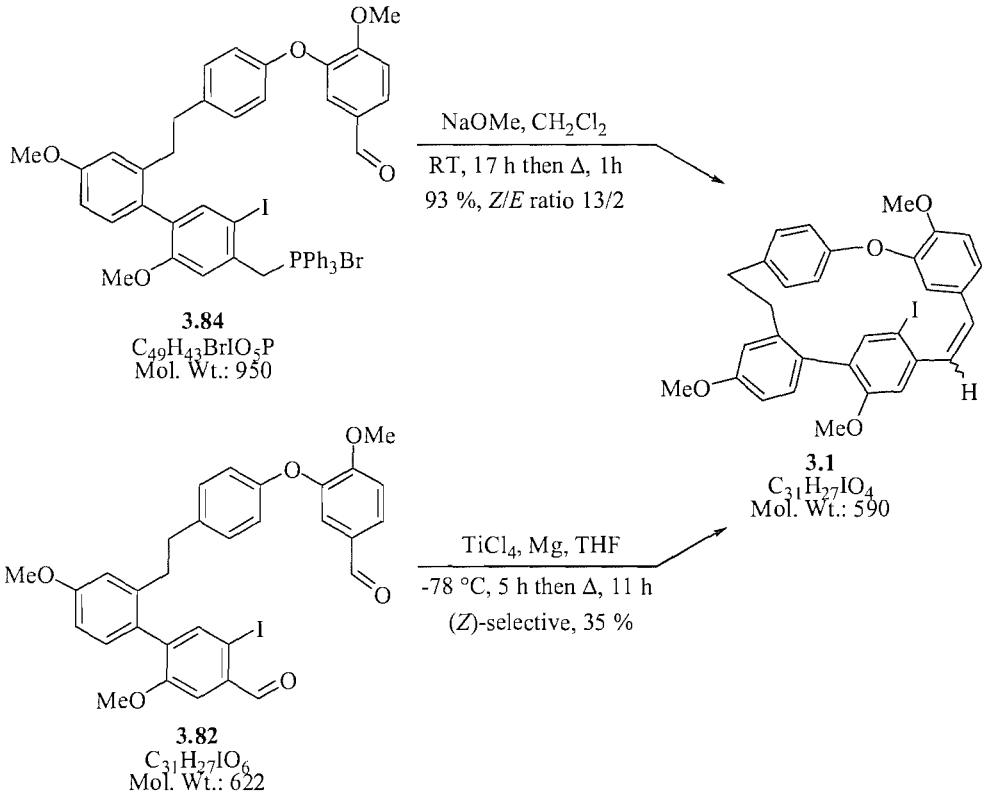
Deprotection:

Pyridinium *p*-toluenesulfonate (1 mg, 4.0 μmol) was added to **3.81** (20 mg, 25.2 μmol) in a mixture of acetone/water (4:1, 10 mL). The reaction mixture was refluxed for 18 h then cooled to RT and the solvent removed *in vacuo*. The resulting oil was partitioned between sat. sodium bicarbonate solution (30 mL) and dichloromethane (10 mL), and the aqueous phase was extracted with further dichloromethane (4 × 10 mL). The organic fractions were combined, dried ($MgSO_4$) and solvent removed *in vacuo*. Purification by column

chromatography (SiO_2, ether/petroleum ether, 2/1) gave **3.82** (13 mg, 20.9 μmol, 83 %) as a colourless oil.

λ_{max}/nm (ε_{max}, CH_2Cl_2)	340 sh (560), 298 sh (1000), 271 (1900), 235 (6000).
ν_{max}/cm^{-1} (film)	2935 (w), 2843 (w), 1685 (s), 1600 (m), 1583 (m), 1504 (s), 1463 (m), 1365 (m), 1273 (s), 1219 (s), 1120 (m), 1041 (m), 1020 (w), 812 (m).
δ_H (400 MHz, $CDCl_3$)	10.04 (1H, s, C*H*O), 9.80 (1H, s, C*H*O), 7.65 (1H, s, Ar*H*), 7.64 (1H, dd, *J* 8.4, 2.0 Hz, Ar*H*), 7.50 (1H, s, Ar*H*), 7.39 (1H, d, *J* 2.0 Hz, Ar*H*), 7.12-7.05 (2H, m, 2 × Ar*H*), 6.94-6.81 (6H, m, 6 × Ar*H*), 3.95 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 2.75 (4H, br. s, 2 × CH_2) ppm.
δ_C (100 MHz, $CDCl_3$)	195.8 (*C*HO), 190.5 (*C*HO), 159.7 (*C*), 157.9 (*C*), 156.3 (*C*), 154.9 (*C*), 146.9 (*C*), 142.7 (*C*H), 141.4 (*C*), 139.1 (*C*), 136.9 (*C*), 134.9 (*C*), 131.0 (*C*H), 130.3 (*C*), 129.8 (2 × *C*H), 128.2 (*C*), 128.0 (*C*H), 119.0 (*C*H), 118.4 (2 × *C*H), 114.8 (*C*H), 112.1 (*C*H), 111.5 (*C*H), 111.4 (*C*H), 90.6 (*C*), 56.4 (*C*H_3), 56.0 (*C*H_3), 55.4 (*C*H_3), 36.5 (*C*H_2), 35.8 (*C*H_2) ppm.
LRMS (ES+)	645 ($[M+Na]^+$, 100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 645.0903. $C_{31}H_{27}IO_6Na$ requires 645.0897.

1,2-dihydro-9,17,22-trimethoxy-3,6-etheno-15,18-(1-iodoetheno)-8,12-metheno-12*H*-7-benzoxacycloeicosine **3.1**



3.84
$C_{49}H_{43}BrIO_5P$
Mol. Wt.: 950

3.1
$C_{31}H_{27}IO_4$
Mol. Wt.: 590

3.82
$C_{31}H_{27}IO_6$
Mol. Wt.: 622

Wittig Protocol:

A solution of Wittig salt **3.84** (800 mg, 0.843 mmol) in dichloromethane (120 mL) was added over 7.5 h to NaOMe (39 mg Na, 1.70 mmol) in dichloromethane (42 mL). The mixture was stirred at RT for a further 17h then heated to reflux for 1 h, cooled to RT, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/3) gave (*Z*)-**3.1** as a white solid (214 mg, 0.36 mmol, 43 %) and then a mixture of (*E*)-**3.1** and (*Z*)-**3.1** (1:3 ratio, 246 mg, 0.42 mmol, 49 %) as a white solid.

McMurry Protocol:

To a solution of magnesium (187 mg, 7.69 mmol) in THF (20 mL) at -78 °C was added titanium tetrachloride (0.80 mL, 7.30 mmol). The mixture was warmed to RT, stirred for 1

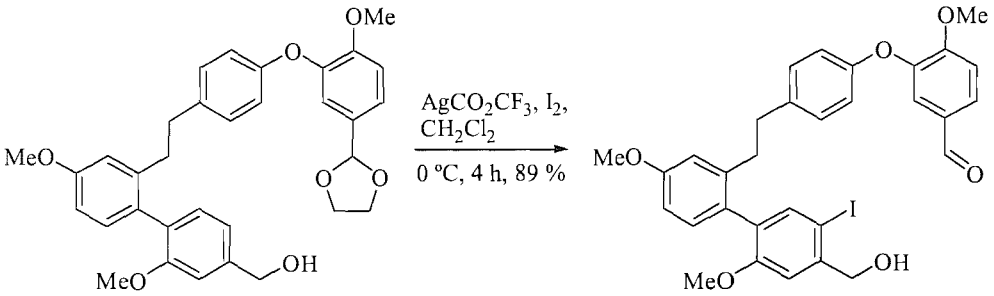
h then cooled to -45 °C. To the resulting black soltuion was added bisaldehyde **3.82** (400 mg, 0.64 mmol) in THF (40 mL). The reaction was allowed to warm to RT, stirred for 11 h at RT then heated at reflux for 48 h. The solvent was removed under reduced pressure and the residue partitioned between water (100 mL) and chloroform (50 mL). The aqueous phase was extracted with chloroform (4 × 30 mL) and the organic phases were combined, washed with water (50 mL) and brine (3 × 20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/2-1/1) gave *Z*-**3.1** (132 mg, 0.22 mmol, 35 %) as a white solid which was recrystallised from ethanol.

Data for (*Z*)-**3.1**.

MP	236-237 °C (ethanol)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	329 (4450), 296 (4400), 230 (12000).
ν_{max}/cm^{-1} (neat)	2931 (w), 2836 (w), 1606 (m), 1505 (s), 1462 (m), 1367 (m), 1264 (m), 1227 (s), 1165 (w), 1123 (m), 1042 (m), 908 (m), 814 (w), 730 (s).
δ_H (400 MHz, $CDCl_3$)	7.46 (1H, s, Ar*H*), 7.13 (1H, d, *J* 8.5 Hz, Ar*H*), 6.97-6.73 (10H, m, 10 × Ar*H*), 6.40 (1H, d, *J* 12.4 Hz, ArC*H*=), 6.25 (1H, d, *J* 12.4 Hz, ArC*H*=), 3.97 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.53 (3H, s, OCH_3), 3.13-2.70 (4H, s, 2 × CH_2) ppm.
δ_C (100 MHz, $CDCl_3$)	159.5 (*C*), 156.3 (*C*), 152.5 (*C*), 149.1 (*C*), 148.8 (*C*), 142.3 (*C*), 141.8 (*C*H), 140.0 (*C*), 139.4 (*C*), 133.0 (*C*H), 130.9 (*C*H), 130.9 (*C*), 130.1 (*C*H), 130.0 (*C*H), 129.7 (*C*H), 128.7 (*C*), 128.3 (*C*), 124.8 (*C*H), 122.9 (*C*H), 121.1 (*C*H), 116.0 (*C*H), 113.4 (*C*H), 112.5 (*C*H), 111.6 (*C*H), 111.5 (*C*H), 87.2 (*C*), 56.1 (*C*H_3), 55.4 (*C*H_3), 55.3 (*C*H_3), 38.5 (*C*H_2), 35.5 (*C*H_2) ppm.

LRMS (ES+)	613 ($[M+Na]^+$, 95 %), 236 (100 %) amu.
CHN	Found C 62.84 %, H 4.49 %. $C_{31}H_{27}IO_4$ requires C 63.06 %, H 4.51 %.

3-{4-[2-(4'-Hydroxymethyl-5'-iodo-4,2'-dimethoxy-biphenyl-2-yl)-ethyl]-phenoxy}-4-methoxy-benzaldehyde **3.83**



1.74
$C_{33}H_{34}O_7$
Mol. Wt.: 543

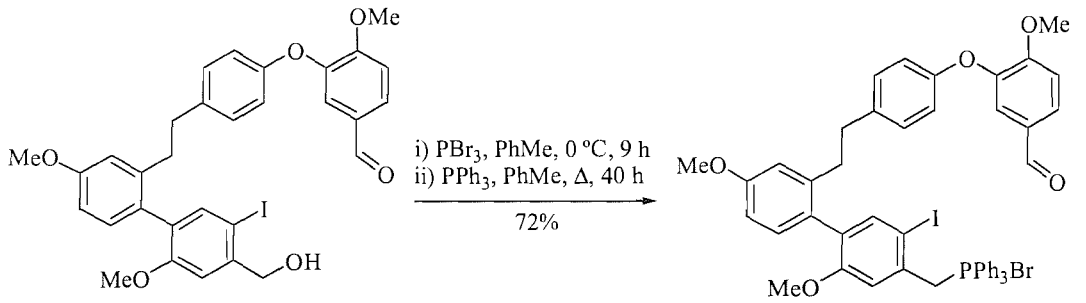
3.83
$C_{31}H_{29}IO_6$
Mol. Wt.: 624

To a cooled (0 °C) solution of benzyl alcohol **1.74** (4.33 g, 7.98 mmol) in dichloromethane (100 mL) was added silver(I) trifluoroacetate (1.85 g, 8.38 mmol).[40] A solution of iodine (2.21 g, 8.70 mmol) in dichloromethane (300 mL) was added dropwise over 2 h. The mixture was stirred for a further 2 h then warmed to RT, filtered through Celite, washed with sat. sodium thiosulphate (2 × 50 mL) and brine (3 × 30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 9/1) gave **3.83** (4.43 g, 7.09 mmol, 89 %) as a viscous oil that solidified to a foam on standing.

λ_{max}/nm (ε_{max}, CH_2Cl_2)	275 (15600), 232 (36600).
ν_{max}/cm^{-1} (neat)	3430 (br. w), 2934 (w), 2841 (w), 1688 (m), 1599 (m), 1505 (s), 1462 (m), 1372 (m), 1273 (s), 1223 (s), 1160 (m), 1121 (m), 1047 (m), 1019 (m), 905 (s), 811 (m).
δ_H (400 MHz, $CDCl_3$)	9.80 (1H, s, C*H*O), 7.63 (1H, dd, *J* 8.3, 2.0 Hz, Ar*H*),

	7.53 (1H, s, Ar*H*), 7.38 (1H, d, *J* 2.0 Hz, Ar*H*), 7.15 (1H, s, Ar*H*), 7.09 (1H, d, *J* 8.5 Hz, Ar*H*), 7.07 (1H, d, *J* 8.3 Hz, Ar*H*), 6.97-6.94 (2H, m, 2 × Ar*H*), 6.87-6.79 (3H, m, 3 × Ar*H*), 6.67 (1H, d, *J* 8.5 Hz, Ar*H*), 4.71 (2H, s, ArCH_2OH), 3.95 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 2.74 (4H, br. s, 2 × ArCH_2), 2.37 (1H, br. s, O*H*) ppm.
δ_C (100 MHz, $CDCl_3$)	190.6 (*C*H), 159.3 (*C*), 157.7 (*C*), 156.3 (*C*), 154.8 (*C*), 147.1 (*C*), 143.0 (*C*), 141.7 (*C*), 141.3 (*C*H), 137.4 (*C*), 131.9 (*C*), 131.4 (*C*H), 130.3 (*C*), 129.8 (2 × *C*H), 129.2 (*C*), 127.9 (*C*H), 119.0 (*C*H), 118.4 (2 × *C*H), 114.7 (*C*H), 112.1 (*C*H), 111.4 (*C*H), 111.2 (*C*H), 85.3 (*C*), 69.4 (CH_2), 56.4 (CH_3), 55.8 (CH_3), 55.4 (CH_3), 36.4 (CH_2), 35.7 (CH_2) ppm.
LRMS (ES+)	647 ($[M+Na]^+$, 100 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 647.0915. $C_{31}H_{29}IO_6Na$ requires 647.0901.

{2'-(2-[4-(5-formyl-2-methoxy-phenoxy)-phenyl]-ethyl)-5-iodo-2,4'-dimethoxy-biphenyl-4-benzyl} triphenyl phosphonium bromide **3.84**



3.83
$C_{31}H_{29}IO_6$
Mol. Wt.: 624

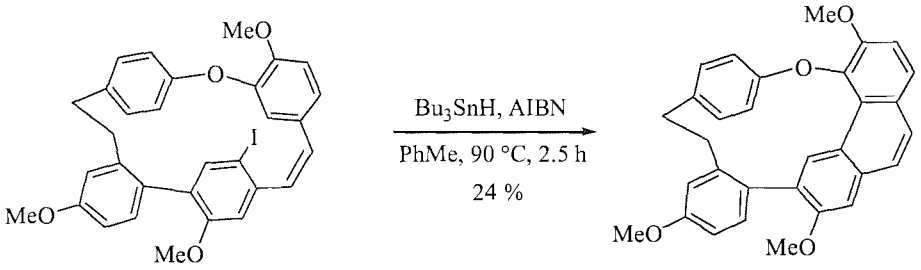
3.84
$C_{49}H_{43}BrIO_5P$
Mol. Wt.: 950

To a cooled (0 °C) solution of benzyl alcohol **3.83** (1.40 g, 2.24 mmol) in toluene (125 mL) was added phosphorous tribromide (80 μL, 0.84 mmol). The mixture was warmed to RT and stirred for 9 h. The solvent was removed *in vacuo*, and the crude product dissolved in dichloromethane (100 mL). The organic phase was washed with sat. sodium bicarbonate solution (3 × 20 mL) and brine (3 × 20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude benzyl bromide was then dissolved in toluene (150 mL) and triphenylphosphine (590 mg, 2.25 mmol) added. The solution was heated to reflux for 40 h then cooled to RT and filtered to yield phosphonium salt **3.84** (1.54 g, 1.62 mmol, 72 %) as a white foam.

λ_{max}/nm (ε_{max}, CH_2Cl_2)	276 (2300), 271 (2300), 231 (62000).
ν_{max}/cm^{-1} (film)	2934 (w), 2842 (w), 1687 (m), 1599 (m), 1505 (s), 1479 (m), 1463 (m), 1438 (m), 1367 (w), 1275 (s), 1219 (s), 1168 (m), 1111 (m), 1014 (w), 908 (s), 829 (m).
δ_H (400 MHz, $CDCl_3$)	9.76 (1H, s, C*H*O), 7.75-7.65 (10H, m, 10 × Ar*H*), 7.64-7.50 (7H, m, 7 × Ar*H*), 7.23 (1H, s, Ar*H*), 7.21 (1H, d, *J* 2.5 Hz, Ar*H*), 7.05 (1H, d, *J* 8.3 Hz, Ar*H*), 6.94 (1H, d, *J* 8.0 Hz, Ar*H*), 6.90 (2H, d, *J* 8.5 Hz, 2 × Ar*H*),

	6.79 (2H, d, *J* 8.5 Hz, 2 × Ar*H*),
	6.74 (1H, d, *J* 2.3 Hz, Ar*H*),
	6.73 (1H, dd, *J* 8.3, 2.5 Hz, Ar*H*),
	5.91 (1H, br. s, ArC*H*H),
	5.32 (1H, br. s, ArC*H*H),
	3.88 (3H, s, OCH_3),
	3.76 (3H, s, OCH_3),
	3.41 (3H, s, OCH_3),
	2.70-2.65 (4H, m, 2 × CH_2) ppm.
δ_C (100 MHz, $CDCl_3$)	190.4 (*C*H), 159.5 (*C*), 157.7 (d, *J* 3.9 Hz, *C*), 156.4 (*C*), 155.0 (*C*), 146.9 (*C*), 141.4 (*C*H), 141.2 (*C*), 137.0 (*C*), 135.4 (d, *J* 2.9 Hz, 3 × *C*H), 134.8 (d, *J* 9.7 Hz, 6 × *C*H), 133.2 (*C*), 131.4 (*C*H), 130.7 (*C*), 130.4 (d, *J* 8.7 Hz, 6 × *C*H), 129.7 (2 × *C*H), 128.4 (*C*), 128.3 (*C*H), 118.8 (*C*H), 118.4 (2 × *C*H), 118.1 (*C*), 117.6 (d, *J* 85.4 Hz, 3 × *C*), 115.5 (C*H*), 114.6 (*C*H), 112.2 (*C*H), 111.4 (*C*H), 92.6 (*C*), 56.5 (*C*H_3), 56.2 (*C*H_3), 55.4 (*C*H_3), 36.2 (*C*H_2), 35.5 (d, *J* 47.5 Hz, *C*H_2), 35.4 (*C*H_2) ppm.
LRMS (ES+)	870 ([MH-Br]$^+$, 50 %), 869 ([M-Br]$^+$, 100 %) amu.
CHN	Found C 61.75 %, H 4.40 %. $C_{49}H_{43}BrIO_5P$ requires C 61.97 %, H 4.56 %.

Dihydrocavicularin methylether **3.2**



3.1
$C_{31}H_{27}IO_4$
Mol. Wt.: 590

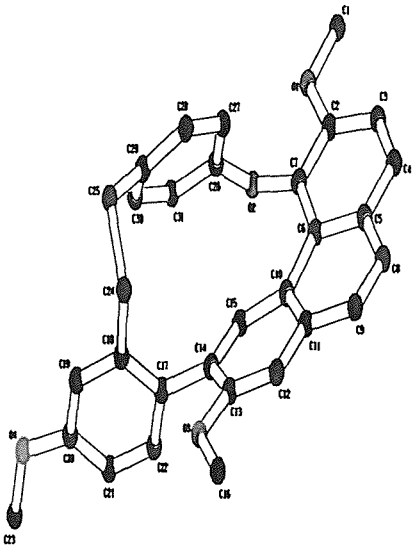
3.2
$C_{31}H_{26}O_4$
Mol. Wt.: 463

A solution of iodide **3.1** (65 mg, 0.11 mmol) and tri-*n*-butyltin hydride (36 μL, 0.13 mmol) in toluene (30 mL) was heated to 90 °C, then AIBN (32 mg, 0.20 mmol) was added. After 2.5 h the mixture was cooled and stirred vigorously with aq. KF (10 % solution, 20 mL) for 0.5 h then extracted with ether (3 × 30 mL). The combined organic fractions were washed with water (20 mL) and brine (3 × 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (firstly SiO_2, ether/petroleum ether, 1/9, then SiO_2, CH_2Cl_2), followed by HPLC (ethyl acetate/hexane, 1/4) and recrystallisation from ethanol gave phenanthrene **3.2** (12 mg, 26 μmol, 24 %) as a white solid.

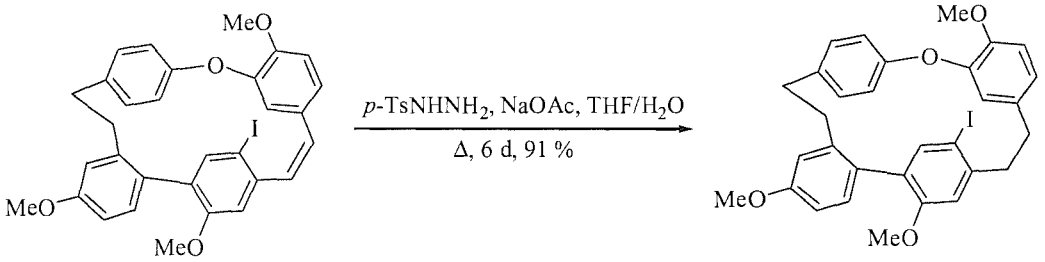
MP	218-220 °C (ethanol)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	320 (15000), 274 (50700), 230 (42600).
ν_{max}/cm^{-1} (solid)	2920 (w), 1600 (m), 1498 (m), 1462 (m), 1419 (m), 1373 (w), 1275 (s), 1228 (s), 1162 (m), 1104 (s), 1040 (m), 930 (m), 845 (s), 818 (s).
δ_H (400 MHz, $CDCl_3$)	7.72 (1H, d, *J* 8.8 Hz, Ar*H*), 7.66 (1H, d, *J* 8.8 Hz, Ar*H*), 7.49 (1H, d, *J* 8.5 Hz, Ar*H*), 7.42 (1H, d, *J* 8.5 Hz, Ar*H*), 7.41 (1H, s, Ar*H*), 7.03 (1H, s, Ar*H*),

	6.93 (1H, d, *J* 2.0 Hz, Ar*H*), 6.89 (1H, dd, *J* 8.3, 2.5 Hz, Ar*H*), 6.79-6.76 (2H, m, 2 × Ar*H*), 6.32 (1H, dd, *J* 8.5, 2.3 Hz, Ar*H*), 6.21 (1H, dd, *J* 8.3, 2.0 Hz, Ar*H*), 5.73 (1H, dd, *J* 8.3, 2.5 Hz, Ar*H*), 4.07 (3H, s, OC*H*$_3$), 3.92 (3H, s, OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 2.99 (1H, dt, *J* 12.8, 3.7 Hz, C*H*H), 2.85 (1H, dt, *J* 12.8, 3.7 Hz, C*H*H), 2.63 (1H, td, *J* 12.8, 3.7 Hz, C*H*H), 2.01 (1H, td, *J* 12.8, 3.7 Hz, C*H*H) ppm.
δ_C (100 MHz, $CDCl_3$)	159.0 (*C*), 155.6 (*C*), 154.9 (*C*), 152.1 (*C*), 142.7 (*C*), 139.8 (*C*), 134.7 (*C*), 133.8 (*C*), 132.0 (*C*), 131.3 (*C*H), 130.6 (*C*H), 130.2 (*C*H), 129.1 (*C*), 128.3 (*C*H), 128.2 (*C*), 127.8 (*C*H), 125.5 (*C*H), 124.9 (*C*H), 122.7 (*C*), 121.0 (*C*), 117.9 (*C*H), 115.2 (*C*H), 113.1 (2 × *C*H), 111.5 (*C*H), 106.5 (*C*H), 57.5 (*C*H$_3$), 55.6 (*C*H$_3$), 55.4 (*C*H$_3$), 38.3 (*C*H$_2$), 38.3 (*C*H$_2$) ppm.
LRMS (ES+)	949 ($[2M+Na]^+$, 20 %), 485 ($[M+Na]^+$, 100 %), 236 (70 %), 227 (70 %) amu.
HRMS (ES+)	Found $[M+Na]^+$: 485.1726. $C_{31}H_{26}O_4Na$ requires 485.1723.

X-ray



1,2,13,14-tetrahydro-9,17,22-trimethoxy-3,6-etheno-15,18-(1-iodoetheno)-8,12-metheno-12*H*-7-benzoxacycloeicosine **3.86**



3.1
$C_{31}H_{27}IO_4$
Mol. Wt.: 590

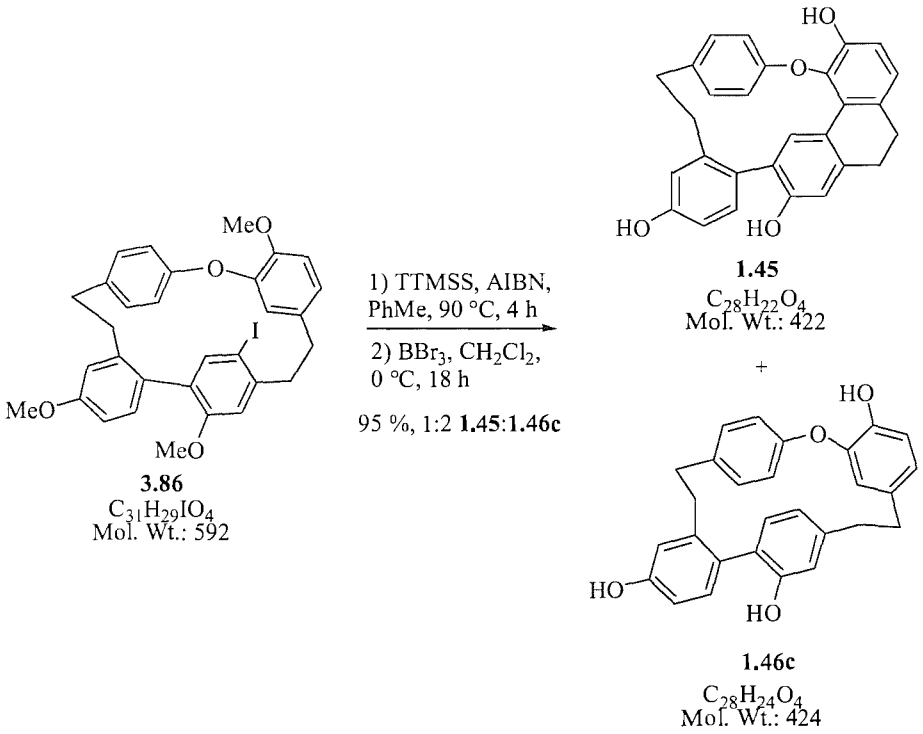
3.86
$C_{31}H_{29}IO_4$
Mol. Wt.: 592

A biphasic solution of stilbene **3.1** (246 mg, 0.417 mmol) and sodium acetate (208 mg, 2.54 mmol) and *p*-toluenesulfonyl hydrazide (466 mg, 2.50 mmol) in THF/water (80 mL, 1/1) was heated at reflux for 24 h. Further sodium acetate (480 mg, 5.84 mmol) and *p*-toluenesulfonyl hydrazide (868 mg, 4.66 mmol) was added at this juncture, and at each 24 h interval over a 4 day period. 20 h after the final addition, the solution was cooled to RT and sat. aq. potassium carbonate (50 mL) added. After a further 18 h the reaction mixture was extracted with dichloromethane (4 × 50 mL), dried ($MgSO_4$) and the solvent removed *in*

vacuo. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/4) gave **3.86** (225 mg, 0.38 mmol, 91 %) as a white solid.

MP	>250 °C (methanol)
λ_{max}/nm (ε_{max}, CH_2Cl_2)	330 sh (1500), 295 sh (7000), 230 (29500).
ν_{max}/cm^{-1} (film)	2933 (w), 2836 (w), 1606 (m), 1505 (s), 1478 (m), 1464 (m), 1369 (m), 1261 (s), 1228 (s), 1165 (m), 1128 (m), 1042 (m), 906 (m), 729 (s).
δ_H (400 MHz, $CDCl_3$)	7.42 (1H, s, Ar*H*), 7.07 (1H, d, *J* 8.5 Hz, Ar*H*), 6.96 (1H, d, *J* 2.8 Hz, Ar*H*), 6.92-6.72 (7H, m, 7 × Ar*H*), 6.38 (1H, s, Ar*H*), 5.34 (1H, d, *J* 2.1 Hz, Ar*H*), 3.96 (3H, s, OC*H*$_3$), 3.89 (3H, s, OC*H*$_3$), 3.63 (3H, s, OC*H*$_3$), 3.09-2.63 (8H, m, 4 × C*H*$_2$) ppm.
δ_C (100 MHz, $CDCl_3$)	159.6 (*C*), 156.5 (*C*), 152.9 (*C*), 149.4 (*C*), 147.3 (*C*), 143.6 (*C*), 143.3 (*C*), 142.8 (*C*H), 139.8 (*C*), 133.3 (*C*), 132.8 (*C*H), 130.4 (*C*), 129.7 (*C*H), 129.6 (*C*H), 129.1 (*C*), 122.8 (*C*H), 122.3 (*C*H), 121.9 (*C*H), 116.2 (*C*H), 115.8 (*C*H), 113.1 (*C*H), 112.3 (*C*H), 111.7 (*C*H), 90.0 (*C*), 56.4 (*C*H$_3$), 55.5 (*C*H$_3$), 55.4 (*C*H$_3$), 42.1 (*C*H$_2$), 38.4 (*C*H$_2$), 36.9 (*C*H$_2$), 35.7 (*C*H$_2$) ppm.
LRMS (ES+)	615 ([M+Na]$^+$, 100 %) amu.
HRMS (ES+)	Found [M+Na]$^+$: 615.1018. $C_{31}H_{29}O_4Na$ requires 615.1003.

Cavicularin **1.45** & riccardin C **1.46c**



A solution of iodo arene **3.86** (40 mg, 67.6 μmol) and TTMSS (30 μL, 97.2 μmol) in toluene (12 mL) was heated to 90 °C, then AIBN (3.2 mg, 19.5 μmol) was added. After 2 h further portions of TTMSS (30 μL, 97.2 μmol) and AIBN (3.2 mg, 19.5 μmol) were added. After a further 2 h the mixture was cooled to RT and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/7) gave a mixture of two products (28 mg) which were inseparable.

These were dissolved in dichloromethane (6 mL), cooled to 0 °C and boron tribromide (1M in CH_2Cl_2, 0.36 mL) was added dropwise over 1 min. After 18 h at RT, ice cold water (5 mL) was added. The aqueous phase was extracted with dichloromethane (4 × 10 mL). The organic phases were combined, washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, dichloromethane/methanol, 50/1) gave firstly cavicularin **1.45** (9 mg, 21.3 μmol, 32 % over two steps) as a white solid, then riccardin C **1.46c** (18 mg, 42.5 μmol, 63 % over two steps) as a white solid.

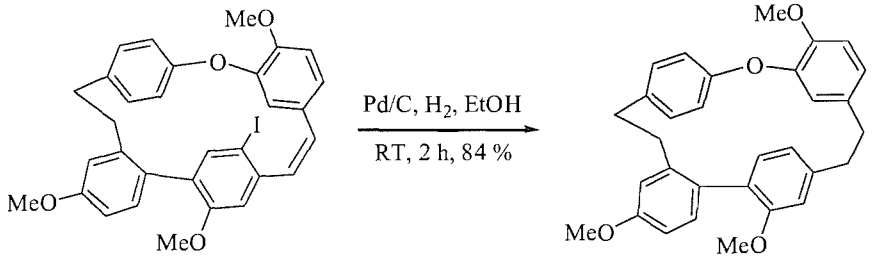
Data for cavicularin **1.45**

MP	214 °C (ether/petroleum ether) [Lit. 244-246 °C (EtOAc/hexane][33]
λ_{max}/nm (ε_{max}, MeOH)	318 sh (5300), 305 sh (5500), 285 (8800), 203 (30600).
δ_H (400 MHz, $CDCl_3$)	6.99 (1H, d, *J* 8.0 Hz, Ar*H*), 6.94 (1H, d, *J* 8.0 Hz, Ar*H*), 6.88 (1H, d, *J* 2.5 Hz, Ar*H*), 6.83 (1H, d, *J* 8.3 Hz, Ar*H*), 6.76 (1H, dd, *J* 8.3, 2.5 Hz, Ar*H*), 6.72 (1H, dd, *J* 8.3, 2.5 Hz, Ar*H*), 6.69 (1H, s, Ar*H*), 6.47 (1H, dd, *J* 8.5, 2.3 Hz, Ar*H*), 6.41 (1H, s, Ar*H*), 6.16 (1H, dd, *J* 8.3, 2.3 Hz, Ar*H*), 6.12 (1H, dd, *J* 8.5, 2.5 Hz, Ar*H*), 6.11 (1H, s, O*H*), 4.82 (1H, s, O*H*), 4.74 (1H, s, O*H*), 2.99-2.92 (2H, m, CH_2), 2.79-2.63 (4H, m, 2 × CH_2), 2.56 (1H, app. td, *J* 13.0, 3.7 Hz, C*H*H), 2.29 (1H, app. td, *J* 13.0, 3.7 Hz, CH*H*) ppm.
δ_C (100 MHz, $CDCl_3$)	155.6 (*C*), 153.8 (*C*), 150.2 (*C*), 147.9 (*C*), 141.6 (*C*), 140.5 (*C*), 138.5 (*C*), 135.0 (*C*), 131.7 (*C*), 131.7 (*C*H), 131.1 (*C*H), 130.1 (*C*H), 128.9 (*C*), 127.8 (*C*H), 124.0 (*C*), 124.0 (*C*), 123.3 (*C*), 123.0 (*C*H), 117.8 (*C*H), 116.9 (*C*H), 115.1 (*C*H), 114.7 (*C*H), 113.3 (*C*H), 113.0 (*C*H), 38.1 (*C*H_2), 37.4 (*C*H_2), 30.5 (*C*H_2), 30.2 (*C*H_2) ppm.
LRMS (ES+)	867 ($[2M+Na]^+$, 12 %), 445 ($[M+Na]^+$, 100 %), 236 (82 %), 142 (90 %) amu.

Data for riccardin C **1.46c**

MP	199-200 °C (ethanol) [Lit. 194 °C (hexane)][40]
λ_{max}/nm (ε_{max}, MeOH)	283 (8400), 206 (67900).
ν_{max}/cm^{-1} (film)	3408 (br. w), 2926 (w), 1605 (m), 1563 (w), 1505 (s), 1432 (m), 1339 (w), 1270 (m), 1223 (s), 1189 (m), 1110 (w), 907 (s), 814 (m).
δ_H (400 MHz, $CDCl_3$)	7.05 (2H, d, *J* 8.3 Hz, 2 × Ar*H*), 6.98 (1H, d, *J* 2.8 Hz, Ar*H*), 6.93 (1H, d, *J* 8.0 Hz, Ar*H*), 6.82-6.77 (4H, m, 4 × Ar*H*), 6.74 (2H, dd, *J* 8.0, 2.0 Hz, 2 × Ar*H*), 6.40 (1H, d, *J* 1.3 Hz, Ar*H*), 6.25 (1H, dd, *J* 7.8, 1.5 Hz, Ar*H*), 5.62 (1H, s, ArO*H*), 5.38 (1H, d, *J* 1.8 Hz, Ar*H*), 5.19 (1H, br. s, ArO*H*), 4.81 (1H, s, ArO*H*), 3.03 (2H, br. s, CH_2), 2.93 (2H, br. s, CH_2), 2.72 (2H, br. s, CH_2), 2.55 (2H, br. s, CH_2) ppm.
δ_C (100 MHz, $CDCl_3$)	156.1 (*C*), 152.8 (*C*), 152.0 (*C*), 146.5 (*C*), 144.0 (*C*), 143.5 (*C*), 142.2 (*C*), 140.0 (*C*), 133.3 (*C*), 133.0 (*C*H), 131.6 (*C*H), 129.4 (2 × *C*H), 128.4 (*C*), 124.6 (*C*), 122.6 (2 × *C*H), 122.4 (*C*H), 121.9 (*C*H), 117.7 (*C*H), 116.3 (*C*H), 116.2 (*C*H), 115.1 (*C*H), 114.5 (*C*H), 38.3 (*C*H_2), 37.9 (*C*H_2), 37.2 (*C*H_2), 35.2 (*C*H_2) ppm.
LRMS (ES+)	871 ([2M+Na]$^+$, 10 %), 447 ([M+Na]$^+$, 100 %), 236 (10 %) amu.

1,2,13,14-tetrahydro-9,17,22-trimethoxy-3,6:15,18-dietheno-8,12-metheno-12*H*-7-benzoxacycloeicosine **3.88**



3.1
$C_{31}H_{27}IO_4$
Mol. Wt.: 590

3.88
$C_{31}H_{30}O_4$
Mol. Wt.: 467

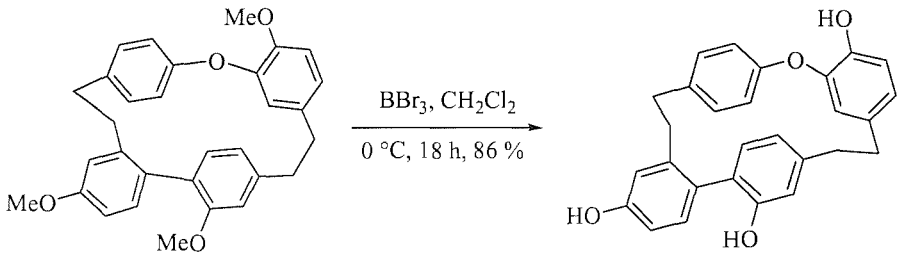
To a solution of alkene **3.1** (84 mg, 0.14 mmol) in ethanol (15 mL) was added palladium on carbon (5 % w/w, 20 mg, 0.19 g.atom). The mixture was stirred vigorously under an atmosphere of hydrogen at RT for 2 h, then filtered through Celite and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 1/2) gave **3.88** (56 mg, 0.12 mmol, 84 %) as a viscous oil.

The spectroscopic and physical data attained compares well with literature values.[30,31,40]

MP	152-154 °C [Lit. 155 °C][40]
λ_{max}/nm (ε_{max}, MeOH)	281 (4000), 206 (36000).
ν_{max}/cm^{-1} (film)	2997 (w), 2930 (m), 2853 (w), 2833 (w), 1604 (m), 1504 (s), 1462 (m), 1441 (m), 1418 (m), 1258 (s), 1227 (s), 1163 (m), 1126 (s), 1037 (m), 904 (s).
δ_H (400 MHz, $CDCl_3$)	7.07 (1H, d, *J* 8.5 Hz, Ar*H*), 6.98 (1H, d, *J* 2.5 Hz, Ar*H*), 6.90 (1H, d, *J* 8.0 Hz, Ar*H*), 6.85-6.75 (7H, m, 7 × Ar*H*), 6.45 (1H, d, *J* 1.5 Hz, Ar*H*), 6.27 (1H, dd, *J* 7.5, 1.5 Hz, Ar*H*), 5.41 (1H, d, *J* 1.8 Hz, Ar*H*), 3.96 (3H, s, OC*H*$_3$), 3.90 (3H, s, OC*H*$_3$), 3.69 (3H, s, OC*H*$_3$),

	3.15-3.05 (1H, m, C*H*H),
	3.00-2.70 (4H, m, 4 × C*H*H),
	2.69-2.55 (3H, m, 3 × C*H*H) ppm.
δ_C (100 MHz, $CDCl_3$)	159.3 (*C*), 156.2 (*C*), 152.9 (*C*), 148.9 (*C*), 147.1 (*C*), 143.4 (*C*), 141.4 (*C*), 139.9 (*C*), 134.0 (*C*), 132.6 (*C*H), 132.6 (*C*H), 131.1 (*C*), 129.4 (*C*H), 129.3 (*C*H), 127.8 (*C*), 122.5 (2 × *C*H), 121.9 (*C*H), 121.6 (*C*H), 116.9 (*C*H), 115.5 (*C*H), 112.0 (*C*H), 111.6 (*C*H), 111.4 (*C*H), 56.3 (CH_3), 55.4 (CH_3), 55.4 (CH_3), 38.4 (CH_2), 38.3 (CH_2), 37.4 (CH_2), 35.8 (CH_2) ppm.
LRMS (ES+)	956 ($[2M+Na]^+$, 23 %), 489 ($[M+Na]^+$, 100 %) amu.

Riccardin C **1.46c**



3.88
$C_{31}H_{30}O_4$
Mol. Wt.: 467

1.46c
$C_{28}H_{24}O_4$
Mol. Wt.: 424

To a cooled (0 °C) solution of arene **3.88** (32 mg, 68.6 μmol) in dichloromethane (5 mL) was added boron tribromide (1M in CH_2Cl_2, 0.36 mL) dropwise over 10 min. After stirring for 3 h at this temperature, the reaction was warmed to RT and ice cold water (5 mL) was added. The aqueous phase was extracted with dichloromethane (4 × 10 mL). The organic phases were combined, washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (SiO_2, ether/petroleum ether, 2/1) gave riccardin C **1.46c** (25 mg, 59.0 μmol, 86 %) as a white solid.

Data coincides with that reported above.

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Table 1. Crystal data and structure refinement.

Identification code	**04sot0828 (TW4135/21)**	
Empirical formula	$C_{31}H_{26}O_4$	
Formula weight	462.52	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*C2/c*	
Unit cell dimensions	a = 25.060(5) Å	α = 90°
	b = 16.703(3) Å	β = 116.18(3)°
	c = 12.935(3) Å	γ = 90°
Volume	4858.7(17) Å^3	
Z	8	
Density (calculated)	1.265 Mg / m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	1952	
Crystal	Block; pale orange	
Crystal size	0.30 × 0.28 × 0.20 mm^3	
θ range for data collection	2.98 – 27.50°	
Index ranges	$-31 \le h \le 32, -21 \le k \le 17, -16 \le l \le 16$	
Reflections collected	14220	
Independent reflections	5578 [R_{int} = 0.0602]	
Completeness to θ = 27.50°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9836 and 0.9756	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5578 / 0 / 421	

Goodness-of-fit on F^2	1.035
Final R indices $[F^2 > 2\sigma(F^2)]$	$R1 = 0.0644$, $wR2 = 0.1642$
R indices (all data)	$R1 = 0.1067$, $wR2 = 0.1820$
Extinction coefficient	0.0029(7)
Largest diff. peak and hole	0.256 and −0.321 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction 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. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: Solvent moieties were removed using the Squeeze module of Platon.

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.*
C1	5723(1)	1288(2)	7107(3)	51(1)	1
C2	4937(1)	1947(1)	5532(2)	34(1)	1
C3	5325(1)	2489(1)	5400(2)	35(1)	1
C4	5099(1)	3031(2)	4517(2)	33(1)	1
C5	4491(1)	3076(1)	3770(2)	30(1)	1
C6	4075(1)	2569(1)	3933(2)	27(1)	1
C7	4328(1)	1984(1)	4814(2)	30(1)	1
C8	4282(1)	3633(1)	2832(2)	31(1)	1
C9	3709(1)	3660(1)	2056(2)	29(1)	1
C10	3441(1)	2668(1)	3163(2)	25(1)	1
C11	3273(1)	3163(1)	2179(2)	26(1)	1
C12	2677(1)	3179(1)	1327(2)	27(1)	1
C13	2248(1)	2726(1)	1433(2)	26(1)	1
C14	2392(1)	2275(1)	2452(2)	24(1)	1
C15	2972(1)	2288(1)	3299(2)	24(1)	1
C16	1478(1)	3217(2)	−337(2)	35(1)	1
C17	1930(1)	1808(1)	2629(2)	24(1)	1
C18	1637(1)	1136(1)	1957(2)	25(1)	1
C19	1225(1)	732(1)	2208(2)	26(1)	1
C20	1104(1)	953(1)	3119(2)	26(1)	1
C21	1393(1)	1613(1)	3789(2)	29(1)	1
C22	1795(1)	2028(1)	3525(2)	28(1)	1
C23	512(1)	749(2)	4117(2)	33(1)	1
C24	1774(1)	788(1)	1019(2)	28(1)	1
C25	2127(1)	−13(1)	1391(2)	32(1)	1
C26	3646(1)	883(1)	4231(2)	34(1)	1
C27	3681(1)	771(1)	3203(2)	34(1)	1
C28	3200(1)	404(1)	2292(2)	35(1)	1
C29	2707(1)	134(1)	2416(2)	31(1)	1
C30	2735(1)	152(1)	3516(2)	35(1)	1
C31	3203(1)	523(1)	4431(2)	35(1)	1
O1	5108(1)	1346(1)	6333(2)	45(1)	1
O2	3997(1)	1417(1)	5073(1)	36(1)	1
O3	1667(1)	2686(1)	631(1)	32(1)	1
O4	705(1)	479(1)	3289(1)	32(1)	1

Table 3. Bond lengths [Å] and angles [°].

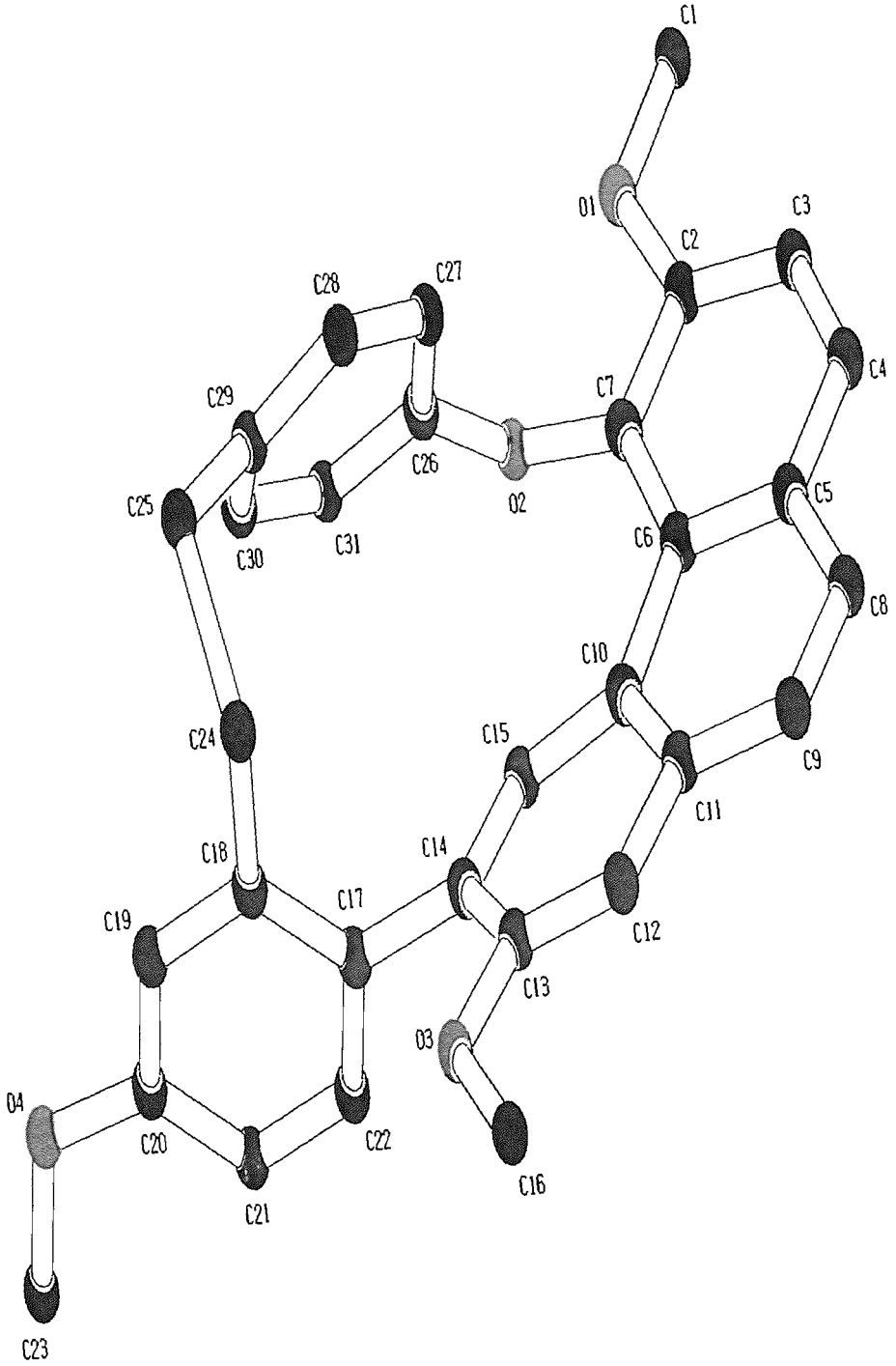
C1–O1	1.423(3)	C19–C20	1.390(3)
C1–H1A	1.00(3)	C19–H19	1.00(2)
C1–H1B	1.01(3)	C20–O4	1.368(2)
C1–H1C	0.96(3)	C20–C21	1.392(3)
C2–O1	1.368(3)	C21–C22	1.384(3)
C2–C3	1.394(3)	C21–H21	0.96(2)
C2–C7	1.395(3)	C22–H22	0.93(2)
C3–C4	1.370(3)	C23–O4	1.428(2)
C3–H3	0.96(3)	C23–H23A	1.04(2)
C4–C5	1.400(3)	C23–H23B	1.00(3)
C4–H4	0.98(2)	C23–H23C	1.01(3)
C5–C6	1.429(3)	C24–C25	1.559(3)
C5–C8	1.433(3)	C24–H24A	0.94(2)
C6–C7	1.420(3)	C24–H24B	1.03(2)
C6–C10	1.466(3)	C25–C29	1.494(3)
C7–O2	1.393(3)	C25–H25A	0.96(2)
C8–C9	1.341(3)	C25–H25B	0.96(2)
C8–H8	0.98(2)	C26–O2	1.382(3)
C9–C11	1.436(3)	C26–C31	1.384(3)
C9–H9	0.98(2)	C26–C27	1.384(3)
C10–C15	1.414(3)	C27–C28	1.402(4)
C10–C11	1.417(3)	C27–H27	0.95(2)
C11–C12	1.412(3)	C28–C29	1.389(3)
C12–C13	1.371(3)	C28–H28	1.02(2)
C12–H12	0.99(2)	C29–C30	1.394(3)
C13–O3	1.367(3)	C30–C31	1.391(4)
C13–C14	1.418(3)	C30–H30	1.06(3)
C14–C15	1.381(3)	C31–H31	1.08(3)
C14–C17	1.495(3)		
C15–H15	0.98(2)	O1–C1–H1A	109.6(16)
C16–O3	1.434(3)	O1–C1–H1B	103.7(16)
C16–H16A	0.99(3)	H1A–C1–H1B	118(2)
C16–H16B	1.05(3)	O1–C1–H1C	108.1(19)
C16–H16C	0.98(2)	H1A–C1–H1C	102(2)
C17–C22	1.393(3)	H1B–C1–H1C	115(2)
C17–C18	1.412(3)	O1–C2–C3	124.5(2)
C18–C19	1.387(3)	O1–C2–C7	115.0(2)
C18–C24	1.514(3)	C3–C2–C7	120.5(2)

C4–C3–C2	118.5(2)	H16A–C16–H16B	106(2)
C4–C3–H3	123.1(15)	O3–C16–H16C	109.2(14)
C2–C3–H3	118.4(15)	H16A–C16–H16C	115(2)
C3–C4–C5	122.4(2)	H16B–C16–H16C	111.8(19)
C3–C4–H4	120.2(15)	C22–C17–C18	118.06(19)
C5–C4–H4	117.4(14)	C22–C17–C14	118.67(19)
C4–C5–C6	120.6(2)	C18–C17–C14	123.23(17)
C4–C5–C8	120.0(2)	C19–C18–C17	118.80(18)
C6–C5–C8	119.4(2)	C19–C18–C24	117.14(19)
C7–C6–C5	115.5(2)	C17–C18–C24	123.93(19)
C7–C6–C10	126.1(2)	C18–C19–C20	122.2(2)
C5–C6–C10	118.40(19)	C18–C19–H19	120.4(12)
O2–C7–C2	113.7(2)	C20–C19–H19	117.3(12)
O2–C7–C6	124.0(2)	O4–C20–C19	115.53(19)
C2–C7–C6	122.3(2)	O4–C20–C21	125.07(18)
C9–C8–C5	121.8(2)	C19–C20–C21	119.40(19)
C9–C8–H8	118.9(14)	C22–C21–C20	118.56(19)
C5–C8–H8	119.3(14)	C22–C21–H21	119.6(13)
C8–C9–C11	120.9(2)	C20–C21–H21	121.8(13)
C8–C9–H9	122.1(13)	C21–C22–C17	123.0(2)
C11–C9–H9	116.9(13)	C21–C22–H22	114.8(14)
C15–C10–C11	116.1(2)	C17–C22–H22	122.1(14)
C15–C10–C6	125.16(19)	O4–C23–H23A	113.0(12)
C11–C10–C6	118.72(19)	O4–C23–H23B	104.4(14)
C12–C11–C10	120.34(19)	H23A–C23–H23B	109(2)
C12–C11–C9	119.9(2)	O4–C23–H23C	109.8(13)
C10–C11–C9	119.8(2)	H23A–C23–H23C	106.8(18)
C13–C12–C11	121.2(2)	H23B–C23–H23C	114(2)
C13–C12–H12	118.4(14)	C18–C24–C25	112.35(18)
C11–C12–H12	120.3(14)	C18–C24–H24A	106.1(12)
O3–C13–C12	124.80(19)	C25–C24–H24A	112.2(12)
O3–C13–C14	115.43(18)	C18–C24–H24B	112.1(13)
C12–C13–C14	119.7(2)	C25–C24–H24B	105.8(13)
C15–C14–C13	118.50(19)	H24A–C24–H24B	108.3(18)
C15–C14–C17	120.05(18)	C29–C25–C24	109.27(19)
C13–C14–C17	121.4(2)	C29–C25–H25A	109.5(14)
C14–C15–C10	123.3(2)	C24–C25–H25A	109.7(13)
C14–C15–H15	114.7(13)	C29–C25–H25B	109.9(13)
C10–C15–H15	122.0(13)	C24–C25–H25B	110.3(12)
O3–C16–H16A	107.0(15)	H25A–C25–H25B	108.2(17)
O3–C16–H16B	107.7(14)	O2–C26–C31	114.6(2)

O2–C26–C27	123.8(2)
C31–C26–C27	121.2(2)
C26–C27–C28	118.0(2)
C26–C27–H27	121.2(16)
C28–C27–H27	120.6(16)
C29–C28–C27	121.6(2)
C29–C28–H28	118.1(13)
C27–C28–H28	120.1(13)
C28–C29–C30	117.7(2)
C28–C29–C25	121.2(2)
C30–C29–C25	120.0(2)
C31–C30–C29	121.4(2)
C31–C30–H30	120.9(14)
C29–C30–H30	117.6(14)
C26–C31–C30	118.6(2)
C26–C31–H31	117.7(14)
C30–C31–H31	122.9(15)
C2–O1–C1	117.6(2)
C26–O2–C7	119.21(17)
C13–O3–C16	117.65(18)
C20–O4–C23	116.84(17)

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}
C1	31(2)	58(2)	45(2)	5(2)	−2(1)	2(2)
C2	30(1)	34(1)	31(1)	−3(1)	8(1)	2(1)
C3	24(1)	41(1)	36(1)	−6(1)	10(1)	−1(1)
C4	28(1)	36(1)	36(1)	−7(1)	15(1)	−4(1)
C5	31(1)	32(1)	30(1)	−6(1)	16(1)	−4(1)
C6	28(1)	29(1)	26(1)	−3(1)	12(1)	−1(1)
C7	27(1)	31(1)	30(1)	−2(1)	11(1)	−4(1)
C8	33(2)	33(1)	33(1)	−6(1)	21(1)	−6(1)
C9	36(2)	29(1)	24(1)	0(1)	15(1)	−2(1)
C10	27(1)	25(1)	23(1)	−4(1)	12(1)	−3(1)
C11	30(1)	24(1)	25(1)	−2(1)	14(1)	0(1)
C12	32(1)	25(1)	23(1)	2(1)	12(1)	1(1)
C13	27(1)	25(1)	22(1)	−2(1)	7(1)	2(1)
C14	26(1)	22(1)	22(1)	−1(1)	10(1)	2(1)
C15	26(1)	24(1)	20(1)	0(1)	8(1)	−1(1)
C16	37(2)	32(1)	28(1)	6(1)	8(1)	3(1)
C17	22(1)	24(1)	24(1)	2(1)	7(1)	2(1)
C18	26(1)	27(1)	17(1)	2(1)	7(1)	3(1)
C19	26(1)	25(1)	23(1)	−1(1)	9(1)	0(1)
C20	23(1)	28(1)	28(1)	4(1)	11(1)	2(1)
C21	31(1)	32(1)	25(1)	−4(1)	13(1)	−1(1)
C22	29(1)	27(1)	23(1)	−3(1)	9(1)	−1(1)
C23	35(2)	39(2)	31(1)	−3(1)	19(1)	−3(1)
C24	32(1)	31(1)	22(1)	−2(1)	11(1)	−5(1)
C25	38(2)	28(1)	34(1)	−8(1)	20(1)	−6(1)
C26	30(1)	30(1)	35(1)	5(1)	6(1)	2(1)
C27	28(1)	29(1)	46(2)	−3(1)	18(1)	−1(1)
C28	36(2)	28(1)	46(2)	−7(1)	22(1)	2(1)
C29	33(2)	21(1)	40(1)	−2(1)	16(1)	2(1)
C30	34(2)	29(1)	35(1)	5(1)	10(1)	−1(1)
C31	35(2)	30(1)	34(1)	8(1)	8(1)	0(1)
O1	31(1)	48(1)	37(1)	8(1)	−1(1)	0(1)
O2	31(1)	41(1)	28(1)	6(1)	5(1)	−6(1)
O3	29(1)	36(1)	25(1)	8(1)	6(1)	1(1)
O4	35(1)	35(1)	34(1)	−5(1)	21(1)	−7(1)


C1
O1
C2
C3
C4
C5
C6
C7
C8
C9
C10
C11
C12
C13
C14
C15
C16
C17
C18
C19
C20
C21
C22
C23
C24
C25
C26
C27
C28
C29
C30
C31
O2
O3
O4

CHAPTER VI – References

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