UNIVERSITY OF SOUTHAMPTON

Faculty of Engineering, Science and Mathematics

School of Chemistry

The Total Synthesis of Macrocyclic bisBibenzyl Natural Products

by

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A Thesis Submitted for the Degree of Doctor of Philosophy

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ABSTRACT

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This thesis is concerned with the total synthesis of two related macrocyclic natural products, cavicularin and riccardin C. Cavicularin is particularly noteworthy owing to its interesting structure: its 14-membered macrocyclic core imparts sufficient strain on the system to force one of the arenes in this paracycophane to adopt a boat-shaped conformation, deviating from planarity. The natural product also exhibits optical activity despite containing no chiral centres, this being due to axial and planar chirality in the molecule. Herein, routes to these two natural products are presented. Key steps include a highly chemoselective hydrogenation and a Wittig macrocyclisation and, in the case of cavicularin, regioselective halogenation and radical induced transannular ring contraction.

This work also furnished a number of highly strained macrocycles as precursors to the natural products. These structures were found to contain boat-shaped aromatic rings, in addition to twisted olefin functionalities. A discussion of these features is presented in Chapter 6, with full crystallographic data provided in the Appendix.

A review of these and related bisbibenzyl natural products is presented in Chapter 1, including their isolation, characterisation, an overview of their biological activity and previous synthetic work. Experimental procedures and characterisation data are provided in Chapter 7.

Contents

The research described in this thesis was carried out under the supervision of Prof. D. C. Harrowven at the University of Southampton and at GlaxoSmithKline, Tonbridge between October 2006 and September 2009. No part of this thesis has previously been submitted for a degree.

The work described is entirely my own, except where I have *either* acknowledged help from a named person *or* given a reference to a published source or a thesis. Text taken from another source is enclosed in quotation marks and a reference given. Pictures taken from another source are clearly indicated in the caption.

For Grandma and Grandad

Acknowledgements

First and foremost I should like to thank Prof. David Harrowven for giving me the opportunity to carry out this research in his laboratory and under his supervision, and for the proof reading of this thesis. Secondly, thank you to Dr. Leo Dudin for helpful suggestions, endless enthusiasm and a warm welcome at Tonbridge.

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Finally, thank you to my wonderful fiancé Alexander for all of his patience, diligent proof reading and support.

SLK, 2009

Abbreviations

2D	two dimensional
$[\alpha]_D$	optical rotation
Ac	acetyl
AD	(Sharpless) asymmetric dihydroxylation
app.	apparent
aq.	aqueous
Bn	benzyl
br.	broad
Bu	butyl
c	concentration
°C	degrees centigrade
CD	circular dichroism
CI	chemical ionisation
cm^{-1}	wavenumber
CoA	coenzyme A
COSY	correlated spectroscopy
Cy	cyclohexyl
d	doublet
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DIBAL-H	diisobutylaluminium hydride
DIPE	diisopropyl ether
DMAP	4-dimethylaminopyridine
DME	dimethyl ether
DMF	*N*-*N*-dimethylformamide
dppf	1,1'-bis(diphenyl-phosphino)ferrocene
ED	effective dose
EI	electron ionisation
ES+	electospray ionisation (positive mode)
ES–	electrospray ionisation (negative mode)
ESI	electrospray ionisation
Et	ethyl
GSK	GlaxoSmithKline
h	hour(s)
HMTA	hexamethylenetetramine
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple-quantum correlation
HPLC	High performance liquid chromatography
HWE	Horner-Wadsworth-Emmons
Hz	hertz
IC	inhibitory concentration
J	coupling constant
JMOD	J-Modulated Spin-Echo
kJ	kilojoule
LCMS	Liquid chromatography-mass spectrometry
LXR	liver X receptor
M	molar
m	medium/multiplet
m	meta
MALDI	matrix-assisted laser desorption/ionization
MD	molecular dynamics
Me	methyl
MIC	minimal inhibitory concentration
min	minute(s)
mL	millilitre(s)
mM	millimolar
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl ether
MP	melting point
MS	mass spectrometry
m/z	mass/charge ratio
n	normal
NAD	nicotinamide adenine dinucleotide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
o	ortho
obsc.	obscured
p	*para*
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
PPTS	pyridinium *p*-toluene-sulfonate
q	quartet
rac	racemic
RCM	ring-closing metathesis
RT	room temperature
s	singlet/strong
sat.	saturated
S_NAR	nucleophilic aromatic substitution
t	triplet
t	tertiary
tert	tertiary

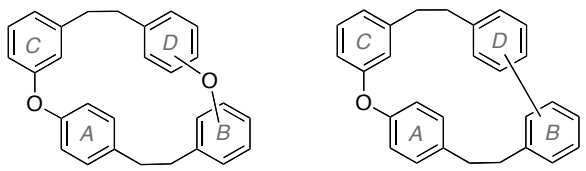
TBDMS	*tert*-butyldimethylsilyl	υ_{max}	absorption maxima
TEA	triethylamine	VAZO	1,1′-azobis(cyclo-hexanecarbonitrile)
Tf	triflate		
TFA	trifluoroacetic acid	VBSCF	valence-bond self-consistent field
THF	tetrahydrofuran		
TLC	thin layer chromatography	*viz*.	*videlicet*
TMS	trimethylsilyl	VT	variable temperature
ToF	time of flight	w	weak
Ts	tosyl	W	watt
TTMSS	*tris*-trimethylsilylsilane		
uv	ultraviolet		

Chapter 1: Introduction to the Macrocyclic bisBibenzyl Natural Products

1.1 Background

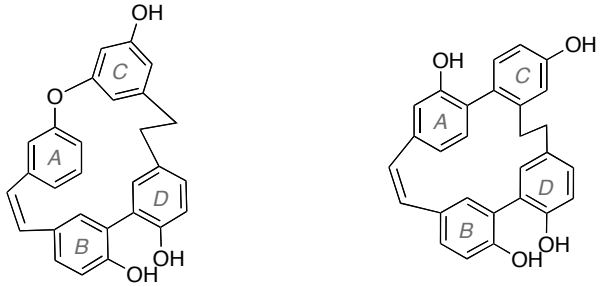
The macrocyclic bisbibenzyls are a class of naturally-occurring compounds found in bryophytes, mainly liverworts,[1] which DNA analyses have revealed to be the earliest land plants.[2] Until recently, these compounds were thought to be exclusive to the bryophyte family. However, the isolation of riccardin C, a macrocyclic bisbibenzyl of this class, from the perennial herbaceous plant *Primula macrocalyx* Bge. (Primulaceae) has refuted this, showing the potential for the isolation of further macrocyclic bisbibenzyls from higher flowering plants.[3]

The core structure of macrocyclic bisbibenzyls comprises four aromatic rings, labelled *A*, *B*, *C* and *D* as shown in Figure 1, with ethano bridges conjoining both the *A* and *B* and *C* and *D* rings.[4] The remaining linkages create two main sub-classes: natural products containing two diphenyl ethers (*e.g.* **1a**) and those containing one diphenyl ether and one biaryl bond (*e.g.* **1b**). Common to the majority of natural bisbibenzyls are the almost invariable *para*-substitution of the *A* ring and the regiochemistry of the *C* ring, in which the pendant ethano bridge is positioned *meta* to the ethereal oxygen. A notable exception to these general rules is the isoplagiochin class, in which the *A* ring is either *meta*-substituted with an ethereal linkage, or *para*-substituted featuring two biaryl bonds (Figure 2).



1a **1b**

Figure 1



Isoplagiochin A **1.2** Isoplagiochin C **1.3**

Figure 2

Further diversity in these classes arises from the regiochemistry of the connectivity between the arenes and from the degree of oxygenation (*e.g.* the riccardins and marchantins) and halogenation (*e.g.* the bazzanins). In general, the connectivity denotes the family, with the degree of oxygenation affording family members referred to as A, B, C *etc*.[4]

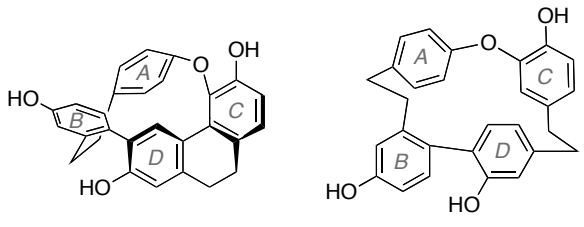
1.2 Isolation and Structural Elucidation

The past 20 years have seen the isolation and identification of a plethora of macrocyclic bisbibenzyls. A major source of these natural products is Japanese liverworts, and much of this work has been carried out by, or in collaboration with, Yoshinori Asakawa at the Institute of Pharmacognosy, Tokushima Bunri University, Japan.[1]

This rich area of natural product research has revealed a number of structurally unusual and interesting compounds, attracting considerable attention from the scientific community. Cavicularin **1.4** and isoplagiochin C **1.3** are two such examples selected for detailed discussion (see Section 1.2.1),[5, 6] with the major families of macrocyclic bisbenzyls summarized in Section 1.2.2.

1.2.1a Cavicularin

(+)-Cavicularin **1.4** was isolated by Asakawa and co-workers in 1996 from samples of the liverwort *Cavicularia densa* Steph. (Blasiaceae), collected on Mount Ishizuchi on the island of Shikoku in Japan in 1995. This species of liverwort had not previously been investigated phytochemically.[6]



(+)-Cavicularin **1.4** Riccardin C **1.5**

Figure 3

The structure of (+)-cavicularin **1.4** was conclusively established by extensive 2D-NMR studies and X-ray crystallographic analysis. Structurally similar to riccardin C **1.5**, (+)-cavicularin has the added complexity of a second biaryl bond, creating a dihydrophenanthrene unit. This places sufficient strain on the macrocyclic core to force arene *A* into a boat-like configuration, 15° out of planarity (Figure 4). This was the first reported example of the isolation of such a compound from Nature.

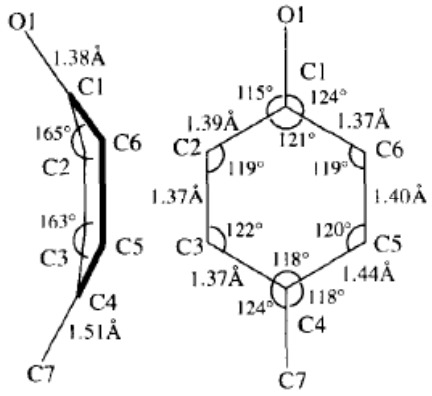
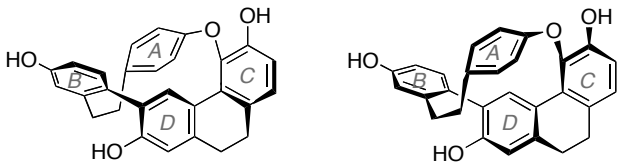


Figure 4 – Diagram of ring *A* of **1.4** showing bond lengths, dihedral and inter-bond angles.[6]

Although (+)-cavicularin **1.4** has no chiral carbon centres, Asakawa *et al*. found that it possessed optical rotation, with an $[\alpha]_D$ of +168.2 (*c* 0.25, MeOH), and that its circular dichroism (CD) spectrum exhibited Cotton effects. These phenomena suggested that **1.4** possessed both planar and axial chirality: it is the assembly of atoms in (+)-cavicularin that exhibits overall asymmetry, resulting in optical activity.

NMR studies of the (1*S*)-(–)-camphanyl triester confirmed the enantiomeric purity of the isolated sample, suggesting that (+)-cavicularin is biosynthesised in enantiopure form in *C. densa*. The absolute configuration is not known (Figure 5).



1.4a **1.4b**

Figure 5 – Restricted absolute structures for (+)-cavicularin.

(+)-Cavicularin was isolated with riccardin C **1.5**, a macrocyclic bisbibenzyl found in a variety of liverwort species from the same family. Thus far, (+)-cavicularin has been found only in *Cavicularia densa* Steph. (Blasiaceae), and not alongside riccardin C in other liverworts. Interestingly, *Blasia pusilla* (Blasiaceae), a liverwort from which riccardin C is also isolated, produces a number of dimers of riccardin C, named pusilatins A–D **1.5i–iv** (Figure 6b).[7] These have not been identified in *C. densa*.[6]

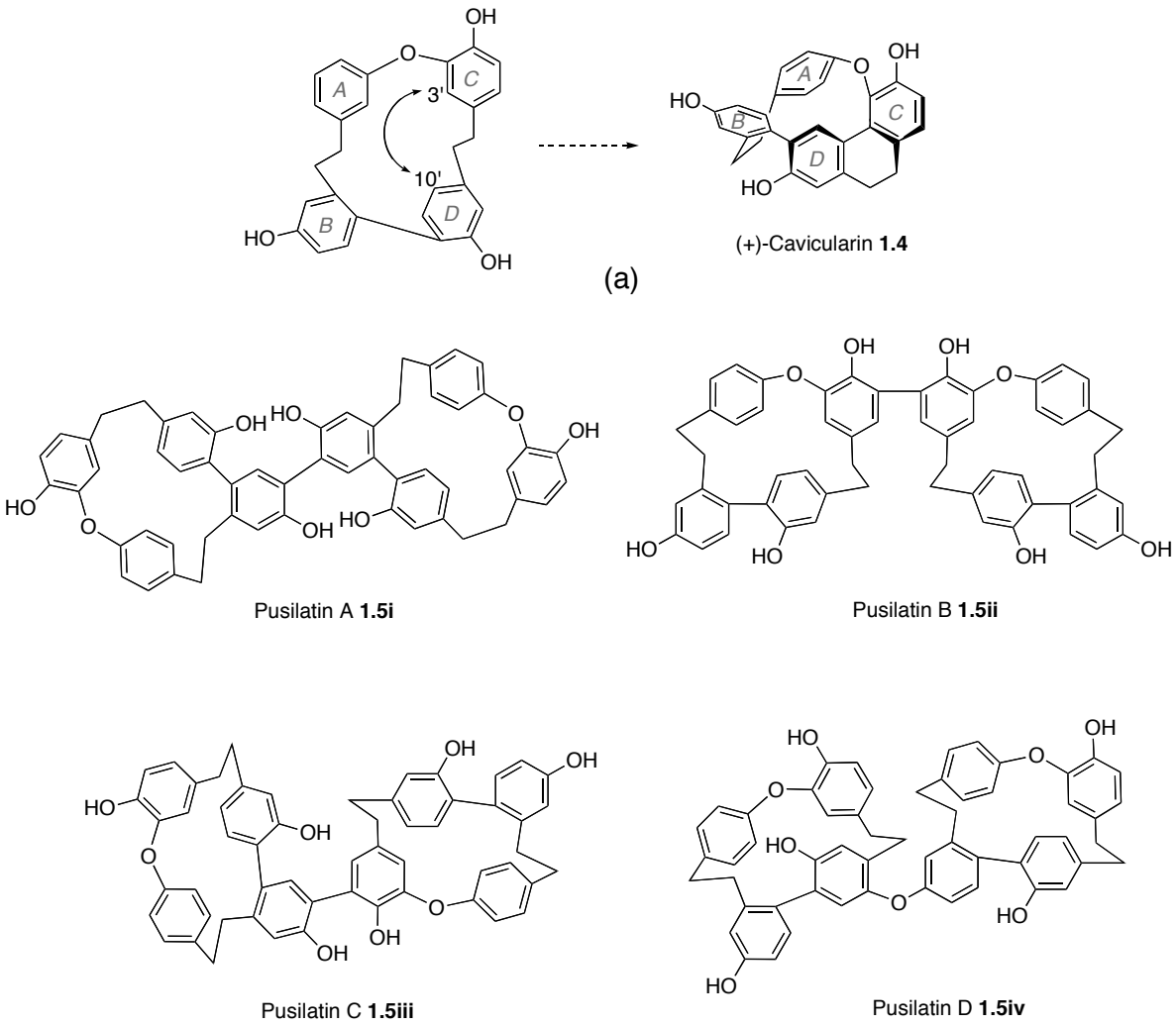
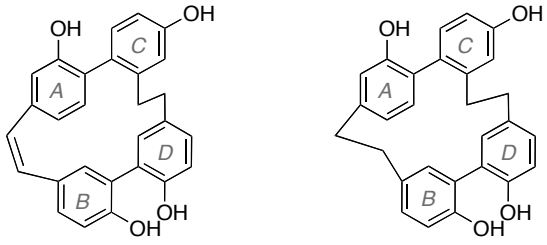


Figure 6

It is speculated that *C. densa* might generate (+)-cavicularin through an intramolecular oxidative phenolic coupling between the 3' and 10' positions of riccardin C **1.5**. Conversely, the pusilatins A–D are thought to be biosynthesised by intermolecular coupling between two molecules of riccardin C **1.5**. It is believed that these different biosynthetic pathways are specific to each species.[6]

1.2.1b Isoplagiochin C

Isoplagiochin C **1.3** and the related natural product isoplagiochin D **1.6**, which lacks the *cis*-stilbene functionality of **1.3**, are two further macrocyclic bisbibenzyls isolated from liverworts (Figure 7).[5] At first glance, isoplagiochins C and D could appear to be achiral. Though possessing two biaryl axes, the small phenol moieties in the *ortho* and *ortho'* positions of arenes *B* and *D* would not be expected to impart configurational stability. This assumption is afforded credence by the observation that natural samples isolated from the liverwort *Plagiochilla fruticosa* were optically inactive.[5]



Isoplagiochin C **1.3** Isoplagiochin D **1.6**

Figure 7

In 1995, Nógrádi *et al*. investigated the possibility of relatively stable chiral conformations of macrocyclic bisbibenzyls,[8] noting that *"it is apparent that any of their non-planar conformations is asymmetric."* Their study resulted in the detection of enantiomeric conformations of macrocyclic bisbibenzyls by X-ray analysis, NMR and chiral HPLC experiments, and a degree of separation for some samples on analytical scale chiral HPLC columns. The authors concluded that information about the chiroptical properties of a natural product of this class would give a valuable insight into its biosynthesis.

Subsequently, isoplagiochin C **1.3** from *Lepidozia incurvata* showed optical activity with a reported $[\alpha]_D$ of +42.5 (*c* 0.2, MeOH).[9] More recently, isoplagiochins C **1.3** and D **1.6** were isolated as optically active samples from *Herbertus sakuraii,* in this instance with $[\alpha]_D$ values of +74.8 and +47.5, respectively (*c* 0.67, MeOH).[10] As with (+)-cavicularin, the CD spectra indicated the presence of atropisomers.[11]

Bringmann *et al*. have published a comprehensive study of the stereochemical features of isoplagiochin C **1.3**, drawing on extensive NMR and CD studies and computational molecular dynamics (MD) experiments.[11] They concluded that isoplagiochin C **1.3** owes its chirality to the presence of two biaryl axes and a helical subunit whose configurational stability is greatly enhanced by its cyclic array. Much like (+)-cavicularin, its optical activity is due to axial and planar chirality.

The biaryl axis labeled **A**, was identified as the most stable of the three stereogenic elements, with an atropisomerisation barrier not overcome at room temperature. The isomerisation barriers of the biaryl axis labeled **B** and the helical stilbene moiety labeled **C** are considerably lower, resulting in a mixture of interconverting diastereomers for each of the two enantiomeric series of molecules (Figure 8).

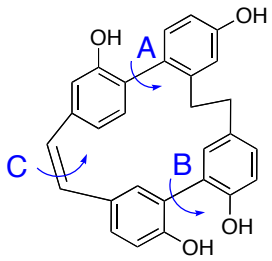
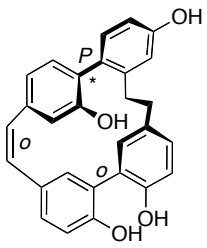


Figure 8 – Possible conformational barriers A, B and C in isoplagiochin C **1.3**.

In this study, Bringmann *et al*. used a natural sample of isoplagiochin C **1.3** isolated from *Plagiochila deflexa*. They found that isoplagiochin C **1.3** from *Plagiochila deflexa* is not enantiomerically pure, occurring in an 85:15 ratio of enantiomers. Interestingly, it is laevorotatory, opposite to that from *Lepidozia incurvata* and *Herbertus sakuraii*, with an $[\alpha]_D$ of –49.0 (*c* 0.75, MeOH).

Using conformational analysis and MD studies, Bringmann *et al*. were able to use quantum chemical CD calculations to assign the absolute configuration of the major enantiomer of isoplagiochin C **1.3** isolated from *Plagiochila deflexa* and establish the main stereoisomer as *P*-configured at axis **A** (Figure 9). The calculations also showed that the helical structure of **1.3** is responsible for the observed CD spectrum. The energetic barrier for enantiomerisation was deduced experimentally to be 101.6 kJ/mol and theoretically calculated at 115.1 kJ/mol.



Isoplagiochin C **1.3**

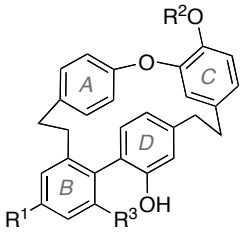
Figure 9 – Absolute configuration of (–)-isoplagiochin C **1.3** from *P. deflexa* (*o* = configurationally unstable, one of the most stable diastereomers is shown; * = configurationally stable).

Other natural products in this class of macrocyclic bisbibenzyls have also been shown to exhibit optical activity, notably some other isoplagiochins, bazzanins and marchantins.[9, 12, 13] The molecules are not typically isolated in enantiopure form, with the enantiomeric ratio varying with natural source and isolation procedure.

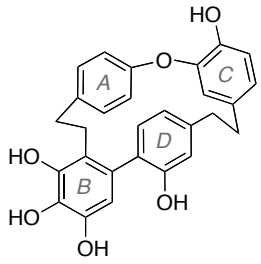
1.2.2a Riccardins, Isoriccardins and Asterelins

The riccardin family of macrocyclic bisbibenzyls, with the exception of riccardin B **1.13**, all feature one diphenyl ether and one biphenyl linkage.[14-17] The *A* ring is invariably *para*-disubstituted (Figure 10). These natural products are found in a variety of liverwort species and were first reported in the 1980s, with the most recent addition to this group, isorricardin D [*sic*]*, reported in 2007.[16] Riccardin C **1.5** is noteworthy as the only macrocyclic bisbibenzyl to date to be isolated from a source other than a bryophyte. In 2007 Kosenkova *et al*. identified it as a constituent of the heptane/acetone extract of a primrose collected in the Altai Republic, a federal subject of Russia.[3]

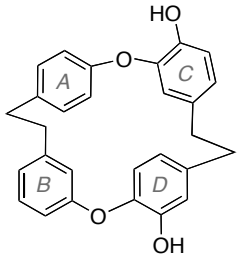
*Hereafter referred to isoriccardin D in accordance with the established naming conventions for this class.



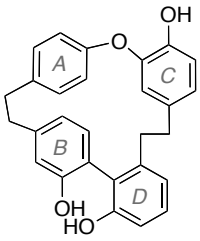
		R^1	R^2	R^3
1.7	Riccardin A	OMe	H	H
1.5	Riccardin C	OH	H	H
1.8	Riccardin D	H	H	OH
1.9	Riccardin E	H	H	OMe
1.10	Riccardin F	OH	Me	H
1.11	Riccardin G	H	Me	H



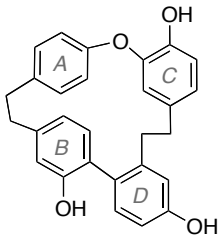
1.12 Riccardin H



1.13 Riccardin B



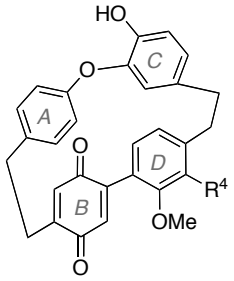
1.14 Isoriccardin C



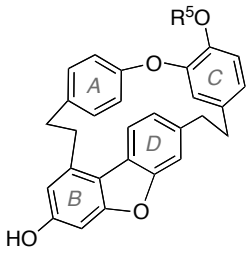
1.15 Isoriccardin D

Figure 10

In 2002, Cui *et al*. reported the isolation of two quinone riccardin C derivatives from the Hong Kong liverwort *Marchantia paleacea*, in addition to marchantin C **1.22** and isoriccardin C **1.14**. These new compounds were named isoriccardinquinone A **1.16** and B **1.17** (Figure 11).[18] Subsequently, Lou *et al*. reported the first examples of dibenzofuran bisbibenzyls from the liverwort *Asterella angusta*, collected in Sichuan Province, China.[19] These compounds were named asterelin A **1.18** and B **1.19**. The authors established that the compounds were true natural products and not artefacts by HPLC-UV analysis of the cold diethyl ether extract of *A. angusta* (Figure 11).



		R^4
1.16	Isoriccardinquinone A	OH
1.17	Isoriccardinquinone B	H

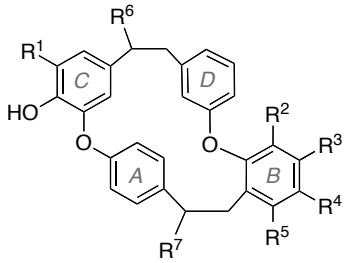


		R^5
1.18	Asterelin A	H
1.19	Asterelin B	Me

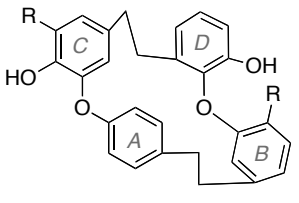
Figure 11

1.2.2b Marchantins, Isomarchantins and Pakyonol

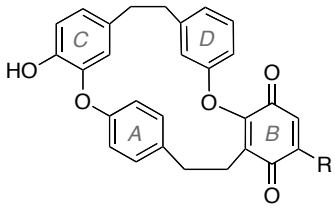
The marchantins represent one of the largest and most frequently isolated families of the macrocyclic bisbibenzyl class, and are characterised by a common bis-diphenyl ether parent structure (Figure 12).[12, 20, 21] They are predominantly isolated from the *Marchantiales* genus of bryophyte. The isomarchantins feature a similar structure, with the connectivity pattern of the *B* and *D* rings the opposite to that found in the marchantins.[20, 22] In addition, two related quinonoid structures, marchantin N **1.36** and marchantinquinone **1.37** have been isolated and identified.[23]



		R1	R2	R3	R4	R5	R6	R7
1.20	Marchantin A	OH	OH	H	H	H	H	H
1.21	Marchantin B	OH	OH	OH	H	H	H	H
1.22	Marchantin C	H	OH	H	H	H	H	H
1.23	Marchantin D	OH	OH	H	H	H	OH	H
1.24	Marchantin E	OH	OH	H	H	H	OMe	H
1.25	Marchantin F	OH	OH	OH	H	H	OH	H
1.26	Marchantin G	OH	OH	H	H	H	=O	H
1.27	Marchantin H	H	OH	OH	H	H	H	H
1.28	Marchantin I	H	H	H	OMe	H	H	H
1.29	Marchantin J	OH	OH	H	H	H	OEt	H
1.30	Marchantin K	OH	OH	OH	H	OMe	H	H
1.31	Marchantin L	OH	OH	H	H	H	H	OH
1.32	Marchantin M	H	OMe	H	H	OH	H	H
1.33	Marchantin O	H	OMe	H	H	H	H	H



		R
1.34	Isomarchantin B	OH
1.35	Isomarchantin C	H

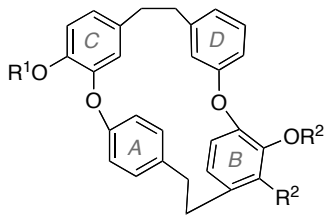


		R
1.36	Marchantin N	OMe
1.37	Marchantinquinone	H

Figure 12

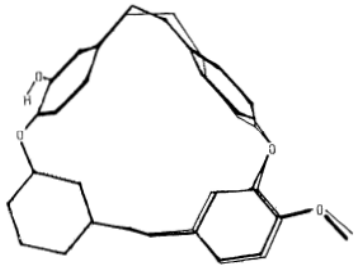
A related series of natural products of the bis-diphenyl ether type is characterised by two *para*-substituted aromatic rings, and comprises neomarchantins A **1.39** and B **1.40** and pakyonol **1.38**.[17, 24] This two *para* two *meta* arrangement forces some unusual bond angles, as observed in the solid state structure of pakyonol, assigned by Böcskei and Kesurü using molecular modelling calculations and X-ray crystallography.[25] The structure proposed by their molecular modelling calculations is shown in Figure 13b. They concluded that:

- The *meta*-substituted rings (*C* and *D*) are nearly coplanar in geometry, with the connecting ethano bridge in an antiperiplanar conformation.
- The planes of the *meta*- and *para*-substituted rings (*i.e. A* and *C* and *B* and *D*) are perpendicular. The connecting ethereal oxygen atoms appear to show slight delocalisation of their non-bonding pairs, deduced by bond angles and bond lengths.
- The para-substituted rings (*A* and *B*) form an angle of 78° in the disordered crystal structure. The connecting ethano bridge is in a gauche conformation.



		R^1	R^2
1.38	Pakyonol	Me	H
1.39	Neomarchantin A	H	H
1.40	Neomarchantin B	H	OH

Figure 13a

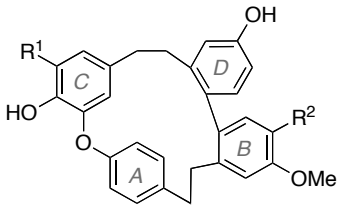


Superposition of the two lowest-energy conformers of pakyonol **1.38** as calculated by Böcskei and Kesurü.

Figure 13b[25]

1.2.2c Plagiochins, Isoplagiochins and Planusin

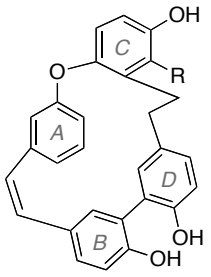
Four members of the plagiochin family, plagiochins A to D **1.41**–**1.44**, were isolated in the late 1980s by Asakawa and co-workers from *Plagiochila acantophyllya japonica*.[26] They all feature a common skeletal structure containing one diphenyl ether and one biaryl linkage, with a *para*-substitution pattern at the *A* ring (Figure 14).



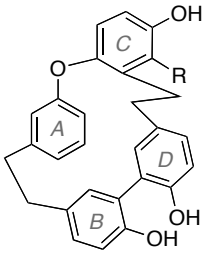
		R^1	R^2
1.41	Plagiochin A	OH	OH
1.42	Plagiochin B	OH	H
1.43	Plagiochin C	H	OH
1.44	Plagiochin D	H	H

Figure 14

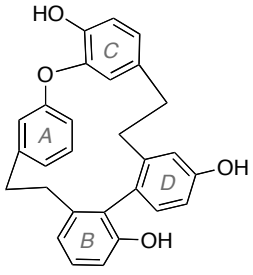
The isoplagiochin class is perhaps the most interesting single nominal family of the macrocyclic bibisbenzyl class, boasting some of the most atypical and diverse structures (Figure 15a and b).[5, 27] Isoplagiochin C **1.3** has already been discussed at length (see Section 1.2.1b) and, with isoplagiochins A **1.2** and B **1.45**, is remarkable for the unsaturation exhibited in one of the ethano chains. This olefin is invariably *cis* in geometry and has also been noted in planusin A **1.50**, a regioisomer of isoplagiochin A **1.2**, isolated from the liverwort *Heteroscyphus planus*.[28] Isoplagiochin C **1.3** differs further, lacking the ubiquitous ethereal *AC* linkage. Isoplagiochins A **1.2** and B **1.45** are also notable for their *meta*-connectivity at the *A* ring. Fully saturated analogues of isoplagiochins A **1.2**, B **1.45** and C **1.3** have all been identified and are named isoplagiochins E **1.46**, F **1.47** and D **1.6** respectively (Figures 15a and b).[5, 29] Isoplagiochin G **1.49**, an aroyl derivative of isoplagiochin B **1.45**, has also been reported.[30]



		R
1.2	Isoplagiochin A	H
1.45	Isoplagiochin B	OH

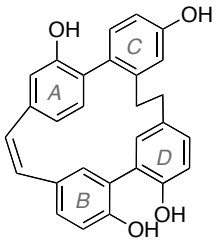


		R
1.46	Isoplagiochin E	H
1.47	Isoplagiochin F	OH

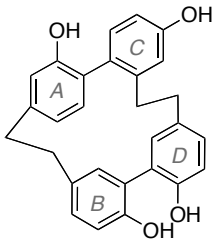


1.48 Plagiochin E

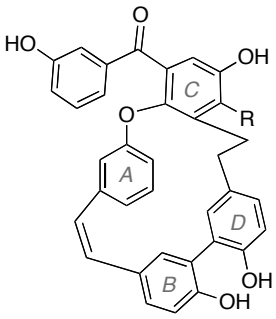
Figure 15a



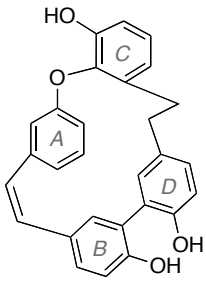
1.3 Isoplagiochin C



1.6 Isoplagiochin D



1.49 Isoplagiochin G

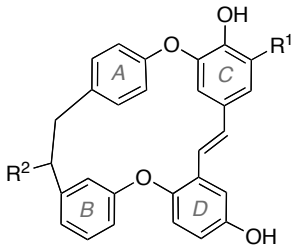


1.50 Planusin A

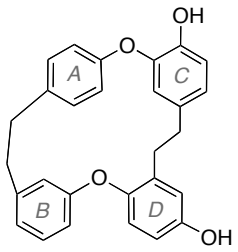
Figure 15b

1.2.2d Ptychantols

Macrocyclic bisbibenzyls featuring a *trans*-stilbene have also been reported by Asakawa *et al*. with the isolation and structural elucidation of ptychantol A **1.51**, B **1.52**, and C **1.53** from the liverwort *Ptychanthus striatus*.[31] These macrocyclic bisbibenzyls are of the bis-diphenyl ether sub-class and have isomarchantin-like structures. The saturated analogue of ptychantol A, dihydroptychantol A **1.54**, was isolated at a later stage from *Asterella angusta* (Figure 16).[19] These compounds are reported to have an $[\alpha]_D$ of zero at room temperature, although no comment is made on the achirality or racemic nature of the samples.



		R^1	R^2
1.51	Ptychantol A	H	H
1.52	Ptychantol B	OH	H
1.53	Ptychantol C	OH	OH

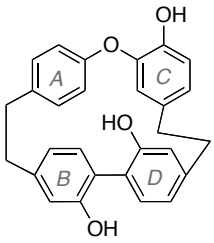


1.54 Dihydroptychantol A

Figure 16

1.2.2e Polymorphatins

In 2007, during a study of the ethereal extract of *Marchantia polymorpha L.*, Lou *et al*. identified a new type of macrocyclic bisbibenzyl, alongside the novel isoriccardin D **1.15** and several known natural products of this class.[16] Named polymorphatin A **1.55** (Figure 17), it features three *para*-connected aromatic rings, with the *C* ring alone having a *meta*-connectivity.

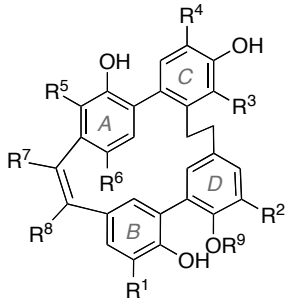


1.55 Polymorphatin A

Figure 17

1.2.2f Bazzanins

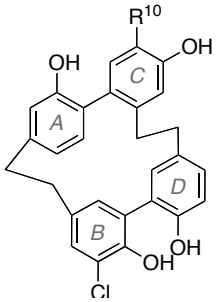
The bazzanins are a family of chlorinated macrocyclic bisbibenzyls based in the most part on the isoplagiochin C/D skeleton.[9, 13, 29] The only exception to this is bazzanin K **1.74**, which contains a phenanthrene subunit and is one of only two molecules in this class to exhibit a fused carbon ring system, the other being cavicularin **1.4** (see Section 1.2.1a).[9]



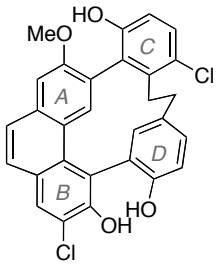
1.56-1.64 Bazzanin A-I
1.65-1.71 Bazzanin L-R

		R1	R2	R3	R4	R5	R6	R7	R8	R9
1.56	Bazzanin A	Cl	H	H	H	H	H	H	H	H
1.57	Bazzanin B	Cl	H	H	H	H	H	Cl	H	H
1.58	Bazzanin C	Cl	H	H	Cl	H	H	Cl	H	H
1.59	Bazzanin D	Cl	H	H	H	Cl	H	Cl	H	H
1.60	Bazzanin E	Cl	H	H	Cl	Cl	H	Cl	H	H
1.61	Bazzanin F	Cl	H	Cl	H	H	Cl	Cl	H	H
1.62	Bazzanin G	Cl	Cl	Cl	H	Cl	H	Cl	H	H
1.63	Bazzanin H	Cl	H	Cl	H	Cl	Cl	Cl	H	H
1.64	Bazzanin I	Cl	Cl	H	Cl	Cl	Cl	Cl	H	H
1.65	Bazzanin L	H	H	Cl	Cl	Cl	H	H	H	Me
1.66	Bazzanin M	H	H	Cl	Cl	Cl	H	H	H	H
1.67	Bazzanin N	H	Cl	Cl	Cl	Cl	H	H	H	H
1.68	Bazzanin O	Cl	H	Cl	Cl	Cl	Cl	H	H	Me
1.69	Bazzanin P	Cl	Cl	Cl	Cl	Cl	H	H	H	H
1.70	Bazzanin Q	Cl	Cl	Cl	Cl	Cl	Cl	H	H	H
1.71	Bazzanin R	Cl	Cl	Cl	Cl	Cl	Cl	Cl	Cl	H

Figure 18a



		R^{10}
1.72	Bazzanin J	Cl
1.73	Bazzanin S	H

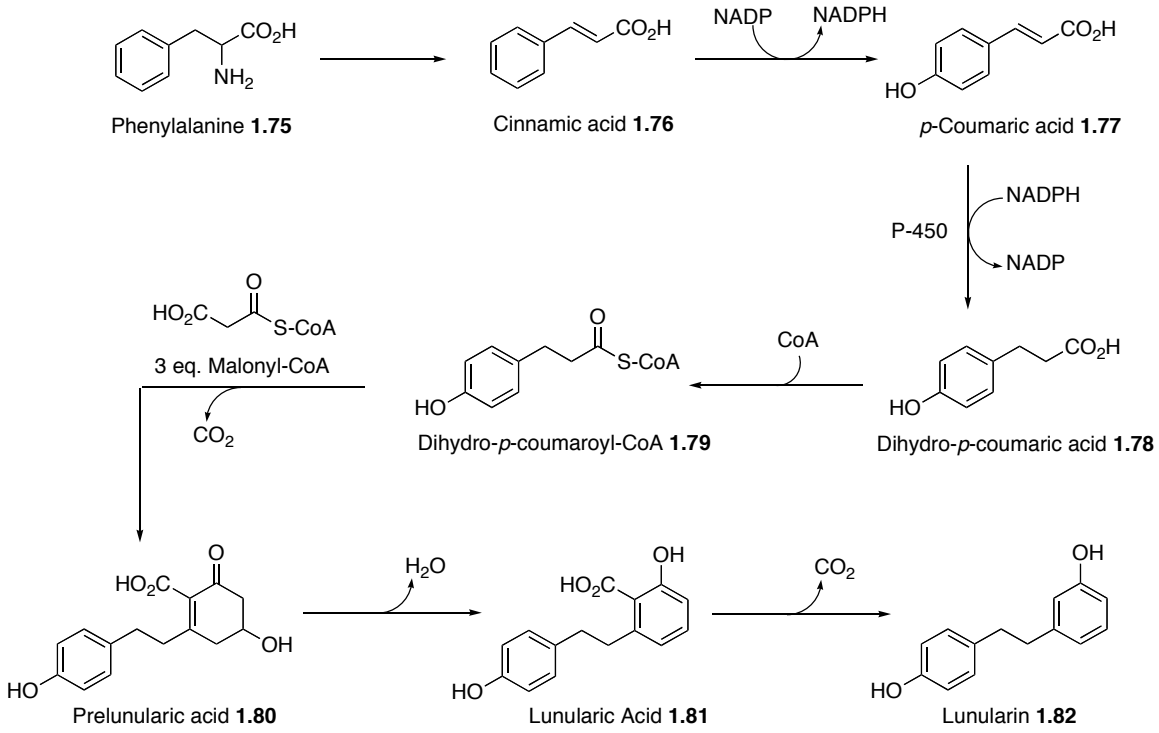


1.74 Bazzanin K

Figure 18b

1.3 Biosynthesis of Macrocyclic bisBibenzyls

Asakawa has proposed a biosynthesis of macrocyclic bisbibenzyls from lunularin **1.82**, which is found in all liverwort species from which bisbibenzyls have been isolated.[32] Pryce established that an enzyme specific to liverworts is responsible for the generation of lunularin **1.82** from lunularic acid **1.81** and a biosynthesis proposed by Friederich *et al*. of lunularin from phenylalanine is shown below (Scheme 1).[33, 34]

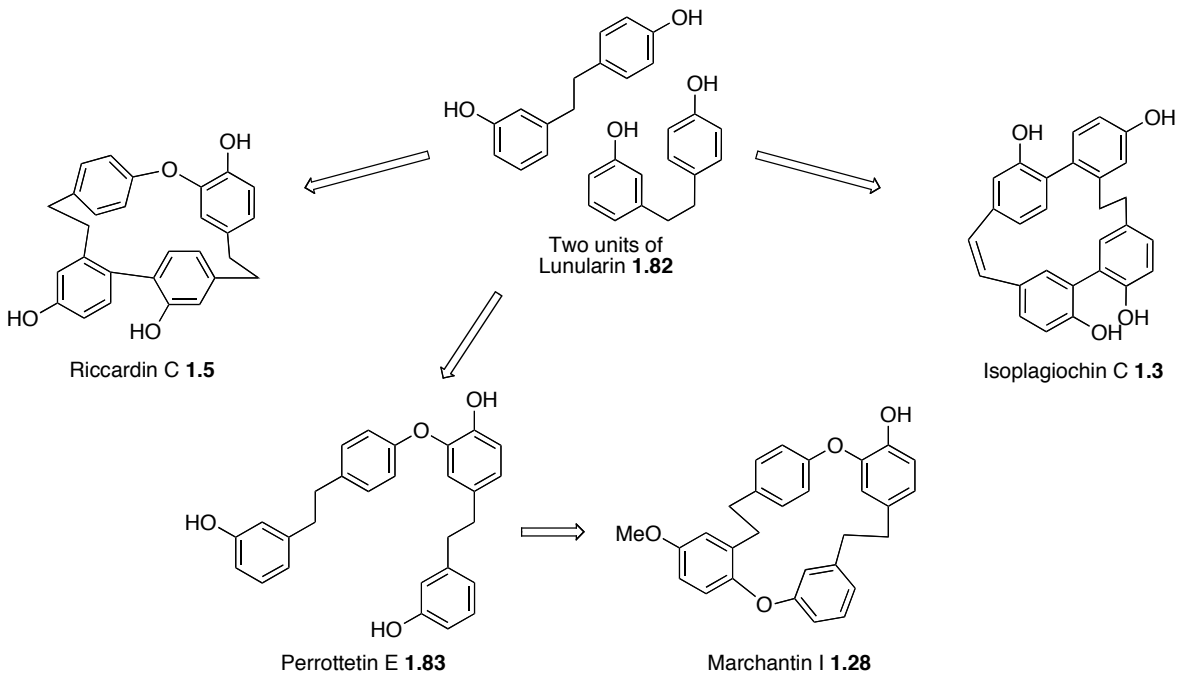


Scheme 1

Phenylalanine **1.75** is transformed into cinnamic acid **1.76** by phenylalanine ammonia lyase (PAL). Cinnamic acid-4-hydroxylase then catalyses the formation of *p*-coumaric acid **1.77**, followed by reduction to dihydro-*p*-coumaric acid **1.78**. The steps to generate prelunularic acid **1.80** have yet to be established conclusively at the enzymatic level, but are thought to involve three units of malonyl-CoA. Enzymatic decarboxylation of lunularic acid affords lunularin, a two arene building block for the bisbibenzyls (Scheme 2).

Union and manipulation of two units of lunularin **1.82** through various enzyme-catalysed couplings, oxidations/reductions and methylations is widely accepted as

the biosynthetic route to the perrottetins, isolated from liverworts by Asakawa, and the other families of macrocyclic bisbibenzyls (Scheme 2). Asakawa *et al*. have used precursor feeding experiments using isotope-labelled substrates to show that lunularic acid **1.81** is the sole substrate for the biosynthesis of marchantin C.[34]



Scheme 2

The biosynthetic pathway of halogenation of macrocyclic bisbibenzyls to afford the bazzanins was not initially clear, with some speculation that the bazzanins were in fact artefacts of external factors outside the liverwort. To establish conclusively the origin of the bazzanins, Speicher *et al*. investigated the *in vitro* reactions between a synthetic sample of isoplagiochin C **1.3** and a chemoenzymatic chloroperoxidase solution of KCl/H_2O_2 in a buffered aqueous medium. MALDI-TOF Mass spectrometry analysis of these reactions indicated the presence of bazzanins.[35] Speicher *et al.* subsequently reported the detection of chloroperoxidase in bryophytes.[36] This research offers sufficient evidence to conclude that the bazzanins are genuine natural products produced by the liverwort or an endosymbiotic metabolism.

1.4 Biological Activity of Macrocyclic bisBibenzyls

Traditional medicine in the Far East utilises a wide variety of lichens, mosses, ferns and some liverwort species. Liverworts of the genus *Marchantiales* are extensively used as components in Japanese folk medicine. Extracts from liverworts are typically applied in four therapeutic areas: diuretics, anti-tumour agents, antibacterial agents and antifungal agents. It was this evidence for biological activity which prompted Asakawa and his co-workers to launch a systematic study of the active constituents of liverwort species indigenous to Japan, ultimately leading to the isolation and study of the macrocyclic bisbibenzyls.[4, 32]

1.4.1 Marchantins and Riccardins

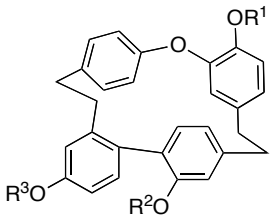
The marchantins and riccardins have been the focus of considerable biological investigation and pharmacological testing, exhibiting diverse and often potent biological activity. Marchantin A **1.20** displays antibacterial and antimycotic effects against a variety of microorganisms (MIC values of 3.13–100 μg/mL), while marchantins A **1.20**, D **1.23** and E **1.24** and riccardin A **1.7** inhibit 5-lipoxygenase (**1.7** inhibits at 4 μM) and calmodulin (ID_{50} values: **1.20**=1.85 μg/mL, **1.23**=6 μg/mL, **1.24**=7 μg/mL and **1.7**=20 μg/mL).[17, 37]

In addition, marchantins A **1.20** and B **1.21** and a number of riccardins showed cytotoxic effects in P-388 mouse leukaemia cells, as well as in KB cell lines originating from nasopharyngeal carcinomas.[4, 15] Marchantin C **1.22** has recently been discovered to have powerful inhibitory effects on cell growth (human glioma A 172 cells), triggering apoptosis. Subsequently, a 59% relative decrease in tumour size in murine models at doses of 20 mg/kg of **1.22** was reported.[38] Asakawa *et al*. have also reported that some riccardins stimulated the growth of nerve endings in the central nervous system and that marchantin A tri-*O*-methyl ether exhibited skeletal muscle relaxation effects.[32]

In 2005 Nishimaki-Mogami, Asakawa and co-workers identified riccardin C **1.5** as a partial liver X receptor (LXR) α agonist and LXRβ antagonist, and riccardin F **1.10** as an LXRα antagonist. These LXRs play a critical role in maintaining lipid

homeostasis by coordinatively regulating several genes involved in the efflux, transport and excretion of cholesterol. The authors found that riccardin C **1.5** exhibited atypical activity when compared to other synthetic LXR agonists,[39] leading them to claim that "*riccardin C may provide a novel tool for identifying subtype-function and drug development*."

This research resulted in a collaborative effort between Asakawa and Fukuyama and their co-workers to establish the role of the phenolic hydroxy groups of riccardin C **1.5** in its activity as an LXRα agonist.[40] Synthetic samples of riccardin C **1.5** and its seven selectively *O*-methylated analogues (Figure 19) were tested, with results indicating that all three phenolic moieties are needed for activity. This conclusion was supported by research by Dodo *et al*., which tested riccardin C analogues lacking oxygenation on each ring in turn. No analogue exhibited the same potency as riccardin C **1.5**.[41]



		R^1	R^2	R^3
1.5	Riccardin C	H	H	H
1.7	Riccardin A	H	H	Me
1.84		H	Me	H
1.10	Riccardin F	Me	H	H
1.85		H	Me	Me
1.86		Me	H	Me
1.87		Me	Me	H
1.88		Me	Me	Me

Figure 19

1.4.2 Plagiochins, Isoplagiochins and Bazzanins

Though the marchantins and riccardins have been the main focus of biological studies, there are noteworthy reports of diverse biological activity in other families of macrocyclic bisbibenzyls. Plagiochin A **1.41**, for example, is reported to display interesting neurotrophic activity in the culture of the cerebral hemisphere of a foetal rat, showing both acceleration of neurite sprouting and enhancement of chlorine acetyl transferase activity.[42] Reports of biological activity within the isoplagiochin series are limited to discussion of antifungal activity, with isoplagiochin D **1.6** displaying resistance against *Botrytis cinerea*, *Cladosporium cucumerinum*, *Pyricularia oryzae*, *Phythophthora infestans*, and *Septoria tritici* with IC_{50} values of 14.2, 11.4, 4.1, 0.9, and 10.0 mg/mL, respectively.[43] Similarly, members of the

bazzanin family have been reported to display antimicrobial activity against fungi and bacteria.[13]

1.5 Macrocyclisation Strategies in the Synthesis of Riccardin C and other Macrocyclic bisBibenzyls

Macrocyclisation can be a difficult synthetic endeavour. Blankenstein and Zhu, in a recent review of macrocyclisation methods, noted that "*most of the cyclisation reactions reported in the literature are effected under conditions of high dilution. However, the inefficiency in bringing head and tail together often leads to prolonged reaction times and side-reactions, for example, cyclodimerisation*".[44] It is therefore no surprise that the most frequently discussed difficulty in macrocyclic bisbibenzyl syntheses is the cyclisation step.

Considering riccardin C **1.5** as an example, macrocyclisation could in theory be effected at any linkage point in the molecule: at the ethereal bond between the *A* and *C* rings, at the biaryl bond between the *B* and *D* rings, or at either ethano bridge. It is this final strategy which has proved most popular in the published syntheses of natural products in this class, with most key macrocyclisation steps occurring at one of the ethano bridges. There are, however, some examples of macrocyclisation at the biaryl bond, invariably using palladium-catalysed aryl-aryl cross coupling methodology. To date, there have been no reported syntheses of macrocyclic bisbibenzyls which effect macrocyclisation at the ethereal *A*-*C* linkage, although similar Ullmann-type cyclisations have been reported in the total synthesis of other macrocyclic natural products. Figure 20 summarises the strategies used in published syntheses of riccardin C **1.5**.

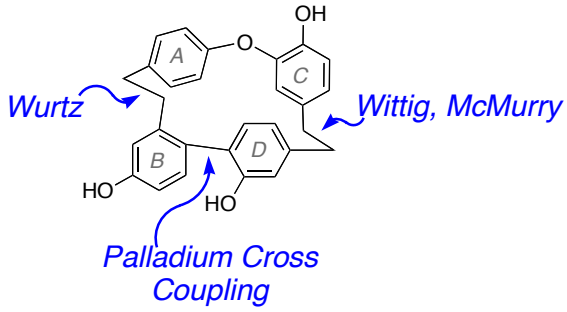
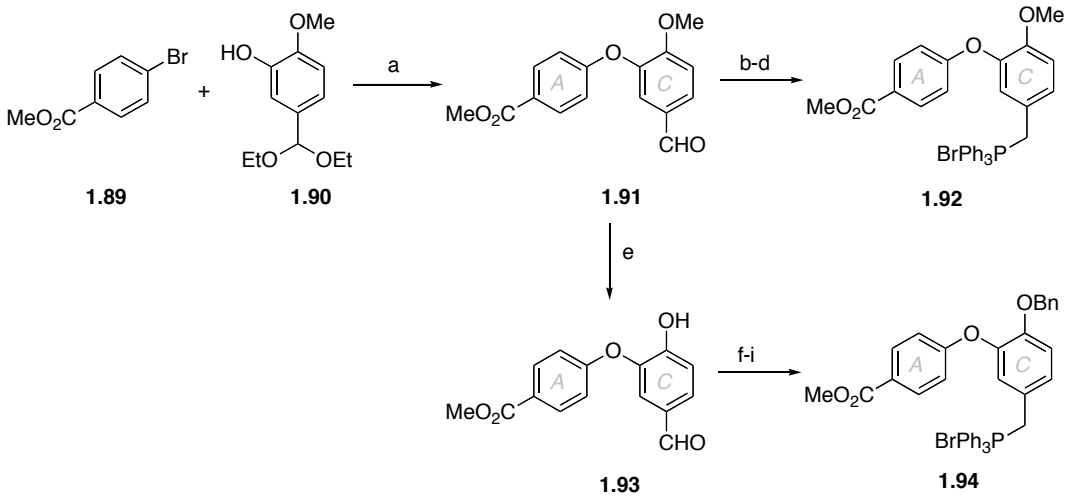


Figure 20 – Summary of the position and method of macrocyclisation in riccardin C syntheses.

1.5.1 The Wurtz Reaction

The Wurtz reaction is the sodium-mediated coupling of two alkyl halides to afford an alkane, and has been used to great effect by Nógrádi and co-workers in their syntheses of macrocyclic bisbibenzyls, including the first total synthesis of riccardin C **1.5** in 1988.[45, 46] Their synthesis of *AC* fragments **1.92** and **1.94** began using an Ullmann ether synthesis with aldehyde deprotection occurring in the work up *viz.* **1.90**→**1.91**. Straightforward reduction and functional group manipulation then gave **1.92**. An alternative protecting group strategy was used to allow access to riccardin A **1.7** *via* **1.94** (Scheme 3).

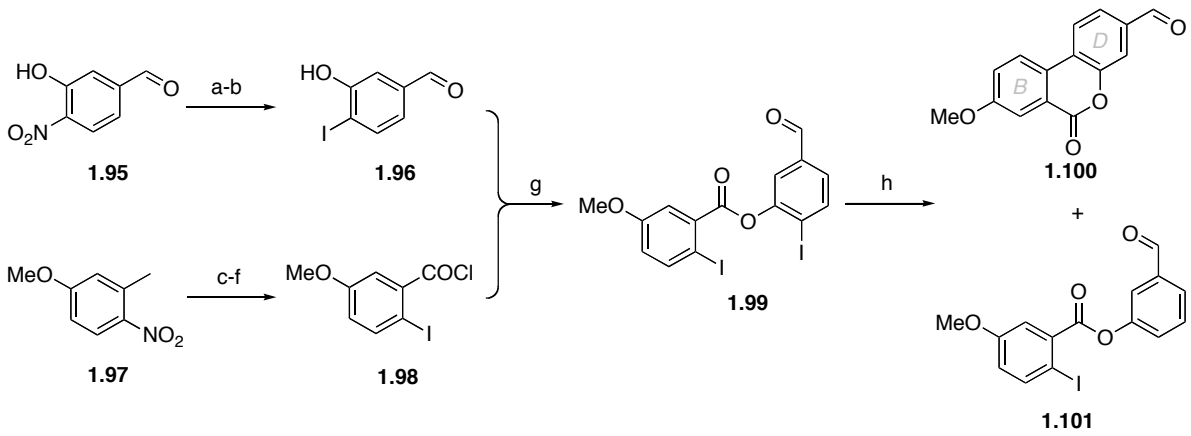


1.89 **1.90** **1.91** **1.92** **1.93** **1.94**

a). CuO, K_2CO_3, 30%; b). $NaBH_4$, 90%; c). aq. HBr; d). PPh_3, 76%; e). $AlCl_3$, 73%; f). BnCl, K_2CO_3, 60%; g). $NaBH_4$; h). PBr_3; i). PPh_3, 84%.

Scheme 3

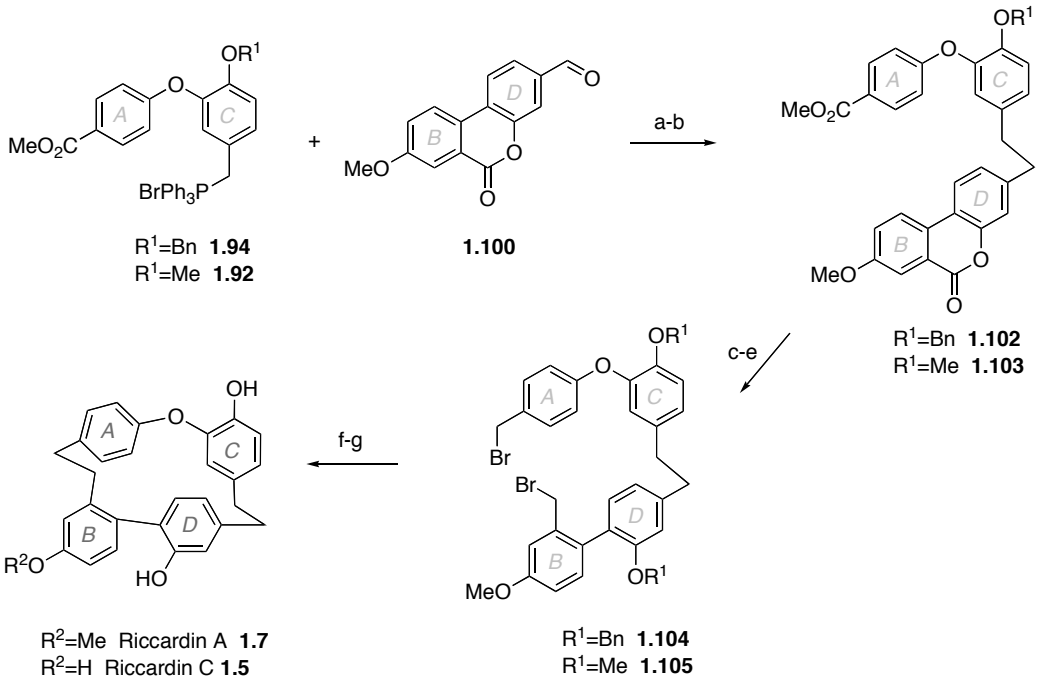
BD Fragment **1.100** presents a more interesting synthetic approach, showcasing a nickel(0)-assisted intramolecular aryl-aryl bond formation from diiodide **1.99** to lactone **1.100**. This reaction proceeded in low yield (17%), with selective deiodination (*viz.* **1.99**→**1.101**, 30%) proving the favoured reaction pathway. The synthesis of diiodide **1.99** was not in itself without difficulty, with sequential nitro-group reduction and Sandmeyer reactions of **1.95** giving iodide **1.96** in 20% yield over the two steps (Scheme 4). With fragments **1.92** and **1.94** and **1.100** in hand, their union was achieved using Wittig chemistry followed by hydrogenation to **1.102** and **1.103** (Scheme 5). Simultaneous reduction of both the lactone and ester functionalities, followed by protection of the unmasked phenol and bis-bromination of the resultant diols gave **1.104** and **1.105**.



a). $SnCl_2.2H_2O$, HCl; b). $NaNO_2$, NaI, 20% over 2 steps; c). Pd/C, H_2; d). $NaNO_2$, KI, 60% over 2 steps; e). $KMnO_4$, 54%; f). $SOCl_2$ followed by g). **1.96** + **1.98**, 63% over two steps; h). $Ni(PPh_3)_4$, 17% **1.100** with 30% **1.101**.

Scheme 4

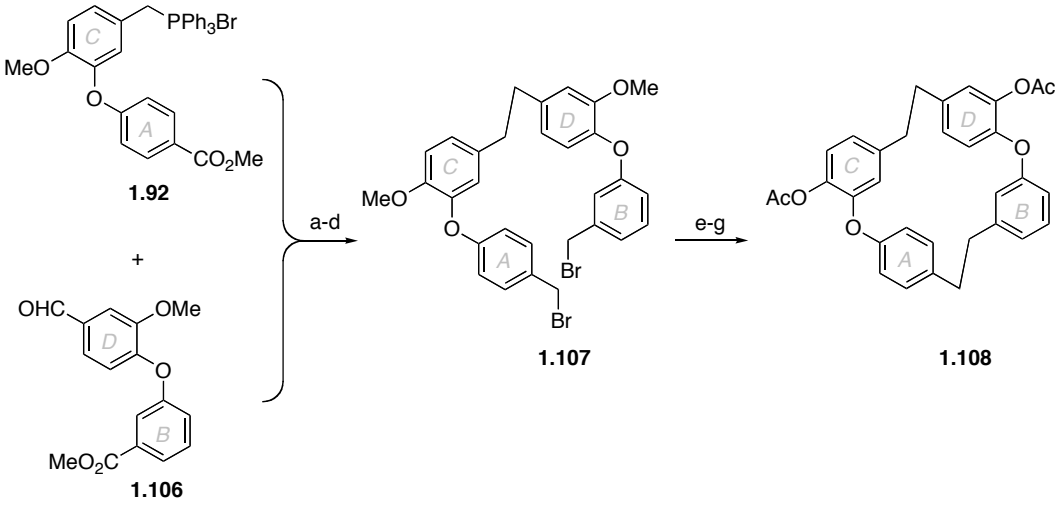
Treatment of dibromide **1.105** with sodium metal and tetraphenylethene then effected cyclisation in a modest 37% yield. Finally, deprotection gave riccardin C **1.5** in 14 steps (Scheme 5). The Wurtz coupling of riccardin A precursor **1.104** did not proceed as efficiently, with the reaction conditions inducing partial and total debenzylation. Complete debenzylation of the crude product then gave riccardin A **1.7** in 15% yield over both steps. These represented the first total syntheses of riccardins A **1.7** and C **1.5**, but are both very low in overall yield.[46]



Riccardin A: a). NaOMe, 64%; b). Pd/C, H_2, 100%; c). $LiAlH_4$, 80%; d). BnBr, 91%; e). PBr_3, 100%; f). Na, $(Ph_2C)_2$; g). BBr_3, 15% over 2 steps.
Riccardin C: a). NaOMe; b). Pd/C, H_2, 55% over 2 steps; c). $LiAlH_4$; d). CH_2N_2, 30% over 2 steps; e). PBr_3, 100%; f). Na, $(Ph_2C)_2$, 30%; g). BBr_3, 37%.

Scheme 5

In the same publication, the authors report the total synthesis of riccardin B **1.13**. The *AC*, and in this case *BD*, fragments **1.92** and **1.106** were again obtained *via* Ullmann ether formation and subsequent reduction and functional group manipulation. Union of the two *via* Wittig chemistry gave dibromide **1.107** following hydrogenation, reduction and treatment with phosphorus tribromide. Cyclisation as described above gave riccardin B dimethyl ether as the only isolable product in 27% yield. Deprotection with boron tribromide completed the total synthesis, although the compound was characterised at the diacetate (Scheme 6). A similar synthetic strategy has also been used by Nógrádi *et al*. to complete the total synthesis of pakyonol **1.38**.[47]

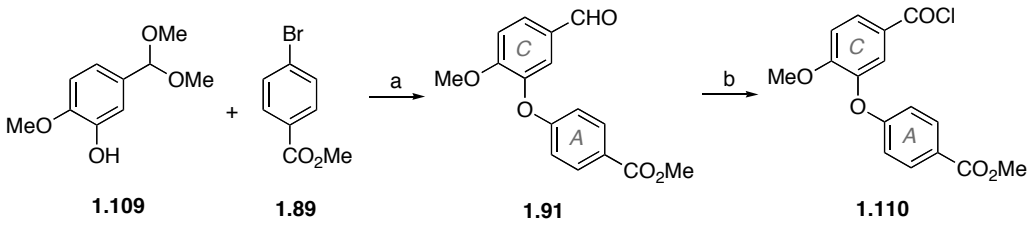


a). NaOMe, 55%; b). H_2, 100%; c). $LiAlH_4$, 87%; d). PBr_3, 100%; e). Na, $(Ph_2C)_2$, 27%; f). BBr_3; g). Ac_2O, 60% over 2 steps.

Scheme 6

Bis-benzyl bromide **1.107** had already featured in a total synthesis of riccardin B **1.13**, with Iyoda *et al*. reporting a nickel-catalysed intramolecular macrocyclisation in 1988.[48] Their approach began with the synthesis of *AC* and *BD* fragments **1.110** and **1.112** as detailed in Schemes 7 and 8. Union of these was achieved using a Fujisawa modified Negishi reaction followed by a Clemmensen reduction with sequential treatment with lithium aluminium and thionyl chloride affording **1.114**. This underwent cyclisation to give the desired product under high dilution conditions in the presence of a reported active nickel complex, prepared *in situ* from $NiBr_2(PPh_3)_2$ (2 equivalents), activated zinc (15 equivalents) and tetraethyl ammonium iodide (4 equivalents). Deprotection then completed the total synthesis

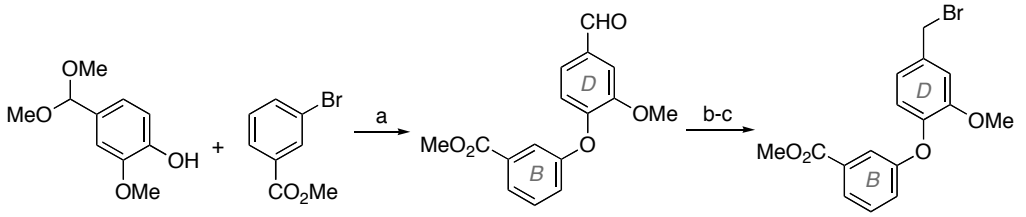
(Scheme 9). The authors also reported the cyclisation of bis-benzyl bromide **1.107** under the same conditions in high yield, although an exact figure is not given.



1.109 **1.89** **1.91** **1.110**

a). CuCl, pyridine, 82%; b). (i). CrO_3, (ii). $(COCl)_2$, 97%.

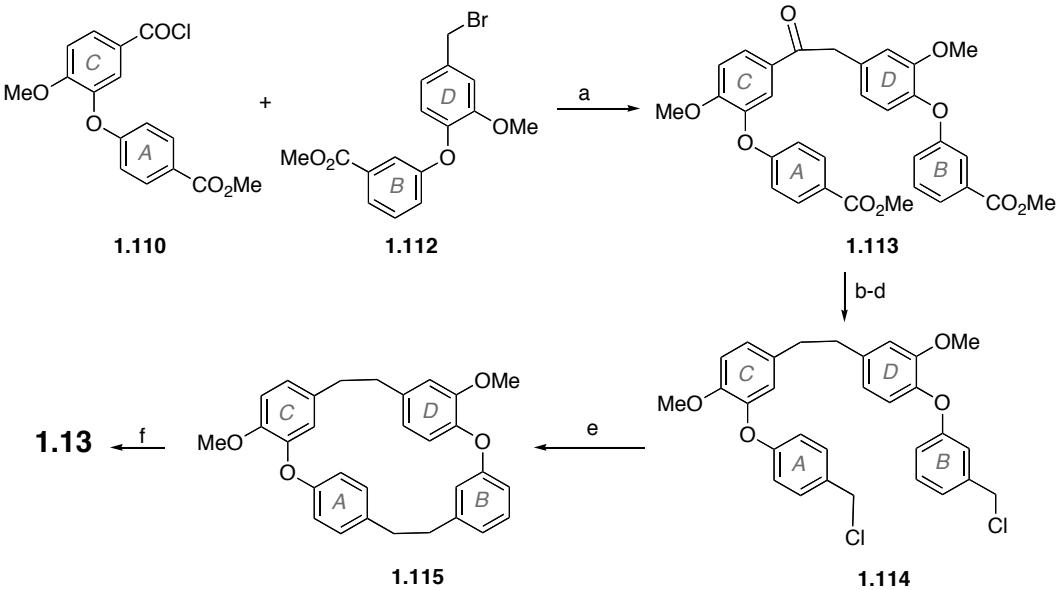
Scheme 7 – Synthesis of the *AC* fragment.



1.109 **1.111** **1.106** **1.112**

a). CuCl, pyridine, 74%; b). $NaBH_4$; c). PBr_3, 72% over 2 steps.

Scheme 8 – Synthesis of the *BD* fragment.

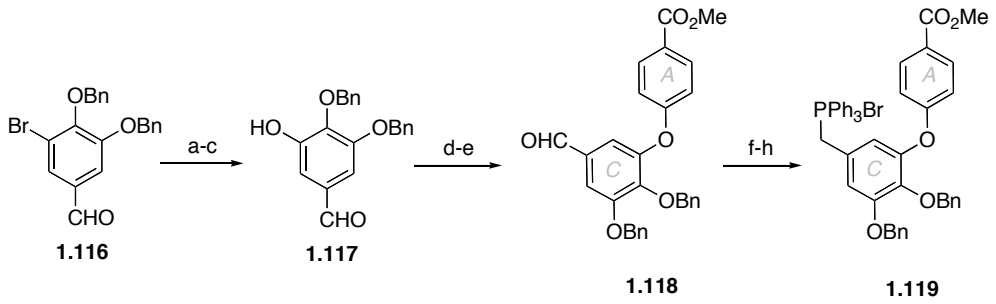


1.110 **1.112** **1.113** **1.114** **1.115**

a). $PdCl_2(PPh_3)_2$, Zn, 50%; b). Zn-Hg, HCl, 91%; c). $LiAlH_4$, 88%; d). $SOCl_2$, 84%; e). $NiBr_2(PPh_3)_2$, Zn, Et_4NI, 83%; f). BBr_3, 95%.

Scheme 9 – Completing the synthesis.

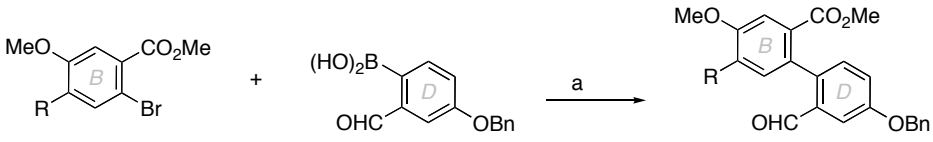
Nógrádi later published routes to plagiochins A **1.41** and B **1.42**,[49] and then plagiochins C **1.43** and D **1.44**,[50] again using Wurtz macrocyclisation reactions mediated by sodium and tetraphenylethene. In each case, the *AC* diaryl ether fragment was constructed using Ullmann chemistry, with **1.119** common to the syntheses of plagiochins A **1.41** and B **1.42** (Scheme 10) and **1.94** common to plagiochins C **1.43** and D **1.44** (synthesis already described – see Scheme 3).



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 **1.89**, CuO, 60%; f). $NaBH_4$, 92%; g). PBr_3, 91%, h). PPh_3, 75%.

Scheme 10

However, for the synthesis of the *BD* fragments Suzuki cross coupling chemistry was used in place of the low-yielding nickel(0)-catalysed cyclisation used in Nógrádi's earlier work. Biaryl fragment **1.124**, for the syntheses of plagiochins A **1.41** and C **1.43**, was obtained in a 60% yield, whilst biaryl **1.122**, for the syntheses of plagiochins B **1.42** and D **1.44**, was obtained in a more modest 35% yield (Scheme 11)



R=H **1.120**
R=OBn **1.121**

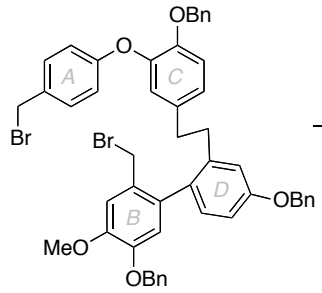
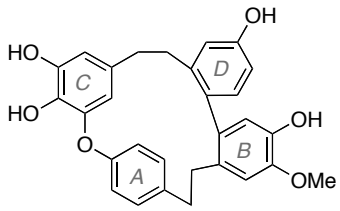
R=H **1.123**
R=OBn **1.124**

R=H a). $Pd(PPh_3)_4$, aq. $NaHCO_3$, 35%.
R=OBn a). $Pd(PPh_3)_4$, aq. $NaHCO_3$, 60%.

Scheme 11

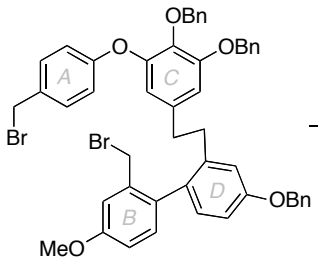
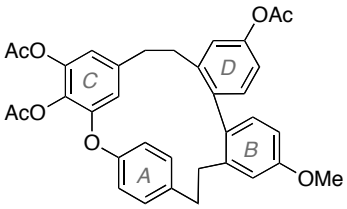
The key Wurtz macrocyclisation reaction and subsequent deprotection (and where appropriate, re-protection) steps for each of these natural product syntheses are shown below in Scheme 12. Yields were typically low, ranging from a mere 4% for plagiochin B **1.42** to a more impressive 35% for plagiochin C **1.43**. Owing to difficulties in the isolation and purification of these compounds, Nógrádi *et al*. isolated and characterised some as the acetate analogues rather than as the phenolic natural product. A similar strategy was employed by Nógrádi and co-workers to complete the total syntheses of marchantins B **1.21**, H **1.27** and I **1.28**.[51]

Thus, the Wurtz reaction has proven to be a useful synthetic tool for the synthesis of macrocyclic bisbibenzyls, having been used to complete the syntheses of a number of macrocyclic bisbibenzyl natural products in the early 1990s. However, as the best reported yields for macrocyclisation are typically modest, it has limited appeal and in more recent years has been superseded by other macrocyclisation strategies.

1.119 + **1.124** ⟹  a-c → 

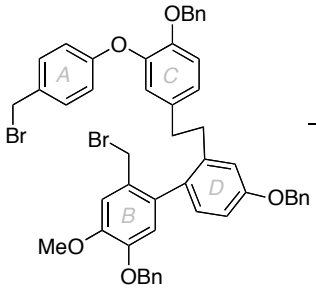
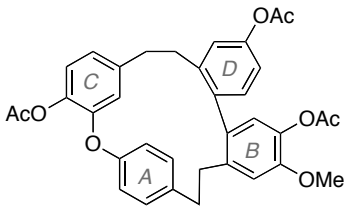
1.125 **1.41**

a). Na, $(Ph_2C)_2$, 8%; b). H_2, Pd/C, 74%.

1.119 + **1.123** ⟹  a-c → 

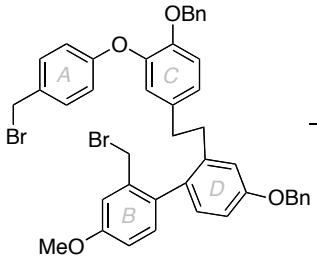
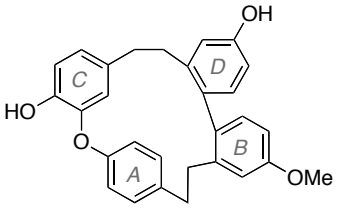
1.126 **1.127**

a). Na, $(Ph_2C)_2$, 4%; b). H_2, Pd/C; c). Ac_2O, 64% over 2 steps.

1.94 + **1.124** ⟹  a-c → 

1.128 **1.129**

a). Na, $(Ph_2C)_2$, 34%; b). H_2, Pd/C; c). Ac_2O, 78% over 2 steps.

1.94 + **1.123** ⟹  a-c → 

1.130 **1.44**

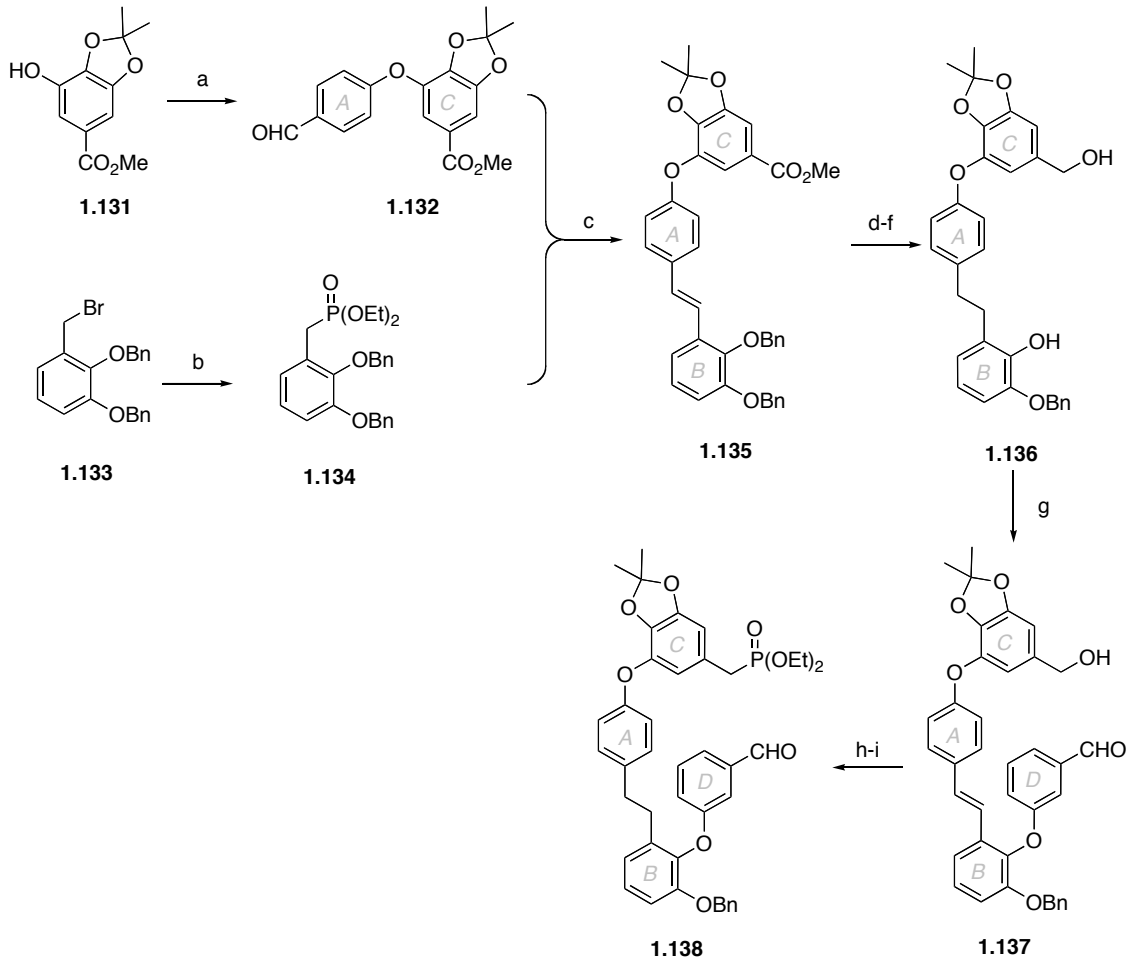
a). Na, $(Ph_2C)_2$; b). H_2, Pd/C, 17% over 2 steps.

Schemes 12i-iv

1.5.2 Wittig Methodology

The Wittig reaction is a coupling reaction between a carbonyl group and an alkyl phosphonium ylide or phosphonate carbanion (more commonly referred to as a Horner-Wadsworth-Emmons HWE reaction) to give an olefin. It was this versatile methodology that Kodama *et al*. used for their early total syntheses of marchantin A **1.20** and riccardin B **1.13** in 1988.[52]

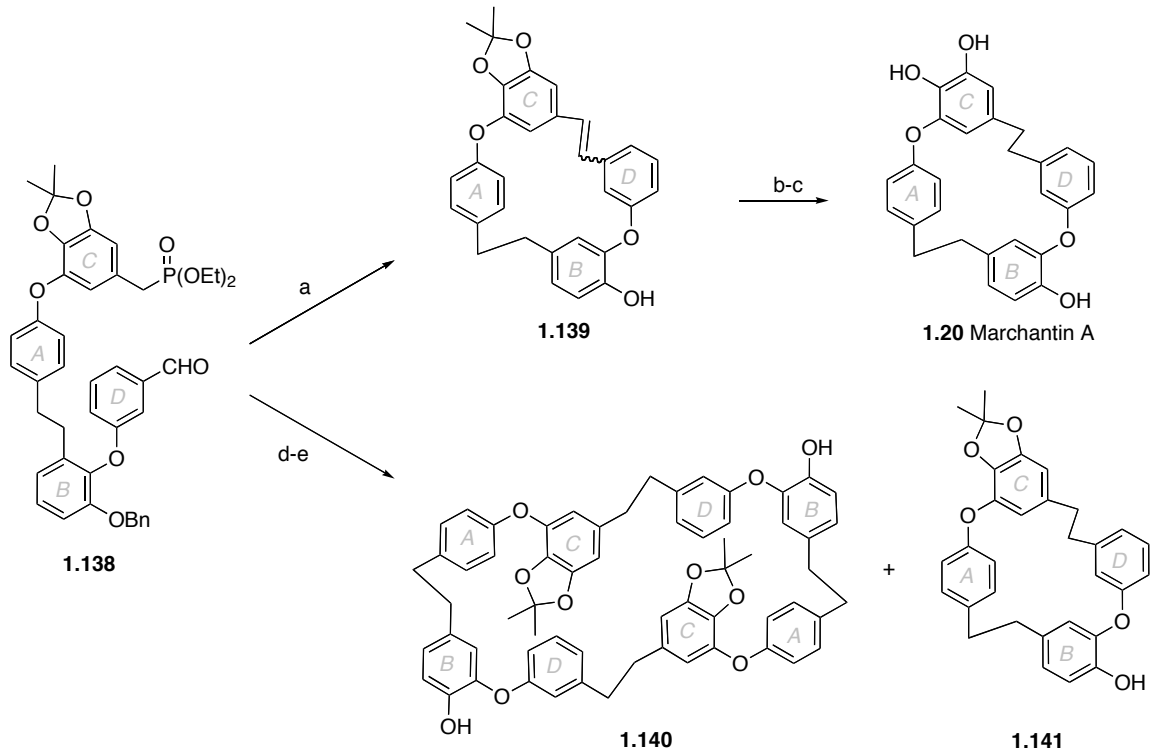
Kodama *et al*. envisaged an intramolecular HWE cyclisation for the construction of ethano bridge between rings *C* and *D* in their synthesis of marchantin A **1.20**, *viz.* **1.138**→**1.139** (Scheme 14). The key acyclic intermediate **1.138** was synthesised using sequential Ullmann ether formation. Bi-phenyl ether **1.132** underwent a HWE reaction with phosphonate **1.134** to give stilbene **1.135** in 74% yield. A short series of functional group manipulations then gave phenol **1.136**, which was subjected to a second Ullmann reaction. For reasons that are not clear, this reaction yielded only 42%, even at high temperatures and with prolonged reaction times. Sequential bromination and Arbuzov reaction gave desired precursor **1.138**.



a). *p*-bromobenzaldehyde, K_2CO_3, CuO, 69%; b). $P(OEt)_3$, 74%; c). *t*-BuOK, 71% *trans* exclusively; d). H_2, Pd/C, 96%; e). benzyl bromide, K_2CO_3, 67%; f). $LiAlH_4$, 94%; g). *m*-bromobenzaldehyde, K_2CO_3, CuO, 42%; h). $SOBr_2$; i). $P(OEt)_3$, 60% over 2 steps.

Scheme 13

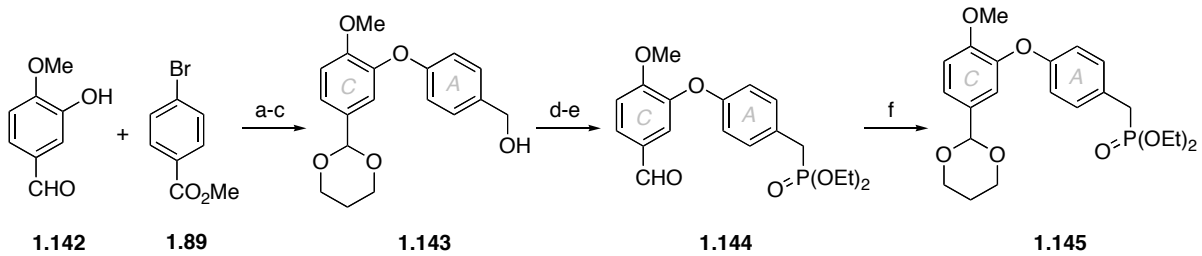
Treatment of phosphonate **1.138** with potassium *tert*-butoxide in DMF at high dilution (1.4 mM) at 0 °C afforded the desired macrocycle **1.139** in a satisfactory 60% yield as a mixture of *cis* and *trans* isomers. Hydrogenation and deprotection reactions then completed the total synthesis of marchantin A **1.20** (Scheme 14). Interestingly, the authors noted that if the key HWE cyclisation was carried out at higher concentration (2.8 mM), the reaction afforded a substantial amount of a dimer which was characterised after reduction as **1.140**.



a). *t*-BuOK, (1.4 mM conc.), 60%, mixture of *cis* and *trans*; b). H_2, Pd/C, 87%; c). HCl, 80%; d). *t*-BuOK, (2.8 mM conc.); e). H_2, Pd/C, 17% of dimer **1.140** and 36% **1.141** over 2 steps.

Scheme 14

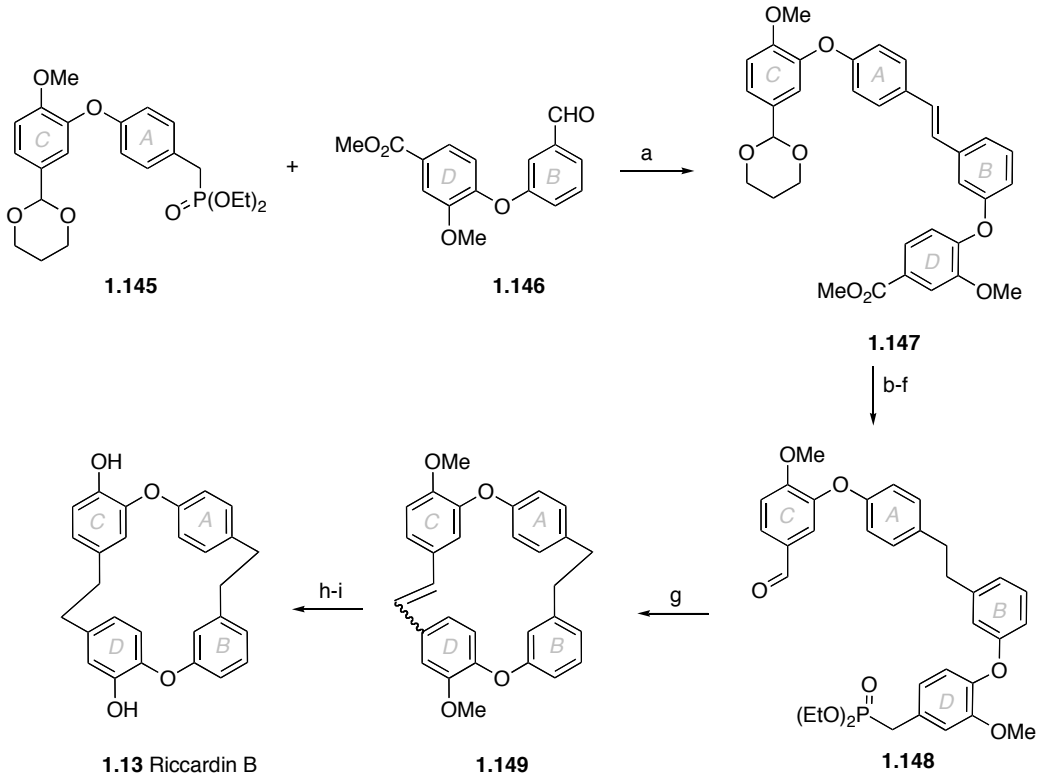
For the synthesis of riccardin B **1.13**, Kodama *et al*. employed a convergent strategy similar to that subsequently reported by Nógrádi.[46] Choosing to synthesise the two *AC* and *BD* diphenyl ether fragments **1.145** and **1.146** *via* Ullmann ether formation, they went on to couple these components using HWE methodology (Scheme16). *AC* Fragment **1.145** was obtained *via* a lengthy sequence of coupling and functional group interconversion reactions (Scheme 15), while *BD* fragment **1.146** was achieved in 1 step from *m*-bromobenzaldehyde and methyl-4-hydroxy-3-methoxy-benzoate by heating in pyridine-quinoline at 170 °C in the presence of K_2CO_3 and CuO.



a). K_2CO_3, CuO, 79%; b). $(HOCH_2)_2CH_2$, PPTS, 97%; c). $LiAlH_4$, 77%; d). $SOBr_2$; e). $P(OEt)_3$, 86% over 2 steps; f). as b, 95%.

Scheme 15

Union of phosphonate **1.145** and aldehyde **1.146** was *trans*-selective, giving **1.147** in 84% yield. Reduction and simple functional group manipulation then afforded diethyl phosphonate **1.148**, the key precursor for macrocyclisation using a second HWE reaction. Treatment of **1.148** with potassium *tert*-butoxide in DMF at high dilution gave the desired macrocycle in an impressive 89% yield as a mixture of *cis* and *trans* isomers in a 1:3 ratio. Reduction and deprotection completed the total synthesis of this natural product in 15 steps, allowing for unambiguous structural assignment (Scheme 16).

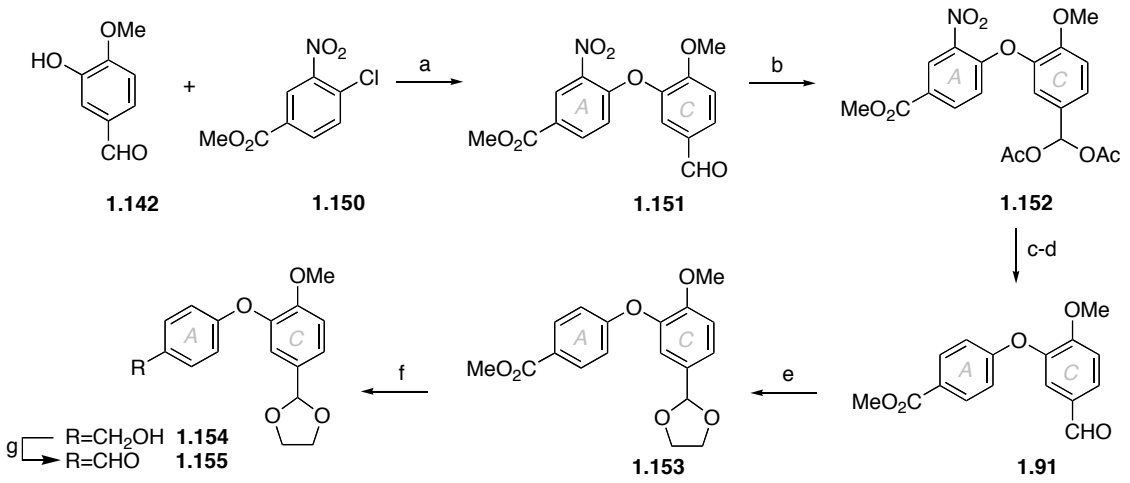


a).*t*-BuOK, 84%, *trans* exclusively; b). H_2, PtO_2, 100%; c). $LiAlH_4$; d). HCl, 82% over 2 steps; e). $SOBr_2$; f). $P(OEt)_3$, 76% over 2 steps; g). *t*-BuOK, 89%; h). H_2, PtO_2, 90%; i). BBr_3, 92%.

Scheme 16

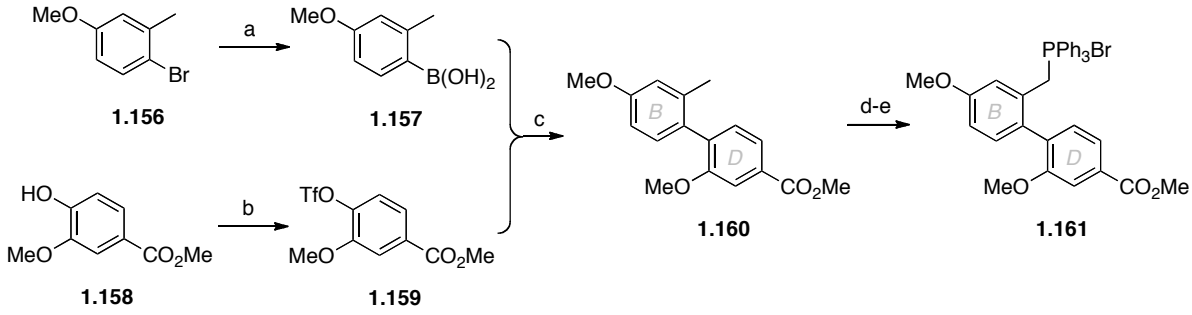
In 1998, Eicher *et al*. published total syntheses of marchantin I **1.28**, riccardin C **1.5** and isoplagiochins C **1.3** and D **1.6**, in each case using a Wittig macrocyclisation strategy.[53] Notably, the authors elected to effect macrocyclisation at the *C-D* ethano bridge, in variance with Nógrádi's synthesis of riccardin C **1.5**,[46] which used a Wurtz reaction to construct the ethano bridge between rings *A* and *C* as the macrocyclisation step.

Their synthesis began with the preparation of diphenyl ether **1.151** from isovanillin **1.142** and **1.150** by nucleophilic aromatic substitution. The resulting diphenyl ether **1.151** was next subjected to aldehyde protection to give **1.152**, then nitro group reduction and reductive deamination with concomitant acetal hydroysis afforded diphenyl ether **1.91**. Subsequent reprotection of the aldehyde moiety (to **1.153**), reduction of the ester (to **1.154**) and reoxidation gave *AC* fragment **1.155** in 7 steps and an overall yield of 34% (Scheme 17). *BD* Fragment **1.161** was obtained *via* a Suzuki-Miyaura reaction between boronic acid **1.157** and aryl triflate **1.159**. Radical bromination of the resulting biaryl **1.160** and phosphonium salt formation then gave **1.161** (Scheme 18).



a). NaH, 88%; b). Ac_2O, H_2SO_4, 86%; c). H_2, Pd/C; d). $NaNO_2$, H_3PO_4, 74% over 2 steps; e). $(HOCH_2)_2$, Al_2O_3, 85%; f). $LiAlH_4$, 84%; g). PCC/Al_2O_3, 95%.

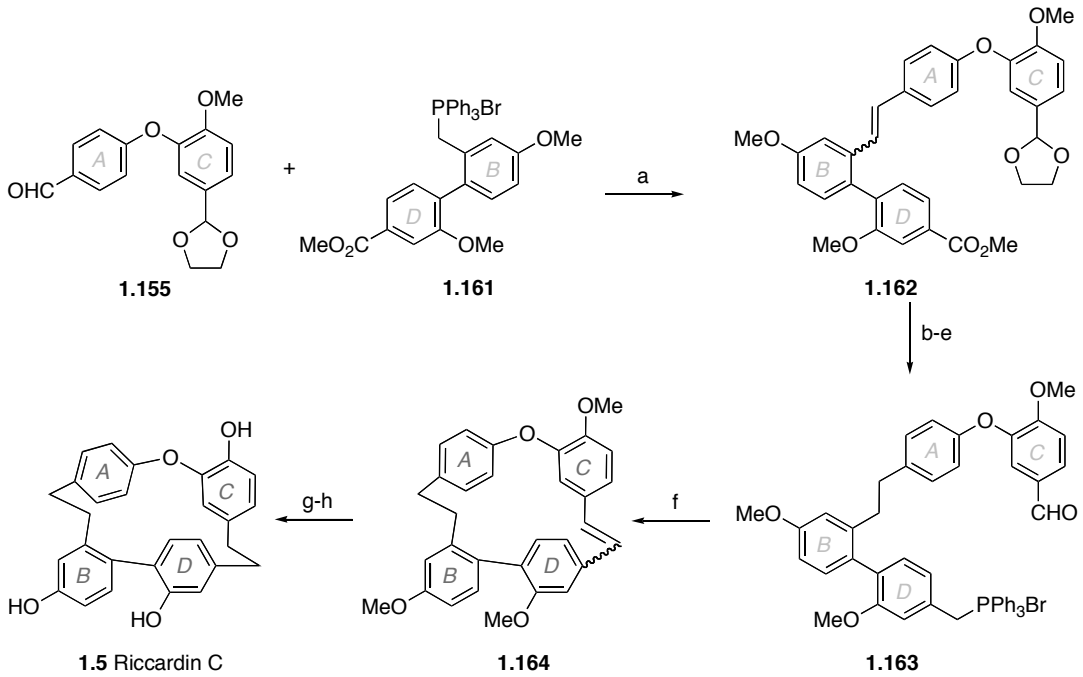
Scheme 17 – Synthesis of *AC* fragment **1.155**.



a). (i). Mg, (ii). $B(On\text{-}Bu)_3$, (iii). HCl, 75%; b). Tf_2O, 95%; c). $Pd(PPh_3)_4$, K_3PO_4, 93%; d). NBS, AIBN; e). PPh_3, 68% over 2 steps.

Scheme 18 – Synthesis of *BD* fragment **1.161**.

These fragments **1.155** and **1.161** were next conjoined by a Wittig reaction using K_2CO_3, aided by the addition of 18-crown-6, to give **1.162** as a mixture of *cis* and *trans* isomers, the ratio of which is not reported. Hydrogenation and further functional group manipulation led to phosphonium salt **1.163**, the intramolecular Wittig cyclisation of which proceeded readily and in excellent yield. Reduction and deprotection then furnished riccardin C **1.5** in 15 steps overall (Scheme 19).[53]



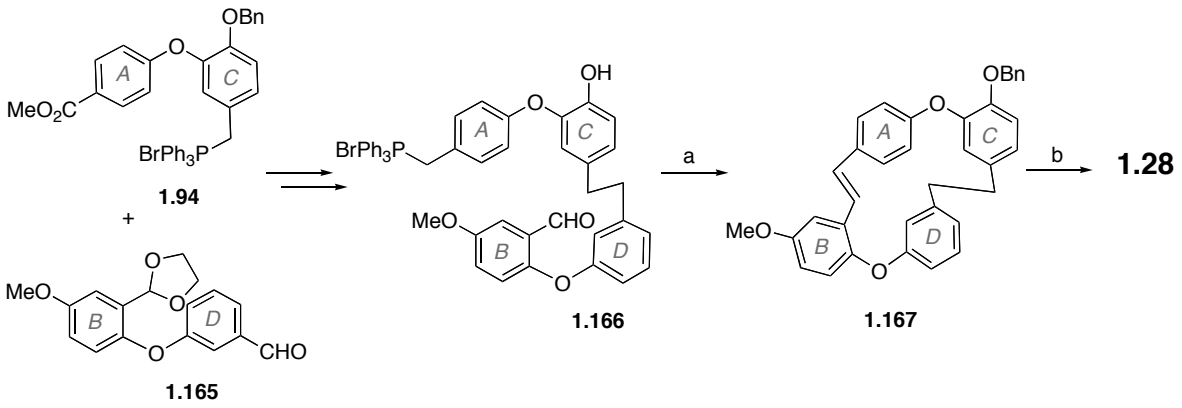
a). K_2CO_3, 18-crown-6, 85%; b). H_2, Pd/C, 93%; c). $LiAlH_4$, 88%; d). HBr; e). PPh_3, 77% over 2 steps; f). NaOMe, 80%; g). H_2, Pd/C, 92%; h). BBr_3, 88%.

Scheme 19

The use of this route was recently reported by Dodo *et al*. for their syntheses of riccardin C **1.5** and a series of riccardin C analogues lacking the phenolic groups.[41] Their published route is made shorter by the use of Harrowven's two step protocol to diphenyl ether **1.155** (see Section 1.6). Dodo and co-workers' success in synthesing six different analogues, diverging in the earliest stages of the syntheses, is testimony to the robustness of Eicher's strategy.

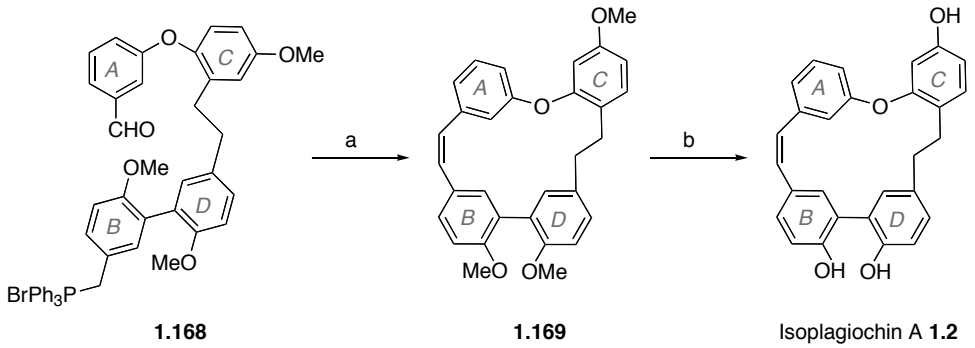
As noted, Eicher *et al*. also report their use of this strategy in a total synthesis of marchantin I, using Ullmann chemistry to obtain *AC* and *BD* fragments **1.94** and **1.164**. Wittig macrocyclisation of **1.166** proceeded in 81% yield to afford the *trans*-stilbene **1.167** exclusively. Concomitant hydrogenation and hydrogenolysis

completed the synthesis (Scheme 20). In this case, macrocyclisation was effected at the *A*-*B* ethano bridge in a disconnective approach reminiscent of that employed by Nógrádi *et al*. in their synthesis of isoplagiochin A **1.2**, published the previous year.[49] Notably, in that case, Wittig macrocyclisation of **1.169** was achieved in a more modest 32% yield and gave the *cis*-stilbene **1.2**, doubtless reflecting the higher degree of strain in that system (Scheme 21).



a). NaOMe, 81%; b). H_2, Pd/C, 90%.

Scheme 20 – The key steps in Eicher's total synthesis of marchantin A **1.28**.

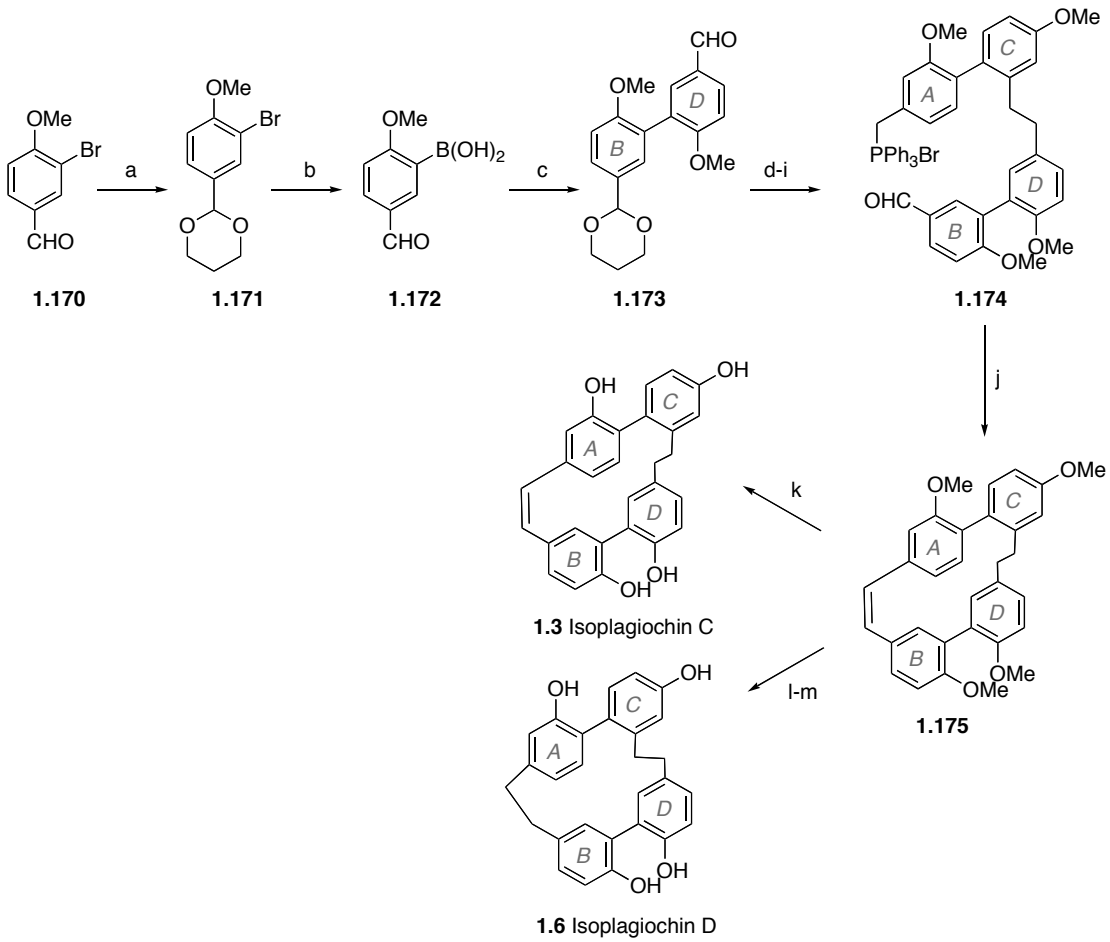


a). KO^{t}Bu, 32%; b). BBr_3, 32%.

Scheme 21 – Nógrádi's macrocyclisation step in the synthesis of isoplagiochin A.

Eicher's report additionally describes an entry to of the isoplagiochin family, achieving the total synthesis of isoplagiochin C **1.3** and its saturated analogue isoplagiochin D **1.6**. A Suzuki reaction allowed access to biaryl **1.173** in high yield, which was conjoined with phosphonium salt **1.161** (synthesis in Scheme 18) using a Wittig reaction. Once again, functional group manipulation afforded the key precursor **1.174**, with the subsequent Wittig macrocyclisation proceeding efficiently in 74% yield to afford stilbene **1.175** with exclusively the desired *cis*-geometry.

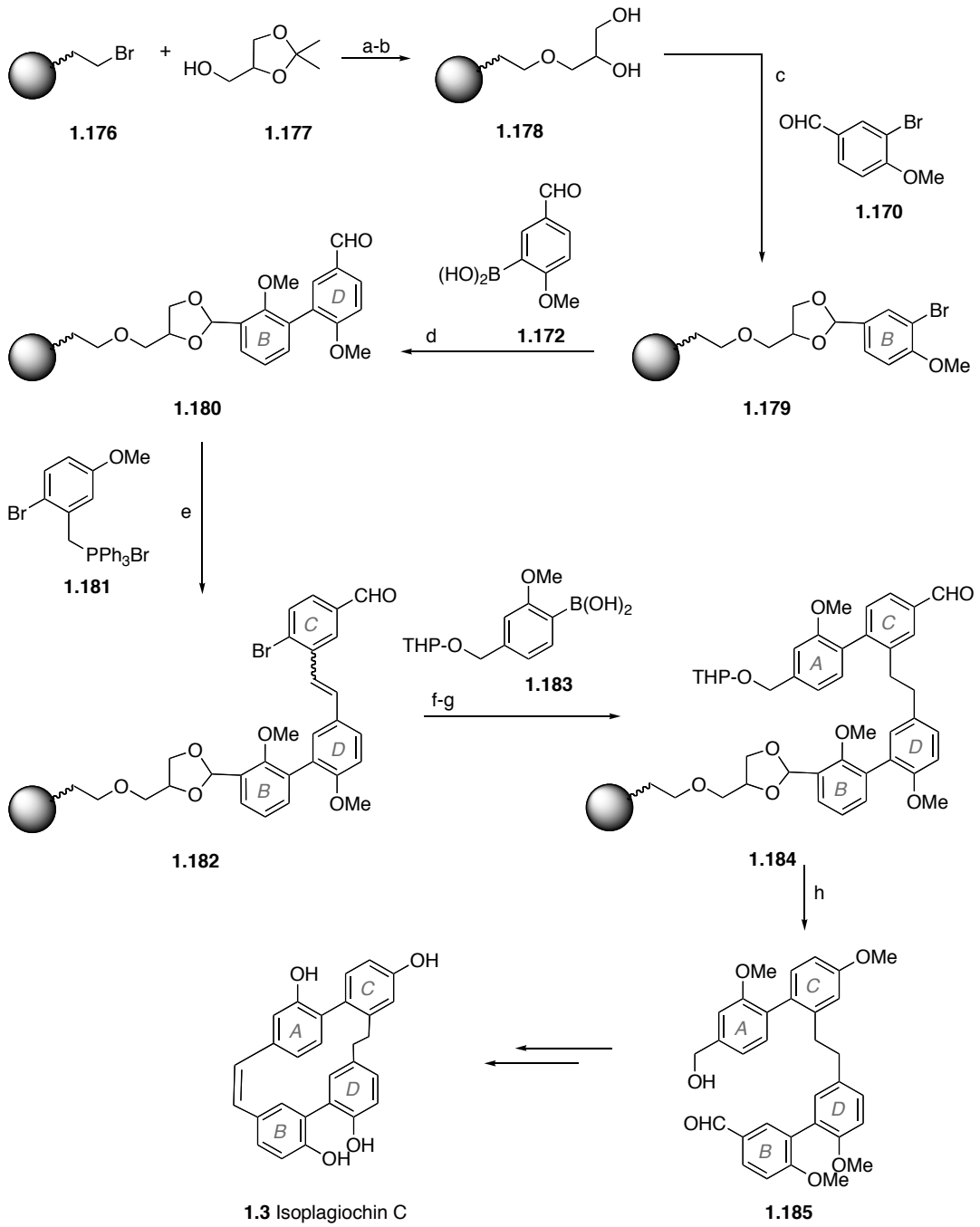
Deprotection or hydrogenation and deprotection afforded isoplagiochins C **1.3** and D **1.6** respectively (Scheme 22). Using a very similar strategy, Speicher subsequently reported the total syntheses of bazzanins A **1.56** and J **1.72**, using a series of Suzuki couplings and Wittig reactions to synthesise these chlorinated macrocyclic bisbibenzyl natural products.[54]



a). $(HOCH_2)CH_2$, PPTS, 97%; b). (i). *n*-BuLi, (ii). $B(On\text{-}Bu)_3$, (iii). HCl, 75%; c). **1.170**, $Pd(PPh_3)_4$, Na_2CO_3, 86%; d). **1.161,** K_2CO_3, 18-crown-6, 88%, mixture of *cis* and *trans*; e). H_2, Pd/C, 93%; f). $LiAlH_4$; g). AcOH, 93% over 2 steps; h). PBr_3; i). PPh_3, 60% over 2 steps; j). NaOMe, 74%; k). BBr_3, 85%; l). H_2, Pd/C, 91%; m). BBr_3, 82%.

Scheme 22

Wittig methodology using phosphonium ylides or phosphonate anions is now the most widely reported macrocyclisation strategy in the synthesis of macrocyclic bisbibenzyls. In addition to the aforementioned reports, it has also been used by Speicher and co-workers in their recent solid phase formal total synthesis of isoplagiochins C **1.3** and D **1.6**, the first example of the synthesis of a natural product of this class using solid phase methods (Scheme 23).[55]



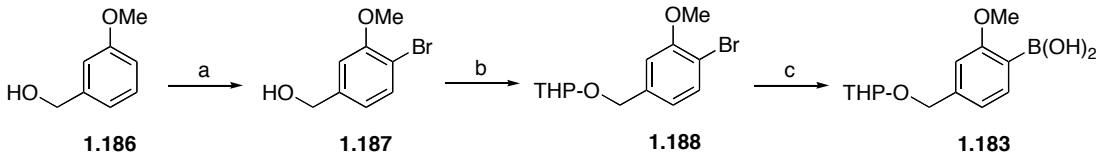
a). Na; b). HCl; c). **1.170**, *p*-TsOH, Na_2SO_4; d). **1.172**, $Pd(PPh_3)_4$, K_2CO_3; e). **1.181**, NaOMe; f). **1.183**, $Pd(PPh_3)_4$, Cs_2CO_3; g). H_2, $Rh(PPh_3)_3Cl$, NaOAc; h). HCl, 25% over 8 steps.

Scheme 23

Their synthesis began with the solid support TentaGel–Br **1.176**, to which a glycerol linker was added. The first arene, ring *B* was appended through acetal formation between the aldehyde moiety of **1.170** and the 1,2-diol of **1.178** to give **1.179**. Suzuki reaction of the polymer-bound aryl bromide **1.179** with boronic acid **1.172** and subsequent Wittig reaction with phosphonium salt **1.181** then afforded **1.182** as mixture of *cis* and *trans* isomers. A further Suzuki protocol attached the

fourth aromatic ring to give *ACDB* fragment **1.184** after hydrogenation with Wilkinson's catalyst. Treatment with acid liberated the fragment from the solid support and simultaneously unmasked the benzyl alcohol functionality to afford precursor **1.185** (Scheme 23), the spectroscopic data for which is reported to be identical to that of the same fragment in Eicher's earlier synthesis (Scheme 22). Owing to the nature of the synthesis (*i.e.* the solid support strategy) the yield is given for the target molecule when liberated from the solid support over the entire sequence.

The synthesis of boronic acid **1.183** used an interesting regioselective bromination procedure *viz.* **1.186**→**1.187**. The alcohol was then masked as the corresponding tetrahydropyran-*O*-ether and the aryl bromide transformed to boronic acid **1.183** *via* halogen-lithium exchange (Scheme 24). However, in our hands this reaction afforded a different product, a full discussion of which is presented in Chapter 3.



1.186 **1.187** **1.188** **1.183**

a). $NaBrO_3$, $NaHSO_3$, 88%; b). 2,3-dihydropyran, *p*-TsOH, 74%; c). (i). *n*-BuLi, (ii). $B(OMe)_3$, (iii). H_2O, 100% crude.

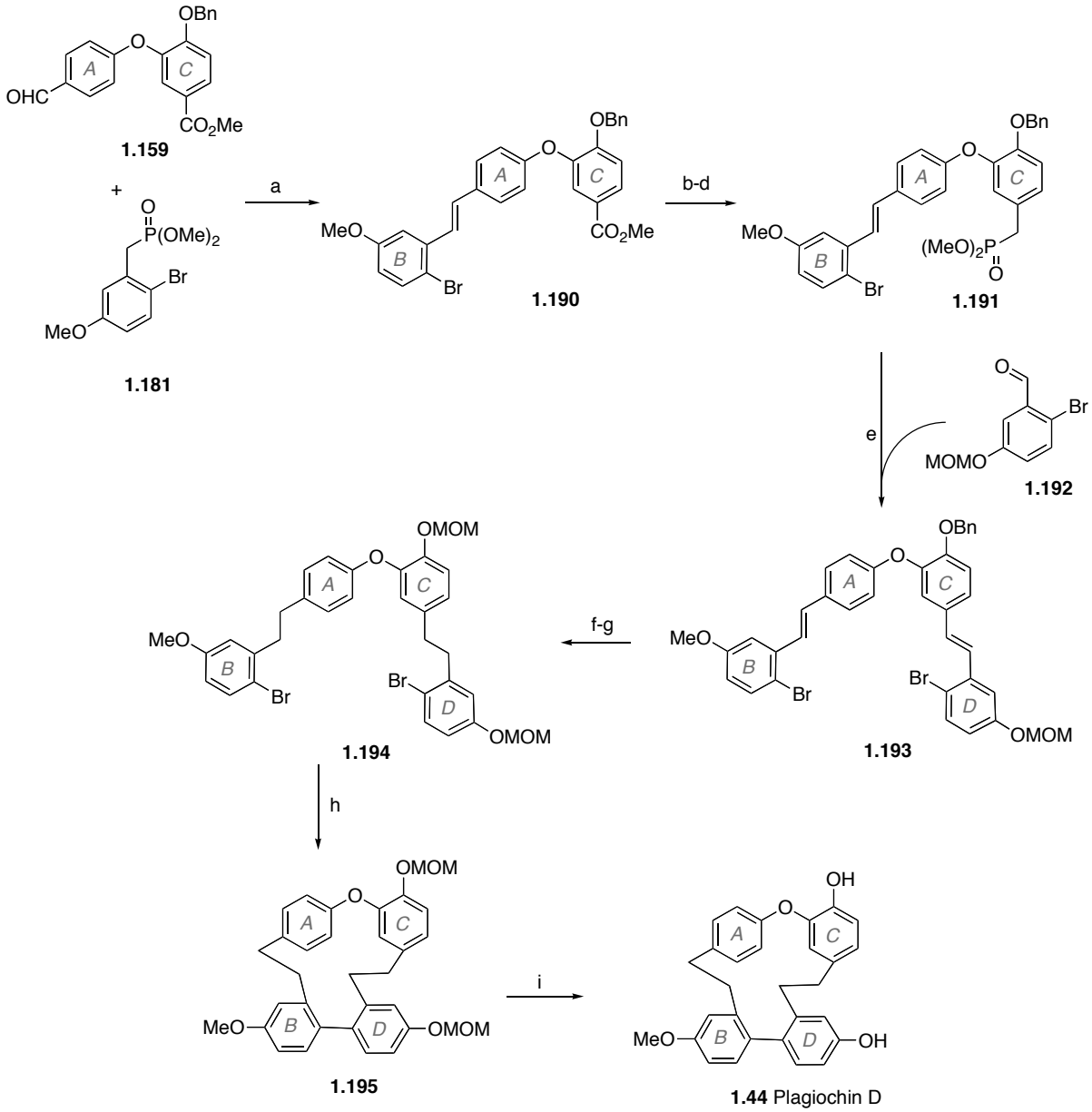
Scheme 24

1.5.3 Metal-Catalysed Aryl-Aryl Coupling Strategies

Macrocyclisation at the aryl-aryl bond of macrocyclic bisbibenzyls has been reported in pioneering work by Fukuyama and co-workers. Using this approach, they have achieved the total syntheses of plagiochin D **1.44**, isoplagiochin D **1.6** and, most recently, riccardin C **1.5**.[40, 42, 56]

For their synthesis of plagiochin D **1.44**, Fukuyama *et al*. adopted a linear approach, using sequential HWE reactions to append the *B* and *C* rings, *viz*. **1.189**+**1.181**→**1.190** and **1.191**+**1.192**→**1.193**, in turn.[42] Catalytic hydrogenation of the olefins in **1.193** was achieved with PtO_2, as the use of palladium on carbon resulted in competitive hydrogenolysis of the aryl bromide bonds. A number of

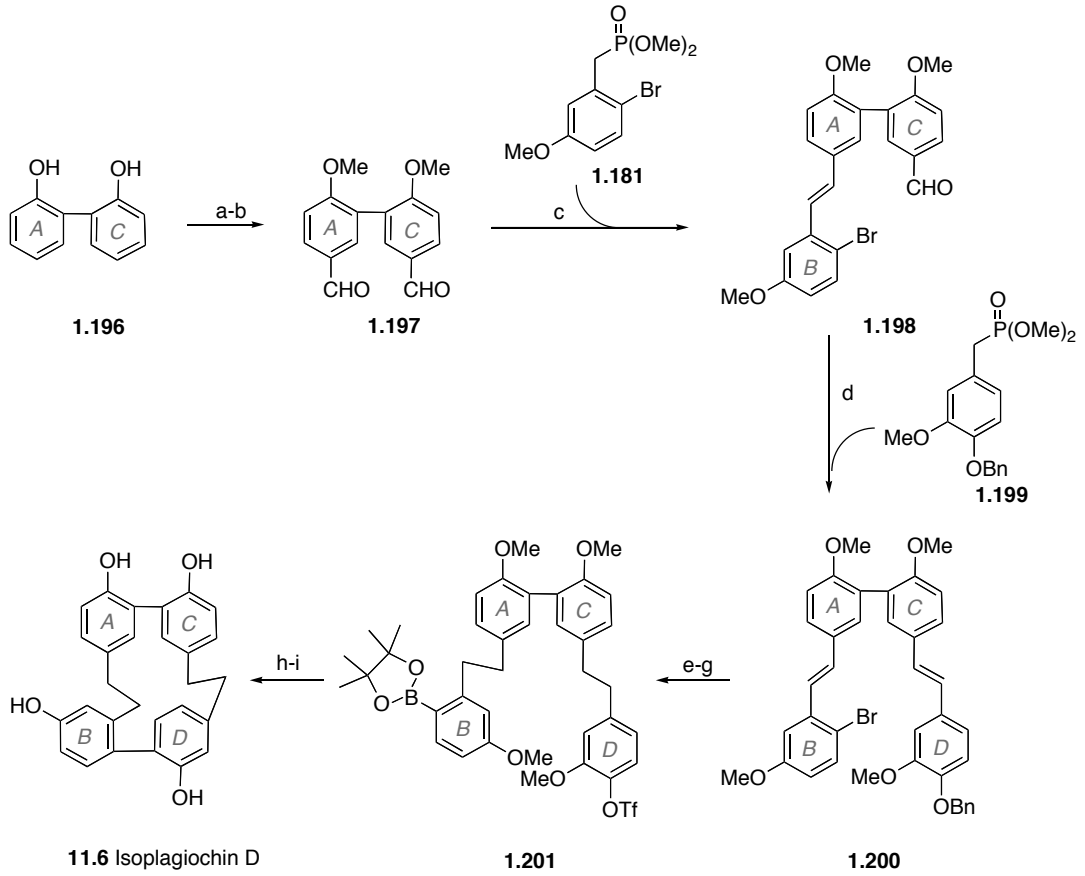
transition metal-catalysed aryl-aryl bond forming reactions were then tried in an attempt to effect macrocyclisation, with both nickel(0)-mediated coupling and tandem Suzuki cross coupling with bis(pinacolato)diborane failing. Cyclisation was achieved *via* Stille-Kelly reaction, albeit in a modest 17% yield, with dimer accounting for *circa.* 15% of the mass balance. Deprotection completed the synthesis (Scheme 25).



a). NaH, 94%; b). $LiAlH_4$; c). CBr_4, PPh_3; d). $P(OMe)_3$, 81% over 3 steps; e). **1.192** NaH, 89%; f). H_2, PtO_2; g). NaH, MOMCl, 73% over 2 steps; h). $(Me_3Sn)_2$, $Pd(PPh_3)_4$, 17%; i). HBr, 87%.

Scheme 25

By contrast, in their 2004 synthesis of isoplagiochin D **1.6**, the corresponding tin-catalysed Stille-Kelly intramolecular cyclisation was not successful prompting the adoption of an orthogonal prophylaxis strategy (Scheme 26) which allowed for the selective unmasking of one phenol and its subsequent triflation.[56] A Suzuki-Miyaura reaction sequence gave some cyclisation, with optimisation to 41% yield of desired product reported. Proto-dehalogenation and -deborylation were the main competing reactions.

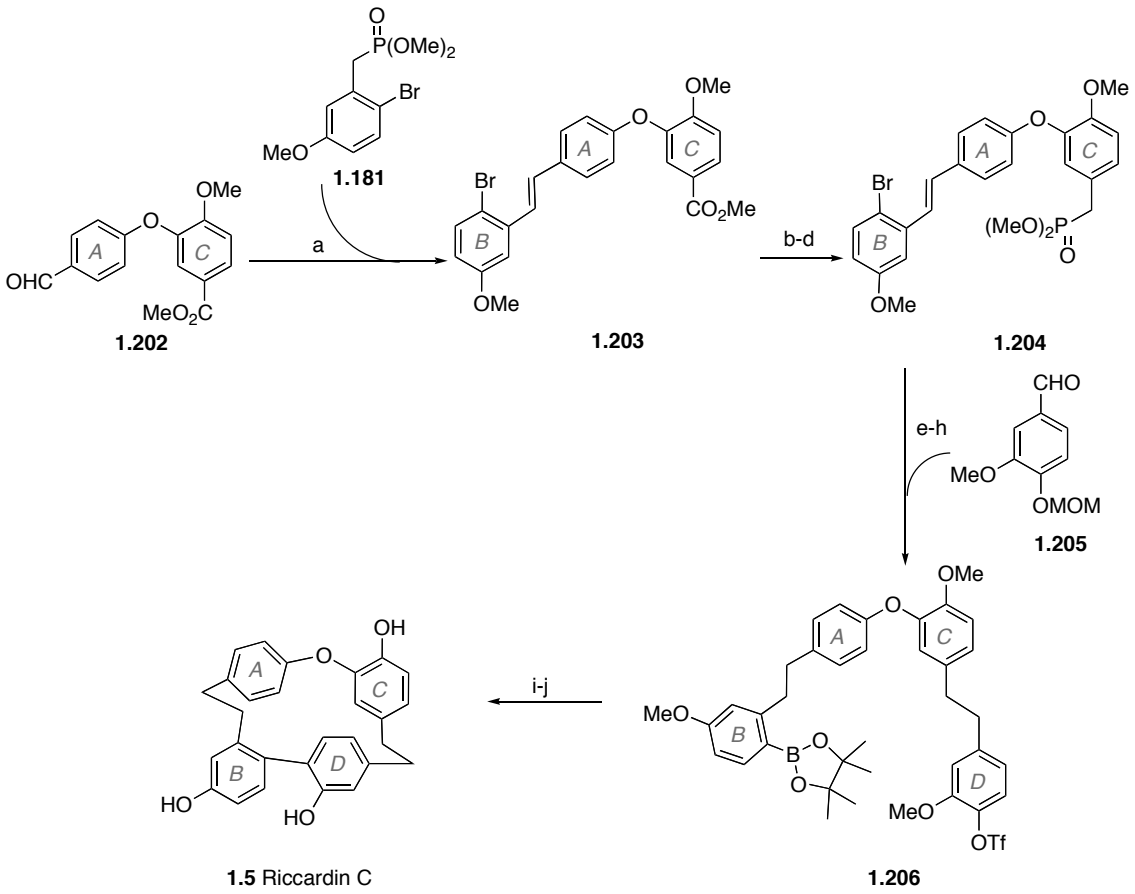


a). MeI, K_2CO_3; b). HMTA, TFA, 72% over 2 steps; c). **1.181**, NaH, 73%; d). **1.199**, NaH, 75%; e). H_2, PtO_2; f). Tf_2O, 97% over 2 steps; g). $PdCl_2(dppf)$, bis(pinacolato)diboron, 76%; h). $Pd(PPh_3)_4$, K_3PO_4, 41%; i). BBr_3, 86%.

Scheme 26

Fukuyama *et al*. reported a related total synthesis of riccardin C **1.5** in 2008, beginning the synthesis with *AC* diphenyl ethyl **1.202** and appending in turn rings *B* and *D* using successive HWE reactions.[40] Once again, the protecting group strategy allowed for selective triflation and selective borylation to facilitate the key macrocyclisation reaction.

In the initial cyclisation attempts, using conditions analogous to those employed earlier, conversion was low, yielding only 9% of the desired product. Use of the Buchwald ligand SPhos improved yields significantly, with 37% yield being realised when Na_2CO_3 was used as the base and DMF as the solvent. Dimerisation was the main competing reaction, which high dilution conditions failed to suppress. Deprotection to unmask the phenolic groups furnished the natural product (Scheme 27).



a). NaH, 99%; b). $LiAlH_4$, 90%; c). NBS, Me_2S; d). $P(OMe)_3$, 98% over 2 steps; e). NaH, **1.205**, 87%; f). Et_3SiH, TFA, 74%; g). *N*-phenyl-bis(trifluoromethanesulfonamide), Cs_2CO_3, 96%; h). $Pd(PPh_3)_4$, bis(pinacolato)diboron, K_3PO_4, 95%; i). Pd_2dba_3, SPhos, Na_2CO_3, 37%; j). BBr_3, 97%.

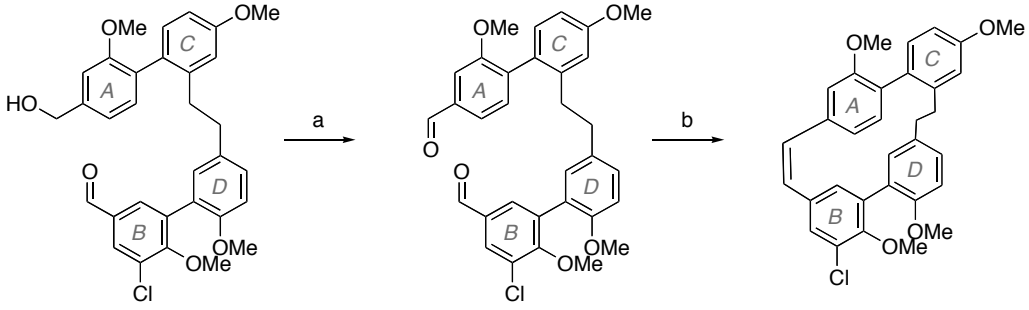
Scheme 27

1.5.4 Other Cyclisation Methods

McMurry Reaction

The McMurry reaction is a metal-mediated pinacol coupling between two carbonyls, followed by diol elimination to furnish an olefin. Speicher *et al*. reported the use of a McMurry reaction to achieve stereoselective *cis*-cyclisation in their

total synthesis of bazzanin A **1.56**, although a stereoselective Wittig reaction was used in their final route (Scheme 28).[54] Harrowven *et al*. also used a McMurry macrocyclisation in the first total synthesis of cavicularin **1.4**, a sequence which additionally yielded the related natural product riccardin C **1.5**.[57] For a full discussion of this approach, see Section 1.6.



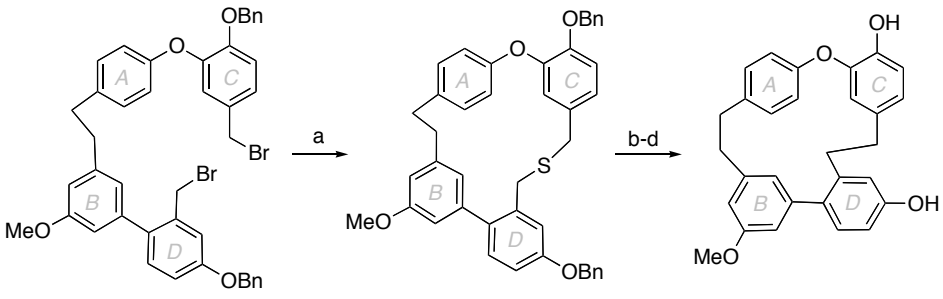
1.207 **1.208** **1.209**

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

Scheme 28

Stevens Reaction

In their earlier efforts towards the total synthesis of plagiochin C **1.43**, Fukuyama *et al*. reported the use of a double nucleophilic displacement of bis-benzylbromide **1.210** with the sulfide anion to form thioether **1.211**, which proceeded in modest yield. The transformation of this thioether to the desired carbon-carbon bond using the Stevens reaction, however, could only furnish the natural product in a 1% yield, with poor reproducibility of results (Scheme 29).[42]

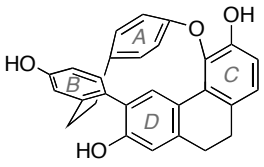


1.210 **1.211** **1.212**

a). Na_2S (10^{-2} M), 25%; b). anthranilic acid, isoamyl nitrite; c). Na; d). H_2, Pd/C, 1% over 3 steps.

Scheme 29

1.6 Cavicularin: Reported Total Synthesis



1.4 Cavicularin

Figure 21

The synthesis of cavicularin **1.4** presents two clear obstacles for special consideration: the kinetic barrier to closure of such a strained macrocycle, and the thermodynamic barrier associated with the bending of an aromatic ring. Harrowven *et al*. overcame these difficulties by using a radical-induced transannular ring contraction as the key step, first surmounting the macrocyclisation by forming the larger 18-membered ring of riccardin C using a McMurry reaction.[57] This placed the bulk of the kinetic burden on the ring contraction step. The close spatial relationship of the carbon-centred radical and arene *C* then facilitated cyclisation, which is thought to occur without substantial distortion of arene *A*. Rather, it is believed that distortion of arene A takes place with the rearomatisation of arene *C*, which compensates for the thermodynamic penalty of bending arene *A* (Figure 22).

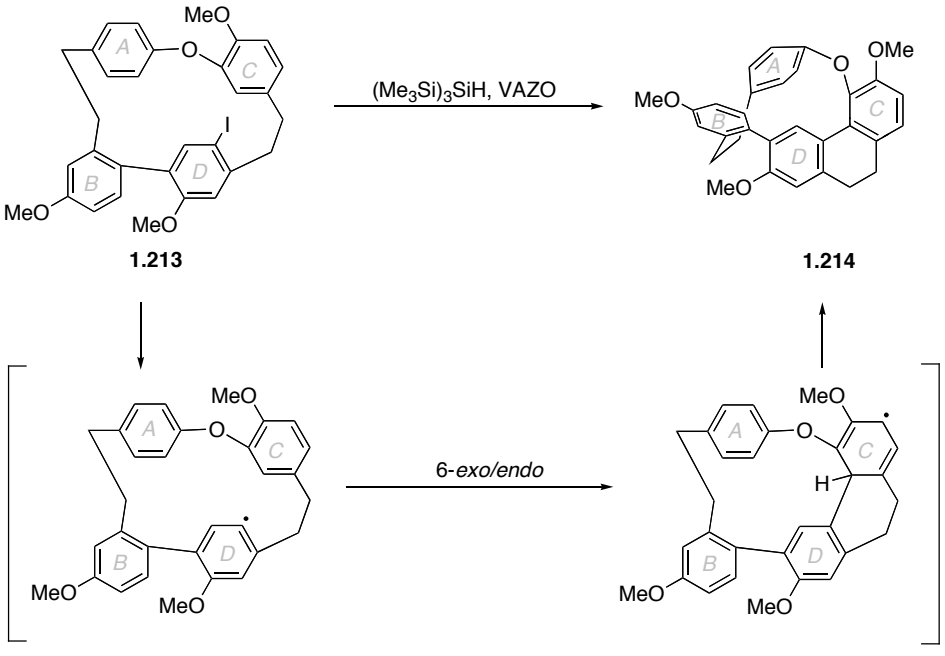
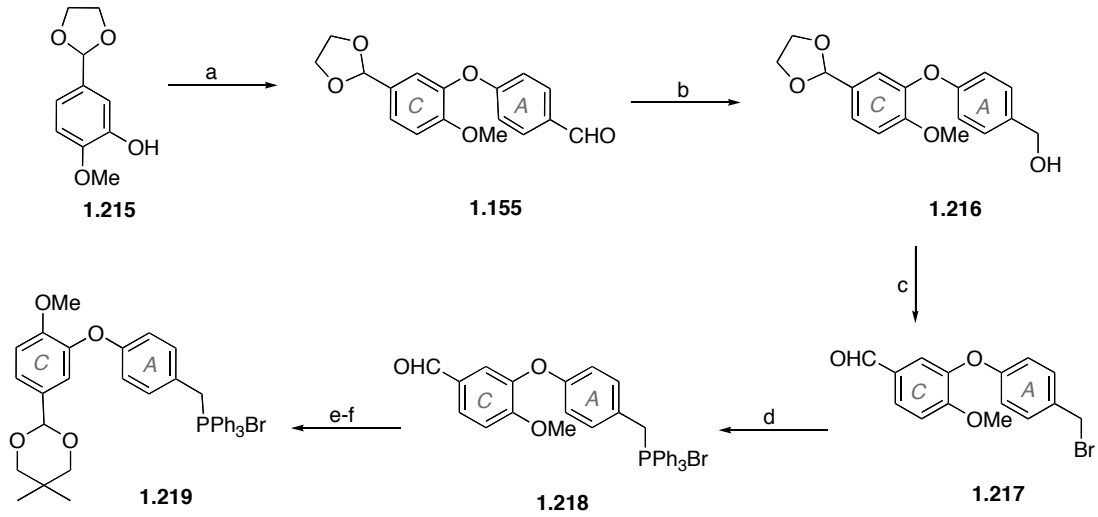


Figure 22

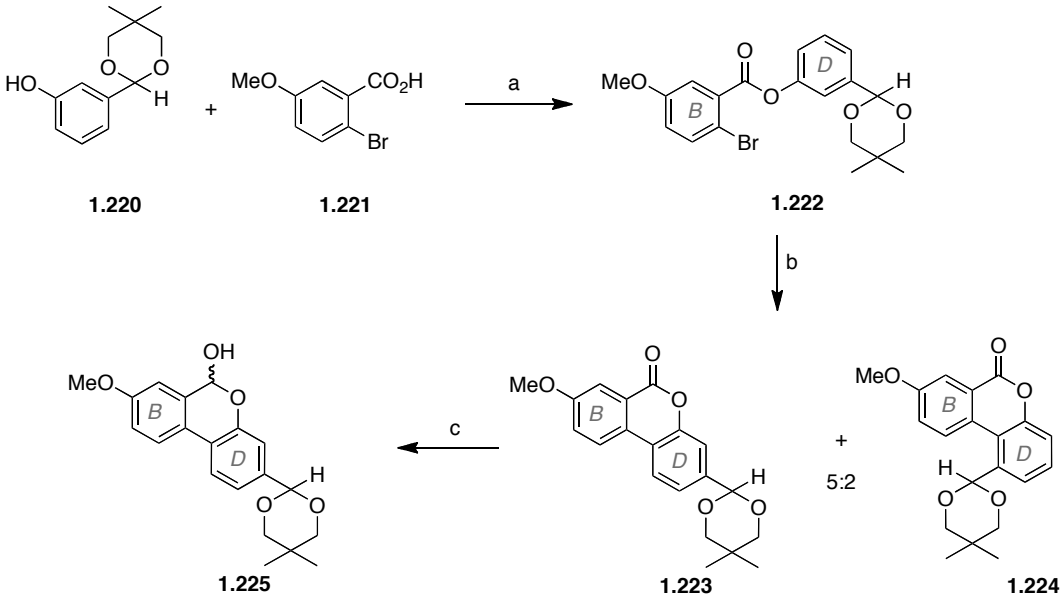
The synthesis begins with the assembly of two bis-arene building blocks, **1.219** and **1.225**. Harrowven *et al*. use the nucleophilic aromatic substitution of 4-fluorobenzaldehyde to obtain diphenyl ether **1.155**. Using a reverse functionality strategy to that reported by Eicher *et al*., straightforward functional group manipulation afforded phosphonium salt **1.219** in a further 4 steps. Notably, benzyl bromide formation induced acetal deprotection, *viz.* **1.216**→**1.217** necessitating the final protection step.



a). 4-fluorobenzaldehyde, K_2CO_3, DMF, 94%; b). $NaBH_4$, MeOH, 92%; c). CBr_4, PPh_3, DCM, 87%; d) PPh_3, PhMe, 86%; e). 2,2-dimethylpropan-1,3-diol, PPTS, 97%.

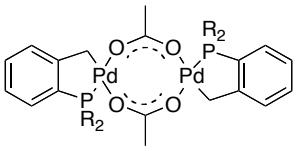
Scheme 30

For the construction of the *BD* biaryl bond, the authors envisaged a tethered palladium-catalysed C-H insertion reaction. To that end, the synthesis began with acetal protection of 3-hydroxybenzaldehyde followed by DCC-coupling with 2-bromo-5-methoxybenzoic acid to give ester **1.222**, the key fragment for this reaction. Treatment with Herrmann catalyst **1.226** (Figure 23) at high temperature afforded the desired benzo[*c*]chromen-6-one **1.223** in a modest 27% yield, with **1.224** and **1.222** the major isolated biproducts. Reduction of **1.223** with DIBALH then furnished lactol **1.225** which is appropriately functionalised for Wittig coupling with *AC* fragment **1.219**, a reaction that simultaneously unmasked the latent phenol moiety.



a). DCC, DMAP, 92%; b). Herrmann catalyst **1.226**, NaOAc, 38% (+**1.220**, 35%); c). DiBAL-H, 60%.

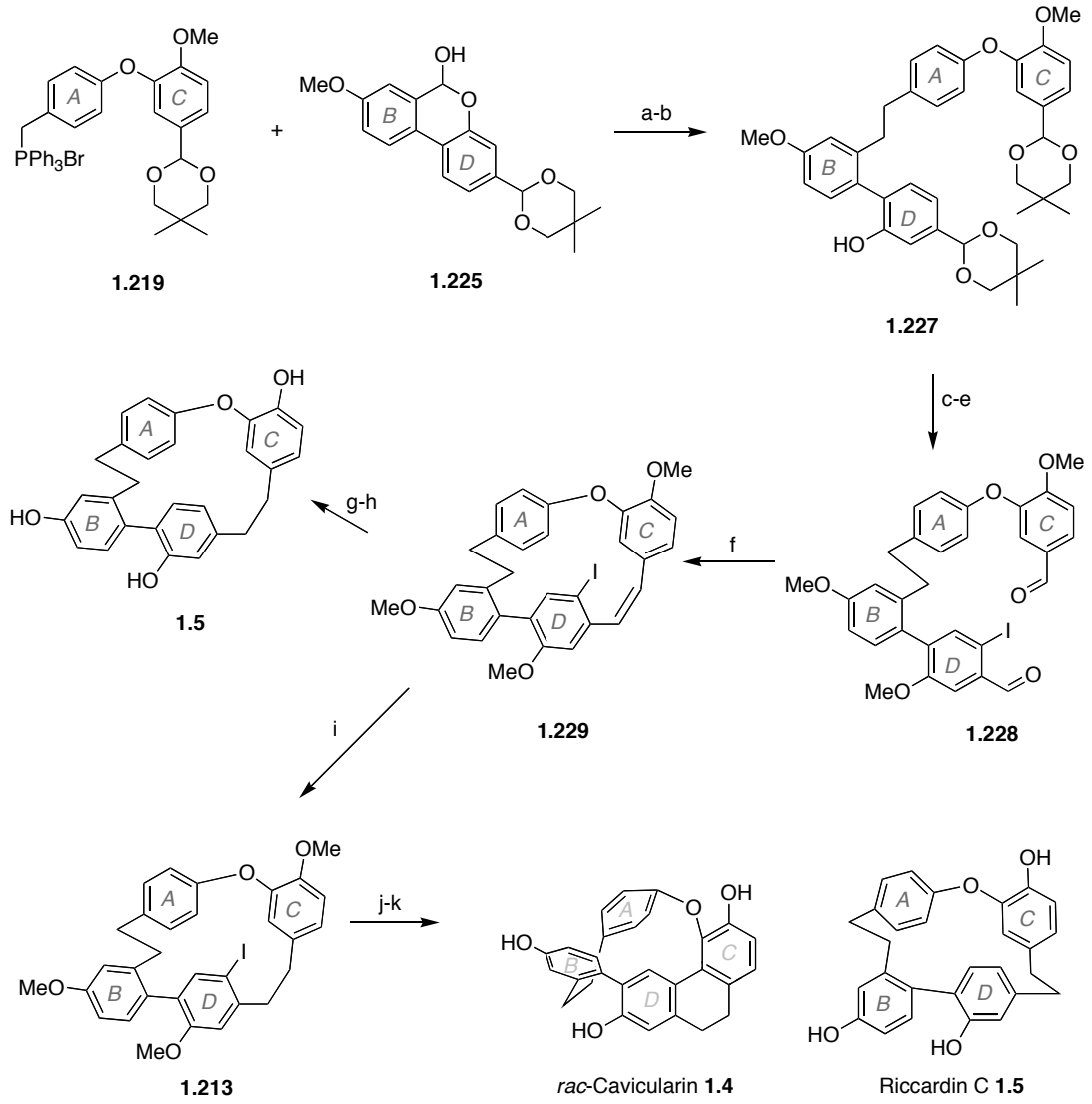
Scheme 31



R=*o*-tolyl
Herrmann catalyst **1.226**

Figure 23

Union of **1.219** and **1.225** proceeded smoothly with the addition of K_2CO_3 and 18-crown-6 to give the stilbene in a 2:1 *trans*:*cis* ratio. Catalytic hydrogenation, regioselective iodination, phenolic protection and acetyl hydrolysis afforded bisaldehyde **1.228**, which underwent macrocyclisation upon treatment with low-valent titanium (McMurry conditions) in 35% yield with complete *cis*-selectivity. Diimide reduction then reduced the stilbene functionality without concomitant protodehalogenation. Carbon-iodine bond homolysis using tristrimethylsilylsilane and AIBN effected the desired radical transannular ring contraction, in addition to simple hydrogen atom abstraction, yielding an inseparable mixture of riccardin C trimethyl ether and cavicularin trimethyl ether in a 2:1 ratio. Finally, treatment with boron tribromide unmasked the phenols to give a separable mixture of the two natural products (Scheme 32), completing the only published total synthesis of cavicularin **1.4** to date.



a). K_2CO_3, 18-crown-6, 66%, 2:1 ratio *trans*:*cis*; b). H_2, PtO_2, Et_3N, 89%; c). NaI, NaOCl, NaOH, 73%; d). MeI, K_2CO_3, 88%; e). PPTS, 83%; f). $TiCl_4$, Mg, 35%; g). H_2, Pd/C, 86%; h). BBr_3, 86%; i). $TsNHNH_2$, NaOAc, 91%; j). TTMSS, AIBN, k). BBr_3, 95% over 2 steps, 2:1 ratio **1.4**:**1.5**.

Scheme 32

Notably, simultaneous hydrogenation and hydrogenolysis of **1.229** using palladium on carbon and hydrogen gave access to riccardin C tri-*O*-methyl ether **1.88**, and hence riccardin C **1.5**, in good yield. This unified approach provided a starting point for the work described in the remainder of this thesis, directed towards a second generation synthesis of these natural product targets.

1.7 Conclusions

To date, over one hundred molecules in the macrocyclic bisbibenzyl family have been identified and isolated. With only one exception to date, the macrocyclic bisbibenzyls are isolated from bryophytes. These natural products have attracted considerable interest from the scientific community for their diverse biological activity and unusual structural features and motifs. A biosynthetic route to all molecules in this family has been proposed, with investigation deducing then an enzymatic chlorination reaction is responsible for the occurrence of chlorinated natural products of this class. A number of these molecules have been the subject of reported total syntheses, with Wurtz and Wittig reactions most commonly used for the key macrocyclisation step. Other methods reported are transition metal or mediated, using McMurry, Suzuki and Stille-Kelly protocols.

Chapter 2: Our Approach

2.1 Our Aims

Our primary aim is to address the unified second generation synthesis of cavicularin **1.4** and riccardin C **1.5**, addressing the low yielding steps in the 2006 synthesis. These are the palladium-catalysed C–H insertion reaction to obtain *BD* fragment **1.223**, which proceeded in only 27%, the McMurry macrocylisation step and the competitive hydrogen atom abstraction in the key transannular ring contraction.

Key to this new synthetic strategy is the potential to secure an asymmetric total synthesis of (+)-cavicularin **1.4**. Our idea exploits temporary stereogenic centres to force the macrocycle to preferentially adopt a conformation wherein attack of the radical intermediate occurs to the *Re* face of arene *C*. Four sites within the molecule show promise, these being the benzylic positions in the chains tethering the *A* and *B* rings and the *C* and *D* rings (Figure 24).

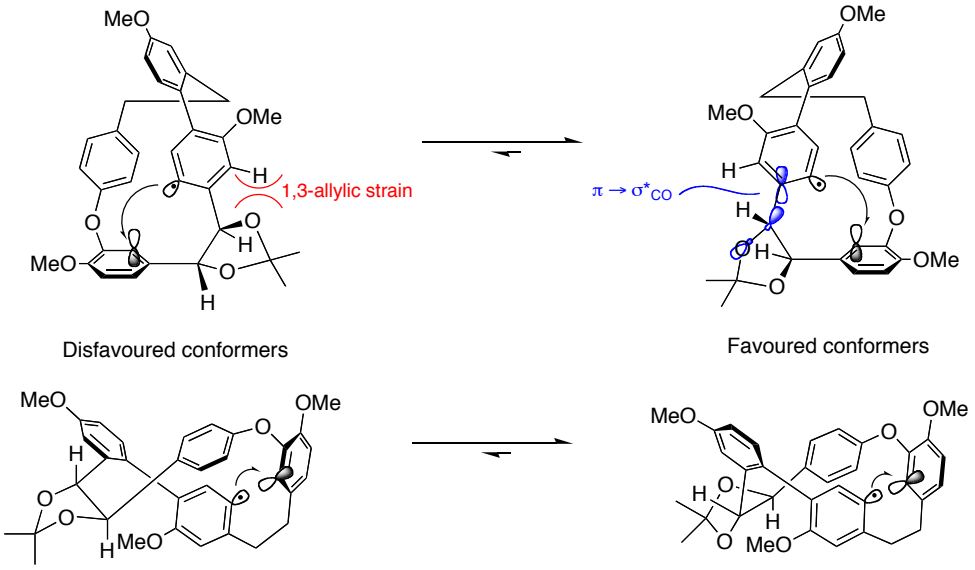


Figure 24 – Predicted reaction conformations for the transannular ring contraction step.

The synthesis of suitable *AC* fragment **1.155** has already been established by Harrowven *et al*. (Scheme 30),[57] and it was with this established work that we began our approach (Figure 25).

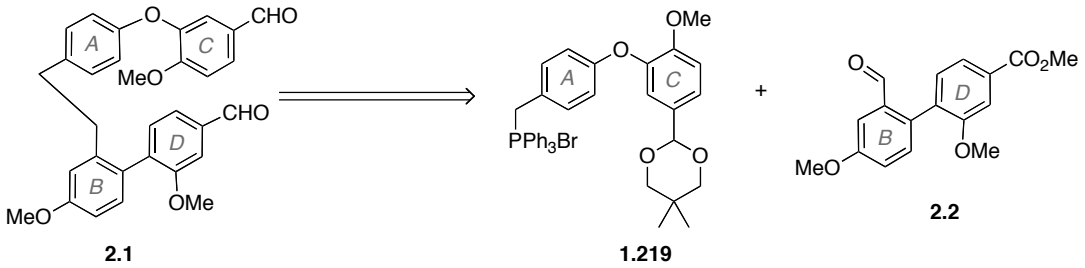
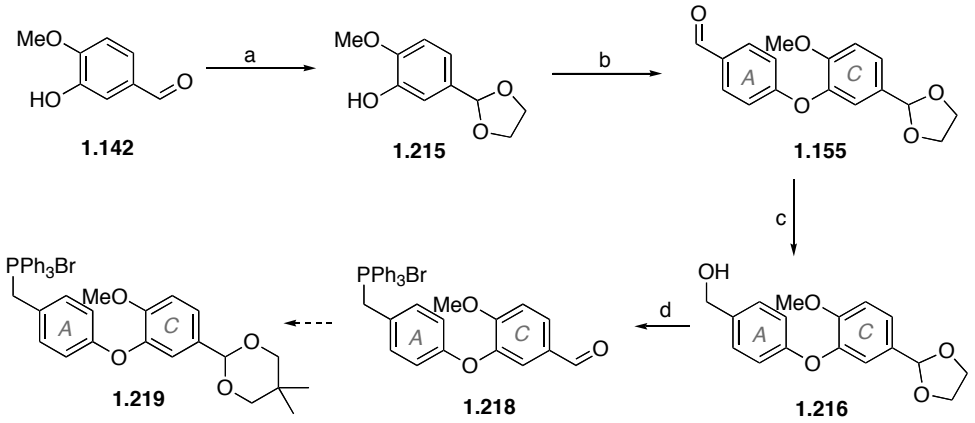


Figure 25

Thus, isovanillin **1.142** was first protected as the acetal **1.215**, then S_NAR chemistry formed the diphenyl ether **1.155**. As reported, benzyl bromide formation caused acetal hydrolysis unmasking the aldehyde. This necessitates reprotection of the subsequent phosphonium salt before Wittig olefination, inconveniently lengthening the sequence.



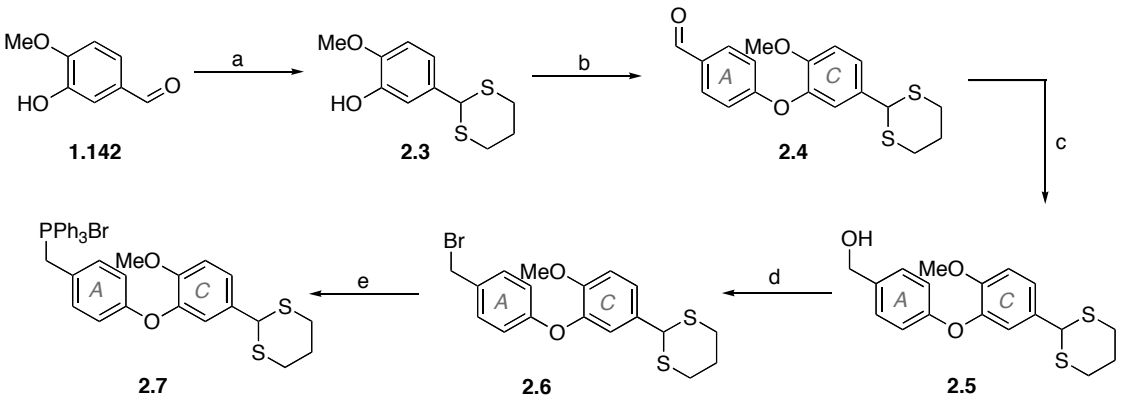
a). $(HOCH_2)_2$, PPTS, PhMe, 110 ºC, 24 h, 84%; b). 4-fluorobenzaldehyde, K_2CO_3, DMF, 155 ºC, 48 h, 87%; c). $NaBH_4$, MeOH, 0 ºC,1 h, 80%; d). CBr_4, PPh_3, DCM, 0 ºC–RT, 68 h, 70%, then PPh_3, PhMe, 110 ºC–0 ºC, 21 h, 73%.

Scheme 33

With a mind to circumventing the need for this second protection step, the use of a 1,3-dithiane protecting group was investigated, anticipating that this functionality would exhibit greater acid tolerance. The use of a dithiane offered further potential for synthetic exploitation, allowing umpolung chemistry to be investigated, either to effect macrocyclisation or simply the union of the *AC* fragment **2.4** with a suitable *BC* fragment, such as a benzyl bromide

Thus, isovanillin **1.142** was protected as dithiane **2.3** with propan-1,3-dithiol and catalytic acid in DCM in very good yield. An alternative procedure in glacial acetic

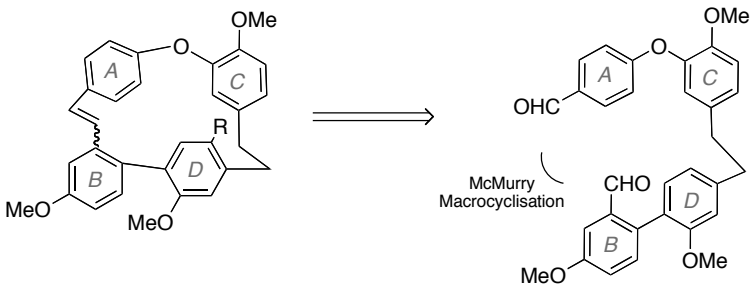
acid with catalytic BF_3.etherate afforded similar yields. Aromatic nucleophilic substitution to **2.4** and subsequent reduction to **2.5** proceeded without difficulty, albeit with the necessary addition of THF as a co-solvent to aid solubility in the reduction step. Surprisingly, bromination under established conditions once again induced partial deprotection of the aldehyde, with only 12% of the desired product **2.6** isolated. Though this was readily converted to phosphonium salt **2.7** (Scheme 34), it was clear that the use of a dithiane protecting group had not improved the synthesis as the yield for formation of the benzyl bromide was disappointingly poor.



a). propan-1,3-dithiol, BF_3.etherate, AcOH, 0ºC–RT, 6 h, 89% or propan-1,3-dithiol, PPTS, DCM, RT, 24 h then reflux, 24 h, 88% (yield based on propan-1,3-dithiol; b). 4-fluorobenzaldehyde, K_2CO_3, DMF, 115 ºC, 48 h, 79%; c). $NaBH_4$, MeOH, THF, 0 ºC–RT, 2.5 h, 73%; d). CBr_4, PPh_3, DCM, 0 ºC–RT, 8 h, 12% (impure); e). PPh_3, PhMe, 110 ºC–0 ºC, 32% (impure).

Scheme 34

Given the length of these sequences and the low yield reported in the 2006 work for the synthesis of *BD* fragment **1.225** (Scheme 31), a new synthetic approach was devised. When selecting an appropriate strategy, the potential for the later inclusion of stereogenic centres had to be considered. Whilst either of the ethano bridges linking the *A*-*B* and *C*-*D* rings could be targeted, it was the former that we selected for investigation. As a consequence, we chose to effect macrocyclisation at this linkage, *viz*. **2.9**→**2.8** (Figure 26), leaving a stilbene judiciously positioned for 1,2-diol installation using Sharpless asymmetric dihydroxylation chemistry.[58] In their previous synthesis of cavicularin **1.4**, Harrowven *et al*. used a free phenol on arene *D* to direct regioselective iodination.[57] To that end, we anticipated the use of an orthogonal protection group strategy in the synthesis of cavicularin **1.4**. However, in the early synthetic work, global methyl protection of the phenol groups was used to aid spectroscopic analysis (Figure 26).

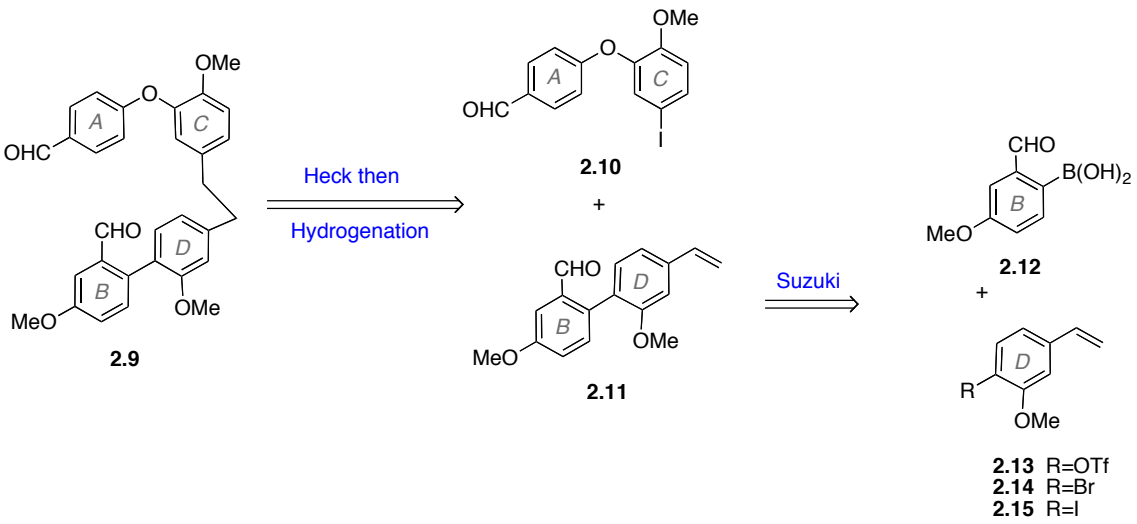


1.88 R=H Riccardin C trimethyl ether
2.8 R=I Precursor for Cavicularin

2.9

Figure 26

A disconnection to the bis-aldehyde offered the McMurry reaction as an obvious macrocyclisation strategy, with the potential for reduction and functional group manipulation to allow access to other macrcocyclisation approaches. For the synthesis of *ACDB* fragment **2.9**, two palladium-catalysed reaction strategies were envisaged. In the first a Suzuki-Miyaura reaction was planned to construct the biaryl bond followed by a Heck reaction to obtain the corresponding stilbene (Figure 27). In the second route a Heck reaction provides access to *ACB* fragment **2.16**, while a final Suzuki-Miyaura installs arene *B* (Figure 28). In each case a hydrogenation step was envisgaed to reduce the stilbene functionality. These routes each feature three sequential palladium-catalysed steps, offering the potential for telescoping these reactions into one-pot tandem procedures.



2.9

2.10

+

2.11

2.12

+

2.13 R=OTf
2.14 R=Br
2.15 R=I

Figure 27 – Route A retrosynthetic analysis.

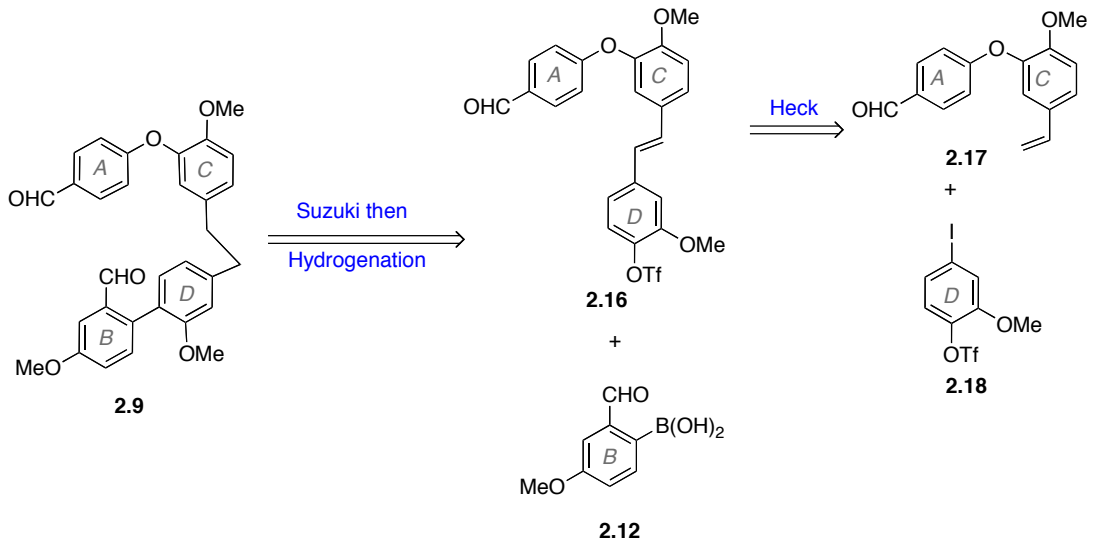


Figure 28 – Route B retrosynthetic anaylsis.

Chapter 3: Results and Discussion

A Total Synthesis of Riccardin C

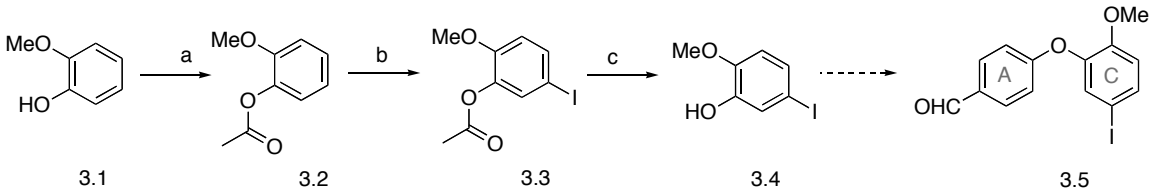
3.1 Assembling the *ACDB* Fragment

Having chosen to target the *A*-*B* ethano bridge for the key macrocyclisation reaction, work began on the development of an efficient synthetic route to a suitable acyclic precursor bis-aldehyde **3.38**. Two approaches, named herein Route A and Route B, were investigated simultaneously.

3.1.1 Route A

3.1.1a Synthesis of the *AC* Fragment

This approach to tetra-arene **3.38** envisaged a Heck reaction to couple *AC* fragment **2.10** and *BD* fragment **2.11**. To that end, attention first turned to the synthesis of diphenyl ether **2.10**. The regioselective iodination of guaiacol (*viz.* **3.1**→**3.4**) is documented in the literature, using a temporary acetate protection strategy to bias the regioselectivity in favour of the *para* directing effect of the methoxy group.[59] A nucluophilic substitution reaction would then be used to install arene *A* (Scheme 35).

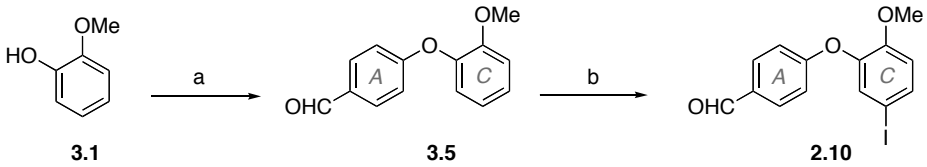


3.1 3.2 3.3 3.4 3.5

a).Ac2O; b). ICl; c). LiOH, H2O, 71% over three steps.

Scheme 35

The presence of the electron-withdrawing aldehyde moiety on arene *A* in the desired fragment offered a more elegant approach. Thus, the reaction of guaiacol **3.1** with 4-fluorobenzaldehyde in the presence of base gave diphenyl ether **3.5**. Treatment with iodine monochloride then effected a completely regioselective, albeit slow, iodination to give *AC* fragment **2.10** in two steps and 91% overall yield.

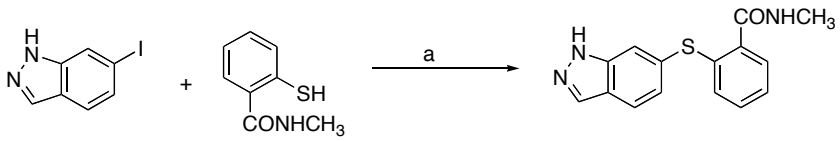


3.1 **3.5** **2.10**

a). 4-fluorobenzaldehyde, K_2CO_3, DMF, 155 ºC, 24 h, 91 %; b). ICl, DCM, RT, 7 d, 100%.

Scheme 36

In early synthetic work, a standard reductive work up for the iodination step was used, first quenching the reaction with saturated aqueous $Na_2S_2O_3$. The material was of high purity and did not require a purification step. However, on a number of occasions, subsequent established palladium-catalysed reactions with *AC* fragment **2.10** proved unsuccessful, giving only recovered starting material and no evidence for the initial oxidative insertion step. After purification of **2.10** by flash column chromatography, these reactions proceeded as expected. We attributed this caprice to catalyst poisoning by a trace impurity in some samples. This observation has been noted in the literature previously for a palladium-mediated coupling reaction following an iodination reaction. For example, Vaidyanathan and colleagues at Pfizer reported inconsistencies in the manufacturing process of Axitinib, in which the first step is the Migita coupling of **3.6** and **3.7** (Scheme 37).[60]

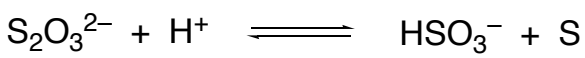


3.6 **3.7** **3.8**

a). Pd_2dba_3, Xanphos, CsOH, NMP.

Scheme 37

The authors determined that “poor” batches of **3.6** contained traces of elemental sulfur, a well-known poison of transition metal catalysts, deposited by the decomposition of $Na_2S_2O_3$ under acidic conditions (Scheme 38).



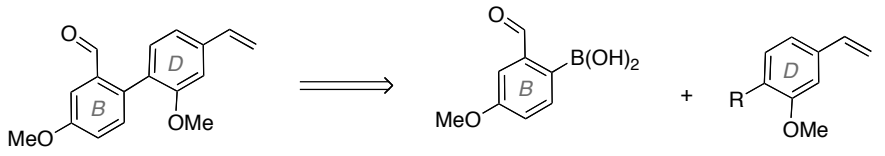
Scheme 38

Vaidyanathan *et al*. established that while the quantity of sulfur in the product can be moderated by solvent choice and careful control of the pH during work up, it cannot be completely eliminated. As a consequence, alternative quenches ($NaHSO_3$ and L-ascorbic acid) are recommended in place of the conventional thiosulfate work up for halogenation reactions in which the product is to be used in a transition metal-catalysed reaction.

The similarly capricious natural of batches of aryl iodide **2.10** was attributed to this phenomenon, although the precise cause of sulfur precipitation in certain cases and not in others is not known. By replacing $Na_2S_2O_3$ with $NaHSO_3$ for the reductive work up at the end of the reaction, no further problems with subsequent palladium-catalysed coupling reactions of **2.10** were encountered.

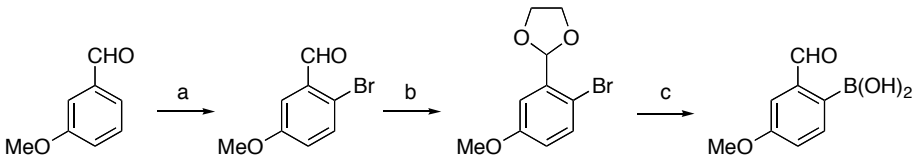
3.1.1b Synthesis of the *BC* Fragment

With *AC* fragment **2.10** in hand, attention turned to the synthesis of *BD* fragment **2.11**, for which we envisaged a Suzuki-Miyaura reaction to obtain the key aryl-aryl bond (Scheme 39). Boronic acid **2.12** is commercially available, but prohibitively expensive and so was prepared in three steps from *m*-anisaldehyde **3.9** (Scheme 40).[61]



2.11 **2.12** **2.13** R=OTf **2.14** R=Br **2.15** R=I

Scheme 39 – Suitable *B* and *D* fragments.

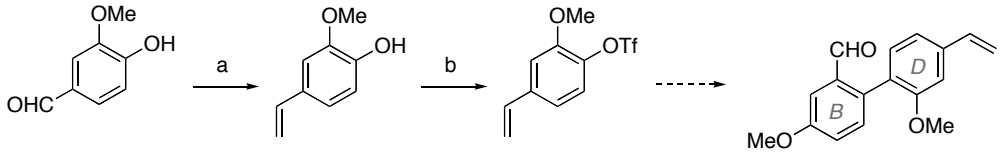


3.9 **3.10** **3.11** **2.12**

a). Br_2, $CHCl_3$, 0 ºC–RT, 6 h, 74%; b). $(HOCH_2)_2$, PPTS, PhMe, 110 ºC, 19 h, 97%; c). (i). *n*-BuLi, (ii). $B(On\text{-}Bu)_3$, (iii). HCl, 63%.

Scheme 40 – Synthesis of boronic acid **2.12**.

Triflation of 4-hydroxy-3-methoxystyrene **3.12** gave the most rapid entry to a suitable *D* ring unit. Once again, although **3.12** is commercially available, it proved more economically viable to synthesise it from vanillin in one step *via* a Wittig reaction, *viz.* **1.142**→**2.13**,[62] giving the desired triflate **2.13** in two steps and good yield (Scheme 41). Disappointingly, initial attempts at the Suzuki-Miyaura coupling of **2.13** and **2.12** with $Pd(dppf)Cl_2$ and K_2CO_3 in THF all failed. Similar results were obtained when $Pd(PPh_3)_3$ was used as catalyst, although prolonged microwave irradiation of the reaction did give traces of desired product **2.11**.

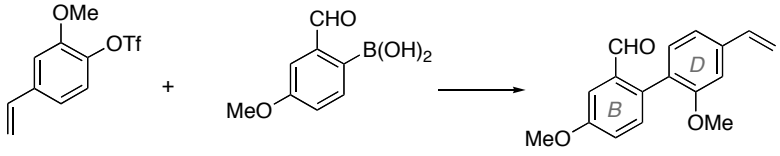


1.142 **3.12** **2.13** **2.11**

a). $MePPh_3Br$, KO*t*-Bu, THF, 0 ºC–RT, 18 h, 77%; b). Tf_2O, pyridine, DCM, 0 ºC, 4 h, 88%.

Scheme 41

Published Suzuki-Miyaura reactions using triflates often report the addition of KBr or LiCl to the reaction.[63] These salt additives are believed to alter the mechanistic pathway of the reaction from the ionic mechanism associated with oxidative insertion into carbon-triflate bonds to the neutral mechanism more commonly associated with oxidative insertion into carbon-halogen bonds. In our hands, the addition of KBr did improve conversion, with a yield of 17% obtainable with high catalyst loading and prolonged reflux times. The use of LiCl with microwave irradiation further enhanced the yield to 20% (Scheme 42). Ligandless conditions, using $Pd(OAc)_2$ as catalyst with no additional phosphine ligand, were consistently unsuccessful.

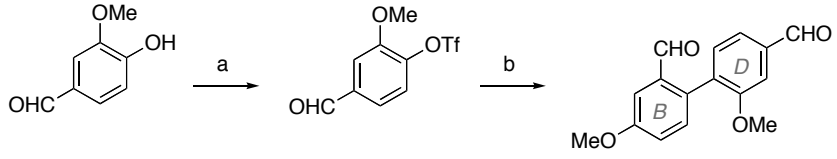


2.13 **2.12** **2.11**

Conditions:
KBr, Et_3N, $Pd(dppf)Cl_2$, dioxane, 101 ºC, 19 h, 2%.
KBr, Et_3N, $Pd(dppf)Cl_2$, dioxane, 101 ºC, 64 h, 17%.
LiCl, Et_3N, $Pd(dppf)Cl_2$, dioxane, microwave, 1 h, 20%.

Scheme 42

These low yields were attributed in part to an unfavourable oxidative insertion step into the carbon-triflate bond. Electronically, an electron-poor substrate is deemed most favourable for the initial oxidative insertion step.[64] Triflate **2.13**, with an *ortho* methoxy substitution, is an electron rich arene. This hypothesis is leant some credence by the ready reaction of triflate **3.13** under similar reaction conditions, without even the need for the addition of LiCl (Scheme 43). In this case, we believe that the electron-donating effect of the *ortho* methoxy group is moderated by the *para* formyl substitution.

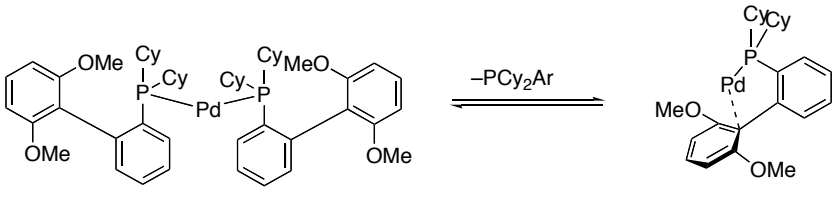


1.142 **3.13** **3.14**

a). Tf_2O, pyridine, DCM, 0–5 ºC, 2 h, 42%; b). **2.12**, Et_3N, Pd(dppf)Cl_2, dioxane, 101 ºC, 64%.

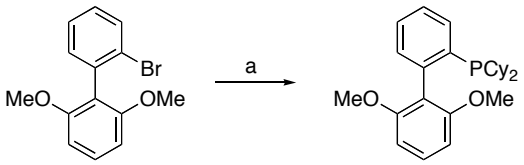
Scheme 43

Recent advances in phosphine ligand chemistry have expanded the scope of palladium-catalysed reactions, with Buchwald monophosphines increasingly used to effect difficult cross coupling reactions in which more conventional catalyst systems have failed. An example of such a ligand is SPhos **3.15**, which is believed to facilitate oxidative insertion *via* an *ipso*-stabilised palladium species **3.17** (Scheme 44).[65] SPhos **3.15** is now commercially available, or can be synthesised in one step from biaryl **3.18** (Scheme 45).[65] In combination with LiCl and Cs_2CO_3 as base, yields of **2.11** in excess of 70% were consistently obtainable in only a few hours (Scheme 46). The reaction also proceeded at room temperature. Both freshly synthesised **3.15** and commercially sourced **3.15** gave identical results in our hands.



3.16 **3.17**

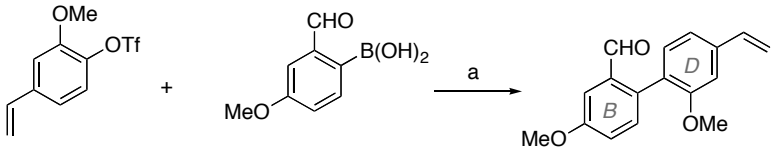
Scheme 44 – Pd-C (*ipso*) interaction promotes $L_2Pd(0)$ to LPd(0).



3.18 **3.15**

a). (i). *n*-BuLi, THF, –78 ºC, 5 min, (ii). Cy_2PCl, –78 ºC, 1 h, then 0 ºC, 2 h, 50%.

Scheme 45 – Synthesis of SPhos **3.15**.



2.13 **2.12** **2.11**

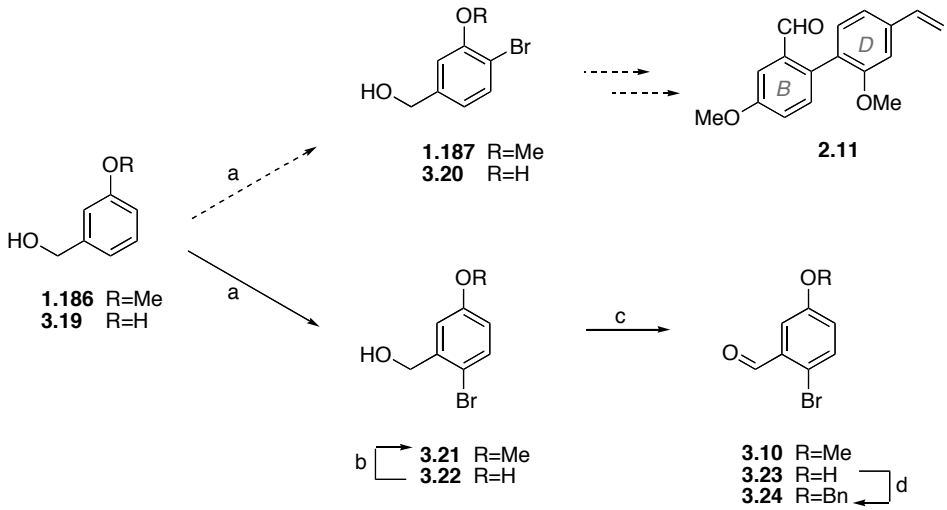
a). LiCl, Cs_2CO_3, $Pd(OAc)_2$, SPhos **3.15**, dioxane, 101 ºC, 3 h, 76%,

Scheme 46 – Optimised conditions for the synthesis of *BC* fragment **2.11**.

While the aforementioned optimisation was being undertaken, we began to explore alternative approaches to biaryl **2.11**. Theorising that our difficulties arose primarily from triflate **2.13**, we investigated halogenation at the relevant position. In the vast majority of reported cases, halogenation of arenes of this type occurs preferentially *para* to the methoxy substitution, which would give the undesired regiochemistry in the halogenation of *m*-anisaldehyde **3.9** (Scheme 40) and styrene **3.12**. However, Speicher *et al*. reported the use of a highly regioselective bromination of benzyl alcohol **1.186** in their formal total synthesis of isoplagiochin C **1.3** on a solid support (Scheme 24, Section 1.5.2).[55] This bromination procedure, with uses $NaBrO_3$ and $NaHSO_3$ in acetonitrile and water to generate hydrobromous acid *in situ* had also been reported earlier for the same substrate.[66]

With the desired regiochemistry for the aryl bromide in place, simple oxidation and Wittig methenylation would afford **2.14**. Despite its length, this approach presented two advantages over the use of triflate **2.13**: namely, the potential for simple orthogonal group protection for our eventual cavicularin **1.4** synthesis (**2.9**→**2.8** and *vide supra*: Chapter 2) and the opportunity to use arene *D* as the boronic acid fragment through halogen lithium exchange and borylation, thereby reversing the unfavourable electronic effects in the Suzuki-Miyaura reaction. Bromination of

benzyl alcohol **1.186** proceeded as described by Speicher in acceptable yield (Scheme 47). Pleasingly, bromination of **3.19** proceeded smoothly, with methylation of the phenol confirming an identical regiochemical outcome. Simple oxidation and functional group interconversion afforded the boronic acids, which underwent Suzuki-Miyaura reactions with aryl bromide **3.10**. However, the ^{1}H and ^{13}C NMR data obtained for the Suzuki product did not match that obtained from Scheme 46.



a). R=Me: $NaBrO_3$, $NaHSO_3$, H_2O, MeCN, 0 ºC–RT, 5 h, 50%, R=H: $NaBrO_3$, $NaHSO_3$, H_2O, MeCN, 0 ºC–RT, 2 h, 60%; b). MeI, K_2CO_3, acetone, RT, 19 h, 100%; c). R=Me: activated MnO_2, DCM, RT, 19 h, 74%, R=H: activated MnO_2, DCM, RT, 74%; d). BnBr, KI, K_2CO_3, THF, reflux, 19 h, 79%.

Scheme 47 – Regioselective bromination procedures.

The regiochemistry of our *B* ring appeared secure thanks to the wealth of literature precedent relating to aryl bromide **3.10**.[67] However, the data for our sample of **1.187** proved a good match for that given in the literature (See Tables 1 and 2) by Lee *et al*. and subsequently by Speicher *et al*. Moreover, Speicher and coworkers had used this compound as a building block in their formal total synthesis of isoplagiochin C **1.3**, thereby verifying the structure.

^{1}H Data reported by Speicher *et al.* ($CDCl_3$, 500 MHz)[55]	**^{1}H Data obtained in our hands ($CDCl_3$, 400 MHz)**
7.40 (d, *J*=8.8 Hz)	7.42 (d, *J*=8.8 Hz)
7.05 (d, *J*=3.1 Hz)	7.07 (d, *J*=3.0 Hz)
6.70 (dd, *J*=8.8, 3.1 Hz)	6.73 (dd, *J*=8.8, 3.0 Hz)
4.69 (s)	4.71 (d, *J*=6.0 Hz)
3.80 (s)	3.81 (s)
2.14 (br. s)	2.07 (t, *J*=6.0 Hz)

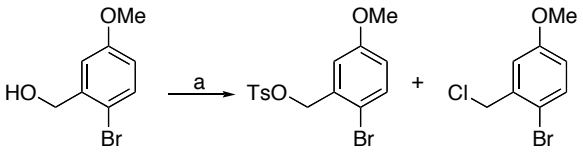
Table 1

^{13}C Data (75 MHz, $CDCl_3$)	
Obtained Data	159.5, 140.9, 133.3, 115.0, 114.5, 112.7, 65.2, 55.7
Literature Data[55]	159.3, 140.7, 133.1, *144.8*, *144.2*, 112.5, 65.0, 55.5

The figures in italics are thought to be typing errors.

Table 2

Further confusion arose when a sample of "**1.187**" was oxidised to the corresponding aldehyde. Now the spectral data was a perfect match for the regioisomeric aldehyde **3.10**! Thus, to resolve the matter an X-ray crystal of its tosylated derivative **3.25** was obtained (Scheme 48 and Figure 29). This confirmed our suspicion that the reported regiochemistry of the bromide was incorrect. It also helped to explain the low yields obtained for the Suzuki reactions (Scheme 42), doubtless resulting from the crowded steric environment around the biaryl bond.



3.22 **3.25** **3.26**

a). TsCl, Et_3N, DMAP, DCM, 0–5 ºC, 2.5 h, 69% of **3.25**.

Scheme 48 – Tosylation of **3.22**.

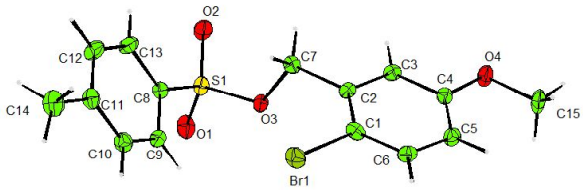
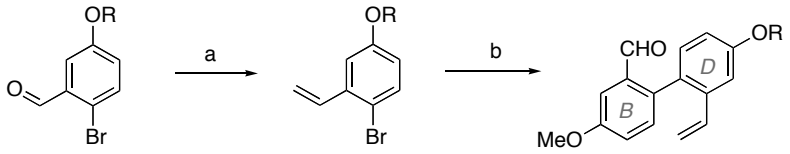


Figure 29 – Crystal structure of **3.25**.



3.10 R=Me
3.24 R=Bn

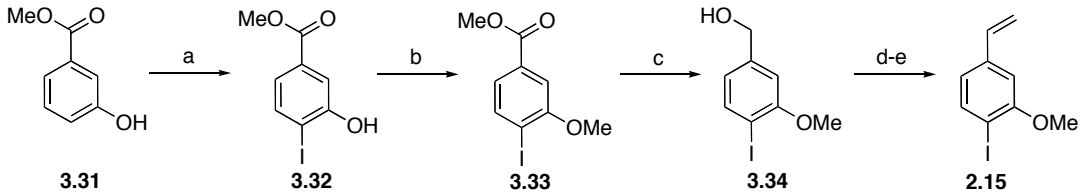
3.27 R=Me
3.28 R=Bn

3.29 R=Me
3.30 R=Bn

For R=Me: a). $MePPh_3Br$, KO*t*-Bu, THF, 0 ºC–RT, 1 h, 81%; f). (i). *n*-BuLi, THF, 0 ºC, 20 min, (ii). $B(On\text{-}Bu)_3$, 0 ºC–RT, 4 h, (iii). HCl, 15 min then **3.10**, K_2CO_3, $Pd(dppf)Cl_2$, THF, 60 ºC, 19 h, 31%.
For R=Bn: a). $MePPh_3Br$, KO*t*-Bu, THF, 0 ºC–RT, 1 h then 65 ºC, 19 h, 55%; f). (i). *n*-BuLi, THF, 0 ºC, 10 min, (ii). $B(On\text{-}Bu)_3$, 0 ºC–RT, 3 h, (iii). HCl, 10 min then **3.10**, K_2CO_3, $Pd(dppf)Cl_2$, THF, 60 ºC, 19 h, 33%.

Scheme 49 – Incorrect regioisomer work towards the *BD* fragment.

To advance the synthesis it was necessary to obtain a haloarene with the correct regiochemistry. Attention next turned to the synthesis of aryl iodide **2.15**. A lengthy but high-yielding sequence of regioselective iodination of ester **3.31**, methylation of the resulting phenol **3.32**, followed by reduction to alcohol **3.33** and re-oxidation to aldehyde **3.34** and Wittig olefination gave the desired aryl iodide **2.15** (Scheme 50).

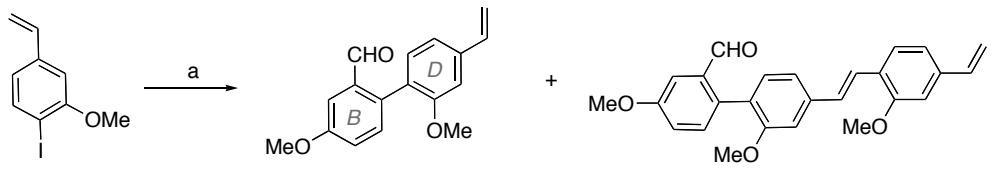


3.31 **3.32** **3.33** **3.34** **2.15**

a). I_2, Na_2CO_3, H_2O, RT, 20 h, 77%; b). MeI, K_2CO_3, acetone, RT, 68 h, 97%; c). DiBAL-H, DCM, –78 ºC–RT, 4 h, 55%; d). activated MnO_2, DCM, RT, 18 h, 67% of **3.35**; e). $MePPh_3Br$, KO*t*-Bu, THF, 0 ºC–RT, 6 h, 96%.

Scheme 50

The Suzuki reaction of aryl iodide **2.15** and boronic acid **2.12** appeared to proceed well, with complete consumption of **2.15** and formation of the desired product **2.11** detected by TLC. However, yields of **2.11** were typically low (38%), with triarene **3.36** accounting for much of the remaining mass balance (Scheme 51). This unwanted side reaction could not be suppressed. Though disappointing, contemporaneous work had optimised the earlier Suzuki-Miyura reaction of triflate **2.13** and boronic acid **2.12** to acceptable levels, so work suppressing the formation of **3.36** was no longer warranted.



2.15 **2.11** **3.36**

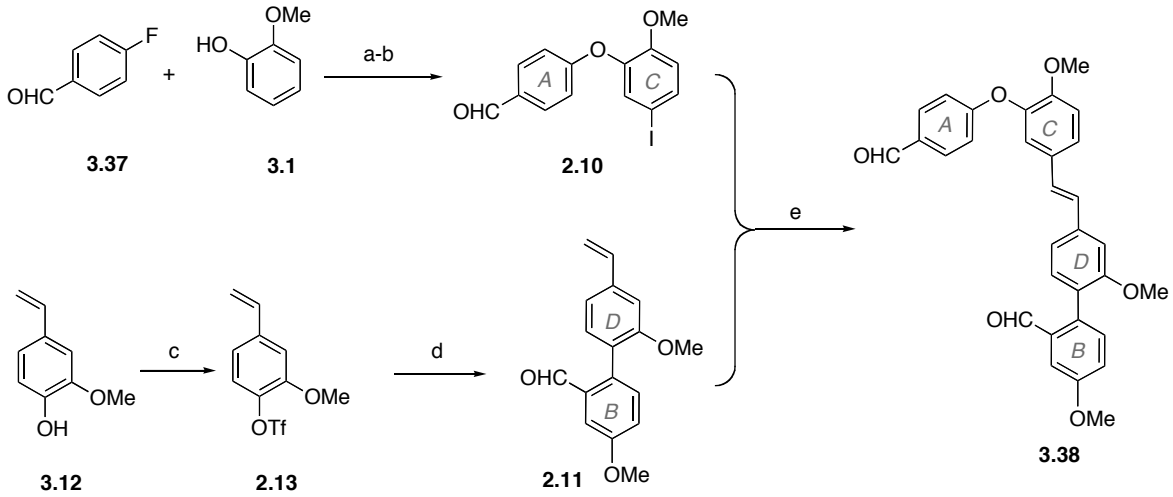
a). **2.12**, $Pd(dppf)Cl_2$, Et_3N, dioxane, 101 ºC, 19 h, 38% of **2.11**.

Scheme 51

In conclusion, a short, efficient route to biaryl **2.11** was achieved in two steps from commercially available starting materials *via* the triflation of **3.12** and subsequent Suzuki-Miyaura reaction with boronic acid **2.12**. High yields for the Suzuki-Miyaura step were obtained using SPhos **3.15** as the ligand, with Cs_2CO_3 as the base. Owing to prohibitively high costs, boronic acid **2.12** and styrene **3.12** were prepared by synthesis rather than bought from a commercial supplier.

3.1.1c Union of the *AC* and *BD* fragments

The union of *AC* fragment **2.10** and *BD* fragment **2.11** was achieved *via* a ligandless Heck reaction in very good yield to give exclusively the *trans*-stilbene **3.38**. Summarised below (Scheme 52) is the complete Route A approach to tetraarene **3.38** in 57% overall yield and longest linear sequence of three steps from commercially available starting materials.



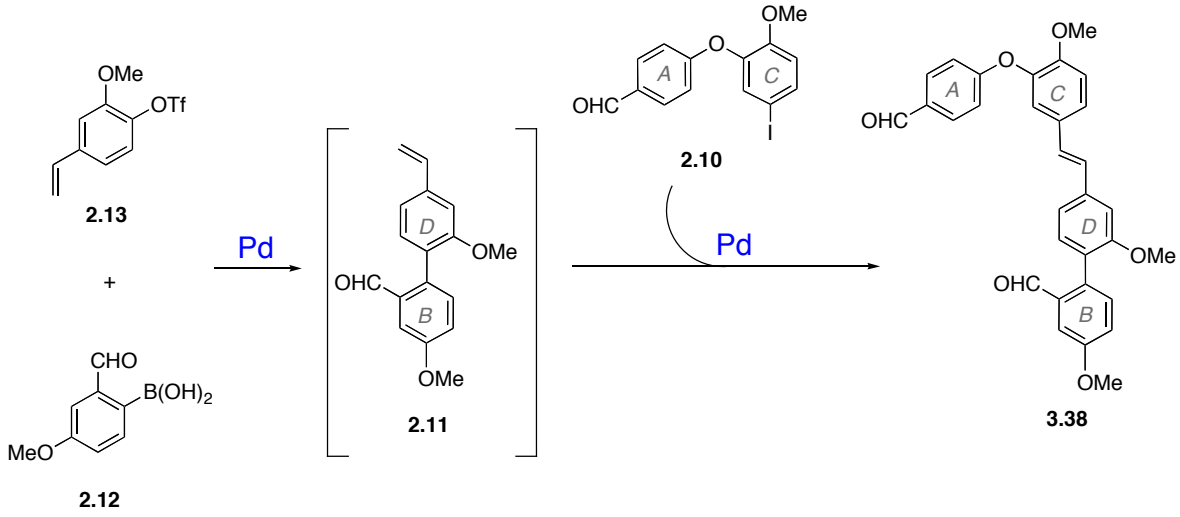
3.37 **3.1** **2.10** **3.38**

3.12 **2.13** **2.11**

a). 4-fluorobenzaldehyde, K_2CO_3, DMF, 155 ºC, 24 h, 91 %; b). ICl, DCM, RT, 7 d, 100%; c). Tf_2O, pyridine, DCM, 0 ºC,4 h, 88%; d). **2.12,** LiCl, Cs_2CO_3, $Pd(OAc)_2$, SPhos **3.15**, dioxane, 101 ºC, 3 h, 76%; e). $Pd(OAc)_2$, Et_3N, 101 ºC, 19 h, 83%.

Scheme 52

With each of the two steps in this palladium-catalysed sequence optimised, we began to investigate the potential for telescoping these reactions in a one pot tandem protocol. As the Suzuki-Miyaura reaction *viz*. **2.13**→**2.11** had proved the most condition-specific reaction, these optimised condition were used first. Thus, Suzuki-Miyaura coupling of **2.12** and **2.13** proceeded under established conditions to completion, then aryl iodide **2.10** was added and the reaction once again heated at reflux. Disappointingly, yields were always low, using both $Pd(OAc)_2$ and $PdCl_2$ and varying the reflux times of both stages, with 10% yield over the steps representing the best obtained yield (Scheme 53). In each case, catalyst demise and palladium black precipitation occurred in the Heck stage. Although this work does establish the principle for telescoping palladium-catalysed steps in the synthesis of macrocyclic bisbibenzyls of this type, further optimisation is clearly needed. Future work could use flow chemistry methods and solid supported catalysts to improve this route.



LiCl, Cs_2CO_3, $Pd(OAc)_2$, SPhos **3.15**, dioxane, reflux, 21 h, then **2.10**, reflux, 18 h, 10%.

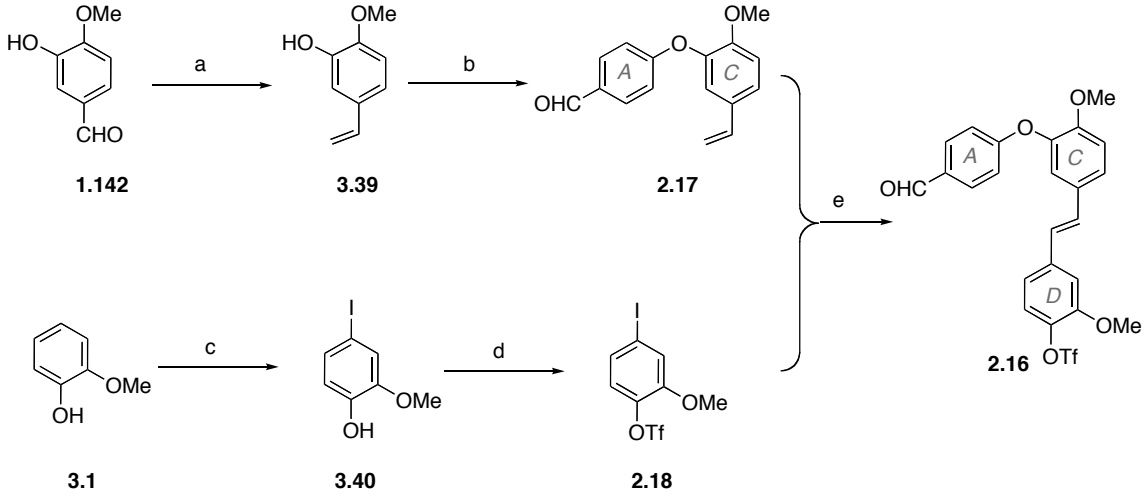
Scheme 53

3.1.2 Route B

Our second route to precursor **3.38** represents a more stepwise approach, first synthesising *ACD* fragment **2.16** *via* a Heck reaction then appending the *B* arene using a Suzuki-Miyaura reaction analogous to that described above.

3.1.2a Synthesis of the *ACD* Fragment

AC Fragment **2.17** was given in excellent yield by a Wittig methenylation of isovanillin **1.142** followed by nucleophilic aromatic substitution of 4-fluorobenzaldehyde. Regioselective iodination of guaiacol **3.1** under basic conditions with subsequent triflation gave *D* ring precursor **2.18** in excellent yield. The union of these fragments **2.17** and **2.18** again proved high yielding under ligandless Heck reaction conditions to give triarene **2.16** in 82% yield (Scheme 54).



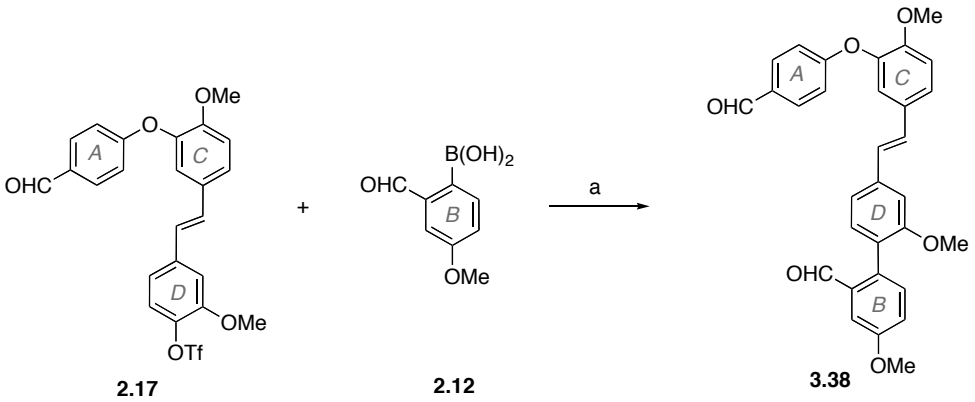
a). $MePPh_3Br$, KO*t*-Bu, 65 ºC, 19 h, THF, 91%; b). **3.37,** K_2CO_3, DMF, 100 ºC, 20 h, 99%; c). NaOCl, NaI, NaOH, MeOH, 0 ºC, 2 h, 86%; d). Tf_2O, pyridine, DCM, 0 ºC, 1 h, 93%; e). $Pd(OAc)_2$, Et_3N, dioxane, 100 ºC, 18 h, 82%.

Scheme 54

3.1.2b Installing the Fourth Arene

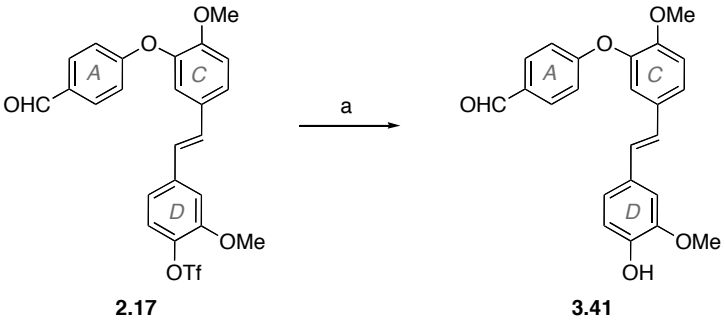
The Suzuki-Miyaura reaction with boronic acid **2.12** to install the fourth arene underwent a similar optimisation process to that described above. The same optimised reaction conditions also proved successful in this case, affording *ADCB* tetraarene **3.38** in 71% yield for the Suzuki-Miyaura step, and 43% overall yield from commercially available starting materials (Scheme 55). Interestingly, during

optimisation, hydrolysis of the triflate moiety to give phenol **3.41** was observed when aqueous NaOH was used as base for the Suzuki-Miyaura reaction (Scheme 56).



a). $Pd(OAc)_2$, SPhos, LiCl, Cs_2CO_3, dioxane, 100 ºC, 18 h, 71%

Scheme 55 – Installing the fourth arene – optimised conditions.



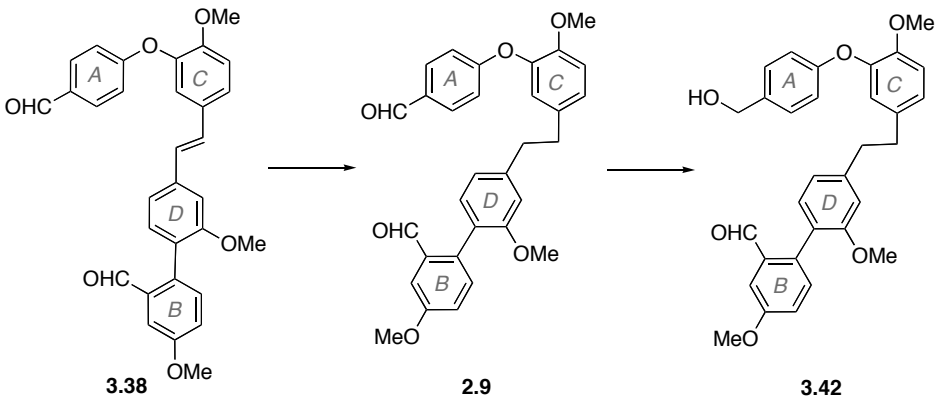
a). **2.12**, $Pd(dppf)Cl_2$, 2 M NaOH, dioxane, microwave, 1 h, 27%.

Scheme 56 – Hydrolysis of the triflate moiety.

Both routes A and B gave rapid access to *ACDB* tetraarene **3.38** in acceptable overall yield (58% and 47% over three and four steps yields respectively). Route A was preferable owing not only to its higher yield but also to the ease of purification of **3.38**. Using route B, **3.38** and **2.17** are of similar polarity making purification of the final step more difficult, whereas **3.38** is easily separable from **2.10** and **2.11**. Route A was used to repeatedly obtain multigram quantities of **3.38**.

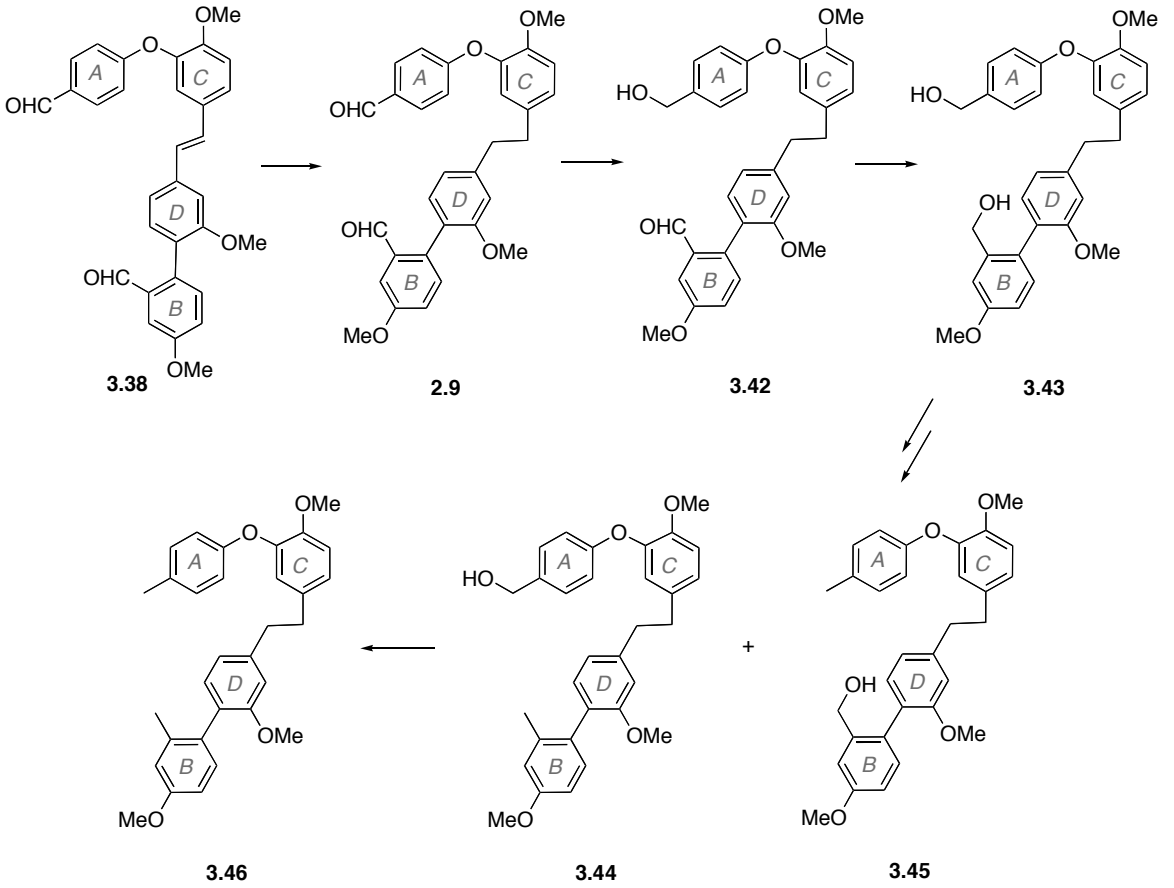
3.1.3 Hydrogenation

With tetraarene **3.38** in hand, attention next turned to hydrogenation of the stilbene functionality. Strategically it seemed appropriate to perform the reduction at this juncture as it would impart greater flexibility to the molecule, allowing sufficient flexibility for macrocyclisation to the desired 18-membered ring of riccardin C. Yields for the hydrogenation step were typically low (52%), with over-reduced alcohol **3.42** accounting for the remaining mass balance, necessitating a subsequent reoxidation step (*viz*. **3.42**→**2.9**, Scheme 57). The extent of hydrogenation in the reaction appeared to depend on a number of factors, with over-reduced diol **3.43** and toluene functionalities **3.44**, **3.45** and **3.46** all obtained on occasion. Interestingly, ^{1}H NMR, TLC, HPLC and LCMS analyses of the reaction indicated that the initial hydrogenation steps occur sequentially (Scheme 58), with hydrogenation of the stilbene functionality (*viz*. **3.38**→**2.9**) occurring first, followed by reduction of the *A* ring aldehyde moiety (*viz*. **2.9**→**3.42**) and then reduction of the second aldehyde (*viz*. **3.42**→**3.43**).



a). H_2, Pd/C, DCM, MeOH, RT, 20 min, 52% of **2.9** or H_2, Pd/C, DCM, MeOH, RT, 20 min then MnO_2, DCM, RT, 19 h, 92% of **2.9**.

Scheme 57



Scheme 58 – Sequential hydrogenation steps.

The hydrogen uptake profile of this reaction sequence was monitored using an Argonaut Endeavour hydrogenation system at GSK Tonbridge with the assistance of Dr. Gary Kelly (Figure 30). The first two molar equivalents of hydrogen are indicated by the dotted lines and these show that the first two reduction steps (**3.38**→**2.9**→**3.42**) occur at similar rates, with the third reduction step (**3.42**→**3.43**) proceeding considerably more slowly. We attributed the higher isolated yields of alcohol **3.42** (89%) to this rate difference.[•] Of interest is the order of reduction in this reaction. We speculate that the steric encumbrance around the biaryl bond is the cause of this selectivity; indeed, variable temperature (VT) ^{1}H NMR analysis of diol **3.43** indicated restricted rotation at this position (Figure 31).

[•] It should be noted that isolated yields were variable and difficult to replicate.

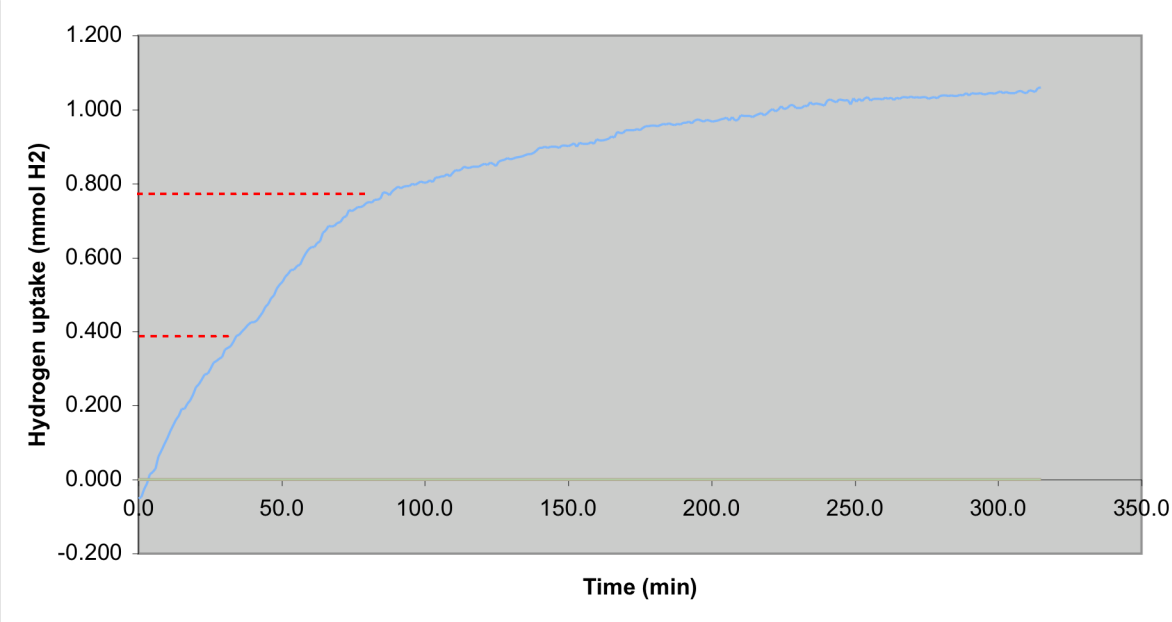


Figure 30 – Hydrogen uptake profile with 0.4 mmol **3.38** performed on an Argonaut Endeavour.

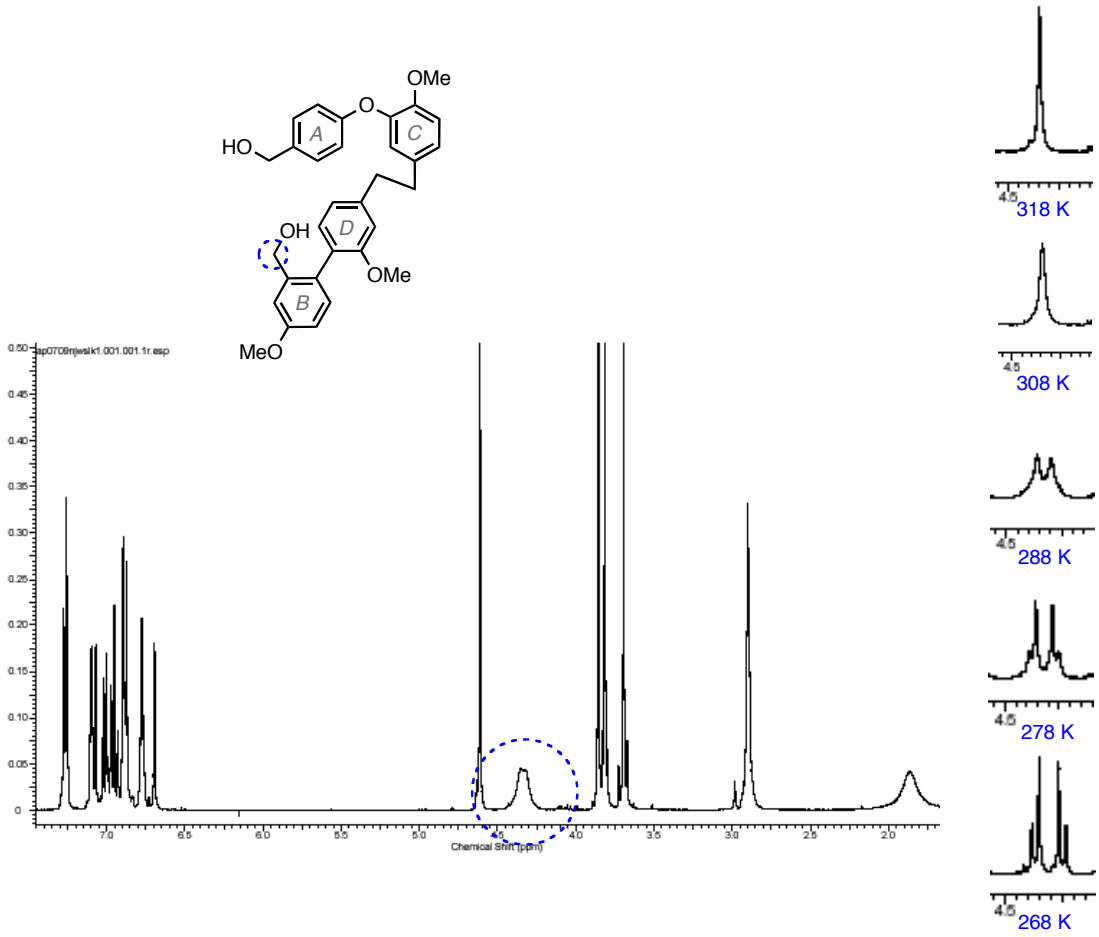
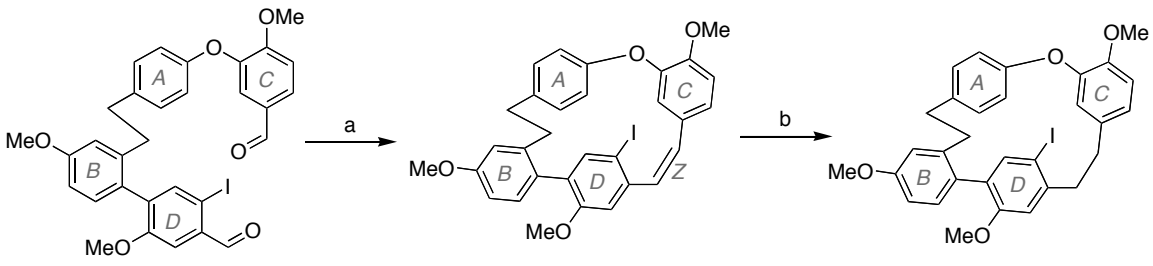


Figure 31 – VT NMR studies on **3.43** show the restricted rotation about the *C–O* bond on the *B* arene. The major spectrum was recorded at 298 K.

3.2 Completing the Synthesis: Macrocyclisation Strategies

3.2.1 McMurry

The first macrocyclisation strategy investigated was a McMurry reaction, previously used by Harrowven *et al*. to effect macrocyclisation at the *C*-*D* linkage in their synthesis of iodinated riccardin C **1.213**. The authors reported a 35% yield of exclusively *cis* stilbene **1.229** after reflux (Scheme 59).[57]

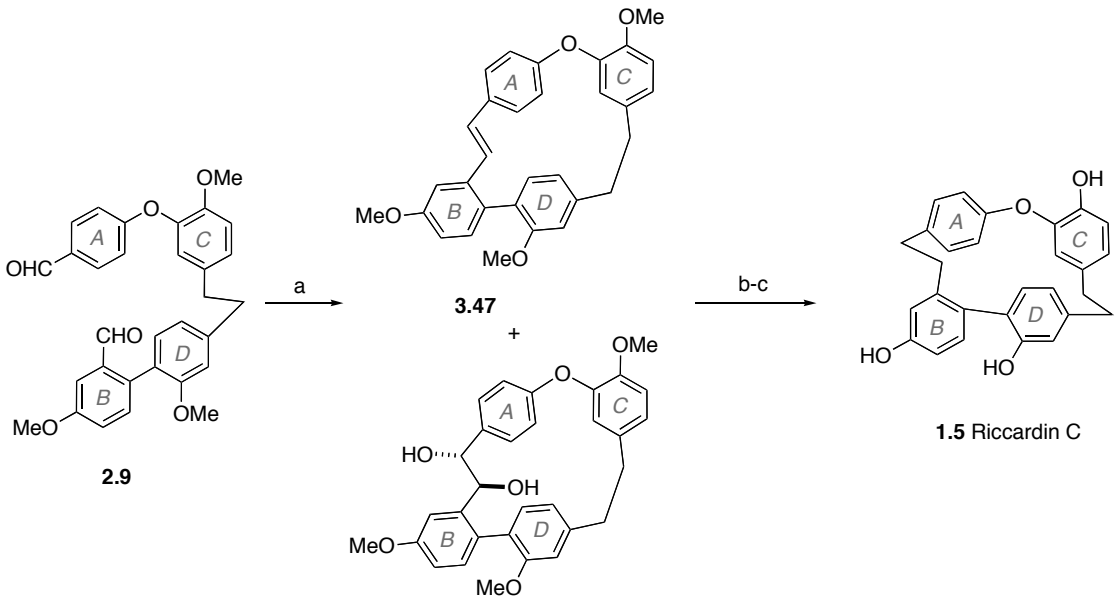


1.228 **1.229** **1.213**

a). $TiCl_4$, Mg, THF, –78 °C, 5 h, then reflux, 11 h, 35%; b). $TsNHNH_2$, NaOAc, THF, H_2O, 90 °C, 91%.

Scheme 59

Exposure of **2.9** to the same low-valent titanium species, formed by reduction of $TiCl_4$ with magnesium turnings, at high dilution afforded a mixture of products after reflux. The desired 18-membered macrocycle **3.47** was identified, interestingly as the *trans*-stilbene, in modest yield, with the remaining mass balance comprising 1,2-diol **3.48** and what we believe to be polymerised material which could not be characterised. Resubmission of diol **3.48** to the reaction conditions did not afford the desired stilbene, even after prolonged reflux, returning only starting material. Thus, we tentatively assigned a *threo* configuration to **3.48**, believing that this diastereoisomer is too constrained by the 18-membered macrocycle for the alcohol moieties to achieve sufficient planarity for elimination to occur. Exposure of the entire reaction mixture to hydrogen in the presence of palladium on carbon yielded riccardin C tri-*O*-methyl ether **1.88** through concomitant hydrogenation of the alkene and hydrogenolysis of the diol in **3.47** and **3.48** respectively. Deprotection with BBr_3 then unmasked the phenol moieties, completing the total synthesis of riccardin C **1.5** (Scheme 60).



a). $TiCl_4$, Mg, THF, –78 ºC, 19 h; b). H_2, Pd.C, DCM, MeOH, RT, 1 h, 20% over 2 steps; c). BBr_3, DCM, 0 ºC, 3.5 h, 85%.

Scheme 60

3.2.2 Ring Closing Metathesis

Though we had achieved a short total synthesis of riccardin C **1.5**, the McMurry macrocyclisation step was far from satisfactory. The low yield, capricious nature on scale up and formation of a complex product mixture in the key step left considerable room for improvement. To that end, the next strategy considered was ring closing metathesis. Thus, bis-styrene **3.51** was obtained from bis-aldehyde **2.9** in good yield using a double Wittig reaction, then treated with Grubbs' second generation catalyst **3.49** (Figure 32)[68] at high dilution. Alas, none of the desired product was observed by TLC or HPLC analyses, with *trans*, *trans* C_2 symmetric dimer **3.52** identified as the only isolable product in 33% yield (Scheme 61). Similar results were also obtained when repeating the reaction with Hoveyda-Grubbs' second generation catalyst **3.50** (Figure 32).[69]

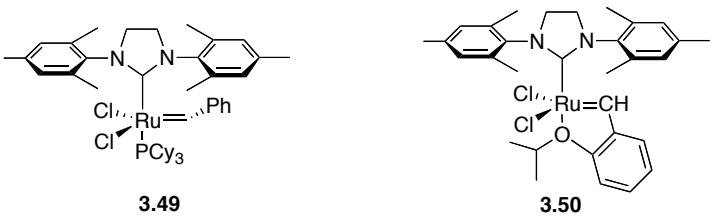
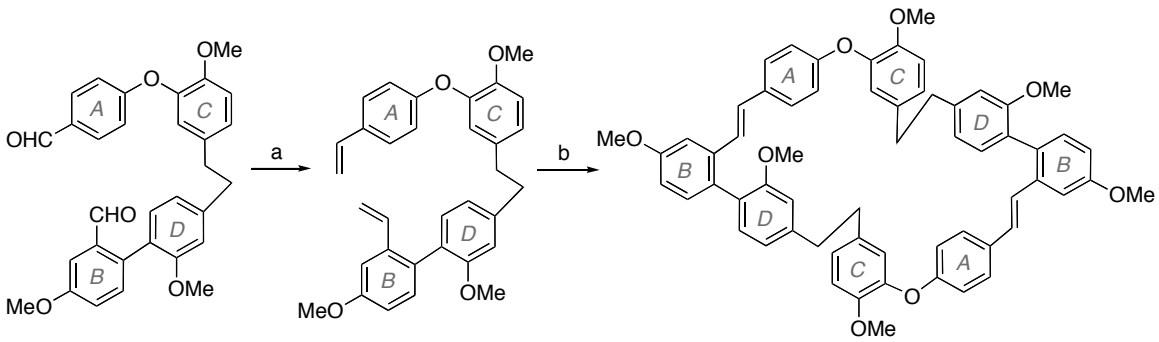


Figure 32



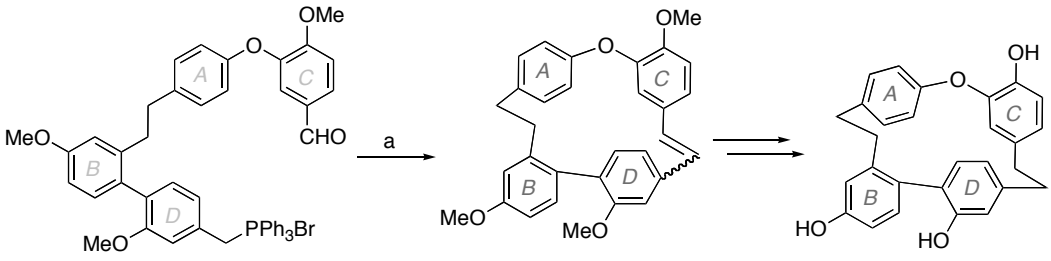
2.9 **3.51** **3.52**

a). MePPh$_3$Br, KO*t*-Bu, THF, RT, 1.5 h, 72%; b). **3.49**, DCM, reflux, 21 h, 33%.

Scheme 61

3.2.3 Wittig

Attention next turned to Wittig macrocyclisation methods, which have been used to achieve the total syntheses of a number of macrocyclic bis-bibenzyls, [41, 52, 54, 70] including riccardin C **1.5**.[41, 53] The Wittig reaction reported by Eicher *et al*. in their total synthesis of riccardin C1.5 effected macrocyclisation at the *C*-*D* ethano bridge and led to a mixture of *cis*- and *trans*- stilbenes (Scheme 62).[53]



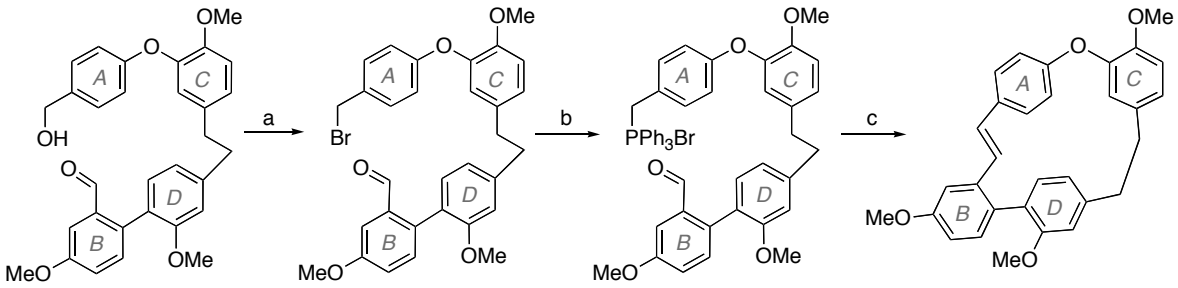
1.163 **1.164** **1.5** Riccardin C

a). NaOMe, DCM, 80%.

Scheme 62

By contrast, our macrocyclisation was to be effected at the *A*-*B* ethano bridge. To gain access to the required aldehyde phosphonium salt **3.54**, we were able to utilise the previously unwanted over-reduction of **3.38** in the hydrogenation step, *viz.* **3.38**→**3.42**, Scheme 58. Thus, treatment of alcohol **3.42** with PBr_3 afforded benzyl bromide **3.53**, which was immediately converted to the corresponding phosphonium salt **3.54** without further purification. Pleasingly, exposure of **3.54** to

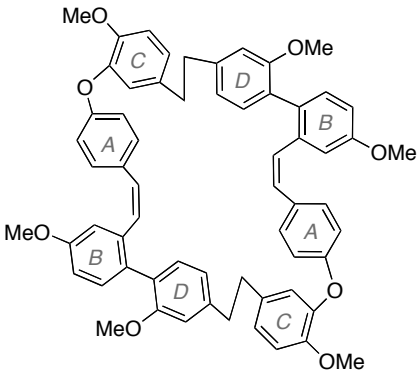
base under high dilution conditions gave the desired macrocycle **3.42**, in 45% yield exclusively as the *trans*-stilbene (Scheme 63). Much of the remaining mass balance comprised a dimer (33%) which was characterised as the all *cis*-bis-stilbene and was confirmed by X-ray crystallography (Figure 33). The total synthesis of riccardin C **1.5** was completed by a straightforward sequence of hydrogenation and deprotection, *viz*. **3.47**→**1.5** (Scheme 64).



3.42 **3.53** **3.54** **3.47**

a). PBr_3, DCM, 0 °C–RT, 3 h; b). PPh_3, PhMe, reflux,18 h, 91% over 2 steps; c). NaOMe, DCM, RT then reflux, 23 h, 45%.

Scheme 63



3.55

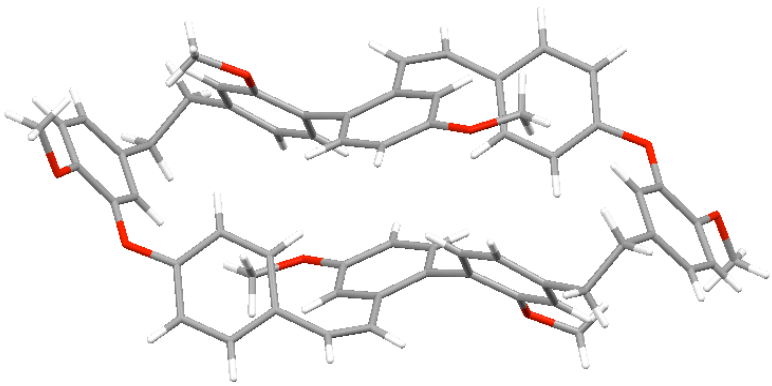
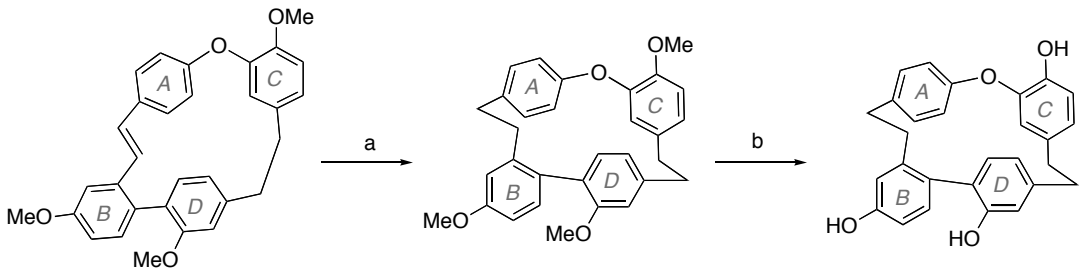


Figure 33



3.47 **1.88** **1.5** Riccardin C

a). H_2, Pd.C, DCM, MeOH, RT, 3 h 90%; b). BBr_3, DCM, 0 ºC, 3.5 h, 85%.

Scheme 64

We were also able to obtain X-ray data for *trans*-stilbene **3.47**, the crystal structure for which exhibits considerable strain including a boat-shaped aromatic ring and a twisted olefin (Figure 34). A full discussion of these structural features is presented in Chapter 6. We believe that the enthalpic and entropic gain associated with the liberation of triphenylphosphine oxide in the Wittig reaction compensates for the energetic penalty of creating this strained macrocycle.

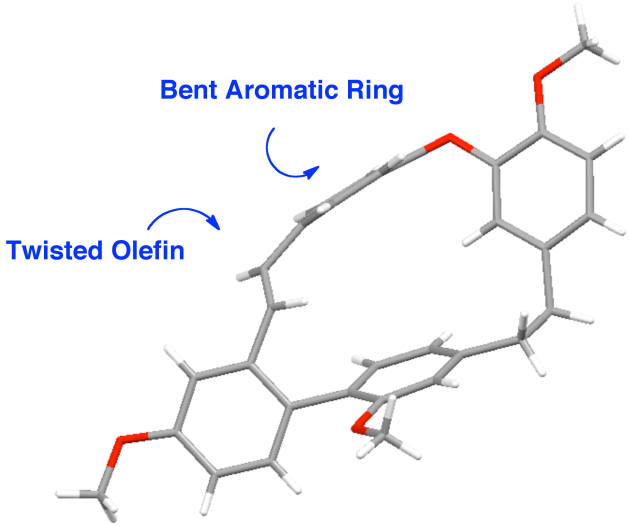


Figure 34

3.3 Conclusions

The total synthesis of riccardin C **1.5** has been achieved, effecting macrocyclisation at the less commonly reported *A*-*B* linkage. Two short and efficient routes to tetraarene **3.38** were established, each showcasing a series of

palladium-catalysed coupling reactions. The hydrogenation of tetraarene **3.38** exhibited sequential, chemoselective reduction steps, the rates of which were monitored using hydrogen uptake profiles. A number of macrocyclisation strategies were investigated, with both McMurry and Wittig reactions affording the desired stilbene **3.47**, in each case as the *trans*-isomer exclusively. No evidence for the corresponding *cis*-stilbene was found. An X-ray crystal structure was obtained for stilbene **3.47** revealing some unusual structural features including a bent aromatic ring (akin to that found in cavicularin **1.4**) and a twisted olefin. To our knowledge, no macrocyclic bisbibenzyl, natural or unnatural, other than cavicularin **1.4**, has been reported to exhibit a boat-shaped arene.

Chapter 4: Results and Discussion

Elaborating to Cavicularin

4.1 Installing the Halogen

4.1.1 Orthogonal Protection Strategies

With a route to riccardin C **1.5** in place, we began to explore orthogonal protecting group strategies to enable the installation of an aryl iodide on arene *D*. Our first approach employed a *tert*-butyldimethylsilyl protecting group for the phenol of arene *D*. For our route A synthesis we envisaged the silyl protection of isovanillin **1.142** then methoxy deprotection followed by Wittig methenylation and triflation to obtain suitable *D* ring fragment **4.4** (Figure 35). The silyl protection of **1.142** to give **4.6** proceeded in good yield. However, standard methyl ether deprotection methods did not give the desired phenol **4.7** (Scheme 65).

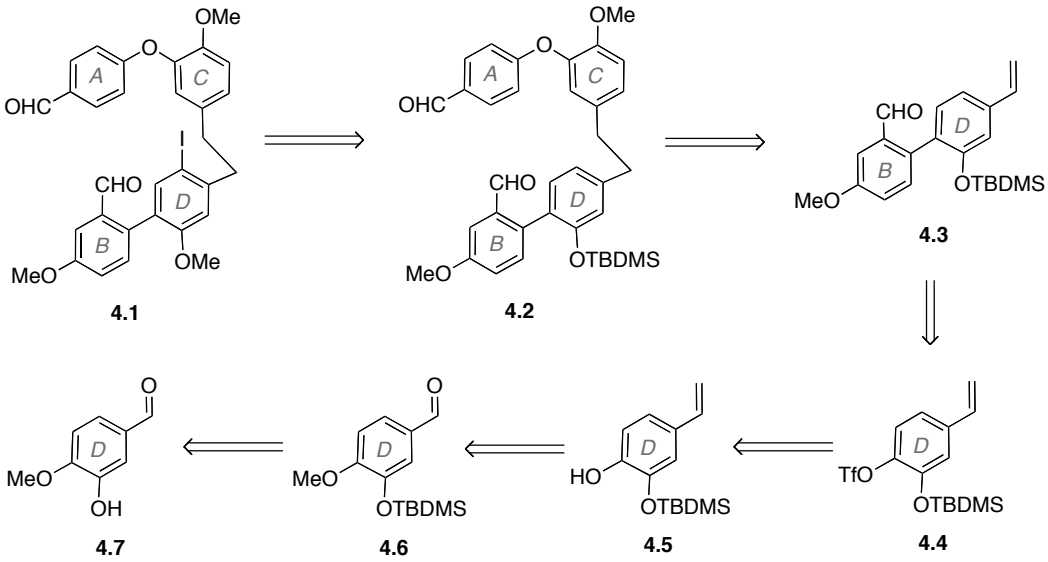
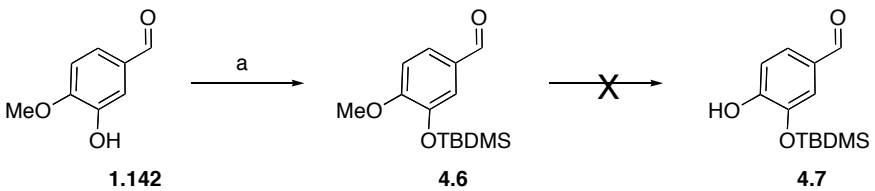


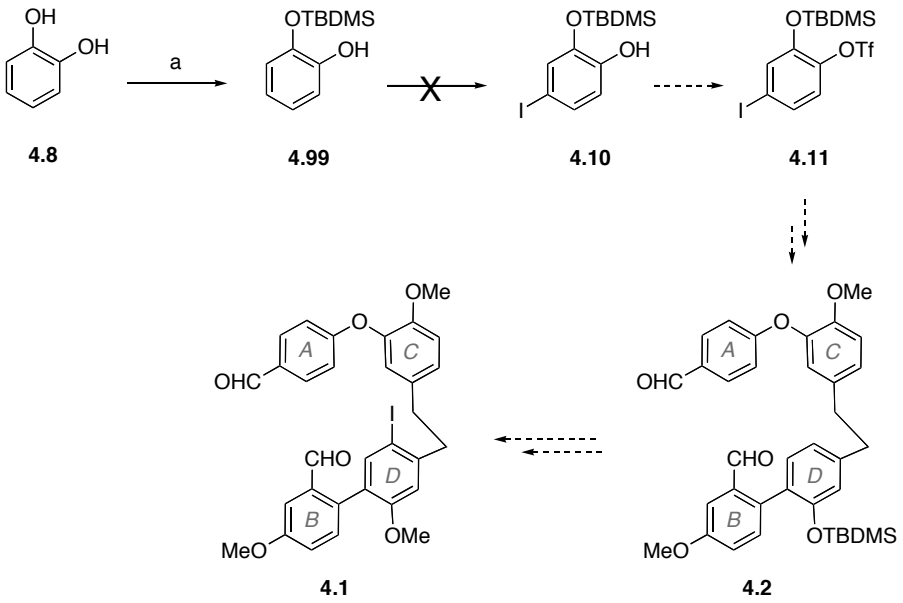
Figure 35



a). imidazole, TBDMSCl, DCM, RT, 19 h, 70%.

Scheme 65

Concurrently, the inclusion of orthogonal protection in our route B strategy was investigated. Thus, catechol **4.8** was mono-silylated with TBDMSCl and imidazole in 61% yield, the greater than statistical distribution of bis-, mono- and unprotected products doubtless a consequence of steric bulk. Unfortunately, suitable iodination conditions could not be found, with protocols either inducing iodination and concurrent deprotection or returning only starting material (Scheme 66)



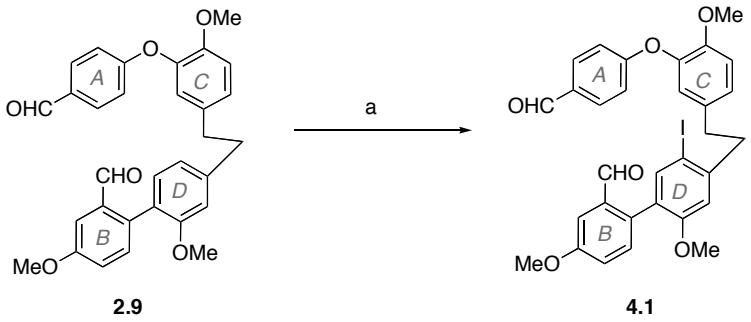
a). imidazole, TBDMSCl, DCM, RT, 7 h, 61%.

Scheme 66

4.1.2 Regioselective Halogenation with Global Protection

With the *tert*-butyldimethylsilyl protecting group proving unsuitable, attention turned to other orthogonal protecting groups, namely acetyl and benzyl moieties. However, we also considered the possibility of direct iodination of tri-*O*-methyl ether **2.9**. Iodination reactions of similar arenes typically show a clear preference for positions *para* to phenolic and ethereal electron-donating groups, as already seen in our route so far, *viz*. **3.5**→**2.10** and **3.1**→**3.40**. Mindful of this, we wondered if iodination of bis-aldehyde **2.9** would occur preferentially at the only available position *para* to a methoxy substituent: the desired position. Pleasingly, treatment of bis-aldehyde **2.9** with either ICl or *N*-iodosuccinimide with a trace of trifluoroacetic acid afforded monoiodide **4.1** as the only product in 98% yield

(Scheme 67). The regiochemistry was confirmed by extensive 2D-NMR analysis and subsequently by completion of the formal total synthesis of cavicularin **1.4**.



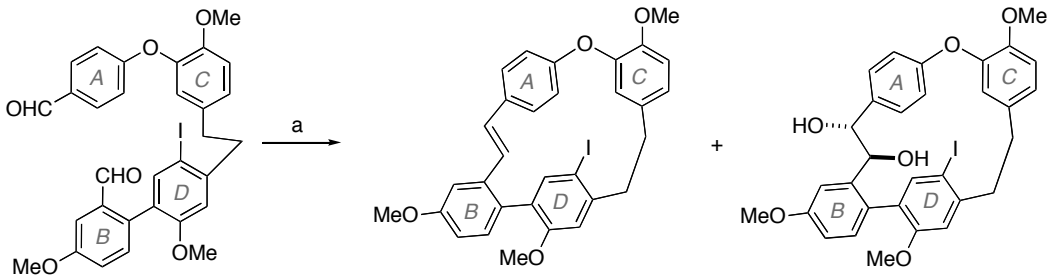
2.9 **4.1**

a). NIS, CF_3COOH, MeCN, 4 h, RT, 98%

Scheme 67

4.2 Macrocyclisation

Hypothesising that the presence of the larger iodine atom in the system may alter the stereoselectivity of the pinacol step of a McMurry reaction (*vide supra* Chapter 3), iodoarene **4.1** was treated with low-valent titanium as described previously. Once again, *trans*-stilbene **4.12** was accompanied by a 1,2-diol, which was stable to the reaction conditions, even when subjected to prolonged reflux (Scheme 68). Thus, it seems likely that this too is the *threo* diastereoisomer **4.13**, though we have been unable to establish this unambiguously by spectroscopic methods.



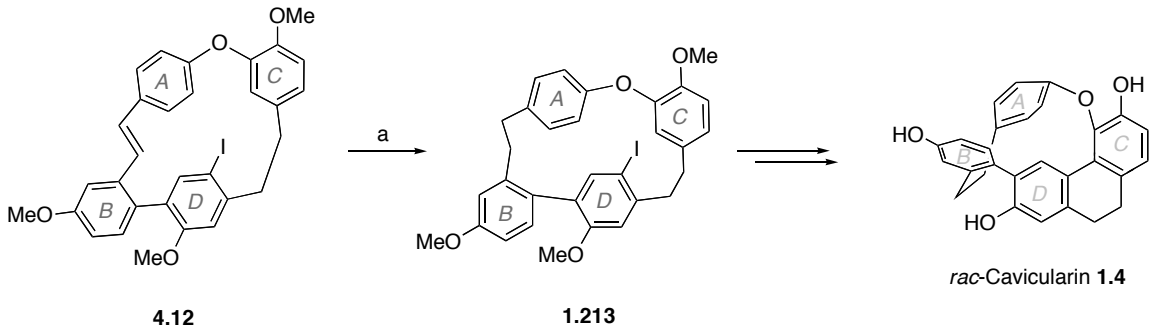
4.1 **4.12** **4.13**

a). $TiCl_4$, Mg, THF, –78 ºC–reflux, 19 h, 5% of **4.12** and 17% of **4.13**.

Scheme 68

The reaction proved too capricious and low-yielding to be suitable for our final synthesis. Nonetheless, stilbene **4.12** was reduced using diimide, generated *in situ*

from tosyl hyrdazone and NaOAc,[71] to give **1.213**, completing a formal total synthesis of (±)-cavicularin **1.4** (Scheme 69).[57]

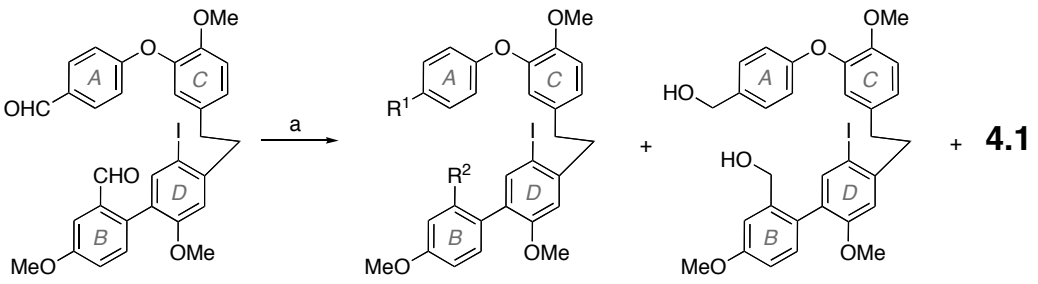


4.12 **1.213** *rac*-Cavicularin **1.4**

a). $TsNHNH_2$, NaOAc, THF, H_2O, reflux, 3 days, 75%.

Scheme 69[57]

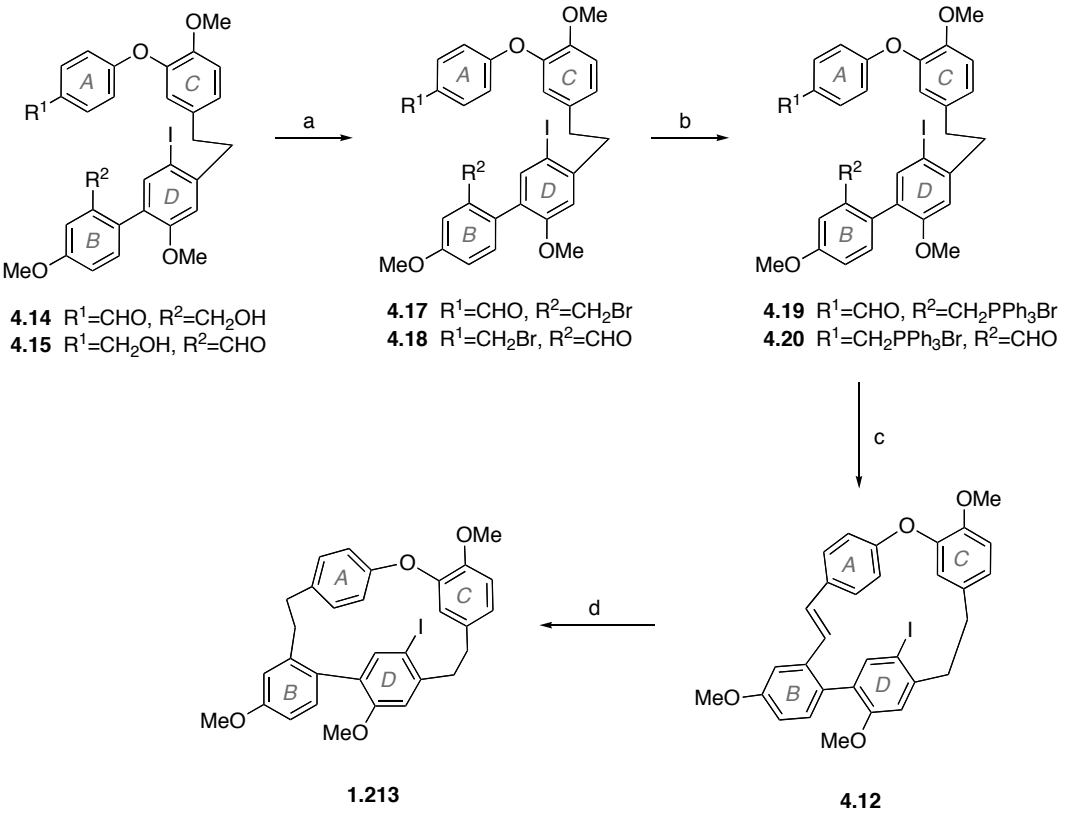
Attention next turned to Wittig macrocyclisation approaches. The presence of the aryl iodide precluded the use of a chemoselective reduction by hydrogenation,[72] so hydride reductants were examined (Scheme 70). Given the different electronic and steric environments of both aldehydes in **4.1**, and the clear sequential reactivity of its precursor **3.38** under hydrogenation conditions, we thought that one aldehyde might be reduced preferentially. However, treatment of **4.1** with DiBAL-H afforded a statistical mixture of alcohols **4.14** and **4.15**, diol **4.16** and recovered starting material. The use of $NaBH(OAc)_3$ resulted in the best selectivity, with reduction of the *A* ring aldehyde favoured (Scheme 70). However, separation of alcohols **4.14** and **4.15** proved intractable (the best sample obtained contained 1:3 **1.14**:**1.15**) so their subsequent conversion to benzyl bromides **4.17** and **4.18**, phosphonium salt formation and macrocyclisation had to be effected on the mixture, making the characterisation of intermediates very challenging (Scheme 71).



4.1 **4.14** R^1=CHO, R^2=CH_2OH **4.16**
4.15 R^1=CH_2OH, R^2=CHO

a). $NaBH(OAc)_3$, DCM, –78 ºC–reflux, 20 h.

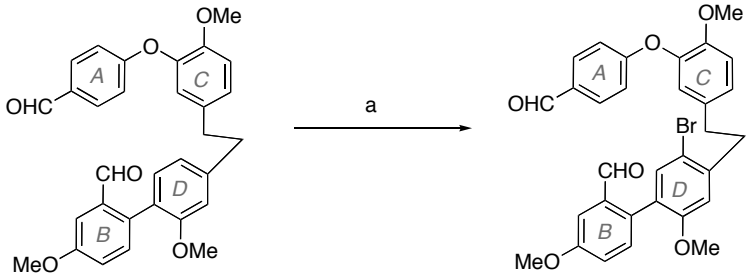
Scheme 70



a). BBr_3,PhMe, 0 ºC, 4 h; b). PPh_3, PhMe, reflux, 18 h; c). NaOMe, DCM, 21 h, 86% for 1 step; d). $TsNHNH_2$, NaOAc, THF, H_2O, reflux, 3 days, 75%.

Scheme 71

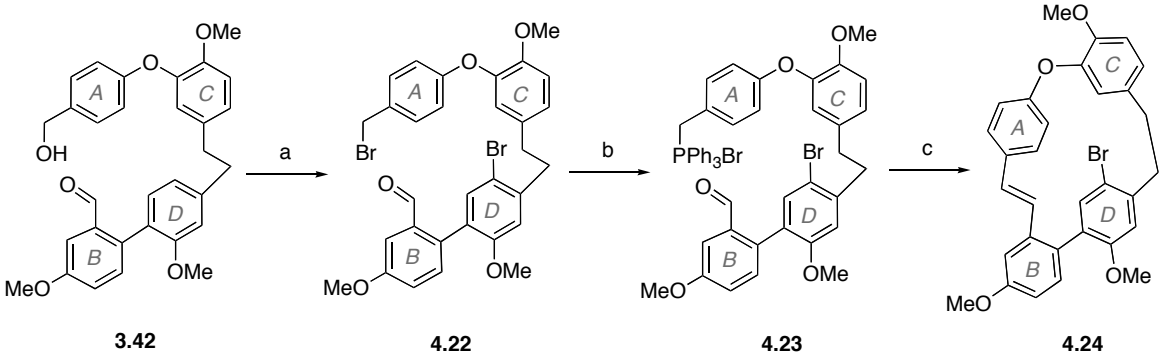
Following these difficulties, the direct iodination of **3.42** was investigated. Pleasingly, ^{1}H NMR analysis of the crude reaction mixture indicated iodination at the correct position, with concomitant benzyl iodide formation and consequent polymerisation. Under the reaction conditions employed, the benzyl iodide proved to be too reactive, leading us to investigate bromination procedures. The use of aryl bromides in similar radical induced biaryl bond formations has been previously reported but generally requires more forcing reaction conditions due to the strength of the C–Br bond. Bromination of bis-aldehyde **2.9** proceeded in high yield with *N*-bromosuccinimide in DMF and led to the desired regiochemistry (Scheme 72), whilst treatment of **3.42** with bromine in glacial acetic acid effected the desired regioselective aromatic bromination with contemporaneous benzyl bromide formation, *viz*. **3.42**→**4.22**. The position of the aryl bromide was confirmed by X-ray crystallographic analysis after Wittig macrocyclisation (Scheme 73). This structure, like that of *trans*-stilbene **3.47**, also exhibits a bent aromatic ring and twisted olefin (Figure 36).



2.9 **4.21**

a). NBS, DMF, RT, 86 h, 74%.

Scheme 72 – Regioselective bromination of **2.9**.



3.42 **4.22** **4.23** **4.24**

a). Br_2, AcOH, RT, 64 h, 81%; b). Ph_3P, PhMe, reflux, 18 h, 93%; c). NaOMe, DCM, RT–reflux, 18 h, 69%

Scheme 73 – Route to **4.24**.

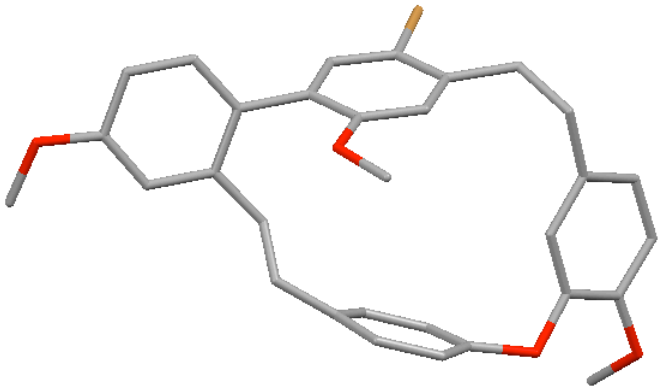
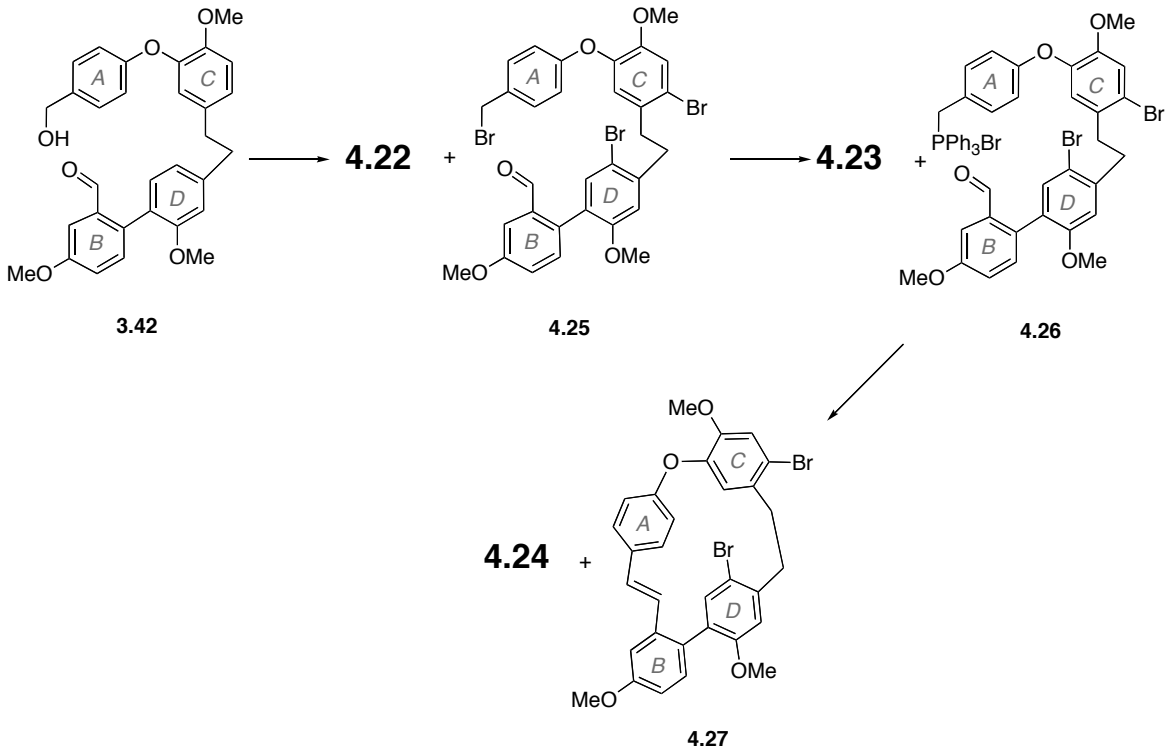


Figure 36 – X-ray crystal structure of **4.24**.

Interestingly, when the bromination of **3.42** to **4.22**, was carried out with an excess of bromine, tribromide **4.25** was formed as a byproduct. Following ylid formation and macrocyclisation the desired bromide **4.24** could be separated from the dibromide **4.27**. Crystallographic analysis showed that the second bromination

occurred on the *C* ring, interestingly *para* to the diphenyl ether ethereal oxygen rather than *ortho* to the methoxy substituent (Figure 37 – The solved structure shows two symmetrically distinct solutions).



Scheme 74

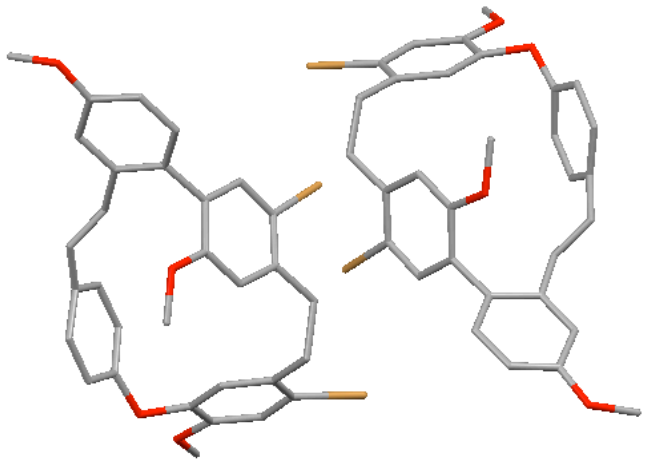
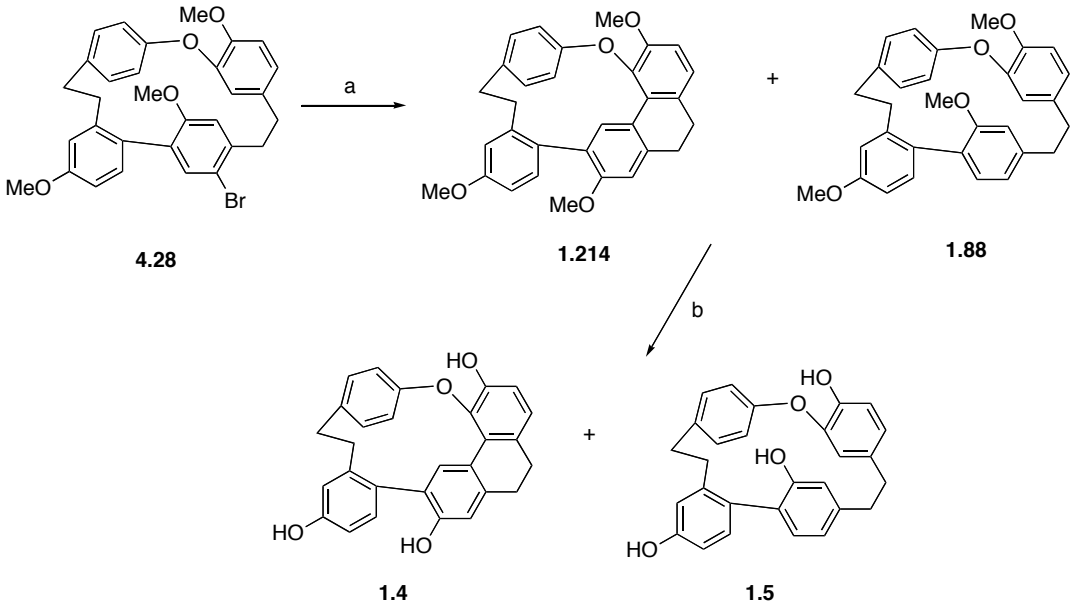


Figure 37

4.3 Completing the Synthesis

The stilbene functionality of macrocycle **4.24** was reduced with diimide generated *in situ* from tosyl hydrazone and NaOAc.[71] We were now ready to effect homolysis of the aryl bromide bond to achieve our transannular ring contraction. Treatment of **4.28** with TTMSS and stoichiometric VAZO and prolonged reflux gave only partial conversion, with further portions of TTMSS and VAZO and heating under microwave irradiation required to force the reaction to completion. Previous work within the group has shown that aryl bromides often require more forcing conditions than the equivalent aryl iodides.[73] Exposure of the resultant inseparable mixture of cavicularin tri-*O*-methyl ether **1.214** and riccardin C tri-*O*-methyl ether (1:2.5 ratio) **1.88** to BBr_3 afforded cavicularin **1.4** and riccardin C **1.5** (Scheme 75).



a). TTMSS, VAZO, reflux, 68 h, then TTMSS, VAZO, microwave, 2 x 30 min; b). BBr_3, DCM, RT, 18 h, 26% of **1.4** and 57% of **1.5.**

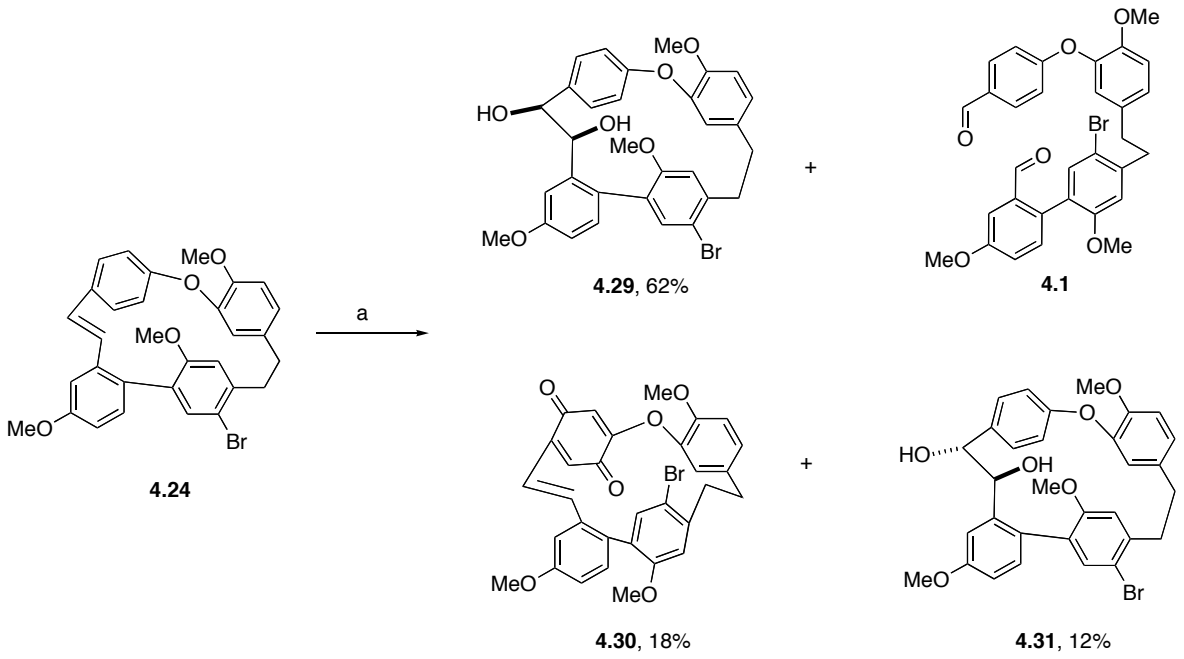
Scheme 75

4.4 An Asymmetric Strategy

At this juncture, we turned our attention to investigating an asymmetric strategy, which envisaged the installation of a chiral 1,2-diol on the *A*-*B* ethano linkage (*vide supra* Chapter 2). A key fragment in the second generation unified synthesis of cavicularin **1.4** and riccardin C **1.5** is macrocyclic *trans*-stilbene **4.24**, which is appropriately functionalised for Sharpless AD chemistry. Thus, **4.24** was treated with AD mix α and methanesulfonate. A number of products were formed (Scheme 76). The desired 1,2-diol **4.29** was obtained, interestingly contaminated with bis-aldehyde **4.1**, the product of an oxidative bond cleavage of the strained macrocycle (these compounds co-eluted).

Two further products were identified. The first was tentatively assigned structure **4.30**, a conclusion supported by IR analysis, which showed a carbonyl stretch, and mass spectroscopy data, in addition to NMR analysis. The formation of this product suggests addition to the bent aromatic ring, arene *A*, in **4.24**, followed by oxidation to the quinone. Like arene *A* in **4.24**, the quinone in **4.30** is most probably non-planar, with considerable bis-α,β-unsaturated ketone character.

The final product **4.31** displayed similar spectroscopic properties to **4.29** and **4.13**, suggesting a second 1,2-diol. However, the significant deviation in δ_H for C**H**OH and C**H**OH suggested a different diastereoisomer, despite the similar H-H coupling constants. Thus, **4.31** was tentatively assigned the structure in Scheme 76. Unfortunately, time and material constraints precluded repetition and further investigation into this reaction, and the clean isolation of **4.29** for our asymmetric strategy.



a). AD mix alpha, methanesulfonate, *t*-BuOH, water, THF, 0–5 °C, 24h.

Scheme 76

4.5 Conclusions

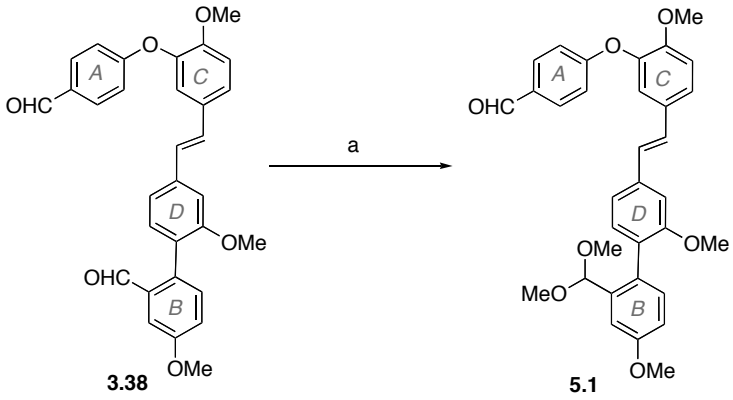
A second generation unified synthesis of cavicularin **1.4** and riccardin C **1.5** has been achieved. Key features include a chemoselective hydrogenation and a Wittig macrocyclisation and, in the case of cavicularin **1.4**, regioselective halogenation and radical induced transannular ring contraction. Crucially, the synthesis furnishes **4.24**, a macrocycle containing a *trans* stilbene functionality. Future work could focus on the elaboration of this molecule to include a chiral 1,2-diol functionality, further investigating an asymmetric approach to (+)-cavicularin **1.4**.

Chapter 5: Results and Discussion

Pot Pourri

5.1 Unusual Hydrogenation Reaction Outcomes

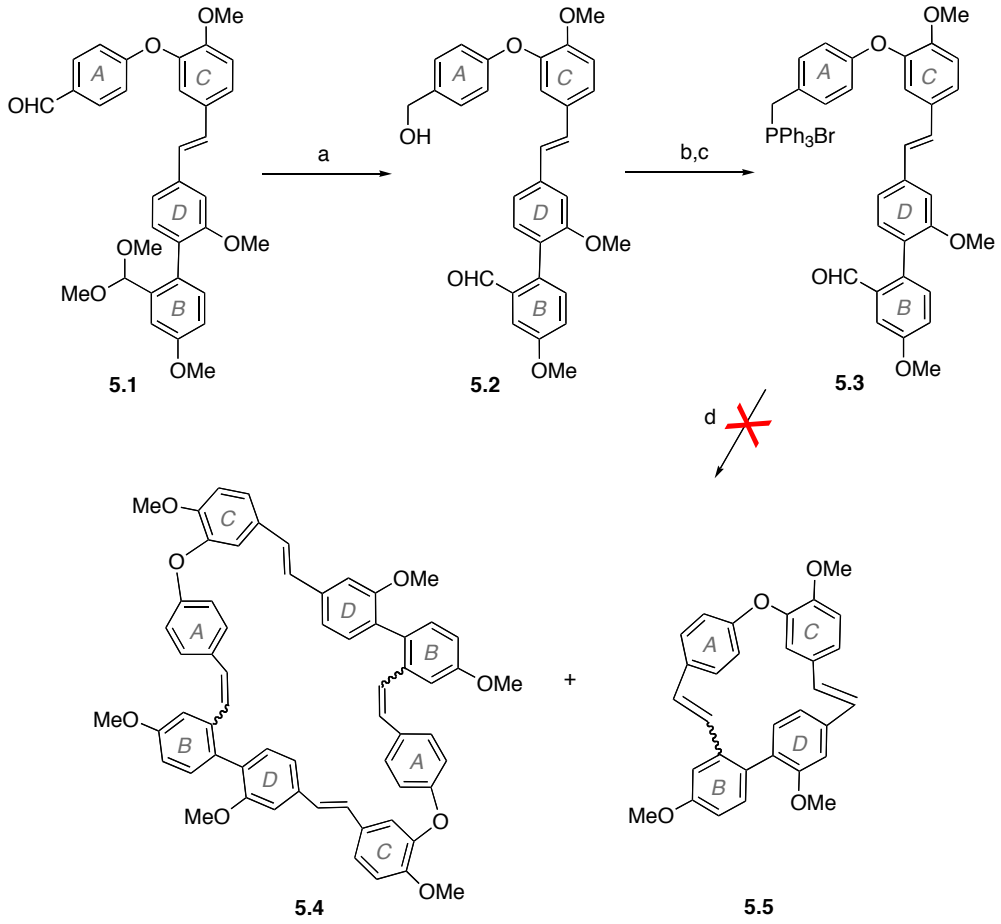
On one occasion when the hydrogenation of **3.38** was attempted, no reduction of stilbene or aldehyde moieties was observed. Instead, unexpected selective acetalisation of the *B* ring aldehyde was observed, with acetal **5.1** isolated in 58% yield (Scheme 77). This batch of palladium on carbon subsequently proved unsuccessful in other hydrogenation reactions in the laboratory.



a). H_2, Pd/C, DCM, MeOH, RT, 3 h then Pd/C, DCM, MeOH, RT, 17 h, 58%.

Scheme 77

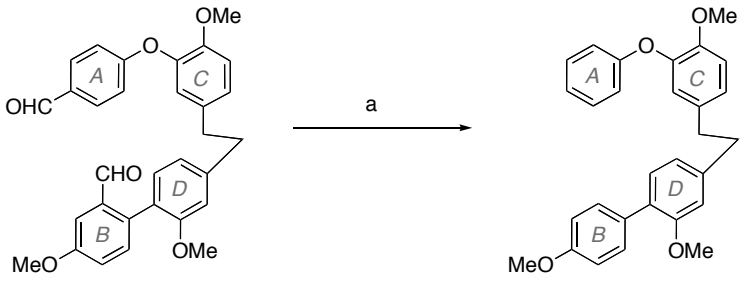
This interesting chemoselectivity afforded the opportunity for selective reduction of the *A* ring aldehyde moiety and subsequent phosphonium salt formation (Scheme 78). As Wittig olefination had proven a reliable means of forming strained macrocycles, we wondered if highly strained bis-stilbene **5.5** could be formed in this manner. Interestingly, treatment of phosphonium salt **5.3** at high dilution led to a crude reaction mixture for which analysis by electrospray mass spectroscopy indicated the formation of products of mass 948 and mass 503, consistent with the formation of **5.4** and **5.5**. However, purification proved intractable and we were unable to characterise these products.



a). $NaBH_4$, THF, 0 ºC–RT, 21 h, then HCl, 95%; b). PBr_3, PhMe, 0 ºC–RT, 19 h; c). PPh_3, PhMe, reflux, 19 h, 33%; d). NaOMe, DCM.

Scheme 78

During the investigation of the chemoselectivity of the reduction steps in the sequential hydrogenation of **3.38** (*vide supra*: Section 3.1.3) the possibility of a transfer hydrogenation[74] protocol was considered. Thus, the chemoselective reduction of one of the aldehyde moieties of **2.9** was attempted using palladium on carbon in refluxing propan-2-ol. Interestingly, no reduction of either aldehyde to the corresponding benzyl alcohol was observed, with decarbonylation of both aldehydes occurring instead (Scheme 79). This same hydrogenation step was successfully achieved using standard palladium on carbon protocols. Clearly, this transfer hydrogenation procedure is not suitable for this reduction, with palladium-catalysed decarbonylation outpacing hydrogenation.



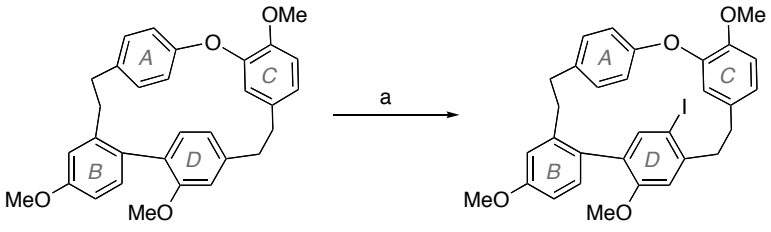
2.9 **5.6**

a). Pd/C, $CH_3CHOHCH_3$, reflux, 19 h, 90%.

Scheme 79

5.2 Regioselective Iodination of Riccardin C Tri-*O*-Methyl Ether

Given the marked preference for *para*-selective iodination in our acyclic systems, we considered the direct iodination of riccardin C tri-*O*-methyl ether **1.88**. In this case, there is greater parity of the electron densities of the aromatic rings, with three rings, namely *B*, *C* and *D* bearing methoxy substituents and no electron-withdrawing aldehyde functionalities. Pleasingly, treatment **1.88** with *N*-iodosuccinimide did afford the desired product **1.213**. However, subsequent iodinations proved more facile than with our acyclic precursors, and much of the mass balance comprised unidentified polyiodinated products. Unfortunately, time and material constraints did not allow us to repeat this procedure with only stoichiometric *N*-iodosuccimide to improve the yield. This direct iodination of riccardin C tri-*O*-methyl ether gives the key intermediate in Harrowven's 2006 total synthesis of cavicularin **1.4**, completing a formal synthesis.[57]



1.88 **1.213**

a). NIS, CF_3COOH, MeCN, RT, 68 h, 16%.

Scheme 80

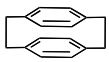
Chapter 6: Results and Discussion

Discussion of X-Ray Structures

6.1 Introduction to Bent Aromatic Rings in the Literature

The molecule that typically functions as a reference compound for aromaticity is benzene. However, since the isolation of benzene in 1825[75] various definitions of aromaticity have been given and the debate about what constitutes aromaticity has become rather complex. Schleyer and Jiao present four criteria for aromaticity, all related to electron delocalisation: electrophilic aromatic substitution rather than addition, equality of bond lengths in the system, enhanced stability through resonance energy and magnetic ‘‘ring current’’ effects, for example, large magnetic anisotropies.[76]

A widely accepted feature of aromatic rings is their planarity. However, the existence of stable boat-shaped “aromatic” rings has been known for many decades, dating from the first synthesis of [2.2]paracyclophane **6.1** in 1949.[77] Extensive studies, both synthetic and theoretical, have demonstrated the bent nature of the rings in highly-strained paracyclophanes, which adopt a boat-type configuration.[78, 79] Evidence for the existence of aromaticity in these systems is that the geometric structures display almost no variation in bond length. NMR Analysis also indicates the aromatic character of the rings. However, unlike benzene, strained paracyclophanes show a preference for addition instead of substitution in their reactivity.[79]



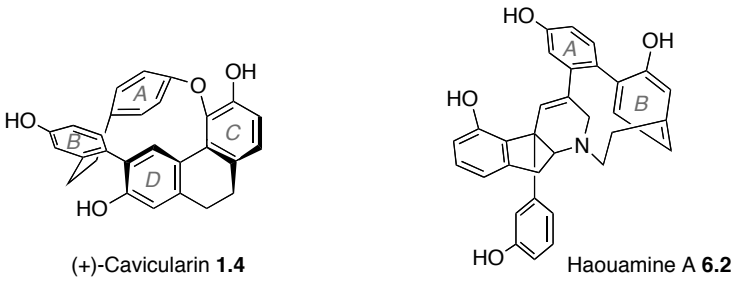
6.1

Figure 38

In 1992, Jenneskens *et al*. reported theoretical analyses of boat-shaped benzenes.[80] Their work indicated that a benzene ring can accommodate deviations from planarity up to 25° without a substantial loss of electron conjugation, and that boat-shaped benzenes are essentially aromatic. Subsequent VBSCF calculations by Dijkstra and van Lenthe led the authors to claim that *“the aromaticity of benzene is not hindered very much by bending the molecule up to 55° in spite of the large*

strain energy." The authors report that the orbitals of the *p* system adapt to the carbon atom framework of the ring to maintain the large overlap required to maintain a Kekulé structure.[79] However, others believe that the high levels of strain prohibit aromaticity in these systems.[81]

Whether these boat-shaped arenes are truly aromatic or not, the strain energy required for such a distortion of bond angles in these systems was thought to preclude their existence in Nature until the isolation of cavicularin **1.4** in 1996 (*vide supra* Section 1.2.1a).[6] As discussed, the structure of this macrocyclic paracyclophane exhibits a boat-shaped arene, bent 15° out of planarity and displaying some variance in bond length around the ring. Subsequently haouamine A **6.2**, which exhibits an even greater degree of strain and an aromatic ring which deviates even further from planarity, was isolated and identified (Figures 39 and 40).[82]



(+)-Cavicularin **1.4** Haouamine A **6.2**

Figure 39

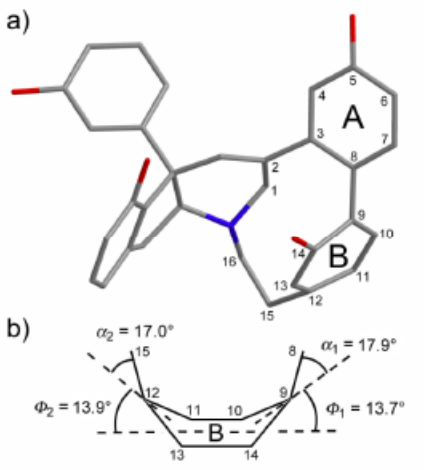
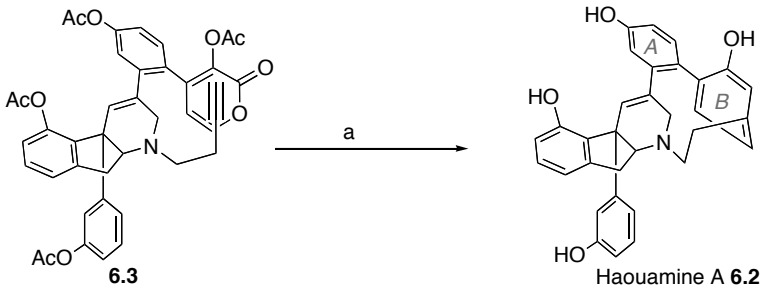


Figure 40 – X-ray crystal structure of haouamine A **6.2** (a) and the deviation of arene *B* from planarity (b).[83]

In achieving the total synthesis of these strained natural products, approaches which compensate energetically for the thermodynamic penalty associated with bending an aromatic ring have been used. In the case of cavicularin **1.4**, a radical induced transannular ring contraction step was used (*vide supra* Section 1.4), with rearomatisation of arene *C* compensating for the bending of arene *A*.[57] In the first reported synthesis of haouamine A **6.2**, Baran *et al*. used this strategy in a different guise, using a cycloaddition and CO_2 extrusion to form the bent aromatic ring (Scheme 81).[84]



a). μ-wave then K_2CO_3, 21%.

Scheme 81

The isolation of cavicularin **1.4** and haouamine A **6.2** has demonstrated the existence of biosynthetic pathways to boat-shaped "aromatic" rings. Theoretical studies on bent benzene systems have indicted that a reasonable degree of deviation from planarity can be tolerated without substantial loss of stabilisation by electron conjugation, although the distortion of bond angles imparts large strain enthalpies. These bent aromatics rings have been shown to exhibit reactive behaviour atypical of aromatic rings, *e.g.* undergoing electrophilic addition rather than substitution.

6.2 Bent Aromatic Rings and Twisted Olefins in Macrocyclic *trans*-Stilbenes

In the course of this route to the second generation unified synthesis of cavicularin **1.4** and riccardin C **1.5** a number of unnatural macrocyclic bisbibenzyl compounds containing *trans* stilbene functionalities were isolated, namely **3.47**, **4.12**, **4.24** and **4.27**. The X-ray crystal structures were solved for several of these, with each structure exhibiting a high degree of strain (**3.47**, **4.12** and **4.24**). In each case, the

compound was obtained by a Wittig macrocyclisation, in which the generation of triphenylphosphine oxide is the driving force for the reaction. Considering the simplest example, stilbene **3.47**, the structure shows a bent aromatic ring, arene *A*, akin to that found in cavicularin **1.4** and haouamine A **6.2**. The deviation from planarity and the variance of bond angles of arene *A* are shown in Figure 41.

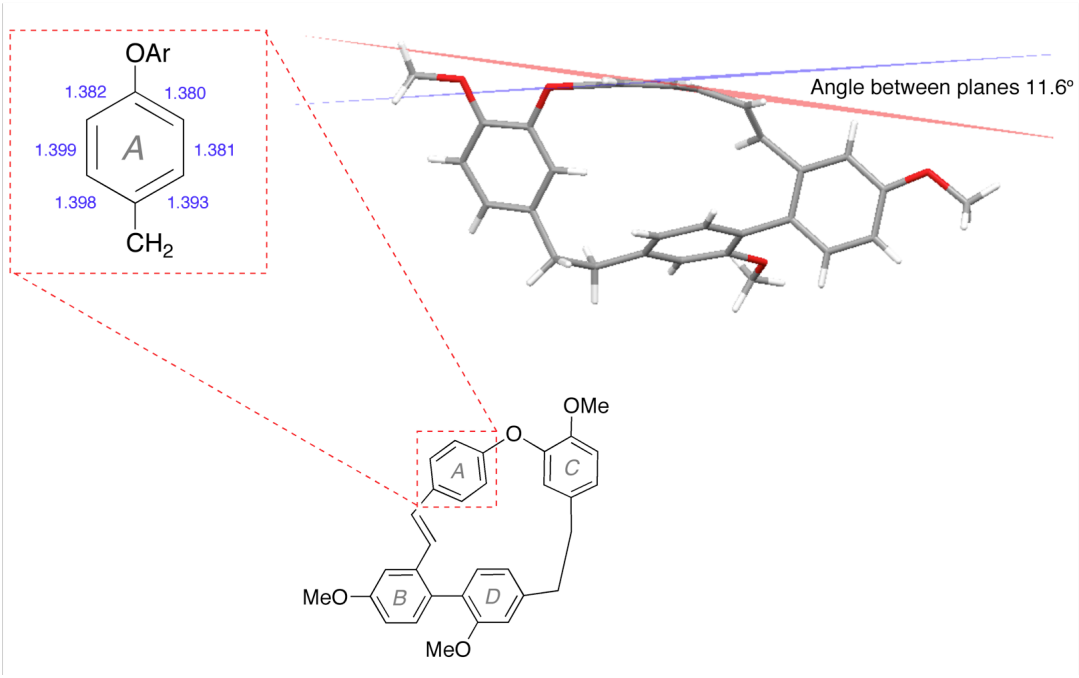


Figure 41 – The boat-shaped aromatic ring of **3.47**.

It is interesting to note the position of proton H-*6** relative to arene *A*. The ^{1}H NMR of **3.47** reveals this proton to be shifted upfield of the aromatic region to δ_H 5.77 ppm, indicating anisotropic effects from both arene *A* and arene *D*. The upfield shift of protons which sit within the macrocyclic core of these bisbibenzyl natural products has been noted in the literature before, and is observed in the NMR data of many natural products of this class. Interestingly, when the unsaturation in the *A*-*B* tether is removed, to give riccardin C tri-*O*-methyl ether **1.88**, and a considerable amount of the strain in the molecule lifted, the anisotropic effects on proton H-*6* are significantly more pronounced (δ_H 5.37 ppm). We postulate that in **3.47**, arene *A* is planar, more "benzene-like" and hence the associated aromatic magnetic field effects are larger. Similar differences in the upfield shift of proton H-*6* can be seen

* It should be noted that the atom labels in this section are derived from the X-ray crystal results, and not IUPAC naming conventions.

when comparing these data of **4.24** and **4.28** (Figure 42) and **4.12** and **1.213** (Table 3).

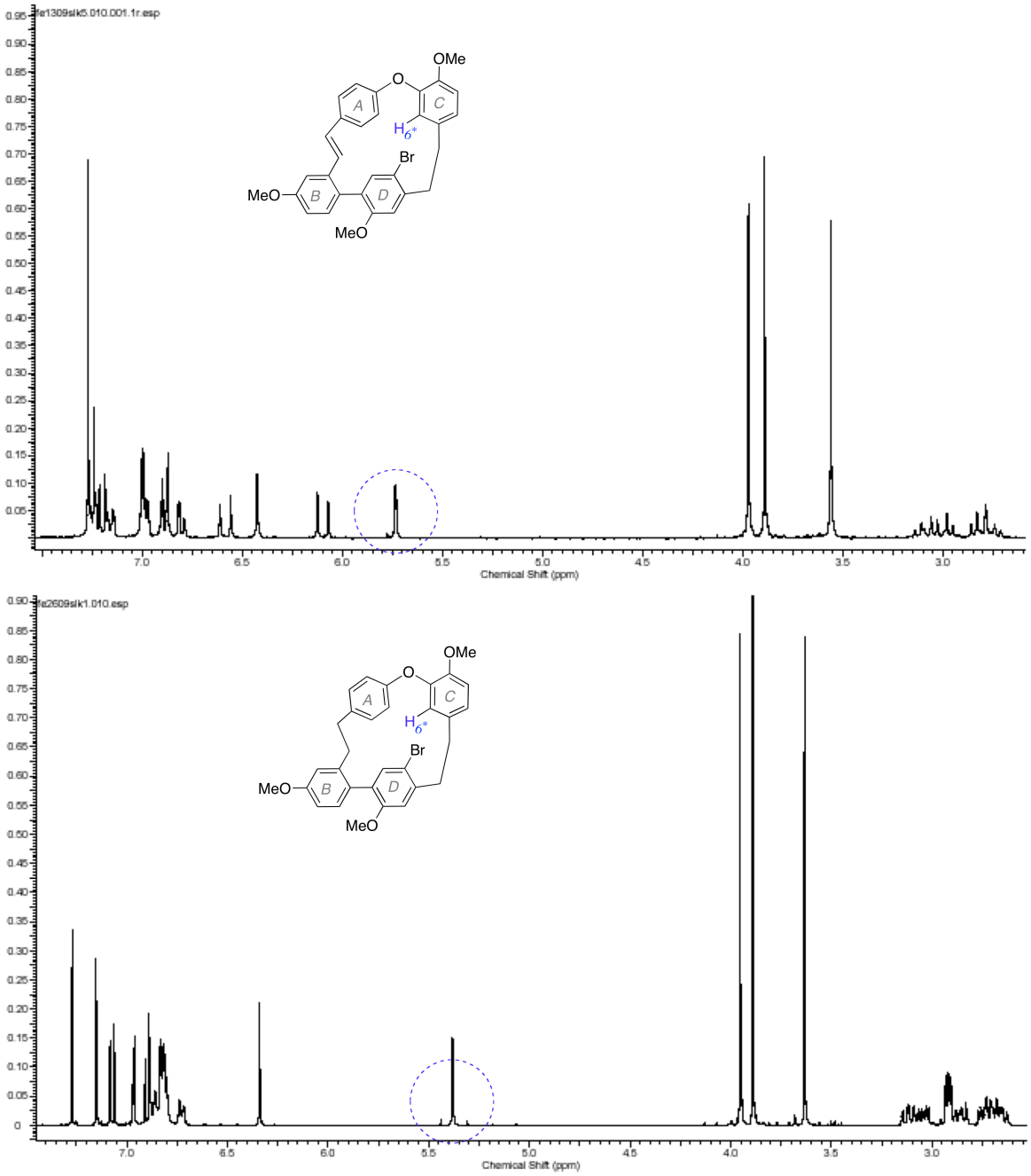


Figure 42 – ^{1}H NMR spectra of **4.24** and **4.28**

Substituent	Unsaturated		Saturated	
	Compound	δ_H (6*)	Compound	δ_H (6*)
H	**3.47**	5.77	**1.88**	5.37
Br	**4.24**	5.73	**4.28**	5.37
I	**4.12**	5.73	**1.213**	5.33

Table 3

In addition to the distortion of arene *A* into a boat shape, the structure shows a high degree of strain about the stilbene functionality. Whilst the *C-C-C* bond angle at carbon-*25* is 120.3°, typical of an sp^2 centre, the *C-C-C* bond angle of carbon-*24* is an atypical 128.9°, placing it somewhere between sp^2 and *sp* in hybridisation (Figure 43). The X-ray crystal structure also reveals a considerable degree of twist in the bond, necessary to accommodate the *trans*-geometry in the 18-membered macrocycle. The torsional angle of this bond is 156°, which represents a significant deviation from the planarity expected for a double bond. The crystal packing structure for **4.24** displays a herringbone-type array and is shown in Figure 44.

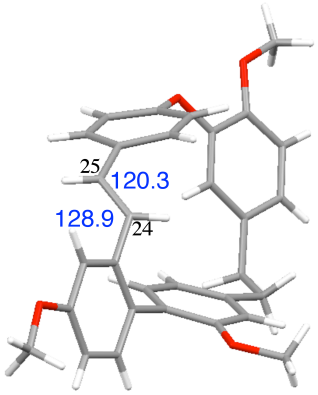


Figure 43

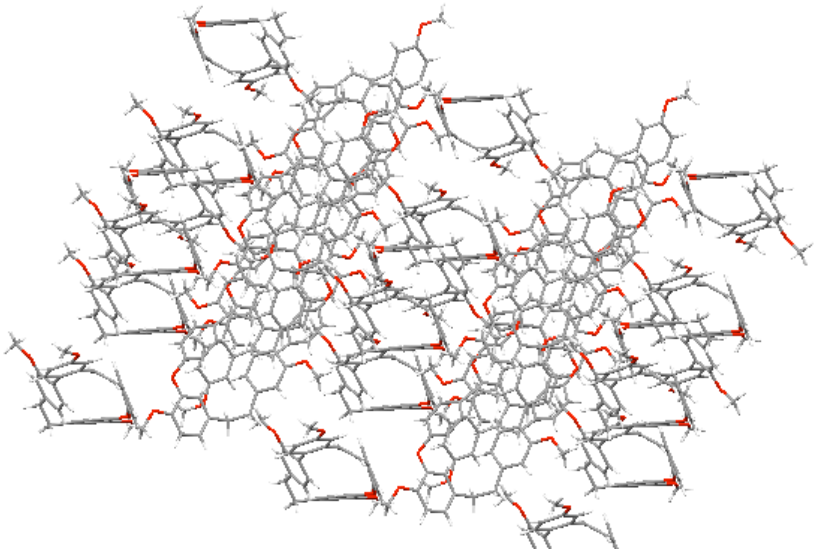


Figure 44 – Packing of **4.24** in the X-ray crystal structure.

Chapter 7: Experimental

7.1 General Experimental Techniques

Melting Points: Melting points were recorded on Reichert Austria apparatus and are uncorrected.

NMR Spectra: Proton (^{1}H) and carbon (^{13}C) spectra were recorded on a Bruker DPX300 (300/75 MHz) or Bruker DPX400 (400/100 MHz) spectrometer at 298 K unless stated otherwise. Chemical shifts are quoted in parts per million downfield of tetramethylsilane with residual solvent as the internal standard. Fluorine (^{19}F) spectra were recorded on a Bruker DPX300 (282 MHz) spectrometer at 298 K. Assignments were made on the basis of chemical shifts, coupling constants, DEPT-135, COSY, HMQC, HMBC and comparison with spectra of related compounds. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), app. (apparent) and br. (broad). Coupling constants (*J*) are given in Hz and are rounded to the nearest 0.1 Hz.

Infrared Spectra: Infrared spectra were recorded neat as an oil film or solid compression using the ATR/golden gate method. Absorption maxima (υ_{max}) are described as s (strong), m (medium) and w (weak) and are quoted in wavenumbers (cm^{-1}).

Mass Spectra: ESI mass spectra were recorded using a VG Platform Quadrupole Electrospray Ionisation mass spectrometer, measuring mono-isotopic masses (mode: ES+ or ES–). EI and CI were measured on a Thermoquest Trace MS. m/z values are reported with their percentage abundance relative to the most intense signal and, where known, the relevant fragment ion in parentheses. Values for the most abundant isotope combination are reported. High resolution mass spectra were recorded by Dr John Langley or Ms. Julie Herniman at the University of Southampton and are calculated to four decimal places from the molecular formula.

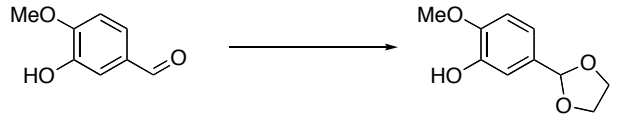
X-ray Crystallography: X-ray crystallographic data was collected using Bruker-Nonius KappaCCD diffractometers by Dr. Mark Light and Dr. Graham Tizzard and structures were similarly solved by the aforementioned.

Chromatography Techniques: Thin layer chromatography was performed on Merck DC-Alufolien 60 F_{254} 0.2 mm precoated plates. Product spots were visualised by the quenching of UV fluorescence (λ_{max}=254 nm) then stained and heated using, most commonly, 5% potassium permanganate in 5% aqueous NaOH solution or 5% anisaldehyde in ethanol as appropriate. Flash column chromatography was carried out on silica gel (200–400 mesh) with the solvent system used given in parentheses.

Solvents and Reagents: Commercially available reagents were purchased and used without further purification. THF and diethyl ether were freshly distilled and dried over a purple solution of sodium and benzophenone, toluene and acetonitrile were freshly distilled over sodium and DCM and choroform were distilled and dried over CaH_2 immediately prior to use.

7.2 Experimental Procedures

3-(1,3-Dioxolan-2-yl)-6-methoxyphenol (1.215)



C_8H_8O
Molecular Weight: 152.15

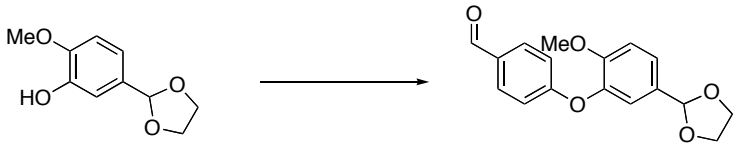
$C_{10}H_{12}O_4$
Molecular Weight: 196.20

To a stirred solution of isovanillin **1.142** (5.00 g, 32.9 mmol) and ethylene glycol (5.5 mL, 98.7 mmol) in toluene (75 mL) was added PPTS (33 mg, 1.13 mmol). The reaction mixture was heated at reflux under a soxhelet extractor filled with 3Å molecular sieves to remove water. After 24 h the reaction mixture was cooled to RT, diluted with DCM (40 mL) and washed with water (3 x 30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (3 x 30 mL). The organic phase was then dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a beige oil (crude mass 5.39 g, 84%). The product was often used crude but recrystallisation from DIPE afforded cream-coloured crystals for characterisation.

MP	57–60 ºC (DIPE) [Lit.[57] quotes as an oil]
υ_{max}	3314 (m), 2970 (w), 2884 (w), 1675 (w), 1618 (m), 1589 (m), 1510 (s), 1443 (s), 1274 (s), 1230 (s), 1166 (s), 1127 (s), 1089 (s), 1020 (s).
δ_H (400 MHz, $CDCl_3$)	7.07 (1 H, d, *J*=2.0 Hz, ArH) 6.98 (1 H, dd, *J*=8.3, 2.0 Hz, ArH) 6.85 (1 H, d, *J*=8.3 Hz, ArH) 5.74 (1 H, s, ArCH) 5.61 (1 H, s, OH) 3.97–4.17 (4 H, m, 2 x OCH_2) 3.90 (3 H, s, OCH_3)
δ_C (100 MHz, $CDCl_3$)	147.7 (C), 146.0 (C), 131.7 (C), 118.8 (CH), 113.1 (CH), 110.7 (CH), 104.0 (CH), 65.4 (2 x OCH_2), 56.4 (CH_3).
LRMS (ES+)	219 ($[M+Na]^+$, 20%), 197 ($[M+H]^+$, 100%).

These data are in accordance with those reported in the literature.[57]

4-[3-(1,3-Dioxolan-2-yl)-6-methoxyphenoxy]benzaldehyde (1.155)



$C_{10}H_{12}O_4$
Molecular Weight: 196.20

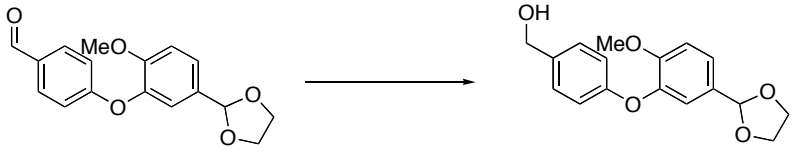
$C_{17}H_{16}O_5$
Molecular Weight: 300.10

To a stirred solution of **1.215** (1.00 g, 5.10 mmol) and 4-fluorobenzaldehyde (0.61 mL, 5.61 mmol) in DMF (5 mL) was added K_2CO_3 (0.77 g, 5.61 mmol). The reaction mixture was heated at reflux for 48 h then cooled to RT and filtered through a glass sinter. The filtrate was poured onto ice (5 mL) and extracted with diethyl ether (4 × 10 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (3:1, petroleum ether:diethyl ether) afforded the title compound as a colourless oil (1.33 g, 87%).

υ_{max}	2880 (w), 2835 (w), 1689 (s), 1599 (s), 1579 (s), 1501 (s), 1430 (m), 1392 (m), 1300 (s), 1271 (s), 1223 (s), 1152 (s), 1123 (s), 1078 (s), 1022 (s), 988 (s), 946 (m), 857 (m), 811 (s).
δ_H (300 MHz, $CDCl_3$)	9.89 (1H, s, CHO) 7.82 (2 H, d, *J*=8.8 Hz, ArH) 7.34 (1 H, ddd, *J*=8.5, 2.0, 0.3 Hz ArH) 7.25 (1 H, d, *J*=2.0 Hz, ArH) 7.04 (1 H, d, *J*=8.5 Hz, ArH) 7.00 (2 H, d, *J*=8.8 Hz, ArH) 5.76 (1 H, s, ArCH) 3.97–4.16 (4 H, m, 2 × OCH_2) 3.81 (3 H, s, OCH_3)
LRMS (ES+)	355 ($[M+Na+MeOH]^+$, 33%), 304 (37%), 301 ($[M+H]^+$, 100%), 282 (31%).

These data are in accordance with those reported in the literature.[57]

4-[3-(1,3-Dioxolan-2-yl)-6-methoxyphenoxy]benzylalcohol (1.216)



$C_{17}H_{16}O_5$
Molecular Weight: 300.10

$C_{17}H_{18}O_5$
Molecular Weight: 302.32

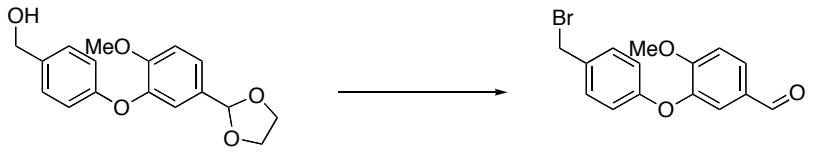
To a stirred solution of **1.155** (1.00 g, 3.33 mmol) in methanol (10 mL) at 0 ºC was added $NaBH_4$ (82 mg, 2.22 mmol) portionwise over 15 min. After 1 h, water (1 mL) was added and the organic solvent removed *in vacuo*. The resultant aqueous solution was partitioned with diethyl ether (10 mL). The organic phase was washed with water (2 × 5 mL) and brine (5 mL) then dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the title compound as a white crystalline solid (804 mg, 80 %).

MP	80–83 °C (ethanol) [Lit.[57] (ethanol) 80 °C]
υ_{max}	3459 (br., w), 2891 (w), 1661 (m), 1607 (m), 1588 (w), 1505 (s), 1477 (s), 1438 (s), 1380 (m), 1350 (m), 1328 (m), 1266 (s), 1213 (s), 1168 (m), 1125 (s), 1077 (s), 1024 (s), 998 (s), 951 (s), 936 (s), 891 (m), 839 (s).
δ_H (300 MHz, $CDCl_3$)	7.28–7.27 (3 H, m, 3 x ArH) 7.10 (1H, d, *J*=2.2 Hz, ArH) 6.98 (1 H, d, *J*=8.4 Hz, ArH) 6.91 (2 H, d, *J*=8.4 Hz, 2 x ArH) 5.69 (1 H, s, ArCH) 4.59 (2 H, s, $ArCH_2$) 4.03–4.07 (2 H, m, OCH_2) 3.93–3.98 (2 H, m, OCH_2) 3.81 (3 H, s, OCH_3) 2.19 (1 H, br. s, OH)
δ_C (75 MHz, $CDCl_3$)	157.4 (C), 152.2 (C), 144.9 (C), 135.1 (C), 131.0 (C), 128.5 (2 x CH), 123.4 (CH), 119.5 (CH), 117.4 (2 x CH), 112.6 (CH), 103.2 (OCHO), 65.2 (2 x OCH_2), 64.8 (OCH_2), 56.1 (OCH_3).

LRMS (ES+) 627 ($[2M+Na]^+$, 11%), 325 ($[M+Na]^+$, 53%), 303 ($[M+H]^+$, 100%).

These data are accordance with those reported in the literature.[57]

3-(4-Bromomethylphenoxy)-4-methoxybenzaldehyde (1.127a)



$C_{17}H_{18}O_5$
Molecular Weight: 302.32

$C_{15}H_{13}BrO_3$
Molecular Weight: 320.17

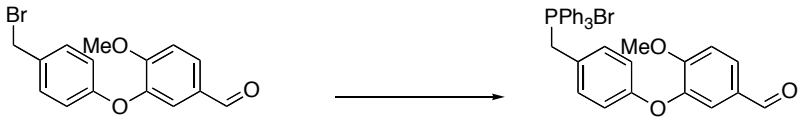
To a stirred solution of **1.127** (725 mg, 2.40 mmol) and triphenylphosphine (943 mg, 3.60 mmol) in DCM (10 mL) at 0 ºC was added carbon tetrabromide (1.19 g, 3.60 mmol) portionwise over 15 min. The reaction mixture was warmed to RT. After 68 h (weekend), the mixture was cooled to RT, silica (~1.2 g) added and the organic solvent removed *in vacuo*. Purification by column chromatography (3:1, petroleum ether:ethyl acetate) afforded the title compound as a white solid (543 mg, 70%) which, owing to its unstable nature, was only partially characterised.

δ_H (300 MHz, $CDCl_3$) 9.82 (1H, s, CHO)
7.68 (1 H, dd, *J*=8.5, 2.0 Hz, ArH)
7.48 (1 H, d, *J*=2.0 Hz, ArH)
7.33 (2 H, d, *J*=8.7 Hz, ArH)
7.10 (1 H, d, *J*=8.5 Hz, ArH)
6.89 (2 H, d, *J*=8.7 Hz, 2 x ArH)
4.48 (2 H, s, $ArCH_2Br$)
3.91 (3 H, s, OCH_3)

δ_C (75 MHz, $CDCl_3$) 190.0 (CHO), 157.3 (C), 156.6 (C), 145.5 (C), 132.6 (C), 130.6 (2 x CH), 130.4 (C), 128.4 (CH), 120.7 (CH), 117.7 (2 x CH), 112.3 (CH), 56.3 (OCH_3), 33.1 (CH_2).

These data are in accordance with those reported in the literature.[57]

[4-(2-Methoxy-5-formylphenoxy)benzyl]triphenylphosphonium bromide (1.218)



$C_{15}H_{13}BrO_3$
Molecular Weight: 320.17

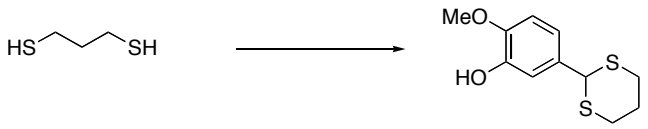
$C_{33}H_{28}BrO_3P$
Molecular Weight: 583.45

Benzyl bromide **1.217a** (520 mg, 1.69 mmol) and triphenylphosphine (443 mg, 1.69 mmol) were dissolved in toluene (30 mL) and heated at reflux for 21 h. Upon cooling to 0 °C white crystals formed, and the title compound was collected by filtration as a white solid (687 mg, 73%).

υ_{max}	2360 (s), 2342 (s), 1683 (m), 1541 (w), 1506 (m), 1436 (m), 1272 (m), 1233 (m), 1118 (m), 749 (w), 724 (w), 688 (m), 669 (m), 642 (w).
δ_H (300 MHz, $CDCl_3$)	9.85 (1 H, s, CHO)
	7.73–7.87 (9 H, m, 9 x ArH)
	7.62–7.70 (7 H, m, 7 x ArH)
	7.40 (1 H, d, *J*=1.8 Hz, ArH)
	7.01–7.14 (3 H, m, 3 x ArH)
	6.74 (2H, d, *J*=8.8 Hz, 2 x ArH)
	5.48 (2H, d, *J*=13.9 Hz, $ArCH_2P$)
	3.91 (3H, s, OCH_3)
LRMS (ES+)	503 ($[M–Br]^+$, 100%)

These data are in accordance with those reported in the literature.[57]

5-(1,3-Dithian-2-yl)-2-methoxyphenol (2.3)



$C_3H_8S_2$
Molecular Weight: 108.23

$C_{11}H_{14}O_2S$
Molecular Weight: 242.36

To a stirred solution of isovanillin **1.142** (15.48 g, 0.1 mol) in DCM (150 mL) was added propan-1,3-dithiol (10.00 g, 92.6 mmol) and PPTS (230 mg, 0.93 mmol). After 24 h the reaction mixture was heated at reflux. After a further 24 h, the reaction mixture was cooled to RT and PPTS (690 mg, 2.78 mmol) was added. The reaction was heated at reflux for a further 8 h, then cooled to RT and poured into saturated aqueous $NaHCO_3$ (100 mL) and the phases separated. The aqueous phase was extracted with DCM (60 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (2:3, DCM:petroleum ether) afforded the title compound as a white solid (13.75 g, 61%). Small scale (1 g) gave an 88% yield.

Alternative procedure:

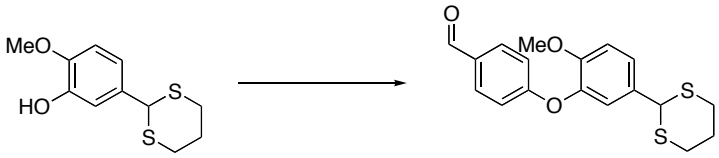
To a stirred solution of isovanillin (1.0 g, 6.58 mmol) in glacial acetic acid (10 mL) at 0 ^oC was added propan-1,3-dithiol (1.07 g, 9.87 mmol) and BF_3.etherate (278 mg, 1.97 mmol). The solution was warmed to RT. After 16 h the resultant white precipitate was collected by filtration, washed with water (10 mL), dissolved in toluene (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the title compound as white solid (1.42 g, 89%).

δ_H (300 MHz, $CDCl_3$) 7.07 (1 H, d, *J*=2.3 Hz, ArH)
6.99 (1 H, dd, *J*=8.3, 2.3 Hz, ArH)
6.81 (1 H, d, *J*=8.3 Hz, ArH)
5.58 (1 H, s, OH)
5.09 (1 H, s, ArCH)
3.88 (3 H, s, CH_3)
3.11–2.99 (2 H, m, SCH_2)
2.95–2.88 (2 H, m, SCH_2)

	2.22–2.17 (1 H, m, C**H**H)
	2.01–1.84 (1 H, m, CH**H**)
δ_C (75 MHz, $CDCl_3$)	146.8 (C), 145.9 (C), 132.7 (C), 119.7 (CH), 114.4 (CH), 110.9 (CH), 56.2 (OCH_3), 51.2 (SCHS), 32.4 (2 x SCH_2), 25.4 (CH_2).
LRMS (ES+)	243 ($[M+H]^+$, 100%), 151 (15%).

These data are in accordance with those reported in the literature.[85]

4-[5-(1,3-Dithian-2-yl)-2-methoxyphenoxy]benzaldehyde (2.4)



$C_{11}H_{14}O_2S$
Molecular Weight: 242.36

$C_{18}H_{18}O_3S_2$
Molecular Weight: 346.46

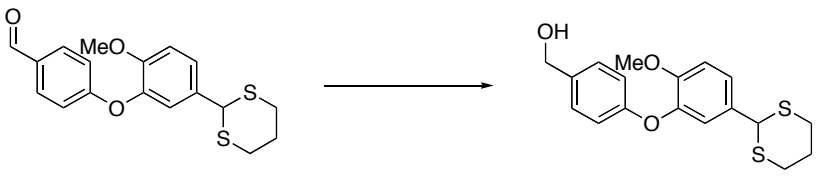
To a stirred solution of **2.3** (1.00 g, 4.12 mmol) and 4-fluorobenzaldehyde (560 mg, 4.53 mmol) in DMF (5 mL) was added K_2CO_3 (630 mg, 4.53 mmol). The reaction mixture was heated at reflux for 48 h, then cooled to RT and poured onto ice (5 mL). The resultant solution was extracted with diethyl ether (4 x 10 mL), then the combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, and the solvent removed *in vacuo* to afford the *title compound* as a white crystalline solid (1.01 g, 79%).

υ_{max}	1693 (s), 1596 (m), 1577 (m), 1503 (s), 1416 (m), 1271 (s), 1249 (m), 1224 (s), 1207 (m), 1181 (w), 1154 (s), 1116 (s), 1016 (s), 877 (w), 853 (w), 839 (w), 824 (s), 818 (s), 771 (s), 757 (s), 700 (m), 677 (m), 636 (m), 605 (m), 551 (m).
δ_H (300 MHz, $CDCl_3$)	9.91 (1 H, s, CHO)
	7.82 (2 H, d, *J*= 8.8 Hz, 2 x ArH)
	7.35 (1 H, dd, *J*=8.4, 2.0 Hz, ArH)
	7.24 (1 H, d, *J*=2.2 Hz, ArH)

	7.00 (3 H, m, 3 x ArH)
	5.12 (1 H, s, ArCH)
	3.79 (3 H, s, OCH_3)
	3.11–2.98 (2 H, m, SC**H**H)
	2.95–2.85 (2 H, m, SCH**H**)
	2.17 (1 H, dm, *J*=14.3 Hz, C**H**H)
	1.99–1.83 (1 H, m, CH**H**)
δ_C (75 MHz, $CDCl_3$)	190.9 (CHO), 163.5 (C), 151.8 (C), 143.2 (C), 132.7 (C), 132.0 (2 x CH), 131.3 (C), 125.8 (CH), 122.2 (CH), 116.6 (2 x CH), 113.3 (CH), 56.2 (CH_3), 50.5 (SCHS), 32.2 (2 x SCH_2), 25.2 (CH_2).
LRMS (ES+)	391 ($[M+CH_3CO_2H+H]^+$, 100%).

These data are in accordance with those reported in the literature.[86]

4-[5-(1,3-Dithian-2-yl)-2-methoxyphenoxy]benzylalcohol (2.5)



$C_{18}H_{18}O_3S_2$
Molecular Weight: 346.46

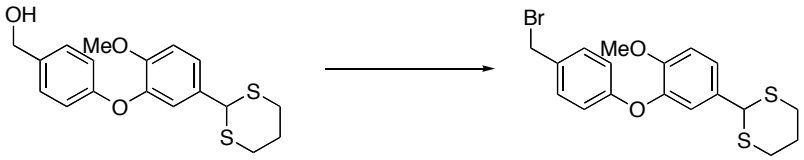
$C_{18}H_{20}O_3S_2$
Molecular Weight: 348.48

To a suspension of **2.4** (2.00 g, 5.76 mmol) in methanol (15 mL) at 0 ºC was added the minimum volume of THF necessary to solubilise the solid (15 mL). To this was added $NaBH_4$ (143 mg, 3.85 mmol) and the reaction mixture warmed to RT. After 2.5 h, water (10 mL) was added and a white precipitate formed. To this suspension was added chloroform (40 mL). The organic phase was separated, washed with water (2 x 20 mL) and brine (20 mL), dried over $MgSO_4$ and the sovent removed *in vacuo* to afford the *title compound* as a white solid (731 mg, 73%).

MP	113–115 ºC (methanol)
υ_{max}	3530 (m), 2920 (w), 2357 (w), 1607 (w), 1581 (w), 1504 (s), 1446 (w), 1416 (m), 1402 (m), 1272 (s), 1247 (m),

	1217 (s), 1180 (m), 1167 (m), 1116 (s), 1021 (s), 1012 (s), 963 (m), 935 (m), 905 (w), 879 (m), 838 (s), 816 (s), 792 (m), 761 (s).
δ_H (300 MHz, $CDCl_3$)	7.31 (2 H, d, *J*=8.8 Hz, 2 × ArH)
	7.26 (1 H, dd, *J*=obsc, 2.2 Hz, ArH)
	7.10 (1 H, d, *J*=2.2 Hz, ArH)
	6.96 (1 H, d, *J*=8.4 Hz, ArH)
	6.95 (2 H, d, *J*=8.8 Hz, 2 x ArH)
	5.07 (1 H, s, ArC**H**)
	4.65 (2 H, s, C**H**$_2$OH)
	3.83 (3 H, s, OCH_3)
	3.08–2.97 (2 H, m, 2 x SCH)
	2.93–2.83 (2 H, m, 2 x SCH)
	2.14 (1 H, app. dm, *J*=14.3 Hz, C**H**H)
	1.98–1.81 (1 H, m, CH**H**)
	1.63 (1 H, br. s, OH)
δ_C (75 MHz, $CDCl_3$)	157.5 (C), 151.6 (C), 145.2 (C), 135.3 (C), 132.4 (C), 128.8 (2 × CH), 124.3 (CH), 120.7 (CH), 117.6 (2 × CH), 113.2 (CH), 65.2 (OCH_2), 56.3 (OCH_3), 50.8 (SCHS), 32.3 (2 × SCH_2), 25.2 (CH_2).
LRMS (ES+)	371 ($[M+Na]^+$, 90%), 349 ($[M+H]^+$, 49%), 331 ($[M–H_2O+H]^+$, 100%).
LRMS (ES–)	347 ($[M–H]^–$, 100%)
HRMS (ES+)	$C_{18}H_{20}NaO_3S_2$ requires 371.0746; Found: 371.0750.

4-[5-(1,3-Dithian-2-yl)-2-methoxyphenoxy]benzyl bromide (2.6)



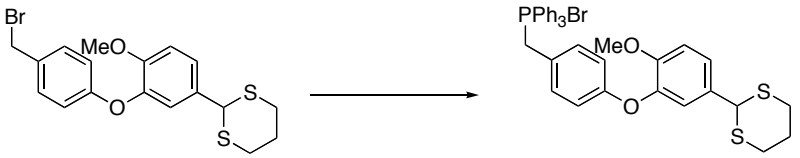
$C_{18}H_{20}O_3S_2$
Molecular Weight: 348.48

$C_{18}H_{19}BrO_2S_2$
Molecular Weight: 411.38

To a stirred solution of **2.5** (686 mg, 1.97 mmol) and triphenylphosphine (772 mg, 2.95 mmol) at 0 °C was added carbon tetrabromide (976 mg, 2.95 mmol) portionwise over 10 min. The reaction mixture was warmed to RT. A mixture of products resulted, to which silica (~2.5 g) was added and the solvent removed *in vacuo*. From this mixture, 99 mg (12 %) of the *title compound* was isolated by flash column chromatography (1:9, ethyl acetate:petroleum ether), contaminated by traces of the deprotected product and characterised only by ^{1}H NMR.

δ_H (300 MHz, $CDCl_3$) 7.32 (2 H, d, *J*=8.7 Hz, 2 x ArH)
7.28 (1 H, obsc., ArH)
7.14 (1 H, d, *J*=2.0 Hz, ArH)
6.97 (1 H, d *J*=8.7 Hz, ArH)
6.89 (2 H, d, *J*=8.7 Hz, 2 × ArH)
5.08 (1 H, s, ArCH)
4.51 (2 H, s, CH_2Br)
3.82 (3 H, s, OCH_3)
3.13–2.95 (2 H, m, 2 x SC**H**H,)
2.94–2.84 (2 H, m, 2 x SCH**H**)
2.15 (1H, dm, *J* =14.0, C**H**H)
1.98–1.82 (1H, m, CH**H**)

[4-(2-Methoxy-5-(1,3-dithian-2-yl))benzyl]triphenylphosphonium bromide (2.7)



$C_{18}H_{19}BrO_2S_2$
Molecular Weight: 411.38

$C_{32}H_{34}BrO_2PS_2$
Molecular Weight: 673.66

Benzylbromide **2.6** (75 mg, 0.17 mmol) and triphenylphosphine (45 mg, 0.17 mmol) were dissolved in toluene (5 mL) and heated at reflux for 24 h. Upon cooling to 0 ºC white crystals formed, which was collected by filtration as a beige solid (39 mg, 32%), albeit with some contamination of aldehyde carried forward.

δ_H (300 MHz, $CDCl_3$) *Peaks attributed to product:*

7.82–7.61 (14 H, m, 14 x ArH)

7.30–7.15 (4 H, m, 4 x ArH)

7.05–6.99 (2 H, m, 2 x ArH)

6.93 (1 H, d, *J*=8.4 Hz, ArH)

6.72 (1 H, d, *J*=8.8 Hz, ArH)

5.40 (2 H, d, *J*=13.5 Hz, CH_2)

3.80 (3 H, s, OCH_3)

3.09–2.97 (2 H, m, 2 x SC**H**H)

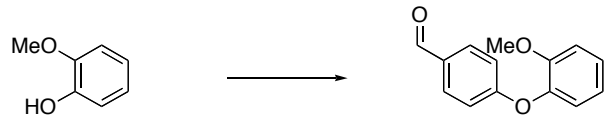
2.95–2.84 (2 H, m, 2 x SCH**H**)

2.21–2.10 (1 H, m, C**H**H)

1.96–1.78 (1 H, m, CH**H**)

LRMS (ES+) (593, $[M–Br]^+$, 100%)).

4-(2-Methoxyphenoxy)benzaldehyde (3.5)



$C_7H_8O_2$
Molecular Weight: 124.14

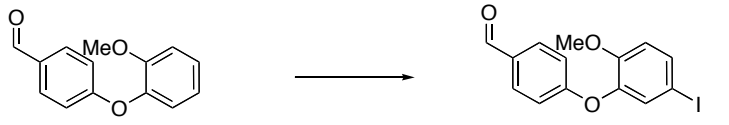
$C_{14}H_{12}O_3$
Molecular Weight: 228.24

To a stirred solution of 2-methoxyphenol (5.00 g, 40.3 mmol) and 4-fluorobenzaldehyde (5.50 g, 44.4 mmol, 4.78 mL) in DMF (25 mL) was added K_2CO_3 (6.12 g, 44.4 mmol). The reaction mixture was heated at reflux for 24 h, then cooled to RT and poured onto ice (50 mL). The resultant emulsion was extracted with ethyl acetate (3 × 50 mL) then the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (chloroform) afforded the title compound as a yellow oil (8.40 g, 91%).

υ_{max}	2360 (m), 1692 (m), 1599 (m), 1581 (m), 1570 (m), 1487 (s), 1461 (w), 1439 (w), 1392 (w), 1292 (m), 1261 (s), 1222 (s), 1176 (s), 1152 (s), 1131 (s), 1104 (w), 1021 (m), 890 (m), 829 (m), 764 (w), 720 (w), 653 (w), 614 (m), 596 (w), 502 (m).
δ_H (400 MHz, $CDCl_3$)	9.90 (1 H, s, CHO) 7.82 (2 H, d, *J*=8.5 Hz, 2 x ArH) 7.27–7.21 (1 H, m, ArH) 7.10 (1 H, dd, *J*=8.0, 1.5 Hz, ArH) 7.05 (1 H, dd, *J*=8.3, 1.3 Hz, ArH) 7.02–7.00 (1 H, m, ArH) 6.99 (2 H, d, *J*=8.5 Hz, 2 x ArH) 3.79 (3 H, s, OCH_3)
δ_C (100 MHz, $CDCl_3$)	191.0 (CHO), 163.9 (C), 152.0 (C), 143.2 (C), 132.1 (2 × CH), 131.2 (C), 126.7 (CH), 122.9 (CH), 121.7 (CH), 116.5 (2 × CH), 113.4 (CH), 56.2 (OCH_3).
LRMS (EI)	228 ($M^{+\cdot}$, 100%), 207 (30%), 185 (20%), 184 (18%), 128 (42%),114 (38%), 77 (55%), 64 (27%), 51 (42%).

These data are in accordance with those reported in the literature.[87]

4-(5-Iodo-2-methoxyphenoxy)benzaldehyde (2.10)



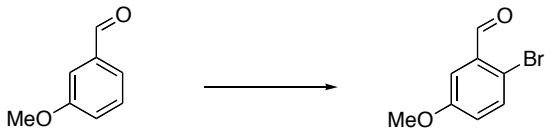
$C_{14}H_{12}O_3$
Molecular Weight: 228.24

$C_{14}H_{11}IO_3$
Molecular Weight: 354.14

To a stirred solution of 4-(methoxyphenoxy)benzaldehyde **3.5** (2.00 g, 9.4 mmol) in DCM (20 mL) was added a solution of ICl (1.83 g, 11.3 mmol) in DCM (5 mL). Light was excluded for 7 days then saturated aqueous $Na_2S_2O_3$ (15 mL) was added. After 1 h the biphasic solution was separated and the aqueous phase extracted with diethyl ether (10 mL + 50 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), then dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the title compound as an orange gum which crystallised on standing (3.31 g, quantitative yield).

MP	48 °C sharp (DCM)
υ_{max}	1682 (s), 1598 (s), 1582 (s), 1495 (s), 1464 (m), 1304 (m), 1264 (s), 1227 (s), 1197 (m), 1175 (s), 1162 (s), 1153 (s), 1110 (s), 1041 (s), 1024 (s), 875 (m), 832 (s), 769 (s), 750 (s), 726 (m), 620 (m), 505 (m).
δ_H (400 MHz, $CDCl_3$)	9.82 (1 H, s, CHO) 7.74 (2 H, d, *J*=8.7 Hz, ArH) 7.43 (1 H, dd, *J*=8.6, 2.1 Hz, ArH) 7.30 (1 H, d, *J*=2.1 Hz, ArH) 6.89 (2 H, d, *J*=8.7 Hz, ArH) 6.70 (1 H, d, *J*=8.6 Hz, ArH) 3.68 (3 H, s, OCH_3)
δ_C (100 MHz, $CDCl_3$)	190.7 (CHO), 163.0 (C), 152.0 (C), 143.9 (C), 135.3 (CH), 132.0 (2 × CH), 131.4 (C), 131.2 (CH), 116.5 (2 × CH), 115.0 (CH), 82.0 (CI), 56.1 (OCH_3).
LRMS (EI)	354 ($M^{+\cdot}$, 100%), 311 (6%), 207 (19%), 184 (24%), 156 (9%), 155 (9%), 128 (14%), 79 (31%), 51 (18%).

2-Bromo-5-methoxybenzaldehyde (3.10)



$C_8H_8O_2$
Molecular Weight: 136.15

$C_8H_7BrO_2$
Molecular Weight: 215.04

To a stirred solution of *m*-anisaldehyde (272 mg, 2.00 mmol, 2.43 mL) in chloroform (20 mL) at 0 ºC was added bromine (318 mg, 2.00 mmol, 0.1 mL) dropwise over 5 min. The reaction mixture was stirred at RT for 6 h, after which time the solution was cooled to 0 °C and further bromine (1.59 g, 10.00 mmol, 4.8 mL) added dropwise over 10 min. The reaction mixture was heated at reflux for 19 h then cooled to RT. Saturated aqueous $Na_2S_2O_3$ (20 mL) was added, then the organic layer was washed with water (20 mL) and brine (20 mL), and the solvent removed *in vacuo*. Purification by flash column chromatography (199:1→19:1, petroleum ether:diethyl ether) afforded the title compound as a beige solid (318 mg, 74%).

Alternative Procedure:

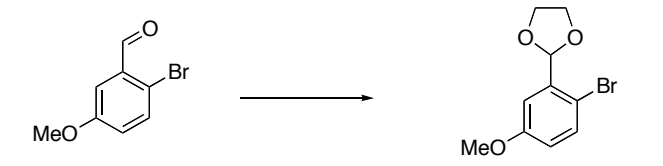
To a stirred solution of *m*-anisaldehyde (20.0 g, 0.15 mol) in glacial acetic acid (500 mL) was added bromine (26.4 g, 0.17 mol) dropwise over 20 min. After 13 days water (300 mL) was added and the reaction left for 19 h without stirring to allow precipitation of the product. The product was collected by filtration, washed with ice water then dried in a desicator for 2 days to yield the title compound as a cream solid (22.66 g, 72%).

MP	60–62 °C (Water) [Lit.[88] 75–76 °C, no solvent given]
υ_{max}	3006 (w), 2941 (w), 2873 (w), 2841 (w), 1674 (m), 1598 (w), 1568 (m), 1463 (m), 1440 (w), 1415 (w), 1381 (m), 1300 (w), 1276 (s), 1233 (m), 1197 (s), 1169 (m), 1134 (w), 1115 (w), 1059 (m), 1010 (m), 930 (s), 864 (s), 819 (s), 752 (m), 685 (w).
δ_H (400 MHz, $CDCl_3$)	10.33 (1 H, s, CHO)
	7.54 (1 H, d, *J*=8.8 Hz, ArH)
	7.43 (1 H, d, *J*=3.3 Hz, ArH)

	7.05 (1 H, dd, *J*=8.8, 3.3 Hz, ArH)
	3.86 (3 H, s, OCH_3)
δ_C (75 MHz, $CDCl_3$)	191.9 (CHO), 159.4 (C), 134.7 (CH), 134.1 (C), 123.3 (CH), 118.1 (CBr), 112.8 (CH), 55.9 (OCH_3).
LRMS (EI)	214 ($M^{+\cdot}$, 100%), 136 (30%), 135 ($[M–Br]^+$, 11%), 109 (7%), 108 (12%), 106 (6%), 63 (35%).

These data are in accordance with those reported in the literature.[67]

2-(2-Bromo-5-methoxyphenyl)-1,3-dioxolane (3.11)



$C_8H_7BrO_2$
Molecular Weight: 215.04

$C_{10}H_{11}BrO_3$
Molecular Weight: 259.10

To a stirred solution of 2-bromo-5-methoxybenzaldehyde **3.10** (2.50 g, 11.68 mmol) in toluene (40 mL) was added ethylene glycol (3.62 g, 58.41 mmol) and PPTS (117 mg, 0.47 mmol). The reaction mixture was heated at reflux under a Dean and Stark apparatus for 19 h then cooled to RT, diluted with diethyl ether (40 mL) and washed with saturated aqueous K_2CO_3 (100 mL) and brine (100 mL). The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the title compound as a colourless oil (2.920 g, 97%).

υ_{max}	2953 (w), 2888 (w), 1595 (w), 1574 (m), 1471 (s), 1420 (m), 1391 (m), 1291 (s), 1233 (s), 1195 (m), 1168 (s), 1139 (m), 1124 (m), 1083 (s), 1052 (s), 1016 (s), 946 (s), 979 (m), 865 (m), 809 (s), 773 (w), 732 (m), 696 (w).
δ_H (300 MHz, $CDCl_3$)	7.42 (1 H, d, *J*=8.7 Hz, ArH)
	7.16 (1 H, d, *J*=3.2 Hz, ArH)
	6.76 (1 H, dd, *J*=8.7, 3.2 Hz, ArH)
	6.03 (1 H, s, ArCH)

	3.97–4.17 (4 H, m, 2 × OCH_2)
	3.77 (3 H, s, OCH_3)
δ_C (300 MHz, $CDCl_3$)	159.0 (C), 137.4 (C), 133.5 (CH), 116.5 (CH), 113.1 (CH), 113.0 (C), 102.4 (ArCH), 65.4 (2 × OCH_2), 55.5 (OCH_3).
LRMS (EI)	258 ($M^{+\cdot}$, 56%), 215 ($[M–C_2H_4O]^+$, 39%), 186 (60%), 179 (45%), 141 (60%), 135 (25%), 119 (26%), 78 (20%), 77 (25%), 76 (31%), 75 (23%), 74 (16%), 73 (100%), 45 ($[C_2H_5O]^+$, 73%).

These data are accordance with those reported in the literature.[61]

2-Formyl-4-methoxyphenylboronic acid (2.12)[61]

$C_{10}H_{11}BrO_3$
Molecular Weight: 259.10

$C_8H_9BO_4$
Molecular Weight: 179.97

To a stirred solution of dioxolane **3.11** (2.00 g, 7.72 mmol) in THF (20 mL) at –78 °C was added *n*-butyllithium (3.92 mL, 8.48 mmol, 2.16 M solution in hexanes) dropwise over 10 min. After 45 min at –78 °C, tri-*n*-butyl borate (2.31 g, 10.05 mmol) was added dropwise over 10 min. The reaction mixture was warmed to RT over 3 h, then HCl (3 mL, 2 M) was added. After 1 h, the biphasic mixture was extracted with NaOH (30 mL, 3 M) and this extract acidified with HCl (approx. 40 mL, 2 M). A white precipitate formed which was collected by filtration and washed with cold water (10 mL). The resultant solid was azeotroped with chloroform (3 × 30 mL) to afford the title compound as a white crystalline solid (873 mg, 63%).

MP	190–192 °C (water)
δ_H (300 MHz, $CDCl_3$)	9.89 (1 H, s, CHO)
	8.24 (1 H, d, *J*=8.5 Hz, ArH)

7.44 (1 H, d, *J*=2.5 Hz, ArH)

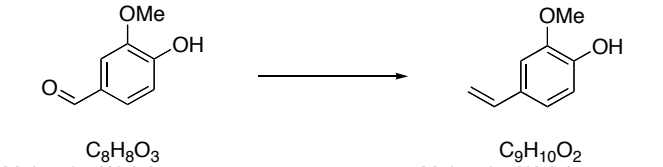
7.20 (1 H, dd, *J*=8.5, 2.5 Hz, ArH)

6.98 (2 H, s, $B(OH)_2$)

3.94 (3 H, s, OCH_3)

This compound is commercially available.

4-Hydroxy-3-methoxystyrene (2.13)



$C_8H_8O_3$
Molecular Weight: 152.15

$C_9H_{10}O_2$
Molecular Weight: 150.17

To a stirred suspension of methyltriphenylphosphonium bromide (7.05 g, 19.74 mmol) in THF (50 mL) at 0 °C was added KO*t*-Bu (2.21 g, 19.74 mmol) portionwise over 5 min. After 30 min at 0 °C vanillin (1.00 g, 6.58 mmol) was added and the reaction heated at reflux for 18 h. The reaction mixture was cooled to RT and the triphenylphosphine oxide removed by filtration. The filtrate was washed with saturated aqueous NH_4Cl (2 × 50 mL) and brine (75 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (7:3, petroleum ether:ethyl acetate) afforded the title compound as pale yellow gum (762 mg, 77%).

υ_{max} 1595 (w), 1509 (s), 1463 (m), 1430 (m), 1417 (m), 1367 (w), 1266 (s), 1232 (s), 1204 (s), 1151 (s), 1121 (s), 1028 (s), 988 (m), 898 (m), 854 (s), 819 (s), 790 (s).

δ_H (300 MHz, $CDCl_3$) 6.95–7.02 (3 H, m, 3 × ArH)

6.71 (1 H, dd, *J*=17.6, 10.9 Hz, C**H**=CH_2)

5.97 (1 H, br. s, OH)

5.67 (1 H, dd, *J*=17.6, 0.6 Hz, CH=CH**H**)

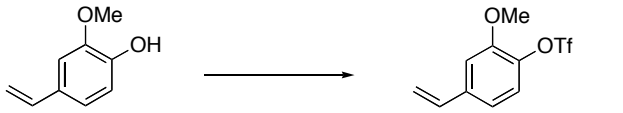
5.20 (1 H, d, *J*=10.9 Hz, CH=C**H**H)

3.91 (3 H, s, OCH_3)

δ_C (75 MHz, $CDCl_3$)	146.7 (C), 145.7 (C), 136.7 (**C**H=CH_2), 130.3 (C), 120.0 (CH), 114.5 (CH), 111.4 (CH=**C**H_2), 108.2 (CH), 55.9 (OCH_3).
LRMS (EI)	150 ($M^{+\cdot}$, 80%), 135 ($[M–CH_3]^+$, 100%), 107 (29%), 79 (27%), 78 (24%), 63 (22%), 52 (18%), 51 (17%).

This compound is commercially available.

2-Methoxy-4-vinylphenyltrifluoromethane sulfonate (2.13)



$C_9H_{10}O_2$
Molecular Weight: 150.17

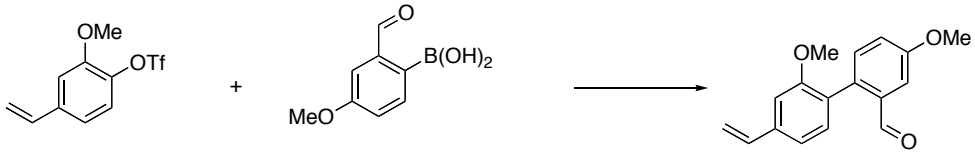
$C_{10}H_9F_3O_4S$
Molecular Weight: 282.24

To a stirred solution of trifluoromethanesulfonic anhydride (2.45 g, 16.3 mmol) in DCM (30 mL) at 0 °C was added a solution of 4-hydroxy-3-methoxystyrene **3.12** (5.07 g, 18.0 mmol) and pyridine (1.55 g, 19.6 mmol) in DCM (30 mL) dropwise over 1 h, keeping the reaction mixture at 0 °C. After a further 3 h at 0 °C ice water (~50 mL) was added and the phases separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (50 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (DCM) afforded the *title compound* as colourless oil (4.03 g, 88%).

υ_{max}	1601 (w), 1502 (m), 1465 (w), 1415 (s), 1277 (w), 1247 (w), 1200 (s), 1135 (s), 1104 (s), 1030 (m), 858 (s), 819 (m), 746 (w), 685 (w), 614 (s), 503 (m).
δ_H (300 Mz, $CDCl_3$)	7.18 (1 H, d, *J*=8.3 Hz, ArH) 7.06 (1 H, d, *J*=1.9 Hz, ArH) 7.01 (1 H, dd, *J*=8.3, 1.9 Hz, ArH) 6.69 (1 H, dd, *J*=17.5, 10.8 Hz, C**H**=CH_2) 5.77 (1 H, d, *J*=17.5 Hz, CH=CH**H**) 5.35 (1 H, d, *J*=10.8 Hz, CH=C**H**H) 3.94 (3 H, s, OCH_3)

δ_C (75 MHz, $CDCl_3$)	151.6 (C), 139.1 (C), 138.3 (C), 135.7 (**C**H=CH_2), 122.6 (CH), 119.0 (CH), 118.9 (q, *J*=320.7 Hz, CF_3), 116.1 (CH=**C**H_2), 110.7 (CH), 56.3 (OCH_3).
δ_F (282 MHz, $CDCl_3$)	–74.13 (CF_3)
LRMS (EI)	282 ($M^{+\cdot}$, 23%), 149 ([M–$SO_2CF_3^+$], 82%), 121 (34%), 103 (28%), 91 (67%), 69 (CF_3^+, 100%), 64 (SO_2^+, 28%), 52 (38%).
HRMS	$C_{10}H_9O_4F_3S$ requires 282.0173; Found: 282.0167.

2',4-Dimethoxy-4'-vinylbiphenyl-2-carbaldehyde (2.11)



$C_{10}H_9F_3O_4S$
Molecular Weight: 282.24

$C_8H_9BO_4$
Molecular Weight: 179.97

$C_{17}H_{16}O_3$
Molecular Weight: 268.31

To a stirred solution of triflate **2.13** (78 mg, 0.28 mmol) and boronic acid **2.12** (10 mg, 0.55 mmol) in dioxane (2 mL) was added LiCl (117 mg, 2.77 mmol), Cs_2CO_3 (326 mg, 1.11 mmol) and SPhos **3.15** (44 mg, 0.11 mmol). The reaction mixture was degassed with sonication under argon for 5 min, then $PdCl_2$ (5 mg, 0.027 mmol) was added and the reaction mixture heated at reflux for 3 h. The reaction was cooled to RT, filtered through a glass sinter, then silica (~1 g) was added to the filtrate and the solvent removed *in vacuo*. Purification by flash column chromatography (4:1, petroleum ether:diethyl ether) afforded the *title compound* (55 mg, 76%) as an off-white solid.

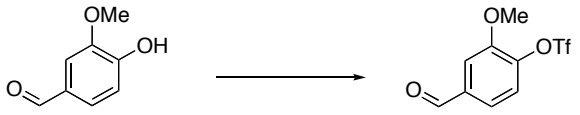
Alternative procedure:

To a stirred solution of triflate **2.13** (4.00 g, 14.18 mmol) and boronic acid **2.12** (2.54 g, 14.18 mmol) in dioxane (80 mL) was added LiCl (6.016 mg, 140.84 mmol), Cs_2CO_3 (23.10 g, 70.92 mmol) and SPhos **3.15** (404 mg, 1.14 mmol). The reaction mixture was degassed with sonication under argon for 10 min, then $Pd(OAc)_2$ (128 mg, 0.57 mmol) was added and the reaction mixture heated at reflux for 3 h. The reaction mixture was cooled to RT, then water (80 mL) added and the reaction

mixture extracted with DCM (3 x 100 mL). The combined organic phases were concentrated *in vacuo*. Purification by flash column chromatography (2:1, petroleum ether:DCM) afforded the *title compound* (1.955 g, 52%) as a yellow crystalline solid.

MP	118–120 °C (heptane/ethylacetate)
υ_{max}	3004 (w), 2936 (w), 2838 (w), 1686 (s), 1603 (s), 1572 (w), 1556 (w), 1512 (w), 1486 (s), 1462 (m), 1393 (m), 1317 (m), 1266 (s), 1246 (s), 1224 (m), 1190 (w), 1162 (s), 1138 (w), 1035 (s), 1000 (w), 934 (w).
δ_H (300 MHz, $CDCl_3$)	9.75 (1 H, s, CHO) 7.50 (1 H, d, *J*=2.7 Hz) 7.31–7.17 (3 H, m, 3 x ArH) 7.12 (1 H, dd, *J*=7.8, 1.4 Hz, ArH) 7.00 (1 H, d, *J*=1.2 Hz, ArH) 6.77 (1 H, dd, *J*=17.6, 10.9 Hz, C**H**=CH_2) 5.82 (1 H, d, *J*=17.6 Hz, C**H**H) 5.33 (1H, d, *J*=10.9 Hz, CH**H**) 3.90 (3 H, s, OCH_3) 3.77 (3 H, s, OCH_3)
δ_C (75 MHz, $CDCl_3$)	192.6 (CHO), 159.4 (C), 156.9 (C), 139.4 (C), 136.5 (CH), 135.1 (C), 134.5 (C), 132.4 (CH), 131.9 (CH), 126.3 (C), 121.4 (CH), 119.3 (CH), 114.8 (CH_2), 109.6 (CH), 108.4 (CH), 55.7 (OCH_3), 55.6 (OCH_3).
LRMS (ES+)	559 ($[2M+Na]^+$, 9%), 291 ($[M+Na]^+$, 100%).
HRMS	$C_{17}H_{16}O_3Na$ requires 291.0992; Found: 291.0994.

2-Methoxy-4-formylphenyl trifluoromethanesulfonate (3.13)



$C_8H_7O_3$
Molecular Weight: 152.15

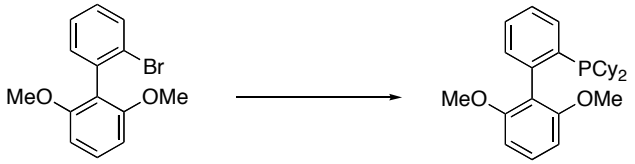
$C_9H_7F_3O_5S$
Molecular Weight: 284.21

To a stirred solution of trifluoromethanesulfonic anhydride (10.20 g, 36.18 mmol) in DCM (25 mL) at 0 °C was added a solution of vanillin (5.00 g, 32.90 mmol) and pyridine (5.20 g, 65.66 mmol) in DCM (50 mL) dropwise over 2 h, maintaining the temperature of the reaction below 5 °C. The reaction mixture was warmed to RT over 30 min, then ice water (~50 mL) was added and the reaction mixture stirred for a further 15 min. The phases were separated and the aqueous phase extracted with DCM (50 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (DCM) afforded the title compound as a pink gum (3.95g, 42%).

υ_{max}	1705 (m), 1605 (m), 1499 (m), 1421 (s), 1388 (m), 1278 (m), 1248 (m), 1205 (s), 1137 (s), 1104 (s), 1029 (m), 874 (s), 822 (m), 780 (w), 734 (m), 717 (m), 615 (s).
δ_H (300 MHz, $CDCl_3$)	9.99 (1 H, s, CHO) 7.57 (1 H, d, *J*=1.8 Hz, ArH) 7.52 (1 H, dd, *J*=8.3, 1.8 Hz, ArH) 7.41 (1 H, d, *J*=8.3 Hz, ArH) 4.00 (3 H, s, OCH_3)
δ_C (75 MHz, $CDCl_3$)	190.5 (CHO), 152.4 (C), 142.9 (C), 137.0 (C), 124.3 (CH), 123.4 (CH), 118.9 (q, *J*=320.7 Hz, CF_3), 112.0 (CH), 56.7 (OCH_3).
δ_F (282 MHz, $CDCl_3$)	–74.2
LRMS (ES+)	299 ($[M+H_2O+H]^+$, 100%).

These data are in accordance with those reported in the literature.[86]

2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (3.15)



$C_{14}H_{13}BrO_2$
Molecular Weight: 293.16

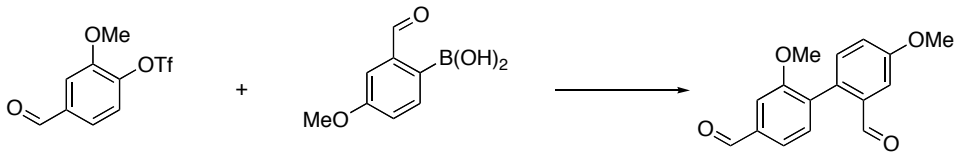
$C_{26}H_{35}O_2P$
Molecular Weight: 410.53

To a stirred solution of biphenyl **3.18** (630 mg, 2.15 mmol) in THF (5 mL) at –78 °C was added *n*-butyllithium (0.95 mL, 2.5 M, 2.36 mmol) dropwise over 5 min. Dicyclohexylphosphine chloride (500 mg, 2.15 mmol) was added and the reaction mixture maintained at –78 °C for 1 h, then warmed to RT over 2 h. The reaction mixture was filtered through silica with additional ethyl acetate (10 mL) then concentrated *in vacuo*. Recrystallisation from acetone afforded the title compound as a white crystalline solid (235 mg). The filtrate was concentred *in vacuo* and a second recystallisation procedure afforded further product as a white crystalline solid (206 mg), giving an overall yield of 50%.

MP	164–165 °C (acetone)
	[Commercial sample 162–162.5 °C (acetone)]
δ_H (400 MHz, $CDCl_3$)	7.57 (1 H, d, *J*=7.5 Hz, ArH)
	7.42–7.37 (1 H, m, ArH)
	7.34 (1 H, dd, *J*=7.0, 1.5 Hz, ArH)
	7.30 (1 H, d, *J*=8.0 Hz, ArH)
	7.20–7.15 (1 H, m, ArH)
	6.59 (2 H, d, *J*=8.5 Hz, 2 x ArH)
	3.68 (6 H, s, 2 x OCH_3)
	1.83–1.58 (12 H, m, 6 x C**H**H)
	1.33–0.97 (10 H, m, 5 x C**H**H)

This compound is commercially available.

2',4-Dimethoxy-4'-formyl-biphenyl-2-carbaldehyde (3.14)



$C_9H_7F_3O_5S$
Molecular Weight: 284.21

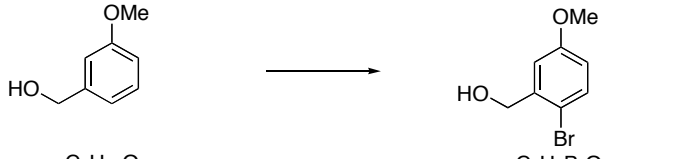
$C_8H_9BO_4$
Molecular Weight: 179.97

$C_{16}H_{14}O_4$
Molecular Weight: 270.28

To a stirred solution of triflate **3.13** (1.00 g, 7.04 mmol) and boronic acid **2.12** (631 mg, 7.04 mmol) in dioxane (15 mL) was added triethylamine (2.85 g, 28.17 mmol). The reaction mixture was degassed with sonication under argon for 10 min, then $Pd(dppf)Cl_2$ was added and the reaction mixture heated at reflux for 8 h. The reaction mixture was cooled to RT, silica (~4 g) added and the solvent removed *in vacuo*. Purification by flash column chromatography (4:1, petroleum ether:diethyl ether) afforded the *title compound* (608 mg, 64%) as a white solid.

MP	130–132 °C (petroleum ether)
υ_{max}	2843 (w), 1690 (s), 1603 (m), 1577 (w), 1509 (w), 1487 (w), 1463 (w), 1413 (w), 1389 (w), 1318 (w), 1276 (m), 1266 (m), 1246 (w), 1224 (w), 1191 (w).
δ_H (400 MHz, $CDCl_3$)	10.00 (1 H, s, CHO) 9.81 (1 H, s, CHO) 7.58 (1 H, d, *J*=1.7 Hz, ArH) 7.55 (1 H, d, *J*=2.8 Hz, ArH) 7.52 (1 H, dd, *J*=8.3, 1.7 Hz, ArH) 7.42 (1 H, d, *J*=8.3 Hz, ArH) 7.27 (1 H, d, *J*=8.3 Hz, ArH) 7.21 (1 H, dd, *J*=8.3, 2.8 Hz, ArH) 4.01 (3 H, s, OCH_3) 3.94 (3 H, s, OCH_3)
δ_C (100 MHz, $CDCl_3$)	191.8 (CHO), 191.7 (CHO), 159.9 (C), 157.5 (C), 137.8 (C), 135.1 (C), 133.7 (C), 133.1 (C), 132.4 (CH), 132.3 (CH), 124.6 (CH), 121.3 (CH), 110.3 (CH), 109.3 (CH), 55.9 (OCH_3), 55.8 (OCH_3).
LRMS (ES+)	325 ($[M+Na+MeOH]^+$, 100%).
HRMS	$C_{16}H_{14}NaO_4$ requires 293.0784; Found: 293.0787.

2-Bromo-5-methoxybenzyl alcohol (3.21)



$C_8H_{10}O_2$
Molecular Weight: 138.16

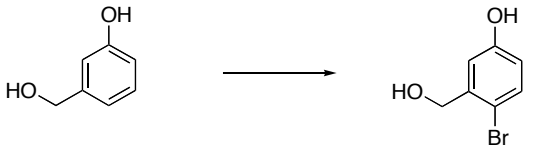
$C_8H_9BrO_2$
Molecular Weight: 217.06

To a stirred solution of 3-methoxybenzyl alcohol (5.00 g, 36.2 mmol) in 1:1 v/v acetonitrile and water (250 mL) at 0 °C was added $NaBrO_3$ (9.53 g, 63.5 mmol). $NaHSO_3$ (6.6 g, 63.5 mmol) was then added portionwise over 5 min. The reaction mixture was warmed to RT and after 1 h, saturated aqueous $Na_2S_2O_3$ (200 mL) was cautiously added. After 1 h, the reaction mixture was extracted with diethyl ether (3 × 100 mL). The combined organic phases were washed with saturated aqueous Na_2CO_3 (100 mL) and water (100 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. The resultant cream solid was purified by flash column chromatography (9:1, chloroform:methanol) to afford the title compound as a white solid (4.00 g, 51%) contaminated with small amounts of a dibrominated compound.

MP	45–48 °C (petrol) [Lit.[55] 49 °C]
υ_{max}	3267 (br. w), 1593 (w), 1574 (m), 1469 (s), 1440 (m), 1409 (m), 1359 (w), 1294 (s),1269 (s), 1237 (s), 1190 (w), 1158 (s), 1135 (w), 1116 (m), 1047 (s), 1012 (s), 983 (m)), 916 (w), 864 (w), 853 (m), 817 (w), 806 (m), 791 (m), 737 (m), 689 (m), 617 (m), 589 (m).
δ_H (400 MHz, $CDCl_3$)	7.42 (1 H, d, *J*=8.8 Hz, ArH) 7.07 (1 H, d, *J*=3.0 Hz, ArH) 6.73 (1 H, dd, *J*=8.8, 3.0 Hz, ArH) 4.71 (2 H, d, *J*=6.0 Hz, OCH_2) 3.81 (3 H, s, OCH_3) 2.07 (1 H, t, *J*=6.0 Hz, OH)
δ_C (100 MHz, $CDCl_3$)	159.5 (C), 140.9 (C), 133.3 (CH), 115.0 (CH), 114.5 (CH), 112.7 (C), 65.2 (OCH_2), 55.7 (OCH_3).
LRMS (EI)	218 ($M(^{81}Br)^{+\cdot}$, 13%), 77 (26%), 65 (28%), 63 (100%).

These data are in accordance with those reported in the literature.[67]

2-Bromo-5-hydroxybenzylalcohol (3.22)



$C_7H_8O_2$
Molecular Weight: 124.14

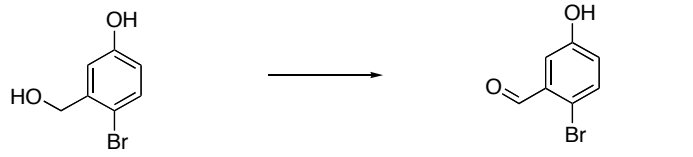
$C_7H_7BrO_2$
Molecular Weight: 203.03

To a stirred solution of 3-hydroxybenzyl alcohol (5.00 g, 40.3 mmol) in 1:1 v/v acetonitrile and water (250 mL) at 0 °C was added $NaBrO_3$ (10.6 g, 70.6 mmol). $NaHSO_3$ (7.34 g, 70.6 mmol) was then added portionwise over 5 min. The reaction mixture was warmed to RT and after 2 h, saturated aqueous $Na_2S_2O_3$ (200 mL) was cautiously added. After 1 h, the reaction mixture was extracted with diethyl ether (3 × 100 mL). The combined organic phases were washed with saturated aqueous Na_2CO_3 (100 mL) and water (100 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (4:1, petroleum ether:ethyl acetate) afforded the title compound as an off-white solid (4.88 g, 60%).

MP	127–129 °C (ethyl aceate/petroleum ether)
	[Lit.[89] 140 °C, PhH]
υ_{max}	3367 (br. w), 3157 (br. w), 1593 (w), 1579 (w), 1468 (m), 1437 (s), 1372 (w), 1326 (w), 1283 (s), 1240 (s), 1223 (s), 1160 (s), 1116 (w), 1047 9s), 1018 (s), 983 (w), 957 (w), 939 (w), 852 (m), 799 (s), 745 (w), 689 (w).
δ_H (300 MHz, DMSO-d_6)	7.29 (1 H, d, *J*=8.6 Hz, ArH)
	6.99 (1 H, d, *J*=3.0 Hz, ArH)
	6.58 (1 H, dd, *J*=8.6, 3.0 Hz, ArH)
	5.33 (1 H, t, *J*=5.6 Hz, OH)
	4.41 (2 H, d, *J*=5.6 Hz, CH_2)
LRMS	Did not fly by EI or ES+.

These data are in accordance with those reported in the literature.[89]

2-Bromo-5-hydroxybenzaldehyde (3.23)



$C_7H_7BrO_2$
Molecular Weight: 203.03

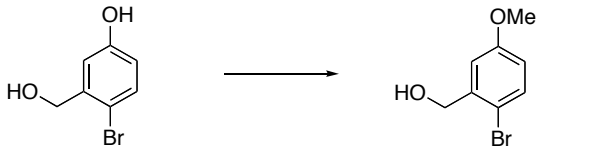
$C_7H_5BrO_2$
Molecular Weight: 201.12

Powdered MnO_2 (15.25 g, 177 mmol) was azeotroped with toluene (2 × 150 mL). To the dry residue was added THF (75 mL) and to this stirred suspension was added 4-bromo-3-hydroxybenzyl alcohol **3.22** (1.800 g, 8.9 mmol). At 19 h, filtration through Celite® and concentration *in vacuo* afforded a cream solid. Purification by flash column chromatography (7:3, petroleum etherl:ethyl acetate) afforded the title compound as a white solid (1.31 g, 74%).

MP	128–130 °C (Petroleum ether) [Lit.[90] 130 °C, $CDCl_3$]
υ_{max}	3315 (br. w), 1673 (s), 1590 (s), 1437 (s), 1395 (s), 1303 (s), 1233 (s), 1168 (s), 1112 (m), 1035 (m), 973 (s), 865 (s), 831 (s), 761 (s), 686 (s), 656 (s), 585 (s).
δ_H (300 MHz, DMSO-d_6)	10.19 (1 H, s, OH) 10.13 (1 H, s, CHO) 7.52–7.61 (1 H, dd, *J*=8.7 Hz, ArH) 7.22 (1 H, dd, *J*=3.0, Hz, ArH) 7.00–7.06 (1 H, dd, *J*=8.7, 3.0 Hz, ArH)
δ_C (75 MHz, d_6-acetone)	191.9 (CHO), 158.3 (CH), 138.2 (C), 135.7 (CH), 135.2 (C), 124.2 (CH), 116.4 (CBr).
LRMS (EI)	207 (25%), 201 (66%), 200 ($M^{+\cdot}$, 83%), 199 (66%), 171 ($[M–CO]^+$, 17%), 143 (8%), 120 (10%), 63 (100%).

These data are in accordance with those reported in the literature.[90]

2-Bromo-5-hydroxybenzyl alcohol (3.21)



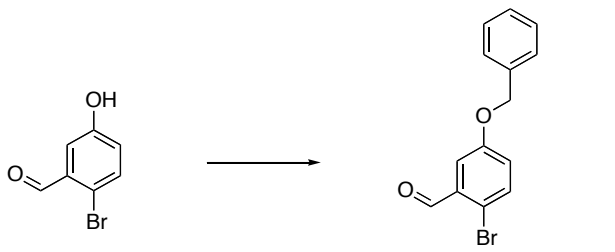
$C_7H_7BrO_2$
Molecular Weight: 203.03

$C_8H_9BrO_2$
Molecular Weight: 217.06

To a stirred solution of benzyl alcohol **3.22** (30 mg, 0.15 mmol) in acetone (3 mL) was added K_2CO_3 (61 mg, 0.44 mmol) and methyl iodide (84 mg, 0.60 mmol). After 19 h, water (3 mL) was added and the reaction extracted with DCM (2 x 5 mL). The combined organic phases were washed with water (2 x 5 mL) and brine (5 mL), then dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the title compound (32 mg, 100%).

The data were identical to those previously reported.[55]

3-Benzyloxy-5-bromobenzaldehyde (3.24)



$C_7H_5BrO_2$
Molecular Weight: 201.12

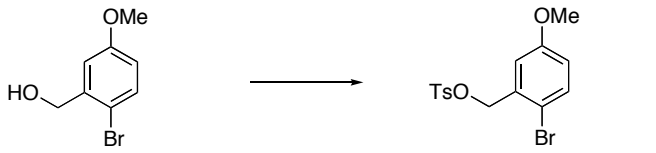
$C_{14}H_{11}BrO_2$
Molecular Weight: 291.14

To a stirred solution of 4-bromo-3-hydroxybenzaldehyde **3.23** (500 mg, 2.5 mmol) and benzyl bromide (556 mg, 3.3 mmol) in THF (15 mL) was added KI (664 mg, 4.0 mmol) and K_2CO_3 (483 mg, 3.5 mmol). The reaction mixture was heated at reflux for 19 h then cooled to RT. Water (15 mL) was added and the reaction mixture extracted with chloroform (2 × 15 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (19:1, petroleum ether:diethyl ether) afforded the title compound as a viscous colourless oil (320 mg, 79%).

υ_{max}	1689 (s), 1589 (m), 1567 (w), 1497 (w), 1454 (m), 1408 (w), 1385 (m), 1307 (m), 1269 (s), 1228 (s), 1163 (s), 1133 (w), 1110 (w), 1046 (w), 1008 (s), 944 (w), 910 (w), 735 (s), 695 (s), 625 (s).
δ_H (300 MHz, $CDCl_3$)	10.31 (1 H, s, CHO) 7.52 (1 H, d, *J*=8.8 Hz, ArH) 7.52 (1 H, d, *J*=3.3 Hz, ArH) 7.46–7.32 (5 H, m, ArH) 7.10 (1 H, dd, *J*=8.8, 3.2 Hz, ArH) 5.099 (2 H, s, OCH_2)
δ_C (75 MHz, $CDCl_3$)	191.6 (CHO), 158.4 (C), 136.0 (C), 134.7 (CH), 134.0 (C), 128.8 (2 × CH), 128.4 (CH), 127.6 (2 × CH), 123.7 (CH), 118.2 (C), 114.0 (C), 70.5 (CH_2).
LRMS (EI)	290 ($M^{+\cdot}$, 4%), 108 (18%), 91 ($C_7H_7^+$, 100%), 65 (6.2%).

These data are in accordance with those reported in the literature.[50]

2-Bromo-5-methoxybenzyl tosylate (3.25)

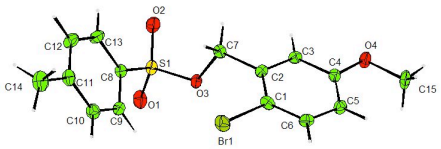


$C_8H_9BrO_2$
Molecular Weight: 217.06

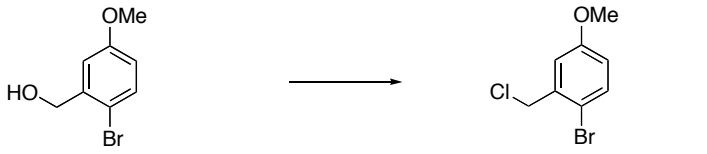
$C_{15}H_{15}BrO_4S$
Molecular Weight: 371.25

To a stirred solution of 4-bromo-3-methoxybenzyl alcohol **3.22** (500 mg, 2.3 mmol) in DCM (5 mL) at 0 °C was added tosyl chloride (482 mg, 2.5 mmol) in 5 portions over 15 min. A solution of TEA (465 mg, 4.6 mmol, 0.64 mL) and DMAP (5 mg, 0.05 mmol) in DCM (1 mL) was then added dropwise over 5 min. The reaction mixture was maintained at 0–5 °C. After 2.5 h, water (5 mL) and DCM (5 mL) were added and the mixture extracted with DCM (2 × 5 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (7:3, petroleum ether:diethyl ether) afforded the *title compound* as a crystalline white solid (591 mg, 69%).

MP	102–103 °C (Petrol)
υ_{max}	1595 (w), 1573 (w), 1465 (w), 1462 (w), 1420 (w), 1349 (m), 1301 (w), 1292 (w), 1278 (w), 1258 (m), 1185 (w), 1166 (s), 1134 (m), 1118 (w), 1094 (w), 1060 (w), 1024 (w), 985 (w), 943 (s), 036 (s), 897 (s), 843 (s), 813 (s), 744 (m), 707 (m), 666 (s).
δ_H (400 MHz, $CDCl_3$)	7.84 (2 H, d, *J*=8.2 Hz, 2 × ArH) 7.38 (1 H, d, *J*=8.8 Hz, ArH) 7.34 (2 H, d, *J*=8.2 Hz, 2 x ArH) 6.93 (1 H, d, *J*=3.0 Hz, ArH) 6.74 (1 H, dd, *J*=8.8, 3.0 Hz, ArH) 5.11 (2 H, s, CH_2) 3.77 (3 H, s, OCH_3) 2.45 (3 H, s, CH_3)
δ_C (100 MHz, $CDCl_3$)	159.3 (C), 145.1 (C), 134.0 (C), 133.6 (CH), 132.2 (CH), 130.0 (2 x CH), 128.3 (2 x CH), 116.5 (C), 115.7 (CH), 113.4 (C), 71.1 (CH_2), 55.8 (CH_3), 21.8 (CH_3).
LRMS (ES+)	398 (11%), 393 ([M+Na]$^+$, 12%), 182 (100%).
X-Ray:	



2-Bromo-5-methoxybenzyl chloride (3.26)



$C_8H_9BrO_2$
Molecular Weight: 217.06

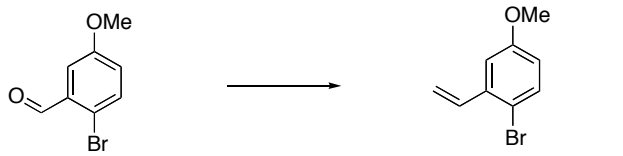
C_8H_8BrClO
Molecular Weight: 235.51

To a stirred solution of 4-bromo-3-methoxybenzyl alcohol **3.22** (2.00 g, 9.2 mmol) in DCM (20 mL) at 0 °C was added tosyl chloride (1.93 g, 10.0 mmol) in 5 portions over 30 min. A solution of TEA (1.860 g, 18.4 mmol, 2.56 mL) and DMAP (22 mg, 0.2 mmol) in DCM (5 mL) was then added dropwise over 15 min. The reaction mixture was maintained at 0–5 °C. After 2.5 h, when the starting material was no longer present by TLC, 0.15 mL of methanol was added and the reaction was heated to reflux for 19 h. The reaction mixtrure was cooled to RT, water (50 mL) and DCM (50 mL) were added and the mixture extracted with DCM (2 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (4:1, petroleum ether:diethyl ether) afforded the title compound as a waxy white solid (375 mg, 17%).

MP	73–75° C (ethanol) [Lit.[91] 75.4–76 (ethanol)]
υ_{max}	1600 (w), 1573 (s), 1450 (m), 1439 (m), 1414 (m), 1299 (m), 1285 (s), 1260 (m), 1250 (s), 1192 (w), 1166 (m), 1152 (s), 1135 (w), 1052 (m), 1016 (m), 928 (w), 874 (m).
δ_H (300 MHz, $CDCl_3$)	7.47 (1 H, d, *J*=8.8 Hz, ArH) 7.05 (1 H, d, *J*=3.0 Hz, ArH) 6.77 (1 H, dd, *J*=8.8, 3.0 Hz, ArH) 4.67 (2 H, s, CH_2) 3.82 (3 H, s, CH_3)
δ_C (75 MHz, $CDCl_3$)	159.3 (C), 137.6 (C), 133.9 (CH), 116.4 (CH), 116.1 (CH), 114.4 (C), 55.7 (OCH_3), 46.4 (CH_2Cl).
LRMS (EI)	234 ($M^{+\cdot}$, 35.8%), 199 ($[M–Cl]^+$, 100%), 51 (68%).

These data are in accordance with those reported in the literature.[91]

2-Bromo-5-methoxystyrene (3.27)



$C_8H_7BrO_2$
Molecular Weight: 215.04

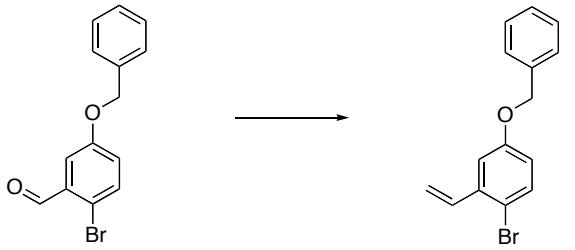
C_9H_9BrO
Molecular Weight: 213.07

To a stirred suspension of methyltriphenylphosphonium bromide (9.96 g, 27.9 mmol) in THF (100 mL) at 0 °C was added KO*t*-Bu (3.12 g, 27.9 mmol). After 1 h at 0 °C, a solution of 2-bromo-5-methoxy-benzaldehyde **3.10** (3.00 g, 14.0 mmol) in THF (30 mL) was added. After 5 min the reaction mixture was filtered through a glass sinter. The filtrate was washed with saturated aqueous NH_4Cl (2 × 100 mL) and brine (100 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (4:1, petroleum ether:diethyl ether) afforded the title compound as a colourless oil (2.410 g, 81%).

υ_{max}	1591 (w), 1564 (m), 1462 (s), 1417 (s), 1301 (w), 1200 (s), 1231 (s), 1165 (s), 1129 (w), 1115 (w), 1066 (w), 1033 (w), 1015 (s), 984 (m), 915 (m), 871 (w), 852 (m), 800 (m), 506 (m).
δ_H (300 MHz, $CDCl_3$)	7.45 (1 H, d, *J*=8.8 Hz, ArH) 7.11 (1 H, d, *J*=3.0 Hz, ArH) 7.06 (1H, dd, *J*=17.4, 10.9 Hz, C**H**=CH_2) 6.72 (1H, dd, *J*=8.8, 3.0 Hz, ArH) 5.72 (1 H, dd, *J*=17.4, 1.1 Hz, CH=C**H**H) 5.39 (1H, dd, *J*=10.9, 1.1 Hz, CH=CH**H**) 3.81 (3 H, s, OCH_3)
δ_C (75 MHz, $CDCl_3$)	159.2 (C), 138.4 (C), 136.1 (CH), 133.6 (CH), 116.9 (CH_2), 115.5 (CH), 114.5 (CBr), 112.1 (CH), 55.7 (OCH_3).
LRMS (EI)	212 ($M^{+\cdot}$, 100%), 197 ($(M\text{-}CH_3)^+$, 22%), 169 (22%), 133 ($[M–Br]^+$, 44%), 118 ($(M\text{-}Br\text{-}CH_3)^+$, 49%), 90 (46%), 89 (62%), 63 (39%).

These data are in accordance with those reported in the literature.[92]

3-Benzyloxy-5-bromostyrene (3.28)



$C_{14}H_{11}BrO_2$
Molecular Weight: 291.14

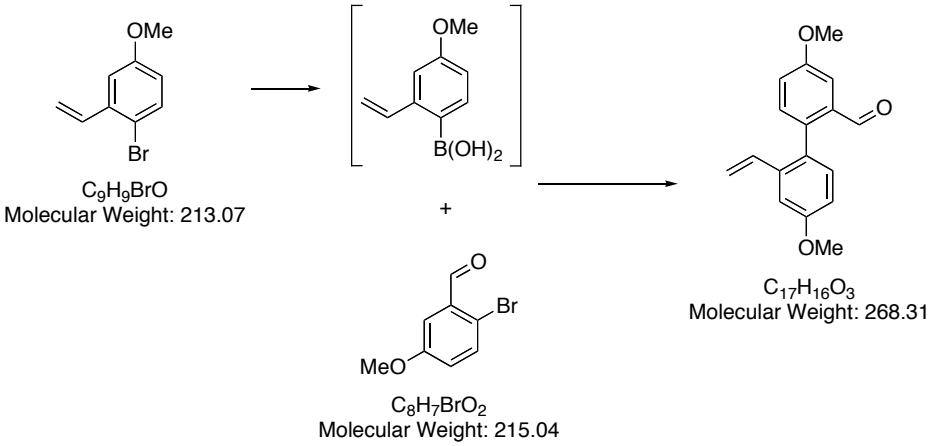
$C_{15}H_{13}BrO$
Molecular Weight: 289.17

To a stirred suspension of methyltriphenylphosphine bromide (1.23 g, 3.5 mmol) in THF (50 mL) at 0 °C was cautiously added potassium *tert*-butoxide (386 mg, 3.5 mmol). The resultant yellow solution was warmed to RT over 30 min, after which time a solution of 3-benzyloxy-4-bromobenzaldehyde **3.28** (500 mg, 1.7 mmol) in THF (5 mL) was added dropwise over 5 min. After 1 h, the reaction was heated at reflux for 19 h then cooled to RT and the precipitated triphenylphosphine oxide removed by filtration. The filtrate was washed with saturated aqueous NH_4Cl (2 × 50 mL), water (50 mL) and brine (40 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (19:1, petroleum ether:diethyl ether) afforded firstly the *title compound* as a colourless oil (275 mg, 55%) and then recovered starting material **3.28** (84 mg, 17%).

υ_{max}	3080 (w), 1590 (s), 1562 (s), 1462 (s) 1418 (s), 1378 (m), 1284 (s), 1225 (s), 1171 (s), 1129 (s), 1115 (m), 1009 (s), 984 (s), 916 (s), 872 (m), 850 (m), 798 (s), 731 (s), 694 (s), 650 (s).
δ_H (300 MHz, $CDCl_3$)	7.51–7.33 (5 H, m, 5 × ArH) 7.19 (1 H, d, *J*=2.9 Hz, ArH) 7.04 (1 H, dd, *J*=17.2, 11.0 Hz, C**H**=CH_2) 6.79 (1 H, d, *J*=11.0 Hz, ArH) 5.68 (1 H, dd, *J*=17.4, 0.9 Hz, CH=C**H**H) 5.38 (1 H, dd, *J*=11.0, 0.9 Hz, CH=CH**H**) 5.08 (2 H, s, CH_2)
δ_C (75 MHz, $CDCl_3$)	158.4 (C), 138.4 (C), 136.7 (C), 136.0 (**C**H=CH_2), 133.6 (CH), 128.8 (2 × CH), 128.3 (CH), 127.7 (2 × CH), 116.9

	(CH=**C**H_2), 116.2 (CH), 114.8 (CBr) 113.3 (CH), 70.5 (OCH_2).
LRMS (EI)	288 ($M^{+\cdot}$, 12%), 209 ($[M–Br]^+$, 5%), 118 ($[M–Br–OBn]^+$, 9%), 91 ($PhCH_2^+$, 100%), 89 (33%), 65 (34%), 63 (12%)
HRMS	Not obtained.

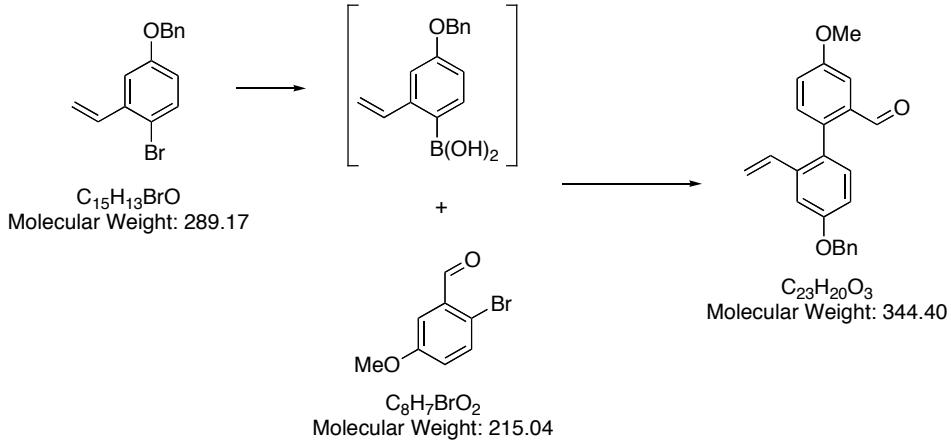
4,4'-Dimethoxy-2'-vinyl-biphenyl-2-carbaldehyde (3.29)



To a stirred solution of **3.27** (660 mg, 3.10 mmol)) in THF (8 mL) at –78 °C was added *n*-butyllithium (1.4 mL, 3.10 mmol, 2.28 M solution in hexanes) dropwise over 4 min. After 20 min at –78 °C, trimethyl borate (1.7 mL, 15.50 mmol) was added. The reaction mixture was warmed to RT. After 4 h water (8 mL) was added then sufficient THF to obtain a monophasic solution (2 mL) was added followed by 5 drops of HCl (2 M solution). After 15 min, the reaction mixture was extracted with DCM (2 × 20 mL), and the combined organic phases dried over $NaSO_4$, and concentrated *in vacuo*. The resultant grey oil and **3.10** (663 mg, 3.10 mmol) were dissolved in THF (50 mL), to which were added $PdCl_2$(dppf) (76 mg, 0.09 mmol) and K_2CO_3 (1.71 g, 12.40 mmol). The reaction mixture was degassed with sonication under argon for 15 min then heated at reflux for 19 h. The reaction mixture was cooled to RT then silica (~4 g) added and the solvent removed *in vacuo*. Purification by flash column chromatography (7:3, petroleum ether:diethyl ether) afforded the *title compound* as colourless oil (255 mg, 31%).

υ_{max}	1684 (s), 1600 (s), 1478 (s), 1416 (w), 1390 (m), 1274 (s), 1225 (s), 1190 (w), 1161 (s), 1060 (w), 1039 (m), 998 (m), 915 (m), 869 (w), 816 (m), 770 (m).
δ_H (300 MHz, $CDCl_3$)	9.81 (1 H, s, CHO) 7.63 (1 H, d, *J*=2.6 Hz, ArH) 7.29–7.41 (4 H, m, ArH) 7.04 (1 H, dd, *J*=8.3, 2.6 Hz, ArH) 6.54 (1 H, dd, *J*=17.5 10.9, C**H**=CH_2) 5.80 (1 H, dd, *J*=17.5, 0.7 Hz, CH=C**H**H) 5.31 (1 H, dd, *J*=10.9, 0.7 Hz, CH=CH**H**) 4.04 (3 H, s, OCH_3) 4.03 (3 H, s, OCH_3)
δ_C **(75 MHz, $CDCl_3$)**	192.3 (CHO), 159.7 (C), 159.2 (C), 138.6 (C), 137.3 (C), 135.4 (C), 135.07 (CH), 133.0 (CH), 132.3 (CH), 128.8 (C), 121.3 (CH), 116.3 (CH=**C**H_2), 113.6 (CH), 110.4 (CH), 109.6 (CH), 55.7 (OCH_3), 55.5 (OCH_3).
LRMS (EI)	268 ($M^{+\cdot}$, 79%), 253 ($[M–CH_3]^+$, 12%), 240 (32%), 239 ($[M–CHO]^+$, 100%), 225 (35%), 224 (35%), 209 (26%), 208 (20%), 181 (16%), 165 (56%), 153 (40%), 152 (52%), 139 (16%).
HRMS	$C_{17}H_{16}O_3$ requires 268.1099; Found: 268.1099.

4'-Benzyloxy-4-methoxy-2'-vinyl-biphenyl-2-carbaldehyde (3.30)

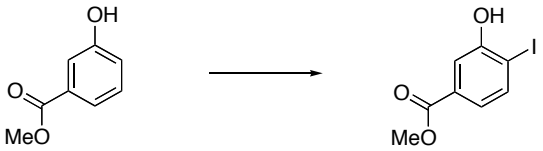


To a stirred solution of benzyl ether **3.28** (288 mg, 1.00 mmol) in THF (3 mL) at –78 °C was added *n*-butyllithium (0.52 mL, 1.10 mmol, 2.1 M in hexanes) dropwise over 3 min. After 10 min at –78 °C, trimethyl borate (618 mg, 6 mmol) was added and the reaction mixture warmed to RT. After 3 h, water (3 mL) was added then sufficient THF to obtain a monophasic solution (0.5 mL), followed by 3 drops of HCl (2 M). After a further 10 min the reaction mixture was extracted with DCM (3 × 5 mL), and the combined organic phases dried over Na_2SO_4 and concentrated *in vacuo*. The resultant grey oil and **3.10** (214 mg, 1.00 mmol) were dissolved in THF (15 mL), to which were added $PdCl_2$(dppf) (24 mg, 0.03 mmol) and K_2CO_3 (552 mg, 4.00 mmol). The reaction was degassed with sonication under argon for 15 min, then heated at reflux for 19 h. The reaction was cooled to RT then silica (~3 g) added and the solvent removed *in vacuo*. Purification by flash column chromatography (19:1→3:2, petroleum ether:diethyl ether) afforded the *title compound* as a colourless oil (115 mg, 33%).

υ_{max}	1597 (w), 1574 (m), 1484 (w), 1454 (w), 1441 (w), 1379 (w), 1285 (m), 1256 (s), 1239 (m), 1155 (s), 1025 (m), 989 (m), 908 (m), 875 (w), 853 (w), 781 (m), 730 (s), 714 (m), 694 (s).
δ_H (300 MHz, $CDCl_3$)	9.68 (1 H, s, CHO)
	7.33–7.52 (6 H, m, 6 × ArH)
	7.10–7.28 (4 H, m, 4 × ArH)
	6.96 (1 H, dd, *J*=8.4, 2.7 Hz, ArH)
	6.39 (1 H, dd, *J*=17.4, 10.9 Hz, C**H**=CH_2)

	5.63 (1 H, d, *J*=17.4 Hz, CH=C**H**H)
	5.13–5.20 (3 H, m, CH=CH**H**, CH_2Ph)
	5.14 (3 H, s, OCH_3)
δ_C (75 MHz, $CDCl_3$)	192.4 (CHO), 159.3 (C), 159.0 (C), 138.7 (C), 137.4 (C), 136.9 (C), 135.5 (C), 135.1 (CH), 133.0 (**C**H=CH_2), 132.4 (CH), 129.1 (C), 128.8 (CH), 128.3 (2 x CH), 127.7 (2 x CH), 121.4 (CH), 116.4 (CH=**C**H_2), 114.3 (CH), 111.6 (CH), 109.6 (OCHO), 70.4 (OCH_2), 55.7 (OCH_3).
LRMS (ES+)	367 ($[M+Na]^+$, 100%)
HRMS	Not obtained

Methyl 4-iodo-5-hydroxybenzoate (3.32)



$C_8H_8O_3$
Molecular Weight: 152.15

$C_8H_7IO_3$
Molecular Weight: 278.04

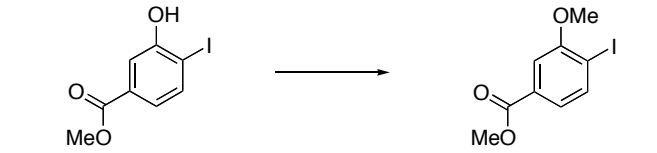
To a stirred suspension of ester **3.31** (1 g, 6.60 mmol) in saturated aqueous Na_2CO_3 (30 mL) and water (10 mL) was added iodine (1.68 g, 6.60 mmol). After 20 h, HCl (5 mL, 2M) was added. The suspended solid was collected by filtration and washed with water to give the title compound as a cream semi-solid (1.405 g, 77%).

MP	143–145 °C (water)
υ_{max}	3311 (br. s), 1690 (s), 1581 (m), 1436 (m), 1408 (s), 1310 (s), 1242 (s), 1211 (m), 1110 (w), 1019 (w), 763 (m).
δ_H (300 MHz, d_6-acetone)	9.39 (1 H, br. s, OH)
	7.86 (1 H, d, *J*=8.2 Hz, ArH)
	7.54 (1 H, d, *J*=1.8 Hz, ArH)
	7.25 (1 H, dd, *J*=8.2, 1.8 Hz, ArH)

	3.85 (3 H, s, OCH_3)
δ_C (75 MHz, d_6-acetone)	166.8 (C), 157.8 (C), 140.6 (CH), 132.8 (C), 122.9 (CH), 116.0 (CH), 91.0 (C), 52.57 (OCH_3).

These data are in accordance with those reported in the literature.[86]

Methyl 4-iodo-5-methoxybenzoate (3.33)



$C_8H_7IO_3$
Molecular Weight: 278.04

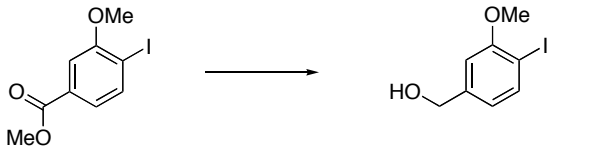
$C_9H_9IO_3$
Molecular Weight: 292.07

To a stirred solution of phenol **3.32** (1.00 g, 3.62 mmol) in acetone (50 mL) was added K_2CO_3 (1.50 g, 10.87 mmol) and MeI (2.057 g, 14.49 mmol). After 68 h, the reaction mixture was filtered then the solvent removed *in vacuo* to afford the title compound as a white waxy solid (1.014 g, 97%).

υ_{max}	2950 (w), 1717 (s), 1586 (m), 1571 (m), 1462 (m), 1433 (m), 1398 (m), 1287 (s), 1233 (s), 1184 (m), 1108 (m), 1038 (m), 1016 (m), 985 (w), 875 (w), 786 (m), 756 (s), 679 (w), 589 (w).
δ_H (300 MHz, $CDCl_3$)	7.84 (1 H, d, *J*=8.0 Hz, ArH) 7.44 (1 H, d, *J*=1.5 Hz, ArH) 7.35 (1 H, dd, *J*=8.0 Hz, 1.5 Hz, ArH) 3.93 (3 H, s, OCH_3) 3.91 (3 H, s, OCH_3)
δ_C (100 MHz, $CDCl_3$)	166.7 (C), 158.4 (C), 139.7 (CH), 131.8 (C), 123.5 (CH), 111.38 (CH), 92.8 (C), 56.7 (OCH_3), 52.5 (OCH_3).
LRMS (ES+)	598 (100%), 347 ($[M+Na+MeOH]^+$, 67%).

These data are in accordance with those reported in the literature.[86]

2-Iodo-4-methoxybenzyl alcohol (3.34)



$C_9H_9IO_3$
Molecular Weight: 292.07

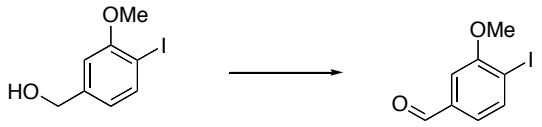
$C_8H_9IO_2$
Molecular Weight: 264.06

To a stirred solution of ester **3.33** (7.40 g, 25.61 mmol) in DCM (150 mL) at –78 °C was added diisobutylaluminium hydride (56.3 mL, 56.34 mmol, 1 M in hexanes) dropwise over 30 min. The reaction mixture was warmed to RT. After 4 h, the reaction was cooled to –78 °C and methanol (50 mL) cautiously added. DCM (50 mL) and a saturated aqueous solution of Rochelle salts (100 mL) were added and the reaction mixture vigorously stirred for 3 h. The phases were separated and the aqueous phase extracted with DCM (100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (7:3→1:1, petroleum ether:diethyl ether) afforded the title compound as a white solid (3.71 g, 55%).

MP	74–76 °C (petroleum ether:diethyl ether)
υ_{max}	3209 (br. m), 2942 (w), 2879 (w), 1586 (w), 1576(m), 1463 (s), 1451 (m), 1403 (s), 1279 (s), 1255 (s), 1173 (s), 1036 (s), 998 (s), 860 (s), 810 (s).
δ_H (300 MHz, $CDCl_3$)	7.71 (1 H, d, *J*=8.1 Hz, ArH) 6.85 (1 H, s, ArH) 6.68 (1 H, d, *J*=8.1 Hz, ArH) 4.64 (2 H, d, *J*=5.1 Hz, CH_2OH) 3.88 (3 H, s, OCH_3) 2.13 (1 H, app. br. m, OH)
LRMS (EI)	264 ($M^{+\cdot}$, 100%), 138 ($[M+H-I]^+$, 17%), 135 (27%), 109 (51%).

These data are in accordance with those reported in the literature.[86]

2-Iodo-4-methoxybenzaldehyde (3.35)



$C_8H_9IO_2$
Molecular Weight: 264.06

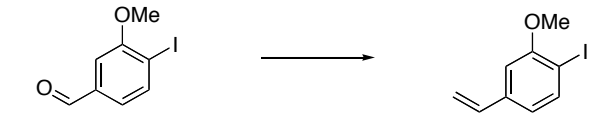
$C_8H_7IO_2$
Molecular Weight: 262.04

MnO_2 (24.102 g, 277.3 mmol) was azeotroped with toluene (2 x 100 mL). To this dry residue was added a solution of benzyl alcohol **3.34** (3.661 g, 13.9 mmol) in DCM (150 mL). After 18 h, the reaction mixture was filtered through Celite® and the solvent removed *in vacuo* to afford the title compound as a white crystalline solid (2.433 g, 67%).

MP	65–66 °C (DCM/Petroleum ether).
υ_{max}	2938 (w), 2841 (w), 2732 (w), 1700 (s), 1685 (s), 1580 (s), 1571 (m), 1462 (m), 1409 (m), 1382 (m), 1303 (w), 1285 (w), 1267 (m), 1251 (m), 1156 (w), 1037 (m), 1016 (m), 956 (w), 921 (w), 864 (w), 812 (w), 777 (w), 734 (m).
δ_H (300 MHz, $CDCl_3$)	9.96 (1H, s, CHO) 8.00 (1H, d, *J*=7.9 Hz, ArH) 7.30 (1H, d, *J*=1.7 Hz, ArH) 7.19 (1H, dd, *J*=7.9, 1.7 Hz, ArH) 3.96 (3H, s, OCH_3)
δ_C (75 MHz, $CDCl_3$)	191.1 (CHO), 158.6 (C), 140.0 (CH), 137.6 (C), 124.7 (CH), 108.3 (CH), 95.0 (C), 56.3 (OCH_3).

These data are in accordance with those reported in the literature.[86]

4-Iodo-5-methoxystyrene (2.15)



$C_8H_7IO_2$
Molecular Weight: 262.04

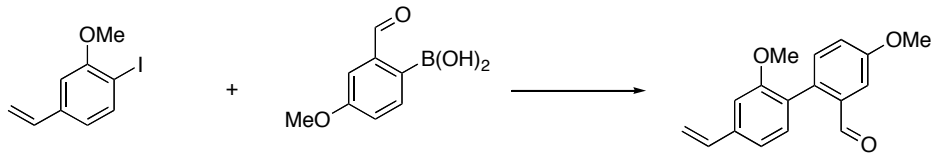
C_9H_9IO
Molecular Weight: 260.07

To a stirred suspension of methyltriphenylphosphonium bromide (2.31 g, 6.47 mmol) in THF (50 mL) at 0 ºC was added KO*t*-Bu (724 mg, 6.47 mmol). After 30 min at 0 °C, a solution of benzaldeyde **3.35** (847 mg, 3.23 mmol) in THF (15 mL) was added and the reaction mixture warmed to RT. After 6 h, water (50 mL) was added and the reaction mixture extracted with ethyl acetate (4 x 50 mL). The combined organic phases were washed with saturated aqueous NH_4Cl (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (9:1; petroleum ether:diethyl ether) afforded the *title compound* as a pale yellow gum (810 mg, 96%).

υ_{max}	1582 (w), 1561 (s), 1475 (m), 1460 (s), 1398 (s), 1380 (m), 1282 (s), 1255 (s), 1169 (s), 1060 (w), 1042 (s), 1029 (s), 1013 (s), 986 (s), 909 (s), 851 (s), 812 (s), 719 (s), 695 (w), 540 (s).
δ_H (400 MHz, $CDCl_3$)	7.72 (1 H, d, *J*=8.0 Hz, ArH) 6.86 (1 H, d, *J*=2.0 Hz, ArH) 6.78 (1 H, dd, *J*=8.0, 2.0 Hz, ArH) 6.67 (1 H, dd, *J*=17.6, 10.5 Hz, ArH) 5.78 (1 H, d, *J*=17.6 Hz, ArH) 5.30 (1 H, d, *J*=10.5 Hz, ArH) 3.91 (3 H, s, OCH_3)
δ_C (100 MHz, $CDCl_3$)	158.2 (C), 139.4 (C), 139.4 (CH), 136.1 (**C**H=CH_2), 120.5 (CH), 114.8 (CH_2), 108.6 (CH), 85.0 (C), 56.3 (OCH_3).
LRMS	Did not fly by ES+ or EI.

These data are in accordance with those reported in the literature.[86]

2',4-Dimethoxy-4'-vinyl-biphenyl-2-carbaldehyde (2.11)



C_9H_9IO
Molecular Weight: 260.0.7

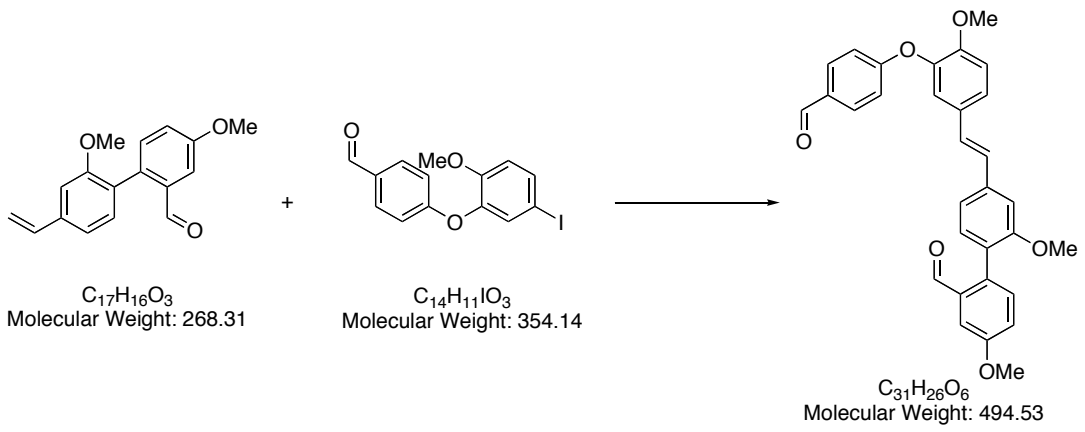
$C_8H_9BO_4$
Molecular Weight: 179.97

$C_{17}H_{16}O_3$
Molecular Weight: 268.31

To a stirred solution of boronic acid **2.12** (5.00 g, 27.93 mmol) and iodide **2.15** (3.63 g, 13.97 mmol) in dioxane (60 mL) was added triethylamine (5.64 g, 55.87 mmol, 7.7 mL). The reaction mixture was degassed with sonication for 10 minutes under argon then $Pd(dppf)Cl_2$ (465 mg, 0.56 mmol) was added and the reaction mixture heated at reflux for 19 h. The solvent was removed *in vacuo* and the residue purified by flash column chromatography (9:1, petroleum ether:diethyl ether) to afford the *title compound* as a pale yellow solid (2.85 g, 38%).

The data obtained were identical to those previously reported.

2',4-Dimethoxy-4'-[3-(4-formyl-phenoxy)-4-methoxy-phenyl-vinyl]-biphenyl-2-carbaldehyde (3.38)



$C_{17}H_{16}O_3$
Molecular Weight: 268.31

$C_{14}H_{11}IO_3$
Molecular Weight: 354.14

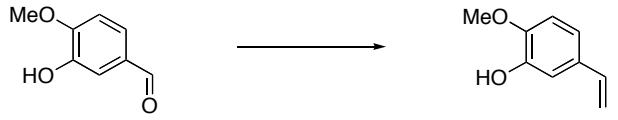
$C_{31}H_{26}O_6$
Molecular Weight: 494.53

To a stirred solution of biaryl **2.11** (1.30 g, 4.49 mmol) and ether **2.10** (1.64 g, 4.49 mmol) in dioxane (30 mL) was added triethylamine (1.96 g, 19.40 mmol). The reaction mixture was degassed with sonication for 10 min under argon then $Pd(OAc)_2$ (43 mg, 0.019 mmol) was added. The reaction mixture was heated at reflux for 19 h then cooled to RT and the solvent removed *in vacuo*. The residue

was purified by flash column chromatography (9:1→3:2, heptane:ethyl acetate) to afford the *title compound* as a white solid (2.00 g, 83 %).

MP	94–95 °C (Petroleum ether)
υ_{max}	2934 (w), 2839 (w), 1689 (s), 1600 (s), 1582 (m), 1501 (s), 1463 (m), 1423 (m), 1271 (s), 1227 (s), 1155 (s), 1128 (w), 1032 (m), 856 (w).
δ_H (400 MHz, $CDCl_3$)	9.94 (1 H, s, CHO) 9.77 (1 H, s, CHO) 7.86 (2 H, d, *J*=8.9 Hz, 2 x ArH) 7.51 (1 H, d, *J*=2.8 Hz, ArH) 7.40 (1 H, dd, *J*=8.5, 1.9 Hz, ArH) 7.35 (1 H, d, *J*=2.0 Hz, ArH) 7.30 (1 H, d, *J*=8.5 Hz, ArH) 7.25 (1 H, d, *J*=7.9 Hz, ArH) 7.23–7.18 (3 H, m, 3 x ArH) 7.10 (1 H, d, *J*=16.3 Hz, CH=C**H**) 7.07–7.04 (3 H, m, 3 x ArH) 7.01 (1 H, d, *J*=16.3 Hz, C**H**=CH) 3.91 (3 H, s, OCH_3) 3.84 (3 H, s, OCH_3) 3.79 (3 H, s, OCH_3)
δ_C (100 MHz, $CDCl_3$)	192.5 (CHO), 190.9 (CHO), 163.6 (C), 159.4 (C), 157.1 (C), 151.7 (C), 143.4 (C), 139.1 (C), 135.1 (C), 134.4 (C), 132.6 (CH), 132.1 (2 x CH), 132.1 (CH), 131.3 (C), 128.2 (CH), 127.6 (CH), 126.2 (C), 125.3 (CH), 121.4 (CH), 120.3 (CH), 119.5 (CH), 116.5 (2 x CH), 113.4 (CH), 109.7 (CH), 108.5 (CH), 56.3 (OCH_3), 55.8 (OCH_3), 55.6 (OCH_3). *N.B. One quaternary carbon centre not observed.*
LRMS	1011 ($[2M+Na]^+$, 37%), 637 (30%), 517 ($[M+Na]^+$, 100%), 183 (99%), 192 (70%).
HRMS	$C_{31}H_{26}NaO_6$ requires 517.1622; Found: 517.1615.

3-Hydroxy-4-methoxystyrene (3.39)



$C_8H_8O_3$
Molecular Weight: 152.15

$C_9H_{10}O_2$
Molecular Weight: 150.17

To a stirred suspension of methyltriphenylphosphonium bromide (7.05 g, 19.7 mmol) in THF (125 mL) at 0 °C was cautiously added KO*t*-Bu (2.211 g, 19.7 mmol). The resultant yellow solution was allowed to warm to RT. After 30 min a solution of 3-hydroxy-4-methoxybenzaldehyde (1.00 g, 6.6 mmol) in THF (5 mL) was added dropwise over 5 min. The reaction mixture was heated at reflux for 20 h, then cooled to RT. The precipitated triphenylphosphine oxide was removed by filtration and the filtrate washed with saturated aqueous NH_4Cl (2 × 75 mL), water (75 mL) and brine (75 mL) then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (7:3, petroleum ether:ethyl acetate) afforded the title compound as a white solid (896 mg, 91%).

MP 56–58 °C (ethyl acetate/petroleum ether)
[Lit.[93] 55–56 °C, no solvent given]

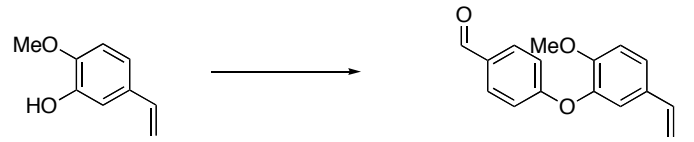
υ_{max} 3319 (br. w), 1577 (m), 1506 (s), 1453 (w), 1439 (m), 1414 (w), 1337 (m), 1287 (w), 1268 (m), 1235 (s), 1178 (m), 1151 (m), 1131 (m), 1045 (w), 1017 (m), 991 (m), 935 (w), 906 (m), 871 (m), 809 (s), 761 (m), 735 (w), 701 (w).

δ_H (300 MHz, $CDCl_3$) 6.98 (1 H, d, *J*=2.1 Hz, ArH)
6.81 (1 H, dd, *J*=8.3, 2.1 Hz, ArH)
6.73 (1 H, d, *J*=8.3 Hz, ArH)
6.55 (1 H, dd, *J*=17.6, 11.0 Hz, C**H**=CH_2)
5.55 (1 H, s, OH)
5.54 (1 H, dd, *J*=17.6, 0.9 Hz, CH=C**H**H)
5.07 (1 H, dd, *J*=11.0, 0.9 Hz, CH=CH**H**)
3.81 (3 H, s, OCH_3)

δ_C (75 MHz, $CDCl_3$)	146.6 (C), 145.8 (C), 136.5 (C**H**=CH_2), 131.6 (C), 119.0 (CH), 112.3 (CH), 111.8 (CH), 111.9 (CH=**C**H_2), 56.2 (OCH_3).
LRMS (EI)	150 ($M^{+\cdot}$, 94%), 135 ($[M–CH_3]^+$, 100%), 107 (46%), 77% (83%), 65 (28%), 63 (25%), 55 (22%), 52 (36%).

These data are in accordance with those reported in the literature.[93]

4-(2-Methoxy-5-vinylphenoxy)-benzaldehyde (2.17)



$C_9H_{10}O_2$
Molecular Weight: 150.17

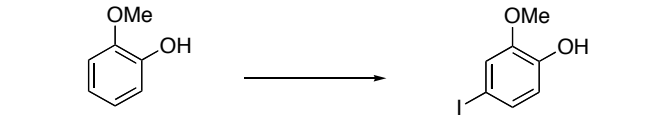
$C_{16}H_{14}O_3$
Molecular Weight: 254.28

To a stirred solution of 3-hydroxy-4-methoxystyrene **3.39** (3.50 g, 23.33 mmol) in DMF (50 mL) was added 4-fluorobenzaldehyde (3.18 g, 25.66 mmol) and K_2CO_3 (3.54 g, 25.66 mmol). The reaction mixture was heated at reflux for 20 h then cooled to RT and poured onto ice water (50 mL). The resultant emulsion was extracted with ethyl acetate (2 × 50 mL) and the combined organic phases washed with brine (70 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (4:1, petroleum ether:ethyl acetate) followed by recrystalisation (ethyl acetate/petroleum ether) gave the *title compound* as yellow crystals (5.87 g, 99%).

MP	46–49 °C (ethyl acetate/petroleum ether)
υ_{max}	2934 (w), 2838 (w), 2735 (w), 1687 (s), 1596 (m), 1582 (m), 1571 (m), 1500 (s), 1462 (w), 1442 (m), 1394 (w), 1297 (m), 1269 (s), 1224 (s), 1185 (w), 1153 (s), 1128 (m), 1119 (m), 1105 (w), 1021 (m), 990 (w), 945 (w), 892 (m), 855 (m), 816 (m).
δ_H (400 MHz, $CDCl_3$)	9.96 (1 H, s, CHO)
	7.88 (2 H, d, *J*=8.8 Hz, 2 × ArH)

	7.32 (1 H, dd, *J*=8.4, 2.1 Hz, ArH)
	7.25 (1 H, d, *J*=2.1 Hz, ArH)
	7.02–7.09 (3 H, m, 3 × ArH)
	6.69 (1 H, dd, *J*=17.5, 10.8 Hz, C**H**=CH_2)
	5.67 (1 H, d, *J*=17.5 Hz, CH=C**H**H)
	5.24 (1 H, d, *J*=10.8 Hz, CH=CH**H**)
	3.84 (3 H, s, OCH_3)
δ_C (75 MHz, $CDCl_3$)	190.1 (CHO), 163.6 (C), 151.5 (C), 143.0 (C), 135.5 (**C**H=CH_2), 132.0 (2 × CH), 131.7 (C), 131.0 (C), 124.7 (CH), 120.0 (CH), 116.3 (2 × CH), 113.1 (CH=**C**H_2), 113.0 (CH), 56.0 (OCH_3)
LRMS (ES+)	309 ($[M+Na+MeOH]^+$, 100%).

4-Iodo-2-methoxyphenol (3.40)



$C_7H_8O_2$
Molecular Weight: 124.14

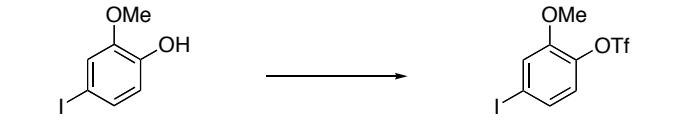
$C_7H_7IO_2$
Molecular Weight: 250.03

To a stirred solution of guaiacol (1.24 g, 10 mmol, 1.11 mL) in methanol (30 mL) was added NaI (3.00 g, 20 mmol) and NaOH (20 mmol). The solution was then cooled to 0 °C and NaOCl (14.9 mL of a solution of >8% concentration) was added dropwise over 2 h at 0 °C. After a further 2 h at 0 °C the reaction mixture was acidified to pH 7 with HCl (2M). The mixture was extracted with ether (2 × 40 mL), and the combined organic phases stirred with saturated aqueous $Na_2S_2O_7$ (100 mL) for 19 h. The organic phase was then separated, dried over $MgSO_4$ and concentrated *in vacuo* to afford an orange oil. ^{1}H NMR analysis indicated <10% diiodinated product. Purification by flash column chromatography (DCM) afforded the title compound as a colourless oil (2.15 g, 86%).

υ_{max}	3501 (br., w), 1602 (w), 1579 (w), 1492 (s), 1461 (m), 1441 (s), 1408 (m), 1355 (m), 1252 (s), 1218 (s), 1116 (s), 1066 (w), 1020 (s), 843 (m), 805 (m), 775 (s).
δ_H (300 MHz, $CDCl_3$)	7.18 (1 H, dd, *J*=8.3, 1.9 Hz, ArH) 7.11 (1 H, d, *J*=1.9 Hz, ArH) 6.69 (1 H, d, *J*=8.3 Hz, ArH) 5.74 (1 H, s, OH) 3.84 (3 H, s, OCH_3)
δ_C (75 MHz, $CDCl_3$)	147.4 (C), 145.6 (C), 130.4 (CH), 119.8 (CH), 116.6 (CH), 81.1 (CI), 56.2 (OCH_3).
LRMS (EI)	250 ($M^{+\cdot}$, 100%), 235 ($[M–CH_3]^+$, 54%), 207 (31%), 127 (I^+, 9%), 80 (40%), 79 (23%), 52 (20%), 51 (29%), 50 (13%).

These data are in accordance with those reported in the literature.[85]

4-Iodo-2-methoxyphenyl-trifluoromethane sulfonate (2.18)



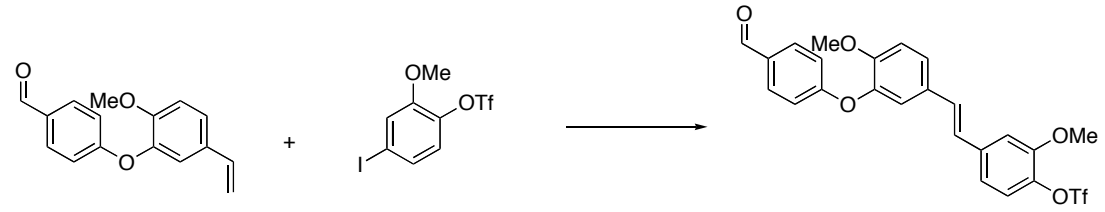
$C_7H_7IO_2$
Molecular Weight: 250.03

$C_8H_6F_3IO_4S$
Molecular Weight: 382.10

To a stirred solution of trifluoromethanesulfonic anhydride (2.28 mg, 8.40 mmol, 1.36 mL) in DCM (10 mL) at 0 °C was added a solution of 4-iodo-2-methoxyphenol **3.40** (2.00 g, 8.00 mmol) and pyridine (783 mg, 9.90 mmol, 0.8 mL) dropwise over 30 min, keeping the reaction at 0 °C. After a further 1 h at 0 °C ice water (50 mL) was added. The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (DCM) afforded the *title compound* as a colourless oil (2.855 g, 93%).

υ_{max}	1596 (w), 1490 (m), 1420 (m), 1394 (w), 1266 (w), 1247 (w), 1202 (s), 1153 (m), 1135 (s), 1107 (s), 1021 (m), 885 (m), 823 (s), 807 (s), 738 (w), 710 (w), 609 (s).
δ_H (300 MHz, $CDCl_3$)	7.30–7.36 (2 H, m, 2 × ArH) 6.95 (1 H, d, *J*=8.1 Hz, ArH) 3.92 (3 H, s, OCH_3)
δ_C (75 MHz, $CDCl_3$)	152.1 (C), 138.9 (C), 130.3 (CH), 124.1 (CH), 122.8 (CH), 93.4 (CI), 56.7 (OCH_3), SO_2CF_3 could not be clearly identified.
δ_F (282 MHz, $CDCl_3$)	–73.99 (CF_3)
LRMS (EI)	382 ($M^{+\cdot}$, 48%), 249 ([M–$SO_2CF_3^+$], 100%), 221 (27%), 191 (14%), 122 ([M–SO_2CF_3–I]$^+$, 14%), 94 (81%), 79 (89%), 69 (CF_3^+, 45%), 51 (92%).
HRMS	$C_8H_6O_4F_3SI$ requires 381.8984; Found: 381.8978.

2-{4-[3-(4-Formylphenoxy)-4-methoxyphenyl]-vinyl}-2-methoxyphenyl-trifluoromethanesulfonate (2.16)



$C_{16}H_{14}O_3$
Molecular Weight: 254.28

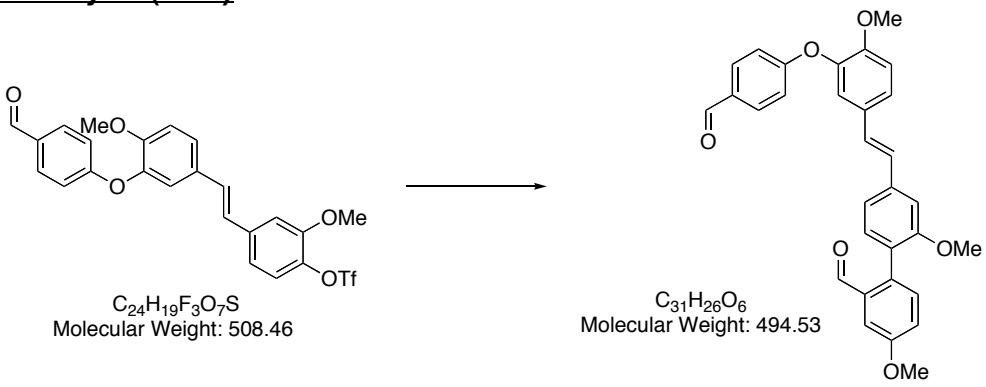
$C_8H_6F_3IO_4S$
Molecular Weight: 382.10

$C_{24}H_{19}F_3O_7S$
Molecular Weight: 508.46

To a stirred solution of diphenyl ether **2.17** (999 mg, 0.39 mmol) and triflate **2.18** (150 mg, 0.39 mmol) in dioxane (6 mL) was added triethylamine (158 mg, 1.57 mmol) and $Pd(OAc)_2$ (3 mg, 0015 mmol). The reaction mixture was degassed with sonication for 15 min, heated at reflux for 24 h, then cooled to RT, silica (~5 g) added and the solvent removed *in vacuo*. Purification by flash column chromatography (4:1→3:2, petroleum ether:diethyl ether) afforded the *title compound* as a white solid (164 mg, 82%).

MP	97–99 °C ($CHCl_3$)
υ_{max}	1688 (m), 1597 (m), 1572 (m), 1512 (m), 1503 (m), 1469 (m), 1419 (s), 1300 (m), 1280 (s), 1248 (s), 1202 (s), 1154 (s), 1136 (s), 1120 (m), 1105 (m), 1052 (m), 1017 (s), 972 (m), 928 (w), 886 (m), 874 (s), 828 (m), 812 (s).
δ_H (300 MHz, $CDCl_3$)	9.93 (1 H, s, CHO) 7.85 (2 H, d, *J*=8.8 Hz, 2 × ArH) 7.37 (1 H, dd, *J*=8.5, 2.1 Hz, ArH) 7.31 (1 H, d, *J*=2.1 Hz, ArH) 7.19 (1 H, d, *J*=8.4 Hz, ArH) 7.12–7.07 (2 H, m, 2 × ArH or CH=CH) 6.93–7.07 (5 H, m, 5 × ArH or CH=CH) 3.96 (3 H, s, OCH_3) 3.83 (3 H, s, OCH_3)
δ_C (75 MHz, $CDCl_3$)	191.0 (CHO), 163.5 (C), 151.9 (C), 151.7 (C), 143.4 (C), 138.8 (C), 132.1 (2 × CH), 131.3 (C), 130.7 (C), 129.4 (CH), 126.5 (CH), 125.4 (CH), 122.8 (C), 122.8 (CH), 120.4 (CH), 119.0 (CH), 116.5 (2 × CH), 113.3 (CH), 110.7 (CH), 56.4 (OCH_3), 56.2 (OCH_3), SO_2**C**F_3 could not be clearly identified.
LRMS (ES+)	531 ([M+Na^+], 100%), 413 (19%), 304 (56%).
HRMS	$C_{24}H_{19}F_3NaO_7S$ requires 531.0696; Found: 531.0695.

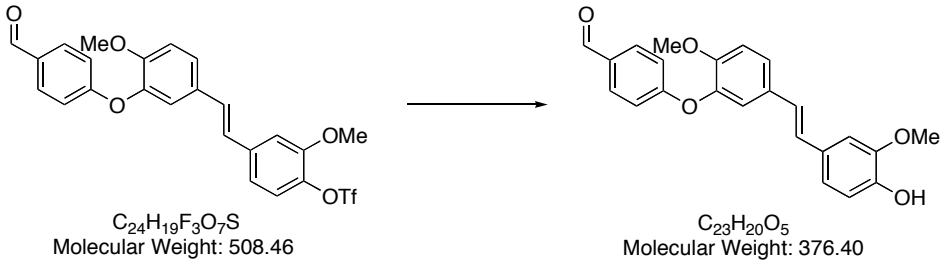
2',4-Dimethoxy-4'-{2-[3-(4-formylphenoxy)-4-methoxyphenyl]}-vinyl-biphenyl-2-carbaldehyde (3.38)



To a stirred solution of triflate **2.17** (142 mg, 0.28 mmol) and boronic acid **2.12** (50 mg, 0.28 mmol) in dioxane (2 mL) was added LiCl (117 mg, 2.77 mmol), Cs_2CO_3 (362 mg, 2.77 mmol), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl **3.15** (22 mg, 0.56 mmol) and $PdCl_2$ (5 mg, 0.028 mmol). The reaction mixture was degassed by sonication under argon for 15 min, then heated at reflux. After 18 h, the reaction mixture was cooled to RT, then silica (~2 g) was added and the solvent removed *in vacuo*. Purification by flash column chromatography (7:3; petroleum ether:diethyl ether) afforded the *title compound* as a white crystalline solid (99 mg, 71%)

The data obtained were identical to those previously reported.

4-{2-[3-(4-Formylphenoxy)-4-methoxyphenyl]vinyl}-2-methoxyphenol (3.41)

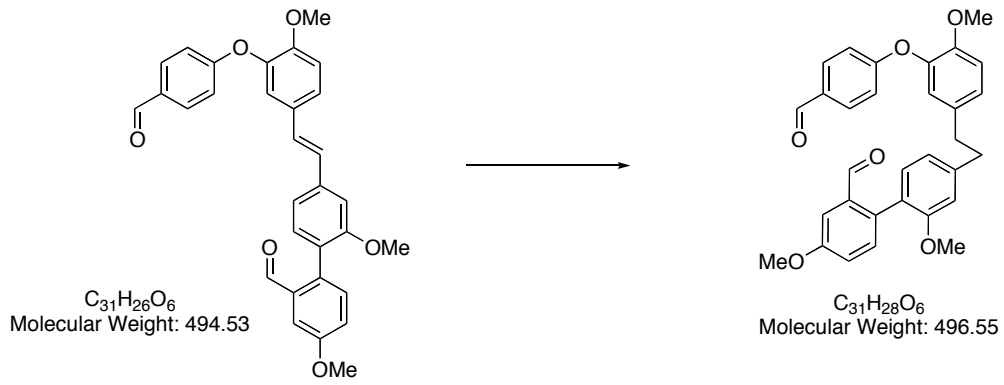


To a solution of triflate **2.17** (74 mg, 0.15 mmol) and boronic acid **2.12** (29 mg, 0.16 mmol) in dioxane (1.5 mL) were added 2 M NaOH (0.22 mL) and $Pd(dppf)Cl_2$ (5 mg, 0.058 mmol). The reaction mixture was stirred under microwave irradiation (300 W) for 1 h, then cooled to RT and partitioned between diethyl ether (2 mL) and brine (2 mL). The phases were separated and the aqueous layer extracted

with diethyl ether (6 x 5 mL). To the combined organic phases silica (~1 g) was added and the solvent removed *in vacuo*. Purification by flash column chromatography (3:2; diethyl ether:petroleum ether) afforded the *title compound* (15 mg, 27%) as a white solid.

δ_H (400 MHz, $CDCl_3$)	9.83 (1 H, s, CHO)
	7.75 (2 H, d, *J*=8.5 Hz, 2 x ArH)
	7.25 (1 H, dd, *J*=8.5, 2.0 Hz, ArH)
	7.20–7.18 (1 H, m, ArH)
	6.97–6.89 (5 H, m, 5 x ArH or CH=CH)
	6.83–6.79 (3 H, m, 3 x ArH or CH=CH)
	5.61 (1 H, br. s, OH)
	3.85 (3 H, s, OCH_3)
	3.72 (3 H, s, OCH_3)
δ_C (100 MHz, $CDCl_3$)	190.8 (CHO), 163.5 (C), 150.9 (C), 146.7 (C), 145.6 (C), 143.1 (C), 131.9 (2 x CH), 131.6 (C), 131.0 (C), 129.8 (C), 127.9 (CH), 125.0 (CH), 124.5 (CH), 120.3 (CH), 119.8 (CH), 116.3 (2 x CH), 114.6 (CH), 113.2 (CH), 108.2 (CH), 56.0 (OCH_3), 55.9 (OCH_3).
LRMS (ES+)	425 (100%), 423 ($[M+2MeOH+H–H_2O]^+$, 97%).

2',4-Dimethoxy-4'-{2-[3-(4-formylphenoxy)-4-methoxyphenyl]-ethyl}-biphenyl-2-carbaldehyde (2.9)



To a stirred solution of tetraaromatic **3.38** (140 mg, 0.283 mmol) in DCM (15 mL) and methanol (15 mL) was added 5% palladium on carbon (280 mg). The flask was evacuated/purged with argon three times then evacuated/purged with hydrogen twice. After 20 min the reaction mixture was filtered through Celite® and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (3:2, petroleum ether:diethyl ether) afforded the title compound as a white solid (73 mg, 52%).

MP	38–39 °C (Petroleum ether/ethyl acetate)
υ_{max}	2938 (w), 2838 (w), 1689 (s), 1602 (m), 1578 (m), 1509 (m), 1488 (m), 1463 (w), 1422 (w), 1273 (s), 1227 (s), 1156 (m), 1124 (w), 1036 (w), 1002 (w), 832 (w).
δ_H (400 MHz, $CDCl_3$)	9.78 (1 H, s, CHO)
	9.60 (1 H, s, CHO)
	7.70 (2 H, d, *J*=8.8 Hz, 2 x ArH)
	7.39 (1 H, d, *J*=2.6 Hz, ArH)
	7.18–7.12 (2 H, m, 2 x ArH)
	7.09 (1 H, dd, *J*=8.4, 2.8 Hx, ArH)
	7.05 (1 H, d, *J*=7.7 Hz)
	6.98 (1 H, dd, *J*=8.4, 2.0 Hz, ArH)
	6.90–6.85 (3 H, m, 3 x ArH)
	6.81 (1 H, d, *J*=2.0 Hz, ArH)
	6.76 (1 H, dd, *J*=7.6, 1.3 Hz, ArH)
	3.81 (3 H, s, OCH_3)
	3.69 (3 H, s, OCH_3)

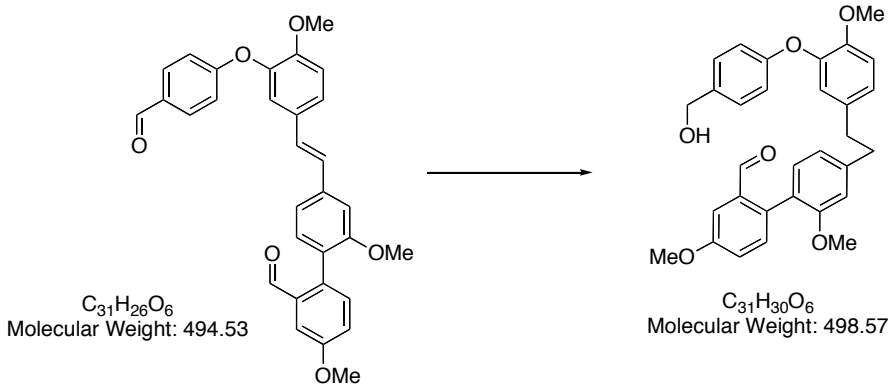
3.60 (3 H, s, OCH_3)

2.87 (4 H, app. s, CH_2CH_2)

δ_H (100 MHz, $CDCl_3$) 192.9 (CHO), 191.1 (CHO), 164.0 (C), 159.5 (C), 157.0 (C), 150.4 (C), 143.8 (C), 143.0 (C), 135.3 (C), 135.3 (C), 135.0 (C), 132.9 (CH), 132.3 (2 x CH), 131.9 (CH), 131.3 (C), 126.7 (CH), 124.7 (C), 123.2 (CH), 121.6 (CH), 121.5 (CH), 116.6. (CH), 116.5 (CH), 113.5 (CH), 111.4 (CH), 109.9 (CH), 56.5 (OCH_3), 56.0 (OCH_3), 55.8 (OCH_3), 38.5 (CH_2), 37.2 (CH_2).

LRMS (EI) 1015 ($[2M+Na]^+$, 97%), 519 ($[M+Na]^+$, 100%).

2',4-Dimethoxy-4'-{2-[3-(4-hydroxymethylphenoxy)-4-methoxyphenyl]-ethyl}-biphenyl-2-carbaldehyde (3.42)

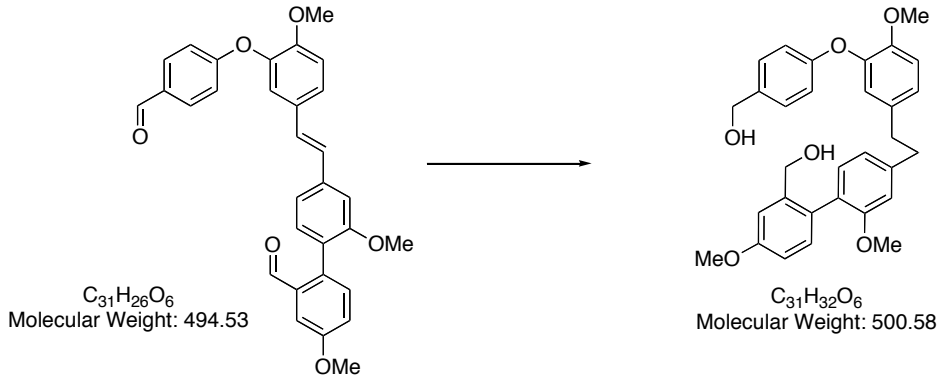


To a stirred solution of **3.38** (230 mg, 0.47 mmol) in DCM (20 mL) and methanol (20 mL) was added 10% palladium on carbon (460 mg). The flask was evacuated/purged with argon three times then evacuated/purged with hydrogen twice. After 20 min the reaction mixture was filtered through Celite® and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (2:3, diethyl ether:petroleum ether) afforded the title compound as a white foam (206 mg, 89%).

υ_{max} 3434 (br. w), 2935 (w), 2837 (w), 1686 (m), 1605 (m), 1578 (w), 1505 (s), 1488 (m), 1463 (m), 1420 (m), 1315 (w), 1269 (s), 1222 (s), 1163 (m), 1125 (m), 1035 (m),

	1002 (m), 935 (w), 910 (w), 818 (m), 768 (w), 729 (m), 648 (w).
δ_H (300 MHz, $CDCl_3$)	9.66 (1 H, s, CHO)
	7.49 (1 H, d, *J*=2.6 Hz, ArH)
	7.29–7.23 (2 H, m, 2 x ArH)
	7.19 (1 H, dd, *J*= 8.4, 2.6 Hz, ArH)
	7.14 (1 H, d, *J*=7.7 Hz, ArH)
	6.98–6.88 (3 H, m, 3 x ArH)
	6.89 (2 H, d, *J*=8.8 Hz, 2 x ArH)
	6.83 (1 H, dd, *J*=7.7, 1.5 Hz, ArH)
	6.78 (1 H, d, *J*=1.8 Hz, ArH)
	6.69 (1 H, d, *J*=1.5 Hz, ArH)
	4.62 (2 H, s, C**H**$_2$OH)
	3.90 (3 H, s, OCH_3)
	3.83 (3 H, s, OCH_3)
	3.68 (3 H, s, OCH_3)
	2.95–2.88 (4 H, m, 2 x CH_2)
δ_C (75 MHz, $CDCl_3$)	192.7 (CHO), 159.0 (C), 157.6 (C), 156.4 (C), 143.5 (C), 134.9 (C), 134.8 (C), 134.5 (C), 132.5 (CH), 131.4 (CH), 128.5 (CH), 124.8 (2 x CH), 124.1 (C), 121.5 (CH), 121.3 (CH), 121.1 (CH), 117.0 (2 x CH), 112.8 (CH), 111.0 (CH), 109.3 (CH), 64.9 (CH_2), 56.1 (OCH_3), 55.6 (OCH_3), 55.3 (OCH_3), 38.1 (CH_2), 36.8 (CH_2).
	N.B. Three quaternary carbon centres were not observed.
LRMS (ES+)	1019 ($[2M+Na]^+$, 33%), 521 ($[M+Na]^+$, 100%).
HRMS	$C_{31}H_{30}NaO_6$ requires 521.1935; Found: 521.1935.

2',4-Dimethoxy-4'-{2-[3-(4-hydroxymethylphenoxy)-4-methoxyphenyl]-ethyl}-biphenyl-2-benzyl alcohol (3.42)



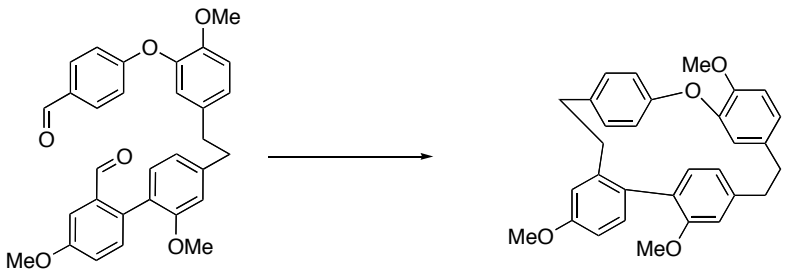
To a stirred solution of bis-aldehyde **3.38** in methanol (10 mL) and DCM (10 mL) was added 5% palladium on carbon (25 mg). The flask was evacuated/purged with argon three times then evacuated/purged with hydrogen twice. After 3 h, the reaction mixture was filtered through Celite® and concentrated *in vacuo*. Purification by flash column chromatography (1:1 petroleum ether:diethyl ether) afforded the title compound (12 mg, 100%) as a waxy solid.

υ_{max}	3245 (br., w), 2933 (w), 1607 (w), 1506 (s), 1460 (m), 1426 (w), 1267 (m), 1239 (m), 1226 (s), 1164 (m), 1124 (m), 1028 (s), 910 (s), 856 (w), 826 (m), 763 (w), 727 (s), 644 (m).
δ_H (400 MHz, $CDCl_3$)	7.28 (2 H, d, *J*=8.5 Hz, 2 x ArH)
	7.11 (1 H, d, *J*=2.5 Hz, ArH)
	7.08 (1 H, d, *J*=8.5 Hz, ArH)
	7.03 (1 H, d, *J*=7.5 Hz, ArH)
	6.99 (1 H, dd, *J*= 8.5, 2.0, ArH)
	6.95 (1 H, d, *J*=8.5 Hz, ArH)
	6.92–6.87 (1 H, m, ArH)
	6.90 (2 H, d, *J*=8.5 Hz, 2 x ArH)
	6.80–6.77 (2 H, m, 2 x ArH)
	6.71 (1 H, s, ArH)
	4.62 (2 H, s, C**H_2**OH)
	4.35 (2 H, br. s, C**H_2**OH)
	3.87 (3 H, s, OCH_3)
	3.82 (3 H, s, OCH_3)

	3.70 (3 H, s, OCH_3)
	2.91 (4 H, app. s, 2 x CH_2)
	2.27–1.56 (2 H, br. m, 2 x OH)
δ_C (100 MHz, $CDCl_3$)	159.2 (C), 157.7 (C), 156.4 (C), 149.8 (C), 144.4 (C), 142.5 (C), 140.8 (C), 134.8 (C), 134.7 (C), 131.4 (CH), 131.4 (CH), 129.5 (C), 128.5 (2 x CH), 127.1 (C), 124.8 (CH), 121.6 (CH), 121.1 (CH), 116.9 (2 x CH), 113.3 (CH), 113.1 (CH), 112.9 (CH), 111.4 (CH), 64.9 (CH_2OH), 63.7 (CH_2OH), 56.1 (OCH_3), 55.7 (OCH_3), 55.3 (OCH_3), 38.0 (CH_2), 36.8 (CH_2).
LRMS (ES+)	523 ($[M+Na]^+$, 100%).

These data are in accordance with those reported in the literature.[45]

1,2,13,14-Tetrahydro-9,17,22-trimethoxy-3,6:15,18-dietheno-8,12-metheno-12*H*-7-benzooxacycloeicosine (1.88)



$C_{31}H_{28}O_6$
Molecular Weight: 496.55

$C_{31}H_{30}O_4$
Molecular Weight: 466.57

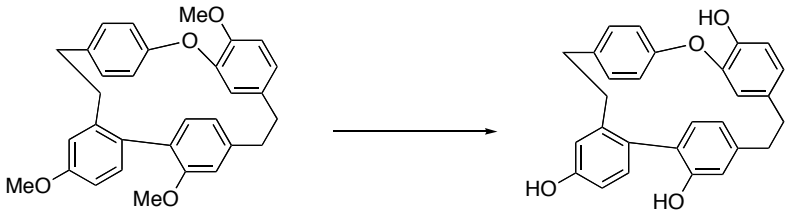
To a cooled aliquot of THF (5 mL) at –78 °C containing magnesium (80 mg, 3.29 gatom) was added titanium tetrachloride (666 mg, 3.51 mmol, 0.39 mL) dropwise over 5 min. The reaction mixture was allowed to warm to RT and stirred for 2 h. The resultant black solution was cooled to –78 °C and a solution of tetraaromatic **2.9** (81 mg, 0.163 mmol) in THF (10 mL) was added dropwise over 10 min. After 19 h at RT the reaction mixture was partitioned between water (15 mL) and chloroform (15 mL). The aqueous phase was re-extracted with chloroform (15 mL) and the combined organic phases dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was redissolved in DCM (15 mL) and methanol (15 mL). To this solution 5% palladium on carbon (150 mg) was added and the

flask evacuated/purged with argon three times then evacuated/purged with hydrogen twice. After 1 h, the reaction mixture was filtered and concentrated *in vacuo*. Purification by flash column chromatography (3:7, diethyl ether:petroleum ether) afforded the title compound as a viscous oil (15 mg, 20%) which crystallised on trituration with petroleum ether.

MP	153–154 °C (Petrol) [Lit. 155 °C]
υ_{max}	2926 (m), 2853 (w), 1604 (m), 1505 (s), 1463 (m), 1419 (w), 1261 (s), 1231 (s), 1164 (m), 1128 (s), 1040 (m).
δ_H (400 MHz, $CDCl_3$)	7.07 (1 H, d, *J*=8.5 Hz, ArH) 6.97 (1 H, d, *J*=2.7 Hz, ArH) 6.89 (1 H, d, *J*=8.1 Hz, ArH) 6.86–6.70 (7 H, m, 7 x ArH) 6.45 (1 H, d, *J*=1.3 Hz, ArH) 6.25 (1 H, dd, *J*=7.6, 1.6 Hz, ArH) 5.37 (1 H, d, *J*=2.0 Hz, ArH) 3.95 (3 H, s, OCH_3) 3.98 (3 H, s, OCH_3) 3.68 (3 H, s, OCH_3) 3.01–2.75 (5 H, m, 5 x CH_2) 2.71–2.54 (3 H, m, 3 x CH_2)
δ_C (100 MHz, $CDCl_3$)	159.3 (C), 156.1 (C), 152.9 (C), 148.8 (C), 147.1 (C), 143.4 (C), 141.4 (C), 139.9 (C), 134.0 (C), 132.6 (2 x CH), 131.1 (C), 129.5 (CH – heavily attenuated), 129.4 (CH – heavily attenuated), 127.8 (C), 122.5 (2 x CH), 121.9 (CH), 121.6 (CH), 116.8 (CH), 115.6 (CH), 112.0 (CH), 111.6 (CH), 111.3 (CH), 56.3 (OCH_3), 55.4 (2 x OCH_3), 38.4 (CH_2), 38.3 (CH_2), 37.4 (CH_2), 35.8 (CH_2)
LRMS	447 ($[M+H_2O+H]^+$, 100%).

These data are in accordance with those reported in the literature.[57]

1,2,13,14-Tetrahydro-9,17,22-trihydroxy-3,6:15,18-dietheno-8,12-metheno-12*H*-7-benzooxacycloeicosine (1.5)



$C_{31}H_{30}O_4$
Molecular Weight: 466.57

$C_{28}H_{24}O_4$
Molecular Weight: 424.49

To a stirred solution of riccardin C tri-*O*-methyl ether **1.88** (8 mg, 17.12 μmol) in DCM (2 mL) at 0 °C was added boron tribromide (0.09 mL, 1 M solution in DCM, 85.65 μmol) dropwise over 5 min. After 3.5 h at 0 °C, ice water (3 mL) and DCM (3 mL) were added. The aqueous phase was separated and extracted with DCM (4 x 5 mL), then the combined organic phases washed with brine (15 mL) was concentrated *in vacuo*. Purification by flash column chromatography (3:2, petroleum ether:diethyl ether) afforded the title compound as a white solid (6 mg, 85%).

MP 195–197 °C (petroleum ether), [Lit.[57] 194 °C (hexane)]

υ_{max} 3402 (br. m), 2928 (m), 2856 (w), 1605 (m), 1505 (s), 1443 (m), 1339 (w), 1270 (m), 1224 (s), 1189 (m), 1164 (m), 1110 (w), 975 (w), 908 (m), 851 (w), 815 (m), 732 (m), 648 (w).

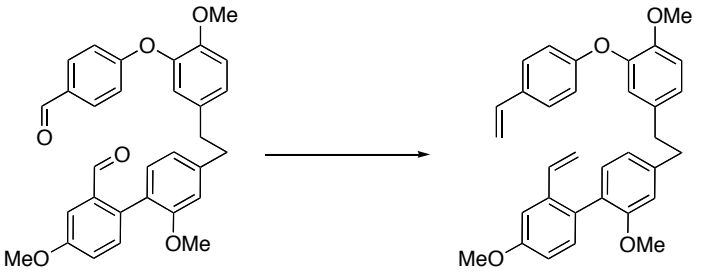
δ_H (300 MHz, $CDCl_3$) 7.05 (1 H, d, *J*=8.1 Hz, ArH)
6.98 (1 H, d, *J*=2.9 Hz, ArH)
6.92 (1 H, d, *J*=8.1 Hz, ArH)
6.89–6.70 (7 H, m, 7 x ArH)
6.40 (1 H, d, *J*=1.8 Hz, ArH)
6.24 (1 H, dd, *J*=7.7, 1.5 Hz, ArH)
5.60 (1 H, s, OH)
5.37 (1 H, d, *J*=2.2 Hz, ArH)
5.07 (1 H, br. s, OH)
4.79 (1 H, s, OH)

3.11–2.59 (8 H, m, CH_2)

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), 133.1 (CH), 131.6 (CH), 129.4 (2 x CH – heavily attenuated), 128.5 (C), 124.5 (C), 122.4 (2 x CH), 122.4 (CH), 121.9 (CH), 117.7 (CH), 116.2 (CH), 116.2 (CH), 115.1 (CH), 114.5 (CH), 38.3 (CH_2), 38.0 (CH_2), 37.3 (CH_2), 35.2 (CH_2).

These data are in accordance with those reported in the literature.[57]

2',4-Dimethoxy-2-vinyl-4'-{2-[3-(4-vinylphenoxy)-4-methoxyphenyl]-ethyl}biphenyl (3.51)



$C_{31}H_{28}O_6$
Molecular Weight: 496.55

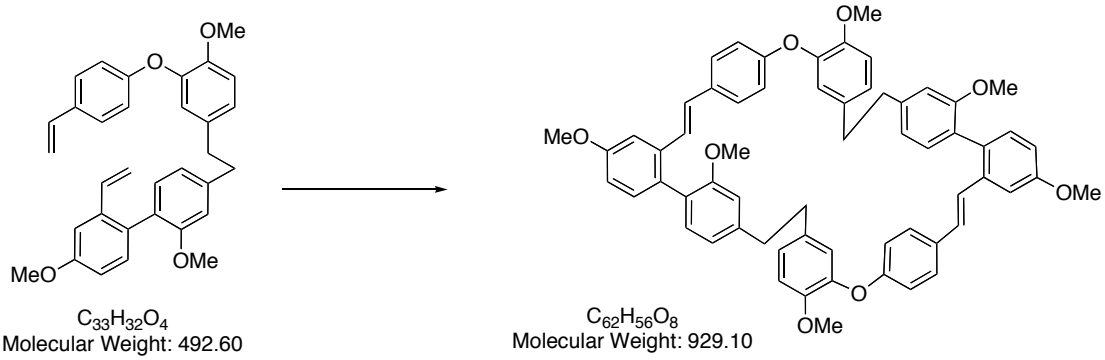
$C_{33}H_{32}O_4$
Molecular Weight: 492.60

To a stirred suspension of methyltriphenylphosphonium bromide (135 mg, 0.38 mmol) in THF (1 mL) at 0 °C was added KO^{t}Bu (42 mg, 0.38 mmol). After 20 min, bis-aldehyde **2.9** (47 mg, 0.097 mmol) was added as a solution in THF (1 mL). The reaction mixture was allowed to warm to RT. After 1.5 h, saturated aqueous NH_4Cl (1 mL) and DCM (2 mL) were added, the phases separated and the aqueous phase extracted with DCM (2 x 2 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (9:1; petroleum ether:ethyl acetate) afforded the *title compound* as a colourless oil (34 mg, 73 %).

υ_{max} 2933 (w), 2834 (w), 2174 (w), 2156 (w), 1603 (w), 1559 (w), 1505 (s), 1483 (w), 1458 (w), 1420 (w), 1271 (m), 1225 (m), 1166 (m), 1125 (w), 1032 (w), 1002 (w), 908 (w), 837 (w), 813 (w).

δ_H (400 MHz, $CDCl_3$)	7.35 (2 H, d, *J*=8.5 Hz, 2 x ArH)
	7.19 (1 H, d, *J*=2.5 Hz, ArH)
	7.13 (1 H, d, *J*=8.5 Hz, ArH)
	7.02 (1 H, d, *J*=7.5 Hz, ArH)
	6.99 (1 H, dd, *J*=8.0, 2.0 Hz, ArH)
	6.97–6.93 (2 H, m, 2 x ArH)
	9.91–6.85 (3 H, m, 3 x ArH)
	6.79 (1 H, dd, *J*=7.5, 1.5 Hz, ArH)
	6.71 (1 H, s, ArH)
	6.70 (1 H, dd, *J*=17.6, 11.0 Hz, C**H**=CH_2)
	6.49 (1 H, dd, *J*=17.6, 11.0 Hz, C**H**=CH_2)
	5.65 (1 H, dd, *J*=17.6, 1.0 Hz, CH=C**H**H)
	5.64 (1 H, dd, *J*=17.6, 1.0 Hz, CH=C**H**H)
	5.17 (1 H, d, *J*=11.0 Hz, CH=CH**H**)
	5.11 (1 H, dd, *J*=11.0, 1.0 Hz, CH=CH**H**)
	3.88 (3 H, s, OCH_3)
	3.83 (3 H, s, OCH_3)
	3.70 (3 H, s, OCH_3)
	2.91 (4 H, app. s, 2 x CH_2)
δ_C (100 MHz, $CDCl_3$)	150.0 (C), 144.5 (C), 142.2 (C), 137.5 (C), 136.1 (CH), 135.8 (CH), 135.7 (C), 135.7 (C), 134.9 (C), 132.0 (C), 131.7 (CH), 131.7 (CH), 130.3 (C), 130.0 (C), 127.4 (2 x CH), 127.1 (C), 124.7 (CH), 121.4 (CH), 120.4 (CH), 117.2 (C), 117.0 (2 x CH), 113.8 (CH_2), 113.4 (CH), 112.9 (CH), 112.3 (CH_2), 111.2 (CH), 109.7 (CH), 56.1 (OCH_3), 55.5 (OCH_3), 55.3 (OCH_3), 38.1 (CH_2), 36.9 (CH_2).
LRMS	1007 ($[2M+Na]^+$, 10%), 515 ($[M+Na]^+$, 100%).
HRMS	$C_{33}H_{32}NaO_4$ requires 515.2193; Found: 515.2189.

(1*E*,25*E*)-13,14,37,38-Tetrahydro-9,17,22,33,41,46-hexamethoxy-3,7:15,18:27,30:39,42-tetraethano-8,12:32,36-dimethano-dibenzo-[7,31-dioxa-*s*-μ]-cyclotetracontine (3.52)

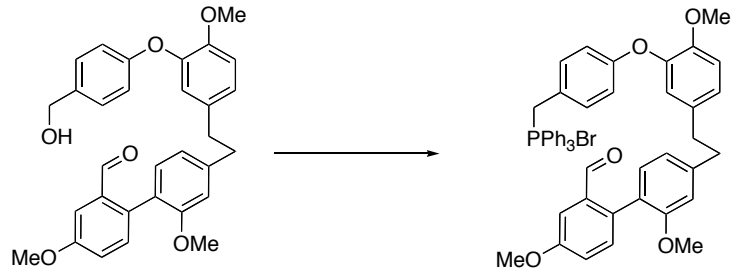


To a stirred solution of bis-styrene **3.51** (179 mg, 0.37 mmol) in DCM was added Grubbs' second generation catalyst **3.49** (5 mg, 0.06 mmol) and the reaction heated at reflux (40 °C) for 1 h. The reaction mixture was cooled to RT, then a further portion of **3.49** (5 mg, 0.06 mmol) was added. The reaction mixture was heated at reflux for 17 h, then cooled to RT and a further portion of **3.49** (5 mg, 0.06 mmol) was added. The reaction mixture was heated at reflux for a further 2 h then cooled to RT, concentrated *in vacuo* and purified by flash column chromatography (7:3, petroleum ether:diethyl ether) to afford the *title compound* as a white crystalline solid (38 mg, 20%), in addition to other unidentified higher oliogmers/isomers.

MP	139–140 °C (DCM/MIBK/Petroleum ether)
υ_{max}	2932 (w), 1600 (m), 1580 (w), 1504 (s), 1463 (m), 1422 (m), 1271 (s), 1226 (s), 1166 (s), 1125 (m), 1038 (m), 1002 (w), 963 (w), 909 (w), 810 (m), 731 (m).
δ_H (400 MHz, $CDCl_3$)	7.29–7.27 (2 H, m, 2 x ArH)
	7.19 (2 H, d, *J*=8.0 Hz, 2 x ArH)
	7.17 (2 H, d, *J*=9.0 Hz, 2 x ArH)
	7.10–7.00 (2 H, obsc. m, 2 x ArH)
	7.08 (2 H, d, *J*=7.5 Hz, 2 x ArH)
	7.03 (2 H, dd, *J*=8.5, 2.0 Hz, 2 x ArH)
	6.96 (2 H, d, *J*=8.0 Hz, 2 x ArH)
	6.92–6.80 (10 H, m, 8 x ArH and 2 x C**H**=CH)
	6.77 (2 H, d, *J*=1.5 Hz, 2 x ArH)

	6.72 (2 H, d, *J*=16.6 Hz, 2 x CH=C**H**)
	3.91 (6 H, s, 2 x OCH_3)
	3.83 (6 H, s, 2 x OCH_3)
	3.70 (6 H, s, 2 x OCH_3)
	2.89 (8 H, s, 4 x CH_2)
δ_C (100 MHz, $CDCl_3$)	158.9 (2 x C), 157.5 (2 x C), 156.9 (2 x C), 149.7 (2 x C), 144.7 (2 x C), 142.4 (2 x C), 137.2 (2 x C), 135.0 (2 x CH), 132.2 (2 x C), 131.9 (2 x CH), 131.9 (2 x C), 130.5 (2 x C), 127.9 (2 x CH), 127.6 (4 x CH), 127.3 (2 x CH), 124.6 (2 x CH), 121.2 (2 x CH), 120.5 (2 x CH), 117.1 (4 x CH), 113.1 (2 x CH), 113.1 (2 x CH), 111.2 (2 x CH), 109.5 (2 x CH), 56.2 (2 x OCH_3), 55.6 (2 x OCH_3), 55.3 (2 x OCH_3), 38.8 (2 x CH_2), 37.5 (2 x CH_2). *N.B. Two quaternary carbons centres were not observed.*
LRMS (HM ES+)	951 ($[M+Na]^+$, 7%), 426 (46%), 219 (100%).

4-{5-[2-(2,4'Dimethyoxy-2'-formyl-biphen-4-yl)ethyl]-2-methoxyphenoxy}-benzyltriphenylphosphoium bromide (3.54)



$C_{31}H_{28}O_6$
Molecular Weight: 498.57

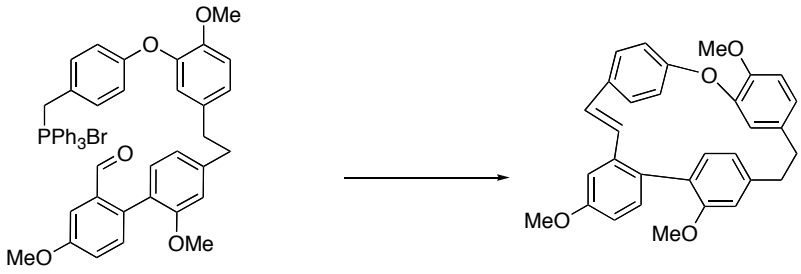
$C_{49}H_{44}BrO_5P$
Molecular Weight: 823.75

To a stirred solution of benzyl alcohol **3.42** (104 mg, 0.21 mmol) in toluene (5 mL) at 0 °C was added PBr_3 (0.019 g, 0.070 mmol). The reaction mixture was allowed to warm to RT and after 3 h, water (2 mL) was added. The phases were separated and the aqueous phase extracted with DCM (3 x 5 mL). The combined organic phases were dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was dissolved in toluene (5 mL) and triphenylphosphine (55 mg, 0.21 mmol)

added. The reaction mixture was heated at reflux for 18 h, then cooled to 0 °C. The resultant precipitate was collected by filtration and washed with petroleum ether, yielding the *title compound* as a white crystalline solid (142 mg, 81%).

MP	145–148 °C (petroleum ether)
υ_{max}	3402 (br. w), 3006 (w), 2936 (w), 2857 (w), 1707 (w), 1687 (m), 1605 (m), 1587 (w), 1505 (s), 1487 (m), 1463 (w), 1438 (m), 1421 (w), 1363 (w), 1317 (w), 1272 (s), 1224 (s), 1164 (w), 1112 (m), 1034 (w), 999 (w), 934 (w), 836 (w), 748 (w), 719 (w), 690 (w), 560 (w), 511 (m).
δ_H (400 MHz, $CDCl_3$)	9.70 (1 H, s, CHO)
	7.83–7.59 (13 H, m, 13 x ArH)
	7.48 (1 H, d, *J*=2.9 Hz, ArH)
	7.28 (1 H, d, *J*=8.4 Hz, ArH)
	7.24–7.17 (2 H, m, 2 x ArH)
	7.13 (1 H, d, *J*=7.7 Hz, ArH)
	7.03 (2 H, dd, *J*=8.6, 2.4 Hz, ArH)
	6.95–6.83 (3 H, m, 3 x ArH)
	6.76–6.66 (5 H, m, 5 x ArH)
	5.37 (2 H, d, *J*=13.2 Hz, CH_2)
	3.88 (3 H, s, OCH_3)
	3.80 (3 H, s OCH_3)
	3.66 (3 H, s, OCH_3)
	2.89 (4 H, app. br. s, 2 x CH_2)
LRMS (ES+)	734 ($[M–Br]^+$, 19%), 621 (18%), 282 (100%).
HRMS	$C_{49}H_{44}O_5P$ requires 743.2921; Found: 743.2933.

13,14-Dihydro-9,17,22-trimethoxy-3,6:15,18-dietheno-8,12-metheno-12*H*-7-benzooxacycloeicosine (3.47)



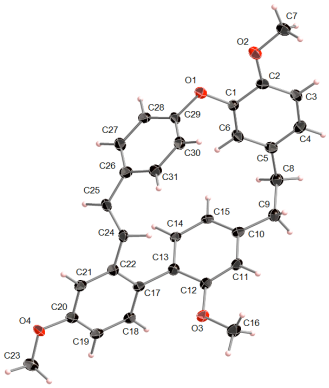
$C_{49}H_{44}BrO_5P$
Molecular Weight: 823.75

$C_{31}H_{29}O_4$
Molecular Weight: 464.55

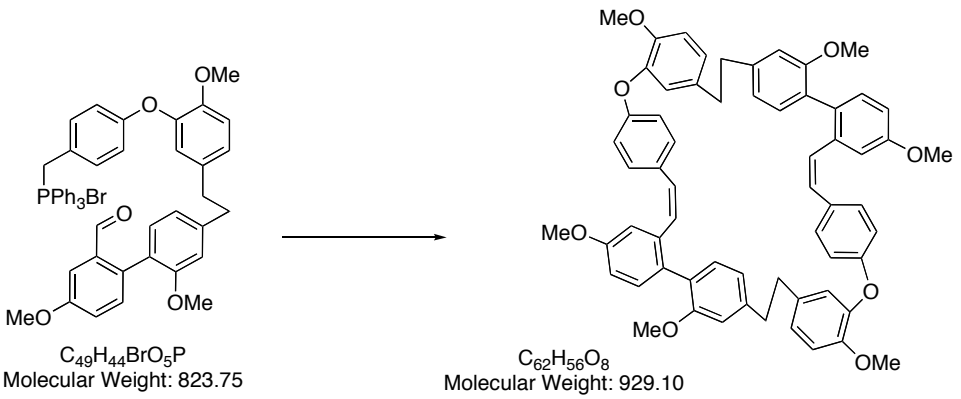
To a stirred solution of NaOMe (15 mg, 0.27 mmol) in DCM (5 mL) was added a solution of phosphonium salt **3.54** (112 mg, 0.137 mmol) in DCM (10 mL) dropwise over 4 h. After 18 h at RT, the reaction mixturewas heated at reflux for 1 h, then cooled to RT, filtered, silica (~4 g) added and the solvent removed *in vacuo*. Purification by flash column chromatography (7:3→2:3 petroleum ether:diethyl ether) afforded the *title compound* as a white solid (30 mg, 47%).

MP	139–140 °C ($CHCl_3$)
υ_{max}	2933 (w), 1602 (m), 1582 (w), 1567 (w), 1510 (s), 1500 (s), 1463 (m), 1417 (m), 1260 (s), 1227 (s), 1161 (s), 1126 (s), 1038 (m), 963 (w), 908 (w), 867 (w), 808 (w), 730 (m).
δ_H (400 MHz, $CDCl_3$)	7.24 (1 H, d, *J*=8.5 Hz, ArH)
	7.22–7.11 (2 H, m, 2 x ArH)
	7.02 (1 H, d, *J*=3.0 Hz, ArH)
	6.95 (1 H. d, *J*=9.0 Hz, ArH)
	6.92–6.88 (2 H, m, 2 x Ar)
	6.86 (1 H, d, *J*=8.0 Hz, ArH)
	6.79 (1 H, dd, *J*=8.5, 2.0 Hz, ArH)
	6.63 (1 H, d, *J*=7.5 Hz, ArH)
	6.58 (1 H, d, *J*=16.1 Hz, CH=C**H**)
	6.52 (1 H, s, ArH)
	6.04 (1 H, d, *J*=16.1 Hz, C**H**=CH)
	5.77 (1 H, d, *J*=2.0 Hz, ArH)
	3.97 (3 H, s, OCH_3)

	3.90 (3 H, s, OCH_3)
	3.66 (3 H, s, OCH_3)
	2.97–2.75 (4 H, m, 2 x CH_2)
δ_C (100 MHz, $CDCl_3$)	158.9 (C), 156.6 (C), 155.4 (C), 150.4 (C), 147.4 (C), 142.5 (C), 139.4 (C), 138.6 (C), 137.9 (CH), 135.8 (C), 131.9 (CH), 131.5 (C), 130.7 (C), 130.1 (CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 122.6 (CH), 122.6 (CH), 122.5 (CH), 119.6 (CH), 116.0 (CH), 112.54 (CH), 111.9 (CH), 110.4 (CH), 110.3 (CH), 56.2 (OCH_3), 55.4 (OCH_3), 55.3 (OCH_3), 36.2 (CH_2), 33.7 (CH_2).
LRMS (ES+)	953 ($(2M+H)^+$, 34%), 951 (44%), 505 (57%), 483 ($(M+H)^+$, 100%)
HRMS	$C_{31}H_{29}O_4$ requires 465.2050; Found: 465.2054.
X-ray:	



(1*Z*,25*Z*)-13,14,37,38-Tetrahydro-9,17,22,33,41,46-hexamethoxy-3,7:15,18:27,30:39,42-tetraethano-8,12:32,36-dimethano-dibenzo-[7,31-dioxa-*s*-μ]-cyclotetracontine (3.55)



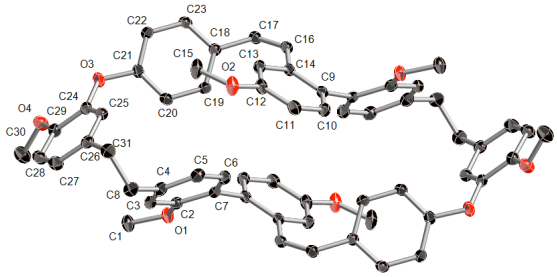
To a stirred solution of NaOMe (15 mg, 0.27 mmol) in DCM (5 mL) was added a solution of phosphonium salt **3.54** (112 mg, 0.137 mmol) in DCM (10 mL) dropwise over 4 h. After 18 h at RT, the reaction mixture was heated at reflux for 1 h, then cooled to RT, filtered, silica (~4 g) added and the solvent removed *in vacuo*. Purification by flash column chromatography (7:3→2:3 petroleum ether:diethyl ether) afforded firstly *trans*-stilbene **3.47** (30 mg, 47%) and then the *title compound* (12 mg, 19%) as a crystalline solid.

Data for **3.47** *identical to those previously reported.*

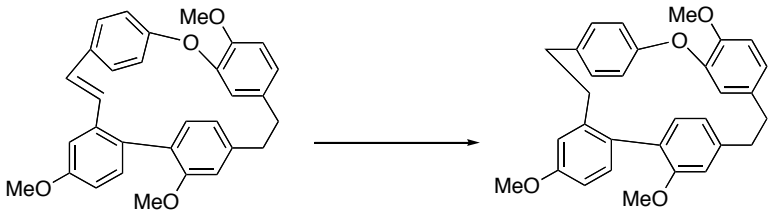
Data for **3.55**:

MP	114–116 °C (DCM/petroleum ether)
υ_{max}	2933 (w), 1602 (m), 1575 (w), 1504 (s), 1463 (m), 1422 (m), 1270 (s), 1227 (s), 1167 (m), 1125 (m), 1038 (m), 1003 (w), 910 (w), 874 (w), 813 (w), 732 (w).
δ_H (300 MHz, $CDCl_3$)	7.17–7.06 (6 H, m, 6 x ArH)
	6.94–6.61 (14 H, m, 14 x ArH)
	6.49 (2 H, s, 2 x ArH)
	6.21 (2 H, d, *J*=12.1 Hz, 2 x C**H**=CH)
	6.15 (2 H, d, *J*=12.1 Hz, 2 x CH=C**H**)
	3.82 (6 H, s, 2 x OCH_3)
	3.62 (6 H, s, 2 x OCH_3)
	3.51 (6 H, s, 2 x OCH_3)
	2.91–2.84 (6 H, s, 2 x OCH_3)

δ_C (100 MHz, $CDCl_3$)	156.6 (2 x C), 156.1 (2 x C), 148.9 (2 x C), 145.3 (2 x C), 141.6 (2 x C), 138.2 (2 x C), 134.2 (2 x C), 131.9 (2 x CH), 131.5 (2 x CH), 131.3 (2 x CH), 130.7 (2 x C), 130.7 (2 x C), 103.4 (4 x CH), 129.6 (2 x CH), 128.7 (2 x C), 127.3 (2 x C), 123.8 (2 x CH), 120.6 (2 x CH), 120.1 (2 x CH), 117.7 (4 x CH), 113.7 (2 x CH), 113.5 (2 x CH), 112.72 (2 x CH), 111.3 (2 x CH), 56.1 (2 x OCH_3), 55.2 (2 x OCH_3), 55.1 (2 x OCH_3), 37.8 (2 x CH_2), 36.6 (2 x CH_2).
LRMS	952 ($[M+H]^+$, 13%), 268 (13%), 217 (100%).
HRMS	$C_{62}H_{56}NaO_8$ requires 951.3867; Found: 951.3865.
X-ray:	



1,2,13,14-Tetrahydro-9,17,22-trimethoxy-3,6:15,18-dietheno-8,12-metheno-12*H*-7-benzooxacycloeicosine (1.88)



$C_{31}H_{30}O_4$
Molecular Weight: 464.55

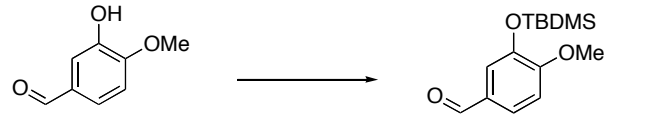
$C_{31}H_{30}O_4$
Molecular Weight: 466.57

To a stirred solution of **3.47** (30 mg, 0.065 mmol) in DCM (2 mL) and methanol (2 mL) was added 10% palladium on carbon (30 mg). The flask was evacuated/purged with argon three times then evacuated/purged with hydrogen

twice. After 3 h the reaction mixture was filtered through Celite® and the solvent removed *in vacuo* to afford the title compound as a white solid (27 mg, 90%).

The data were identical to those previously reported.

4-(Dimethyl-*tert*-butylsilyloxy)-2-methoxylbenzaldehyde (4.6)



$C_8H_8O_3$
Molecular Weight: 152.15

$C_{14}H_{22}O_3Si$
Molecular Weight: 266.41

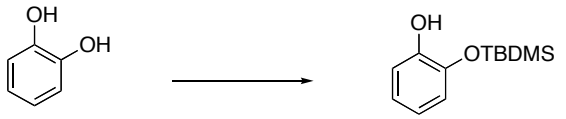
To a stirred solution of isovanillin (1.00 g, 6.58 mmol) in DCM (25 mL) was added imidazole (1.79 g, 26.32 mmol) and *tert*-butyldimethylsilyl chloride (1.98 g, 13.16 mmol). After 18 h at RT the solvent was removed *in vacuo* and purification by flash column chromatography (4:1, petroleum ether:diethyl ether) afforded the title compound as a colourless oil (1.423 g, 70%).

δ_H (400 MHz, $CDCl_3$) 9.80 (1 H, s, CHO)
7.45 (1 H, dd, *J*=8.3, 2.0 Hz, ArH)
7.36 (1 H, d, *J*=2.2 Hz, ArH)
6.94 (1 H, d, *J*=8.3 Hz, ArH)
3.87 (3 H, s, OCH_3)
0.99 (9 H, s, $SiC(C\mathbf{H}_3)_3$)
0.16 (6 H, s, $Si(C\mathbf{H}_3)_2$)

δ_C (100 MHz, $CDCl_3$) 190.7 (CHO), 156.5 (C), 145.5 (C), 130.7 (C), 126.2 (CH), 119.9 (CH), 111.1 (CH), 55.5 (OCH_3), 25.6 ($SiC(\mathbf{C}H_3)_3$), 18.3 ($Si(\mathbf{C}H_3)_2$), –4.7 ($Si\mathbf{C}(CH_3)_3$.

These data are in accordance with those reported in the literature.[94]

2-(Dimethyl-*tert*-butylsilyloxy)phenol (4.9)[95]



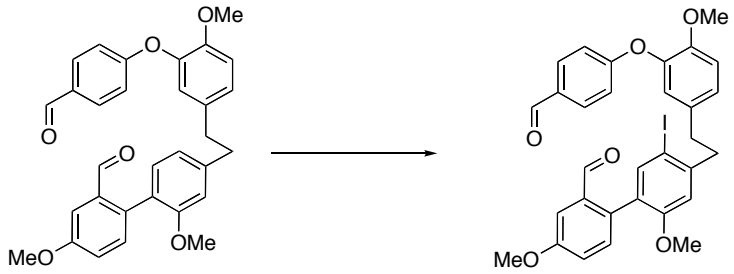
$C_6H_6O_2$
Molecular Weight: 110.11

$C_{12}H_{20}O_2Si$
Molecular Weight: 224.37

To a stirred solution of catechol (2.00 g, 18.20 mmol) in DCM (30 mL) was added imidazole (2.74 g, 18.20 mmol) and *tert*-butyldimethylsilyl chloride (2.48 g, 36.40 mmol). After 7 h, silica (~5 g) was added and the solvent removed *in vacuo*. Purification by flash column chromatography (9:1, petroleum ether:diethyl ether) afforded the title compound as a colourless oil (2.49 g, 61%).

υ_{max}	3543 (w), 2954 (w), 2930 (w), 2858 (w), 1593 (w), 1498 (s), 1471 (w), 1464 (w), 1362 (w), 1267 (s), 1224 (m), 1191 (m), 1100 (m), 1030 (w), 911 (s), 825 (s), 781 (s), 742 (s).
δ_H (400 MHz, $CDCl_3$)	7.00 (1 H, dd, *J*=8.0, 2.0 Hz, ArH) 6.92 (1 H, app. td, *J*=8.0, 1.5 Hz, ArH) 6.88 (1 H, dd, *J*=8.0, 1.5 Hz, ArH) 6.80 (1 H, app. td, *J*=8.0, 1.1 Hz, ArH) 5.56 (1 H, s, OH) 1.08 (9 H, s, $SiC(C\mathbf{H}_3)_3$) 0.33 (6 H, s, $Si(C\mathbf{H}_3)_2$)
δ_C (100 MHz, $CDCl_3$)	147.3 (C), 142.4 (C), 122.2 (CH), 120.0 (CH), 117.9 (CH), 114.9 (CH), 25.7 ($SiC(\mathbf{C}H_3)_3$), 18.2 ($Si\mathbf{C}(CH_3)_3$), –4.4 ($Si(\mathbf{C}H_3)_2$.
LRMS (EI)	209 ($[M–CH_3]^+$, 2%), 167 ($[M–C(CH_3)_3]^+$, 100%), 151 ($[M–OH–C(CH_3)_3]^{+\bullet}$, 73%), 136 ($[M–OH–C(CH_3)_3–CH_3]^{+\bullet}$, 21%), 75 (78%).

4-{2-[3-(4-Formylphenoxy)-4-methoxyphenyl]-ethyl}-2,4'dimethoxy-2'-formyl-5-iodo-biphenyl (4.1)



$C_{31}H_{28}O_6$
Molecular Weight: 496.55

$C_{31}H_{27}IO_6$
Molecular Weight: 622.45

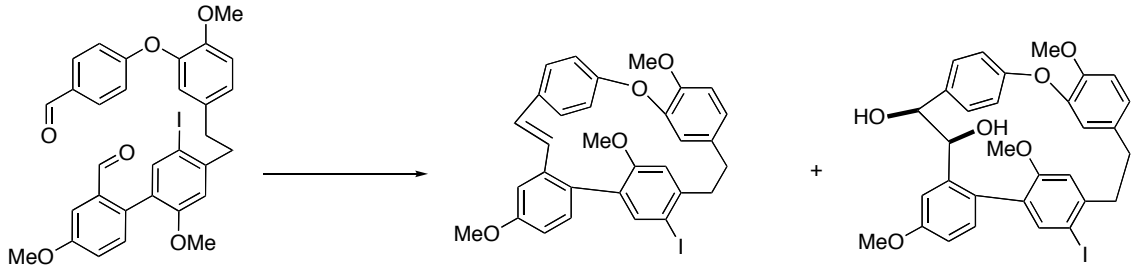
To a stirred solution of bis-aldehyde **2.9** (184 mg, 0.37 mmol) in acetonitrile (3 mL) was added *N*-iodosuccinimide (150 mg, 0.67 mmol) and a trace of trifluoroacetic acid. After 17 h, DCM (3 mL) was added and the reaction mixture washed with saturated aqueous $Na_2S_2O_7$ (10 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography afforded the *title compound* as a white solid (210 mg, 91%), contaminated with traces of succinimide.

υ_{max} 2936 (w), 1689 (s), 1601 (m), 1579 (m), 1502 (s), 1481 (m), 1463 (w), 1442 (w), 1378 (w), 1313 (w), 1272 (s), 1229 (s), 1155 (s), 1124 (m), 1043 (m), 936 (w).

δ_H (400 MHz, $CDCl_3$) 9.88 (1 H, s, CHO)
9.68 (1 H, s, CHO)
7.80 (2 H, d, *J*=8.8 Hz, 2 x ArH)
7.67 (1 H, s, ArH)
7.47 (1 H, app. s, ArH)
7.19 (2 H, app. s, 2 x ArH)
7.12 (1 H, dd, *J*=8.3, 2.1 Hz, ArH)
7.02–6.96 (3 H, m, 3 x ArH)
6.94 (1 H, d, *J*=2.1 Hz, ArH)
6.68 (1 H, s, ArH)
3.90 (3 H, s, OCH_3)
3.79 (3 H, s, OCH_3)
3.65 (3 H, s, OCH3)
3.09–3.01 (2 H, m, CH_2)
2.95–2.87 (2 H, m, CH_2)

δ_C (100 MHz, $CDCl_3$)	192.1 (CHO), 190.9 (CHO), 163.6 (C), 159.5 (C), 156.9 (C), 150.2 (C), 145.2 (C), 142.6 (C), 141.3 (CH), 134.8 (C), 134.4 (C), 132.5 (C), 132.4 (CH), 131.9 (2 x CH), 130.9 (C), 127.0 (C), 126.5 (CH), 122.9 (CH), 121.2 (CH), 116.1 (2 x CH), 113.1 (CH), 112.2 (CH), 109.8 (CH), 89.3 (C), 56.1 (OCH_3), 55.6 (OCH_3), 55.5 (OCH_3), 35.5 (OCH_3), 29.6 (OCH_3).
LRMS (ES+)	623 ($[M+H]^+$, 100%)

<u>*E*-13,14-Dihydro-9,17,22-trimethoxy-3,6-etheno-15,18-iodoetheno-8,12-metheno -12*H*-7-benzooxacycloeicosine (4.12) and *rel*-(1*S*,2*S*)-13,14-Dihydro-1,2-dihydroxy-9,17,22-trimethoxy-3,6-etheno-15,18-iodoetheno-8,12-metheno -12*H*-7-benzooxacycloeicosine (4.13)</u>



$C_{31}H_{27}IO_6$
Molecular Weight: 622.45

$C_{31}H_{27}IO_4$
Molecular Weight: 590.45

$C_{31}H_{29}IO_6$
Molecular Weight: 624.46

To a cooled aliquot of THF (5 mL) at –78 °C containing magnesium (80 mg, 3.29 g-atom) was added titanium tetrachloride (666 mg, 3.51 mmol, 0.39 mL) dropwise over 5 min. The reaction mixture was allowed to warm to RT and stirred for 2 h. The resultant black solution was cooled to –78 °C and a solution of tetraaromatic **4.1** (80 mg, 0.13 mmol) in THF (10 mL) was added dropwise over 9 min. After 12 h at RT the reaction mixture was partitioned between brine (20 mL) and DCM (20 mL). The aqueous phase was re-extracted with DCM (3 x 20 mL) and the combined organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (4:6, diethyl ether:petroleum ether→diethyl ether) afforded firstly the *title compound* **4.12** as a viscous oil (4 mg, 5%) followed by the *title compound* **4.13** as a white foam (14 mg, 17%).

Data for **4.12**:

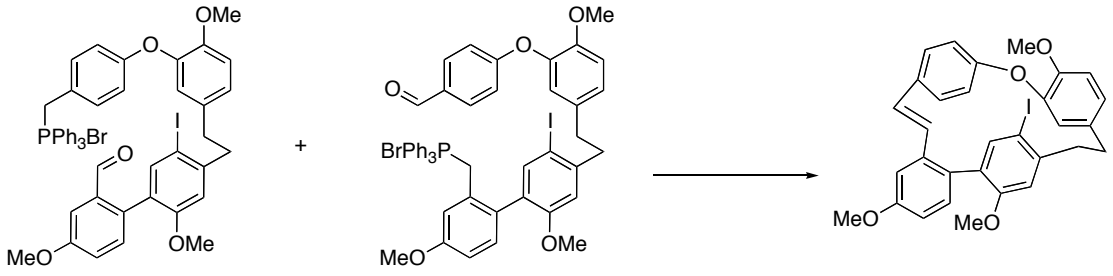
υ_{max}	2932 (m), 1606 (m), 1512 (s), 1505 (s), 1231 (s), 1128 (m).
δ_H **(400 MHz, $CDCl_3$)**	7.50 (1 H, s, ArH) 7.23–7.13 (3 H, m, 3 x ArH) 7.00 (3 H, m, 3 x ArH) 6.93–6.77 (3 H, m, 3 x ArH) 6.58 (1 H, d, *J*=16.1 Hz, C**H**=CH) 6.43 (1 H, s, ArH) 6.09 (1 H, d, *J*=16.1 Hz, CH=C**H**) 5.73 (1 H, app. s, ArH) 3.97 (3 H, s, OCH_3) 3.89 (3 H, s, OCH_3) 3.56 (3 H, s, OCH_3) 3.04–2.75 (4 H, m, 2 x CH_2)
δ_C **(100 MHz, $CDCl_3$)**	159.3 (C), 157.1 (C), 157.0 (C), 150.3 (C), 149.2 (C), 144.7 (C), 144.3 (C), 141.1 (CH), 139.4 (CH), 138.4 (C), 136.2 (C), 135.2 (CH), 131.4 (CH), 130.1 (CH), 129.8 (CH), 127.5 (C), 127.4 (CH), 127.3 (C), 123.6 (CH), 122.7 (CH), 122.0 (CH), 115.9 (CH), 112.7 (CH), 112.0 (CH), 110.6 (CH), 89.2 (C), 56.2 (OCH_3), 55.5 (OCH_3), 55.4 (OCH_3), 41.4 (CH_2), 40.5 (CH_2). *N.B. Some C and CH assignments made by comparison of the spectrum with related compound.*

Data for **4.13**:

υ_{max}	3426 (br. w), 2930 (w), 2357 (w), 1608 (w), 1506 (s), 1478 (m), 1464 (m), 1421 (w), 1372 (w), 1261 (m), 1230 (s), 1163 (m), 1128 (m), 1039 (m), 906 (w).
δ_H **(400 MHz, $CDCl_3$)**	7.56 (1 H, dd, *J*=8.8, 1.3 Hz, ArH) 7.47 (1 H, s, ArH) 7.36 (1 H, d, *J*=2.5 Hz, ArH) 7.11 (1 H, d, *J*=9.0 Hz, ArH)

	7.02 (1 H, dd, *J*=8.5 Hz, 2.0 Hz, ArH)
	6.92 (1 H, d, *J*=8.5 Hz, ArH)
	6.88 (1 H, dd, *J*=9.0, 2.0 Hz, ArH)
	6.83 (1 H, dd, *J*=8.5, 2.0 Hz, ArH)
	6.63 (1 H, dd, *J*=8.5, 2.5 Hz, ArH)
	6.57 (1 H, dd, *J*=8.0, 1.3 Hz, ArH)
	5.95 (1 H, s, ArH)
	5.40 (1 H, d, *J*=2.0 Hz, ArH)
	4.82 (1 H, d, *J*=8.5 Hz, C**H**OH)
	4.74 (1 H, d, *J*=8.5 Hz, C**H**OH')
	3.95 (3 H, s, OCH_3)
	3.92 (3 H, s, OCH_3)
	3.48 (3 H, s, OCH_3)
	3.18 (1 H, ddd, *J*=13.1, 5.5, 2.4 Hz, C**H**H)
	2.85 (1 H, ddd, *J*=13.1, 5.5, 2.0 Hz, CH**H**)
	2.63 (1 H, dd, *J*=13.1, 2.0 Hz, C**H**H)
	2.49 (1 H, dd, *J*=13.1, 2.4 Hz, CH**H**)
	1.59 (2 H, br. s, 2 x OH)
δ_C (100 MHz, $CDCl_3$)	159.6 (C), 155.8 (C), 153.8 (C), 148.2 (C), 147.2 (C), 142.9 (C), 140.9 (C), 140.6 (CH), 137.7 (C), 133.5 (CH), 133.2 (C), 128.3 (C), 128.2 (C), 124.8 (CH), 123.7 (CH), 122.2 (CH), 120.8 (CH), 116.8 (CH), 115.5 (CH), 115.5 (CH), 113.8 (CH), 112.6 (CH), 112.3 (CH), 87.6 (C), 77.1 (CHOH), 73.9 (CHOH), 56.4 (OCH_3), 55.6 (OCH_3), 55.2 (OCH_3), 43.0 (CH_2), 35.0 (CH_2).
LRMS (ES+)	647 ($[M+Na]^+$, 42%), 153 (100%).
HRMS	$C_{31}H_{29}INaO_6$ requires 647.0901; Found: 647.0912.

13,14-Dihydro-9,17,22-trimethoxy-3,6-etheno-15,18-iodoetheno-8,12-metheno-12*H*-7-benzooxacycloeicosine (4.12)



$C_{49}H_{43}BrIO_5P$
Molecular Weight: 949.65

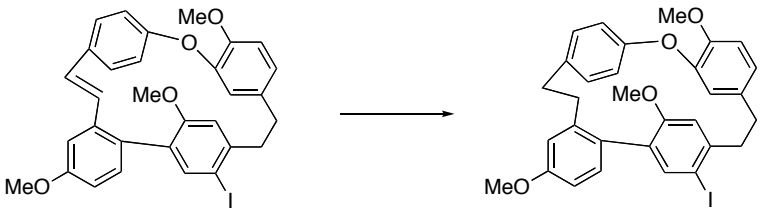
$C_{49}H_{43}BrIO_5P$
Molecular Weight: 949.65

$C_{31}H_{29}O_4$
Molecular Weight: 464.55

To a stirred suspension of NaOMe (6 mg, 0.11 mmol) in DCM (1 mL) was added a solution of combined phosphonium salts **4.19** and **4.20** (0.010 mmol) in DCM (3 mL) dropwise over 3 h. After 18 h at RT, silica (~0.5 g) was added and the solvent removed *in vacuo*. Purification by flash column chromatography (4:1, heptane:ethyl acetate) then by preparative thin layer chromatography (1:1, ethyl acetate:heptane and then 1:1, petroleum ether:diethyl ether) afforded the title compound as a colourless film (4 mg, 86%).

The data obtained were identical to those previously reported.

1,2,13,14-Tetrahydro-9,17,22-trimethoxy-3,6-etheno-15,18-iodoetheno-8,12-metheno-12*H*-7-benzooxacycloeicosine (1.213)



$C_{31}H_{27}IO_4$
Molecular Weight: 590.45

$C_{31}H_{29}IO_4$
Molecular Weight: 592.46

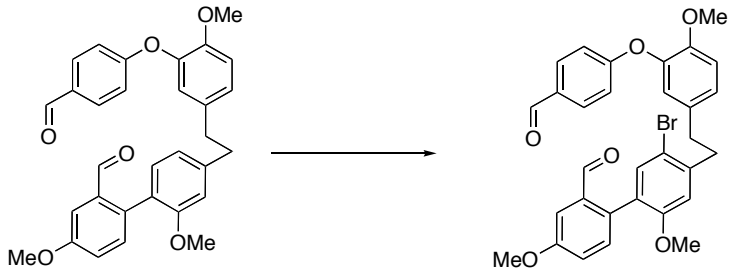
To a stirred solution of stilbene **4.12** (4 mg, 0.006 mmol) in 1:1 v/v THF and water (2 mL each) was added tosylhydrazone (125 mg, 0.06 mmol) and NaOAc (55 mg, 0.06 mmol). The reaction mixturewas heated at reflux for 3 days, then cooled to RT and saturated aqueous K_2CO_3 (2 mL) added. After 3 h, the reaction mixture was extracted with DCM (4 x 5 mL), then the combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography

(4:1; petroleum ether:diethyl ether) afforded the *title compound* as a white solid (3 mg, 75%).

MP	>250 °C (ethanol)
υ_{max}	2932 (w), 2836 (w), 2359 (w), 1606 (w), 1586 (w), 1505 (s), 1479 (m), 1463 (m), 1442 (w), 1420 (w), 1369 (w), 1261 (m), 1231 (s), 1165 (w), 1128 (m), 1043 (m), 1016 (w), 907 (m), 852 (w), 807 (w), 730 (m).
δ_H (400 MHz, $CDCl_3$)	7.41 (1 H, s, ArH) 7.06 (1 H, d, *J*=8.5 Hz, ArH) 6.96 (1 H, d, *J*=2.5 Hz, ArH) 6.92–6.72 (7 H, m, 7 x ArH) 6.37 (1 H, s, ArH) 5.33 (1 H, d, *J*=2.0 Hz, ArH) 3.95 (3 H, s, OCH_3) 3.89 (3 H, s, OCH_3) 3.63 (3 H, s, OCH_3) 3.09–2.63 (8 H, m, 4 x CH_2)
δ_C (100 MHz, $CDCl_3$)	159.4 (C), 156.3 (C), 152.7 (C), 149.2 (C), 147.1 (C), 143.4 (C), 143.2 (C), 142.6 (CH), 139.6 (C), 133.1 (C), 132.6 (CH), 130.2 (C), 129.6 (CH), 129.4 (CH), 128.9 (C), 122.6 (CH), 122.2 (CH), 121.7 (CH), 116.0 (CH), 115.6 (CH), 112.9 (CH), 112.0 (CH), 111.5 (CH), 89.9 (C), 56.2 (OCH_3), 56.2 (OCH_3), 55.3 (OCH_3), 41.9 (CH_2), 38.3 (CH_2), 36.7 (CH_2), 35.5 (CH_2).
LRMS (ES+)	647 ($[M+MeOH+Na]^+$, 56%), 615 ($[M+Na]^+$, 90%), 268 (49%), 183 (100%).

These data are identical to those previously recorded in our laboratory.

4-{2-[3-(4-Formylphenoxy)-4-methoxyphenyl]-ethyl}-2,4'dimethoxy-2'-formyl-5-bromo-biphenyl (4.21)



$C_{31}H_{28}O_6$
Molecular Weight: 496.55

$C_{31}H_{27}BrO_6$
Molecular Weight: 575.45

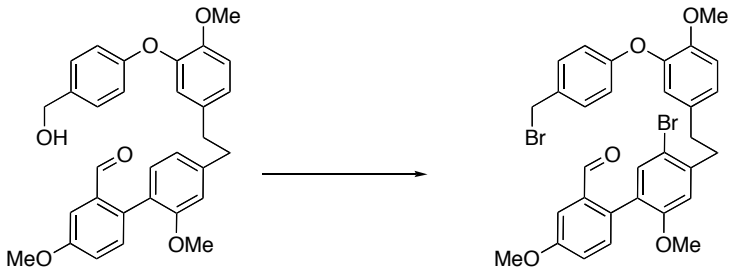
To a stirred solution of bis-aldehyde **2.9** (64 mg, 0.13 mmol) in DMF (2 mL) was added *N*-bromosuccinimide (16 mg, 0.14 mmol). After 64 h, a further portion of *N*-bromosuccinimide (5 mg, 0.4 mmol) was added then after 4 h one further portion (16 mg, 0.14 mmol) was added. After a further 18 h, saturated aqueous $Na_2S_2O_7$ (2 mL) were added and the reaction mixture extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with water (3 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (7:3, petroleum ether:ethyl acetate) afforded the *title compound* as a waxy solid (55 mg, 74%).

υ_{max} 2935 (w), 2841 (w), 1689 (s), 1600 (m), 1579 (m), 1502 (s), 1481 (m), 1463 (w), 1442 (w), 1423 (w), 1393 (w), 1377 (w), 1313 (w), 1271 (s), 1229 (s), 1190 (w), 1155 (s), 1123 (m), 1043 (m), 1014 (w), 935 (w), 910 (w), 856 (w), 833 (m), 771 (w), 731 (m), 609 (w).

δ_H (300 MHz, $CDCl_3$)
9.73 (1 H, s, CHO)
9.52 (1 H, s, CHO)
7.65 (2 H, d, *J*=8.8 Hz, 2 x ArH)
7.33 (1 H, s, ArH)
7.12 (1 H, s, ArH)
7.04 (1 H, s, ArH)
6.96 (1 H, dd, *J*=8.4, 1.8 Hz, ArH)
6.86–6.76 (5 H, m, 5 x ArH)
6.52 (1 H, s, ArH)
3.75 (3 H, s, OCH_3)

	3.64 (3 H, s, OCH_3)
	3.50 (3 H, s, OCH_3)
	2.99–2.87 (2 H, m, CH_2)
	2.84–2.73 (2 H, m, CH_2)
δ_C (100 MHz, $CDCl_3$)	192.1 (CHO), 190.9 (CHO), 163.8 (C), 159.6 (C), 156.0 (C), 150.3 (C), 142.8 (C), 141.9 (C), 135.1 (CH), 135.0 (C), 134.7 (C), 132.8 (C), 132.5 (2 x CH), 132.0 (CH), 131.1 (C), 126.8 (C), 126.6 (CH), 123.0 (CH), 121.3 (CH), 116.2 (2 x CH), 115.3 (C), 113.2 (CH), 113.0 (CH), 110.0 (CH), 56.2 (OCH_3), 55.8 (OCH_3), 55.8 (OCH_3), 38.8 (CH_2), 35.3 (CH_2).
LRMS (ES+)	1171 ($[2M+Na]^+$, 51%), 597 ($[M+Na]^+$, 94%), 575 ($[M+H]^+$, 17%), 284 (20%), 223 (42%), 214 (17%), 167 (24%), 151 (40%).
HRMS	$C_{31}H_{27}BrNaO_4$ requires 597.0883; Found: 597.0882.

3'-Bromo-4,6'-dimethoxy-2-formyl-4'-{2-[3-(4-bromomethylphenoxy)-4-methoxyphenyl]ethyl}biphenyl (4.22)

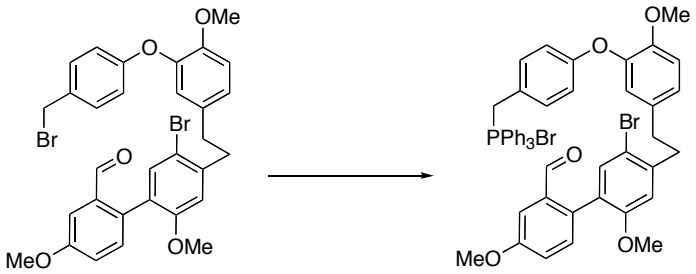


$C_{31}H_{30}O_6$
Molecular Weight: 498.57

$C_{31}H_{28}Br_2O_5$
Molecular Weight: 640.36

To a stirred solution of **3.42** (95 mg, 0.19 mmol) in glacial acetic acid (2 mL) was added a solution of bromine (34 mg, 0.23 mmol) in glacial acetic acid (1 mL). After 64 h at RT, water (2 mL) was added followed by saturated aqueous $Na_2S_2O_3$ (2 mL). The reaction mixture was extracted with DCM (3 x 10 mL), then the combined organic phases dried over $MgSO_4$ and the solvent removed *in vacuo*. The *title compound* was obtained as a colourless oil (99 mg, 81%) and was used immediately in the next step.

4-(5-[2-{5-Bromo-2,4'-dimethoxy-2-formylbiphenyl}-ethyl]-2-methoxy phenoxy)-benzyltriphenylphosphonium bromide (4.23)



$C_{31}H_{28}Br_2O_5$
Molecular Weight: 640.36

$C_{49}H_{43}Br_2O_5P$
Molecular Weight: 902.67

To a stirred solution of **4.22** (99 mg, 0.16 mmol) in toluene (10 mL) was added triphenylphosphine (81 mg, 0.31 mmol). The reaction mixture was heated at reflux for 18 h, then cooled to 0 °C and the *title compound* collected by filtration as a white solid (129 mg, 93%).

υ_{max} 3382 (br. w), 2930 (w), 2849 (w), 1689 (m), 1604 (m), 1505 (s), 1482 (m), 1438 (s), 1394 (w), 1377 (w), 1314 (w), 1270 (s), 1225 (s), 1171 (m), 1112 (s), 1041 (w), 838 (w).

δ_H (400 MHz, $CDCl_3$)
9.70 (1 H, s, CHO)
7.80–7.69 (7 H, m, 7 x ArH)
7.67–7.60 (4 H, m, 4 x ArH)
7.55–7.38 (5 H, m, 5 x ArH)
7.28–7.14 (5 H, m, 5 x ArH)
7.07–6.97 (2 H, m, 2 x ArH)
6.92 (1 H, d, *J*=7.5 Hz, ArH)
6.85–6.75 (1 H, m, ArH)
6.72 (1 H, d, *J*=8.0 Hz, ArH)
6.66 (1 H, s, ArH)
5.40 (2 H, br. s, CH_2)
3.88 (3 H, s, OCH_3)
3.80 (3 H, s, OCH_3)
3.63 (3 H, s, OCH_3)
3.04–2.83 (4 H, m, 2 x CH_2)

LRMS (ES+)	823 ([M–^{89}Br]$^+$, 100%, 821 ([M–Br]$^+$, 54%)
HRMS	$C_{49}H_{43}BrO_5P$ requires 821.2026; Found: 821.2026.

***E*-13,14-Dihydro-9,17,22-trimethoxy-3,6-etheno-15,18-bromoetheno-8,12-metheno -12*H*-7-benzooxacycloeicosine (4.24)**

$C_{49}H_{43}Br_2O_5P$
Molecular Weight: 902.67

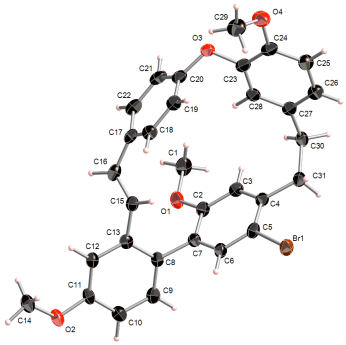
$C_{31}H_{27}BrO_4$
Molecular Weight: 543.45

To a stirred solution of NaOMe (2 mg, 0.04 mmol) in DCM (0.5 mL) was added a solution of phosphonium salt **4.23** (18 mg, 0.2 mmol) in DCM (1.5 mL) dropwise over 20 min. After 4 h, the reaction mixture was heated at reflux for 18 h, then cooled to RT, silica (~1 g) added and the solvent removed *in vacuo*. Purification by preparative thin layer chromatography (diethyl ether) afforded the *title compound* as a white crystalline solid (7.5 mg, 69%).

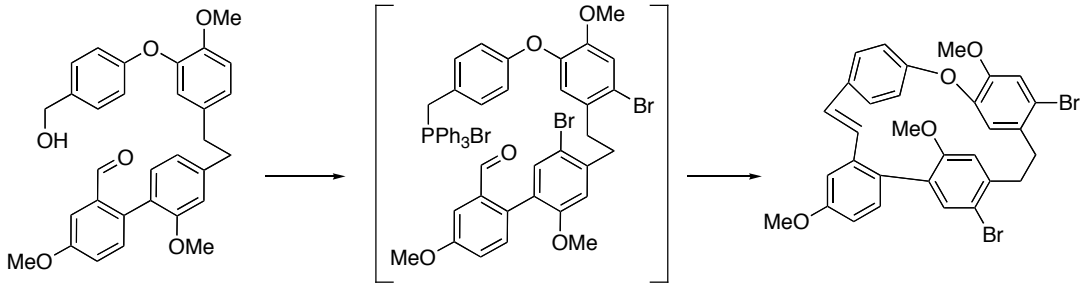
A larger scale procedure (120 mg **4.23**) gave the *title compound* in 53% yield.

MP	196–197 °C (DCM/Petroleum ether)
υ_{max}	2921 (m), 2810 (w), 2358 (m), 1505 (m), 1458 (w), 1437 (s), 1260 (m), 1217 (m), 1161 (m), 1120 (m), 1104 (m), 1028 (w), 718 (s), 693 (s), 640 (m), 542 (m), 517 (m).
δ_H (300 MHz, $CDCl_3$)	7.24 (1 H, obs. d, *J*=8.0 Hz, ArH) 7.24 (1 H, s, ArH) 7.17 (1 H, d, *J*=8.4 Hz, ArH) 7.22–7.13 (1 H, m, ArH) 7.03–6.95 (3 H, m 3 x ArH) 6.89 (1 H, d, *J*=8.1 Hz, ArH) 6.92–6.86 (1 H, m, ArH) 6.82 (1 H, d, *J*=1.8 Hz, ArH)

	6.58 (1 H, d, *J*=16.1 Hz, C**H**=CH)
	6.43 (1 H, s, ArH)
	6.10 (1 H, d, *J*=16.1 Hz, CH=C**H**)
	5.73 (1 H, d, *J*=1.8 Hz, ArH)
	3.97 (3 H, s, OCH_3)
	3.86 (3 H, s, OCH_3)
	3.56 (3 H, s, OCH_3)
	3.15–2.94 (2 H, m, CH_2)
	2.87–2.70 (2 H, m, CH_2)
δ_C (400 MHz, $CDCl_3$)	159.5 (C), 156.1 (C), 155.5 (C), 150.5 (C), 147.6 (C), 141.1 (C), 139.7 (C), 138.6 (C), 136.4 (CH), 135.5 (C), 134.9 (CH), 131.5 (CH), 130.2 (C), 130.0 (CH), 129.9 (C), 127.7 (CH), 127.5 (CH), 123.7 (CH), 122.9 (CH), 122.1 (CH), 116.0 (CH), 114.7 (C), 112.9 (CH), 112.1 (CH), 111.4 (CH), 110.8 (CH), 56.4 (OCH_3), 55.8 (OCH_3), 55.5 (OCH_3), 37.1 (CH_2), 33.21 (CH_2).
LRMS (ES+)	1107 ($[2M+Na]^+$, 23%), 843 (14%), 565 ($[M+Na]^+$, 86%), 301 (27%), 183 (71%).
HRMS	$C_{31}H_{27}BrNaO_4$ requires 565.0985; Found: 565.0970.
X-ray:	



_E_-11-Bromo-13,14-dihydro-9,17,22-trimethoxy-3,6-etheno-15,18-bromoetheno-8,12-metheno -12_H_-7-benzooxacycloeicosine (4.27)



$C_{31}H_{30}O_6$
Molecular Weight: 498.57

$C_{49}H_{42}Br_3O_5P$
Molecular Weight: 981.54

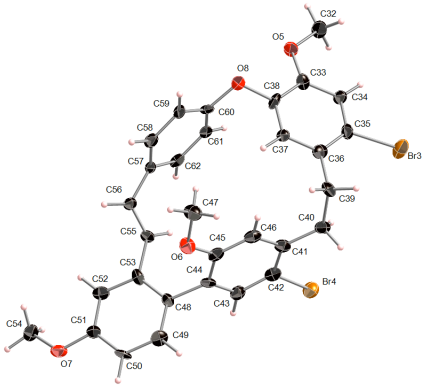
$C_{31}H_{26}Br_2O_4$
Molecular Weight: 622.34

To a stirred solution of benzyl alcohol **3.42** (279 mg, 0.56 mmol) in glacial acetic acid (5 mL) was added bromine (107 mg, 0.67 mL) dropwise over 2 min. After 18 h, aqueous $Na_2S_2O_7$ (3 mL) was added. After 30 min, the reaction mixture was extracted with DCM (2 x 5 mL). Brine (5 mL) was added to the aqueous phase which was further extracted with DCM (3 x 5 mL). The combined organic phases were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo.* ^{1}H NMR analysis of this crude mixture indicated the formation of the desired benzyl bromide. The residue was dissolved in toluene (3 mL) and triphenylphosphine (147 mg, 0.56 mmol) added. The reaction mixture was heated at reflux for 48 h, then cooled to RT and additional triphenylphosphine (294 mg, 1.2 mmol) added. The reaction was heated at reflux for a further 18 h, then cooled to RT, petroleum ether (2 mL) added, and a white precipitate obtained by trituration. Phosphonium salts **4.23** and **4.26** were collected as a white solid by filtration, washed with petroleum ether, then dissolved in DCM (10 mL). This solution was added dropwise over 2 h to a stirred solution of NaOMe (38 mg, 0.67 mmol) in DCM (2 mL). After 18 h, silica (~3 g) was added and the solvent removed *in vacuo*. Purification by flash column chromatography (9:1; petroleum ether:diethyl ether) afforded the *title compound* as a white solid (9 mg, 3%), **4.24** as a white solid (28 mg, 9%) and a mixture of **4.24** and **4.27** in an approximately 1:1 ratio (5 mg).

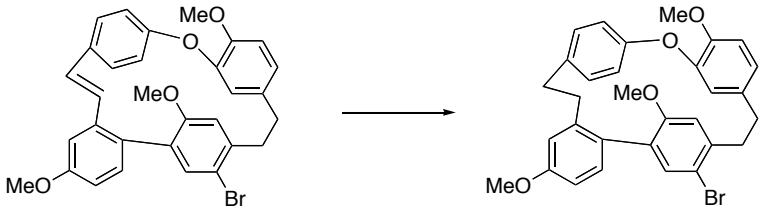
The data for **4.25** *were identical to those previously reported.*

Data for **4.27**:

MP 105–107 °C (DCM/petroleum ether)

υ_{max}	1599 (m), 1499 (s), 1464 (m), 1440 (m), 1378 (m), 1289 (m), 1258 (m), 1210 (s), 1162 (m), 1142 (m), 1045 (m), 1013 (w), 866 (w), 845 (w), 831 (w), 732 (m).
δ_H (400 MHz, $CDCl_3$)	7.24–7.14 (4 H, m, 4 x ArH) 7.14 (1 H, s, ArH) 7.02–6.98 (2 H, m, 2 x ArH) 6.92 (1 H, dd, *J*=8.9, 2.8 Hz, ArH) 6.90 (1 H, dd, *J*=8.6, 2.7 Hz, ArH) 6.63 (1 H, d, *J*=16.0 Hz, CH) 6.34 (1 H, s, ArH) 6.06 (1 H, d, *J*=16.0 Hz, CH) 5.78 (1 H, s, ArH) 3.97 (3 H, s, OCH_3) 3.89 (3 H, s, OCH_3) 3.57 (3 H, s, OCH_3) 2.64–3.23 (4 H, m, 2 x CH_2)
δ_C (100 MHz, $CDCl_3$)	159.3 (C), 155.9 (C), 155.8 (C), 149.5 (C), 148.3 (C), 141.1 (C), 139.0 (C), 138.8 (C), 136.9 (CH), 134.9 (CH), 133.6 (C), 130.9 (CH), 130.0 (C), 129.9 (CH), 129.7 (C), 127.8 (CH), 127.4 (CH), 123.3 (CH), 121.8 (CH), 118.9 (CH), 116.4 (C), 116.4 (CH), 114.5 (C), 112.8 (CH), 111.7 (CH), 110.5 (CH), 56.4 (OCH_3), 55.7 (OCH_3), 55.4 (OCH_3), 35.5 (CH_2), 34.2 (CH_2).
LRMS (ES)	644 ($[M+Na]^+$, 12%), 565 ($[M–Br+H]^+$, 17%), 413 (13%), 317 (22%), 301 (100%), 279 (17%), 268 (40%).
X-ray:	

1,2,13,14-Tetrahydro-9,17,22-trimethoxy-3,6-etheno-15,18-bromoetheno-8,12-metheno-12*H*-7-benzooxacycloeicosine (4.28)



$C_{31}H_{27}BrO_4$
Molecular Weight: 543.45

$C_{31}H_{29}BrO_4$
Molecular Weight: 545.46

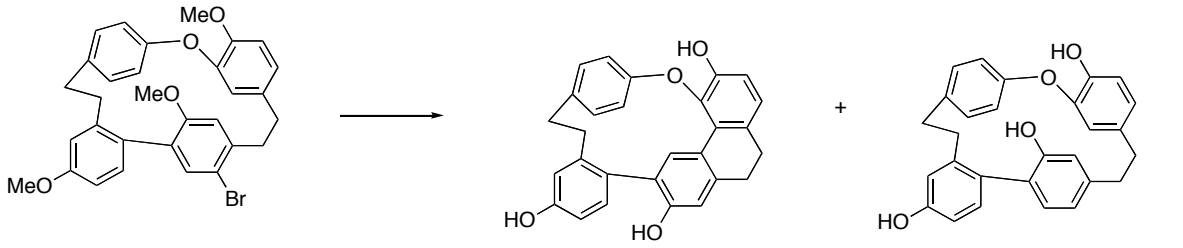
To a stirred solution of stilbene **4.24** (25 mg, 0.046 mmol) in 1:1 v/v THF and water (4 mL each) was added tosylhydrazone (86 mg, 0.46 mmol) and NaOAc (38 mg, 0.46 mmol). The reaction mixture was heated at reflux for 3 days, then cooled to RTand saturated aqueous K_2CO_3 (4 mL) added. After 3 h, the reaction mixture was extracted with DCM (3 x 10 mL), then the combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (4:1; petroleum ether:diethyl ether) afforded the *title compound* as a white foam (20 mg, 75%).

υ_{max} 2929 (m), 2849 (w), 1606 (m), 1512 (s), 1506 (s), 1481 (m), 1464 (m), 1443 (w), 1420 (w), 1375 (w), 1262 (m), 1231 (s), 1166 (m), 1129 (m), 1047 (m), 1017 (m), 851 (w), 807 (w).

δ_H (400 MHz, $CDCl_3$)
7.28 (1 H, s, ArH)
7.15 (1 H, s, ArH)
7.07 (1 H, d, *J*=8.5 Hz, ArH)
6.96 (1 H, d, *J*=2.5 Hz, ArH)
6.92–6.87 (1 H, m, ArH)
6.87–6.78 (4 H, m, 4 x ArH)
6.72 (1 H, d, *J*=8.5 Hz, ArH)
6.34 (1 H, s, ArH)
5.37 (1 H, d, *J*=2.0 Hz, ArH)
3.96 (3 H, s, OCH_3)
3.89 (3 H, s, OCH_3)
3.63 (3 H, s, OCH_3)
3.16–3.00 (2 H, m, CH_2)

	2.94–2.81 (3 H, m, CH_2)
	2.78–2.61 (3 H, m, CH_2)
δ_C (100 MHz, $CDCl_3$)	159.4 (C), 157.2 (C), 155.2 (C), 154.7 (C), 153.7 (C), 152.8 (C), 149.1 (C), 143.1 (C), 139.8 (C), 139.6 (C), 136.1 (CH), 132.6 (CH), 129.5 (CH), 129.4 (CH), 122.5 (CH), 122.0 (CH), 121.6 (CH), 115.9 (CH), 115.6 (CH), 114.7 (C), 113.7 (C), 113.6 (CH), 111.9 (CH), 111.5 (CH), 56.1 (OCH_3), 55.4 (OCH_3), 55.2 (OCH_3), 38.2 (CH_2), 37.8 (CH_2), 36.3 (CH_2), 35.4 (CH_2).
LRMS (ES+)	1111 ($[2M+Na]^+$, 10%), 599 ($[M+Na+MeOH]^+$, 39%), 583 ($[M+K]^+$, 13%), 567 ($[M+Na]^+$, 30%), 364 (18%), 356 (21%), 318 (100%).
HRMS	$C_{31}H_{29}BrNaO_4$ requires 567.1141; Found: 567.1131.

9,10,18,19-Tetrahydro-3,12,21, trihydroxy-5,8:15,17-diethenobenzo[g]-naphtha[1,8-bc]cycloteteadecine (1.4) and 1,2,13,14-Tetrahydro-9,17,22-trihydroxy-3,6:15,18-dietheno-8,12-metheno-12*H*-7-benzooxacycloeicosine (1.5)



$C_{31}H_{29}BrO_4$
Molecular Weight: 545.46

$C_{28}H_{22}O_4$
Molecular Weight: 422.47

$C_{28}H_{24}O_4$
Molecular Weight: 424.49

To a stirred solution of aryl bromide **4.28** (20 mg, 0.037 mmol) in toluene (3 mL) was added TTMSS (14 mg, 0.055 mmol) and VAZO (3 mg, 0.037 mmol). The reaction mixture was heated at reflux for 68 h then cooled and further TTMSS (68 mg, 0.28 mmol) and VAZO (3 mg, 0.037 mmol) added. The reaction mixture was heated under microwave irradiation (120 °C, 300 W) for 30 min then a further portion of VAZO (3 mg, 0.037 mmol) added and the reaction once again heated under microwave irradiation (120 °C, 300 W) for 30 min. Silica (~1 g) was added and the solvent removed *in vacuo*. Purifcation by flash column chromatography

afforded a mixture of two products (20 mg) which were dissolved in DCM (3 mL). To this stirred solution at 0 °C was added boron tribromide (0.36 mL, 1 M in DCM, 0.36 mmol) dropwise over 5 min. The reaction mixture was warmed to RT and after 18 h, ice water (3 mL) was added The aqueous phase was extracted with DCM (4 x 5 mL). The combined organic phases were dried over $MgSO_4$, silica (~1 g) was added and the solvent removed *in vacuo*. Purification by flash column chromatography (50:1, DCM:methanol) afforded firstly cavicularin **1.4** (4 mg, 26%, not clean and characterised only by ^{1}H NMR) and secondly riccardin C **1.5** (9 mg, 57%).

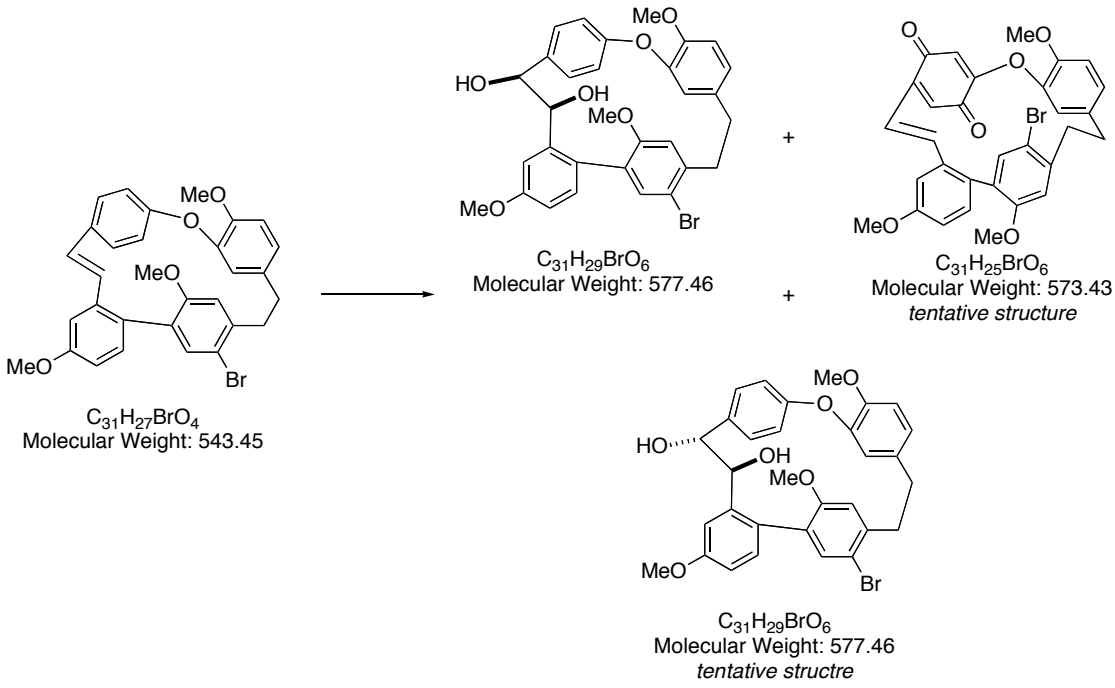
Data for cavicularin **1.4**:

δ_H (400 MHz, $CDCl_3$) 6.99 (1 H, d, *J*=8.0 Hz, ArH)
6.93 (1 H, d, *J*=8.0 Hz, ArH)
6.89 (1 H, d, *J*=2.6 Hz, ArH)
6.83 (1 H, d, *J*=8.1 Hz, ArH)
6.75 (1 H, dd, *J*=8.2, 2.6 Hz, ArH)
6.71 (1 H, dd, *J*=8.4, 2.6 Hz, ArH)
6.69 (1 H, s, ArH)
6.47 (1 H, dd, *J*=8.4, 2.2 Hz, ArH)
6.41 (1 H, s, ArH)
6.16 (1 H, dd, *J*=8.2, 2.2 Hz, ArH)
6.13–6.09 (2 H, m, ArH and OH)
5.00 (1 H, br. s, OH)
4.78 (1 H, s, OH)
3.02–2.88 (2 H, m, 2 x C**H**H)
2.81–2.49 (5 H, m, 5 x C**H**H)
2.37–2.22 (1 H, m, C**H**H)

These data are in accordance with the literature.[57]

The data for riccardin C **1.5** *were identical to those previously recorded.*

rel-(1*S*,2*S*)-13,14-Dihydro-1,2-dihydroxy-9,17,22-trimethoxy-3,6-etheno-15,18-bromoetheno-8,12-metheno -12*H*-7-benzooxacycloeicosine (4.29) and _rel_-(1*R*,2*S*)-13,14-Dihydro-1,2-dihydroxy-9,17,22-trimethoxy-3,6-etheno-15,18-bromoetheno-8,12-metheno -12*H*-7-benzooxacycloeicosine (4.31) and (4.30)



To AD mix α (39 mg) was added water (2 mL) and *tert*-butanol (2 mL). The reaction mixture was stirred vigorously for 30 min until two distinct phases formed. The reaction mixture was then cooled to 0 °C and methanesulfonamide (2.6 mg, 0.028 mmol) and a solution of stilbene **4.24** (15 mg, 0.028 mmol in 0.5 mL THF) were added. After 24 h at 0 °C–5 °C, saturated aqueous Na_2CO_3 (5 mL) was added and the reaction mixture extracted with DCM (5 x 5 mL). The combined organic phases were washed with NaOH (2 M, 20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography afforded firstly *title compound* **4.30** (3 mg, 18%, *tentative structure*), then *title compound* **4.29** (10 mg, 62%) contaminated with bis-aldehyde **4.1** (~10% of sample), and finally *title compound* **4.31** (2 mg, 12%, *tentative structure*).

Data for **4.30** *tentative structure*:

υ_{max} 2922 (m), 2849 (w), 1669 (m), 1601 (m), 1581 (w), 1516 (m), 1502 (w), 1477 (m), 1463 (w), 1417 (w), 1371 (w), 1264 (s), 1230 (s), 1196 (w), 1159 (s), 1128 (s), 1034 (m), 1013 (w), 908 (w), 820 (w), 730 (m).

δ_H (400 MHz, $CDCl_3$)	7.92 (2 H, br. s, 2 x CH)
	7.44 (1 H, d, *J*=3.0 Hz, ArH)
	7.29 (1 H, obsc., ArH)
	7.14 (1 H, dd, *J*=8.5, 3.0 Hz, ArH)
	7.03 (1 H, d, *J*=8.5 Hz, ArH)
	6.90 (1 H, d, *J*=8.0 Hz, ArH)
	6.84 (1 H, dd, *J*=8.0, 2.3 Hz, ArH)
	6.28 (1 H, s, ArH)
	5.63 (1 H, d, *J*=2.3 Hz, ArH)
	5.31 (2 H, s, 2 x CH)
	3.98 (3 H, s, OCH_3)
	3.94 (3 H, s, OCH_3)
	3.53 (3 H, s, OCH_3)
	3.06–2.81 (4 H, m, 2 x CH_2)
δ_C (100 MHz, $CDCl_3$)	181.8 (2 x C), 161.8 (C), 159.5 (C), 156.5 (C), 147.0 (C), 146.5 (C), 141.7 (C), 138.1 (C), 135.6 (CH), 134.1 (C), 133.2 (CH), 127.7 (C), 123.1 (C), 122.6 (CH), 119.7 (CH), 115.9 (CH), 115.4 (C), 113.4 (CH), 112.4 (CH), 111.0 (CH), 108.3 (C), 56.4 (OCH_3), 55.8 (OCH_3), 55.7 (OCH_3), 35.8 (CH_2), 33.2 (CH_2).
LRMS (ES+)	595 (18%), 309 (100%).
HRMS	$C_{31}H_{25}BrO_6Na$ requires 595.0732; Found: 595.0691.

Data for **4.29**:

υ_{max}	3432 (br. w), 2930 (m), 2357 (w), 1608 (w), 1506 (s), 1478 (m), 1464 (m), 1261 (m), 1230 (s), 1163 (m), 1039 (m).
δ_H (400 MHz, $CDCl_3$)	*Peaks attributed to product*
	7.56 (1 H, dd, *J*=8.8, 1.8 Hz, ArH)
	7.38–7.34 (1 H, m, ArH)
	7.22 (1 H, s, ArH)
	7.12 (1 H, d, *J*=8.5 Hz, ArH)
	7.02 (1 H, dd, *J*=8.5, 2.5 Hz, ArH)

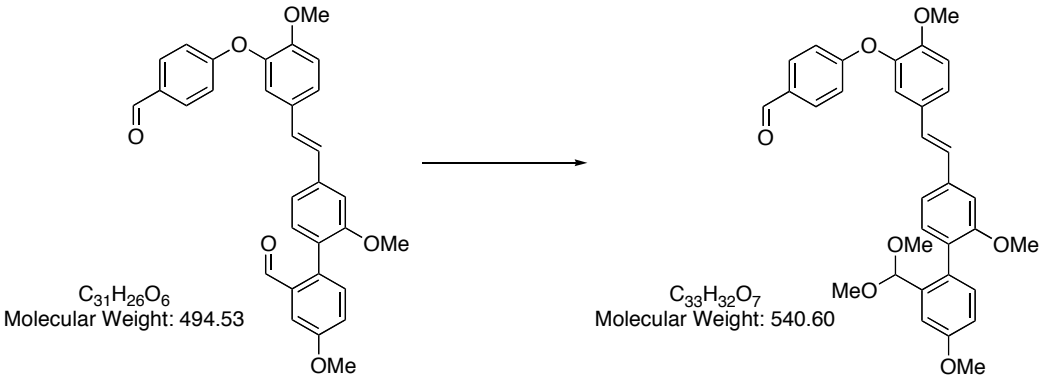
	6.92 (1 H, s, ArH)
	6.89 (1 H, dd, *J*=9.0, 3.0 Hz, ArH)
	6.83 (1 H, dd, *J*=8.0, 2.0 Hz, ArH)
	6.65–6.61 (1 H, m, ArH)
	6.60–6.55 (1 H, m, ArH)
	5.96 (1 H, s, ArH)
	5.40 (1 H, d, *J*=2.0 Hz, ArH)
	4.83 (1 H, d, *J*=8.5 Hz, CH)
	4.76 (1 H, d, *J*=8.5 Hz, CH)
	3.95 (3 H, s, OCH_3)
	3.92 (3 H, s, OCH_3)
	3.49 (3 H, s, OCH_3)
	3.36–3.28 (1 H, m, C**H**H)
	3.12 (1 H, br. s, OH)
	2.91–2.83 (1 H, m, C**H**H)
	2.70–2.61 (1 H, m, C**H**H)
	2.37 (1 H, td, *J*=12.9, 2.3 Hz, C**H**H)
	N.B. One OH not identified.
δ_C (100 MHz, $CDCl_3$)	159.9 (C), 155.0 (C), 154.0 (C), 148.5 (C), 147.4 (C), 141.2 (C), 139.8 (C), 138.0 (C), 134.4 (CH), 133.7 (CH), 133.6 (C), 128.6 (C), 128.4 (CH), 128.1 (C), 125.0 (CH), 123.9 (CH), 122.4 (CH), 121.6 (CH), 121.1 (CH), 117.0 (CH), 116.2 (CH), 114.1 (CH), 113.8 (C), 112.8 (CH), 112.5 (CH), 77.1 (CHOH), 74.2 (CHOH), 56.6 (OCH_3), 55.8 (OCH_3), 55.6 (OCH_3), 39.0 (CH_2), 35.0 (CH_2).
LRMS (ES+)	1177 ($[2M+Na]^+$, 10%), 599 ($[M+Na]^+$, 100%)

Data for **4.31** *tentative structure*:

υ_{max}	3483 (br. w), 2922 (s), 2851 (m), 1607 (w), 1507 (m), 1482 (w), 1464 (w), 1375 (w), 1261 (m), 1230 (s), 1164 (w), 1128 (w), 1045 (m).
δ_H (400 MHz, $CDCl_3$)	7.61 (1 H, dd, *J*=8.5, 2.0 Hz, ArH)
	7.36 (1 H, d, *J*=2.5 Hz, ArH)

	7.32–7.28 (1 H, m, ArH)
	7.08–7.04 (1 H, m, ArH)
	7.03–6.95 (3 H, m, 3 x ArH)
	6.88 (1 H, d, *J*=8.0 Hz, ArH)
	6.80 (1 H, dd, *J*=8.0, 2.0 Hz, ArH)
	6.77 (1 H, dd, *J*=8.0, 2.5 Hz, ArH)
	6.64 (1 H, s, ArH)
	6.39 (1 H, dd, *J*=8.3, 2.3 Hz, ArH)
	5.33 (1 H, d, *J*=2.0 Hz, ArH)
	4.90 (1 H, d, *J*=8.5 Hz, CH)
	4.37 (1 H, d, *J*=8.5 Hz, CH)
	3.95 (3 H, s, OCH_3)
	3.93 (3 H, s, OCH_3)
	3.74 (3 H, s, OCH_3)
	3.01–2.84 (5 H, m, 5 x C**H**H)
	2.77 (1 H, br. s, OH)
	2.48 (1 H, td, *J*=12.7, 3.3 Hz, C**H**H)
	2.28 (1 H, s, OH)
δ_C	Could not be obtained.
LRMS (ES+)	1177 ($[2M+Na]^+$, 6%), 599 ($[2M+2Na]^{2+}$, 29%), 183 (100%).
HRMS	$C_{31}H_{27}BrO_6Na$ requires: 597.0883; Found: 597.0859. *N.B. High resolution spectrum appears to indicate doubly charged dimer.*

4-(3-{2-[(3,4'-Dimethyoxy-6'-dimethoxymethyl)biphenyl]-vinyl}-4-methoxy)-phenoxybenzaldehyde (5.1)



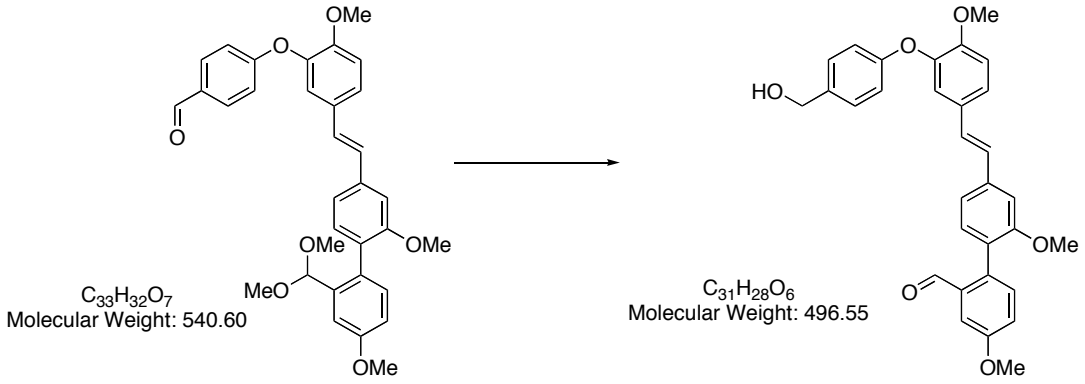
To a stirred solution of bis-aldehyde **2.9** (480 mg, 0.97 mmol) in methanol (10 mL) and DCM (10 mL) was added 10% palladium on carbon (48 mg). The flask was evacuated/purged with argon three times then evacuated/purged with hydrogen twice. After 3 h, the atmosphere of hydrogen was removed and the reaction left under an atmosphere of argon. After 17 h, the reaction mixture was filtered through Celite® and concentrated *in vacuo*. Purification by flash column chromatography afforded the *title compound* (304 mg, 58%) as a waxy yellow solid.

N.B. The palladium on carbon reagent was subsequently found to be unsuccessful in other hydrogenation procedures in the group.

δ_H (400 MHz, $CDCl_3$) 9.83 (1 H, s, CHO)
7.76 (2 H, d, *J*=9.0 Hz, 2 x ArH)
7.30 (1 H, dd, *J*=8.5, 2.5 Hz, ArH)
7.24 (1 H, d, *J*=2.5 Hz, ArH)
7.14 (1 H, d, *J*=2.5 Hz, ArH)
7.05 (2 H, d, *J*=1.5 Hz, ArH)
6.98–6.93 (7 H, m, 5 x ArH and CH=CH)
6.83 (1 H, dd, *J*=8.5, 3.0 Hz, ArH)
4.97 (1 H, s, C**H**$(OMe)_2$)
3.77 (3 H, s, OCH_3)
3.73 (3 H, s, OCH_3)
3.70 (3 H, s, OCH_3)
3.21 (3 H, s, OCH_3)
3.07 (3 H, s, OCH_3)

δ_c (100 MHz, $CDCl_3$)	190.7 (CHO), 163.4 (C), 159.0 (C), 156.8 (C), 151.3 (C), 143.1 (C), 138.0 (C), 137.8 (C), 131.8 (2 x CH), 131.4 (CH), 131.2 (C), 131.0 (C), 129.8 (C), 128.8 (C), 127.8 (CH), 127.3 (CH), 124.9 (CH), 120.0 (CH), 118.7 (CH), 116.2 (2 x CH), 114.5 (CH), 113.1 (CH), 110.6 (CH), 109.5 (CH), 108.3 (CH), 102.4 (OCHO), 56.0 (OCH_3), 55.4 (OCH_3), 55.3 (OCH_3), 54.4 (OCH_3), 53.5 (OCH_3).
LRMS (ES+)	1103 ($[2M+Na]^+$, 32%), 563 ($[M+Na]^+$, 100%).
HRMS	Sample decomposed before HRMS could be obtained.

5-[2-(2,4'-Dimethoxy-2'-formyl)-4-biphenyl-vinyl]-2-methoxy-phenoxybenzyl alcohol (5.2)

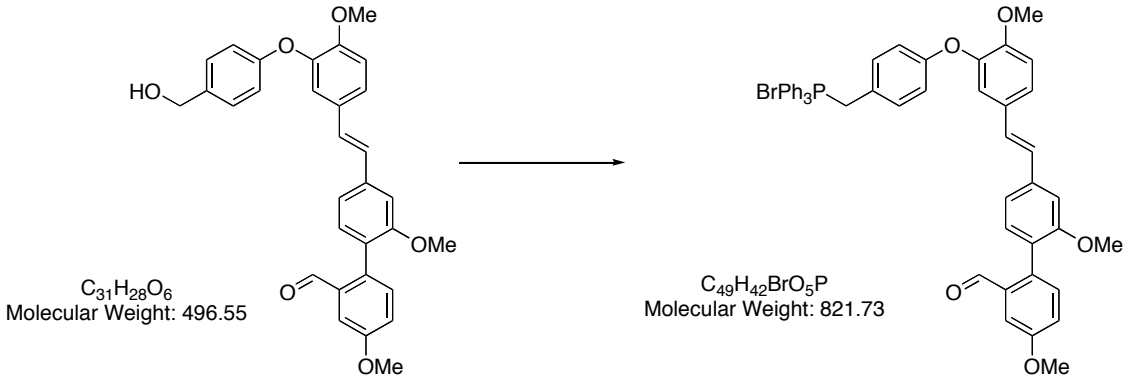


To a stirred solution of acetal **5.1** (250 mg, 0.46 mmol) in THF (5 mL) at –78 °C was added $NaBH_4$ (5 mg, 0.13 mmol + 4 mg, 0.11 mmol) in two portions over 5 min. The reaction mixture was warmed to RT and after 3 h, further $NaBH_4$ (9 mg, 0.24 mmol) was added. After 18 h, HCl (2 M, 2 mL) was added and after a further 30 min the reaction mixture was extracted with DCM (2 x 15 mL). The combined organic phases were dried over $MgSO_4$ and the solvent removed *in vacuo* to afford the *title compound* (217 mg, 95%) as a white crystalline solid.

MP	74–75 °C (DCM/Petrol)
υ_{max}	3420 (br., w), 2948 (w), 2804 (w), 1687 (m), 1602 (m), 1505 (s), 1488 (m), 1423 (w), 1270 (s), 1223 (s), 1192

	(w), 1164 (m), 1126 (w), 1032 (m), 1001 (w), 910 (w), 819 (m), 731 (m).
δ_H (300 MHz, $CDCl_3$)	9.77 (1 H, s, CHO) 7.50 (1 H, d, *J*=2.9 Hz, ArH) 7.38–6.90 (14 H, m, 12 x ArH and CH=CH) 4.68 (2 H, s, CH_2) 3.90 (3 H, s, OCH_3) 3.88 (3 H, s, OCH_3) 3.78 (3 H, s, OCH_3)
δ_C (75 MHz, $CDCl_3$)	192.4 (CHO), 159.1 (C), 157.4 (C), 156.8 (C), 151.3 (C), 145.2 (C), 139.0 (C), 135.1 (C), 134.9 (C), 134.3 (C), 132.4 (CH), 131.7 (CH), 130.6 (C), 128.6 (2 x CH), 128.3 (CH), 126.9 (CH), 125.8 (C), 123.5 (CH), 121.2 (CH), 119.2 (CH), 118.6 (CH), 117.3 (2 x CH), 112.9 (CH), 109.4 (CH), 108.2 (CH), 64.9 (CH_2), 56.1 (OCH_3), 55.5 (OCH_3), 55.4 (OCH_3).
LRMS	1116 ($[2M+Na]^+$, 37%), 519 ($[M+Na]^+$, 100%), 227 (17%), 192 (32%), 183 (26%), 151 (38%), 133 (16%).

4-{5-[2-(2,4'-Dimethoxy-2'-formylbiphen-4-yl)-vinyl]-2-methoxyphenoxy}-benzyltriphenylphosphonium bromide (5.3)



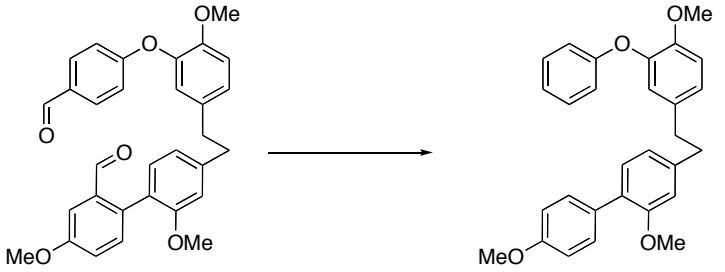
To a stirred solution of benzyl alcohol **5.2** (100 mg, 0.20 mmol) in toluene (5 mL) at 0 °C was added a solution of phosphorus tribromide (18 mg, 0.067 mmol) in toluene (1 mL) dropwise over 5 min. The reaction mixture was warmed to RT then

after 19 h DCM (5 mL) was added and the reaction mixture washed with saturated aqueous $NaHCO_3$ (10 mL). The organic phase was extracted with DCM (2 x 10 mL) and the combined organic phases washed with brine (20 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was dissolved in toluene (10 mL) and triphenylphosphine (53 mg, 0.20 mmol) added. The reaction mixture was heated at reflux for 19 h then cooled to 0 °C. The resultant precipitate was collected by filtration and washed with petroleum either, yielding the *title compound* as a white crystalline solid (59 mg, 33%).

MP	>250°C
υ_{max}	3368 (br. w), 3010 (w), 2935 (w), 2839 (w), 1686 (m), 1603 (m), 1572 (w), 1504 (s), 1487 (m), 1463 (w), 1439 (m), 1317 (w), 1271 (s), 1225 (s), 1165 (m), 1112 (m), 1031 (m), 999 (w), 934 (w), 837 (m), 728 (m), 690 (m).
δ_H (400 MHz, $CDCl_3$)	9.75 (1 H, s, CHO) 7.81–7.72 (10 H, m, 10 x ArH) 7.64 (7 H, m, 7 x ArH) 7.49 (1 H, d, *J*=2.5 Hz, ArH) 7.30–7.27 (1 H, m obsc., ArH) 7.24–6.98 (8 H, m, 6 x ArH and CH=CH) 6.96 (1 H, d, *J*=4.0 Hz, ArH) 6.78 (2 H, d, *J*=8.5 Hz, 2 x ArH) 5.46 (2 H, d, *J*=14.1 Hz, CH_2) 3.89 (3 H, s, OCH_3) 3.84 (3 H, s, OCH_3) 3.77 (3 H, s, OCH_3)
δ_C (100 MHz, $CDCl_3$)	192.4 (CHO), 158.2 (C), 157.9 (C), 156.8 (C), 151.0 (C), 144.8 (C), 139.0 (C), 134.9 (CH), 134.9 (C), 134.5 (4 x CH), 134.4 (4 x CH), 132.9 (CH), 132.4 (CH), 131.8 (CH), 130.7 (C), 130.2 (4 x CH), 130.2 (4 x CH), 128.2 (CH), 127.1 (CH), 125.8 (C), 123.7 (CH), 125.8 (C), 123.7 (CH), 121.1 (CH), 121.0 (C), 120.9 (C), 119.2 (CH), 118.5 (CH), 118.4 (C), 117.7 (CH), 117.5 (C),

	112.8 (CH), 109.5 (CH), 108.3 (CH), 56.1 (OCH_3), 55.5 (OCH_3), 55.5 (OCH_3).
LRMS (ES+)	741 ([M–Br]$^+$, 25%), 521 (20%), 277 (81%), 268 (32%), 128 (100%).
HRMS	$C_{49}H_{42}O_5P$ requires 741.2764; Found: 741.2763.

2',4-Dimethoxy-4'-{2-[3-phenoxy-4-methoxyphenyl]-ethyl}-biphenyl (5.6)



$C_{31}H_{28}O_6$
Molecular Weight: 496.55

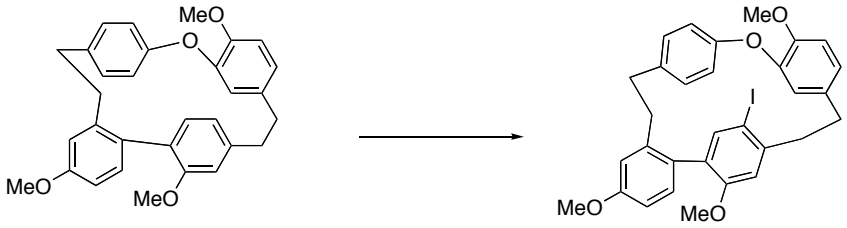
$C_{29}H_{28}O_4$
Molecular Weight: 440.53

To a stirred solution of bis-aldehyde **2.9** (100 mg, 0.20 mmol) in propan-2-ol (5 mL) was added 5% palladium on carbon (500 mg). The reaction mixture was heated at reflux for 19 h, then cooled to RT, filtered and the solvent removed *in vacuo* to afford the *title compound* (80 mg, 90%) as a colourless oil.

υ_{max}	2950 (w), 2845 (w), 1690 (m), 1598 (m), 1501 (s), 1270 (s), 1225 (s), 1191 (m), 1154 (s), 1121 (m), 1088 (m), 1035 (m), 962 (w), 819 (m), 727 (s).
δ_H (400 MHz, $CDCl_3$)	7.54 (2 H, d, *J*=8.8 Hz, 2 x ArH) 7.30 (1 H, d, *J*=7.7 Hz, ArH) 7.20 (1 H, d, *J*=7.7 Hz, ArH) 7.09–6.99 (2 H, m, ArH) 6.99–6.90 (6 H, m, 4 x ArH) 6.85 (1 H, d, *J*=1.8 Hz, ArH) 6.80 (1 H, dd, *J*=7.7, 1.5 Hz, ArH) 6.72 (1 H, d, *J*=1.8 Hz, ArH) 3.85 (3 H, s, OCH_3) 3.83 (3 H, s, OCH_3)

	3.77 (3 H, s, OCH_3)
	2.89 (4 H, app. s, 2 x CH_2)
δ_C (100 MHz, $CDCl_3$)	158.5 (C), 158.0 (C), 156.3 (C), 144.7 (C), 141.9 (C), 134.8 (C), 130.5 (2 x CH), 130.5 (CH), 129.5 (2 x CH), 124.6 (CH), 122.3 (CH), 121.3 (CH), 120.8 (CH), 117.1 (2 x CH), 113.5 (2 x CH). 112.8 (CH), 111.6 (CH), 56.2 (OCH_3), 55.5 (OCH_3), 55.3 (OCH_3), 38.0 (CH_2), 36.9 (CH_2). *N.B. Three aromatic quaternary centres are not observed.*
LRMS (ES+)	903 ($[2M+Na]^+$, 3%), 463 ($[M+Na]^+$, 34%), 133 (100%).

1,2,13,14-Tetrahydro-9,17,22-trimethoxy-3,6-etheno-15,18-iodoetheno-8,12-metheno-12*H*-7-benzooxacycloeicosine (1.213)



$C_{31}H_{30}O_4$
Molecular Weight: 466.57

$C_{31}H_{29}IO_4$
Molecular Weight: 592.46

To a stirred solution of **1.88** (10 mg, 0.022 mmol) in acetonitrile (3 mL) was added *N*-iodosuccinimide (5 mg, 0.23 mmol) and CF_3COOH (trace). After 68 h, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (9:1 petroleum ether:diethyl ether) to afford the title compound as a colourless film (2 mg, 16%). The remaining mass balance comprised poly iodinated products.

The data were identical to those previously reported.

Chapter 8: References

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Table 1. Crystal data and structure refinement.

Identification code	**2007sot0937**	
Empirical formula	$C_{15}H_{15}BrO_4S$	
Formula weight	371.24	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = **13.0954(6) Å**	α = **90°**
	b = **8.9930(3) Å**	β = 10**4.561(2)°**
	c = **13.2468(5) Å**	γ = **90°**
Volume	1509.93(10) Å^3	
Z	4	
Density (calculated)	1.633 Mg / m^3	
Absorption coefficient	2.873 mm-**1**	
$F(000)$	752	
Crystal	Block; Colourless	
Crystal size	0.30 × 0.30 × 0.04 mm^3	
θ range for data collection	3.18 – 27.48°	
Index ranges	$-16 \le h \le 16$, $-11 \le k \le 11$, $-17 \le l \le 17$	
Reflections collected	17591	
Independent reflections	3444 [R_{int} = 0.0510]	
Completeness to θ = 27.48°	99.8 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.8938 and 0.4795	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3444 / 0 / 193	
Goodness-of-fit on F^2	1.048	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0349, $wR2$ = 0.0735	
R indices (all data)	$R1$ = 0.0523, $wR2$ = 0.0805	
Extinction coefficient	0.0037(5)	
Largest diff. peak and hole	0.645 and –0.588 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). S**tructure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure 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:

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Br1	3419(1)	393(1)	6423(1)	26(1)	1
S1	3395(1)	−4643(1)	6053(1)	17(1)	1
O1	3425(2)	−5361(2)	7021(1)	25(1)	1
O2	3703(2)	−5451(2)	5246(2)	26(1)	1
O3	4150(1)	−3262(2)	6379(1)	18(1)	1
O4	8012(1)	−709(2)	6655(1)	23(1)	1
C1	4859(2)	72(3)	6476(2)	19(1)	1
C2	5176(2)	−1213(3)	6052(2)	16(1)	1
C3	6243(2)	−1420(3)	6125(2)	17(1)	1
C4	6986(2)	−367(3)	6620(2)	17(1)	1
C5	6660(2)	915(3)	7037(2)	20(1)	1
C6	5591(2)	1130(3)	6959(2)	20(1)	1
C7	4411(2)	−2391(3)	5532(2)	18(1)	1
C8	2149(2)	−3865(3)	5539(2)	17(1)	1
C9	1734(2)	−2867(3)	6139(2)	19(1)	1
C10	730(2)	−2312(3)	5743(2)	22(1)	1
C11	122(2)	−2724(3)	4759(2)	22(1)	1
C12	551(2)	−3723(3)	4180(2)	26(1)	1
C13	1558(2)	−4292(3)	4554(2)	23(1)	1
C14	−977(2)	−2114(3)	4340(2)	33(1)	1
C15	8809(2)	280(3)	7233(2)	30(1)	1

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

Br1–C1	1.892(3)
S1–O1	1.4281(19)
S1–O2	1.4318(19)
S1–O3	1.5787(17)
S1–C8	1.748(2)
O3–C7	1.477(3)
O4–C4	1.367(3)
O4–C15	1.437(3)
C1–C6	1.387(4)
C1–C2	1.393(3)
C2–C3	1.389(3)
C2–C7	1.501(3)
C3–C4	1.398(3)
C3–H3	0.9500
C4–C5	1.392(4)
C5–C6	1.391(4)
C5–H5	0.9500
C6–H6	0.9500
C7–H7A	0.9900
C7–H7B	0.9900
C8–C13	1.393(3)
C8–C9	1.396(3)
C9–C10	1.380(4)
C9–H9	0.9500
C10–C11	1.396(3)
C10–H10	0.9500
C11–C12	1.388(4)
C11–C14	1.509(4)
C12–C13	1.385(4)
C12–H12	0.9500
C13–H13	0.9500
C14–H14A	0.9800
C14–H14B	0.9800
C14–H14C	0.9800
C15–H15A	0.9800
C15–H15B	0.9800
C15–H15C	0.9800
O1–S1–O2	119.49(12)
O1–S1–O3	103.63(10)
O2–S1–O3	109.18(10)
O1–S1–C8	110.06(12)
O2–S1–C8	108.86(12)
O3–S1–C8	104.52(10)
C7–O3–S1	117.27(14)
C4–O4–C15	117.1(2)
C6–C1–C2	120.9(2)
C6–C1–Br1	118.63(19)
C2–C1–Br1	120.44(19)
C3–C2–C1	118.7(2)
C3–C2–C7	118.7(2)
C1–C2–C7	122.6(2)
C2–C3–C4	120.8(2)
C2–C3–H3	119.6
C4–C3–H3	119.6
O4–C4–C5	124.7(2)
O4–C4–C3	115.2(2)
C5–C4–C3	120.0(2)
C6–C5–C4	119.3(2)
C6–C5–H5	120.4
C4–C5–H5	120.4

C1–C6–C5	120.3(2)
C1–C6–H6	119.8
C5–C6–H6	119.8
O3–C7–C2	106.30(18)
O3–C7–H7A	110.5
C2–C7–H7A	110.5
O3–C7–H7B	110.5
C2–C7–H7B	110.5
H7A–C7–H7B	108.7
C13–C8–C9	120.4(2)
C13–C8–S1	119.9(2)
C9–C8–S1	119.63(18)
C10–C9–C8	119.1(2)
C10–C9–H9	120.5
C8–C9–H9	120.5
C9–C10–C11	121.6(2)
C9–C10–H10	119.2
C11–C10–H10	119.2
C12–C11–C10	118.2(2)
C12–C11–C14	120.8(2)
C10–C11–C14	121.0(3)
C13–C12–C11	121.5(2)
C13–C12–H12	119.2
C11–C12–H12	119.2
C12–C13–C8	119.2(2)
C12–C13–H13	120.4
C8–C13–H13	120.4
C11–C14–H14A	109.5
C11–C14–H14B	109.5
H14A–C14–H14B	109.5
C11–C14–H14C	109.5
H14A–C14–H14C	109.5
H14B–C14–H14C	109.5
O4–C15–H15A	109.5
O4–C15–H15B	109.5
H15A–C15–H15B	109.5
O4–C15–H15C	109.5
H15A–C15–H15C	109.5
H15B–C15–H15C	109.5

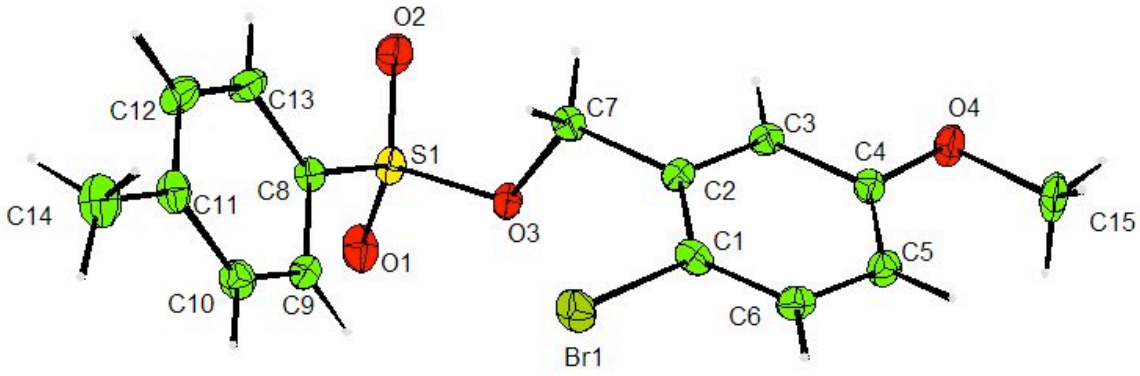
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br1	20(1)	26(1)	34(1)	−2(1)	10(1)	5(1)
S1	14(1)	14(1)	22(1)	0(1)	3(1)	0(1)
O1	22(1)	23(1)	28(1)	9(1)	2(1)	−2(1)
O2	22(1)	20(1)	37(1)	−10(1)	9(1)	0(1)
O3	16(1)	18(1)	18(1)	1(1)	2(1)	−3(1)
O4	15(1)	22(1)	31(1)	−6(1)	3(1)	−3(1)
C1	21(1)	18(1)	19(1)	6(1)	7(1)	4(1)
C2	18(1)	13(1)	14(1)	2(1)	2(1)	0(1)
C3	20(1)	16(1)	15(1)	1(1)	4(1)	1(1)
C4	17(1)	16(1)	16(1)	2(1)	3(1)	−1(1)
C5	23(1)	18(1)	20(1)	0(1)	5(1)	−4(1)
C6	28(1)	14(1)	19(1)	0(1)	7(1)	0(1)
C7	17(1)	19(1)	18(1)	3(1)	4(1)	1(1)
C8	16(1)	16(1)	18(1)	0(1)	4(1)	−1(1)
C9	18(1)	21(1)	19(1)	−4(1)	4(1)	−3(1)
C10	20(1)	20(1)	26(1)	0(1)	7(1)	1(1)
C11	17(1)	22(1)	25(1)	5(1)	3(1)	0(1)
C12	24(1)	32(2)	18(1)	−2(1)	−2(1)	−2(1)
C13	24(1)	24(1)	19(1)	−6(1)	3(1)	−1(1)
C14	20(2)	36(2)	40(2)	6(1)	1(1)	5(1)
C15	15(1)	29(2)	43(2)	−9(1)	4(1)	−8(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

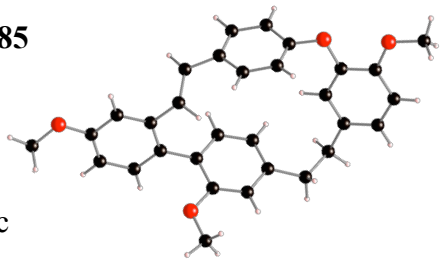
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H3	6470	−2288	5835	21	1
H5	7162	1636	7372	24	1
H6	5361	2005	7238	24	1
H7A	3767	−1933	5085	21	1
H7B	4735	−3038	5093	21	1
H9	2137	−2575	6810	23	1
H10	447	−1632	6150	27	1
H12	144	−4023	3512	31	1
H13	1842	−4965	4144	27	1
H14A	−951	−1263	3885	50	1
H14B	−1262	−1794	4921	50	1
H14C	−1431	−2888	3940	50	1
H15A	8702	1275	6923	44	1
H15B	9507	−90	7212	44	1
H15C	8761	328	7959	44	1



UNIVERSITY OF Southampton
School of Chemistry

Single Crystal X-Ray Diffraction Service
School of Chemistry - University of Southampton
Contact: Dr Mark E Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.



Identification code	**2009sot0385**
Empirical formula	$C_{31}H_{28}O_4$
Formula weight	464.53
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 12.2830(4) Å
	b = 12.1806(6) Å β = 106.521(2)°
	c = 16.4851(7) Å
Volume	2364.58(17) Å^3
Z	4
Density (calculated)	1.305 Mg / m^3
Absorption coefficient	0.085 mm^{-1}
$F(000)$	984
Crystal	Fragment; Colourless
Crystal size	0.1 × 0.07 × 0.02 mm^3
θ range for data collection	2.95 – 25.03°
Index ranges	$-14 \le h \le 14$, $-14 \le k \le 14$, $-19 \le l \le 18$
Reflections collected	25371
Independent reflections	4177 [R_{int} = 0.1505]
Completeness to θ = 25.03°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9983 and 0.9815
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4177 / 0 / 327
Goodness-of-fit on F^2	1.013
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.1071, $wR2$ = 0.2060
R indices (all data)	$R1$ = 0.1843, $wR2$ = 0.2497
Largest diff. peak and hole	0.306 and –0.326 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **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**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **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: All hydrogen atoms were placed in idealised positions and refined using a riding model, except those of the ethylenic group which were freely refined.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 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.*
O1	13978(4)	–1468(4)	–1971(3)	36(1)	1
O2	15676(3)	–2728(3)	–2005(3)	33(1)	1
O3	12683(3)	1084(3)	2485(2)	29(1)	1
O4	9012(3)	4389(3)	556(3)	31(1)	1
C1	14373(5)	–2164(5)	–1296(3)	26(1)	1
C2	15277(5)	–2844(5)	–1316(4)	25(1)	1
C3	15721(5)	–3558(5)	–644(4)	28(1)	1
C4	15212(5)	–3621(5)	7(4)	31(2)	1
C5	14268(5)	–3007(5)	14(4)	30(1)	1
C6	13862(5)	–2264(5)	–653(4)	31(2)	1
C7	16531(5)	–3466(5)	–2083(4)	35(2)	1
C8	13682(6)	–3198(5)	700(4)	35(2)	1
C9	13874(5)	–2335(5)	1398(4)	31(1)	1
C10	13100(5)	–1336(5)	1251(3)	25(1)	1
C11	13297(5)	–559(5)	1897(4)	28(1)	1
C12	12590(5)	335(5)	1861(3)	24(1)	1
C13	11668(5)	511(5)	1129(4)	25(1)	1
C14	11494(4)	–265(5)	484(3)	24(1)	1
C15	12176(5)	–1196(5)	557(3)	24(1)	1
C16	13640(5)	986(6)	3218(4)	38(2)	1
C17	10967(4)	1526(5)	1005(3)	22(1)	1
C18	10224(5)	1749(5)	1486(4)	27(1)	1
C19	9553(5)	2689(5)	1354(4)	29(1)	1
C20	9620(5)	3435(5)	732(4)	26(1)	1
C21	10341(5)	3215(5)	235(4)	29(1)	1
C22	11002(4)	2275(5)	358(3)	24(1)	1
C23	8374(5)	4708(6)	1111(4)	37(2)	1
C24	11760(5)	1982(5)	–159(4)	27(1)	1
C25	11504(5)	1881(5)	–1001(4)	29(1)	1
C26	12217(5)	1203(5)	–1385(4)	32(2)	1
C27	11706(5)	500(5)	–2051(4)	34(2)	1
C28	12296(5)	–371(5)	–2256(4)	32(2)	1
C29	13415(5)	–543(5)	–1807(4)	27(1)	1
C30	13980(5)	213(5)	–1210(4)	31(2)	1
C31	13379(5)	1084(5)	–987(4)	32(2)	1

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

O1–C1	1.373(7)
O1–C29	1.388(7)
O2–C2	1.366(7)
O2–C7	1.415(7)
O3–C12	1.356(7)
O3–C16	1.430(7)
O4–C20	1.368(7)
O4–C23	1.417(7)
C1–C6	1.382(8)
C1–C2	1.393(8)
C2–C3	1.393(8)
C3–C4	1.389(8)
C4–C5	1.383(8)
C5–C6	1.403(8)
C5–C8	1.520(8)
C8–C9	1.528(8)
C9–C10	1.520(8)
C10–C15	1.373(8)
C10–C11	1.394(8)
C11–C12	1.383(8)
C12–C13	1.417(8)
C13–C14	1.393(8)
C13–C17	1.487(8)
C14–C15	1.394(8)
C17–C18	1.395(8)
C17–C22	1.413(8)
C18–C19	1.391(8)
C19–C20	1.390(8)
C20–C21	1.393(8)
C21–C22	1.385(8)
C22–C24	1.475(8)
C24–C25	1.339(8)
C25–C26	1.471(8)
C26–C27	1.393(9)
C26–C31	1.398(8)
C27–C28	1.381(8)
C28–C29	1.380(8)
C29–C30	1.382(9)
C30–C31	1.399(9)

C1–O1–C29	115.1(4)
C2–O2–C7	117.4(5)
C12–O3–C16	117.1(5)
C20–O4–C23	117.7(5)
O1–C1–C6	122.9(5)

O1–C1–C2	116.6(5)
C6–C1–C2	120.3(5)
O2–C2–C3	125.0(5)
O2–C2–C1	115.8(5)
C3–C2–C1	119.1(5)
C4–C3–C2	119.2(6)
C5–C4–C3	122.7(6)
C4–C5–C6	117.0(5)
C4–C5–C8	120.0(6)
C6–C5–C8	122.9(5)
C1–C6–C5	121.4(6)
C5–C8–C9	116.8(5)
C10–C9–C8	118.4(5)
C15–C10–C11	118.3(5)
C15–C10–C9	124.3(5)
C11–C10–C9	117.2(5)
C12–C11–C10	122.1(5)
O3–C12–C11	125.5(5)
O3–C12–C13	114.8(5)
C11–C12–C13	119.7(5)
C14–C13–C12	117.3(5)
C14–C13–C17	120.2(5)
C12–C13–C17	122.3(5)
C13–C14–C15	121.9(5)
C10–C15–C14	120.5(5)
C18–C17–C22	117.9(5)
C18–C17–C13	122.1(5)
C22–C17–C13	120.0(5)
C19–C18–C17	121.8(5)
C20–C19–C18	119.8(5)
O4–C20–C19	124.6(5)
O4–C20–C21	116.1(5)
C19–C20–C21	119.3(6)
C22–C21–C20	121.1(6)
C21–C22–C17	120.2(5)
C21–C22–C24	123.7(5)
C17–C22–C24	116.1(5)
C25–C24–C22	128.4(5)
C24–C25–C26	120.3(6)
C27–C26–C31	118.5(6)
C27–C26–C25	119.6(6)
C31–C26–C25	120.7(6)
C28–C27–C26	121.0(6)
C29–C28–C27	119.8(6)
C28–C29–C30	120.2(6)
C28–C29–O1	119.6(6)
C30–C29–O1	120.2(5)

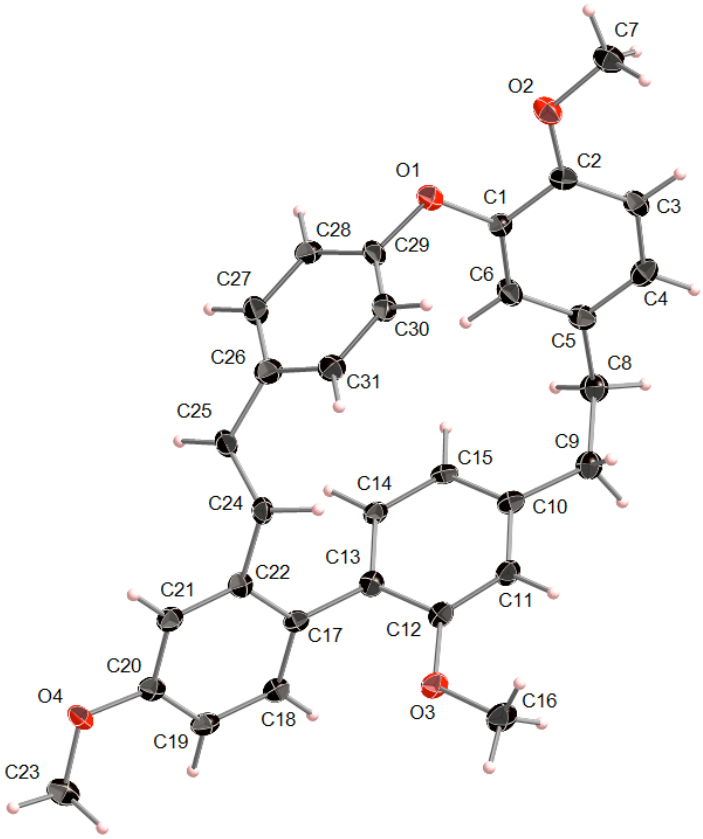
C29–C30–C31	119.7(5)
C26–C31–C30	120.0(6)

Table 4. Anisotropic displacement parameters [Å²× 10³]. 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}
O1	42(3)	40(3)	32(2)	5(2)	18(2)	15(2)
O2	33(2)	28(2)	43(3)	0(2)	19(2)	4(2)
O3	29(2)	30(2)	23(2)	−6(2)	−1(2)	−5(2)
O4	34(2)	27(2)	35(2)	−2(2)	15(2)	10(2)
C1	29(3)	27(3)	23(3)	2(3)	9(2)	4(3)
C2	26(3)	23(3)	27(3)	−6(3)	10(2)	−7(3)
C3	29(3)	20(3)	35(3)	−6(3)	8(3)	0(3)
C4	35(3)	32(4)	27(3)	5(3)	8(3)	−5(3)
C5	33(3)	25(3)	31(3)	−5(3)	11(3)	−3(3)
C6	28(3)	33(4)	38(4)	7(3)	18(3)	5(3)
C7	35(3)	33(4)	42(4)	−3(3)	19(3)	1(3)
C8	44(4)	28(4)	34(4)	3(3)	13(3)	1(3)
C9	30(3)	30(4)	32(3)	2(3)	8(3)	0(3)
C10	29(3)	26(3)	22(3)	3(3)	13(2)	−7(3)
C11	24(3)	36(4)	21(3)	0(3)	2(2)	1(3)
C12	26(3)	22(3)	23(3)	2(3)	5(2)	−6(2)
C13	23(3)	27(3)	26(3)	3(3)	8(2)	−3(2)
C14	19(3)	33(3)	18(3)	−4(3)	2(2)	−2(3)
C15	30(3)	23(3)	18(3)	−5(2)	9(2)	−6(3)
C16	35(4)	43(4)	29(4)	−8(3)	0(3)	0(3)
C17	24(3)	20(3)	19(3)	−7(3)	3(2)	−6(2)
C18	29(3)	29(4)	23(3)	−1(3)	7(2)	−3(3)
C19	28(3)	39(4)	22(3)	−3(3)	11(2)	−4(3)
C20	23(3)	28(3)	25(3)	−8(3)	4(2)	−6(3)
C21	23(3)	40(4)	23(3)	2(3)	7(2)	1(3)
C22	16(3)	31(3)	26(3)	−1(3)	4(2)	−2(2)
C23	33(3)	36(4)	43(4)	−10(3)	15(3)	−1(3)
C24	29(3)	22(3)	28(3)	6(3)	6(3)	5(3)
C25	28(3)	27(3)	34(4)	7(3)	13(3)	9(3)
C26	40(4)	32(4)	27(3)	1(3)	12(3)	1(3)
C27	31(3)	35(4)	36(4)	5(3)	11(3)	9(3)
C28	42(4)	33(4)	23(3)	1(3)	13(3)	5(3)
C29	23(3)	33(4)	31(3)	8(3)	16(3)	7(3)
C30	26(3)	37(4)	33(4)	10(3)	14(3)	0(3)
C31	24(3)	42(4)	30(3)	0(3)	10(3)	1(3)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H3	16365	–3998	–631	34	1
H4	15526	–4104	466	38	1
H6	13222	–1820	–663	37	1
H7A	17238	–3309	–1642	52	1
H7B	16654	–3378	–2641	52	1
H7C	16291	–4221	–2019	52	1
H8A	13937	–3916	968	42	1
H8B	12855	–3253	424	42	1
H9A	13811	–2705	1917	37	1
H9B	14665	–2069	1515	37	1
H11	13937	–646	2378	34	1
H14	10893	–158	–19	29	1
H15	12001	–1737	124	28	1
H16A	13605	281	3495	56	1
H16B	13628	1585	3611	56	1
H16C	14342	1025	3048	56	1
H18	10176	1247	1914	33	1
H19	9051	2820	1688	35	1
H21	10380	3718	–196	34	1
H23A	7761	4178	1073	55	1
H23B	8049	5438	952	55	1
H23C	8872	4728	1693	55	1
H27	10939	623	–2368	40	1
H28	11932	–852	–2706	38	1
H30	14774	143	–952	37	1
H31	13761	1594	–566	38	1
H92	10770(50)	2040(50)	–1330(40)	31(17)	1
H91	12490(60)	1630(60)	190(40)	50(20)	1



Thermal ellipsoids drawn at the 35% probability level.

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Table 1. Crystal data and structure refinement details.

Identification code	**2009sot0355**
Empirical formula	$C_{62}H_{56}O_8$
Formula weight	929.07
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	*P*–1
Unit cell dimensions	a = 8.1351(3) Å α = 68.647(2)°
	b = 11.4747(5) Å β = 81.978(3)°
	c = 14.3414(6) Å γ = 74.307(3)°
Volume	1199.11(9) Å^3
Z	1
Density (calculated)	1.287 Mg / m^3
Absorption coefficient	0.084 mm^{-1}
F(000)	492
Crystal	Slab; Colourless
Crystal size	0.1 × 0.08 × 0.02 mm^3
θ range for data collection	2.96 – 27.45°
Index ranges	$-10 \le h \le 10$, $-14 \le k \le 14$, $-18 \le l \le 18$
Reflections collected	21618
Independent reflections	5438 [R_{int} = 0.0611]
Completeness to θ = 27.45°	99.0 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9975 and 0.9816
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5438 / 0 / 319
Goodness-of-fit on F^2	1.100
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0676, *wR2* = 0.1118
R indices (all data)	*R1* = 0.1009, *wR2* = 0.1259
Largest diff. peak and hole	0.254 and –0.247 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **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**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **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: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 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.*
O1	2709(2)	805(2)	4656(1)	30(1)	1
O2	3710(2)	3626(2)	7476(1)	40(1)	1
O3	–3319(2)	6483(2)	9191(1)	37(1)	1
O4	–4845(2)	8825(2)	9182(1)	38(1)	1
C1	3485(3)	–143(2)	4201(2)	34(1)	1
C2	1093(3)	1512(2)	4392(2)	25(1)	1
C3	111(3)	1258(2)	3803(2)	27(1)	1
C4	–1526(3)	2025(2)	3545(2)	30(1)	1
C5	–2142(3)	3073(2)	3864(2)	31(1)	1
C6	–1179(3)	3302(2)	4477(2)	30(1)	1
C7	427(3)	2521(2)	4775(2)	24(1)	1
C8	–2570(3)	1713(3)	2910(2)	34(1)	1
C9	1342(3)	2731(2)	5512(2)	25(1)	1
C10	2970(3)	2981(2)	5299(2)	28(1)	1
C11	3743(3)	3274(2)	5953(2)	30(1)	1
C12	2889(3)	3300(2)	6863(2)	30(1)	1
C13	1334(3)	2985(2)	7119(2)	28(1)	1
C14	526(3)	2718(2)	6444(2)	25(1)	1
C15	2739(4)	3824(3)	8342(2)	45(1)	1
C16	–1112(3)	2347(2)	6754(2)	28(1)	1
C17	–2359(3)	2724(2)	7369(2)	29(1)	1
C18	–2530(3)	3717(2)	7825(2)	25(1)	1
C19	–2236(3)	4926(2)	7275(2)	26(1)	1
C20	–2467(3)	5867(2)	7706(2)	30(1)	1
C21	–2966(3)	5582(2)	8708(2)	26(1)	1
C22	–3257(3)	4392(2)	9275(2)	27(1)	1
C23	–3057(3)	3469(2)	8832(2)	28(1)	1
C24	–2300(3)	7348(2)	8963(2)	29(1)	1
C25	–552(3)	7022(2)	8770(2)	30(1)	1
C26	438(3)	7909(2)	8566(2)	29(1)	1
C27	–372(3)	9116(2)	8614(2)	35(1)	1
C28	–2117(3)	9448(2)	8822(2)	35(1)	1
C29	–3107(3)	8577(2)	8984(2)	31(1)	1
C30	–5760(4)	10140(3)	8780(2)	46(1)	1
C31	2291(3)	7598(3)	8222(2)	33(1)	1

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

O1–C2	1.367(3)
O1–C1	1.427(3)
O2–C12	1.377(3)
O2–C15	1.433(3)
O3–C24	1.383(3)
O3–C21	1.392(3)
O4–C29	1.374(3)
O4–C30	1.429(3)
C2–C3	1.389(3)
C2–C7	1.405(3)
C3–C4	1.397(3)
C4–C5	1.384(3)
C4–C8	1.515(3)
C5–C6	1.389(3)
C6–C7	1.391(3)
C7–C9	1.494(3)
C8–C31^{i}	1.541(3)
C9–C10	1.399(3)
C9–C14	1.404(3)
C10–C11	1.378(3)
C11–C12	1.397(3)
C12–C13	1.374(3)
C13–C14	1.403(3)
C14–C16	1.469(3)
C16–C17	1.336(3)
C17–C18	1.476(3)
C18–C19	1.391(3)
C18–C23	1.394(3)
C19–C20	1.388(3)
C20–C21	1.380(3)
C21–C22	1.376(3)
C22–C23	1.385(3)
C24–C25	1.384(3)
C24–C29	1.394(3)
C25–C26	1.389(3)
C26–C27	1.385(3)
C26–C31	1.508(3)
C27–C28	1.386(4)
C28–C29	1.385(3)
C31–C8^{i}	1.541(3)

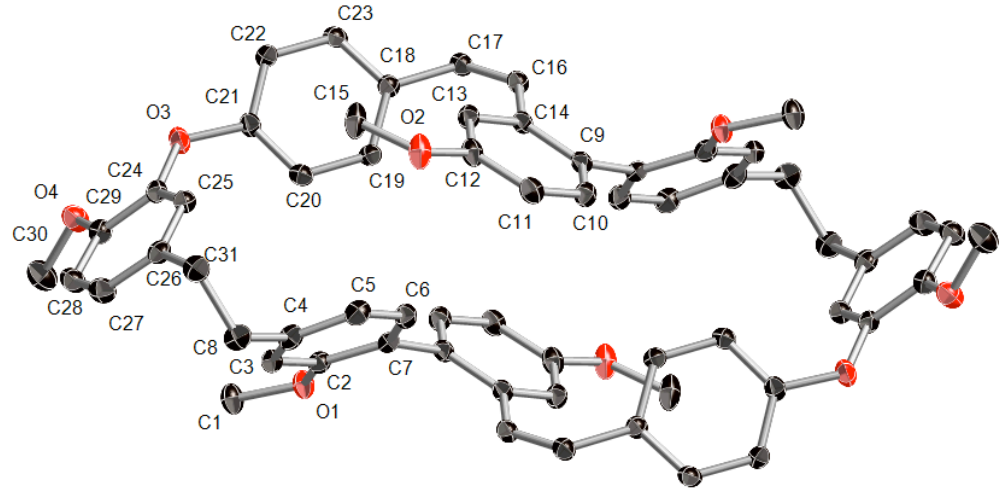
Symmetry transformations used to generate equivalent atoms:
(i) –x,–y+1,–z+1

Table 4. Anisotropic displacement parameters [Å²× 10³]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

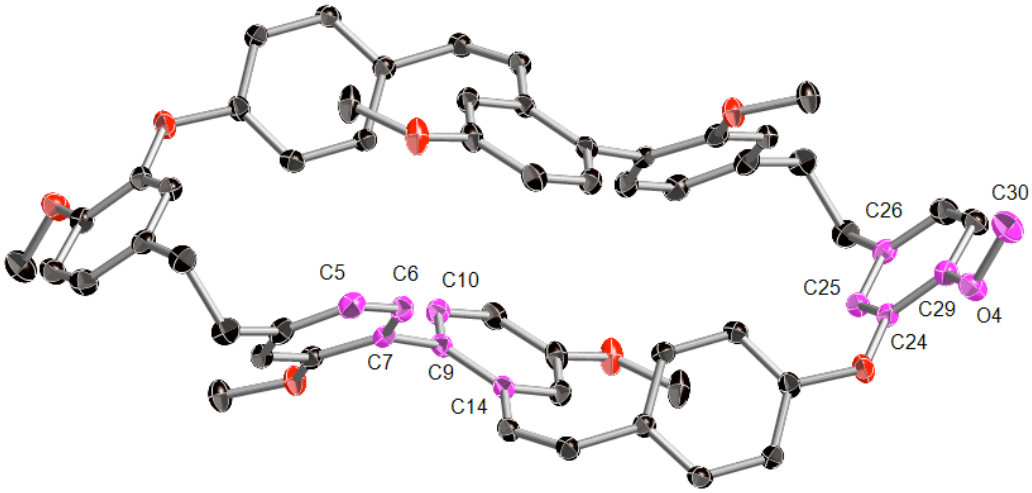
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	28(1)	29(1)	36(1)	−18(1)	−7(1)	2(1)
O2	29(1)	55(1)	48(1)	−35(1)	−8(1)	−2(1)
O3	45(1)	35(1)	44(1)	−25(1)	17(1)	−21(1)
O4	36(1)	29(1)	48(1)	−15(1)	2(1)	−8(1)
C1	30(1)	32(1)	44(2)	−22(1)	−6(1)	2(1)
C2	25(1)	25(1)	22(1)	−6(1)	−2(1)	−4(1)
C3	31(1)	27(1)	25(1)	−11(1)	0(1)	−8(1)
C4	28(1)	37(1)	25(1)	−10(1)	−1(1)	−11(1)
C5	26(1)	34(1)	28(1)	−8(1)	−4(1)	−2(1)
C6	29(1)	29(1)	28(1)	−12(1)	0(1)	−1(1)
C7	27(1)	26(1)	19(1)	−7(1)	0(1)	−6(1)
C8	29(1)	41(2)	33(1)	−11(1)	−4(1)	−12(1)
C9	27(1)	19(1)	26(1)	−8(1)	−4(1)	0(1)
C10	25(1)	28(1)	29(1)	−12(1)	−1(1)	−1(1)
C11	22(1)	28(1)	39(1)	−14(1)	−3(1)	0(1)
C12	27(1)	28(1)	36(1)	−17(1)	−9(1)	3(1)
C13	29(1)	26(1)	26(1)	−12(1)	−3(1)	−1(1)
C14	28(1)	20(1)	26(1)	−9(1)	−2(1)	−1(1)
C15	41(2)	60(2)	44(2)	−36(2)	−8(1)	0(1)
C16	37(1)	23(1)	28(1)	−11(1)	−3(1)	−8(1)
C17	31(1)	25(1)	31(1)	−11(1)	2(1)	−10(1)
C18	23(1)	24(1)	27(1)	−10(1)	1(1)	−6(1)
C19	28(1)	25(1)	23(1)	−6(1)	1(1)	−6(1)
C20	37(1)	23(1)	30(1)	−8(1)	3(1)	−10(1)
C21	25(1)	26(1)	33(1)	−15(1)	3(1)	−7(1)
C22	31(1)	27(1)	23(1)	−10(1)	3(1)	−6(1)
C23	31(1)	22(1)	30(1)	−6(1)	4(1)	−10(1)
C24	39(1)	29(1)	24(1)	−12(1)	4(1)	−15(1)
C25	38(1)	25(1)	26(1)	−10(1)	−2(1)	−7(1)
C26	36(1)	31(1)	21(1)	−7(1)	−7(1)	−8(1)
C27	38(2)	31(1)	39(2)	−11(1)	−4(1)	−15(1)
C28	41(2)	25(1)	41(2)	−12(1)	−3(1)	−9(1)
C29	33(1)	31(1)	29(1)	−12(1)	1(1)	−8(1)
C30	41(2)	34(2)	60(2)	−17(1)	−4(1)	−2(1)
C31	31(1)	36(1)	34(1)	−11(1)	−11(1)	−8(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	2869	–830	4433	51	1
H1B	4680	–506	4386	51	1
H1C	3441	258	3471	51	1
H3	560	552	3572	32	1
H5	–3224	3636	3663	37	1
H6	–1632	4015	4701	36	1
H8A	–3797	1965	3101	40	1
H8B	–2262	771	3053	40	1
H10	3559	2948	4685	33	1
H11	4841	3455	5788	36	1
H13	801	2948	7759	33	1
H15A	1659	4461	8136	67	1
H15B	3393	4139	8684	67	1
H15C	2499	3008	8799	67	1
H16	–1312	1761	6480	34	1
H17	–3262	2293	7536	34	1
H19	–1869	5113	6589	32	1
H20	–2284	6695	7317	36	1
H22	–3593	4205	9965	33	1
H23	–3282	2655	9220	34	1
H25	–18	6174	8776	35	1
H27	284	9729	8501	41	1
H28	–2638	10281	8854	42	1
H30A	–5448	10645	9121	68	1
H30B	–6991	10194	8883	68	1
H30C	–5469	10482	8062	68	1
H31A	2697	6655	8378	40	1
H31B	2978	7859	8596	40	1



Thermal ellipsoids drawn at the 35% probability level



Bond angles deviating most from normal values

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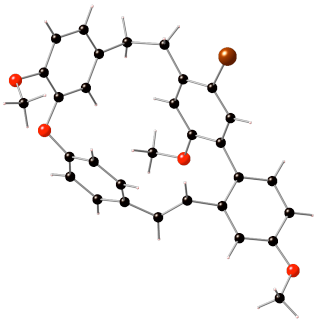
Table 1. Crystal data and structure refinement details.



Identification code	**2009sot0091**
Empirical formula	$C_{31}H_{27}BrO_4$
Formula weight	543.44
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*P*21/*c*
Unit cell dimensions	a = 11.9037(3) Å
	b = 17.7403(4) Å β = 98.3490(10)°
	c = 11.8878(2) Å
Volume	2483.80(9) Å^3
Z	4
Density (calculated)	1.453 Mg / m^3
Absorption coefficient	1.691 mm^{-1}
F(000)	1120
Crystal	Rod; Colourless
Crystal size	0.2 × 0.04 × 0.04 mm^3
θ range for data collection	3.22 – 27.48°
Index ranges	$-14 \le h \le 15$, $-23 \le k \le 22$, $-15 \le l \le 13$
Reflections collected	35115
Independent reflections	5689 [R_{int} = 0.0801]
Completeness to θ = 27.48°	99.6 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9354 and 0.7284
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5689 / 0 / 328
Goodness-of-fit on F^2	1.469
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0598, *wR2* = 0.1129
R indices (all data)	*R1* = 0.0847, *wR2* = 0.1208
Largest diff. peak and hole	1.624 and –0.367 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **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**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **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: All hydrogen atoms were located in the difference map and then placed in corresponding idealised positions and refined using a riding model.
PLAT094_ALERT_2_B Ratio of Maximum / Minimum Residual Density .... 4.43.
Highest peak 1.62 at 0.7220 0.1467 0.4798 [0.97 A from H1A]
No reason for the high residual peak could be found. A twin law was tried for the higher metric symmetry orthorhombic C, but the refinement did not improve.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Br1	5132(1)	2048(1)	7055(1)	31(1)	1
O1	4473(2)	−1310(1)	6588(2)	30(1)	1
O2	8134(2)	−1945(1)	10907(2)	31(1)	1
O3	−473(2)	1(2)	7258(2)	31(1)	1
O4	−1739(2)	1323(2)	6969(2)	40(1)	1
C1	3531(4)	−1608(2)	5818(3)	37(1)	1
C2	4575(3)	−546(2)	6654(3)	25(1)	1
C3	3872(3)	−51(2)	5954(3)	25(1)	1
C4	3995(3)	726(2)	6040(3)	23(1)	1
C5	4867(3)	990(2)	6854(3)	25(1)	1
C6	5575(3)	513(2)	7551(3)	26(1)	1
C7	5438(3)	−268(2)	7477(3)	23(1)	1
C8	6124(3)	−761(2)	8337(3)	22(1)	1
C9	7274(3)	−903(2)	8308(3)	26(1)	1
C10	7917(3)	−1320(2)	9156(3)	27(1)	1
C11	7413(3)	−1590(2)	10067(3)	25(1)	1
C12	6269(3)	−1467(2)	10101(3)	24(1)	1
C13	5622(3)	−1053(2)	9243(3)	23(1)	1
C14	7709(3)	−2109(2)	11947(3)	33(1)	1
C15	4416(3)	−878(2)	9245(3)	24(1)	1
C16	3556(3)	−1348(2)	9284(3)	27(1)	1
C17	2386(3)	−1077(2)	8983(3)	24(1)	1
C18	2092(3)	−351(2)	9284(3)	26(1)	1
C19	1117(3)	−5(2)	8753(3)	28(1)	1
C20	427(3)	−389(2)	7901(3)	28(1)	1
C21	629(3)	−1126(2)	7676(3)	32(1)	1
C22	1607(3)	−1477(2)	8211(3)	32(1)	1
C23	−121(3)	571(2)	6597(3)	28(1)	1
C24	−773(3)	1227(2)	6461(3)	30(1)	1
C25	−476(3)	1792(2)	5748(3)	30(1)	1
C26	473(3)	1714(2)	5205(3)	29(1)	1
C27	1130(3)	1063(2)	5339(3)	25(1)	1
C28	820(3)	493(2)	6033(3)	24(1)	1
C29	−1521(4)	1398(3)	8173(3)	42(1)	1
C30	2113(3)	976(2)	4661(3)	26(1)	1
C31	3267(3)	1261(2)	5237(3)	26(1)	1

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

Br1–C5	1.912(3)
O1–C2	1.361(4)
O1–C1	1.441(4)
O2–C11	1.372(4)
O2–C14	1.431(4)
O3–C23	1.383(4)
O3–C20	1.404(4)
O4–C24	1.384(4)
O4–C29	1.424(5)
C2–C3	1.399(5)
C2–C7	1.401(5)
C3–C4	1.388(5)
C4–C5	1.394(5)
C4–C31	1.524(5)
C5–C6	1.383(5)
C6–C7	1.396(5)
C7–C8	1.495(5)
C8–C9	1.397(5)
C8–C13	1.404(5)
C9–C10	1.389(5)
C10–C11	1.396(5)
C11–C12	1.385(5)
C12–C13	1.395(5)
C13–C15	1.468(5)
C15–C16	1.326(5)
C16–C17	1.468(5)
C17–C22	1.399(5)
C17–C18	1.396(5)
C18–C19	1.382(5)
C19–C20	1.386(5)
C20–C21	1.363(5)
C21–C22	1.390(5)
C23–C28	1.393(5)
C23–C24	1.396(5)
C24–C25	1.391(5)
C25–C26	1.386(5)
C26–C27	1.392(5)
C27–C28	1.388(5)
C27–C30	1.523(5)
C30–C31	1.529(5)
C2–O1–C1	117.2(3)
C11–O2–C14	117.3(3)
C23–O3–C20	113.5(3)
C24–O4–C29	114.1(3)
O1–C2–C3	123.3(3)
O1–C2–C7	116.1(3)

C3–C2–C7	120.6(3)
C4–C3–C2	122.1(3)
C3–C4–C5	116.4(3)
C3–C4–C31	121.9(3)
C5–C4–C31	121.6(3)
C6–C5–C4	122.6(3)
C6–C5–Br1	116.8(3)
C4–C5–Br1	120.6(3)
C5–C6–C7	120.9(3)
C6–C7–C2	117.4(3)
C6–C7–C8	119.3(3)
C2–C7–C8	123.0(3)
C9–C8–C13	118.7(3)
C9–C8–C7	121.8(3)
C13–C8–C7	119.3(3)
C10–C9–C8	121.1(3)
C9–C10–C11	119.5(3)
O2–C11–C12	124.4(3)
O2–C11–C10	115.3(3)
C12–C11–C10	120.2(3)
C11–C12–C13	120.1(3)
C12–C13–C8	120.2(3)
C12–C13–C15	123.1(3)
C8–C13–C15	116.7(3)
C16–C15–C13	128.9(3)
C15–C16–C17	119.7(3)
C22–C17–C18	118.0(3)
C22–C17–C16	120.6(3)
C18–C17–C16	120.3(3)
C19–C18–C17	121.2(3)
C18–C19–C20	119.1(3)
C21–C20–C19	120.7(4)
C21–C20–O3	120.5(3)
C19–C20–O3	118.8(3)
C20–C21–C22	120.0(3)
C21–C22–C17	120.3(4)
O3–C23–C28	122.2(3)
O3–C23–C24	117.8(3)
C28–C23–C24	120.0(3)
O4–C24–C25	118.5(3)
O4–C24–C23	122.4(3)
C25–C24–C23	119.0(3)
C24–C25–C26	120.5(4)
C27–C26–C25	120.8(3)
C28–C27–C26	118.7(3)
C28–C27–C30	122.1(3)
C26–C27–C30	119.1(3)

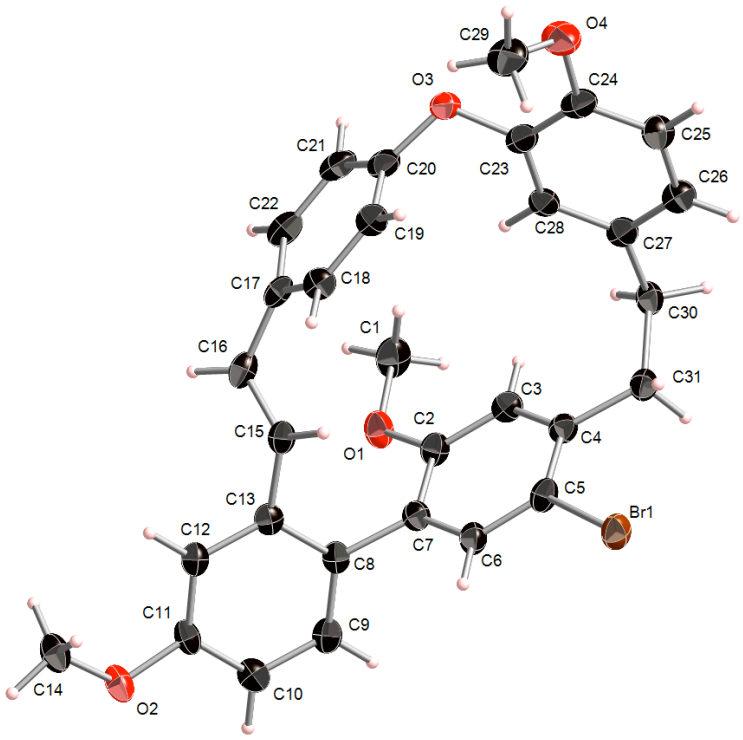
C27–C28–C23	121.0(3)
C27–C30–C31	116.1(3)
C4–C31–C30	117.8(3)

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br1	38(1)	20(1)	33(1)	2(1)	1(1)	−5(1)
O1	40(2)	20(1)	27(1)	−1(1)	−2(1)	0(1)
O2	36(1)	35(2)	21(1)	5(1)	2(1)	11(1)
O3	22(1)	44(2)	27(1)	9(1)	0(1)	−8(1)
O4	30(1)	57(2)	35(2)	3(1)	11(1)	2(1)
C1	51(2)	22(2)	35(2)	−5(2)	−1(2)	−7(2)
C2	32(2)	22(2)	23(2)	−1(1)	5(1)	−2(2)
C3	26(2)	28(2)	20(2)	−4(1)	4(1)	−4(1)
C4	25(2)	25(2)	21(2)	0(1)	6(1)	−1(1)
C5	34(2)	16(2)	27(2)	0(1)	7(2)	−3(1)
C6	28(2)	27(2)	23(2)	5(2)	3(1)	−1(2)
C7	25(2)	26(2)	16(2)	0(1)	2(1)	−1(1)
C8	30(2)	18(2)	18(2)	−3(1)	1(1)	−1(1)
C9	35(2)	25(2)	18(2)	−2(1)	7(2)	1(2)
C10	30(2)	29(2)	23(2)	−4(2)	4(1)	5(2)
C11	33(2)	19(2)	21(2)	0(1)	−1(1)	6(1)
C12	32(2)	20(2)	21(2)	−1(1)	5(1)	1(1)
C13	29(2)	17(2)	22(2)	−4(1)	1(1)	0(1)
C14	40(2)	39(2)	20(2)	4(2)	3(2)	8(2)
C15	30(2)	19(2)	22(2)	0(1)	5(1)	0(1)
C16	38(2)	20(2)	25(2)	0(1)	13(2)	−1(2)
C17	31(2)	24(2)	21(2)	0(1)	12(1)	−6(1)
C18	29(2)	30(2)	21(2)	−5(1)	5(1)	−2(2)
C19	29(2)	29(2)	25(2)	−2(2)	4(2)	−3(2)
C20	24(2)	38(2)	23(2)	2(2)	8(1)	−7(2)
C21	29(2)	39(2)	29(2)	−4(2)	8(2)	−15(2)
C22	37(2)	26(2)	34(2)	−4(2)	13(2)	−9(2)
C23	26(2)	39(2)	19(2)	1(2)	2(1)	−9(2)
C24	24(2)	40(2)	25(2)	−5(2)	6(2)	−5(2)
C25	32(2)	26(2)	31(2)	−1(2)	5(2)	2(2)
C26	30(2)	32(2)	26(2)	−3(2)	6(2)	−3(2)
C27	25(2)	32(2)	17(2)	−4(1)	0(1)	−6(2)
C28	25(2)	26(2)	20(2)	−1(1)	−2(1)	−3(1)
C29	40(2)	58(3)	32(2)	−2(2)	16(2)	−2(2)
C30	30(2)	29(2)	19(2)	4(1)	4(1)	2(2)
C31	27(2)	25(2)	27(2)	5(2)	4(1)	−2(2)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	2819	–1408	6018	55	1
H1B	3529	–2159	5873	55	1
H1C	3606	–1460	5038	55	1
H3	3293	–254	5403	30	1
H6	6164	719	8088	31	1
H9	7621	–710	7697	31	1
H10	8694	–1422	9118	33	1
H12	5925	–1666	10710	29	1
H14A	7426	–1644	12252	50	1
H14B	8321	–2319	12498	50	1
H14C	7089	–2475	11801	50	1
H15	4227	–358	9215	29	1
H16	3697	–1858	9505	32	1
H18	2571	–89	9864	32	1
H19	923	488	8968	33	1
H21	102	–1399	7153	39	1
H22	1746	–1991	8053	38	1
H25	–926	2235	5632	36	1
H26	677	2110	4736	35	1
H28	1256	43	6125	29	1
H29A	–1293	909	8515	64	1
H29B	–2210	1573	8454	64	1
H29C	–909	1765	8379	64	1
H30A	1917	1247	3931	31	1
H30B	2189	435	4482	31	1
H31A	3713	1412	4633	32	1
H31B	3136	1722	5670	32	1

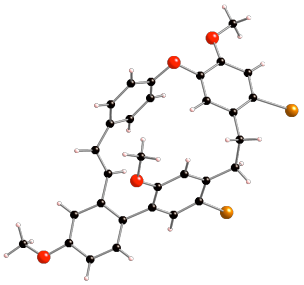


Thermal ellipsoids drawn at the 50% probability level

UNIVERSITY OF Southampton
School of Chemistry

Single Crystal X-Ray Diffraction Service
School of Chemistry - University of Southampton
Contact: Dr Mark E Light, light@soton.ac.uk, ex 29429

Table 1. Crystal data and structure refinement details.



Identification code	**2009sot0386**
Empirical formula	$C_{31}H_{26}Br_2O_4$
Formula weight	622.34
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 18.7857(4) Å
	b = 16.0845(4) Å β = 112.110(1)°
	c = 18.8141(4) Å
Volume	5266.8(2) Å^3
Z	8
Density (calculated)	1.570 Mg / m^3
Absorption coefficient	3.114 mm^{-1}
F(000)	2512
Crystal	Rod; Colourless
Crystal size	0.22 × 0.03 × 0.03 mm^3
θ range for data collection	2.98 – 25.03°
Index ranges	$-22 \le h \le 22$, $-18 \le k \le 19$, $-22 \le l \le 22$
Reflections collected	54975
Independent reflections	9291 [R_{int} = 0.1114]
Completeness to θ = 25.03°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9124 and 0.5374
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9291 / 0 / 668
Goodness-of-fit on F^2	1.598
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0830, $wR2$ = 0.1427
R indices (all data)	$R1$ = 0.1220, $wR2$ = 0.1559
Largest diff. peak and hole	2.329 and –0.852 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **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**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **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: All hydrogen atoms were placed in idealised positions and refined using a riding model.
The structure was refined as a pseudo-merohedral twin, the twin fraction refined to ca 30%, twin law used was 0 0 1 0 -1 0 1 0 0

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Br1	2859(1)	5048(1)	4570(1)	38(1)	1
Br2	3269(1)	1819(1)	5914(1)	31(1)	1
O1	3873(4)	4311(4)	2401(3)	24(2)	1
O2	6647(3)	1912(4)	6492(4)	29(2)	1
O3	7026(4)	–1939(4)	6852(4)	25(2)	1
O4	5185(3)	3714(4)	3361(3)	17(1)	1
C1	3142(6)	4591(7)	1858(6)	32(3)	1
C2	3962(6)	4315(6)	3142(6)	23(2)	1
C3	3435(6)	4618(6)	3437(6)	29(2)	1
C4	3608(6)	4575(7)	4218(6)	26(2)	1
C5	4288(5)	4241(6)	4750(6)	21(2)	1
C6	4800(6)	3938(6)	4431(6)	25(2)	1
C7	4646(5)	3972(6)	3659(5)	17(2)	1
C8	4478(6)	4223(6)	5600(5)	23(2)	1
C9	4196(6)	3465(7)	5895(6)	30(3)	1
C10	4663(6)	2673(6)	6060(5)	21(2)	1
C11	4340(5)	1906(6)	6097(5)	21(2)	1
C12	4763(5)	1176(6)	6282(5)	19(2)	1
C13	5550(5)	1191(6)	6418(5)	19(2)	1
C14	5874(5)	1957(6)	6361(6)	24(2)	1
C15	5435(6)	2681(7)	6185(6)	22(2)	1
C16	6991(6)	2649(7)	6344(7)	34(3)	1
C17	5979(5)	381(6)	6540(6)	20(2)	1
C18	6241(5)	–27(6)	7254(5)	20(2)	1
C19	6592(5)	–792(6)	7327(6)	23(2)	1
C20	6706(5)	–1168(6)	6720(6)	20(2)	1
C21	6493(5)	–750(6)	6022(6)	20(2)	1
C22	6142(5)	10(6)	5931(5)	20(2)	1
C23	7057(7)	–2401(7)	6223(7)	33(3)	1
C24	5897(6)	499(6)	5221(5)	21(2)	1
C25	6349(5)	750(6)	4848(5)	19(2)	1
C26	6079(5)	1426(6)	4279(5)	18(2)	1
C27	6558(5)	2091(6)	4315(5)	23(2)	1
C28	6285(5)	2844(6)	4003(5)	17(2)	1
C29	5490(5)	2932(6)	3615(5)	20(2)	1
C30	5013(6)	2264(7)	3507(6)	23(2)	1
C31	5292(5)	1508(6)	3817(5)	19(2)	1
Br3	4578(1)	–152(1)	7796(1)	40(1)	1
Br4	5869(1)	3246(1)	8148(1)	32(1)	1
O5	2432(4)	563(4)	8837(4)	28(2)	1
O6	6533(4)	3086(4)	11542(4)	28(2)	1
O7	6831(4)	6921(4)	12014(4)	28(2)	1
O8	3404(4)	1189(4)	10131(4)	28(2)	1

C32	1895(6)	204(8)	8150(6)	37(3)	1
C33	3180(5)	577(6)	8913(5)	23(2)	1
C34	3470(5)	264(6)	8394(5)	23(2)	1
C35	4246(6)	348(6)	8545(6)	24(2)	1
C36	4764(6)	720(6)	9189(6)	25(2)	1
C37	4474(5)	1014(6)	9713(5)	17(2)	1
C38	3703(6)	940(6)	9588(5)	22(2)	1
C39	5628(6)	795(6)	9354(6)	31(3)	1
C40	5867(6)	1592(6)	9051(6)	24(2)	1
C41	6032(6)	2377(6)	9527(6)	24(2)	1
C42	6068(5)	3147(6)	9220(5)	22(2)	1
C43	6257(5)	3863(7)	9646(6)	24(2)	1
C44	6400(5)	3846(6)	10433(5)	21(2)	1
C45	6373(5)	3090(6)	10774(5)	23(2)	1
C46	6198(6)	2367(7)	10330(6)	25(2)	1
C47	6388(7)	2337(7)	11872(6)	34(3)	1
C48	6525(5)	4645(6)	10889(5)	19(2)	1
C49	7213(5)	5083(7)	11120(6)	25(2)	1
C50	7308(5)	5830(6)	11499(6)	22(2)	1
C51	6695(5)	6158(6)	11663(5)	19(2)	1
C52	6017(6)	5704(6)	11473(5)	25(2)	1
C53	5926(5)	4950(6)	11083(5)	20(2)	1
C54	6180(6)	7367(7)	12042(6)	29(3)	1
C55	5239(5)	4435(6)	10887(5)	18(2)	1
C56	4876(5)	4161(6)	11319(5)	20(2)	1
C57	4341(5)	3489(6)	11047(5)	15(2)	1
C58	4354(5)	2817(7)	11515(6)	27(2)	1
C59	4032(5)	2054(6)	11229(5)	20(2)	1
C60	3665(5)	1979(6)	10439(5)	20(2)	1
C61	3560(5)	2628(6)	9952(6)	18(2)	1
C62	3890(5)	3387(6)	10254(5)	20(2)	1

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

Br1–C4	1.923(9)
Br2–C11	1.914(9)
O1–C2	1.340(11)
O1–C1	1.440(11)
O2–C14	1.380(11)
O2–C16	1.427(12)
O3–C20	1.360(11)
O3–C23	1.417(13)
O4–C29	1.390(11)
O4–C7	1.393(10)
C2–C3	1.394(13)
C2–C7	1.400(13)
C3–C4	1.381(14)
C4–C5	1.401(14)
C5–C6	1.401(13)
C5–C8	1.502(13)
C6–C7	1.370(13)
C8–C9	1.515(14)
C9–C10	1.510(14)
C10–C15	1.379(14)
C10–C11	1.389(13)
C11–C12	1.387(13)
C12–C13	1.402(13)
C13–C14	1.397(14)
C13–C17	1.503(14)
C14–C15	1.393(14)
C17–C18	1.406(13)
C17–C22	1.423(13)
C18–C19	1.378(13)
C19–C20	1.379(13)
C20–C21	1.392(13)
C21–C22	1.370(13)
C22–C24	1.467(13)
C24–C25	1.349(13)
C25–C26	1.476(13)
C26–C27	1.384(13)
C26–C31	1.410(13)
C27–C28	1.360(14)
C28–C29	1.401(12)
C29–C30	1.364(14)
C30–C31	1.366(14)
Br3–C35	1.919(9)
Br4–C42	1.915(9)
O5–C33	1.358(11)
O5–C32	1.429(12)

O6–C45	1.361(11)
O6–C47	1.428(12)
O7–C51	1.373(12)
O7–C54	1.436(12)
O8–C38	1.397(11)
O8–C60	1.406(12)
C33–C34	1.380(13)
C33–C38	1.406(14)
C34–C35	1.383(13)
C35–C36	1.374(14)
C36–C37	1.378(13)
C36–C39	1.539(14)
C37–C38	1.382(13)
C39–C40	1.537(14)
C40–C41	1.509(14)
C41–C42	1.379(14)
C41–C46	1.425(15)
C42–C43	1.372(14)
C43–C44	1.401(13)
C44–C45	1.385(14)
C44–C48	1.514(13)
C45–C46	1.396(14)
C48–C49	1.390(14)
C48–C53	1.397(13)
C49–C50	1.374(14)
C50–C51	1.401(13)
C51–C52	1.392(13)
C52–C53	1.394(14)
C53–C55	1.459(13)
C55–C56	1.318(12)
C56–C57	1.433(13)
C57–C58	1.388(14)
C57–C62	1.422(13)
C58–C59	1.385(14)
C59–C60	1.387(13)
C60–C61	1.354(13)
C61–C62	1.390(14)
C20–O3–C23	118.6(8)
C29–O4–C7	113.6(6)
O1–C2–C3	126.0(9)
O1–C2–C7	116.4(8)
C3–C2–C7	117.7(9)
C4–C3–C2	119.3(10)
C3–C4–C5	124.5(9)
C3–C4–Br1	115.9(8)
C5–C4–Br1	119.6(7)
C4–C5–C6	114.6(9)

C4–C5–C8	123.8(9)
C6–C5–C8	121.6(9)
C7–C6–C5	122.3(9)
C6–C7–O4	121.2(8)
C6–C7–C2	121.7(8)
O4–C7–C2	117.0(8)
C5–C8–C9	115.4(9)
C8–C9–C10	119.9(8)
C15–C10–C11	116.8(10)
C15–C10–C9	121.3(9)
C11–C10–C9	121.9(9)
C12–C11–C10	123.0(9)
C12–C11–Br2	116.6(7)
C10–C11–Br2	120.4(7)
C11–C12–C13	119.9(9)
C14–C13–C12	117.4(9)
C14–C13–C17	123.6(8)
C12–C13–C17	118.8(9)
O2–C14–C15	125.1(9)
O2–C14–C13	113.5(8)
C15–C14–C13	121.3(9)
C10–C15–C14	121.6(10)
C18–C17–C22	118.0(9)
C18–C17–C13	121.7(8)
C22–C17–C13	120.3(8)
C19–C18–C17	119.7(9)
C20–C19–C18	121.7(9)
O3–C20–C19	116.3(8)
O3–C20–C21	124.2(9)
C19–C20–C21	119.4(9)
C22–C21–C20	120.1(9)
C21–C22–C17	120.9(8)
C21–C22–C24	124.2(9)
C17–C22–C24	114.9(9)
C25–C24–C22	126.3(9)
C24–C25–C26	119.1(9)
C27–C26–C31	118.0(9)
C27–C26–C25	119.6(8)
C31–C26–C25	120.7(8)
C28–C27–C26	122.3(9)
C27–C28–C29	118.0(9)
C30–C29–O4	119.9(9)
C30–C29–C28	120.7(9)
O4–C29–C28	119.4(8)
C29–C30–C31	120.8(9)
C30–C31–C26	119.5(9)
C33–O5–C32	116.9(7)

C45–O6–C47	117.6(8)
C51–O7–C54	117.2(7)
C38–O8–C60	112.8(7)
O5–C33–C34	126.0(9)
O5–C33–C38	116.5(8)
C34–C33–C38	117.5(9)
C35–C34–C33	119.1(9)
C36–C35–C34	124.4(9)
C36–C35–Br3	120.8(7)
C34–C35–Br3	114.7(7)
C35–C36–C37	116.2(9)
C35–C36–C39	123.7(9)
C37–C36–C39	120.1(9)
C36–C37–C38	121.3(9)
C37–C38–O8	122.3(9)
C37–C38–C33	121.4(8)
O8–C38–C33	116.3(8)
C40–C39–C36	115.1(9)
C41–C40–C39	120.1(8)
C42–C41–C46	115.3(9)
C42–C41–C40	122.3(9)
C46–C41–C40	122.3(9)
C41–C42–C43	123.6(9)
C41–C42–Br4	119.6(8)
C43–C42–Br4	116.8(7)
C42–C43–C44	120.3(9)
C45–C44–C43	118.7(9)
C45–C44–C48	120.5(8)
C43–C44–C48	120.6(9)
O6–C45–C46	122.6(9)
O6–C45–C44	117.6(9)
C46–C45–C44	119.7(9)
C45–C46–C41	122.3(10)
C49–C48–C53	119.1(9)
C49–C48–C44	122.4(8)
C53–C48–C44	118.6(8)
C50–C49–C48	121.9(9)
C49–C50–C51	119.1(9)
O7–C51–C52	125.3(9)
O7–C51–C50	115.0(8)
C52–C51–C50	119.6(9)
C53–C52–C51	120.7(9)
C52–C53–C48	119.4(9)
C52–C53–C55	123.4(9)
C48–C53–C55	117.2(8)
C56–C55–C53	130.3(9)
C55–C56–C57	119.2(9)

C58–C57–C62	116.0(9)
C58–C57–C56	121.2(8)
C62–C57–C56	121.5(8)
C59–C58–C57	122.8(9)
C58–C59–C60	117.6(9)
C61–C60–C59	123.0(9)
C61–C60–O8	118.6(9)
C59–C60–O8	118.4(8)
C60–C61–C62	118.2(9)
C61–C62–C57	121.8(9)

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement
factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

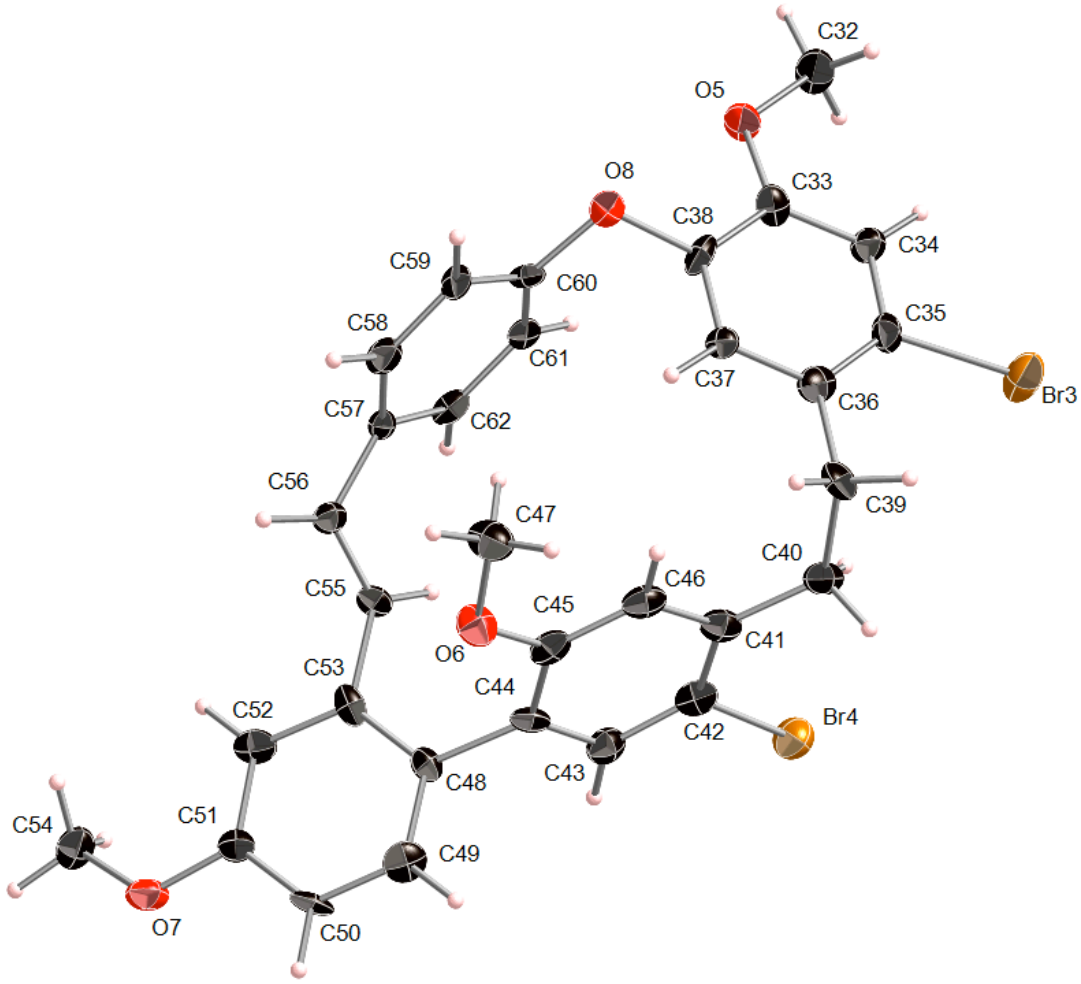
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br1	37(1)	46(1)	39(1)	–1(1)	23(1)	9(1)
Br2	21(1)	32(1)	40(1)	4(1)	13(1)	0(1)
O1	22(4)	36(4)	15(4)	6(3)	8(3)	10(3)
O2	13(3)	33(4)	40(4)	2(3)	9(3)	–8(3)
O3	24(4)	23(4)	24(4)	–1(3)	5(3)	3(3)
O4	21(3)	13(4)	20(3)	2(3)	10(3)	1(3)
C1	23(6)	50(8)	19(5)	7(5)	2(5)	10(5)
C2	39(6)	11(5)	26(6)	2(4)	19(5)	3(4)
C3	19(6)	27(6)	40(7)	–1(5)	11(5)	–3(5)
C4	20(6)	34(7)	30(6)	–3(5)	14(5)	1(5)
C5	25(6)	13(5)	27(6)	–3(4)	13(5)	–5(4)
C6	15(5)	26(6)	31(6)	–2(5)	6(4)	–1(4)
C7	24(5)	9(5)	19(5)	2(4)	11(4)	6(4)
C8	32(6)	17(5)	25(5)	5(4)	17(5)	–1(4)
C9	26(6)	38(7)	29(6)	–5(5)	13(5)	3(5)
C10	28(6)	22(6)	12(5)	1(4)	6(4)	–8(5)
C11	18(5)	28(6)	18(5)	–1(4)	8(4)	2(4)
C12	29(6)	13(5)	14(5)	–2(4)	6(4)	–1(4)
C13	21(5)	22(6)	17(5)	2(4)	8(4)	2(4)
C14	21(5)	24(6)	24(6)	2(5)	4(4)	2(5)
C15	21(6)	24(6)	21(5)	–3(5)	10(5)	–4(5)
C16	25(6)	44(7)	32(6)	–5(6)	8(5)	–18(5)
C17	14(5)	19(5)	25(6)	2(5)	5(4)	–1(4)
C18	11(5)	28(6)	20(5)	2(5)	4(4)	1(4)
C19	20(5)	28(6)	21(5)	6(5)	7(4)	–3(5)
C20	9(5)	18(5)	26(5)	8(5)	0(4)	1(4)
C21	19(5)	13(5)	32(6)	–3(5)	14(5)	–1(4)
C22	12(5)	28(6)	15(5)	7(4)	0(4)	–11(4)
C23	30(7)	19(6)	53(8)	–3(5)	19(6)	4(5)

C24	18(5)	18(6)	19(5)	4(4)	−2(4)	10(4)
C25	24(5)	17(5)	19(5)	1(4)	10(4)	3(4)
C26	21(5)	23(5)	10(5)	−1(4)	5(4)	9(4)
C27	11(5)	33(6)	27(6)	5(5)	10(4)	−3(4)
C28	20(5)	14(5)	17(5)	5(4)	8(4)	1(4)
C29	26(6)	22(6)	17(5)	−3(4)	15(5)	0(4)
C30	19(5)	30(6)	22(5)	2(5)	11(5)	−6(5)
C31	22(5)	16(5)	28(5)	0(4)	18(5)	−4(4)
Br3	39(1)	50(1)	39(1)	−8(1)	23(1)	1(1)
Br4	37(1)	36(1)	25(1)	1(1)	15(1)	−3(1)
O5	17(4)	35(5)	29(4)	−13(3)	6(3)	−7(3)
O6	34(4)	21(4)	27(4)	4(3)	9(3)	0(3)
O7	20(4)	32(5)	32(4)	−2(3)	10(3)	−8(3)
O8	33(4)	27(4)	30(4)	−5(3)	19(3)	−5(3)
C32	18(5)	55(8)	36(6)	−23(6)	7(5)	−10(5)
C33	16(5)	26(6)	21(5)	−4(5)	1(4)	4(4)
C34	22(5)	31(6)	17(5)	−3(4)	8(4)	−4(5)
C35	35(6)	15(5)	25(5)	−2(4)	16(5)	1(5)
C36	25(6)	18(6)	36(6)	3(5)	15(5)	5(5)
C37	18(5)	21(6)	11(5)	2(4)	4(4)	−2(4)
C38	31(6)	21(6)	24(5)	6(5)	20(5)	11(5)
C39	36(6)	18(6)	39(6)	−9(5)	17(5)	1(5)
C40	22(5)	23(6)	31(6)	2(5)	12(5)	−2(4)
C41	14(5)	24(6)	31(6)	3(5)	6(4)	0(4)
C42	18(5)	28(6)	17(5)	10(5)	3(4)	5(5)
C43	21(6)	25(6)	30(6)	4(5)	13(5)	4(5)
C44	12(5)	22(6)	27(6)	1(5)	6(4)	−6(4)
C45	11(5)	34(6)	24(5)	3(5)	6(4)	3(4)
C46	15(5)	29(6)	31(6)	7(5)	9(5)	1(5)
C47	37(7)	35(7)	26(6)	2(5)	8(5)	−9(5)
C48	20(5)	18(5)	17(5)	−3(4)	4(4)	0(4)
C49	16(5)	27(6)	28(6)	8(5)	3(4)	11(5)
C50	13(5)	17(6)	30(6)	2(4)	1(4)	−9(4)
C51	22(5)	16(5)	17(5)	7(4)	7(4)	1(4)
C52	19(5)	34(6)	17(5)	6(5)	2(4)	−1(5)
C53	20(5)	21(6)	9(4)	−1(4)	−5(4)	3(4)
C54	17(6)	42(7)	24(6)	−6(5)	5(5)	1(5)
C55	11(5)	21(5)	18(5)	−1(4)	0(4)	−2(4)
C56	16(5)	23(6)	21(5)	−1(4)	8(4)	−1(4)
C57	14(5)	14(5)	20(5)	−1(4)	9(4)	2(4)
C58	24(6)	40(7)	19(5)	−7(5)	11(5)	−7(5)
C59	36(6)	17(5)	15(5)	4(4)	17(5)	0(4)
C60	17(5)	22(6)	27(6)	0(4)	14(5)	−5(4)
C61	5(5)	27(6)	22(5)	−4(5)	4(4)	2(4)
C62	19(5)	26(6)	17(5)	8(4)	9(4)	7(4)

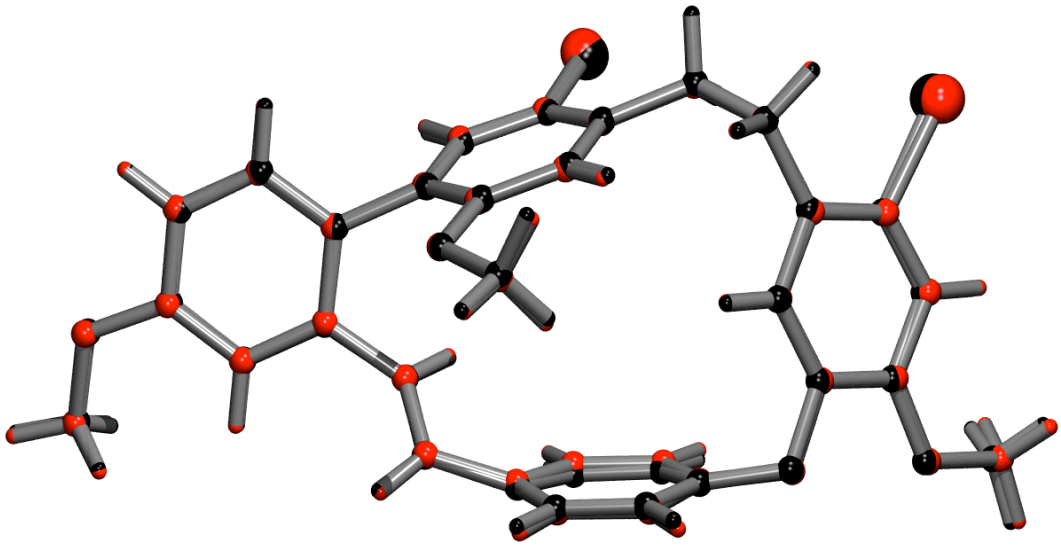
Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	3142	4557	1338	48	1
H1B	3056	5168	1972	48	1
H1C	2732	4238	1895	48	1
H3	2962	4851	3106	34	1
H6	5272	3700	4760	30	1
H8A	4255	4724	5742	27	1
H8B	5043	4258	5866	27	1
H9A	3679	3328	5516	36	1
H9B	4132	3629	6374	36	1
H12	4521	668	6317	23	1
H15	5673	3192	6149	26	1
H16A	7536	2547	6454	51	1
H16B	6940	3100	6673	51	1
H16C	6732	2807	5805	51	1
H18	6176	223	7683	24	1
H19	6760	–1067	7809	28	1
H21	6592	–993	5608	24	1
H23A	7300	–2940	6404	49	1
H23B	7357	–2093	5982	49	1
H23C	6535	–2488	5847	49	1
H24	5371	653	5002	25	1
H25	6833	495	4951	23	1
H27	7097	2019	4566	27	1
H28	6623	3298	4047	21	1
H30	4480	2326	3212	27	1
H31	4960	1041	3723	23	1
H32A	1378	224	8162	56	1
H32B	2037	–376	8110	56	1
H32C	1902	517	7705	56	1
H34	3141	–5	7940	28	1
H37	4810	1272	10170	21	1
H39A	5914	766	9915	37	1
H39B	5786	310	9123	37	1
H40A	6333	1460	8947	29	1
H40B	5455	1724	8551	29	1
H43	6291	4374	9407	29	1
H46	6188	1852	10573	30	1
H47A	6528	2415	12424	51	1
H47B	6696	1885	11785	51	1
H47C	5841	2196	11632	51	1
H49	7630	4859	11014	30	1
H50	7782	6121	11647	26	1
H52	5613	5911	11611	30	1
H54A	6350	7900	12304	43	1

H54B	5931	7038	12321	43	1
H54C	5813	7469	11518	43	1
H55	5018	4270	10364	22	1
H56	4968	4407	11805	24	1
H58	4595	2884	12056	32	1
H59	4061	1599	11560	25	1
H61	3268	2566	9419	22	1
H62	3813	3850	9920	24	1



Molecule 2 in the asymmetric unit, thermal ellipsoids drawn at the 50% probability level.



Fit of the 2 independent molecules in the asymmetric unit.