UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

SCHOOL OF CHEMISTRY

New Syntheses of the Macrocyclic Bisbibenzyl Natural Products, Riccardin D, Riccardin C, Polymorphatin A and an Unnatural Analogue; Formal Total Syntheses of Cavicularin and Asterelin A

by

Faisal Ateeq A. Almalki

Thesis for the degree of Doctor of Philosophy

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ABSTRACT

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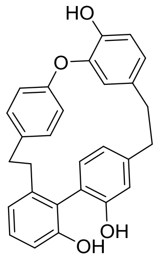
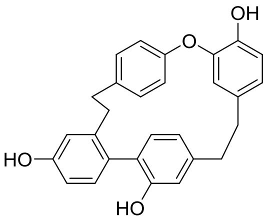
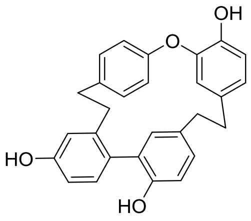
This thesis describes total syntheses of many different macrocyclic bisbibenzyl natural products including riccardin D **1.1**, riccardin C **1.2**, asterelin A **1.4**, cavicularin **1.5** and polymorphatin A **1.6** as well as an unnatural macrocyclic bisbibenzyl analogue **1.3**.



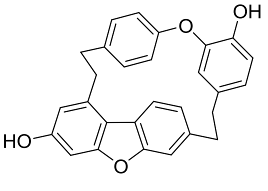
Riccardin D **1.1**



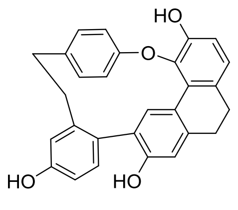
Riccardin C **1.2**



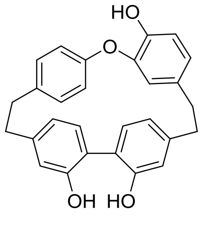
Analogue **1.3**



Asterelin A **1.4**



Cavicularin **1.5**



Polymorphatin A **1.6**

The first approach developed a strategy for the total synthesis of riccardin D **1.1**. The key fragments in the target are synthesised then connected using a Heck reaction. An intramolecular Wittig reaction is then used to achieve macrocyclisation.

The second approach provides access to many natural products in the macrocyclic bisbibenzyl family, including riccardin C **1.2**, asterelin A **1.4** and cavicularin **1.5** as well as an unnatural analogue **1.3**. We have synthesised and connected the key fragments of each target. To close the macrocyclic ring, we have demonstrated for the first time a new strategy involving an alkyllithium mediated displacement reaction to make the macrocycle via a Corey Seebach reaction. We have used the method to complete total syntheses of riccardin C **1.2** and an unnatural analogue **1.3**. The work additionally constitutes formal total syntheses of asterelin A **1.4** and cavicularin **1.5**.

The third approach provided a method to achieve the first total synthesis of polymorphatin A **1.6**. A nickel-mediated cross-coupling reaction was used to effect macrocyclisation and install the strained biaryl linkage connecting its two distorted arenes.

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DECLARATION OF AUTHORSHIP

I, Faisal A. Almalki

declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

New Syntheses of the Macrocyclic Bisbibenzyl Natural Products, Riccardin D, Riccardin C, Polymorphatin A and an Unnatural Analogue; Formal Total Syntheses of Cavicularin and Asterelin A.

I confirm that:

- This work was done wholly or mainly while in candidature for a research degree at this University;
- Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- Where I have consulted the published work of others, this is always clearly attributed;
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- I have acknowledged all main sources of help;
- Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
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Almalki, F.; Harrowven, D.; *Eur. J. Org. Chem.* **2016**, *34*, 5738-5746

Signed:

Date: 31/05/2017

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A special thank goes to my dear mother and father to whom I dedicate this work. May their souls rest in peace.

Definitions and Abbreviations

2D	two dimensional
Å	angstrom
Ac	acetyl
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
br.	broad
Bu	butyl
°C	degrees centigrade
cm^{-1}	wavelength number
Cy$_2$NMe	*N*,*N*-dicyclohexylmethylamine
δ	chemical shift (ppm)
d	day(s)/ doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]-undec-7-ene
DCM	dichloromethane
DCC	*N,N'*-dicyclohexylcarbodiimide
DHP	3,4-dihydro-*2H*-pyran
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMA	*N*,*N*-dimethylacetamide
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNPH	2,4-dinitrophenyl hydrazine
Dtbpf	1,1-bis(di-*tert*-butylphosphino) ferrocene
ee	enantiomeric excess
EI	electron ionisation
equiv.	molar equivalent
ESI	electrospray ionization
Et	ethyl
et al.	*et alia* (Latin: and others)
g	gram
h	hour
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HIV	human immunodeficiency virus
HPLC	high performance liquid
HRMS	high resolution mass spectrometry
HWE	Horner–Wadsworth–Emmons
Hz	hertz
i	iso
i.e.	*id, est* (Latin: that is)
IR	infrared
J	coupling constant
K	kelvin
L	litre
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrometry
M	molar
m	milli/medium/multiplet
Me	methyl
m	meta
min	minute
MHz	megahertz
µ	micro
mol	mole
MP	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
MOM	methoxymethyl ether
m/z	mass/charge ratio
NCS	*N*-chlorosuccinimide
NIS	*N*-iodoosuccinimide
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*

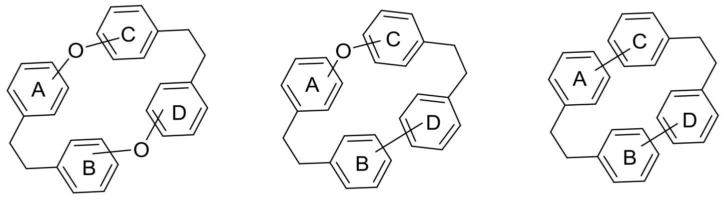
PE	petroleum ether
p-TsOH	*p*-toluenesulfonic acid
pH	potential hydrogen
Ph	phenyl
PMA	phosphomolybdic acid
ppm	part per million
PPTS	pyridinium *p*-toluenesulfonate
q	quartet
quant.	quantitative yield
RSM	recovered starting material
RT	room temperature
s	singlet/strong
sat.	saturated
SPhos	2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
S_NAr	nucleophilic aromatic substitution
t	triplet
t	tertiary (*tert*)
TBAC	tetrabutylammonium chloride
Tf	triflate
TFA	trifluoroacetic acid
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
Ts	*p*-toluenesulfonyl (tosyl)
TTMSS	tris(trimethylsilyl)silane
UV	ultraviolet
VAZO	2,2′-Azobis(2-methylpropionitrile), 2-(azo(1-cyano-1-methylethyl))-2-methylpropane nitrile
VT	variable temperature
w	weak

Chapter 1: Introduction

1.1 Background and biological activity of macrocyclic bisbibenzyls

The macrocyclic bisbibenzyls family of natural products are commonly found in liverworts and other bryophytes.[1] To date, over 70 macrocyclic bisbibenzyl natural products have been isolated. This family has a large number of biological activities associated with it including antifungal, cytotoxicity, anti-HIV activity, anticancer activity, anti-tumour, and antibacterial activity.[2-7] Indeed, liverworts of the genus *Marchantiales* have long been used in Japanese folk medicine to treat four types of diseases, *i.e.* diuretics, antiallergenic, antibacterial agents and antifungal agents.[8] This use of liverworts inspired Asakawa *et al*. to start a systematic study of the active constituents of Japanese liverwort species which led to the discovery of the macrocyclic bisbibenzyls.

Macrocyclic bisbibenzyls are typically composed of four aromatic rings in their core structure (labelled A-D). There are three main categories to connect these rings of macrocyclic bisbienzyl. The first class has two diphenyl ether linkages between rings A and C, and B and D **1.7**. The second class has one diphenyl ether linkage between rings A and C, and one biaryl bond between the B and D rings **1.8**. The last class has biaryl bonds between rings A and C, and B and D **1.9** (Figure 1.1).[8-10]



1.7 **1.8** **1.9**

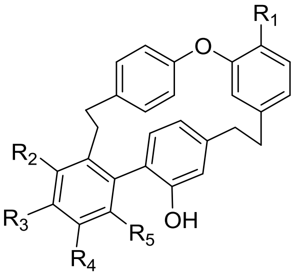
Figure 1.1: General structure of macrocyclic bisbibenzyls

1.2 Bisbibenzyl natural products: isolation and structural elucidation

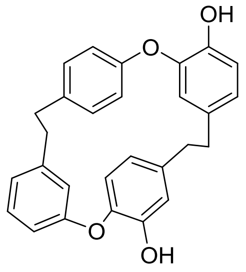
1.2.1 Riccardins, isoriccardins and isoriccardinquinones

The riccardin class of macrocyclic bisbibenzyls has one bisbibenzyl unit connected by a diphenyl ether and one by a direct biaryl linkage (except for riccardin B).[10-16] Table 1.1 shows the compounds that belong to the riccardin class, which have been found in a variety of liverwort species. To data, riccardin C **1.2** is the only example of macrocyclic bisbibenzyl isolated from a non-liverwort species. It was isolated from the perennial herbaceous plant *Primula macrocalyx*

Bge. (Primulaceae). Also, Koesnkova *et al.* reported the identification of riccardin C **1.2** in bryophyte species from the Altai Republic.[17] Riccardin D **1.1** was first isolated in 1988 by Asakawa *et al.* from the New Zealand liverworts *Monocle forsteri*.[11] In 2011, riccardin D **1.1** and isoriccardin C **1.15** were isolated from *Reboulia hemisphaerica* by Lou *et al.* (Figure 1.2).[10] Notably, these two samples were optically active and are enantioenriched rather than enantiopure in nature. Two quinone derivatives of riccardin C **1.2** have been isolated from the Hong Kong liverwort *Marchantia paleacea* by Cui *et al.* in 2002.[18] These compounds were named isoriccardinquinone A **1.18** and B **1.19**.

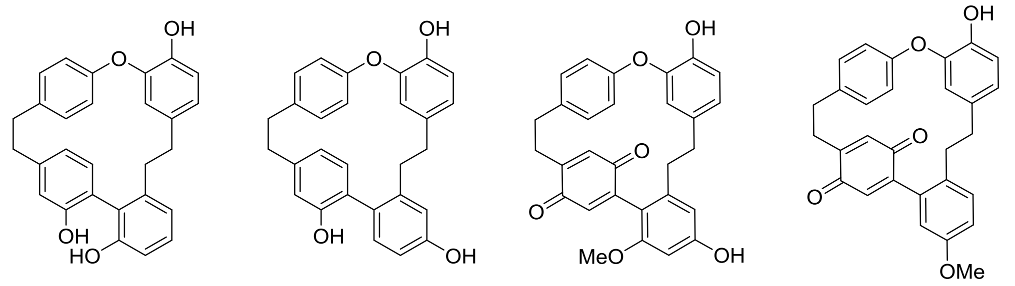


	R_1	R_2	R_3	R_4	R_5
Riccardin A **1.10**	OH	H	OMe	H	H
Riccardin C **1.2**	OH	H	OH	H	H
Riccardin D **1.1**	OH	H	H	H	OH
Riccardin E **1.11**	OH	H	H	H	OMe
Riccardin F **1.12**	OMe	H	OH	H	H
Riccardin G **1.13**	OMe	H	H	H	OH
Riccardin H **1.14**	OH	OH	OH	OH	H



Riccardin B **1.15**

Table 1.1: Riccardins

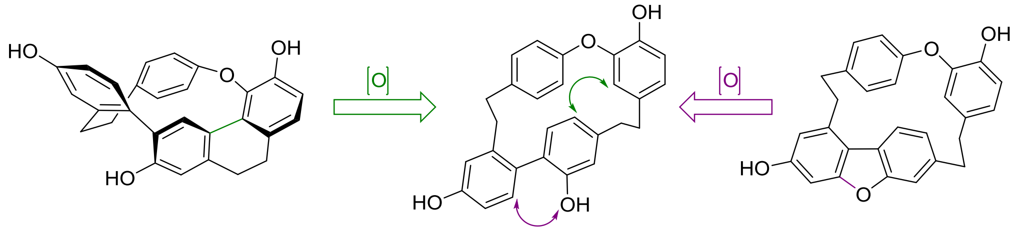


Isoriccardin C **1.16**   Isoriccardin D **1.17**   Isoriccardinquinone A **1.18**   Isoriccardinquinone B **1.19**

Figure 1.2: Isoriccardins and isoriccardinquinones

1.2.2 Cavicularin and asterelins

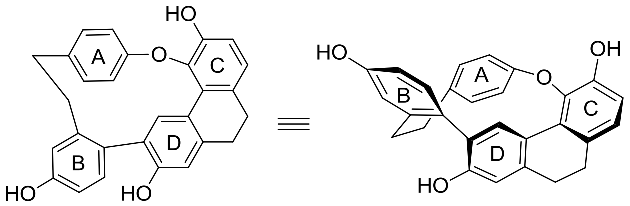
Riccardin C **1.2** is believed to be the biosynthetic precursor of other natural bisbibenzyl products such as cavicularin **1.5** and asterelin A **1.4** through intramolecular oxidative cyclisation (Figure 1.3).[19]



Cavicularin **1.5**   Riccardin C **1.2**   Asterelin A **1.4**

Figure 1.3: Oxidative cyclisation of riccardin C **1.2**[19]

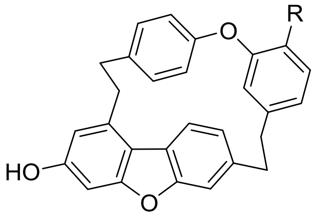
In 1996, (+)-cavicularin **1.5** (Figure 1.4) was first isolated from the liverwort *Cavicularia densa* which was collected on Mount Ishizuchi on the island of Shikoku in Japan.[20] It is a unique example of bisbibenzyl macrocycle because of the highly strained 14-membered ring. (+)-Cavicularin **1.5** has optical activity because of the restricted rotational freedom.[9]



1.5 **1.5**

Figure 1.4: Flat and perspective view of cavicularin **1.5**

The asterelins have a unique structure within the bisbibenzyls family as they contain a dibenzofuran moiety. Lou *et al*. isolated these compounds from the Chine liverwort *Asterella angusta* and named them asterelin A **1.4** and B **1.20** (Figure 1.5).[21]

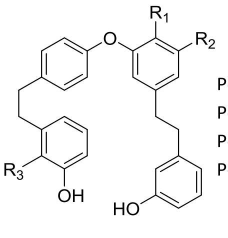


	R
Asterelin A **1.4**	OH
Asterelin B **1.20**	OMe

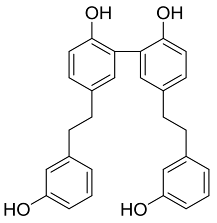
Figure 1.5: Structure of asterelin A **1.4** and B **1.20**

1.2.3 Perrottetins and isoperrottetin A

The perrottetins E **1.21**, F **1.22** and G **1.23** were isolated from liverworts *Radula perrottetii*.[22] The perrottetins are not macrocyclic compounds but are linear analogue of macrocyclic bisbibenzyls (Figure 1.6). Perrottetin H **1.24** was isolated from the ether extract of *Jubula japonica* and this is rare examples of a bisbibenzyl structure isolated from non-liverwort species of higher plants.[23] In 1994, Asakawa *et al.* reported the isolation of isoperrottetin A **1.25** from liverworts *Radula perrottetii*.[24] It is produced in nature by oxidative coupling of two lunularin subunits.



	R_1	R_2	R_3
Perrottetin E **1.21**	OH	H	H
Perrottetin F **1.22**	OH	OH	H
Perrottetin G **1.23**	OMe	OH	H
Perrottetin H **1.24**	OH	OH	OH

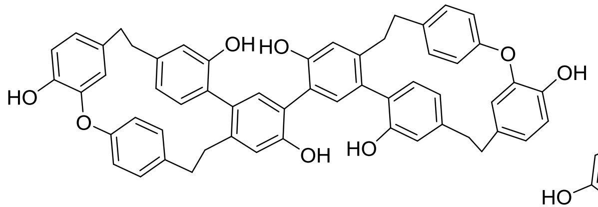


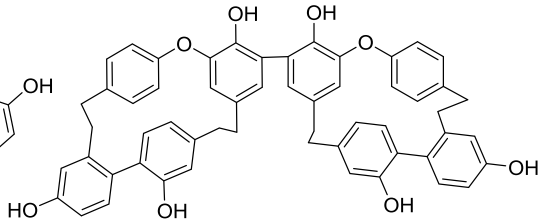
Isoperrottetin A **1.25**

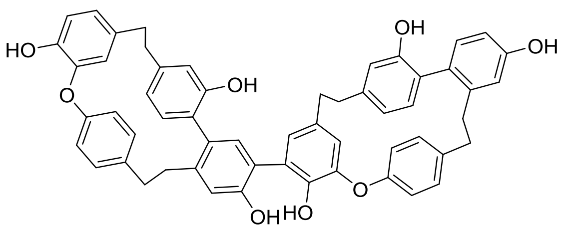
Figure 1.6: Perrottetins and isoperrottetin A

1.2.4 Pusilatins

In 1994, Asakawa *et al*. reported the isolation of bisbibenzyl dimers from *Blasia pusilla*.[25] The pusilatins are formed in nature by oxidative intermolecular coupling between two molecules of riccardin C **1.2**. These dimers of riccardin C are named pusilatins A **1.26**, B **1.27**, C **1.28** and D **1.29** (Figure 1.7).


Pusilatin A **1.26**


Pusilatin B **1.27**


Pusilatin C **1.28**

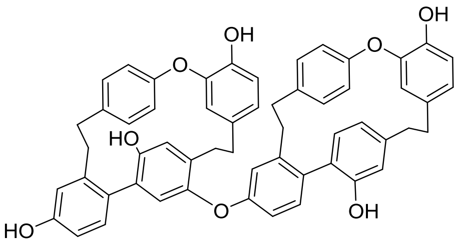

Pusilatin D **1.29**

Figure 1.7: Pusilatins

Becker and co-worker additionally reported the isolation of pusilatin B **1.27** and pusilatin E **1.30** from the liverwort *Ricciocarpos natanis*.[26] In 1997, Asakawa *et al.* isolated pusilatin E **1.30** from the liverwort *Riccardia multifida* subsp. *Decrescens*.[27] They suggested that pusilatin E **1.30** was formed in nature by an intermolecular oxidative coupling between two molecules of riccardin A **1.10** (Figure 1.8).

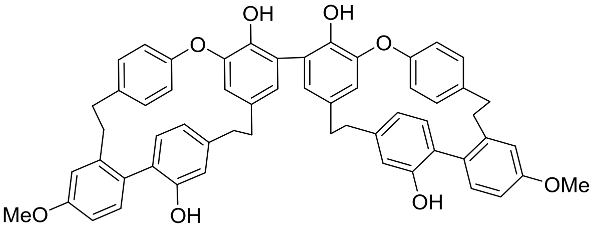
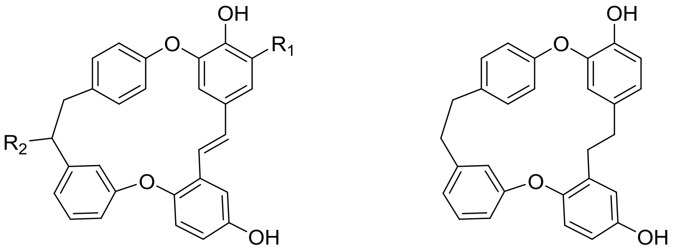


Figure 1.8: pusilatin E **1.30**

1.2.5 Ptychantols

Ptychantols A **1.31**, B **1.32** and C **1.33** were isolated from the liverwort *Ptychanthus striatus* by Asakawa *et al.*[28] These macrocyclic bisbibenzyls feature a *trans*-stilbene within the macrocyclic core, along with two aryl ether linkages (Figure 1.9). Dihydroptychantol A **1.34** was isolated from *Asterella angustI* and is a saturated analogue of ptychantol A **1.31**.[21]



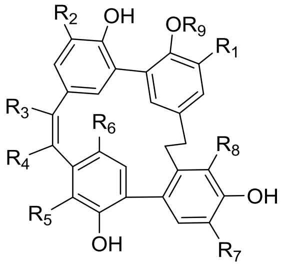
	R_1	R_2
Ptychantol A **1.31**	H	H
Ptychantol B **1.32**	OH	H
Ptychantol C **1.33**	OH	OH

Dihydroptychantol A **1.34**

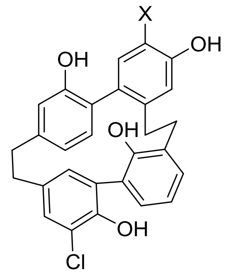
Figure 1.9: Ptychantols and dihydroptychantol A

1.2.6 Bazzanins and Chlorinated derivatives of the isoplagiochin

In 1998, Becker *et al*. isolated a new class of macrocyclic bisbibenzyl natural products which they called the bazzanins. The structure of these natural products contains chlorine atoms which is uncommon in compounds isolated from liverworts. Bazzanins A-J have been isolated from the liverwort *Bazzania trilobata*, while bazzanins L-R have been isolated from the liverwort *Lepidozia incurvata* (Figure 1.10).[29,30] These natural products are based on the isoplagiochin skeleton except the bazzanin K **1.53** which has a phenanthrene subunit.[29]

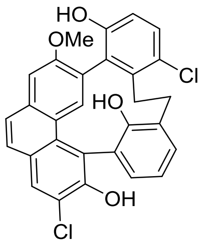


	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9
Bazzanin A **1.35**	H	Cl	H	H	H	H	H	H	H
Bazzanin B **1.36**	H	Cl	H	Cl	H	H	H	H	H
Bazzanin C **1.37**	H	Cl	H	Cl	H	H	Cl	H	H
Bazzanin D **1.38**	H	Cl	H	Cl	Cl	H	H	H	H
Bazzanin E **1.39**	H	Cl	H	Cl	Cl	H	Cl	H	H
Bazzanin F **1.40**	H	Cl	H	Cl	H	Cl	H	Cl	H
Bazzanin G **1.41**	Cl	Cl	H	Cl	Cl	H	H	Cl	H
Bazzanin H **1.42**	H	Cl	H	Cl	Cl	Cl	H	Cl	H
Bazzanin I **1.43**	Cl	Cl	H	Cl	Cl	Cl	Cl	H	H
Bazzanin L **1.44**	H	H	H	H	Cl	H	Cl	Cl	Me
Bazzanin M **1.45**	H	H	H	H	Cl	H	Cl	Cl	H
Bazzanin N **1.46**	Cl	H	H	H	Cl	H	Cl	Cl	H
Bazzanin O **1.47**	H	Cl	H	H	Cl	Cl	Cl	Cl	Me
Bazzanin P **1.48**	Cl	Cl	H	H	Cl	H	Cl	Cl	H
Bazzanin Q **1.49**	Cl	Cl	H	H	Cl	Cl	Cl	Cl	H
Bazzanin R **1.50**	Cl	Cl	Cl	Cl	Cl	Cl	Cl	Cl	H



Bazzanin J **1.51** X=Cl

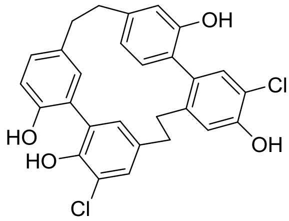
Bazzanin S **1.52** X=H



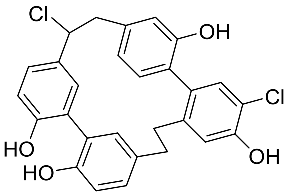
Bazzanin K **1.53**

Figure 1.10: Bazzanins

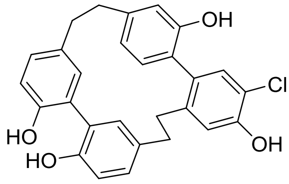
Asakawa *et al*. isolated 2,12-dichloroisoplagiochin D **1.54**, 12,7’-dichloroisoplagiochin D **1.55** and 12,10’-dichloroisoplagiochin C **1.57** fom the liverworts *Herbertus sakuraii* (Figure 1.11).[31] 2,12-Dichloroisoplagiochin D **1.54** and 12-chloroisoplagiochin D **1.56** have also been isolated from *Mastigophora diclados*.



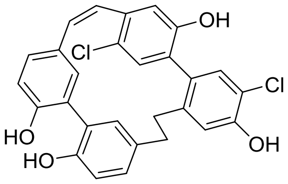
2,12-dichloroisoplagiochin D **1.54**



12,7'-dichloroisoplagiochin D **1.55**



12-chloroisoplagiochin D **1.56**

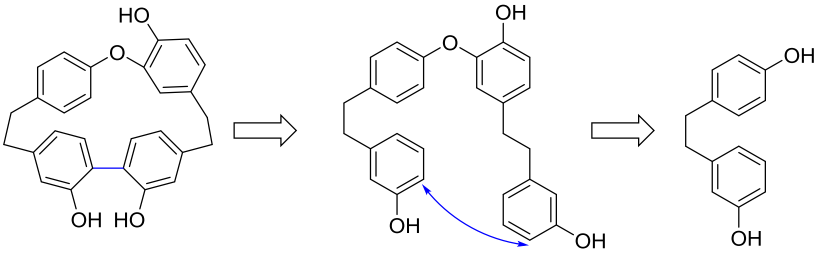


12,10'-dichloroisoplagiochin C **1.57**

Figure 1.11: Chlorinated derivatives of the isoplagiochin

1.2.7 Polymorphatin A

In 2007, Lou *et al.* isolated polymorphatin A **1.6** from a Chinese Liverwort *Marchantia polymorpha* and assigned its name.[32] Polymorphatin A **1.6** is a unique example of bisbibenzyl macrocycle products because of its highly strained ring. In nature, dimer isolation of lunularin **1.58** can generate perrottetin E **1.21** which may then form a macrocycle through coupling of its *para*-carbon centres (as indicated by the blue arrow) to form polymorphatin A **1.6** (Figure 1.12). Speicher *et al*. cast doubt on the authenticity of this product after they synthesised it and found little consistency with reported data (See Section 1.4.5).[46] Our study resolves this conflict (See Chapter 4).

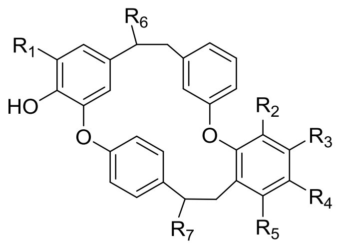


Polymorphatin A **1.6** Perrottetin E **1.21** Lunularin **1.58**

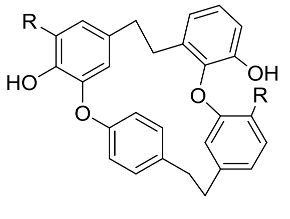
Figure 1.12: Structure of polymorphatin A **1.6** and perrottetin E **1.21** as the biosynthetic precursor to an array of macrocyclic bisbibenzyl ethers

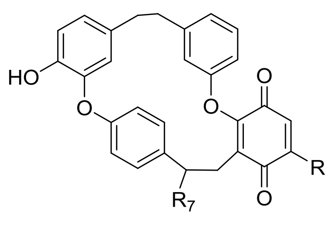
1.2.8 Marchantins, isomarchantins and pakyonol

The most frequently isolated families of the macrocyclic bisbibenzyl class are the marchantins which have a two ether bridges in their macrocyclic bisbibenzyl core. The marchantins were isolated from the *Marchantia polymorpha*.[33-35] Interestingly, the marchantins can be oxidised at the ethylene bridges in nature which is rare in the macrocycle bisbibenzyl class. In 1995, marchantin N **1.72** and marchantinquinone **1.73** were isolated from the Taiwanese liverwort *Reboulia hemisphaerica* and identified by Wu *et al*.[36] These compounds have quinonoid structures as presented in Figure 1.13. The isomarchantins have a similar structure to the marchantins. Isomarchantin C **1.71** was isolated from the Indian liverwort *Marchantia palmate*.[34]



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Marchantin A **1.59**	OH	OH	H	H	H	H	H
Marchantin B **1.60**	OH	OH	OH	H	H	H	H
Marchantin C **1.61**	H	OH	H	H	H	H	H
Marchantin D **1.62**	OH	OH	H	H	H	OH	H
Marchantin E **1.63**	OH	OH	H	H	H	OMe	H
Marchantin F **1.64**	OH	OH	OH	H	H	OH	H
Marchantin G **1.65**	OH	OH	H	H	H	=O	H
Marchantin H **1.66**	H	OH	OH	H	H	H	H
Marchantin I **1.67**	H	H	H	OMe	H	H	H
Marchantin J **1.68**	OH	OH	H	H	H	OEt	H
Marchantin K **1.69**	OH	OH	OH	H	H	OMe	H



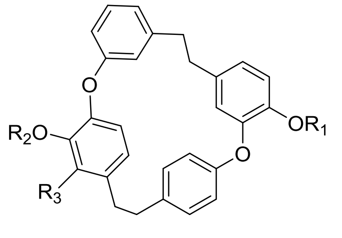


	R
Isomarchantin B **1.70**	OH
Isomarchantin C **1.71**	H

	R
Marchantin N **1.72**	OMe
Marchantinquinone **1.73**	H

Figure 1.13: Marchantins, marchantinquinone and Isomarchantins

Huneck *et al*. reported the isolation of pakyonol **1.74** from the Korean liverwort *Mannia fragrans*, while in 2006, Lou *et al.* isolated neomarchantin A **1.75** from the Chinese liverwort *Marchantia polymorpha* L (Figure 1.14).[37,16] Asakawa and co-workers additionally reported the isolation of neomarchantin A **1.75** and neomarchantin B **1.76** from the New Zealand liverwort *Schistochila glaucescens*.[38]

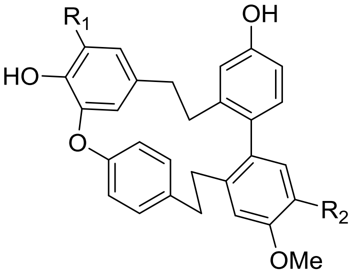


	R_1	R_2	R_3
Pakyonol **1.74**	Me	H	H
Neomarchantin A **1.75**	H	H	H
Neomarchantin B **1.76**	H	OH	OH

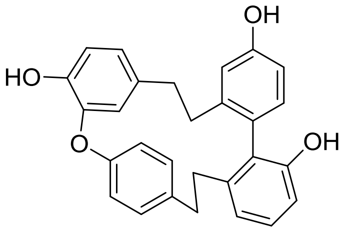
Figure 1.14: Related structures of marchantins

1.2.9 Plagiochins

The common feature in the plagiochins are the diphenyl ether bridge and *ortho*, *ortho*'-biaryl linkage. In 1987, Asakawa and co-workers isolated plagiochins A **1.77**, B **1.78** C **1.79** and D **1.80** from *Plagiochila acanthophylla* subsp. *Japonica* (Figure 1.15).[39] Lou *et al.* reported the isolation of plagiochin E **1.81** from *Marchantia plymorpha*.[16] After Speicher *et al.* had achieved the total synthesis of plagiochin E **1.81**, they cast doubt on the identity of plagiochin E **1.81**.[40] Indeed, they concluded that the data given for plagiochin E **1.81** was similar to that recorded on their synthetic of riccardin D **1.1**. Our study helps to resolve these doubts (See Chapter 2).



	R_1	R_2
Plagiochin a **1.77**	OH	OH
Plagiochin B **1.78**	OH	H
Plagiochin C **1.79**	H	OH
Plagiochin D **1.80**	H	H

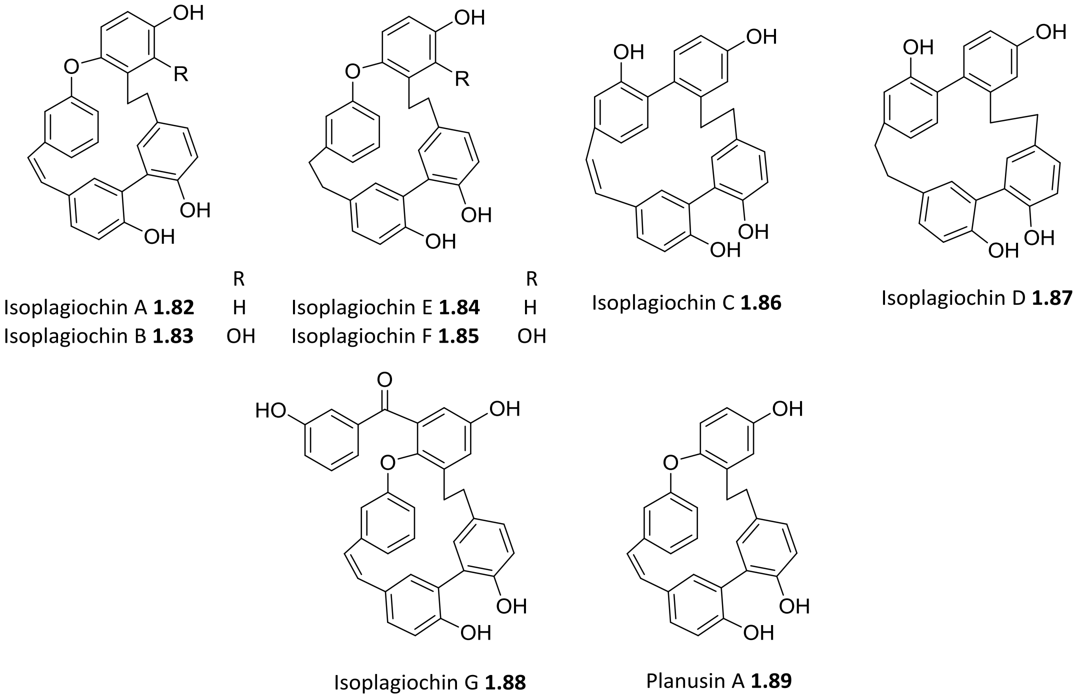


Plagiochin E **1.81**

<u>Figure **1.15**:</u> Plagiochins

1.2.10 Isoplagiochins and planusin

The isoplagiochins class is interesting because it includes variously structured atypical bisbibenzyl natural products (Figure 1.16).[41] In 1996, Asakawa *et al.* isolated isoplagiochins C **1.86** and D **1.87** from liverwort *Plagiochila fruticosa*.[42] These compounds have a common skeletal structure containing one diphenyl ether and one biaryl linkage. However, isoplagiochin C **1.86**, planusin A **1.26** and isoplagiochin G **1.88** have unsaturation in one of the ethano chains. In addition, isoplagiochin G **1.88** has an additional ring in the form of an attached benzoyl group. In 1998, isoplagiochin A **1.82** and planusin A **1.26** were isolated from the liverwort *Heteroscyphus planus* by Nabeta *et al.*[43] Also, isoplagiochin E **1.84**, F **1.85** and D **1.87** have been identified as saturated analogues.[41,42] Isoplagiochins C **1.68** and D **1.87** have been found to be chiral because of their configurational stability. Although the first isolation of these compounds from *plagiochila acantophyllyal* subsp. *japonica* showed no optical activity, isoplagiochins C **1.86** and D **1.87** were sequentially isolated as optically active samples from liverworts *Lepidozia incurvata* with ($[\alpha]_D$ = +42.5, c 0.2, MeOH) and *Herbertus sakuraii* giving an $[\alpha]_D$ of +47.5.[9,30,42] Moreover, Bringmann *et al*. isolated isoplagiochin C **1.84** from *Plagiochila deflexa* as predominantly (*P*)-isoplagiochin C, the sample being laevorotatory with an $[\alpha]_D$ of -49.0 (*c* 0.75, MeOH) and an e.r. of 85 : 15.[44]



	R
Isoplagiochin A **1.82**	H
Isoplagiochin B **1.83**	OH

	R
Isoplagiochin E **1.84**	H
Isoplagiochin F **1.85**	OH

Isoplagiochin C **1.86**

Isoplagiochin D **1.87**

Isoplagiochin G **1.88**

Planusin A **1.89**

Figure 1.16: Isoplagiochins and planusin A

1.3 Biosynthesis of macrocyclic bisbibenzyls

Lunularin **1.58** is considered to be the common precursor in the biosynthesis of macrocyclic bisbibenzyls.[9] The oxidative dimerisation of lunularin **1.58** first produces the natural products perrottetin E **1.21** and isoperrottetin A **1.25**.[19] Further oxidation of isoperrottetin A **1.25** and perrottetin E **1.21** then forms new C-O or C-C bonds between the terminal arenes to give macrocycles such as **1.90**, **1.91**, **1.92** and **1.93** (Figure 1.17). Although analogue **1.3** has a similar constitution to the ring systems in natural macrocyclic bisbibenzyls, the biaryl bond linking arenes B and D is not consistent with macrocyclic bisbibenzyl biosynthesis. This is because these rings are necessarily bound within the macrocycle via *ortho*- and *para*-linkages while in analogue **1.3** they have an *ortho*- and *meta*-linkage (See Section 3.2).[19]

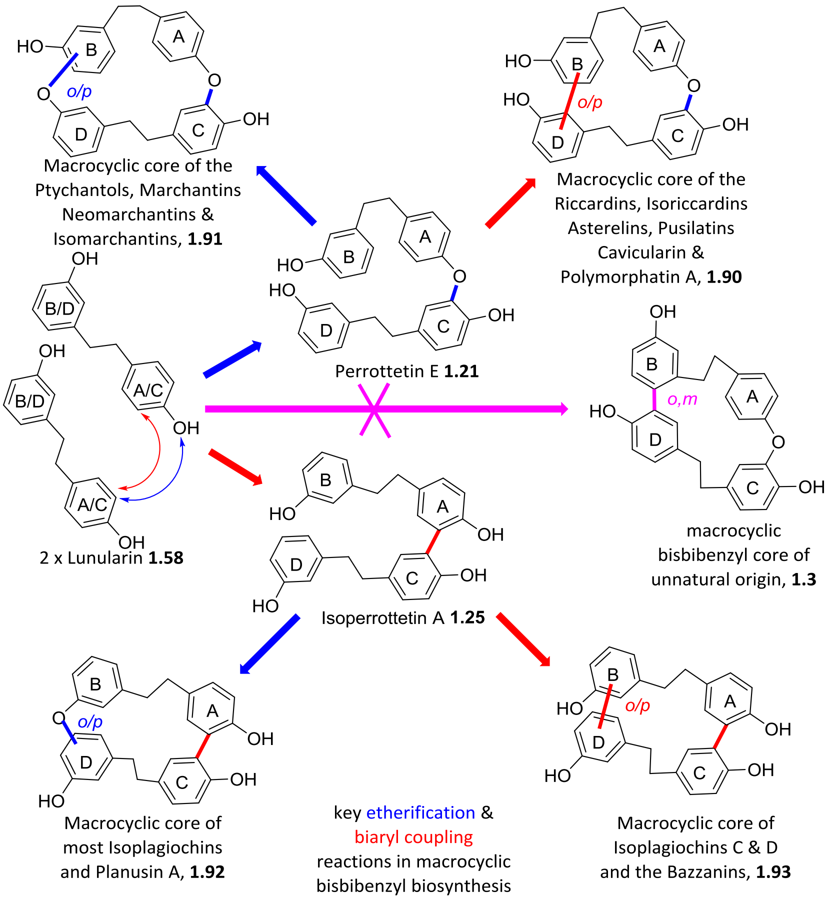


Figure 1.17: Structural relationships in macrocyclic bisbibenzyl natural products and the unnatural analogue[19]

1.4 Previous macrocyclisation strategies in the synthesis of macrocyclic bisbibenzyls

The macrocyclisation reaction is a step which is most often discussed in literature reviews as it is often the most difficult reaction to effect.[9,45] This key step can be used to make one of the ethylene bridges, which is the most common approach, or to make either the biaryl or the biaryl ether bond (Figure 1.18).

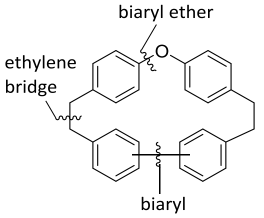


Figure 1.18: Examples of disconnections

1.4.1 Nomenclature

To elaborate on the discussion in this thesis, macrocycles are referred to by the labels of the constituent arenes of the natural product and the associated linkage. Thus, the A and C rings are linked to form a biaryl ether while the B and D rings are linked directly, as shown in Figure 1.19.

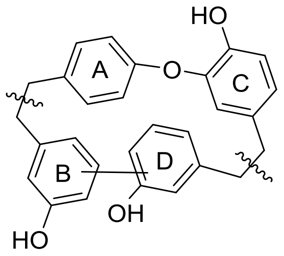


Figure 1.19: Nomenclature used to describe architecture

1.4.2 Macrocyclisation approaches in the synthesis of riccardin D 1.1

A total synthesis of riccardin D **1.1** (Figure 1.20) was reported by Speicher *et al.* in 2009.[40,46] In 2012, Lou and co-workers also completed the total synthesis of riccardin D **1.1**.[6] Both used a Wittig reaction to effect macrocyclisation. Indeed, it has proven to be the most popular strategy because of the reliability of this reaction.[9]

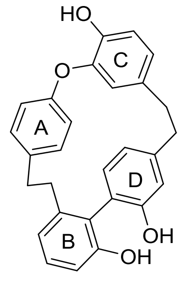
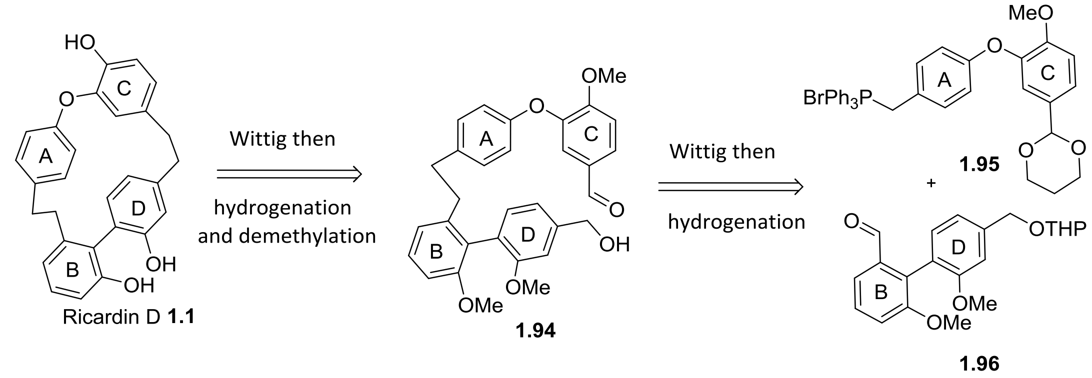


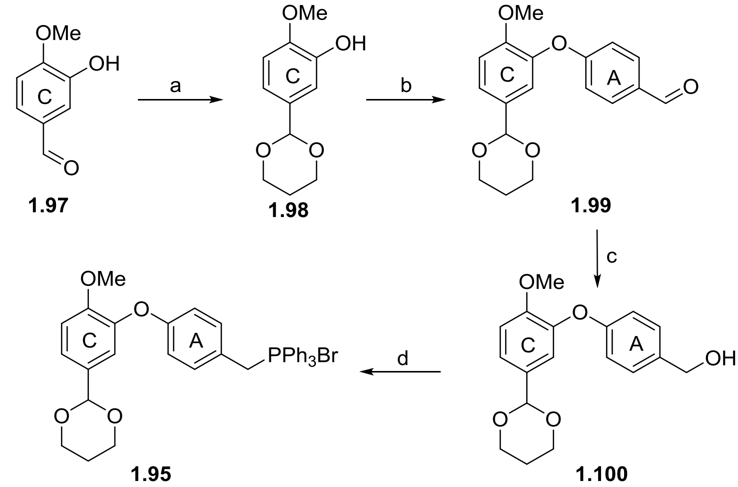
Figure 1.20: Riccardin D **1.1**

Speicher *et al*. also used an intramolecular Wittig reaction to connect their AC **1.95** and BD **1.96** fragments on route to cyclisation precursor **1.94** (Scheme 1.1).[46]



Scheme 1.1: Retrosynthesis of riccardin D **1.1**

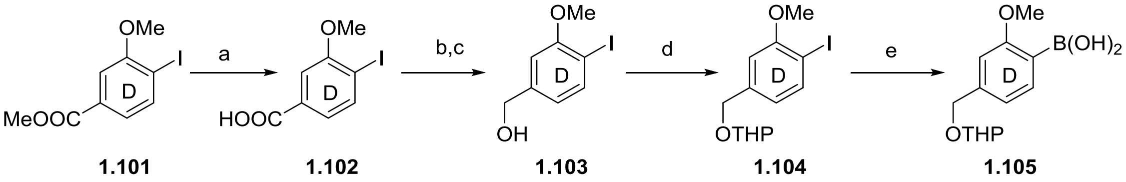
They started their synthesis of the AC **1.95** fragment from commercially available isovanillin **1.97**. The aldehyde of **1.97** was protected to give acetal **1.98** which then underwent a nucleophilic aromatic substitution (S_NAr) reaction to give biaryl ether **1.99**. The aldehyde of **1.99** was reduced to alcohol **1.100**, before bromination and treatment with PPh_3 gave benzylphosphonium salt **1.95** (Scheme 1.2).



Reagents and conditions: a) $CH(OEt)_3$, tetrabutylammonium tribromide,1,3-propanediol, 65 °C, 12 h, 91%; b) 4-fluorobenzaldehyde, K_2CO_3, DMF, 160 °C, 20 h, 93%; c) $NaBH_4$, EtOH, 0 °C to RT, 2 h, 97%; d) $PPh_3{\cdot}HBr$, MeCN, reflux, 2 h, 85%.

Scheme 1.2: Formation of AC **1.95** fragment

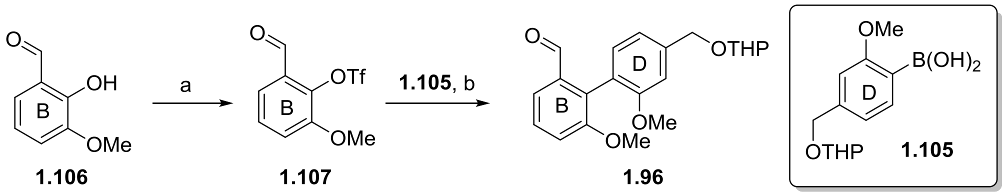
With the AC **1.95** fragment in hand, attention turned to the preparation of the BD **1.96** fragment using a Suzuki-Miyaura reaction. Preparation of the required boronic acid **1.105** began with saponification of ester **1.101** to benzoic acid **1.102**. The latter was then reduced in two steps to benzylic alcohol **1.103** which was protected as its THP ether **1.104**. Finally, boronic acid **1.105** was obtained from ether **1.104** by a halogen/lithium exchange reaction with subsequent scavenging of the organolithium intermediate with $B(OMe)_3$ and hydrolysis with acid (Scheme 1.3).



Reagents and conditions: a) NaOH, 85%; b) $SOCl_2$; c) $NaBH_4$, 1,4-dioxane, 77% over two steps; d) TsOH, DCM, dihydropyran, 76%; e) *n*-BuLi, $B(OMe)_3$, sat. KH_2PO_4, 80%.

Scheme 1.3: Boronic acid **1.105** formation

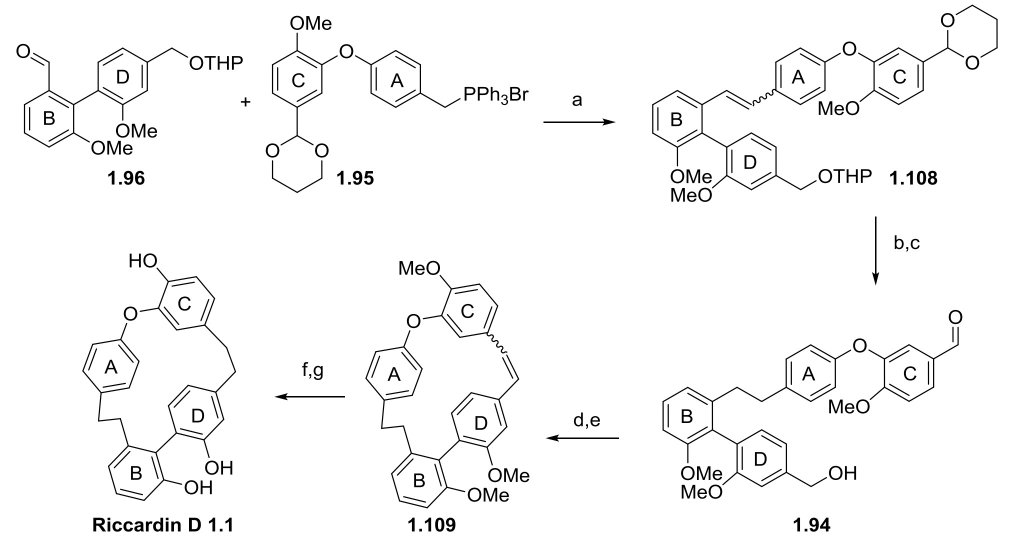
In parallel, triflate **1.107** was prepared from *ortho*-vanillin **1.106**. With **1.105** and **1.107** in hand, a Suzuki reaction was carried out to afford biaryl **1.96** (Scheme 1.4).



Reagents and conditions: a) pyridine, DCM, Tf_2O, 0 °C to RT, 90%;
b) **1.105**, $Pd(PPh_3)_4$, PhMe/EtOH/ 2 M Na_2CO_3, reflux, 16 h, 69%.

Scheme 1.4: The preparation of BD **1.96** fragment

Having the AC **1.95** and BD **1.96** fragments in hand, a Wittig reaction gave stilbene **1.108**. Then, the cyclisation precursor **1.94** was prepared by the hydrogenation of the alkene **1.108**, removal of THP and acetal protection. The alcohol was converted into the corresponding benzylphosphonium salt to facilitate a Wittig cyclisation to macrocycle **1.109**. After hydrogenation and demethylation, a synthetic sample of the natural product riccardin D **1.1** was obtained (Scheme 1.5).



Reagents and conditions: a) K_2CO_3,18-crown-6, DCM, reflux, 24 h, 94%; b) Pd/C (5%), 3 bar H_2, Et_3N, EtOAc, RT, 24 h, 99%; c) 2 M HCl/THF (1:1), RT, 12 h, 96%; d) $PPh_3\cdot HBr$, MeCN, reflux, 16 h; e) NaOMe, DCM, 24 h, 68% over two steps (*E/Z* 1.1:1); f) Pd/C (5%), 3 bar H_2, EtOAc, RT, 24 h, 95%; g) BBr_3 (10 equiv.), DCM, -78 °C to RT, over 5 h, then 10 h at RT, 71%.

Scheme 1.5: The total synthesis of riccardin D **1.1**

After validating the pathway to reach riccardin D **1.1**, Lou *et al*. has also completed the total synthesis of riccardin D **1.1** following the cyclisation approach reported by Speicher *et al*.[6] Lou *et al*. studied the chirality of the riccardin D **1.1** sample they had isolated and found that it was optically active ($[\alpha]_D$ = -3.9, *c* 0.3, acetone).[10] Moreover, they were able to separate methylated analogues of riccardin D **1.1** at ambient temperature using a chiral stationary phase HPLC. As a result, they established that riccardin D **1.1** was enantioenriched rather than enantiopure. Moreover, riccradin D **1.1** had sufficient conformational rigidity to prolong its half-life for atropisomerisation beyond 1000s at room temperature (Figure 1.21).[9]

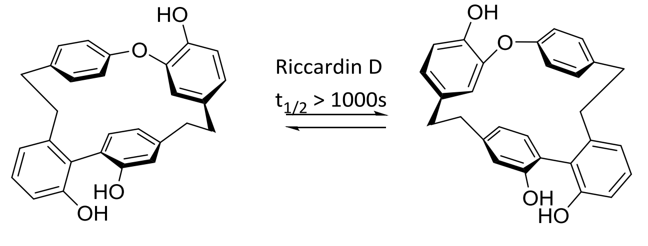


Figure 1.21: Three-dimensional depictions of riccardins D **1.1**

1.4.3 Macrocyclisation approaches in the syntheses of riccardin C 1.2 and cavicularin 1.5

With a growing interest in the biological effects of riccardin C **1.5**, several groups have attempted its total synthesis.[11,13,34] The key macrocyclisation step has been achieved using Wittig, Wurtz and McMurry reactions to form one of the ethano bridges between the AB or CD arenes.[9] The formation of a biaryl bond in macrocyclisation has also been used to obtain riccardin C **1.2** and cavicularin **1.5** by means of a palladium-catalysed cross coupling. The cyclisation steps needed to obtain cavicularin can also be afforded by the *de novo* construction of arene A. Another efficient way to achieve macrocyclisation is by nucleophilic aromatic substitution. To date, there have been no reported syntheses of macrocyclic bisbibenzyls using a Corey-Seebach reaction, as described in the current study.[19] Previous strategies of syntheses of riccardin C **1.2** and cavicularin **1.5** are summarised in Figure 1.22.

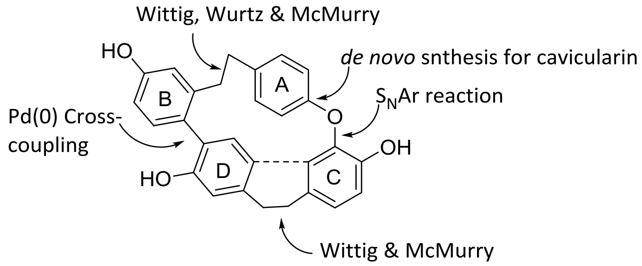
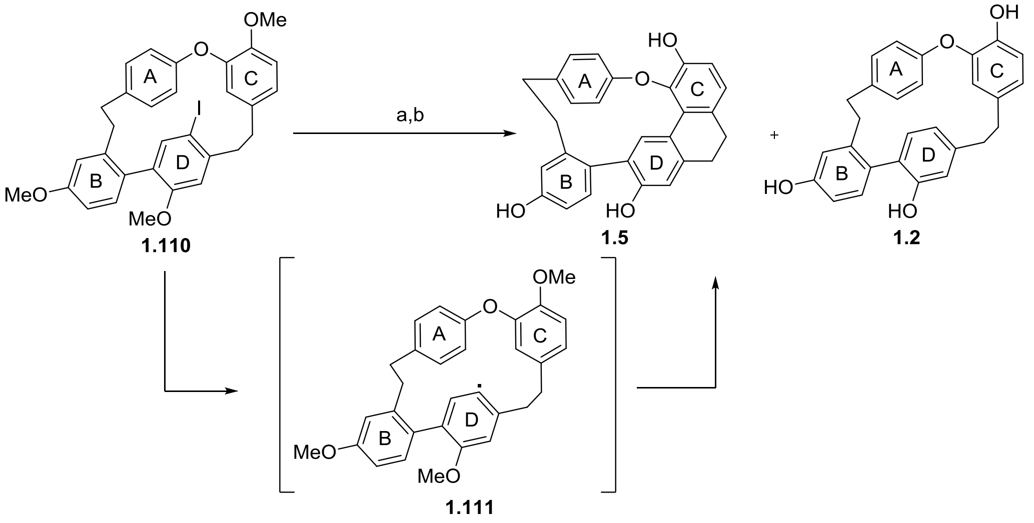


Figure 1.22: Macrocyclisation strategies used to prepare riccardin C **1.2** and cavicularin **1.5**

1.4.3a The McMurry method

The first total synthesis of cavicularin **1.5** was achieved by Harrowven and co-workers through the use of a McMurry macrocyclisation which yielded the protected and iodinated analogue of riccardin C **1.110**. It was treated under radical forming conditions to form the intermediate compound **1.111**. This resulted in a mixture of protected cavicularin and riccardin C which could be separated after deprotection to obtain cavicularin **1.5** and riccardin C **1.2** (Scheme 1.6).[47]

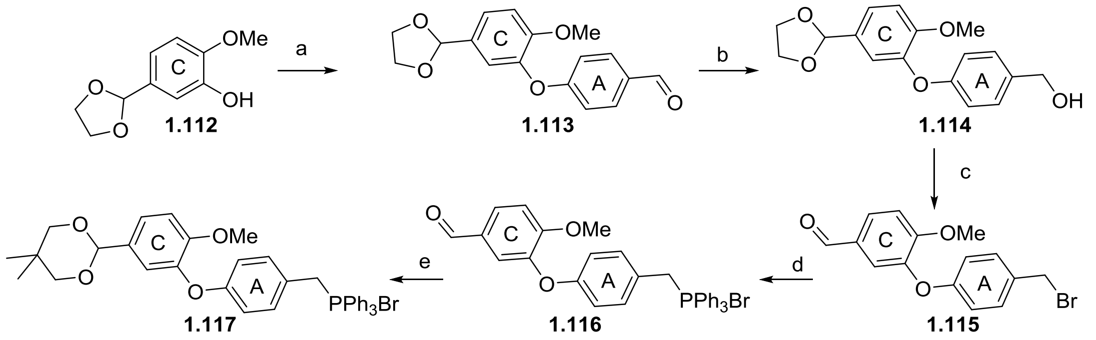


Reagents and conditions: a) AIBN, TTMSS, PhMe; b) BBr$_3$, DCM, 32% of **1.5** and 63% of **1.2** (over two step).

Scheme 1.6: The syntheses of cavicularin **1.5** and riccardin C **1.2**

The synthesis started with the preparation of the AC **1.117** fragment by using S$_N$Ar to obtain diphenyl ether **1.113** (Scheme 1.7). Then, the reduction of the aldehyde in **1.113** gave alcohol

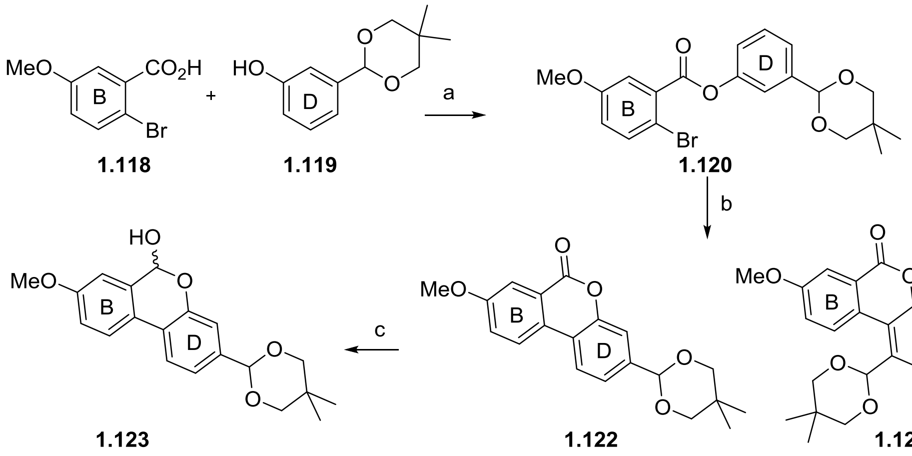
1.114 which was converted into the corresponding benzylphosphonium salt **1.116** in two steps, followed by protection of the aldehyde to obtain **1.117**.[48]



Reagnts and conditions: 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 1.7: Formation of AC **1.117**

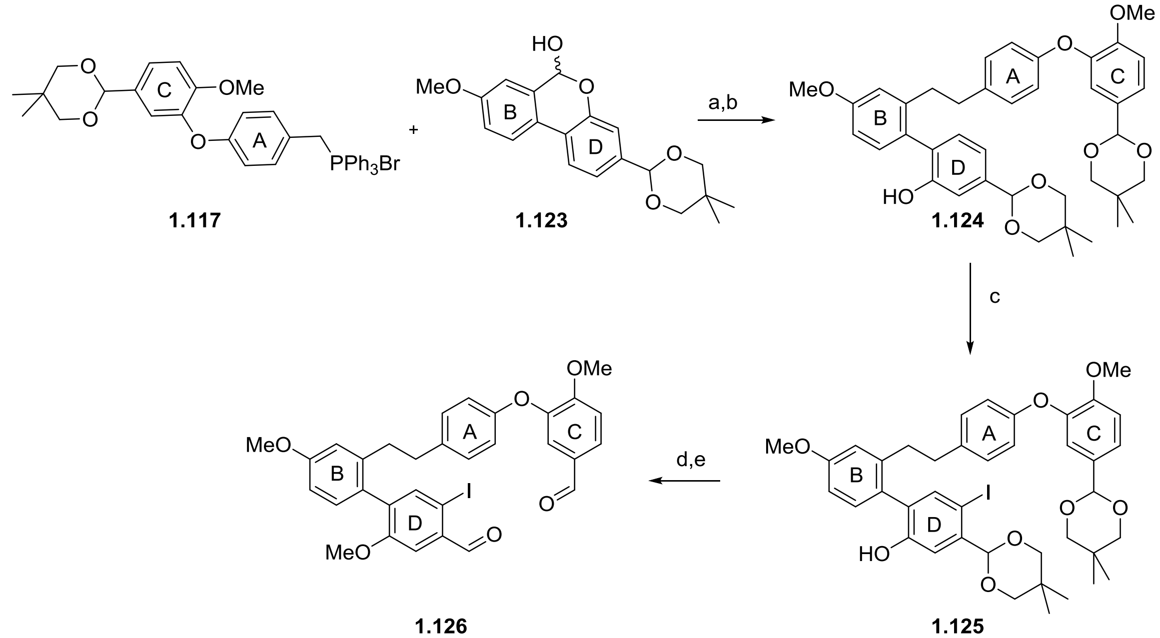
Formation of the BD fragment **1.123** began with acetal protection of 3-hydroxybenzaldehyde to obtain **1.119**, followed by DCC-coupling with 2-bromo-5-methoxybenzoic acid to give ester **1.118**. At high temperature, treatment of **1.120** with Herrmann's catalyst yielded the desired product **1.122** and undesired product **1.121**. Reduction of **1.122** with DIBAL-H then provided lactol **1.123** (Scheme 1.8).



Reagnts and conditions: a) DCC, DMAP, 92%; b) Herrmann's catalyst (4%), NaOAc, **1.122** 38%, **1.121**, 35%; c) DIBAL-H, 60%.

Scheme 1.8: Formation of BD **1.123** fragment

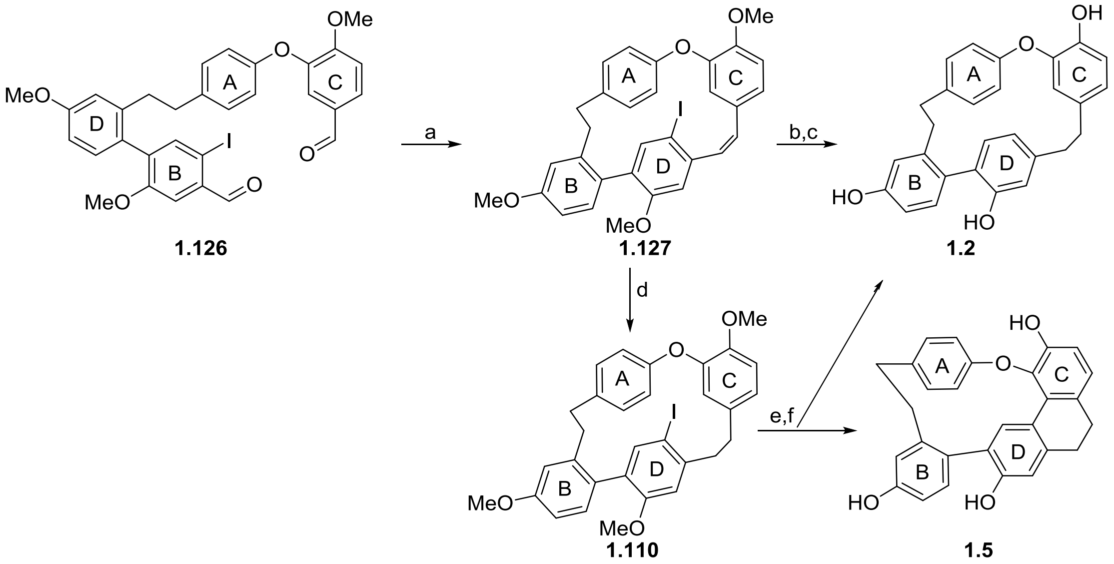
A Wittig reaction coupled fragments AC **1.117** and BD **1.123** to form the stilbene in a 2:1 *trans*:*cis* ratio. This was followed by hydrogenation to afford stilbene **1.124** (Scheme 1.9). A regioselective iodination of phenol next gave the desired product **1.125**. The protection of hydroxyl and acetyl hydrolysis afforded bisaldehyde **1.126**.



Reagnts and conditions: 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%.

Scheme 1.9: Formation of bisaldehyde **1.126**

The cyclisation of dialdehyde **1.126** was achieved by McMurry reaction with low valent titanium and was *cis*-selective to afford **1.127**. Hydrogenation with Pd/C then reduced the alkene and halide to obtain protected riccardin C which was demethylated to give riccardin C **1.2** (Scheme 1.10). Hydrogenation of **1.127** using *p*-toluenesulfonyl hydrazide was also used to access macrocycle **1.110**. This gave protected cavicularin and protected riccardin C when treated under radical forming conditions to induced transannular ring contraction. The mixture of riccardin C trimethyl ether and cavicularin trimethyl ether was inseparable. Consequently they were treated with boron tribromide to remove the protecting groups to give a separable mixture of riccardin C **1.2** and cavicularin **1.5**. This work was the first published total synthesis of cavicularin **1.5**.

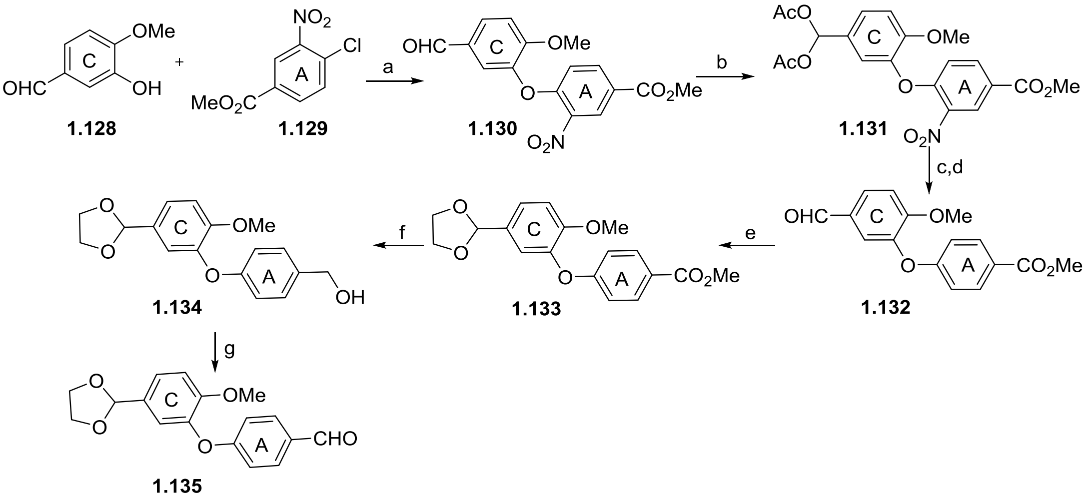


Reagnts and conditions: a) TiCl$_4$, Mg, THF, 35%; b) H$_2$, Pd/C, 86%; c) BBr$_3$ (5 equiv.), DCM, 86%; d) TsNHNH$_2$, NaOAc, THF/ H$_2$O, 91%; e) TTMSS, AIBN, PhMe; f) BBr$_3$, DCM, 95% over two steps, 2:1 ratio **1.5**:**1.2**.

Scheme 1.10: The syntheses of cavicularin **1.5** and riccardin C **1.2**

1.4.3b Wittig method

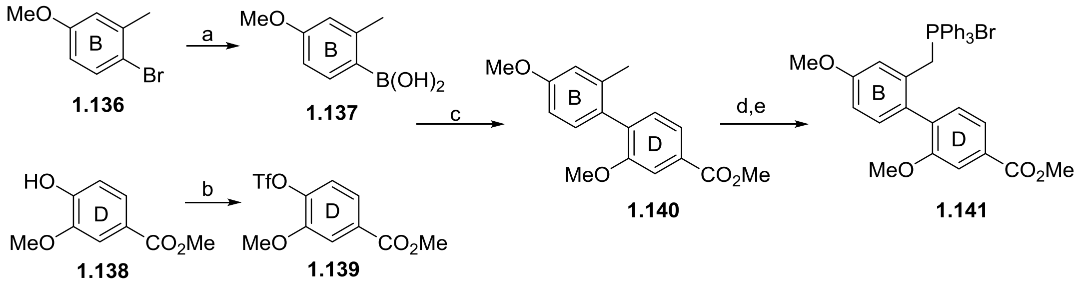
In 1998, Eicher *et al.* used a Wittig reaction to achieve the key macrocyclisation step in their total synthesis of riccardin C **1.2**.[48] They began with the preparation of AC fragment **1.135** from isovanillin **1.128** and aryl chloride **1.129**. First, an S$_N$Ar reaction was used to obtain biaryl ether **1.130** (Scheme 1.11). Then protection of the aldehyde gave **1.131**. Nitro group reduction and reductive deamination with concomitant acetal hydrolysis then afforded diphenyl ether **1.132**. The aldehyde was again protected as acetal **1.133** allowing reduction of the ester moiety to alcohol **1.134**. Its reoxidation then gave AC fragment **1.135**.



Reagents and Conditions: a) NaH, 88%; b) Ac$_2$O, H$_2$SO$_4$, 86%; c) H$_2$, Pd/C; d) NaNO$_2$, H$_3$PO$_4$, 74% over 2 steps; e) (HOCH$_2$)$_2$, 85%; f) LiAlH$_4$, 84%; g) PCC/Al$_2$O$_3$, 95%.

Scheme 1.11: Synthesis of AC **1.135** fragment

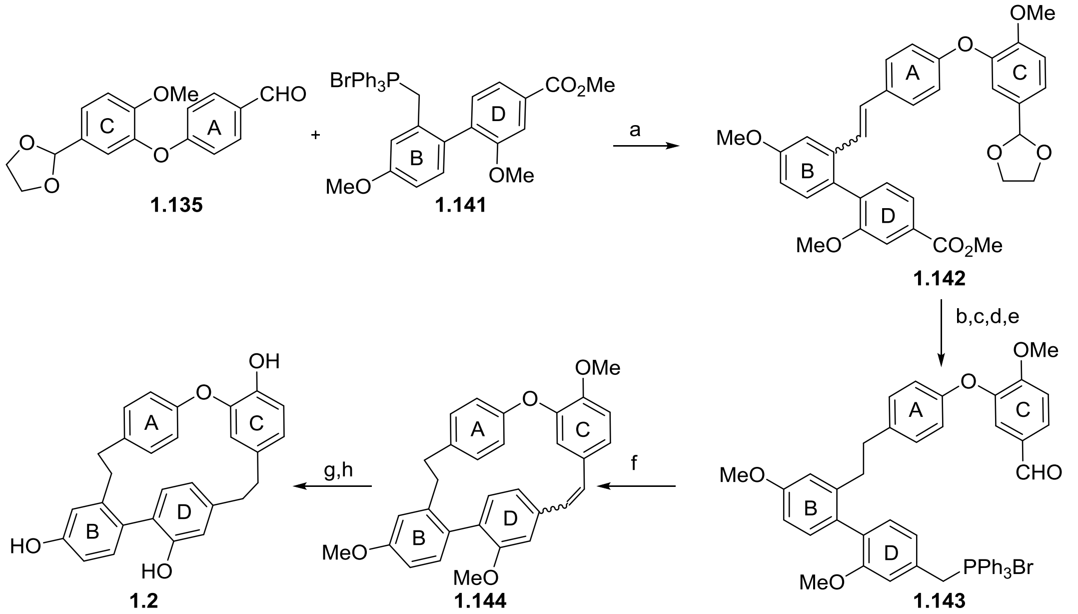
In parallel, a Suzuki–Miyaura reaction between boronic acid **1.137** and aryl triflate **1.139** was achieved to obtain the biaryl compound **1.140**. Then the resulting biaryl was brominated with NBS under radical conditions then transformed into phosphonium salt **1.141** through the action of PPh_3 (Scheme 1.12).



Reagents and Conditions: 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 two steps).

Scheme 1.12: The synthesis of BD **1.141** fragment

Having the AC **1.135** and BD **1.141** fragments in hand, a Wittig reaction was used to provide tetraarene **1.142**. Preparing the cyclisation precursor **1.143** required hydrogenation of alkene in **1.142**, reduction of its ester, bromination and treatment with PPh_3. This sequence gave the key phosphonium salt **1.143**. The critical macrocyclisation reaction was then achieved using a Wittig reaction to obtain stilbene **1.144** in 77% yield. Finally, hydrogenation of the stilbene and deprotection of trimethyl ethers gave riccardin C **1.2** (Scheme 1.13).

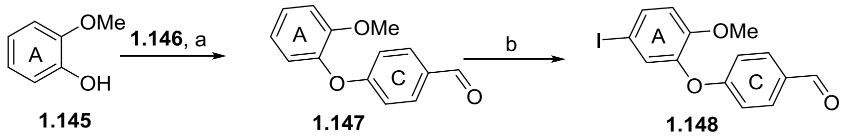


Reagents and Conditions: a) K_2CO_3, 18-crown-6, DCM, 85%; b) H_2, Pd/C, 93%; c) $LiAlH_4$, 88%; d) HBr; e) PPh_3, 77% over two steps; f) NaOMe, 80%; g) H_2, Pd/C, 92%; h) BBr_3, 88%.

Scheme 1.13: The total synthesis of riccardin C **1.2**

After validating the route of Eicher's group, Dodo *et al.* modified the synthesis to prepare riccardin C **1.2** and a series of analogues lacking various phenolic groups.[49] Then Harrowven *et al*. shortened the published route of Eicher *et al*. and Dodo *et al.* to develop an improved synthesis of the key diaryl ether (See Section 1.4.3a).[47]

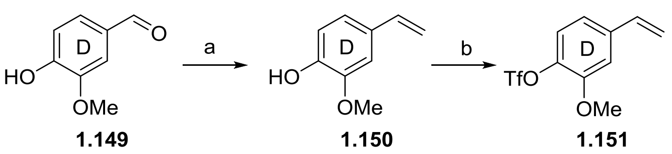
Harrowven *et al.* reported their second generation of total syntheses of riccardin C **1.2** and cavicularin **1.5**.[50] Initially, the synthesis of riccardin C **1.5** started with the development of an efficient synthetic route for the synthesis of the AC **1.148** and BD **1.153** fragments. Formation of the AC subunit **1.147** began with an S_NAr reaction between 4-fluorobenzaldehyde **1.146** and 2-methoxyphenol **1.145** to obtain ether **1.147**. Iodination of the resulting ether **1.147** then gave biaryl ether **1.148** in quantitative yield though the reaction required seven days to run to completion (Scheme 1.14).



Reagents and conditions: a) 4-fluorobenzaldehyde **1.146**, K_2CO_3, DMF, 155 °C, 24 h, 91%; b) ICl, DCM, RT, 7 d, 100%.

Scheme 1.14: AC fragment **1.148** synthesis

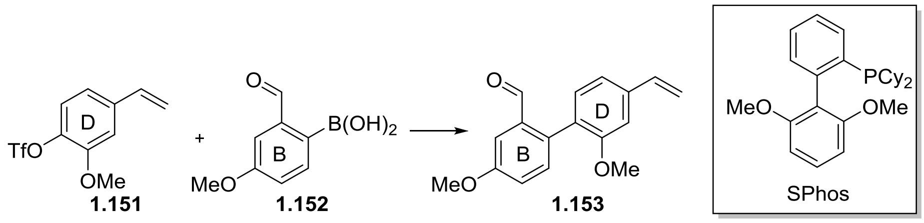
Having the AC **1.148** fragment in hand, their attention turned to the synthesis of BD fragment **1.153** by means of Suzuki-Miyaura reaction to connect arene B **1.152** and arene D **1.151**. Boronic acid **1.152** is commercially available. To prepare arene D **1.151**, the aldehyde in vanillin **1.149** was converted to alkene **1.150** by a Wittig reaction. Then, the phenol was subjected to triflation (Scheme 1.15).



Reagents and conditions: a) $MePPh_3Br$, KO^tBu, THF, 0 °C–RT, 18 h, 77%; b) Tf_2O, pyridine, DCM, 0 °C, 4 h, 88%.

Scheme 1.15: Arene D **1.151** formation

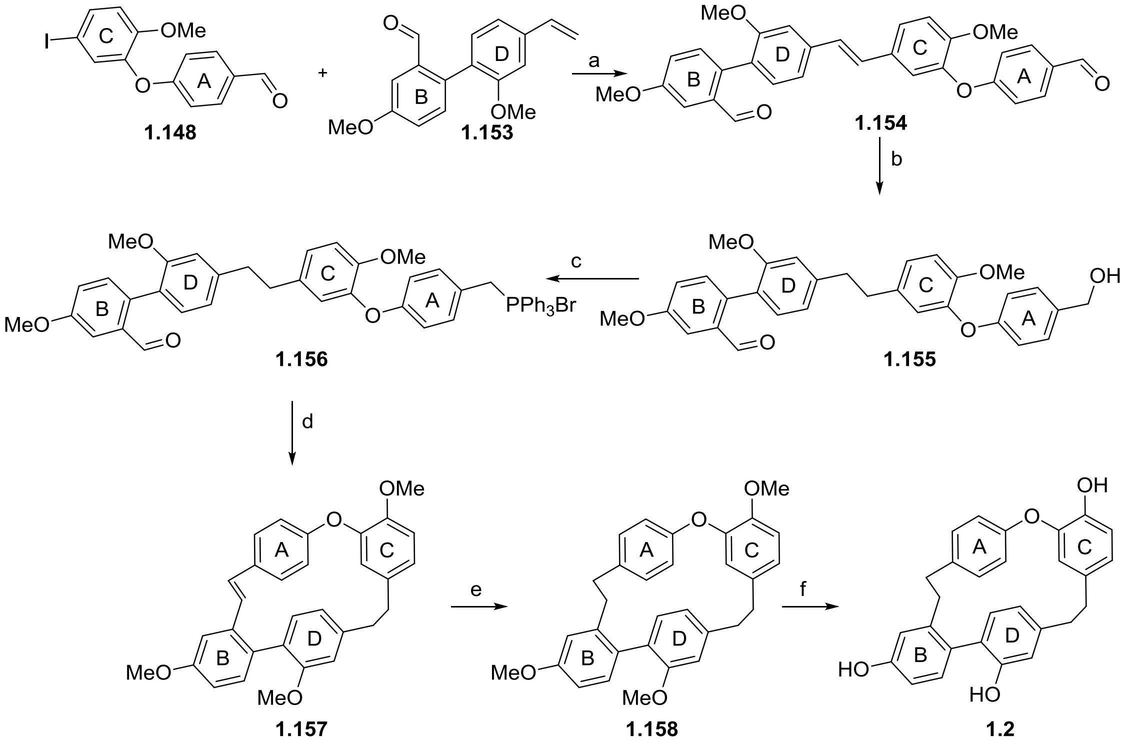
Arenes B **1.152** and D **1.151** were then conjoined in a Suzuki-Miyaura reaction making the key aryl-aryl bond **1.153** in good yield 76% (Scheme 1.16).



Reagents and conditions: LiCl, Cs_2CO_3, $Pd(OAc)_2$, SPhos, 1,4-dioxane, 101 °C, 3 h, 76%.

Scheme 1.16: Formation of BD **1.153** fragment

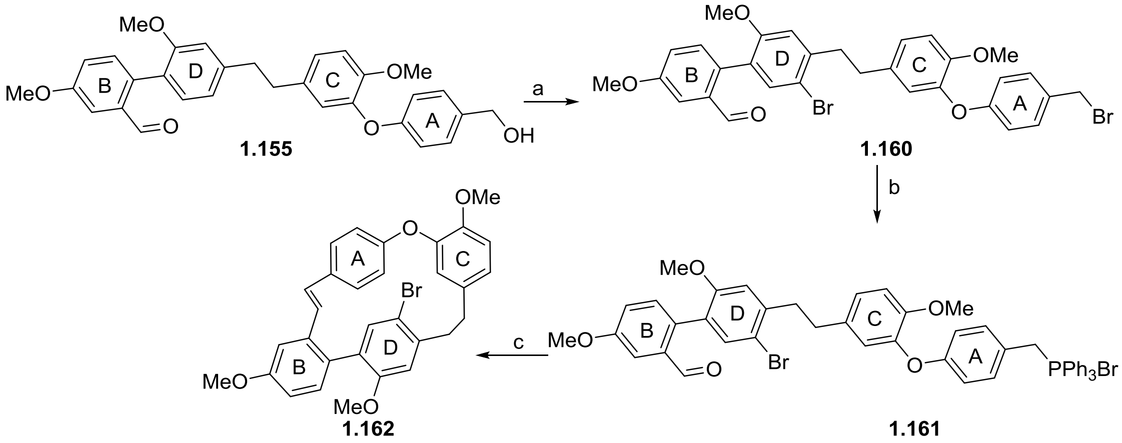
A Heck reaction was next used to connect the AC **1.148** and BD **1.153** fragments giving *trans*-stilbene **1.154**. A subsequent hydrogenation reduced the alkene and a single aldehyde to the corresponding alcohol **1.115**. Bromination of the alcohol cleanly gave the corresponding benzyl bromide which was transformed into the required phosphonium salt **1.156** by treatment with PPh_3. An intramolecular Wittig reaction then gave the desired macrocycle **1.157** in good yield. Hydrogenation to **1.158** was followed by demethylation to give riccardin C **1.2** (Scheme 1.16).



Reagnts and conditions: a) $Pd(OAc)_2$, Et_3N, 1,4-dioxane, 83%; b) H_2, Pd/C, 89%; c) (i) PBr_3, DCM; (ii) Ph_3P PhMe, reflux, 18 h, 91% (over two steps); d) NaOMe, DCM, 47%; e) H_2, Pd/C, DCM, MeOH; f) BBr_3, DCM, 90% (over two steps).

Scheme 1.16: The completion of riccardin C **1.2**

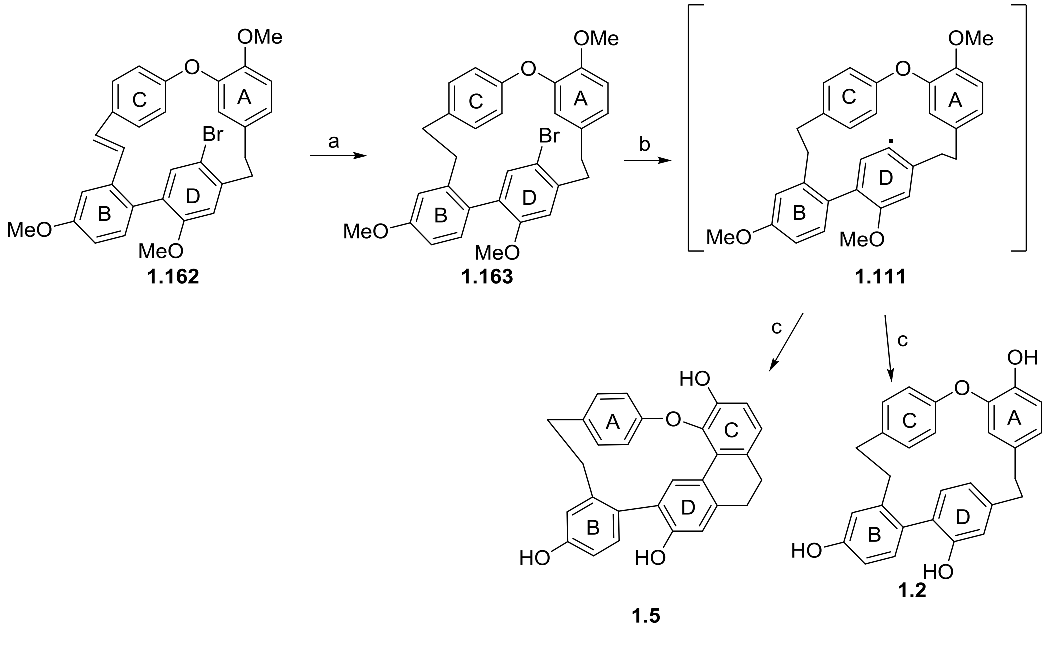
The second total synthesis of cavicularin followed riccardin C **1.2**.[50] Bromination of alcohol **1.155** cleanly gave dibromide **1.160** which was transformed into the required phosphonium salt **1.161** by treatment with PPh_3. An intramolecular Wittig reaction then gave the desired macrocycle **1.162** in good yield 69% (Scheme 1.18).



Reagnts and conditions: 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 1.18: Formation of the macrocycle **1.162**

After macrocyclosation, the resulting alkene in **1.162** was reduced to give **1.163**. Treatment of **1.163** with TTMSS and VAZO in the microwave was effective in promoting homolysis of the C-Br bond and resulted in a mixture of cavicularin tri-*O*-methyl ether and riccardin C tri-*O*-methyl ether which was inseparable. Treatment with BBr_3 then afforded cavicularin **1.5** and riccardin C **1.2** which were separated by column chromatography (Scheme 1.19).

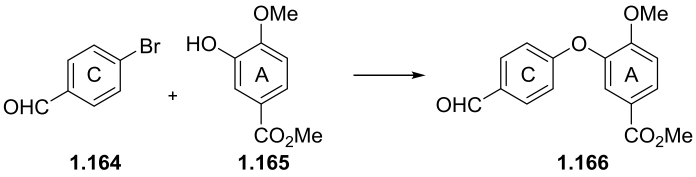


Reagents and conditions: a) NH_2NHTs, NaOAc, 96%; b) 3 equiv. Bu_3SnH, 1 equiv. VAZO, △; c) BBr_3, DCM, 22% **1.5,** 52% **1.2**.

Scheme 1.19: The total synthesis of cavicularin **1.5** and riccardin C **1.2**

1.4.3c By Metal-catalysed aryl-aryl coupling methods

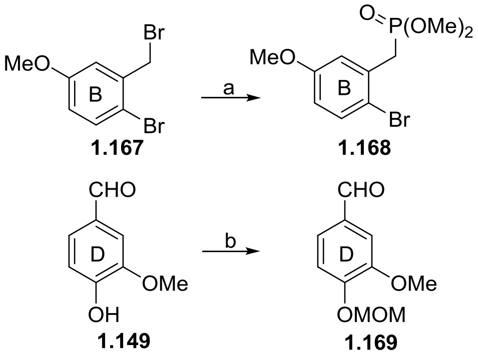
Fukuyama *et al*. reported a total synthesis of riccardin C **1.2** in 2008.[51] With an S_NAr reaction, they were able to prepare the AC **1.166** fragment from commercially available chemicals in one step (Scheme 1.20).



Reagents and Conditions: K_2CO_3, DMSO, 4 h, 68%.

Scheme 1.20: Preparation of AC **1.166** fragment

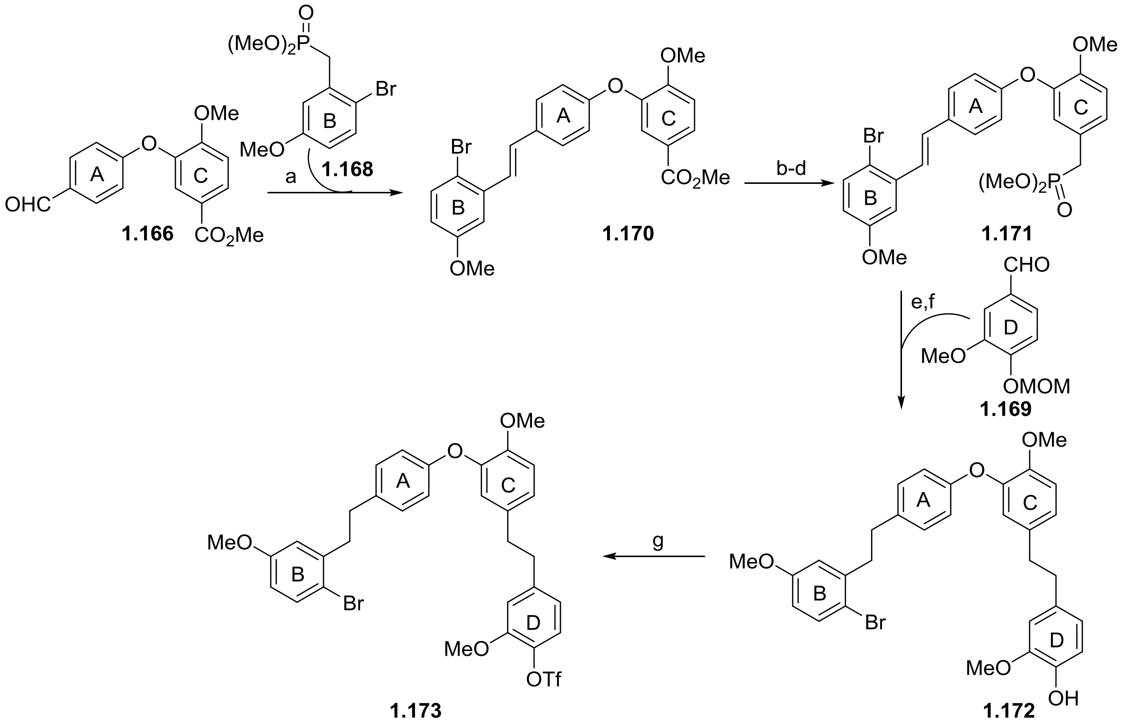
Arenes B **1.168** and D **1.169** were also prepared rapidly. Thus, treatment of benzyl bromide **1.167** with $P(OMe)_3$ afforded arene B **1.168** in good yield while vanillin **1.149** protection as a methoxymethyl (MOM) ether provided arene D **1.169** (Scheme 1.21).



Reagents and Conditions: a) $P(OMe)_3$, 90 °C, 2 h, 98%;
b) MOMCl, NaH, THF, 1.5 h, 84%.

Scheme 1.21: Preparation of arenes B **1.168** and D **1.169**

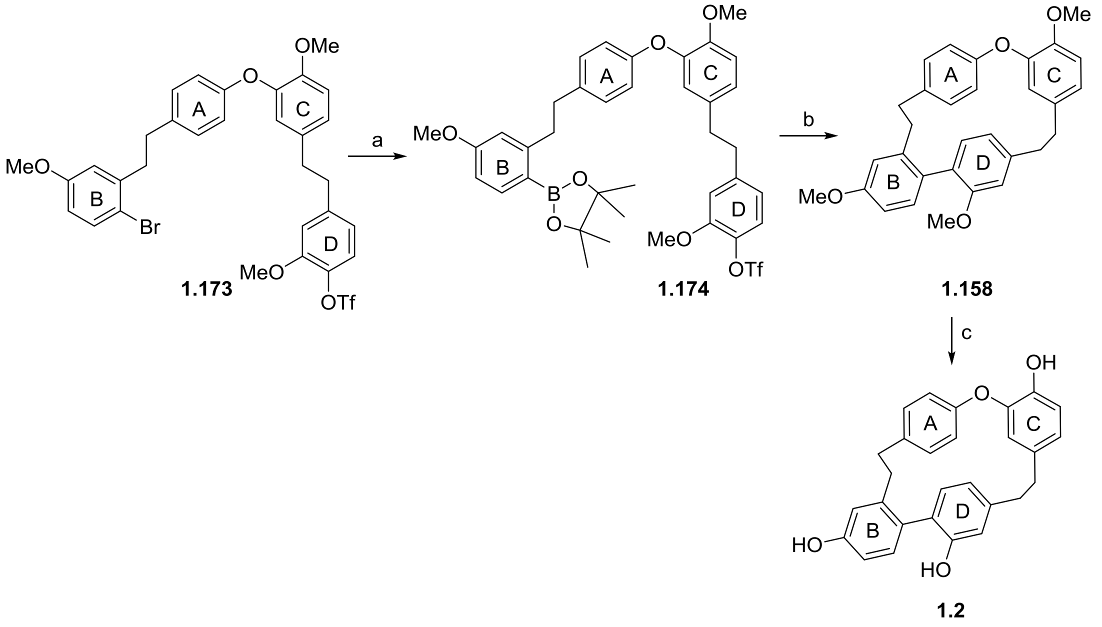
With arenes AC **1.166**, B **1.168**, and D **1.169** fragments in hand, a precursor for macrocyclisation was prepared by a Horner–Wadsworth–Emmons (HWE) reaction. The first HWE reaction coupled the AC **1.166** fragment with arene B **1.168** to obtain **1.170**, and this was followed by a reduction of its ester to an alcohol. Then, the alcohol was converted to **1.171** by bromination and phosphorylation. A second HWE reaction of **1.171** with arene D **1.169** proceeded smoothly with the resulting alkene reduced using triethylsilane in trifluoroacetic acid to **1.172**. During the reduction, the MOM protecting group was removed allowing the resulting phenol **1.172** to be converted to triflate **1.173** (Scheme 1.22).



Reagents and conditions: a) NaH, **57**%; b). LiAlH$_4$, 90%; c) NBS, Me$_2$S; d) P(OMe)$_3$, 98% over 2 steps; e) NaH, **58**, 87%; f) Et$_3$SiH, TFA, 74%; g) *N*-phenyl-bis(trifluoromethanesulfonamide), Cs$_2$CO$_3$, 96%.

Scheme 1.22: Preparation of cyclisation precursor **1.173**

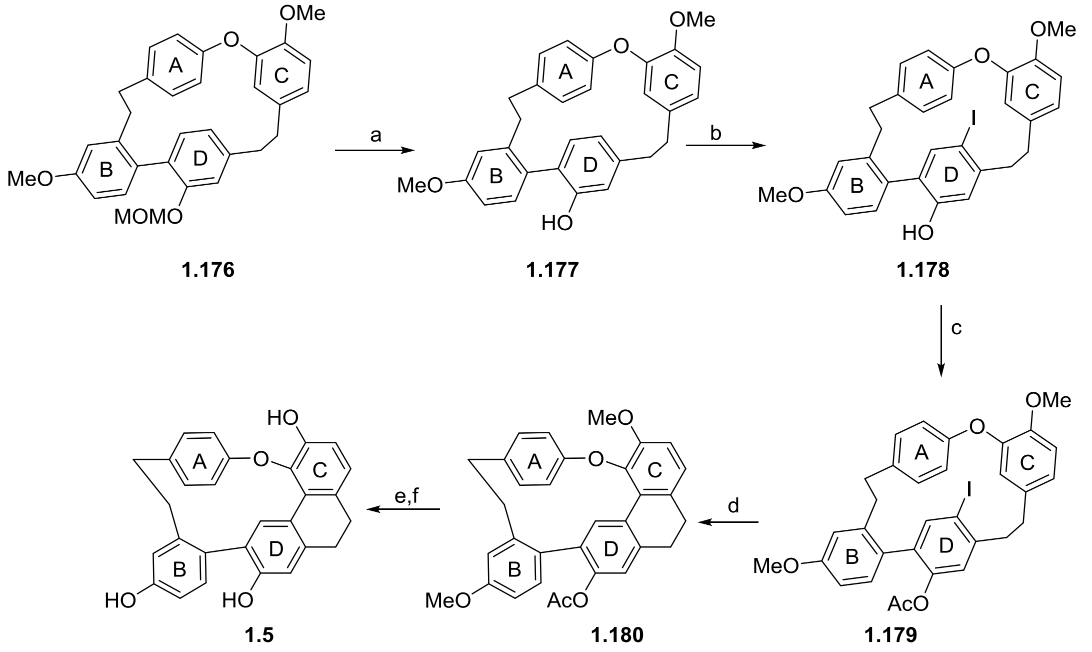
Preparing the cyclisation precursor **1.173** required halogen-boronate exchange. This exchange was achieved by treatment of **1.173** with bis(pinacolato)diboron in the presence of Pd(PPh$_3$)$_4$ affording the desired product **1.174** in good yield. A Suzuki–Miyaura coupling was then employed to achieve the macrocyclisation reaction, affording **1.158** in 39% yield. Riccadin C **1.2** was then obtained by removal of the three *O*-methyl ether residues from riccardin C trimethyl ether **1.158** which was achieved in a good yield (Scheme 1.23).



Reagents and Conditions: a) $Pd(PPh_3)_4$, bis(pinacolato)diboron, K_3PO_4, 4.5 h, 95%; b) $Pd_2(dba)_3$, SPhos, Na_2CO_3, DMF, 37%; c) BBr_3 (12 equiv.), DCM, 7 h, 97%.

Scheme 1.23: Completion of the synthesis of riccardin C **1.2**

In 2013, Fukuyama *et al*. reported a total synthesis of cavicularin **1.5** using a similar methodology to that described above for riccardin C **1.2**.[52] However, the yield for Suzuki-Miyaura reaction increased to 72%. After formation of the 18-membered macrocycle ring **1.176**, the MOM ether protection was removed under acidic conditions to obtain **1.177**. Iodination of phenol **1.177** was regioselectively achieved to obtain **1.178** in good yield and this was followed by a protection of the alcohol with an acetyl group giving **1.179**. Their strategy was similar to that used in Harrowven's group for the total synthesis of cavicularin **1.5**.[47] However, instead of using a radical reaction to achieve a transannular ring contraction to cavicularin, Fukuyama *et al.* heated aryl iodide **1.179** in the presence of palladium acetate to give the protected cavicularin **1.180**. Then, removal of the acetyl group and the two *O*-methyl groups gave cavicularin **1.5** in good yield (Scheme 1.24).

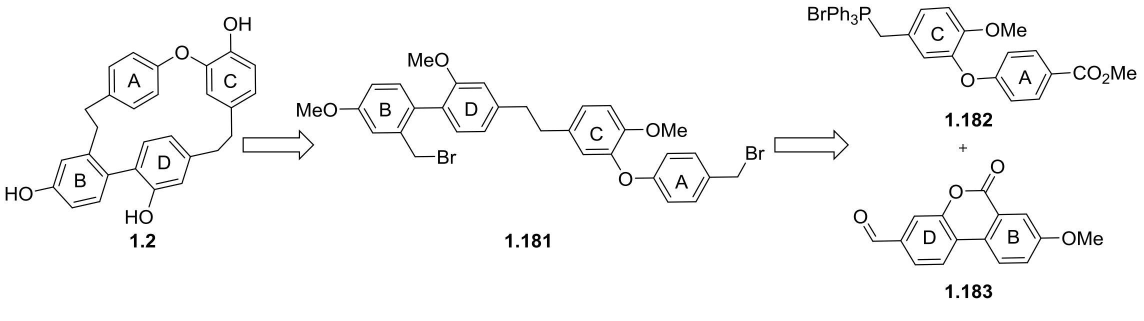


Reagents and Conditions: a) Dowex®, MeOH-EtOAc (2:1), 83%; b) NaI, NaOH, NaOCl, MeOH, 75%; c) Ac_2O, DMAP, THF, 97%; d) $Pd(OAc)_2$, *n*-Bu_3P, Ag_2CO_3, DMF, 50%; e) K_2CO_3, MeOH; f) BBr_3, DCM, 71% (over two steps).

Scheme 1.24: The total synthesis of cavicularin **1.5**

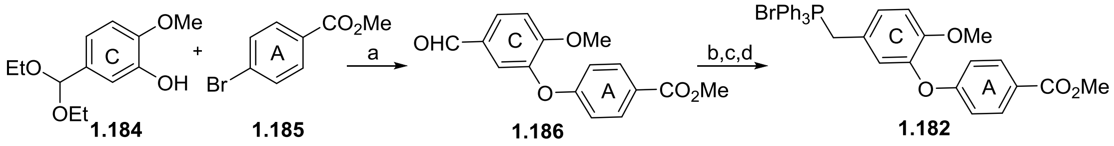
1.4.3d The Wurtz method

Nógrádi and co-workers were first to complete the total synthesis of riccardin C **1.2** and used a Wurtz reaction to achieve macrocyclisation.[9,53,54] They used the same macrocyclisation strategy in several macrocyclic bisbibenzyl syntheses. In this instance, connection of the AC **1.182** and BD **1.183** fragments was achieved using a Wittig reaction to obtain **1.181** (Scheme 1.25).



Scheme 1.25: Nógrádi retrosynthesis of riccardin C **1.2**

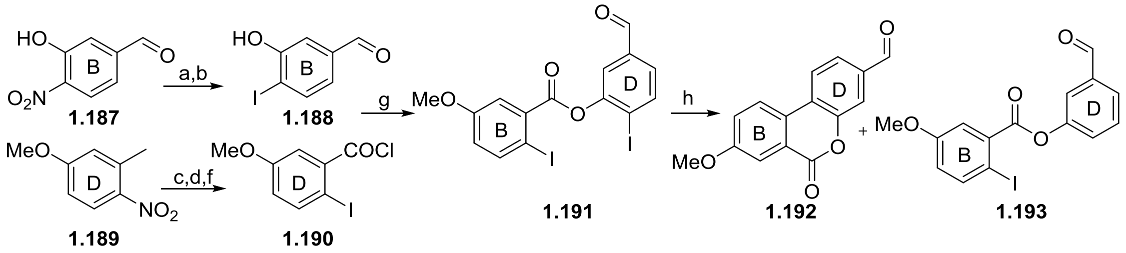
They began their synthesis with the formaion of AC fragment **1.182** using an Ullmann coupling between phenol **1.184** and aryl bromide **1.185** to obtain **1.186**. Then, reduction of the aldehyde, bromination and treatment with PPh_3 gave AC fragment **1.182** (Scheme 1.26).



Reagents and Conditions: a) CuO, K_2CO_3, 30%; b) $NaBH_4$, 90%; c) HBr; d) PPh_3, 76% (over two steps).

Scheme 1.26: Formation of the AC **1.182** fragment

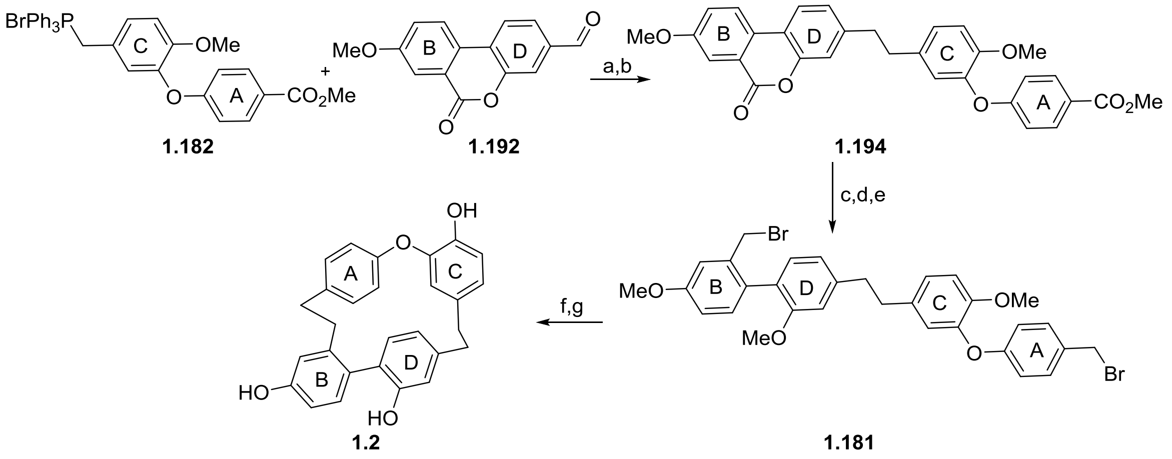
The preparation of BD **1.192** fragment started with the reduction of the nitro-group in arene B **1.187**, followed by a Sandmeyer sequence to prepare iodide **1.188** in 20% yield over the two steps. Arene D **1.190** was prepared in three steps from **1.189**. Coupling arenes B and D next gave diiodide **1.191** which underwent intramolecular biaryl to build its lactone **1.192** by using a Ni(0)-promoted reaction (Scheme 1.27). However, formation of the lactone **1.192** proceeded in low yield as it also gave the byproduct **1.193** in 30% yield by selective deiodination. Thus, while this approach provided an entry to BD fragment **1.192**, it did so in a poor yield and involved many steps.



Reagents and Conditions: 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) $SOCl_2$; g) **1.188**, **1.190**, 63% over two steps; h) $Ni(PPh_3)_4$,17% **1.192**, 30% **1.193**.

Scheme 1.27: BD **1.192** formation

Having AC **1.182** and BD **1.192** fragments in hand, they were connected through a Wittig reaction to obtain **1.194**. Reduction of the lactone and ester functions, protection of the phenol and bis-bromination of the resultant diols gave **1.181** (Scheme 1.28). The cyclisation reaction was then achieved by treatment of dibromide **1.181** with sodium metal to obtain tetraphenylethene in 30% yield. In the final stage, the deprotection of the three methyl ether groups completed the total synthesis of riccardin C **1.2**.



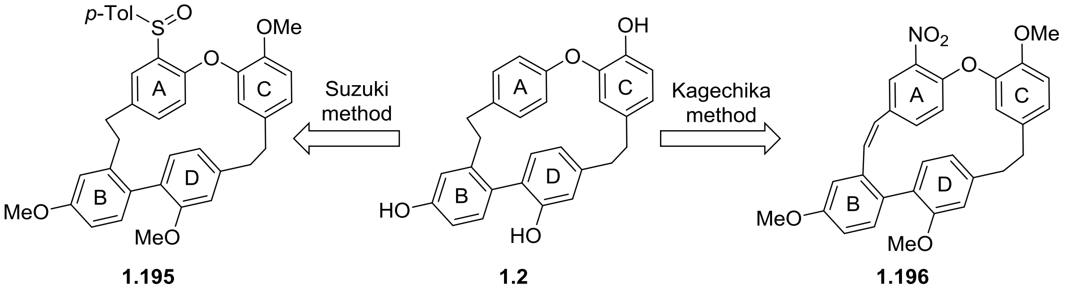
Reagents and Conditions: a) NaOMe; b) Pd/C, H_2, 55% over 2 steps; c) $LiAlH_4$; d) CH_2N_2, 30% over 2 steps; e) PBr_3, 100%; f) Na, $(Ph_2C)_2$, 30%; g) BBr_3, 37%.

Scheme 1.28: First synthesis of riccardin C **1.2**

The Wurtz coupling was used by Nógrádi and co-workers as a key step to achieve many total syntheses, including riccardin C **1.2**, but usually proceeded with a low yield. However, this cyclisation reaction was achieved in a high yield (83%) when Iyoda *et al.* applied a similar strategy in their synthesis of riccardin B **1.15**.[55]

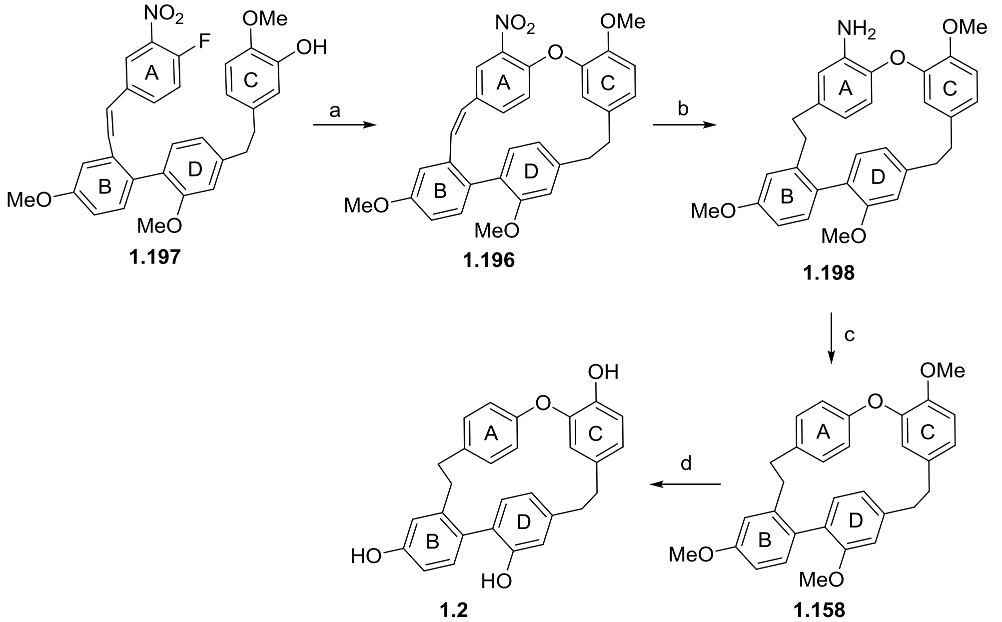
1.4.3e By nucleophilic aromatic substitution method

In 2011, Suzuki *et al.* and Kagechika *et al.* independently used nucleophilic aromatic substitution reactions to achieve the key macrocyclisation step in their total syntheses of riccardin C **1.2**.[56,57] While Kagechika *et al.* used the nitro group as an electron-withdrawing group in the total synthesis of riccardin C **1.2**, Suzuki *et al.* chose to use a sulfoxide as the electron-withdrawing group. The latter method was beneficial in that it proved easier to remove than the nitro group (Scheme 1.29).



Scheme 1.29: Retrosynthesis of riccardin C according to Suzuki *et al.* and Kagechika *et al.*[56,57]

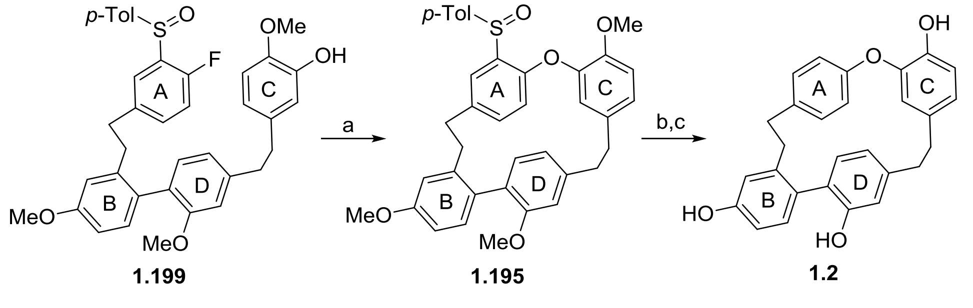
Kagechika *et al.* first formed the cyclisation precursor **1.197**.[57] Then, macroetherification of **1.197** was accomplished in 60% yield through the action of potassium carbonate in DMF. Hydrogenation of product **1.196** then gave amine **1.198** in 92% yield which underwent deamination via the corresponding diazonium salt to give riccardin C trimethyl ether **1.158** (Scheme 1.30). Finally, removal of the protection groups in **1.158** using boron tribromide afforded riccardin C **1.2**.



Reagents and Conditions: a) K_2CO_3, 18-crown-6, DMF, 60%; b) Pd/C, H_2, 92%; c) $NaNO_2$, HCl, H_3PO_2, Cu_2O, 83%; d) BBr_3, DCM, 77%.

Scheme 1.30: Completion of total synthesis of riccardin C **1.2**

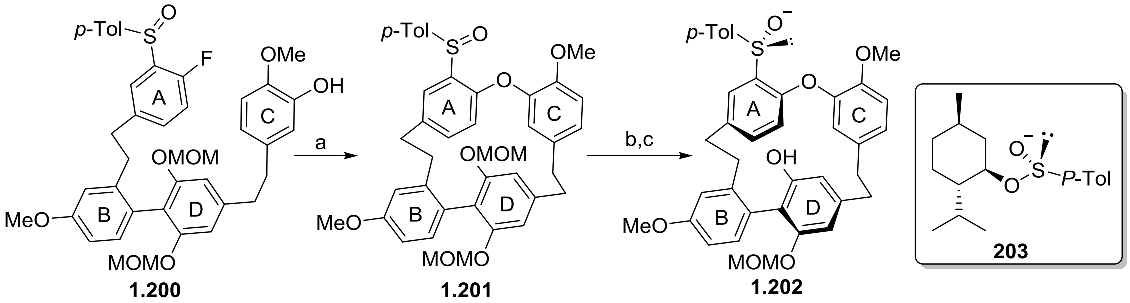
Suzuki *et al.* established an approach for the total synthesis of riccardin C **1.2**, which was then used to effect the total synthesis of (–)-cavicularin after making significant improvements.[56,58] The key macrocyclisation step for both natural products involved an intramolecular S_NAr reaction. The macrocyclisation step for riccardin C **1.2** was achieved in 92% which is very high for macrocyclisation within the bisbibenzyl family (Scheme 1.31). A sulfoxide-lithium exchange was then made on (±)-**1.195** quenching with menthol. Deprotection of the resulting trimethyl ether then gave riccardin C **1.2**.



Reagents and Conditions: a) CsF, $CaCO_3$, 3 Å M. S., DMF, 140 °C, 4 h, 92%; b) ^{t}BuLi, THF, 10 min, MeOH, 10 min, 95%; c) BBr_3, CH_2Cl_2, 2 h, 93%.

Scheme 1.31: The key reactions of riccardin C **1.2**

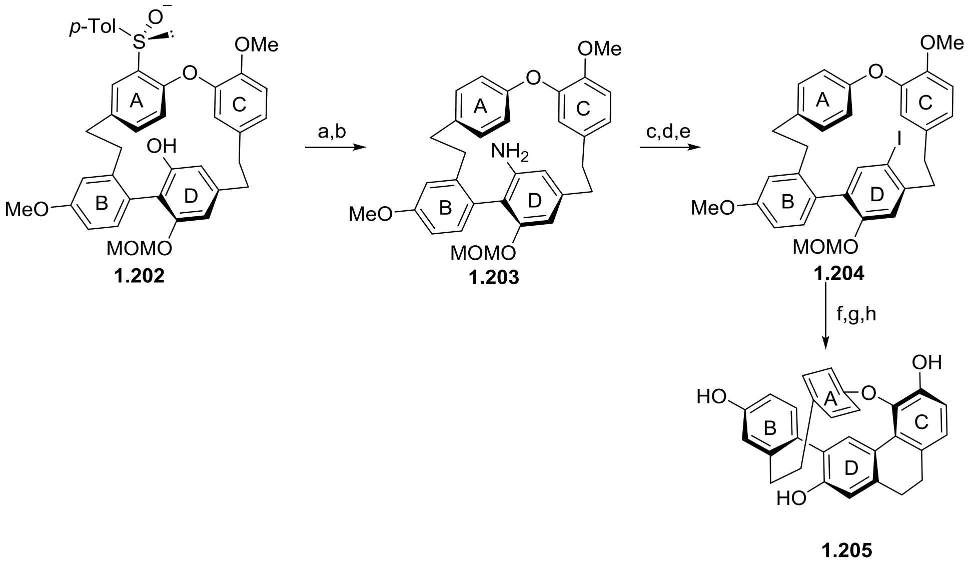
The macrocyclisation step for (–)-cavicularin **1.205** was also achieved by an intramolecular S_NAr reaction in very high yield. To form a single enantiomer (–)-**1.202**, the sulfoxide-lithium exchange was made on (±)-**1.201** and a quench with menthol was achieved, followed by regioselectively deprotection of one of the MOM groups in the ring D (Scheme 1.32).



Reagents and Conditions: a) CsF, $CaCO_3$, 3 Å M.S., DMF, 140 °C, 4 h, 92%; b) ^{t}BuLi, **203**, THF, 73%; c) $SnBr_2$, phloroglucinol, PhMe, 82%.

Scheme 1.32: A single enantiomer (–)-**1.202**

A sulfoxide-lithium exchange was then carried out on (–)-**1.202.** Quenching with menthol followed by triflation and coupling with benzophenone imine gave aniline **1.203** on hydrolysis. Then, regioselective iodination and deamination provided macrocycle (–)-**1.204**. Next, using the same method as Harrowven *et al.*, transannular ring contraction to precursor **1.204** was realised.[47] The highly strained ring system was obtained as an enantiopure compound in high yield. Finally, removal of the protecting groups gave (–)-cavicularin **1.205** (Scheme 1.33), which exhibited spectral and physical characteristics identical to those reported for the natural product.[58]

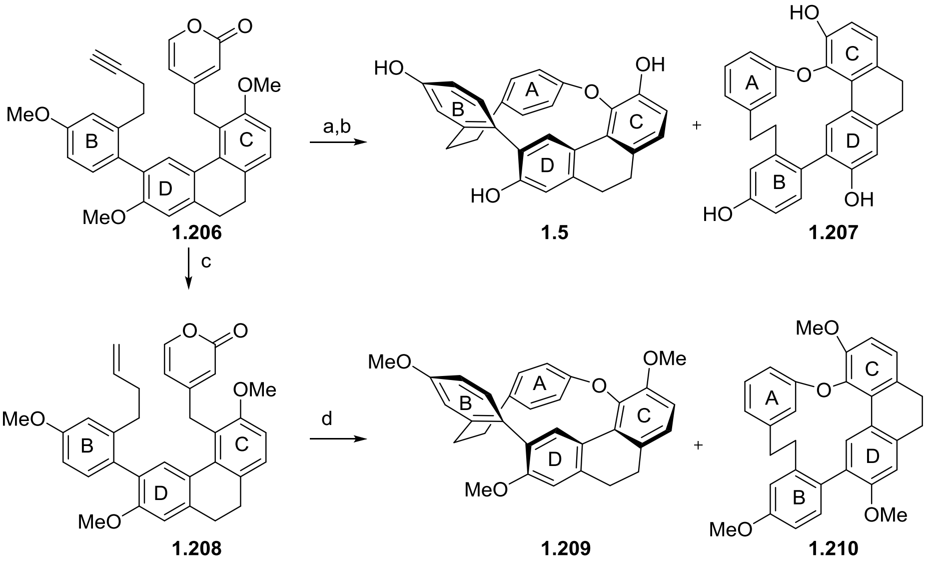


Reagents and Conditions: a) (i) *n*-BuLi, THF, 10 min, (ii) MeOH, 95%; b) K_2CO_3, $PhNTf_2$, acetone, 98 %; c) Benzophenone imine, $Pd(OAc)_2$, binap, Cs_2CO_3, reflux, 3 h; d) HCl (2 M), THF, (86% over two steps); e) $BnNMe_3ICl_2$, DCM, MeOH, 88%; f) $NaNO_2$, AcOH, $Na_2S_2O_3$, THF, H_2O, 42%; g) TTMSS, AIBN, Na_2HPO_4,PhH, 82%; h) BBr_3, 85%.

Scheme 1.33: First formation of (–)-cavicularin **1.205**

1.4.3f By *De novo* synthesis of an aromatic ring

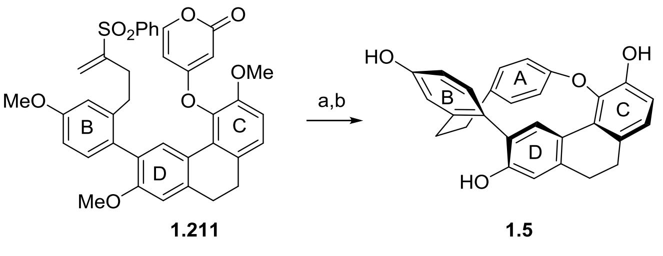
A new macrocyclisation strategy for the total synthesis of cavicularin **1.5** has been developed by Baran *et al.*[9] This strategy involves the *de novo* synthesis of an aromatic ring. An intramolecular Diels-Alder reaction between a pyrone and the alkyne of **1.206** delivered cavicularin **1.5** and regioisomer **1.207** in a 1:3 ratio. Repeating the Diels-Alder reaction with an alkene **1.208**, which was generated from alkyne **1.206** by reduction, yielded cavicularin trimethyl ether **1.209** in an improved yield of ~40% with regioisomer **1.210** accounting for ~25% of the mass balance (Scheme 1.34).



Reagents and Conditions: a) 225 °C, microwave; b) BBr_3, neither yield specified; c) H_2, Lindlar's catalyst, 100%; d) 200 °C, microwave, **1.209** ~40%, **1.210** ~25%.

Scheme 1.34: Formation of cavicularin

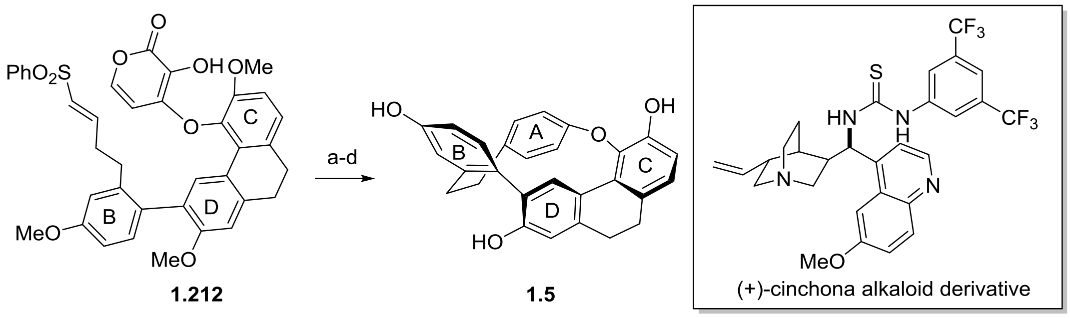
In 2013, Beaudry *et al.* used the method of Baran *et al.* to produce a short and efficient strategy for the total synthesis of cavicularin **1.5**.[9,59] In this approach, a strong electron-withdrawing substituent was used on the alkene **1.211** which helped to achieve regiocontrol and a high yield in the [4+2] cycloaddition (Scheme 1.35). Finally, the removal of the protection groups afforded (+)-cavicularin **1.5**.



Reagents and Conditions: a) 240 °C, microwave, 83%; b) BBr_3, DCM, 80%.

Scheme 1.35: Beaudry *et al.* method for (+)-cavicularin **1.5**

In 2014, Beaudry *et al.* has reported the enantioselective synthesis of (+)-cavicularin **1.5** based on their pervious strategy.[60] They used cinchona-based catalysts to promote enantioselective reactions. An asymmetric intramolecular Diels–Alder reaction with a pyrone gave the desired product as a single regioisomer (Scheme 1.36). Reduction and dealkylation of triflate gave (+)-cavicularin **1.5**.

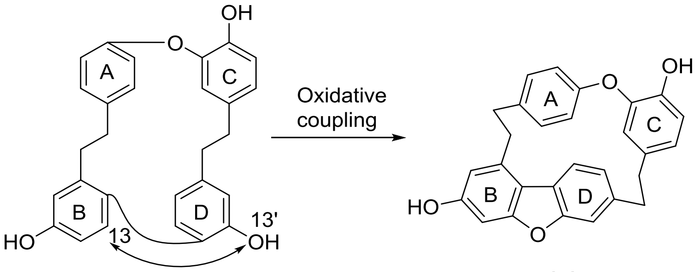


Reagents and Conditions: a) (+)-cinchona alkaloid derivative, EtOAc, 3 Å M.S., 45 °C; b) Tf_2O, DCM, 0 °C, 45% over two steps; c) NH_4CO_2H, Pd/C, MeOH, 70 °C, quant.; d) BBr_3, DCM, 80%.

Scheme 1.36: Beaudry *et al.* method for (+)-cavicularin **1.5**

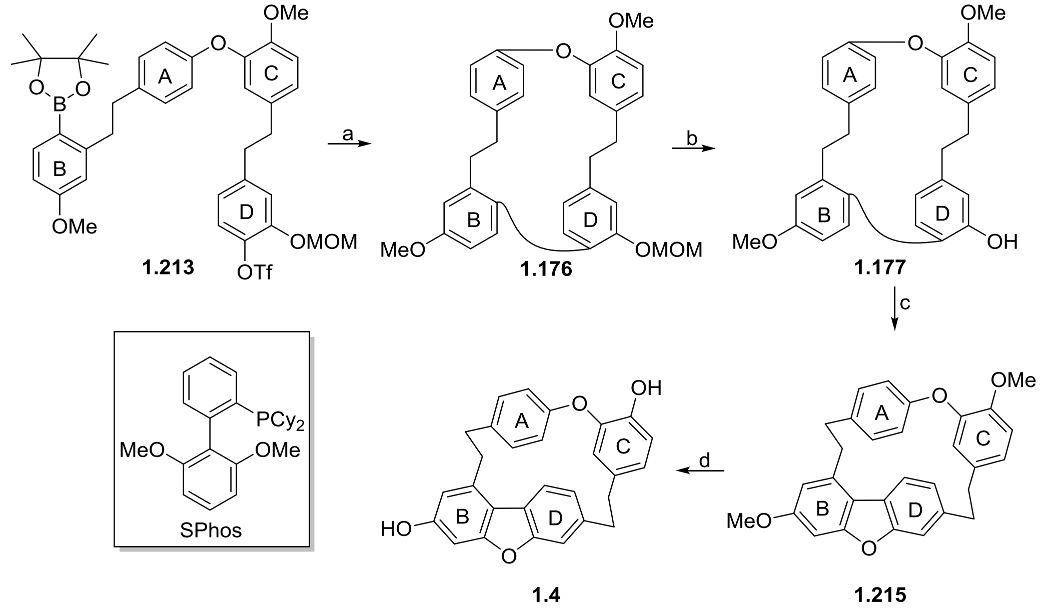
1.4.4 Macrocyclisation approach in the synthesis of asterelin A 1.4

Fukuyama *et al*. were the first to report the total synthesis of asterelin A **1.4** in 2013.[61] Their synthesis was achieved using a biomimetic strategy involving an intramolecular oxidative coupling of a protected analogue of riccardin C **1.2**. The coupling in nature is believed to occur between C-13 in arene B and the 13'-OH in arene D (Scheme 1.37)



Scheme 1.37: The structures of asterelin A **1.4** and riccardin C **1.2**

The macrocyclisation strategy employed (See Section 1.4.3c) involved a Suzuki-Miyaura coupling of **1.213** which was followed by removal of the MOM protecting group in **1.176** to give phenol **1.177**. The intramolecular oxidative coupling of arenes B and D in **1.177** was successfully achieved using $VOCl_3$ to obtain protected asterelin A **1.215** which was treated with BBr_3 to give asterelin A **1.4** (Scheme 1.38).

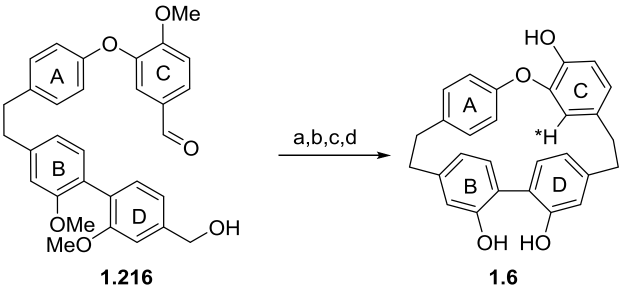


Reagents and conditions: a) $Pd_2(dba)_3$, SPhos, Na_2CO_3, DMF,100 °C,12 h, 53%; b) Dowex®, MeOH/EtOAc 2:1, 70°C, 3 h, 83%; c) $VOCl_3$, DCM, 0 °C, 20 min, 58%; d) BBr_3, DCM, 0 °C, 2 h, 76%.

Scheme 1.38: The total synthesis of asterelin A **1.4**

1.4.5 Macrocyclisation approach in the synthesis of polymorphatin A 1.6

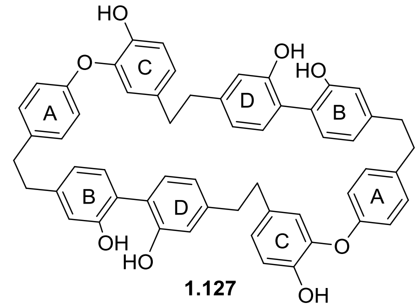
In 1992, Keserü and Nógrádi studied macrocycle **1.6** computationally and suggested that it had excessive molecular strain and was unlikely to be found in nature.[62] However, in 2007, Lou and co-workers isolated the macrocycle from *Marchantia polymorpha* and named it polymorphatin A **1.6**.[32] The fact that it consists of two boat configured aromatic rings made its discovery in nature unusual. Indeed when Speicher *et al*. reported a total synthesis of polymorphatin A **1.6** by using a Wittig cyclisation reaction form **1.216**, they disputed the claimed isolation (Scheme 1.39).[46]



Reagents and conditions: a) PPh_3.HBr, MeCN; b) NaOMe, DCM, 12% over 2 steps; c) H_2, Pd/C, EtOAc, 95%; d) BBr_3, DCM, 89%.

Scheme 1.39: Speicher's group approach

Importantly, their synthetic sample of "polymorphatin A" **1.6** exhibited spectral and physical characterisation that were inconsistent with the data in the isolation paper of Lou and co-workers. Indeed, they differed markedly with one proton (H*) found at *J*=6.37 ppm which was reported at *J*=5.88 ppm in the isolation paper. Neither group supported their product's identity with an X-ray crystal structure, leading us to suggest that the conflict could be explained by formation of a dimer such as **1.127** (Scheme 1.40).[63] Although the HRMS data presented by Speicher *et al.* was in accordance with the molecular formula of polymorphatin A **1.6**, this could also be explained by the presence of a doubly charged dimeric species. Indeed, as has been noted previously, the NMR spectra of the dimer would be very similar but would lack the ubiquitous high-field aromatic resonance for H*.[50]



1.127

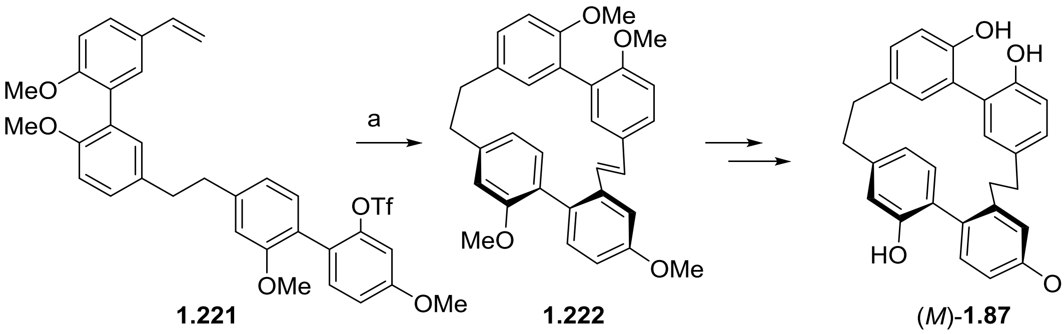
Scheme 1.40: The possible dimerization

1.4.6 Relevant macrocyclisation methods in the synthesis of macrocyclic bisbibenzyls

In this section, approaches relevant to the current study are discussed.

1.4.6a By Heck method

In 2012, Speicher *et al*. reported the total synthesis of isoplagiochin D **1.87** by using an intramolecular Heck coupling to achieve the key macrocyclisation step.[64] They were the first group to use this approach. Although the yield for the ring closure was poor, they found that use a chiral ligand provided (*M*)-isoplagiochin D **1.87** with a 37% enantiomeric excess (Scheme 1.43).

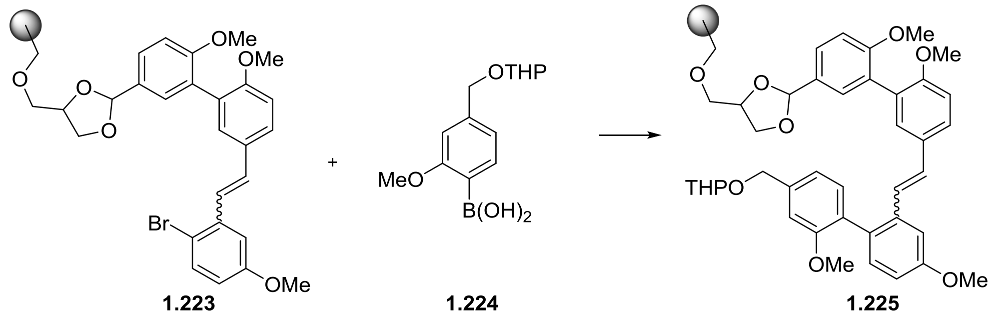


Reagents and conditions: a) Pd[(*M*)-BINAP]$_2$, PMP, DMF, 22%, 37% ee.

Scheme 1.43: Heck appoach for Speicher *et al*.

1.4.6b The Bromination Issue

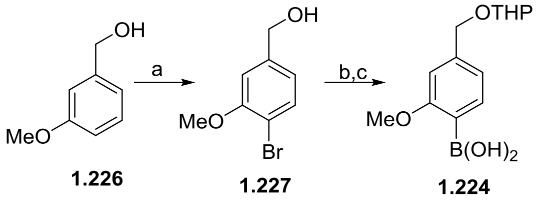
Speicher *et al.* have reported the total synthesis of the isoplagiochins C **1.86** and D **1.87** using solid phase methods.[65] The use of solid support can be advantageous because it makes it easy to remove excess reactant or byproduct from the product by filtration. In the synthesis of Speicher *et al.* coupled the polymer-bound bromide **1.223** and boronic acid **1.224** to obtain **1.225** using a Suzuki-Miyaura reaction (Scheme 1.44).



Reagents and conditions: Pd(PPh_3)$_4$, Cs_2CO_3, EtOH.

Scheme 1.44: Synthesis of **1.225**

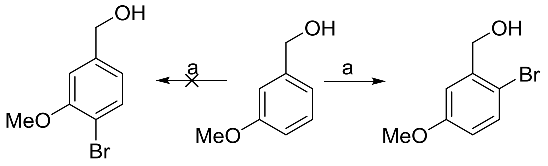
Their claimed synthesis of boronic acid **1.224** started from arene **1.226** which they converted to bromide **1.227** directly. The alcohol was then protected as its THP ether and the aryl bromide was converted to boronic acid **1.224** via halogen-lithium exchange, addition of $B(OMe)_3$ and hydrolysis (Scheme 1.45).



Reagents and conditions: a) $NaBrO_3$, $NaHSO_3$, MeCN / H_2O, 88%; b) DHP, PTSA, DCM, 74%; c) (i) *n*-BuLi, (ii) $B(OMe)_3$, (iii) H_2O, 100%.

Scheme 1.45: Formation of boronic acid **1.224**

However, when this sequence was repeated by Harrowven *et al.* it gave a different product.[9] Indeed, they and others found that the methoxy group in **1.226** directs the bromination reaction to occur in the *para* position, which was proven by X-ray diffraction (Scheme 1.46).[9,66]



1.227 **1.226** **1.228**

Reagents and conditions: a) $NaBrO_3$, $NaHSO_3$, MeCN / H_2O.

Scheme 1.46: Regioselective bromination of **1.226**

1.5 Bent Aromatic Rings

Aromatic rings are usually planar due to their π-systems.[67] However, strain can cause them to adopt a boat-shape. A theoretical analysis of boat-shaped aromatic rings was reported by Jenneskens *et al*. in 1992.[68] They concluded that the benzene ring can be twisted from planarity by up to 25° without significant forfeit of electron conjugation, such that boat-shaped benzenes retain their aromaticity. However, others believe that aromaticity in such systems is compromised by high levels of strain.[69]

Cavicularin **1.5** exists in nature with significant distortion of the bond angles in its *p*-disubstituted arene due to ring strain.[50] 2D-NMR and X-ray crystallographic analysis gave access to the structure of (+)-cavicularin. The formation of a dihydrophenanthrene unit by transannular oxidative coupling between arenes C and D in riccardin C **1.2** causes sufficient strain on the macrocyclic core to force arene A into a boat-like configuration, being some 15° out of planarity (Figure 1.23).

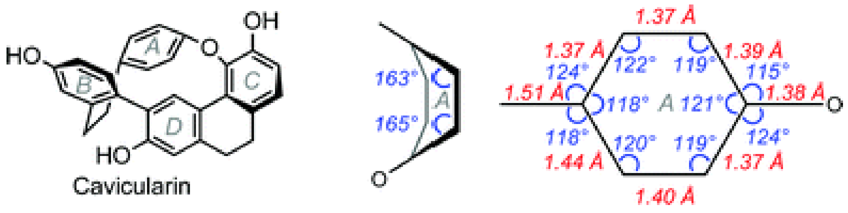


Figure 1.23: The benzene ring A diagram for cavicularin **1.5**

Harrowven *et al.* also studied polymorphatin A **1.6** computationally.[9] Their result indicated that this compound was heavily distorted from planarity with arenes B and D having little conformational freedom (Figure 1.24).

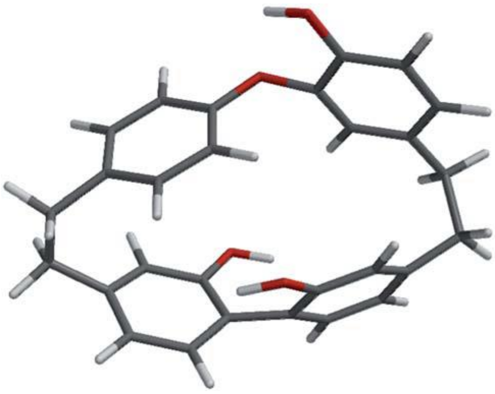


Figure 1.24: The model of polymorphatin A **1.6**

Many biosynthetic pathways leading to boat configured arenes are known, such as those leading to cavicularin **1.5** and polymorphatin A **1.6**. Computational studies on bent benzene systems have indicated that a reasonable degree of deviation from planarity can be tolerated without losing stability arising from electron conjugation.[50] These bent aromatic rings have been shown to exhibit reactively that is atypical of aromatic rings, *e.g.* undergoing electrophilic addition reactions rather than substitution.

1.6 Stereochemical considerations

Molecular chirality plays a critical role in chemistry, biology and medicine. The macrocyclic bisbibenzyl family includes both chiral and achiral natural products.[9] Indeed, several are known to have enantiomeric partners yet are devoid of stereogenic carbon centres. For example, cavicularin **1.6** was isolated as a chiral molecule from natural sources at ambient temperature. By way of contrast, riccardin D **1.2** has always been found in enantioenriched or racemic form, while samples of riccardin C **1.2** never display optical activity.[9] Harrowven *et al*. have noted that chirality within this series is temperature dependant when enantiomeric partners can exist at low temperatures yet interconvert rapidly at higher temperatures.

This was evidenced in a VT-NMR study of riccardin C **1.2**.[50] Figure 1.25 shows that the four ^{1}H resonances associated with the *p*-disubstituted arene appear as broad signals at ambient temperature (298 K). By contrast, at 243 K these resolve into four doublet of doublets as the molecule becomes conformationally restricted, while at 363 K the signals coalesced to the AB quartet expected for an achiral molecule.

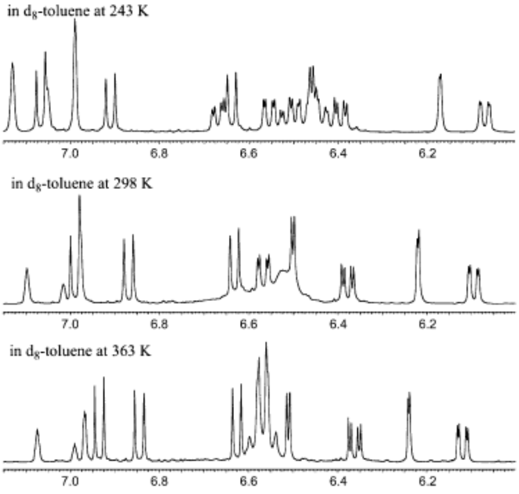


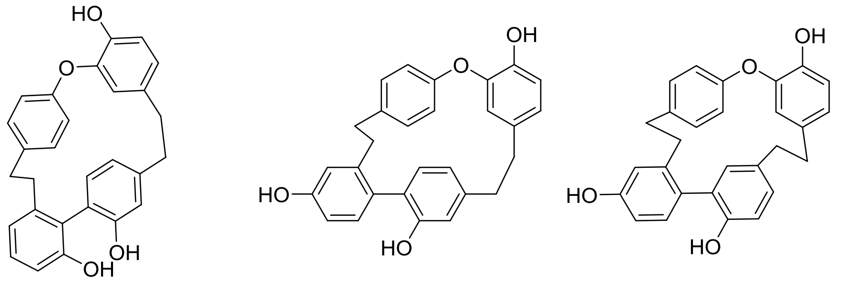
Figure 1.25: The ^{1}H NMR spectra of riccardin C **1.2** in toluene-d$_8$ at 243 K, 298 K and 363 K

Many biaryl compounds are conformationally restricted at ambient temperature and are physically separable. The rule for whether a molecule should be considered chiral and achiral has been arbitrarily defined in relation to the half-life for the interconversion of its enantiomers. Thus, separated atropisomers have a half-life for interconversion that is greater that 1000 s the molecule is considered to be chiral. The appropriateness of this rule for the atropisomers of macrocyclic bisbibenzyl natural products is debatable given the time needed to effect their extraction from natural sources.

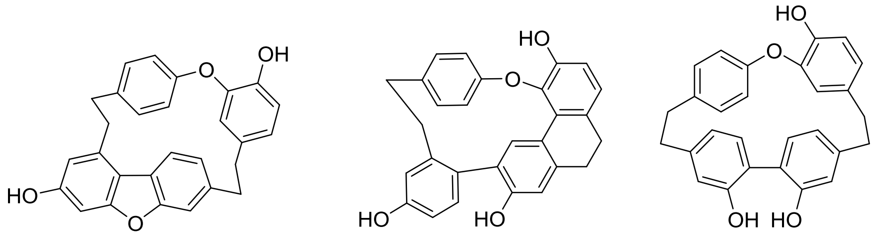
The biosynthesis of macrocyclic bisbibenzyl can give rise to single enantiomers, as evidenced by the isolation of (+)-cavicularin **1.5** as a single enantiomer in nature at ambient temperature. However, a single enantiomer may give enantiomeric mixtures over time. For example, bazzanin K **1.53** has a significant energy barrier for the interconversion of its enantiomeric conformers making its racemisation slow. Nonetheless, it is plausible that the age of the bryophyte and the nature of the isolation procedure cause its partial racemisation.

1.7 Our aim

The aim of this project is to establish useful approaches to the total synthesis of many different macrocyclic bisbibenzyl natural products and unnatural analogues. We aim to use these approaches to complete the total syntheses of riccardin D **1.1**, riccardin C **1.2**, polymorphatin A **1.6** and novel derivatives such as the unnatural macrocyclic bisbibenzyl analogue **1.3**. These studies will also target total syntheses of cavicularin **1.5** and asterelin A **1.4** (Figure 1.26). In addition, we hope to resolve the doubts that have been cast over polymorphatin A **1.6** and plagiochin E **1.81** due to conflicts in data interpretation by synthetic and nature products isolation chemists.[9]



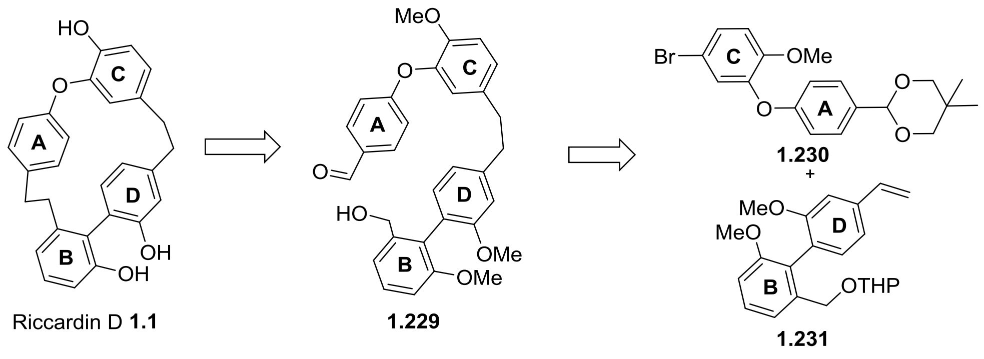
Riccardin D **1.1** Riccardin C **1.2** Analogue **1.3**



Asterelin A **1.4** Cavicularin **1.5** Polymorphatin A **1.6**

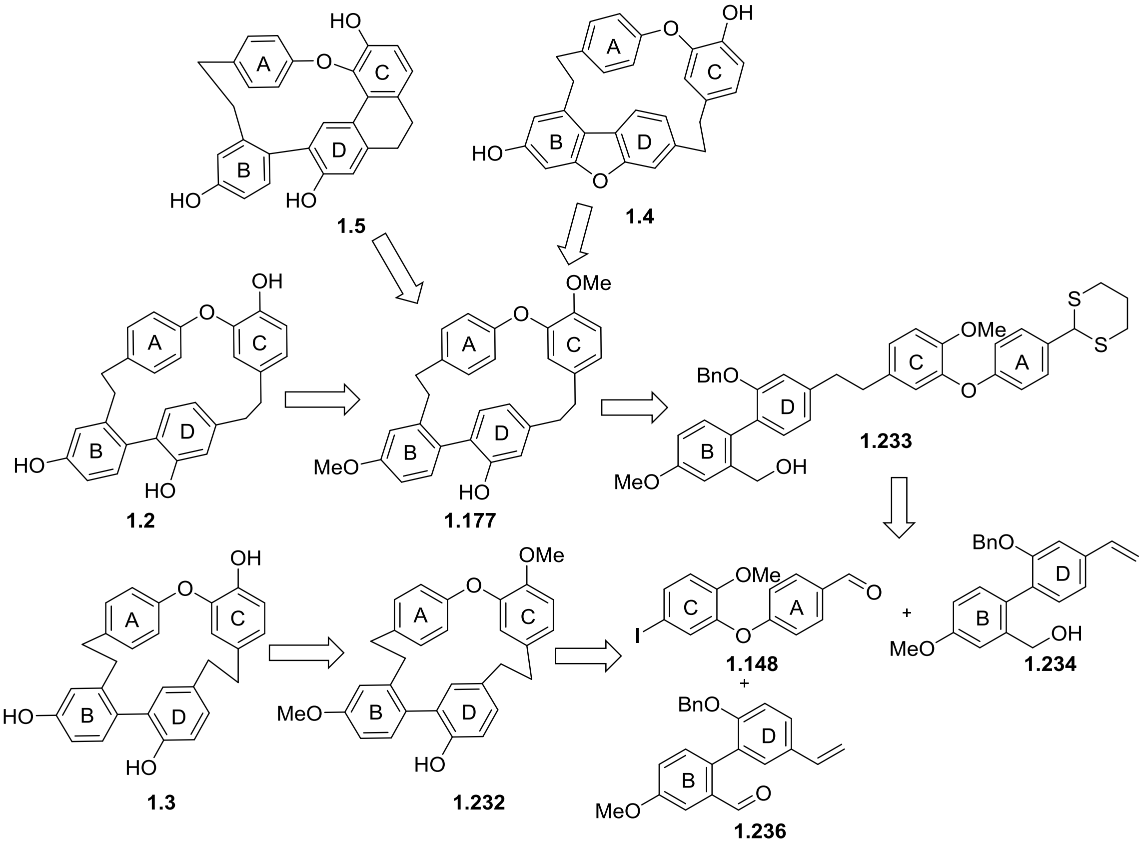
Figure 1.26: Target products

Our first approach proposes a new strategy for the total synthesis of riccardin D **1.1**. The key fragments AC **1.230** and BD **1.231** in the target were to be synthesised then connected by using a Heck reaction. The macrocyclisation envisioned using an intramolecular Wittig reaction (Scheme 1.47). By having riccardin D **1.1** to hand, we would be able to resolve an issue raised by Speicher *et al.* who believed it to be identical to a natural product isolated by Lou *et al.* and named plagiochin E **1.81**.[16,40]



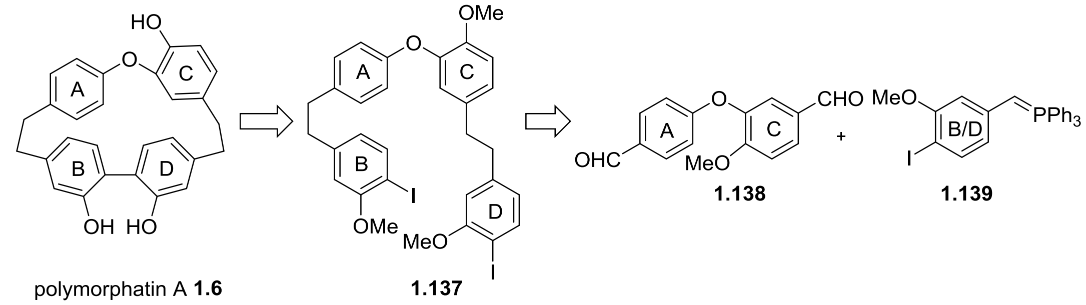
Scheme 1.47: Our retrosynthesis of riccardin D **1.1**

Our second approach sought to provide access to many natural products in the macrocyclic bisbibenzyl family, including riccardin C **1.2**, cavicularin **1.5**, and asterelin A **1.4** as well as a novel derivative of unnatural macrocyclic bisbibenzyl analogue **1.3**. Again the key fragments AC **1.148** and BD **1.236** were to be synthesised then connected using a Heck reaction. To close the ring, we envisioned various approaches including McMurry, Heck, Wittig and Corey-Seebach reactions to obtain **1.232**. The Corey-Seebach approach was particularly interesting to us as it constituted a new strategy for achieving the macrocyclisation step. We would need to synthesise and connect key fragments AC **1.148** and BD **1.234** then macrocyclisation reaction of **1.233** to obtain **1.177**. The approach additionaly offer access to total syntheses of asterelin A **1.4** and cavicularin **1.5** (Scheme 1.48).[52,61]



Scheme 1.48: A macrocyclisation approach using a Corey-Seebach (Umpolung) reaction

The final phase of the study was to achieve the total synthesis of polymorphatin A **1.6**. Harrowven *et al*. had suggested that further validation was needed to secure the identity of polymorphatin A **1.6**.[9] Therefore, we aim to synthesise polymorphatin A **1.6** from a simple starting material using a short synthetic route (Scheme 1.49). Having polymorphatin A **1.6** in hand would allow us to resolve the conflict that has arisen due to different data being reported for a synthetic sample to that reported for the natural product. Moreover, we can investigate the conformational freedom at ambient temperature as it has been suggested in modelling studies that this would be very limited.

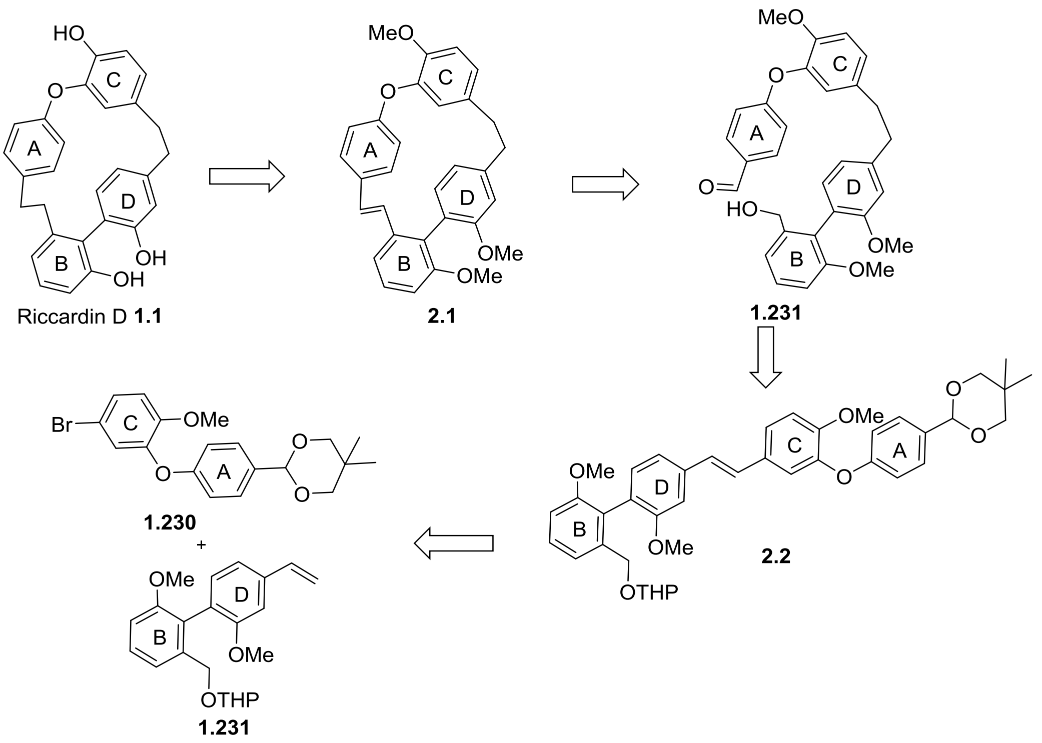


Scheme 1.49: Our retrosynthetic analysis for polymorphatin A **1.6**

Chapter 2: Results and Discussion: A Total Synthesis of Riccardin D 1.1

2.1 The retrosynthesis of riccardin D 1.1

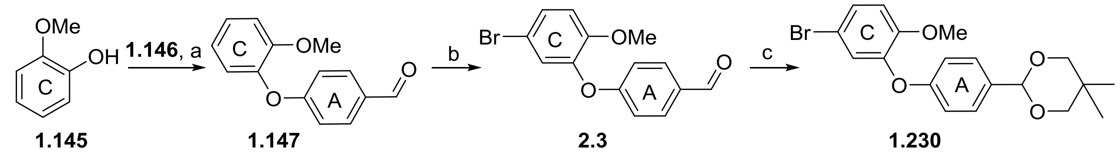
Our plan was to achieve the total synthesis of riccardin D **1.1** using methodology that was used previously within the Harrowven group to prepare riccardin C **1.2**.[50] To that end, we began by preparing AC **1.230** and BD **1.231** fragments. Then a Heck reaction was to be carried out to connect these two fragments. Reduction of the resulting alkene **2.2** would then give access to substrate a **1.231** ready for macrocyclisation using a Wittig reaction. Finally, a second hydrogenation and demethylation would lead to riccardin D **1.1** (Scheme 2.1).



Scheme 2.1: Riccardin D **1.1** retrosynthesis

2.2 Synthesis of AC fragment 1.230

The AC fragment **1.230** was prepared following Harrowven's method for the total synthesis of riccardin C **1.1**.[50] The route began by an S_NAr reaction between 2-methoxyphenol **1.145** and 4-fluorobenzaldehyde **1.146** to obtain biaryl ether **1.147**. Bromination of the resulting ether **1.147** gave then biaryl ether **2.3** (Scheme 2.2). The aldehyde in **2.3** was next protected as its neopentylglycol acetal to give AC fragment **1.230** in 92 % (See also Section 2.5.2).

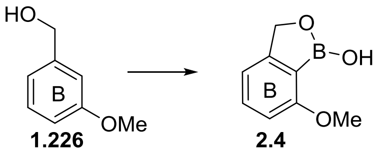


Reagents and conditions: a) 4-fluorobenzaldehyde **1.146**, K_2CO_3, DMF, 96%; b) NBS, MeCN, reflux, 95%; c) PhMe, neopentylglycol, TsOH, 92%.

Scheme 2.2: AC **1.230** fragment formation

2.3 Synthesis of BD 1.231 fragment

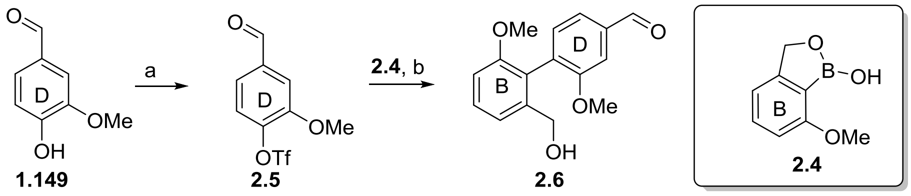
Having prepared the AC arene **1.230**, our attention turned to the preparation of the desired BD fragment **1.231** by a Suzuki-Miyaura reaction. Boronic acid **2.4** was prepared by deprotonation of 3-methoxybenzyl alcohol **1.226** with *n*-BuLi, quenching with trimethyl borate, and hydrolysis (Scheme 2.3).



Reagents and condition: (i) *n*-BuLi (2 equiv.), (ii) $B(OMe)_3$, (iii) aq. HCl (2 M), 54%.

Scheme 2.3: B **2.4** fragment synthesis

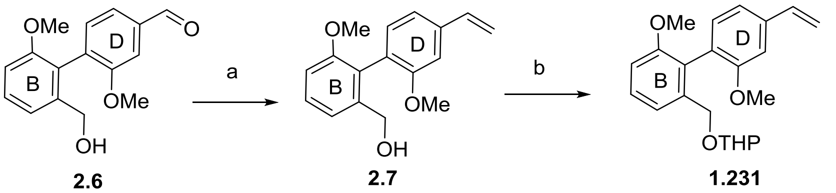
In parallel, vanillin triflate **2.5** was prepared from vanillin **1.149**. With **2.4** and **2.5** in hand, the Suzuki-Miyaura reaction was carried out to afford biaryl **2.6** (Scheme 2.4).



Reagents and conditions: a) Tf_2O, DCM, pyridine, 80%; b) $Pd(PPh_3)_4$, PhMe/EtOH,Cs_2CO_3, 49%.

Scheme 2.4: The Suzuki-Miyaura coupling of B **2.4** and D **2.5** fragments

The aldehyde **2.6** was next converted into styrene **2.7** by a Wittig reaction (Scheme 2.5). Protection of alcohol **2.7** as its THP ether then gave BD fragment **1.231** (See also Section 2.5.1).



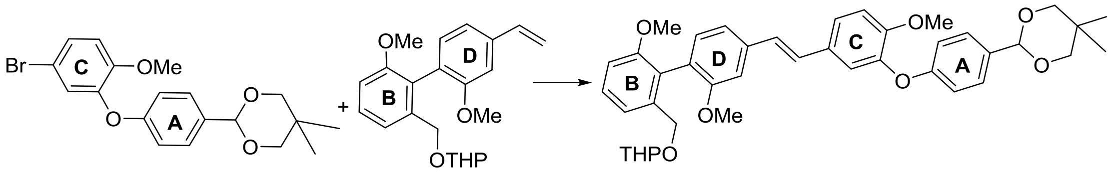
2.6 **2.7** **1.231**

Reagents and conditions: a) $MePPh_3Br$, KO^tBu, THF, 0 °C to RT, 86%; b) DCM, *p*-$TsOH.H_2O$, 3,4-dihydro-2*H*-pyran, RT, 90%.

Scheme 2.5: BD **1.231** fragment synthesis

2.4 Connection of the AC 1.230 and BD 1.131 fragments

Having prepared the AC **1.230** and BD **1.231** fragments, *trans*-stilbene **2.2** was next obtained using a Heck reaction. Conditions for the Heck reaction were examined in detail and Table 2.1 shows the range of conditions employed. The first attempt to obtain **2.2** used $Pd(OAc)_2$ in the presence of Et_3N in 1,4-dioxane but gave a low yield.[50] The yield of tetraarene **2.2** was increased to 23% by using Yang's conditions (Entry 2, Table 2.1).[70] Pleasingly, using Sweeney's conditions, tetraarene **2.2** was formed in 79% yield (Entry 3, Table 2.1).[71]



1.230 **1.231** **2.2**

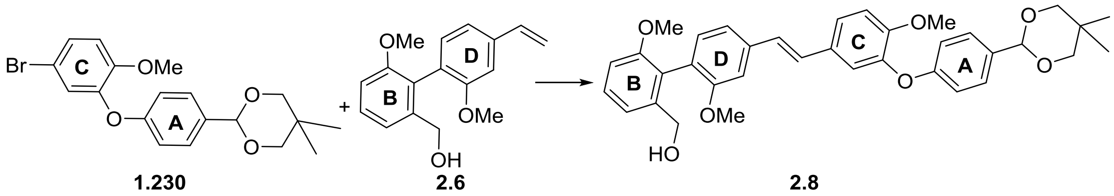
Entry	Conditions	Yield (%)
1	$Pd(OAc)_2$, 1,4-dioxane, Et_3N, reflux, 15 h	5
2	$Pd(OAc)_2$, K_3PO_4, DMA, 140 °C, 13 h	23
3	$Pd(dtbpf)Cl_2$, TBAC, Cy_2NMe, DMA, 80 °C, 13 h	79

Table 2.1: Results from the Heck conditions screen

2.5 Existence of protecting groups

2.5.1 Alcohol protection by THP ether in BD fragment

With an unprotected alcohol in the BD fragment **2.6**, its coupling with the AC **1.230** fragment was investigated under a range of conditions. The desired product **2.8** was obtained in many of these reactions and Table 2.2 shows the various conditions examined. The data shows that Sweeney's conditions (Entry 3, Table 2.2) gave the desired product in 25% yield while Yang's protocol (Entry 4, Table 2.2) gave a yield of 30%. As these yield were low we decided to protect alcohol **2.6** as its THP ether in the hope that this would lead to an increase in the yield of the Heck reaction.

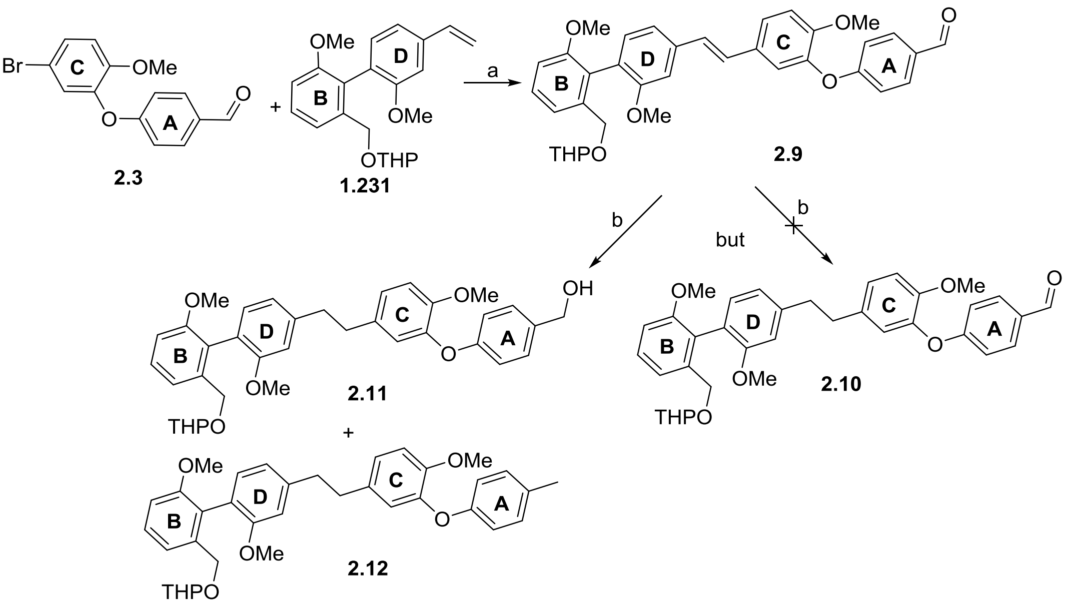


Entry	Conditions	Yield (%)
1	Pd(OAc)$_2$, 1,4-dioxane, Et$_3$N, reflux, 18 h	RSM
2	Pd(dtbpf)Cl$_2$, TBAC, Cy$_2$NMe, DMA, 80 °C, 18 h	25
3	Pd(OAc)$_2$, K$_3$PO$_4$, DMA, 140 °C, 18 h	30

Table 2.2: Results from the Heck conditions screen

2.5.2 Aldehyde protection by neopentylglycol

Protection of the aldehyde in the AC fragment **1.230** was also required for its hydrogenation to proceed efficiently. With an unprotected aldehyde in **2.9**, the hydrogenation reaction leading to **2.10** was unsuccessful. Using a classical hydrogenolysis protocol, a mixture of alchohol **2.11** and alkane **2.12** was given rather than the desired product (Scheme 2.6).

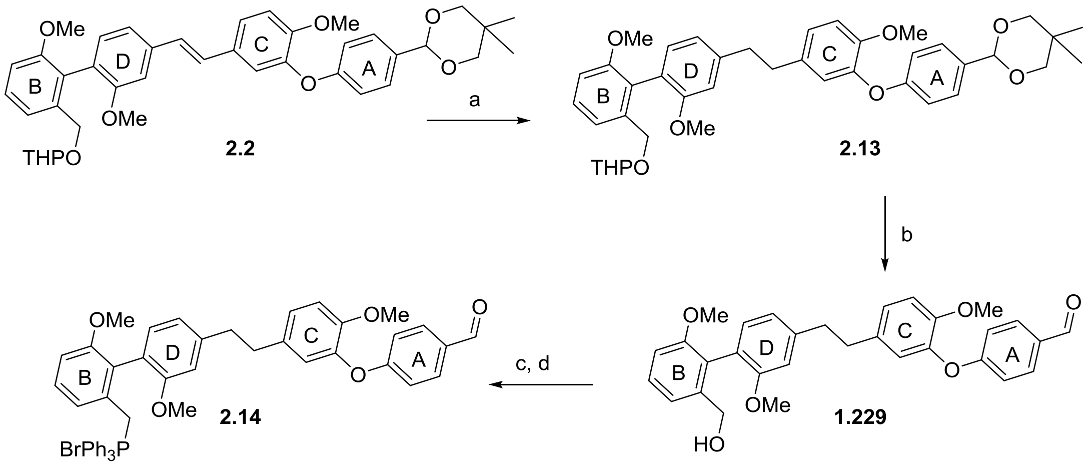


Reagents and conditions: a) Pd(OAc)$_2$, Et$_3$N, 1,4-dioxane, 26%; b) Pd/C (5%), H$_2$, THF, 10 min, (**2.11**) 37%, (**2.12**) 25%.

Scheme 2.6: Failed attempt to form tetraarene **2.10**

2.6 Preparation of cyclisation precursor 2.14

For macrocyclisation we needed to prepare the Wittig salt **2.14**. The alkene **2.2** from the Heck reaction was reduced to the tetraarene **2.13** by hydrogenation using PtO_2 in the presence of Et_3N to help prevent hydrogenolysis of the acetal group.[48] The acetal group and THP ether in **2.13** were then removed under acidic conditions to obtain the tetraarene **1.229**. Bromination of the alcohol moiety in **1.229** and subsequent treatment of the resulting benzyl bromide with PPh_3 gave the corresponding benzylphosphonium salt **2.14** as a cyclisation precursor (Scheme 2.7).

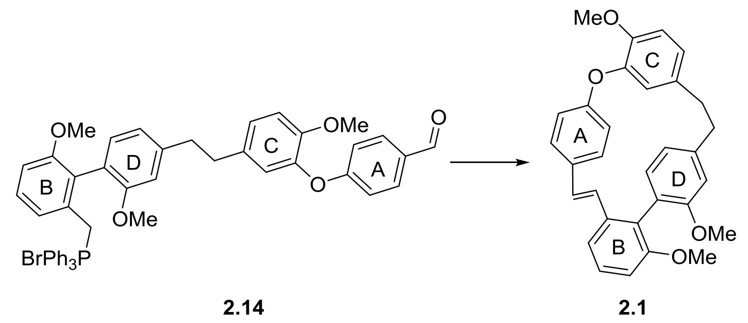


Reagents and conditions: a) H_2, PtO_2, DCM, EtOH, Et_3N, 95%; b) THF, HCl (2M), H_2O, 76%; c) PhMe, PBr_3, 0° C,15 h; d) PhMe, PPh_3, reflux, 16h.

Scheme 2.7: The preparation of cyclisation precursor **2.14**

2.7 Ring closure by a Wittig reaction

After preparation of the cyclisation precursor **2.14**, our attention turned to the ring closure step using a base. The use of NaOMe failed to achieve the Wittig cyclisation. However, when the reaction was carried out using KO^{t}Bu it succeeded in giving macrocycle **2.1** in a yield of 29%. Repeating the Wittg reaction with the addition of the base over 1 hour and then with heating for 13 h, increased the yield to 50% and resulted in cyclisation to *trans*-stilbene **2.1** (Scheme 2.8).

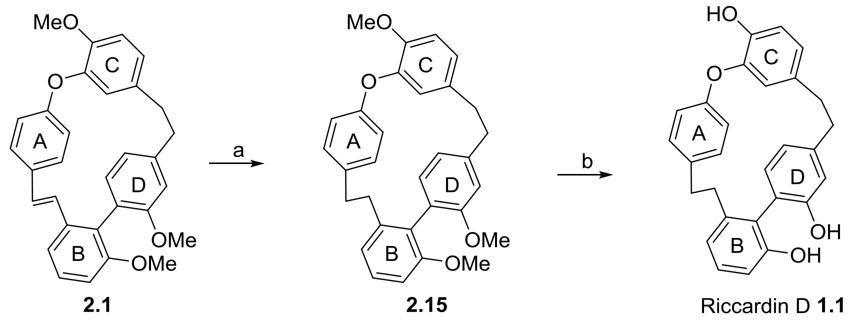


Reagent and condition: DCM, KO^{t}Bu (0.1 M), 1 h at RT then 13 h at 50 °C, 50% over three steps.

Scheme 2.8: Formation *trans*-cyclisation **2.1**

2.8 The final steps for the total synthesis of riccardin D 1.1

Riccardin D trimethyl ether **2.15** was then obtained by reducing the alkene in **2.1** under standard hydrogenation conditions. Deprotection of the three methyl ether residues then afforded riccardin D **1.1** (Scheme 2.9).

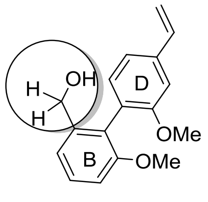


Reagents and conditions: a) Pd/C (10%), H_2, DCM, MeOH, 4 h, 94%; b) BBr_3, DCM, 61%.

Scheme 2.9: The preparation of the total synthesis of ricardin D **1.1**

2.9 NMR analysis

At this juncture it is sensible to highlight some features about the ^1H NMR spectra given by products in this project. The ^1H NMR for BD fragment **2.6** has a pair of protons for the benzyl alcohol that are diastereotopic (Scheme 2.10).[72] As a consequence each is observed as a 1 H, doublet.



2.6

Scheme 2.10: Diastereotopic protons

When the alcohol in BD fragment **2.6** was protected as a tetrahydropyranyl ether, the CH_2 group is now within a chiral molecule that has two interchanging diastereoisomeric forms (**A** and **B**, Figure 2.1). In the ^1H NMR, we see signals for both diastereomers due to slow atropisomerism (See Section 1.6).

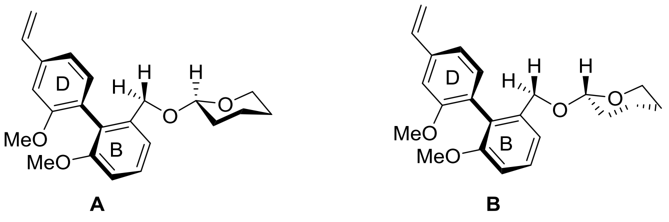


Figure 2.1: Diastereoisomers

For example, in the ^{1}H NMR proton of **1.231** the acetal CH of the THP gives rise to two doublets at δ_H 4.61 and 4.52 ppm (Figure 2.2). Additionally, the protons of the benzyl ether CH_2 each appear as two doublets (δ_H 4.63, 4.54, 4.27 and 4.19).

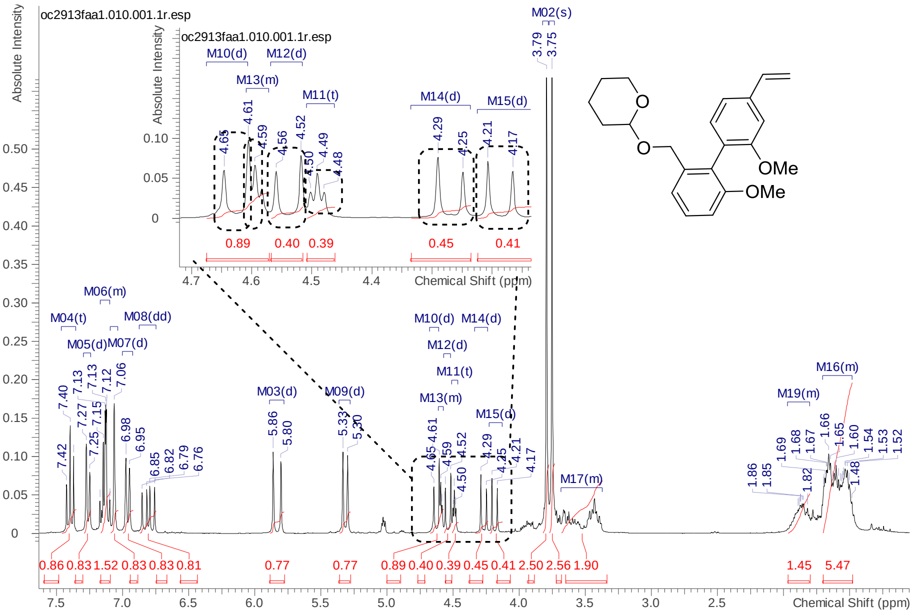
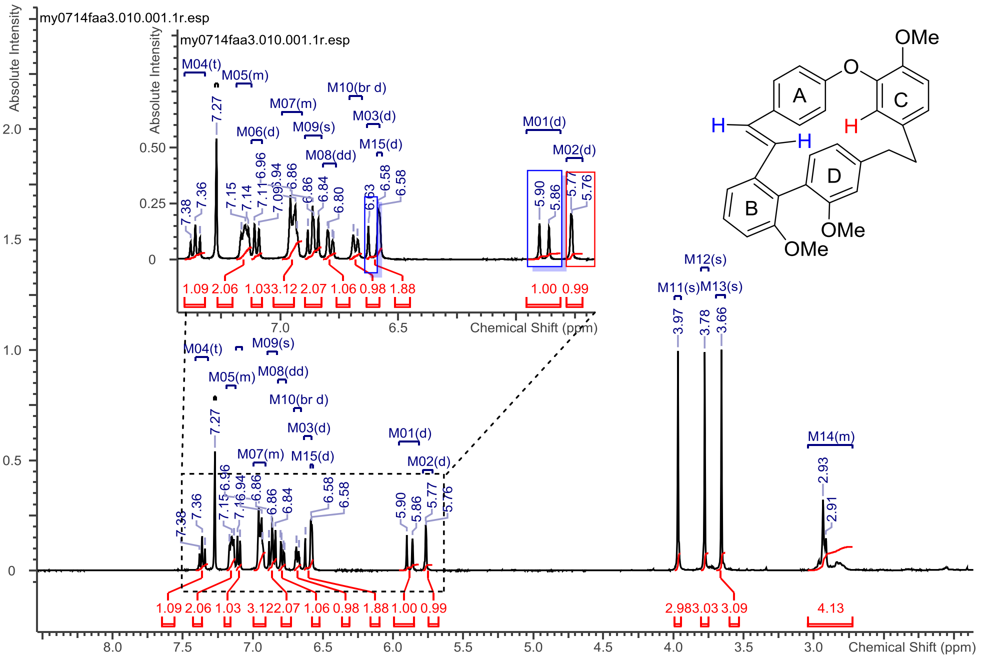


Figure 2.2: ^{1}H NMR spectral of **1.231**

The ^{1}H NMR spectra for macrocycle **2.1** indicated that we had achieved macrocyclisation and formed a *trans*-alkene. This was evidenced by a *J*-coupling of 16 Hz for the alkene protons (Figure 2.4). Moreover, it has been shown that in such cyclic bisbibenzyls the isolated CH in arene C (highlighted in red) is usually shifted upfield to ~δ_H 5.8 ppm due to the anisotropic effect of arenes A and D.[50] In our riccardin D precursor **2.1** this signal was observed at δ_H 5.77 ppm. These characteristics provide strong evidence that we had achieved clean macrocyclisation to *trans*-stilbene **2.1**.



<u>Figure 2.4:</u> ^{1}H NMR spectra of **2.1**

The NMR data of our synthetic sample of riccardin D **1.1** matched those published by Asakawa *et al*. for natural riccardin D **1.1** as well as those reported by Speicher *et al*. for their synthetic sample.[11,40] Through total synthesis, Speicher *et al*. had cast doubt about the structure assigned to plagiochin E **1.81** by Lou *et al*. following its isolation.[16,40] Speicher had achieved a total synthesis of plagiochin E **1.81** and found that the data it exhibited did not match that reported by Lou *et al*. Rather, Lou’s data was consistent that exhibited by riccardin D **1.1**. For completeness, we have made the same comparison (Table 2.3) of ^{1}H and ^{13}C NMR data for these compounds. This leads us to support the claim of Speicher *et al*. that Lou *et al*. had isolated riccardin D **1.1** not plagiochin E **1.81**.

^{1}H NMR data of isolation plagiochin E **1.81** and synthetic riccardin D **1.1** (acetone-d_6)		
Plagiochin E **1.81** data by Lou *et al*. (600 MHz)	Riccardin D **1.1** data by Speicher *et al*. (500 MHz)	Our sample riccardin D **1.1** data (400 MHz)
-	7.68 (br. s, O**H**),	7.66 (br. s, 2 x O**H**),
7.22 (t, *J*=7.8 Hz, Ar-**H**),	7.21 (dd, *J*=8.0,7.8 Hz, Ar-**H**),	7.18 (t, *J*=7.8 Hz, Ar-**H**),
-	7.15 (br.s, O**H**),	6.99 (br.s, O**H**),
7.01 (dd, *J*=7.8, 1.1 Hz, Ar-**H**),	7.02 (br.m, Ar-**H**),	7.01 (br.m, Ar-**H**),
7.00-7.05 (m, Ar-**H**),	6.99 (dd, *J*=7.8,1.3 Hz, Ar-**H**),	6.96 (dd, *J*=7.7,1.1 Hz, Ar-**H**),
6.90-6.98 (m, Ar-**H**),	6.92 (br.m, Ar-**H**),	6.87 (br.m, Ar-**H**),
6.86 (d, *J*=7.8 Hz, Ar-**H**),	6.85 (d, *J*=8.0 Hz, Ar-**H**),	6.81 (d, *J*=8.1 Hz, Ar-**H**),
6.85 (d, *J*=7.8 Hz, Ar-**H**),	6.84 (d, *J*=8.0 Hz, Ar-**H**),	6.81 (d, *J*=8.2 Hz, Ar-**H**),
6.80 (dd, *J*=7.8, 1.1 Hz, Ar-**H**),	6.79 (dd, *J*=8.0,1.3 Hz, Ar-**H**),	6.76 (dd, *J*=7.9, 1.2 Hz, Ar-**H**),
6.77-6.79 (m, Ar-**H**),	6.77 (br.m, Ar-**H**),	6.74 (br.m, Ar-**H**),
6.75-6.78 (m, Ar-**H**),	6.77 (br.m, Ar-**H**),	6.74 (br.m, Ar-**H**),
6.74 (dd, *J*=7.8, 1.8 Hz, Ar-**H**),	6.72 (dd, *J*=8.0,2.0 Hz, Ar-**H**),	6.69 (dd, *J*=8.1,2.1 Hz, Ar-**H**),
6.32-6.35 (m, Ar-**H**),	6.32 (d, *J*=1.8 Hz, Ar-**H**),	6.29 (d, *J*=1.7 Hz, Ar-**H**),
6.32-6.35 (m, Ar-**H**),	6.31 (dd, *J*=7.9,1.8 Hz, Ar-**H**),	6.28 (dd, *J*=7.8,1.7 Hz, Ar-**H**),
5.46 (d, *J*=1.8 Hz, Ar-**H**),	5.45 (d, *J*=2.0 Hz, Ar-**H**),	5.41 (d, *J*=2.0 Hz, Ar-**H**),
2.94-2.56 (m, 8**H**).	2.94-2.56 (m, 8**H**).	2.94-2.54 (m, 8**H**).
^{13}C NMR data of isolation plagiochin E and synthetic riccardin D (acetone-d_6)		
156.18, 155.65, 154.96, 148.95,	155.59, 155.06, 154.36, 148.35,	156.1, 155.6, 154.9, 148.9,
145.96, 145.61, 143.28, 141.93,	145.34, 145.01, 142.67, 141.33,	145.8, 145.5, 143.2, 141.8,
134.29, 134.18, 130.91, 130.65,	133.70, 133.57, 130.32, 130.05,	134.2, 134.1, 130.8, 130.6,
129.99, 126.65, 123.71, 123.40,	129.39, 126.06, 123.12, 122.85,	129.9, 126.6, 123.6, 123.4,
123.40, 123.17, 121.82, 121.74,	122.79, 122.57, 121.21, 121.14,	123.3, 123.1, 121.7, 121.7,
118.48, 118.41, 117.29, 114.47,	117.90, 117.81, 113.87, 116.69,	118.4, 118.3, 117.2, 114.4,
39.08, 39.10, 38.11, 36.29.	38.48, 38.51, 37.48, 35.69.	39.0, 39.0, 38.0, 36.2.

Table 2.3: A comparison of the NMR data

2.10 Conclusion and future work

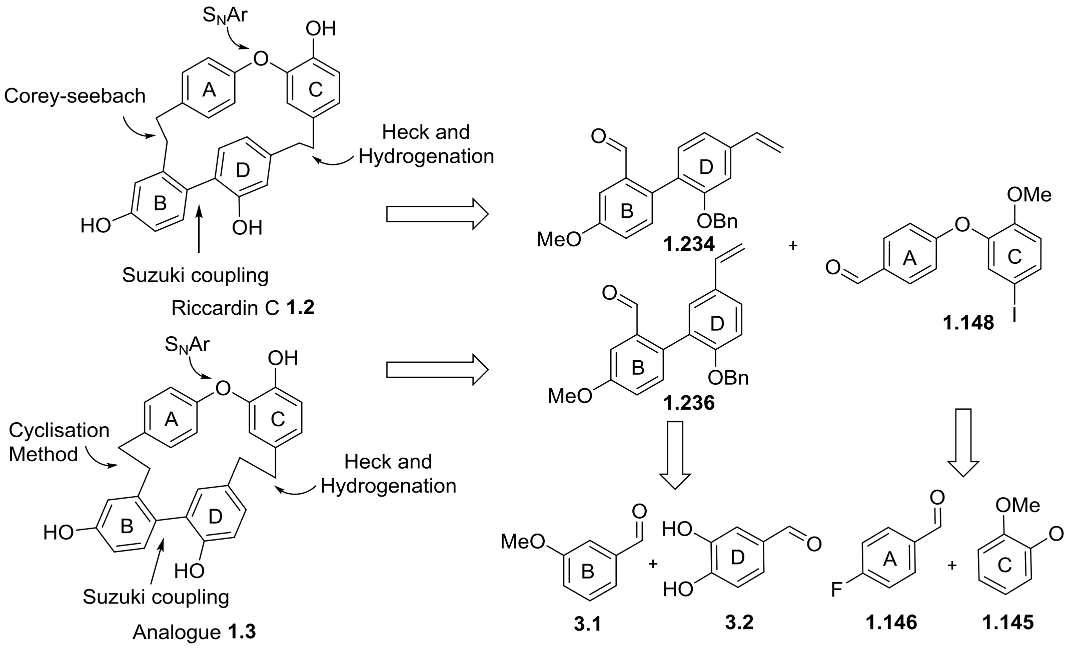
The total synthesis of riccardin D **1.1** was achieved by effecting macrocyclisation at the AB linkage. A Wittig reaction was used for that key reaction and afforded the desired product exclusively as a *trans*-stilbene **2.1**. The NMR data recorded on our synthetic sample of riccardin D **1.1** supports the view of Speicher *et al*. that the compound isolated by Lou *et al*. and assigned as plagiochin E **1.81** was in fact riccardin D **1.1**. With interest growing in respect of the biological effects of riccardin D

1.1, we can envision other researchers using this approach to produce both the natural product and analogues for screening as lead compounds in pharmaceutical research.

Chapter 3: Results and discussion: A total syntheses of riccardin C 1.2 and analogue 1.3; Formal total syntheses of asterelin A 1.4 and cavicularin 1.5

3.1 The retrosynthesis of riccardin C 1.2 and a novel macrocyclic bisbibenzyl analogue 1.3

Our attention now switched to developing a second approach to provide more general access to the macrocyclic bisbibenzyl family including riccardin C **1.2** and a novel derivative of unnatural origin **1.3**. Our starting point was the synthesis of the required AC **1.148** and BD fragments **1.234** and **1.236** which were prepared from simple starting materials. The AC fragment **1.148** can be obtained in two-steps. Syntheses of the BD fragments **1.248** and **1.236** each began with *m*-anisaldehyde **3.1** and 3,4-dihydroxybenzaldehyde **3.2** and required regiocontrolled coupling (Scheme 3.1). Various cyclisation reactions including McMurry, Wittig, metathesis, Heck and Corey-Seebach reactions are examined to make the macrocycle analogues.[46- 48,50,64,73,74] The latter of these would introduce a new strategy for achieving the macrocyclisation step.[75-79]



Scheme 3.1: The retrosynthesis of riccardin C **1.2** and analogue **1.3**

Macrocyclisation is often the most difficult step to realise in macrocyclic bisbibenzyl syntheses.[9] Therefore, we need to consider the best strategy to achieve a successful macrocyclisation in high yield.

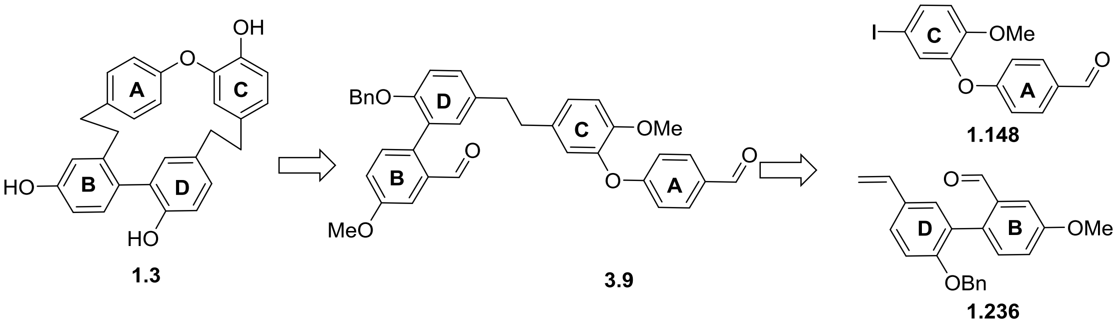
3.2 A novel derivative of macrocyclic bisbibenzyl (analogue) 1.3

There are limited examples of macrocyclic bisbibenzyl derivatives of unnatural origin. Lou *et al.* have recently reported two derivatives of riccardin D (riccardin D-26) and (RD-N).[80,81] In 2013, Miyachi *et al*. reported the total syntheses of a series of macrocyclic bisbibenzyl derivatives based on the riccardin, isoplagiochin and marchantin class of structures.[73] They studied biological activity within these series of macrocyclic bisbibenzyl derivatives evaluating their antibacterial activity towards methicillin-resistant *Staphylococcus aureus* (anti-MRSA activity). Dodo *et al*. also investigated the biological activity of riccardin C **1.2** and some derivatives lacking oxygenation on each ring.[49] It was concluded that the analogues were not as active as riccardin C **1.2**.

The ring system in our novel derivative **1.3** has a constitution similar to those found in nature.[19] However, the biaryl arenes B and D in the analogue are not consistent with macrocyclic bisbibenzyl biosynthesis. In nature, the biaryl arenes B and D rings are necessarily bound within the macrocycle through *ortho* and *para* linkages.[9] We simply activated the *meta*-carbon atom in arene D to be able to gain access to the unnatural product series. McMurry, Wittig, metathesis, Heck and Corey-Seebach reactions were investigated for macrocyclisation.

3.2.1 Macrocyclic reaction by McMurry

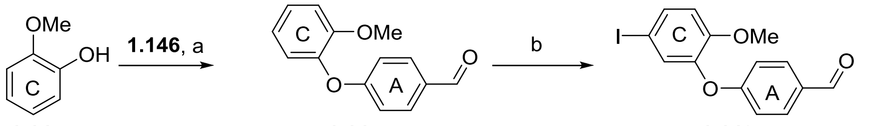
Harrowven *et al.* and Speicher *et al.* have each reported the use of a McMurry reaction in total syntheses of macrocycle bisbibenzyl compounds.[46,47,82,83] This approach requires the use of a low valent titanium reagent to effect a coupling between two carbonyls and the elimination of the resulting diol to give an alkene. Having chosen a McMurry reaction for the key macrocyclisation step, our attention turned to the synthesis of AC **1.148** and BD **1.236** fragments and their connection by means of a Heck reaction (Scheme 3.2).



Scheme 3.2: Retrosynthesis of unnatural product analogue **1.3**

3.2.1a Synthesis of the AC 1.148 fragment

The preparation of the AC fragment **1.148** began with the union of 4-fluorobenzaldehyde **1.146** and 2-methoxyphenol **1.145** to produce biaryl ether **1.147** in an S_NAr reaction. Iodination then gave biaryl ether **1.148** (Scheme 3.3). We developed new conditions for the iodination reaction. Previously the Harrowven group has reported that the iodination was complete after seven days which is a long time to wait.[50] Therefore, we examined the use of *N*-iodosuccinimide in an attempt to effect the iodination in a shorter time. However, the reaction failed to yield the desired product **1.148**. When trifluoroacetic acid was also added, to activate *N*-iodosuccinimide.[84,85] We were pleased to obtain the required AC fragment **1.148** in a high yield. Indeed, these conditions have reduced the time required for the iodination reaction to 13 hours and proceeded to a single regioisomer.



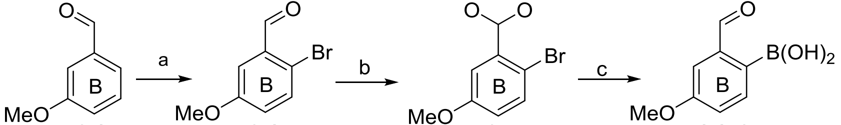
1.145 **1.147** **1.148**

Reagents and conditions: a) 4-fluorobenzaldehyde **1.146**, K_2CO_3, DMF, 155 °C, 24 h, 96%; b) NIS, CF_3COOH, MeCN, 13 h, 90%.

Scheme 3.3: AC fragment **1.148** formation

3.2.1b Synthesis of the BD fragment 1.236

With the AC fragment **1.148** in hand, our attention turned to the preparation of the BD fragment **1.236** using a Suzuki-Miyaura reaction. Boronic acid **1.152** is commercially available as described in the total synthesis of riccardin C **1.2** (See Section 1.4.3b).[50] To avoid the high expense, arene B **1.152** was prepared in three steps from *m*-anisaldehyde **3.1**. Bromination of *m*-anisaldehyde **3.1** first gave the desired bromide **3.4** which was subjected to protection of its aldehyde to give acetal **3.5**.[86] Finally, boronic acid **1.152** was prepared by halogen-boronate exchange through treatment of **3.5** with *n*-BuLi, then quenching with tributyl borate followed by an acidic work-up (Scheme 3.4).

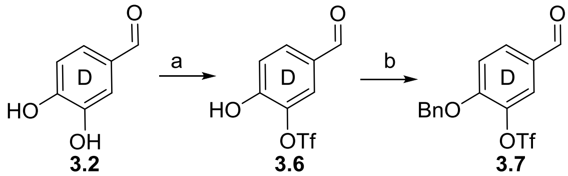


3.1 **3.4** **3.5** **1.152**

Reagents and conditions: a) Br_2, AcOH, 92%; b) Ethylene glycol, PPTS, 99%; c) (i) *n*-BuLi, (ii) $B(On\text{-}Bu)_3$,(iii) HCl (2 M), 85%.

Scheme 3.4: B fragment **1.152** formation

We started our preparation of arene D **3.7** with 3,4-dihydroxybenzaldehyde **3.2** which was selectively triflated at the *meta* position to obtain **3.6**. Then, the *para*-hydroxy group **3.6** was protected with a benzyl group to give ether **3.7** (Scheme 3.5).

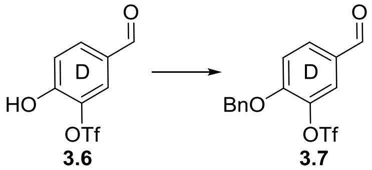


3.2 **3.6** **3.7**

Reagents and conditions: a) Tf_2O, pyridine, DCM, 74%;
b) BnBr, K_2CO_3, 72%.

Scheme 3.5: Preparation of **3.7**

Protection of the *para*-hydroxy group required considerable effort to improve its yield. Indeed, we investigated the effect of both concentration and solvent on its outcome. Acetone was first used as the solvent at a concentration of 0.09 M and led to the desired product in 43% yield (Entry 1, Table 3.1). Acetonitrile was next examined and the yield of the reaction improved. Further improvements came by increasing the concentration from 0.1 to 0.4 M. However, when the concentration was increased further to 0.7 M, the yield decreased to 59% (Entry 5, Table 3.1), suggesting that the optimal concentration for this reaction is close to 0.4 M.



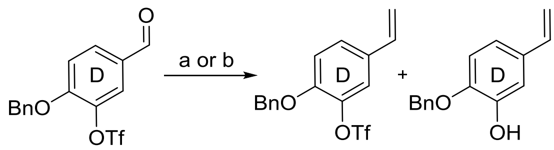
3.6 **3.7**

Reagent and condition: BnBr, K_2CO_3, solvent table 5

Entry	Solvent	[M]	Yield (%)
1	Acetone	0.09	43
2	Acetone	0.1	37
3	Acetonitrile	0.1	65
4	Acetonitrile	0.4	72
5	Acetonitrile	0.7	59

Table 3.1: The impact of concentration and solvents on the protection reaction

The subsequent Wittig methylenation reaction using KO^{t}Bu afforded styrene **3.8** in low yield together with phenol **3.9** (Scheme 3.6). The phenol **3.9** appeared because of our use of KO^{t}Bu as a base as this removed the triflate in **3.8** which was not our aim. To improve the yield of the Wittig reaction, NaH was used as a base. The phosphonium salt was slowly added to a mixture of the triflate and the base to obtain styrene **3.8** in good yield.

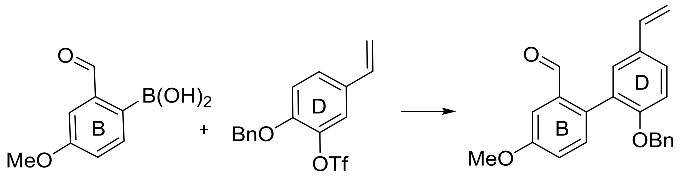


3.7 **3.8** **3.9**

Reagents and Conditions: a) KO^{t}Bu, MePPh$_3$Br, **3.8** (16%) **3.9** (21%),
b) NaH,MePPh$_3$Br, **3.8** (76%).

Scheme 3.6: Formation of arene D **3.8**

Having arenes B **1.152** and D **3.8** in hand, a Suzuki–Miyaura coupling was employed to prepare the BD biaryl fragment **1.236** (Scheme 3.7).[50]



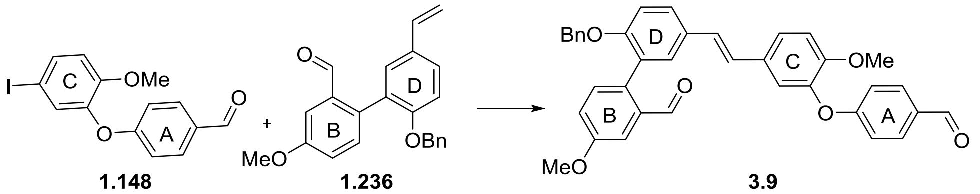
1.152 **3.8** **1.236**

Reagents and Conditions: Pd(PPh$_3$)$_4$, PhMe/EtOH/H$_2$O, Cs$_2$CO$_3$, reflux, 90%.

Scheme 3.7: BD **1.236** synthesis

3.2.1c Connecting the AC 1.148 and BD 1.236 fragments

A Heck reaction was next used to connect the AC **1.148** and BD **1.236** fragments giving *trans*-stilbene **3.9**. Various catalysts were examined for the Heck reaction. The first attempt to obtain **3.9** used Pd(OAc)$_2$ in the presence of Et$_3$N in 1,4-dioxane and proceeded in reasonable yield.[50] Table 3.2 shows these conditions and others used for effecting the Heck reaction (entry 3).[70]



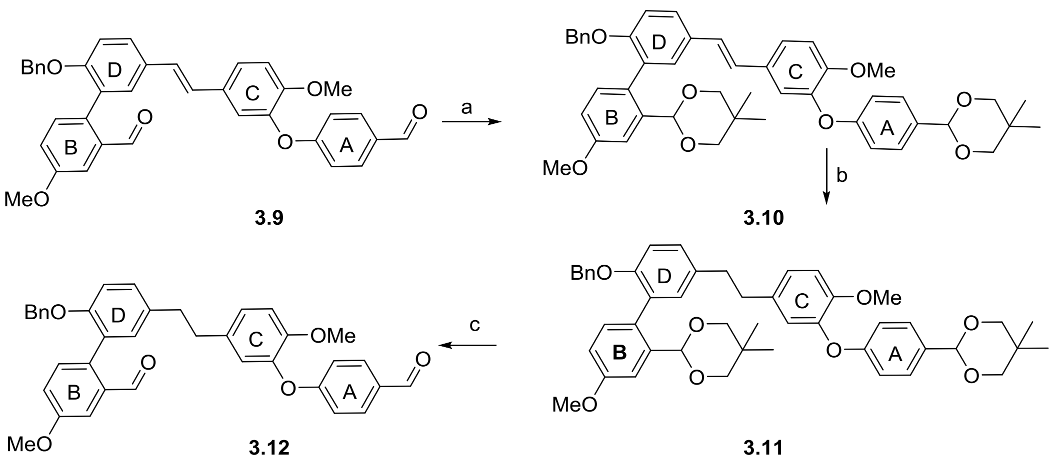
1.148 **1.236** **3.9**

Entry	Catalyst	Yield (%)
1	Pd(OAc)$_2$, 1,4-dioxane, Et$_3$N, reflux, 13 h	71
2	Pd(PPh$_3$)$_4$, 1,4-dioxane, Et$_3$N, reflux, 13 h	42
3	Pd(OAc)$_2$, K$_3$PO$_4$, DMA, reflux, 13 h	72

Table 3.2: Conditions effect on Heck reaction

3.2.1d Formation of cyclisation precursor 3.12

Then, both aldehydes in **3.9** were protected to obtain **3.10**. The alkene was then reduced using tosylhydrazone and NaOAc to generate diimide to give **3.11** with the benzyl ether group intact. Deprotection of both aldehydes in **3.11** was then achieved under acidic conditions to obtain cyclisation precursor **3.12** (Scheme 3.8).

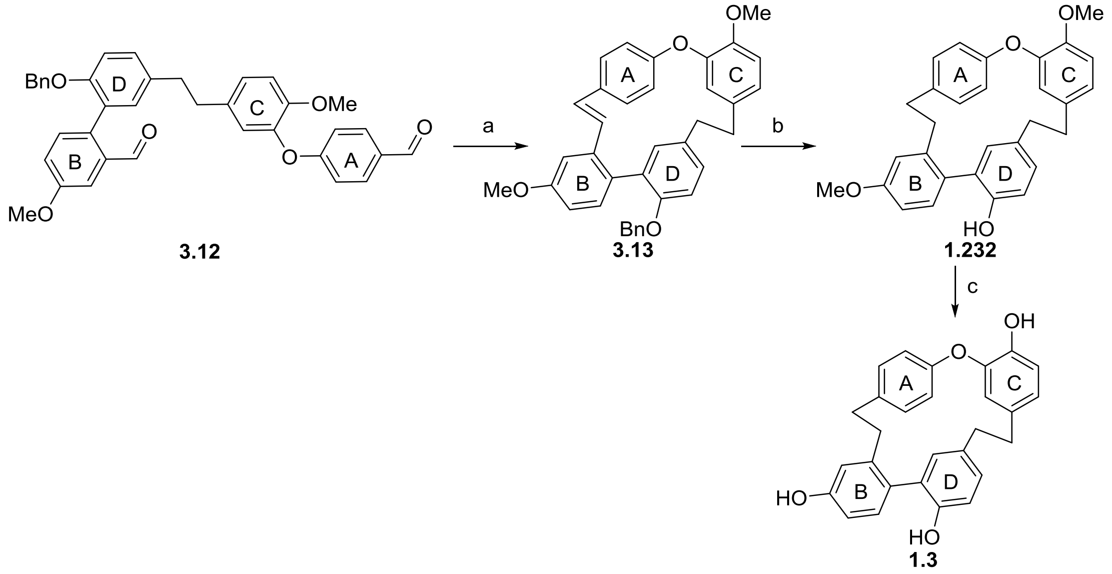


Reagents and conditions: a) neopentylglycol, PhMe, *p*-TsOH, 98%; b) tosylhydrazone, NaOAc, 1:1 v/v THF and water, 76%; c) PPTS, acetone, water, 84%.

Scheme 3.8: Preparation of cyclisation precursor **3.12**

3.2.1e Ring Closure by McMurry reaction and obtaining the final target

Having the cyclisation precursor **3.12**, a McMurry reaction was used to obtain the macrocycle **3.13** in 26% yield as the *trans*-stilbene. A hydrogenation reaction then reduced the alkene and removed the benzyl group to give dimethyl ether analogue **1.232** (Scheme 3.9). The total synthesis of analogue **1.3** was completed by demethylation of two methyl ethers.

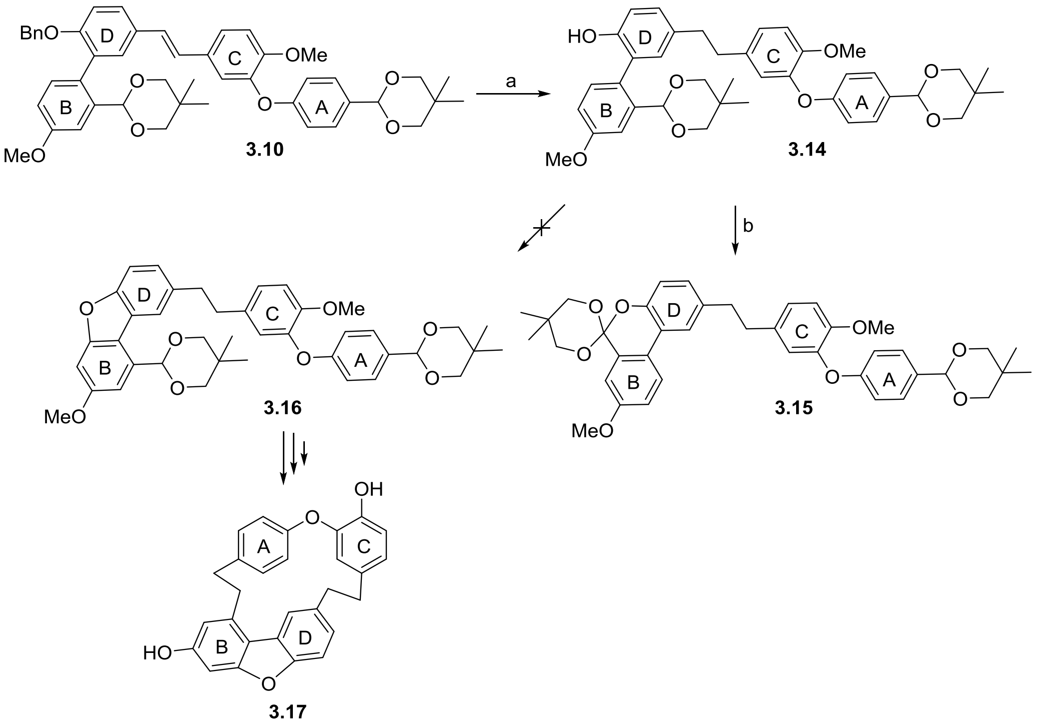


Reagents and conditions: a) $TiCl_4$, Mg, THF, 26%; b) 10% Pd/C, EtOH, DCM, 71%; c) BBr_3, DCM, 92%.

Scheme 3.9: Formation of protected analogue **1.3**

3.2.1f A failed attempt to effect intramolecular oxidative coupling

We next sought to extend this approach to another derivative **3.17** which contains a dibenzofuran moiety such as asterelin A **1.4**. To that end, tetraarene **3.10** was subjected to hydrogenation to obtain **3.14**. We hoped oxidative intramolecular coupling of arenes D and B would lead to **3.16**. However, it proved unsuccessful using the same method of Fukuyama *et al.*[61] Indeed, instead of giving the dibenzofuran moiety. It yielded orthoacetal **3.15** (Scheme 3.10).

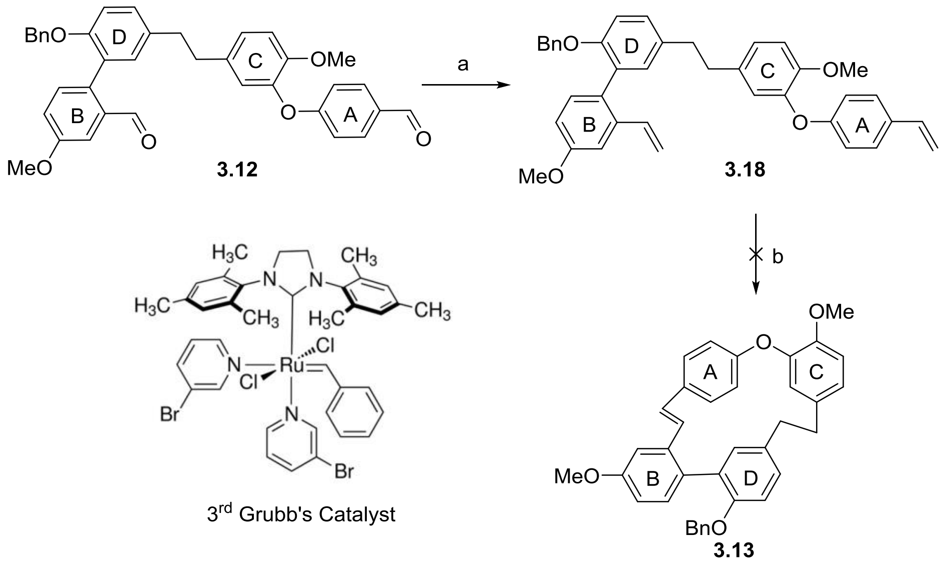


Reagents and Conditions: a) PtO_2, Et_3N, H_2, EtOH/DCM, 75%; b) $VOCl_3$, DCM, 0 °C, 20 min, **314** (15%).

Scheme 3.10: Failed attempt to perform oxidative intramolecular coupling

3.2.2 Macrocyclisation by Ring-Closing Metathesis

Although the McMurry reaction had successfully delivered the macrocyclic compound **3.13**, it proceeded in low yield. To improve the yield of macrocyclisation, we decided to examine the metathesis reaction. Harrowven's group has previously used Grubbs' second generation catalyst for macrocyclisation in the bisbibenzyl series and a symmetric dimer was obtained instead of the desired product.[50] Taking into account the potential for dimer formation, we decided to examine the metathesis reaction using Grubbs's third generation catalyst under conditions of high dilution. Grubbs's 3rd generation catalyst is more efficient and contains two pyridine ligands instead of the phosphine ligand that is in the 2nd generation catalyst. Pyridine ligands help because they are weakly connected with the ruthenium centre and tend to dissociate more easily. To that end, a double Wittig reaction was performed on bis-aldehyde **3.12** to obtain the bis-styrene **3.18** (Scheme 3.11). Alas, its exposure to Grubbs's third generation catalyst failed to give the desired product leading instead to a complex product mixture.

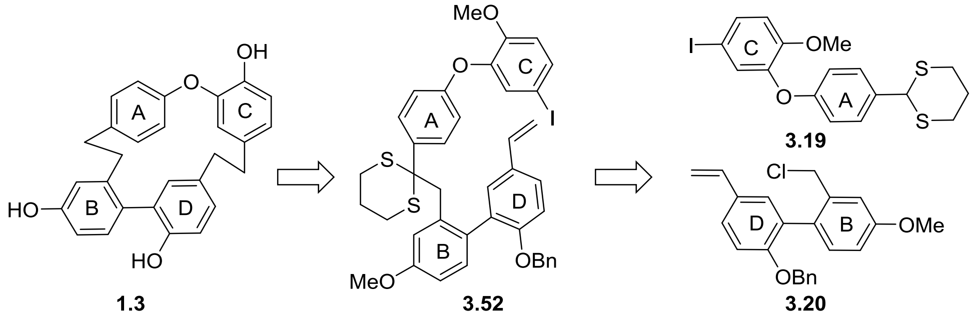


Reagents and conditions: a) KO^{t}Bu, MePPh$_3$Br, 72%. b) 3rd Grubb's Catalyst.

Scheme 3.11: Preparation of cyclisation **3.13**

3.2.3 Macrocyclisation by a Heck cross coupling

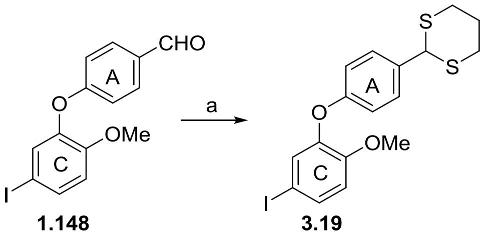
Given the disappointing result of the metathesis, we next sought to use an intramolecular Heck cross coupling for the macrocyclisation reaction in an attempt to improve the yield. Although macrocyclisation using a Heck reaction was reported recently to achieve the synthesis of a related natural product in low yield, we hoped the yield might improve with our system.[64] To that end, we planned to develop syntheses of the AC **3.19** and BD **3.20** fragments and connect these to obtain precursor **3.52** (Scheme 3.12).



Scheme 3.12: Retrosynthesis of unnatural product analogue **1.3**

3.2.3a Preparation of the AC fragment 3.19

The required AC fragment **3.19** was readily prepared by protection of the aldehyde in **1.148** with 1,3-propanedithiol. This was achieved 81% yield (Scheme 3.13).[87]

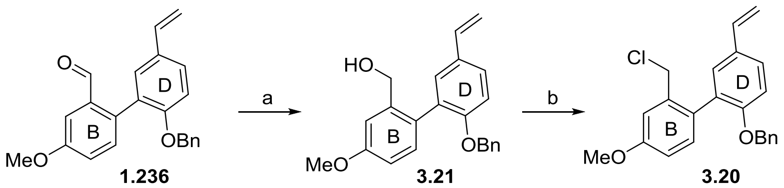


Reagents and conditions: a) 1,3-propanedithiol, PPTS, DCM, 81%.

Scheme 3.13: The formation of AC **3.19** fragment

3.2.3b Preparation of the BD fragment 3.20

The BD fragment **3.20** was then prepared by reduction of the aldehyde in **1.236** to alcohol **3.21**. Then the alcohol was converted into chloride **3.20** by the action of methanesulfonyl chloride (Scheme 3.14).

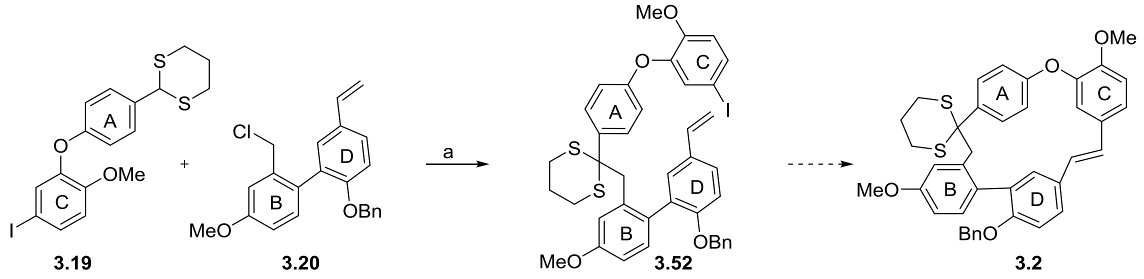


Reagents and conditions: a) $NaBH_4$, MeOH, DCM, 99%. b) MsCl, DBU, DCM, 96%.

Scheme 3.14: Preparation of the BD fragment **3.20**

3.2.3c Attempt to effect macrocyclisation using a Heck reaction

Our plan to effect macrocyclisation using a Heck reaction required us to prepare precursor **3.52**. The AC **3.19** and BD **3.20** fragments were treated with LDA under a variety of conditions but even our best protocol gave the desired product **3.52** in low yield (Scheme 3.15).[88] Consequently, we decided to adopt a different strategy.

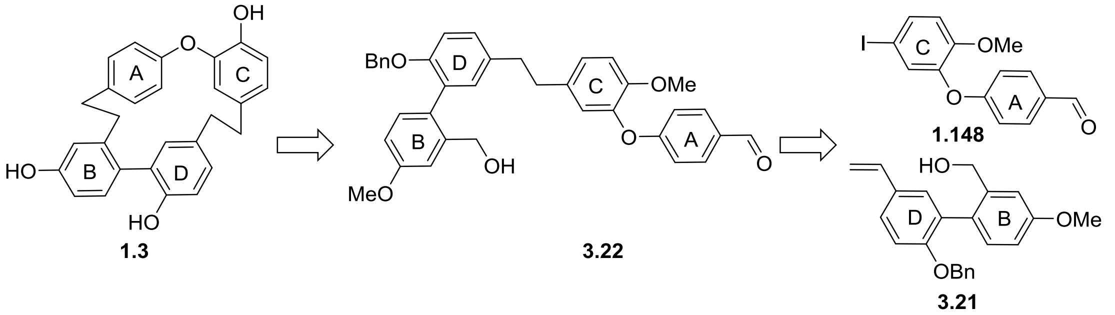


Reagents and conditions: a) THF, LDA, -78 °C- RT, 18%.

Scheme 3.15: Attempt to make the cyclisation reaction by Heck reaction

3.2.4 Macrocyclic reaction by an intramolecular Wittig coupling

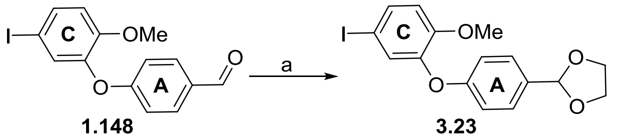
The Wittig macrocyclisation reaction has become established as the most useful method for achieving macrocyclisation to reach different targets in the bisbibenzyl family of natural products. A number of total syntheses have been achieved using the Wittig reaction so our attention turned to using this for the macrocyclic reaction.[46,47,48,50,73] Also, having completed the total synthesis of riccardin D by using A Wittig reaction (See Section 3.6); we had experience of the method. To that end, we need to prepare two fragments **1.148** and **3.21** and connect them together. Then we would be able to advance via **3.22** to a Wittig precursor to make the macrocyclic analogue (Scheme 3.16).



Scheme 3.16: Retrosynthesis of the analogue **1.3**

3.2.4a First attempt to form AC 3.23 fragment

To avoid reduction of the aldehyde during the hydrogenation, we decided to protect the aldehyde in AC **1.148** fragment using ethylene glycol to obtain acetal **3.23** in 64 % (Scheme 3.17).

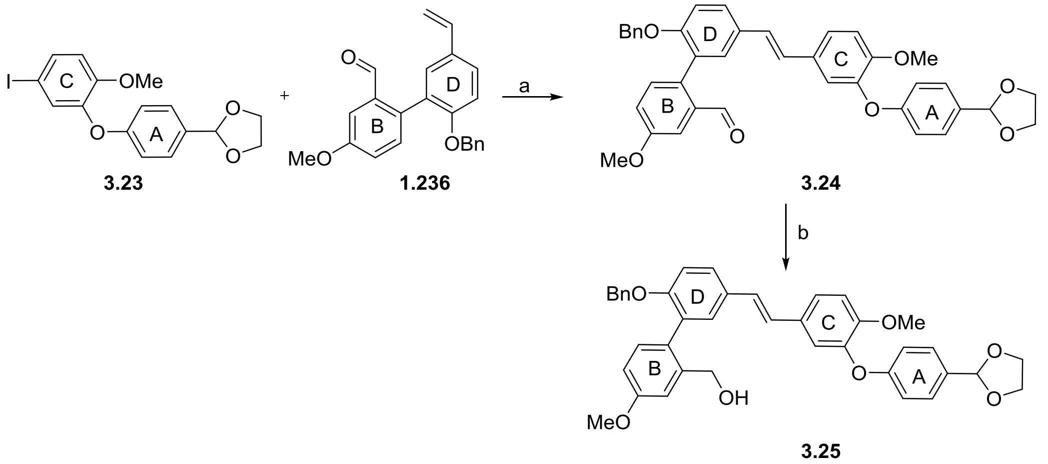


Reagents and conditions: a) ethylene glycol, PPTS, 64%.

Scheme 3.17: Protection of AC **3.23** fragment

3.2.4b Connecting AC 3.23 and BD 1.236 fragments

Having the AC **3.23** and BD **1.236** fragments in hand, a Heck reaction was then carried out to obtain stilbene **3.24**. Then, the aldehyde in **3.24** was reduced by $NaBH_4$ to produce alcohol **3.25** in excellent yield (Scheme 3.18).

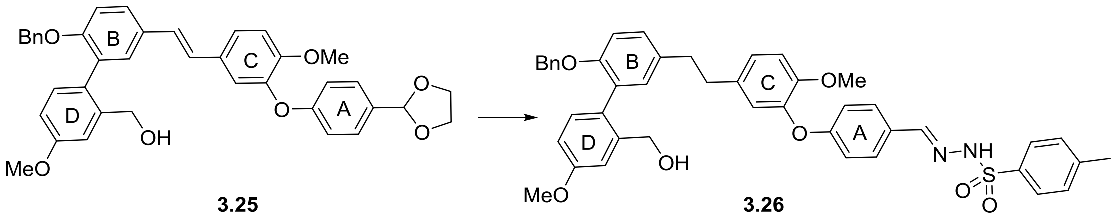


Reagents and conditions: a) $Pd(OAc)_2$, K_3PO_4, DMA, 82%; b) $NaBH_4$, MeOH, DCM, 92%.

Scheme 3.18: The formation of stilbene **3.25**

3.2.4c Failure in the preparation of the cyclisation precursor

The catalytic hydrogenation of stilbene **3.25** to the desired precursor was unsuccessful using classical methods. Moverover, when using *p*-toluenesulfonyl hydrazide and NaOAc, deprotection of the acetal in **3.25** occurred and the transient aldehyde reacted with tosyl hydrazine to give the undesired product **3.26** (Scheme 3.19).

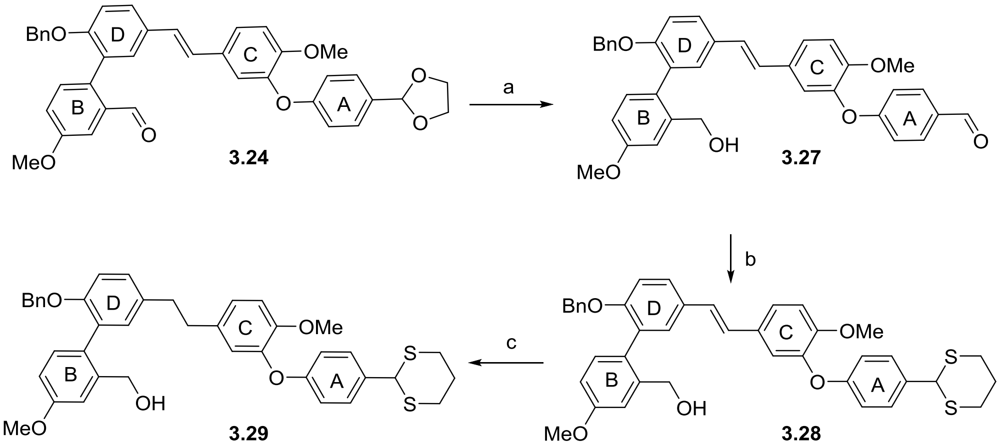


Reagents and conditions: $TsNHNH_2$, NaOAc, THF, H_2O, 18 h, 55%.

Scheme 3.19: Failed attempt to perform the hydrogenation

3.2.4d Second attempt to prepar the cyclisation precursor

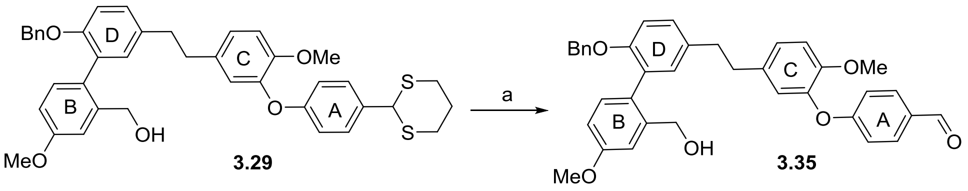
To overcome the problem of aldehyde deprotection, we decided to use a more stable protecting group for the aldehyde. Thus, we reduced the aldehyde in **3.24** to alcohol, followed by removal of the protecting group from the aldehyde to give **3.27** (Scheme 3.20). Then, the aldehyde was protected using 1,3-propanedithiol to obtain dithiane **3.28**. Hydrogenation with diimide then gave the desired product **3.29** in good yield.[50]



Reagents and conditions: a) $NaBH_4$, MeOH, DCM, 1 h, 2M HCl, 83%; b) 1,3-propanedithiol, PPTS, DCM, 91%; c) $TsNHNH_2$, NaOAc, 91%.

Scheme 3.20: The formation of **3.29**

Mercury(II) oxide and mercury(II) chloride were next used to remove the 1,3-propanedithiol protection group in **3.29**.[89] When mercury(II) oxide was used to remove the protecting group in **3.29** was removed and then some of the aldehydes were reduced in **3.35** to methyl groups giving an undesired product which was unexpected. The ^{1}H NMR analysis of the crude reaction mixture indicated the aldehyde reduction. As alternative method for the hydrolytic removal of dithianes is to use methyl iodide with $CsCO_3$.[90] These conditions provided a mild deprotection method for **3.29**, giving **3.35** in 87% yield (Scheme 3.21). Nonetheless, taking into consideration the length of the route we were developing to access the Wittig macrocyclisation precursor, we decided to adopt a different strategy.



Reagents and conditions: a) MeI, $CaCO_3$, H_2O, MeCN, 87%.

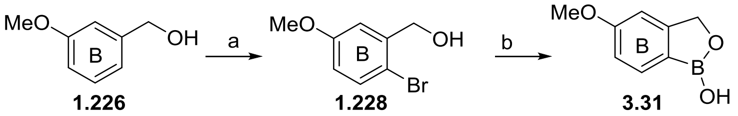
Scheme 3.21: Formation of **3.35**

3.2.5 Achievement of an efficient route to the Wittig precursor

The length of the previous route prompted us to develop a short and efficient pathway to make the Wittig macrocyclisation precursor. We aimed to use a stable acetal protecting group for the aldehyde in the AC fragment and develop a short way to make the required BD fragment.

3.2.5a A new method to prepare BD 3.21 fragment

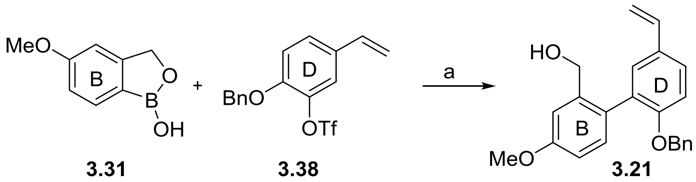
Our new plan was to make the BD fragment **3.21** using a Suzuki-Miyaura reaction. The required arene B **3.31** was prepared in two steps (Scheme 3.22).[63] Thus, bromination of 3-methoxybenzyl alcohol was achieved using NBS to give bromide **1.228**. Then halogen-lithium exchange was effected through the treatment of **1.228** with *n*-BuLi, quenching with trimethyl borate, and hydrolysis to boronic acid **3.31**.



Reagents and conditions: a) NBS, MeCN, 99%; b) NaH, *n*-BuLi, THF, $B(OMe)_3$, 57%.

Scheme 3.22: Synthesis of boronic acid **3.31**

Having boronic acid **3.31** and styrene **3.38** in hand, a Suzuki–Miyaura coupling was employed to prepare the BD **3.21** biaryl fragment (Scheme 3.23).

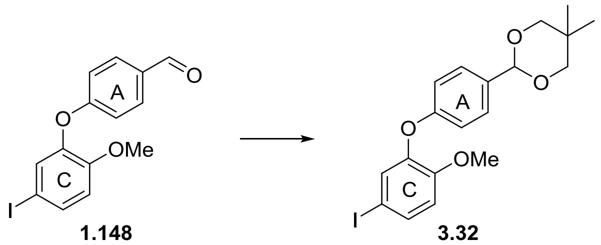


Reagents and conditions: a) $Pd(PPh_3)_4$, Cs_2CO_3, $PhMe/EtOH/H_2O$, 48%.

Scheme 3.23: Preparation of the BD **3.21** biaryl fragment

3.2.5b The protection of aldehyde in AC arene by neopentylglycol

Protection of aldehyde in AC fragment **1.148** was required to achieve good yields for the subsequent hydrogenation reaction. Thus, aldehyde **1.148** was protected using neopentylglycol to obtain acetal **3.32** in high yield (Scheme 3.24).



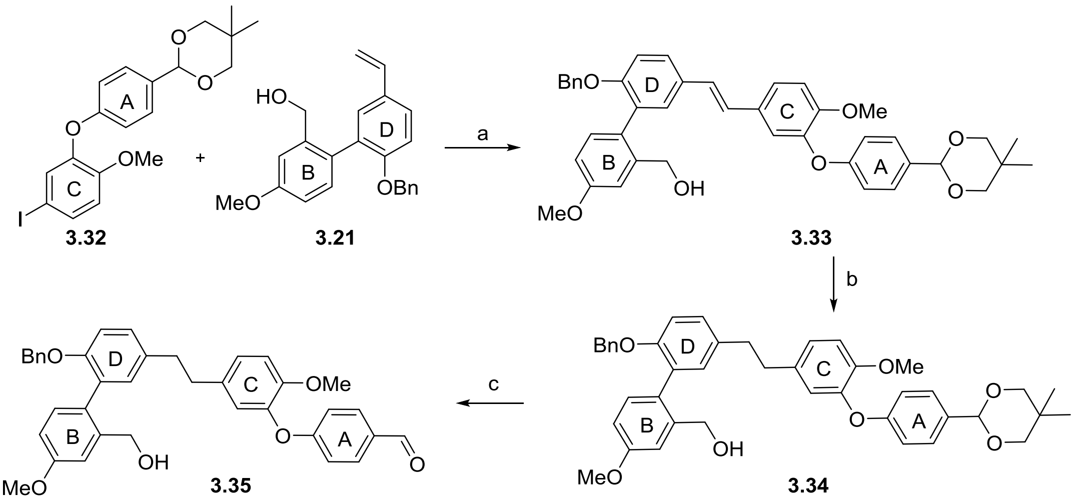
1.148 **3.32**

Reagents and conditions: neopentylglycol, *p*-TsOH, PhMe, 93%.

Scheme 3.24: Protection of the aldehyde AC **3.32** fragment

3.2.5c Preparation of cyclisation precursor 3.35

A Heck reaction between the AC **3.32** and BD **3.21** fragments next gave *trans*-stilbene **3.33**. The alkene in **3.33** was then reduced by using tosylhydrazone and NaOAc to give **3.34**. Deprotection of the acetal in **3.34** then gave aldehyde **3.35** in modest yield (Scheme 3.25).



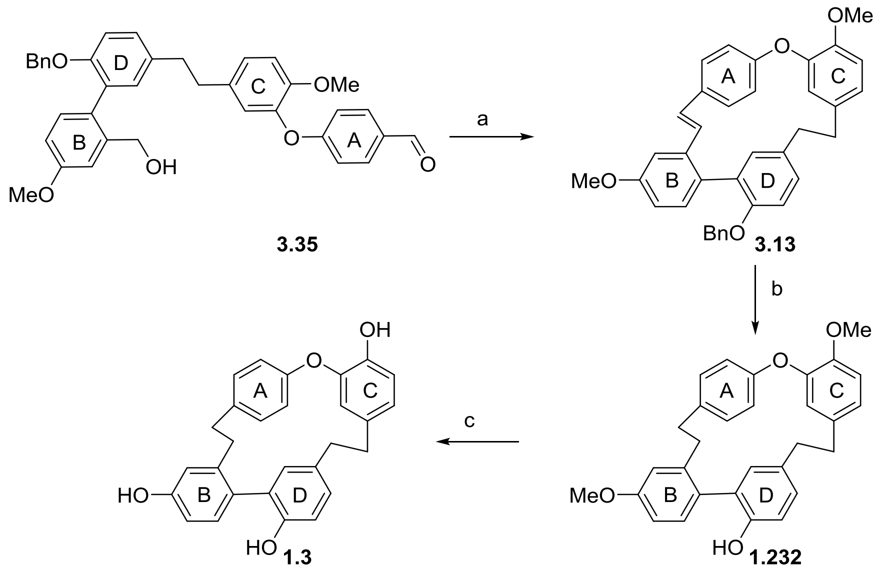
3.32 **3.21** **3.33** **3.34** **3.35**

Reagents and conditions: a) K_3PO_4, DMA, $Pd(OAc)_2$, 59%; b) $TsNHNH_2$, NaOAc, 82%; c) 2M HCl, THF, 58%.

Scheme 3.25: Production of **3.35**

3.2.5d Ring closure by an intramolecular Wittig reaction

Finally, the cyclisation precursor **3.35** was treated with $PPh_3.HBr$ leading to bromination of the alcohol moiety and subsequent displacement with PPh_3 to give the corresponding phosphonium salt as a cyclisation precursor. Then Wittig reaction was acheived by using KO^{t}Bu and gave macrocycle **3.13** in 10% yield over the two steps (Scheme 3.26). Although the cyclisation was reacted using the Wittig reaction is reliable in the macrocyclisation bisbibenzyl the reaction gave poor yield. It is possible that the low yield in the cyclisation step was due to strain in the resulting macrocyclic compound **3.13**. It could also be that the use of PPh_3.HBr had contributed to the poor yield. After the preparation of the macrocycle compound **3.13**, a hydrogenation reaction reduced its alkene and removed the benzyl protecting group to obtain **1.232**. Deprotection of the two remaining methyl ether residues then afforded the analogue **1.3**.



Reagents and conditions: a) (i) PPh_3.HBr, MeCN; (ii) KO^{t}Bu, DCM, 10% (over two steps); b) H_2, Pd/C (10%), EtOH, DCM, 95%; c) BBr_3, DCM, 92%.

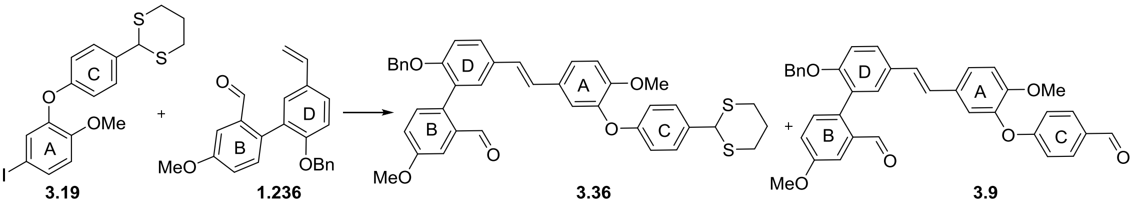
Scheme 3.26: The preparation analogue **1.3**

3.2.6 Macrocyclic reaction by a Corey-Seebach reaction

In each of the aforementioned approaches to **1.3**, using both the McMurry and Wittig cyclisation reactions, the yield of the macrocycle reaction was poor. Consequently, we decided to develop a new strategy wherein a Corey-Seebach reaction would be used to achieve the critical macrocyclisation step. Notably, this reaction has been widely used for the synthesis of macrocyclisation precursors, but it is rarely used in the context of macrocyclisation.[74,91] To that end, we closed to follow the general concepts developed in the previous routes, beginning with an S_NAr reaction to prepare the AC fragment.[50] Then, the preparation of the BD fragment would be achieved using a Suzuki-Miyaura reaction, before connecting the AC and BD fragments using a Heck reaction. Macrocyclisation would then be attempted using a Corey-Seebach reaction.

3.2.6a Union of the AC 3.19 and BD 1.236 fragments

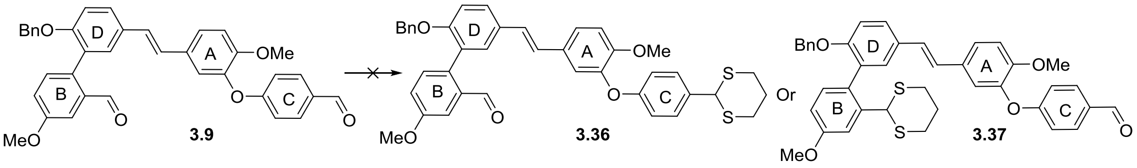
A Heck reaction to connect the AC **3.19** and BD **1.236** fragments gave *trans*-stilbene **3.36**. Two concentrations of the solvent were examined. Surprisingly, we found that the dithiane residue was removed hydrolytically when the concentration of DMA was 1 molar leading to a mixture of aldehyde **3.36** and bisaldehyde **3.9** (Table 3.3 entry 1). At a concentration of 0.1 M, coupling led to the desired product **3.36** but the yield was 38%.



Entry	Conditions	Yield (%)
1	K_3PO_4, DMA (1 M), $Pd(OAc)_2$	Mixture of **3.36** and **3.9**
2	K_3PO_4, DMA (0.1 M), $Pd(OAc)_2$	**3.36** (38)

Table 3.3: Conditions of Heck reaction

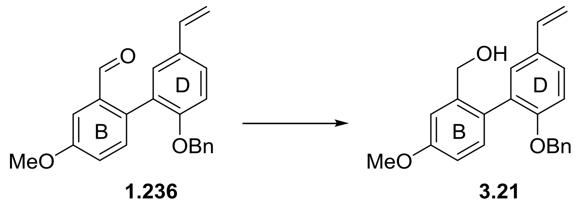
It is widely known that palladium-based catalysts can be poisoned by sulfur.[92,93,94,95] This might be the reason for the low yield of Heck reaction. To avoid this issue, we have tried to selectively protect one of the aldehyde in tetraarene **3.9** by 1,3-propanedithiol (Scheme 3.27). However, the selection of one of the aldehydes was not successful. According to TLC, it is very clear that there were three compounds in the crude product mixture. Moreover, a ^{1}H NMR of that mixture showed that the protecting group had added to both aldehydes.



Reagents and conditions: 1,3-propanedithiol, PPTS, DCM.

Scheme 3.27: Failed selective protection of tetraarene **3.9**

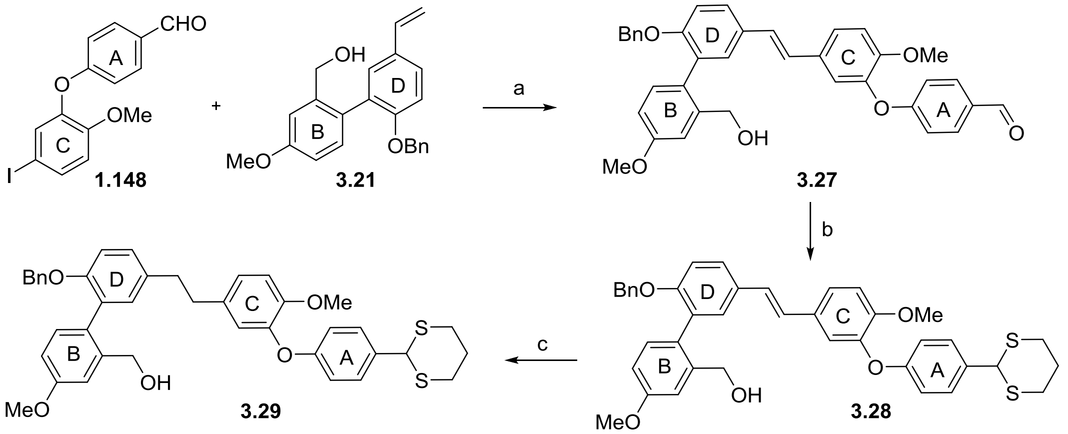
As an alternative, we decided to reduce one of the aldehydes before coupling to form tetraarene **3.27**. We can make this reduction of the aldehyde either in the AC fragment **1.148** or the BD fragment **1.236**. Therefore, reduction of the aldehyde in BD arene **1.236** to alcohol **3.21** was accomplished in a good yield (Scheme 3.28).



Reagents and conditions: $NaBH_4$, MeOH, DCM, 99%.

Scheme 3.28: The reduction of aldehyde in BD **3.21** Fragment

Having AC **1.148** and BD **3.21** fragments in hand, *trans*-stilbene **3.27** was obtained by a Heck reaction. Then, the aldehyde **3.27** was protected with 1,3-propanedithiol to obtain dithiane **3.28** in 91%. Using tosylhydrazone and NaOAc, the alkene was then reduced to give tetraarene **3.29** (Scheme 3.29).

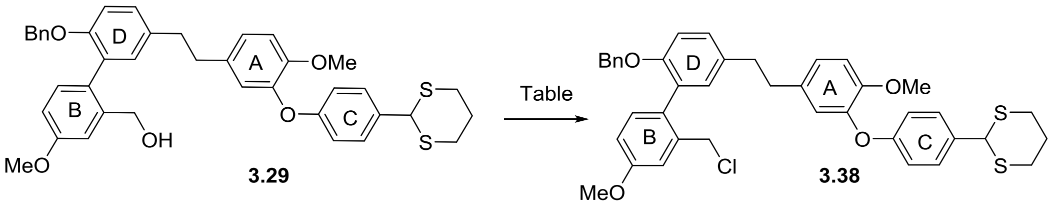


Reagents and conditions: a) K_3PO_4, DMA, $Pd(OAc)_2$, 75%; b) 1,3-propanedithiol, PPTS, DCM, 91%; c) $TsNHNH_2$, NaOAc, THF, water, 91%.

Scheme 3.29: Formation of **3.29**

3.2.6b Ring closure by a Corey-Seebach reaction

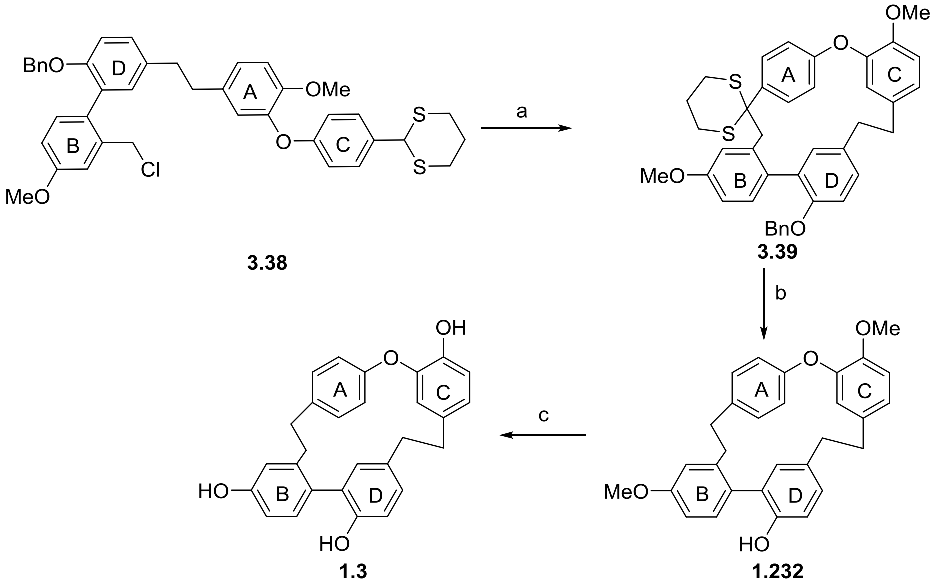
Our attention now turned to preparing the cyclisation precursor **3.38**. To that end, various conditions to effect the chlorination reaction were examined (Table 3.4). The first attempt to obtain **3.38** by using triphenylphosphine and *N*-chlorosuccinimide was unsuccessful due to side reactions involving the dithiane protecting group.[96] The tetraarene **3.38** was formed using 2,6-lutidine, methanesulfonyl chloride and lithium chloride (Entry 2, Table 3.4) though the yield was modest.[97] Using methanesulfonyl chloride and 1,8-diazabicyclo[5.4.0]undec-7-ene, tetraarene **3.38** was formed in 63% yield (Entry 3, Table 3.4).[87] When lithium chloride was added to the aforementioned conditions, the yield increased further to 88% (Entry 4, Table 3.4).



Entry	Conditions	Yield %
1	PPh_3, NCS, DCM	-
2	2,6-lutidine, MsCl, LiCl, DCM	44
3	MsCl, DBU, DCM	63
4	MsCl, DBU, LiCl, DCM	88

Table 3.4: The conditions of chlorination reaction

The cyclisation reaction was now achieved by applying the Corey-Seebach approach. Thus, treatment of **3.38** with *n*-BuLi induced cyclisation giving macrocycle **3.39** in 48% yield (Scheme 3.30). Alas, attempts to reduce the dithiane to precursor **1.232** using raney nickel failed.[98,99] By contrast, using $NiCl_2.6H_2O$ and $NaBH_4$ succeeded via in situ generation of an active nickel bond, and after standard hydrogenation gave bismethyl ether **1.232** in high yield.[100,101] The synthesis of analogue **1.3** was completed by demethylation an its identity was confirmed by X-ray crystallography (Figure 3.1). The crystal was obtained by dissolving the compound **1.3** in $CDCl_3$ and allowing the solvent to evaporate slowly. Once the solution was saturated the crystal formed.



Reagents and conditions: a) *n*-BuLi, THF, 48%; b) (i) $NiCl_2.6H_2O$, DMF, $NaBH_4$, THF, 59%; (ii) 10% Pd/C, H_2, 74%; c) BBr_3, DCM, 92%.

Scheme 3.30: The completion of the synthesis of analogue **1.3**

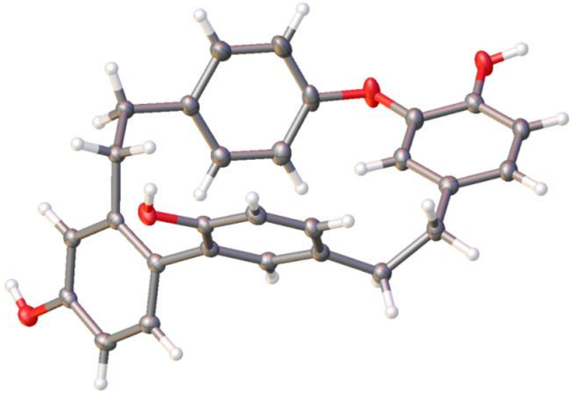


Figure 3.1: X-ray crystal structure of analogue **1.3** (full crystallographic data provided in the Appendix)

Unexpectedly, in its ^{1}H NMR spectra the proton H* in arene A of the analogue **1.3** appeared as a very broad singlet at 6.37 ppm. It has been reported in the literature that the signal of such protons is usually shifted upfield in macrocyclic bisbibenzyls due to anisotropic effects from both arene A and arene D (Figure 3.2).[50]

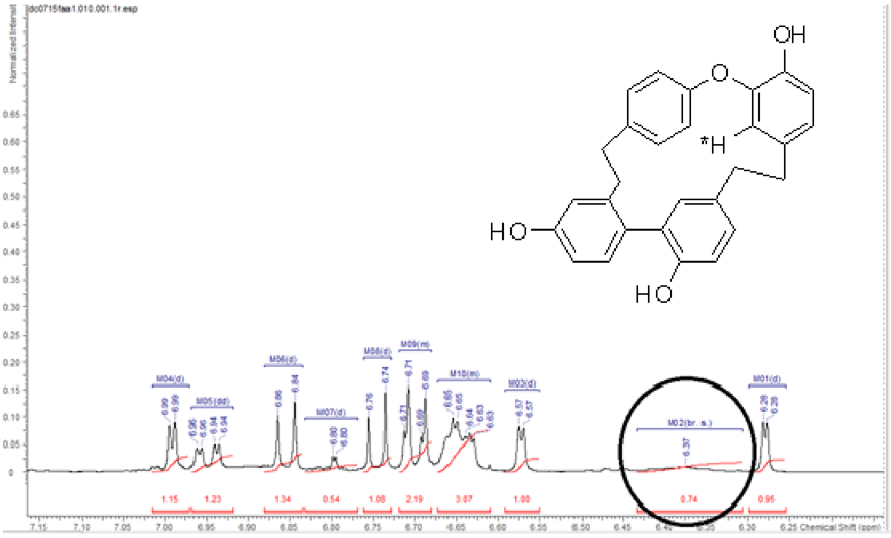
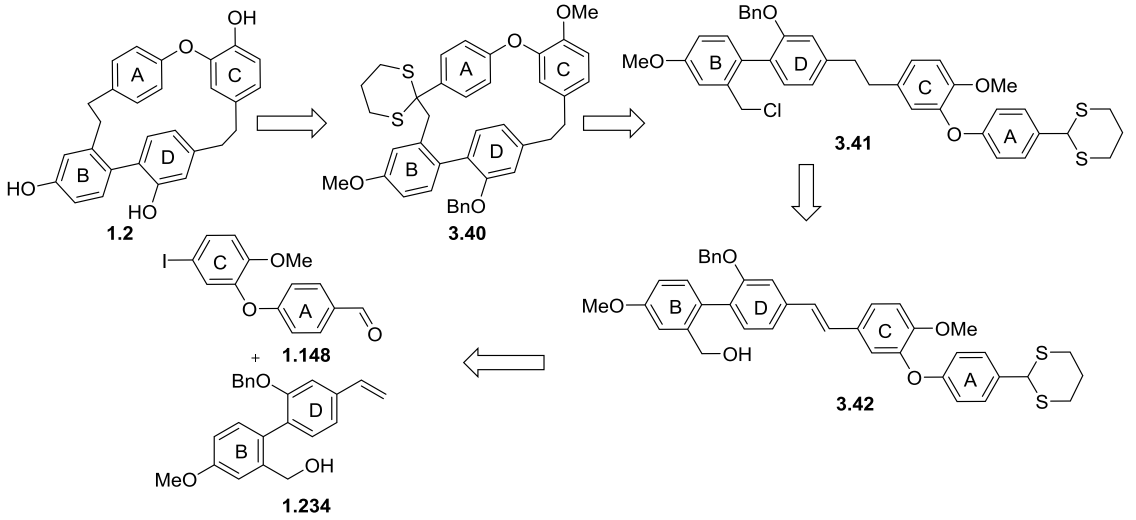


Figure 3.2: Aromatic region of ^{1}H NMR spectrum of the analogue **1.3**

3.3 The total synthesis of riccardin C 1.2

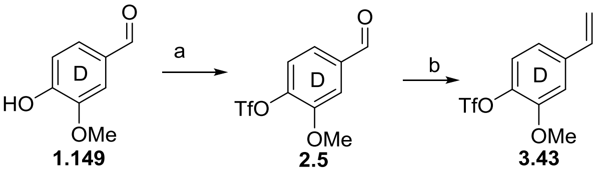
Having achieved a synthesis of analogue **1.3**, we next sought to adopt the approach to effect a total synthesis of riccardin C **1.2** using a Corey-Seebach macrocyclisation reaction. The AC **1.148** and BD **1.234** fragments needed to be prepared and connected by a Heck reaction. A Corey-Seebach reaction could then be used to close the macrocyclic ring **3.40** for advancement to riccardin C **1.2** (Scheme 3.31).



Scheme 3.31: The retrosynthesis of riccardin C **1.2**

3.3.1 The formation of BD 1.234 fragment

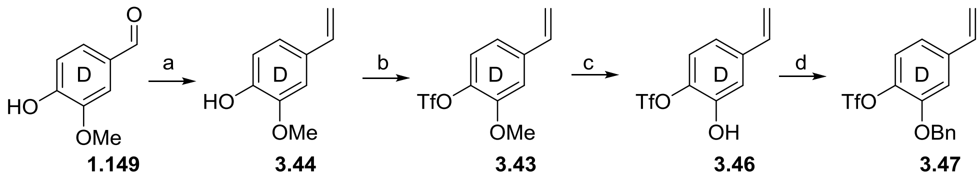
Two routes have been developed to prepare arene D **3.47**. The first route began with vanillin **1.149** and made arene D **3.47** in four steps. Thus, vanillin triflate **2.5** was obtained from vanillin **1.149** by triflation, then a Wittig reaction was used to convert the aldehyde to styrene **3.43**. Alas, this reaction proceeded in low yield due to removal of the triflate group (Scheme 3.32).



Reagents and Conditions: a) Tf_2O, pyridine, DCM at 0 °C, 80%; b) $MePPh_3Br$, KO^tBu, THF, 0 °C to RT, 3 h, 18%.

Scheme 3.32: Preparation of styrene **3.43**

Due to the low yield obtained for styrene **3.43**, we developed an improved route by undertaking the Wittig reaction as a first step to obtain styrene **3.44** in a high yield. Triflation then gave **3.45**. Demethylation of **3.43** was next achieved using BBr_3 to obtain **3.46**. Arene D **3.47** was then prepared by protection of the alcohol in **3.46** with a benzyl group (Scheme 3.33).

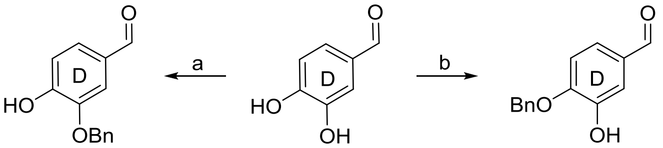


Reagents and Conditions: a) $MePPh_3Br$, KO^tBu, THF, 0 °C to RT, 3 h, 99%; b) Tf_2O, pyridine, DCM, 0 °C, 91%; c) BBr_3, DCM, 0 °C, 39%; d) BnBr, K_2CO_3, MeCN, 86%.

Scheme 3.33: The preparation of D **3.47** fragment

The purification of **3.46** and **3.47** in the aforementioned route proved to be difficult and the yield of the demethylation reaction was poor. To overcome these difficulties, we developed another route that was more efficient than the first because it took only three steps to prepare the arene D **3.47**.

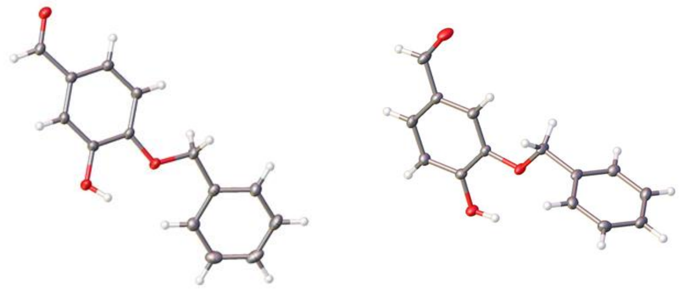
Thus, our new preparation of arene D **3.47** began with 3,4-dihydroxybenzaldehyde **3.2** which was first protected with a benzyl group in the *meta* position to give mono-ether **3.48** (Scheme 3.34). This addition of a benzyl group was needed to achieve optimal regioselectivity. Various conditions were examined for this reaction. Our first attempt used 1 equiv. Et_3N or DBU, followed by the addition of benzyl bromide. However, this led to protection of the *para*-hydroxyl group leading to **3.49**, which was confirmed by X-ray analysis (Figure 3.3). To solve this problem, two equivalents of the sodium hydride (60 % dispersion in mineral oil) were used to deprotonate both hydroxyl groups in **3.2**. Addition of 1 equiv. of BnCl then gave regioisomer **3.48**.[102] We were again able to confirm the structure of **3.48** by X-ray for analysis (Figure 3.3). The crystals were obtained by evaporating hexane into a diethyl ether solution of the two regioisomers **3.49** and **3.48**.



3.48 **3.2** **3.49**

Reagents and conditions: a) BnCl, NaH (2 equiv.), DMF, 72%; b) BnCl, DBU, 79%.

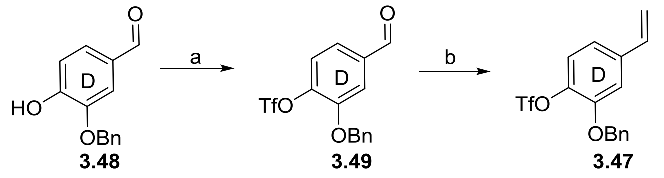
Scheme 3.34: Formation of **3.49** and **3.48**



3.49 **3.48**

Figure 3.3: The addition of a benzyl group to 3,4-dihydroxybenzaldehyde (full crystallographic data provided in the Appendix)

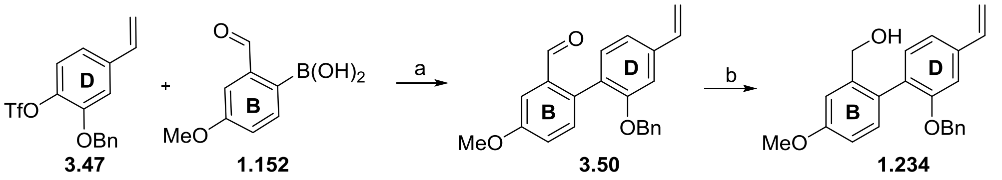
The phenol in **3.48** was next triflated to give **3.49**. Then a Wittig methylenation reaction was achieved in high yield using NaH as a base. The phosphonium salt was slowly added to a mixture of the triflate and the base to obtain styrene **3.47** in 87% (Scheme 3.35).



Reagents and conditions: a) Tf_2O, pyridine, DCM, 70%; b) NaH, $MePPh_3Br$, 87%.

Scheme 3.35: Formation of styrene **3.47**

Disappointingly, our first attempt at the Suzuki-Miyaura coupling of fragments D **3.47** and B **1.152** with $Pd(PPh_3)_4$ and Cs_2CO_3 gave a low yield. The second conditions employed SPhos with the combination of LiCl and Cs_2CO_3 in the presence of $Pd(OAc)_2$ improved this reaction considerably giving **3.50** in 75% yield (Scheme 3.36). Then, the aldehyde in **3.50** was reduced to give alcohol **1.234**.[50,103]

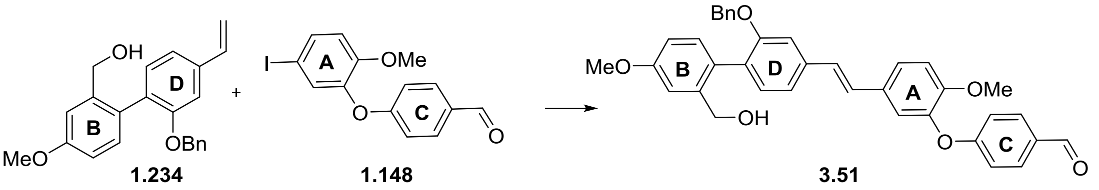


Reagents and conditions: a) LiCl, SPhos, $Pd(OAc)_2$, Cs_2CO_3, 1,4-dioxane, 75%; b) $NaBH_4$, MeOH, DCM, 94%.

Scheme 3.36: The preparation of BD fragment **1.234**

3.3.2 Preparation of the cyclisation precursor 3.41

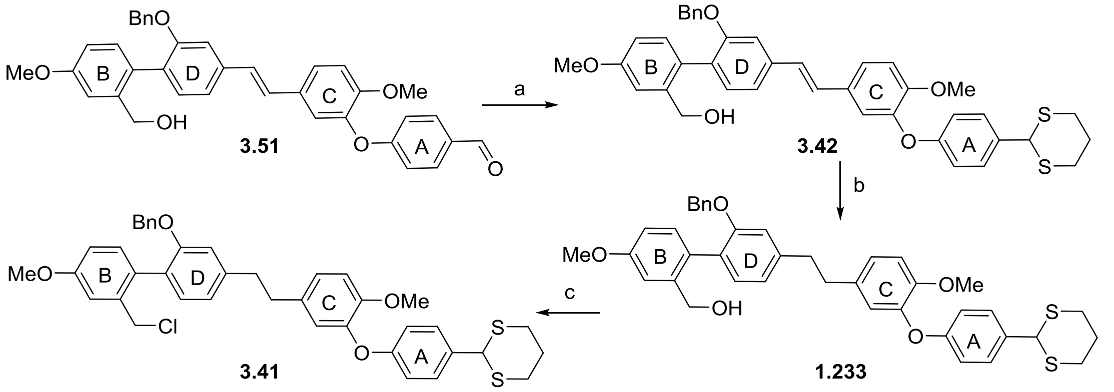
The AC **1.148** and BD **1.234** fragments were next coupled using a Heck reaction and gave *trans*-stilbene **3.51** (Scheme 3.37).



Reagents and conditions: K_3PO_4, DMA, $Pd(OAc)_2$, 67%.

Scheme 3.37: A Heck cross coupling

Then, the aldehyde **3.51** was protected using a 1,3-propanedithiol to give **3.42**. This was followed by reduction of the alkene using tosylhydrazone and NaOAc to give **3.52**. Then, the cyclisation precursor **3.41** was prepared by chlorination using $SOCl_2$ and pyridine (Scheme 3.38).[104] The alcohol **1.233** could also be was transformed into chloride **3.41** through the action of MsCl, but the method using $SOCl_2$ proceeded in a slightly better yield.

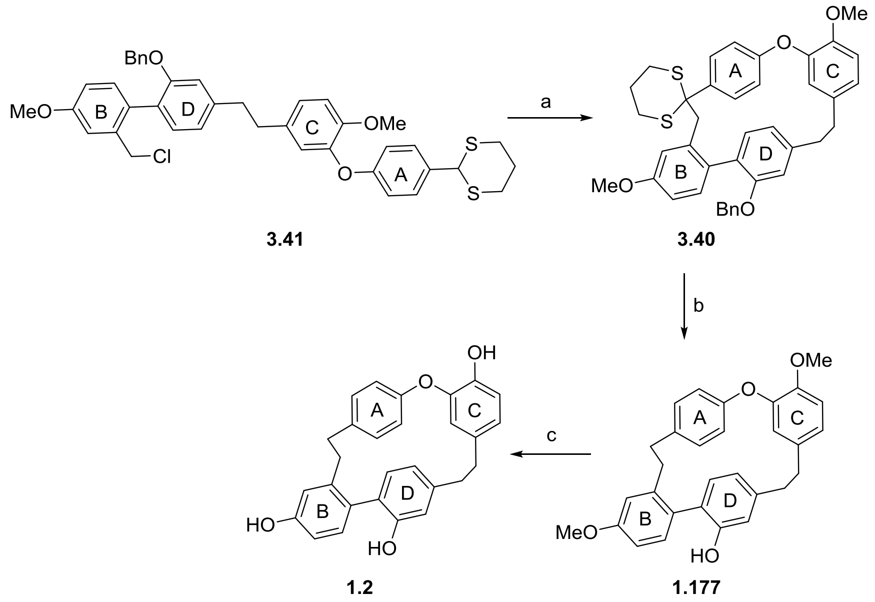


Reagents and conditions: a) 1,3-propanedithiol, PPTS, DCM, 91%; b) $TsNHNH_2$, NaOAc, 62%; c) $SOCl_2$, DCM, pyridine, 67%; or MsCl, DBU, LiCl, DCM, 63%.

Scheme 3.38: The preparation of the cyclisation precursor **3.41**

3.3.3 Ring closure by a Corey-Seebach reaction and the total synthesis of riccardin C 1.2

After preparation of the cyclisation precursor **3.41**, the macrocyclisation reaction to **3.40** was achieved using a Corey-Seebach reaction. Unexpectedly, this was unsuccessful using LDA but was achieved in 33% yield using *n*-BuLi (Scheme 3.39). Then, as before, $NiCl_2.6H_2O$ and $NaBH_4$ achieved the reductive removal of the dithiane group via in situ generation of an active nickel bond. Standard hydrogenation then gave the key compound **1.177**. We were able to obtain X-ray data for this **1.177** (Figure 3.4). Although this compound was reported to be an oil, we obtained it as a white solid and confirmed its identity by X-ray analysis.[52] The crystal was obtained by evaporating hexane into a solution of macrocycle **1.177** in diethyl ether. The total synthesis of riccardin C **1.2** was completed by the demethylation of the two methyl ethers.



Reagents and conditions: a) *n*-BuLi, THF, 33%; b) (i) $NiCl_2.6H_2O$, DMF, $NaBH_4$, THF, 34%; (ii) 10% Pd/C, H_2, 71%; c) BBr_3, DCM, 71%.

Scheme 3.39: The total synthesis of riccardin C **1.2**

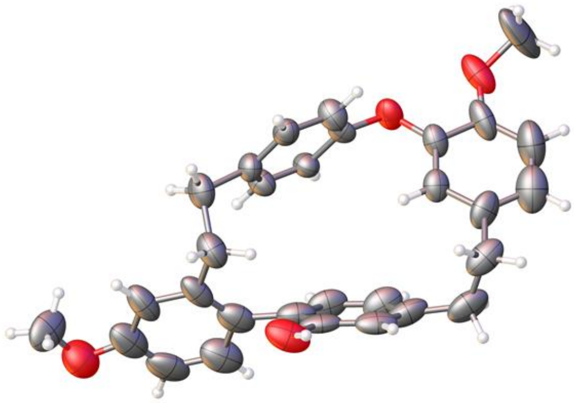
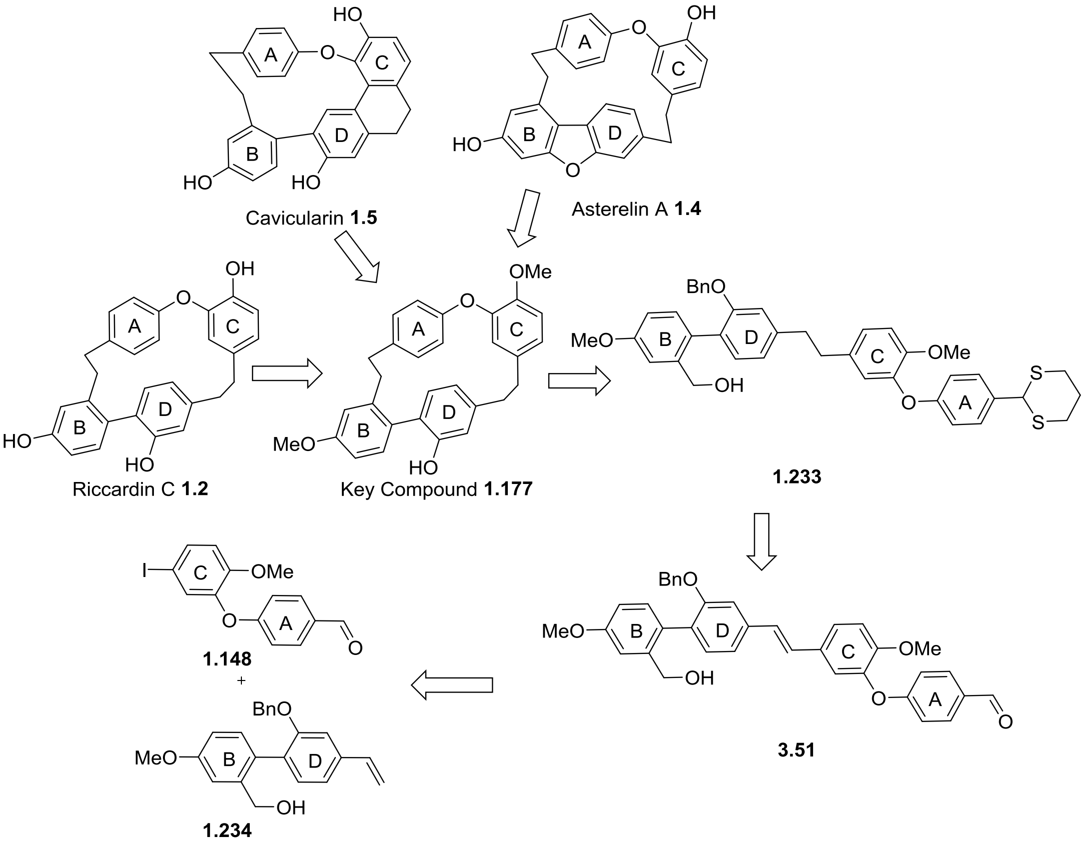


Figure 3.4: X-ray data for the key compound **1.177** (full crystallographic data provided in the Appendix)

3.4 Formal total syntheses of asterelin A 1.4 and cavicularin 1.5

3.4.1 The retrosynthesis of asterelin A 1.4 and cavicularin 1.5

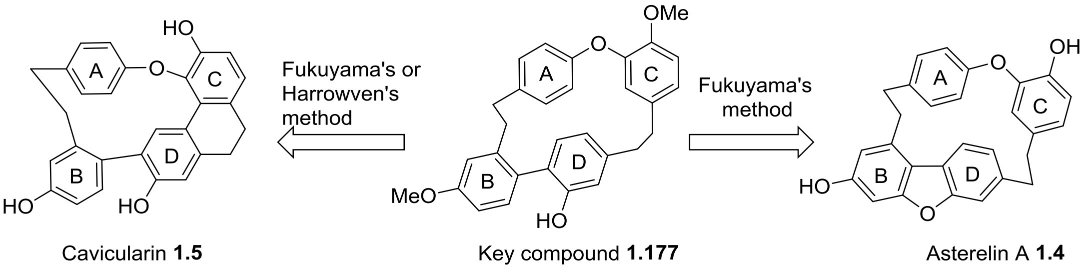
For total syntheses of asterelin A **1.4** and cavicularin **1.5**, we are required to make the macrocyclic compound **1.177** (Scheme 3.40).[19,52,61] Its synthesis is described in section 3.3.3. From this compound, we have completed the synthesis of riccardin C **1.2** by demethylation.[19] Fukuyama *et al*. have reported the transformation of key compound **1.177** into asterelin A **1.4** and cavicularin **1.5** as detailed in the introductory chapter (See sections 1.4.4, and 1.4.3c).[51,61] Therefore, we have formally achieved syntheses of asterelin A **1.4** and cavicularin **1.5** by intersection with Fukuyama's syntheses.



Scheme 3.40: The retrosynthesis of riccardin C **1.2**, asterelin A **1.4** and cavicularin **1.5**

3.4.2 Towards syntheses of cavicularin 1.5 and asterelin A 1.4

From the key compound **1.177**, we can prepare cavicularin **1.5** in four steps, and asterelin A **1.4** in two steps by using the method of Fukuyama *et al*. (Scheme 3.41).[52,61] They completed the total synthesis of asterelin A **1.4** by an intramolecular oxidative coupling and demethylation reaction. Harrowven's group successfully achieved cavicularin **1.5** by a radical reaction from a similar macrocyclic compound.[50]



Scheme 3.41: Details towards syntheses of cavicularin **1.5** and asterelin A **1.4**

3.5 Conclusion and future work

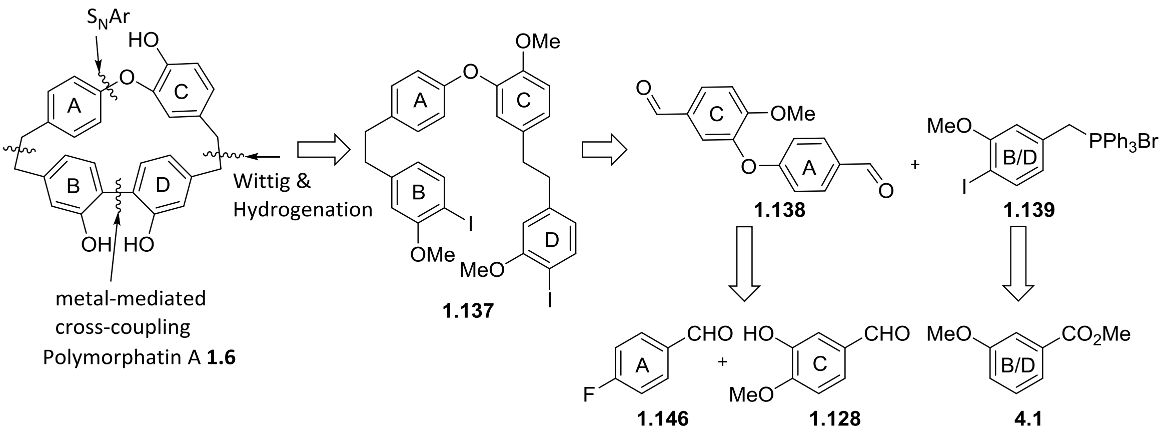
This approach was developed to provide access to many natural products in the macrocyclic bisbibenzyl family, *i.e.* riccardin C **1.2**, asterelin A **1.4** and cavicularin **1.5** as well as novel unnatural macrocyclic bisbibenzyl analogues such as **1.3**. We have succeeded in synthesising all these targets using key fragments approach that facilitates analogue production. For the macrocyclisation reaction, we have demonstrated various approaches including McMurry, Wittig and Corey-Seebach reactions. Moreover, Corey-Seebach approach constitutes a new strategy involving an alkyllithium mediated displacement reaction to achieve the macrocyclisation step. It was exemplified with total syntheses of riccardin C **1.2** and an unnatural analogue **1.3**. This approach offers access to cavicularin **1.5** and asterelin A **1.4**.

Future research will examine the potential of the Corey-Seebach approach for accomplishing the the total synthesis (−)-cavicularin **1.205** and/or (+)-cavicularin **1.5** by using chiral protecting groups. Also, the approach provides a means to complete the total synthesis of asterelin A **1.4** by an intramolecular oxidative coupling and demethylation (Scheme 3.41). With interest growing into the biological effects of riccardin C **1.2**, the approach could be used to produce it on large scale as it is robust and very reliable. Novel derivatives of riccardin C could also be prepared easily by adding functional groups to advanced intermediates or key building blocks. Additionally, the unnatural analogue **1.3** has not been tested for biology activity and we welcome such an investigation.

Chapter 4: Results and discussion: A total synthesis of Polymorphatin A 1.6

4.1 The retrosynthesis of polymorphatin A 1.6

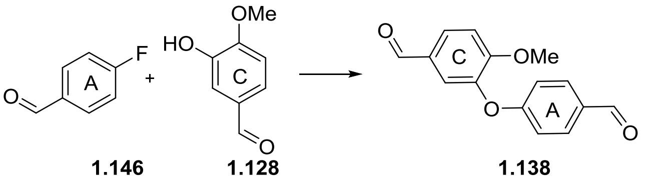
The doubts surrounding the identity of polymorphatin A **1.6** all stem from inconsistent in data reported in the isolation and total synthesis papers.[9] This prompted us to propose a new approach to polymorphatin A **1.6** which will allow us to compare our data with theirs and establish which was correctly assigned. Our approach is interesed in the excessive molecular strains that makes the bent aromatic rings. Consequently, for our retrosynthesis analysis we decided to disconnect at the biaryl bond linking arenes B and D as it could come from a metal-mediate cross coupling reaction. The required dihalide precursor **1.137** was then to be prepared by a double Wittig reaction between the AC **1.138** and B/D **1.139** fragments, followed by alkene reduction to obtain **1.137** (Scheme 4.1).[63] The biaryl ether **1.138** was to be made from the aldehydes **1.146** and **1.128** by an S_NAr reaction. The corresponding phosphonium **1.139** was to be prepared using a known sequence from methyl 3-hydroxybenzoate **4.1**.



Scheme 4.1: Retrosynthesis of natural product polymorphatin A **1.6**

4.2 Synthesis of AC 1.138 fragment

A synthesis of the AC fragment **1.138** was achieved by an S_NAr reaction between isovanillin **1.128** and 4-fluorobenzaldehyde **1.146** which gave biaryl ether **1.138** in 90% yield (Scheme 4.2).[105]

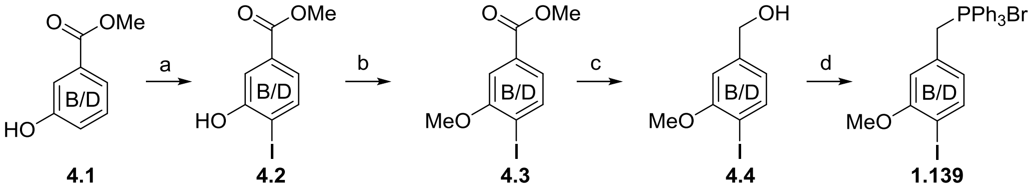


Reactions and conditions: K_2CO_3, DMF, 100%.

Scheme 4.2: Formation of AC **1.138** fragment

4.3 Synthesis of B/D 1.139 arene

In parallel, we synthesised the B/D **1.139** fragment from methyl 3-hydroxybenzoate **4.1**. A highly regioselective iodination of ester **4.1** first led to aryl iodide **4.2**. The phenol was next protected by methylation to give **4.3** which was reduced to alcohol **4.4** in good yield by the action of DIBAL-H (Scheme 4.3).[50,63] Bromination of the alcohol moiety in **4.4** and subsequent treatment of the benzyl bromide with PPh_3 then gave the required benzylphosphonium salt **1.139**.[63]

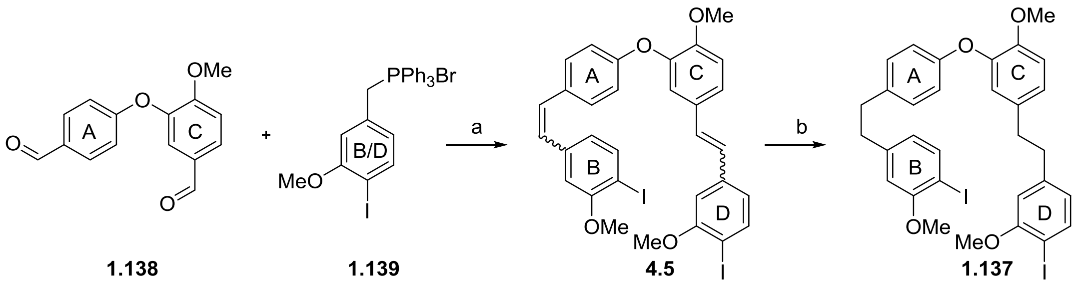


Reactions and conditions: a) I_2, Na_2CO_3, H_2O, 78%; b) MeI, K_2CO_3, AcMe, 66%; c) DIBALH, DCM, 73%; d) i) PPh_3, NBS, THF; ii) PPh_3, PhMe, 84%.

Scheme 4.3: The preparation of phosphonium salt **1.139**

4.4 Connecting the AC 1.138 and B/D 1.139 Fragments

Having both the AC **1.138** and B/D **1.139** fragments in hand, a Wittig reaction was next achieved to give bis-stilbene **4.5** as a mixture of geometric isomers. Then, 12,12'-diiodoperrottetin E trimethyl ether **1.137** was obtained by reducing the mixture of bis-stilbenes **4.5** using diimide.[63]

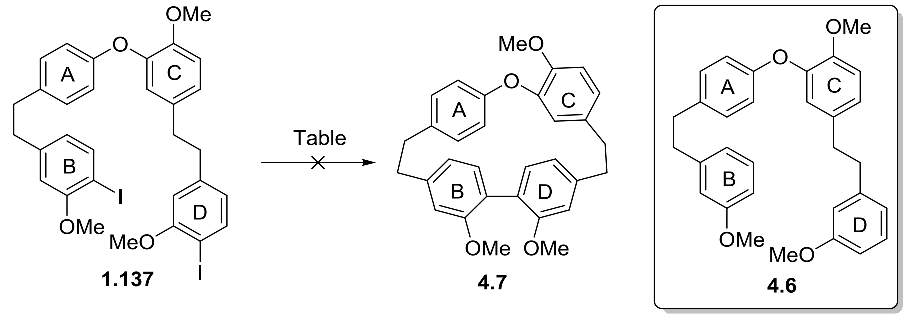


Reactions and conditions: a) NaH, THF; b) $TsNHNH_2$, NaOAc,THF/H_2O, 98% (over two steps).

Scheme 4.4: The preparation of dihalide precursor **1.137**

4.5 Cyclisation attempts

With 12,12’-diiodoperrottetin E trimethyl ether **1.137** in hand, attention turned to the cyclisation reaction to achieved macrocycle **4.7**. We had envisaged various conditions to accomplish this as shown in Table 4.1. The halogen-lithium exchange on diiodide **1.137** and subsequent transmetalation to copper(I) led to the reduction of both aryl iodides leading to perrottetin E-trimethyl ether **4.6** (Entry 1-2, Table 4.1).[106,107] The use of the conditions of Cahiez *et al.*, to effect an iron-catalyzed homo-coupling reaction of the bis-aryl Grignard reagents also resulted in reduction and gave other undesired products that could not be identified (Entry 3, Table 4.1).[108] Cyclisation by reductive metalation of the aryl iodides was also studied but as exemplified by the conditions outlined in Entry 4 these failed to induce the cyclisation reaction.[109] Likewise, using Stille-Kelly conditions led only to reduction and no cyclisation was evidenced (Entry 6, table 4.1).[107,110,111] Similarity, standard radical reaction examined and these too gave perrottetin E-trimethyl ether **4.6** (entry 7-10, table 4.1).[50,112] The selenium dioxide in 1,1,1,3,3,3-hexafluoroisopropanol also failed to induce reductive coupling to form the key Aryl-Aryl bond.[13]

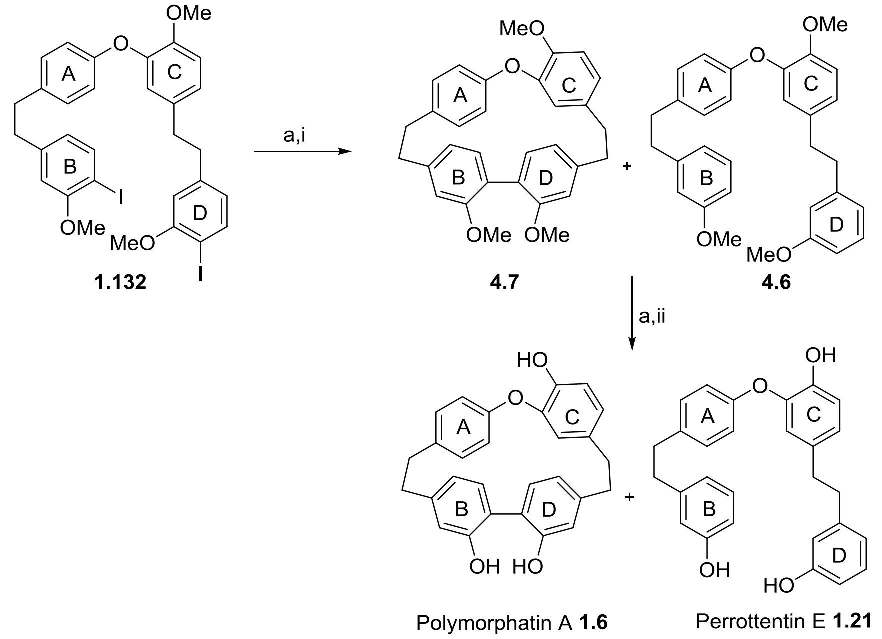


Entry	Conditions	Products (%)
1	*n*-BuLi, THF, CuI	**4.6** (42)
2	*n*-BuLi, THF, CuCN	**4.6** (45)
3	(i) *i*-PrMgBr, THF; (ii) $BrCH_2CH_2Br$, $FeCl_2$	**4.6** (67)
4	$Pd(OAc)_2$, K_2CO_3, MeCOEt, 120 °C	RSM
5	$(CH_3)_3SnSn(CH_3)_3$, $Pd_2(dba)_3$, PhMe	No desired product
6	$(CH_3)_3SnSn(CH_3)_3$, $Pd(PPh_3)_4$, PhMe	No desired product
7	TTMSS, VAZO, PhMe, refluxed	**4.6** (54)
8	Bu_3SnH, VAZO, PhMe, microwave	**4.6** (41)
9	TTMSS, VAZO, PhMe, microwave	**4.6** (64)
10	Bu_3SnH, VAZO, PhMe, refluxed	**4.6** (52)
11	Cu Powder, PhMe, microwave	RSM
12	SeO_2, HFIP, 100 °C	RSM

Table 4.1: Attempts of cyclisation reaction

4.6 The final stage for the total synthesis of polymorphatin A 1.6

Although the cyclisation reaction had proven very challenging, our effects were rewarded when we turned to using the conditions of Semmelhack *et al.*, in a nickel-promoted biaryl coupling. This resulted in a mixture of polymorphatin A-trimethyl ether **4.7** and perrottetin E-trimethyl ether **4.6** (Scheme 4.5).[114] We explored many conditions to effect separation of polymorphatin A-trimethyl ether **4.7** chromatographically from the crude product mixture, but found it was co-polar with perrottetin E-trimethyl ether **4.6**. However, we managed to get a pure sample by crystalisation of polymorphatin A-trimethyl ether **4.7** from the mixture, as perrottetin E-trimethyl ether **4.6** is known to be as oil and polymorphatin A-trimethyl ether **4.7** is solid. Thus, we were able to confirm that we had indeed made polymorphatin A-trimethyl ether **4.7** though X-ray analysis (Figure 4.1). importantly, we also proved that we had accomplished the first total synthesis of polymorphatin A **1.6** following demethylation. Pleasingly, it was readily separated from perrottetin E **1.21**.



Reactions and conditions: a) i) $NiCl_2(PPh_3)_2$, Zn Powder, DMF, PPh_3; ii) BBr_3, DCM, **1.6** 26%, **1.21** 6%.

Scheme 4.5: The total syntheses of **1.6** and **1.21**

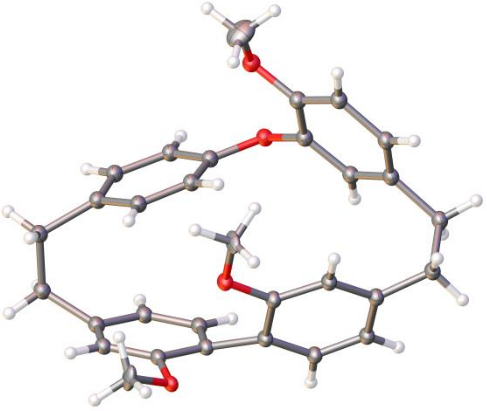
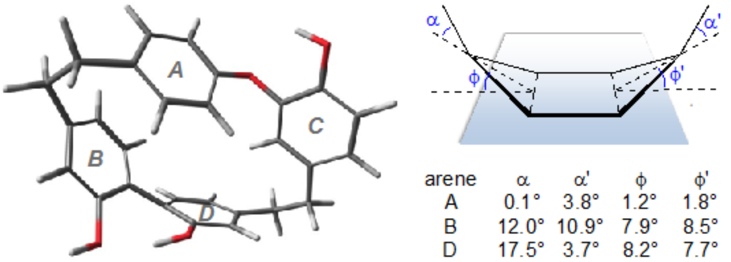


Figure 4.1: X-ray crystal structure of polymorphatin A trimethyl ether **4.7** with full crystallographic data provided in the Appendix

4.7 Bent Aromatic Rings and 1H NMR analysis for Polymorphatin A-trimethyl ether 4.7

Dr. Sun, who is member of the Harrowven group, has performed a computational analysis of polymorphatin A trimethyl ether **4.7**.[a] The study suggested that each of the arenes in the biaryl subunit would adopt a boat-like conformation, with arenes B and D each bent out of planarity by about 16^{o} (Figure 4.2).



arene	α	α'	ϕ	ϕ'
A	0.1°	3.8°	1.2°	1.8°
B	12.0°	10.9°	7.9°	8.5°
D	17.5°	3.7°	8.2°	7.7°

Figure 4.2: Computationally generated model of polymorphatin A-trimethyl ether **4.7** showing significant distortion from planarity in arenes B and D

From the X-ray crystal structure of polymorphatin A-trimethyl ether **4.7**, we have discovered that it adopts two crystallographically independent structural forms in the solid state (Figure 4.3). These forms seem very similar visually, as the differences were mainly confined to distortions

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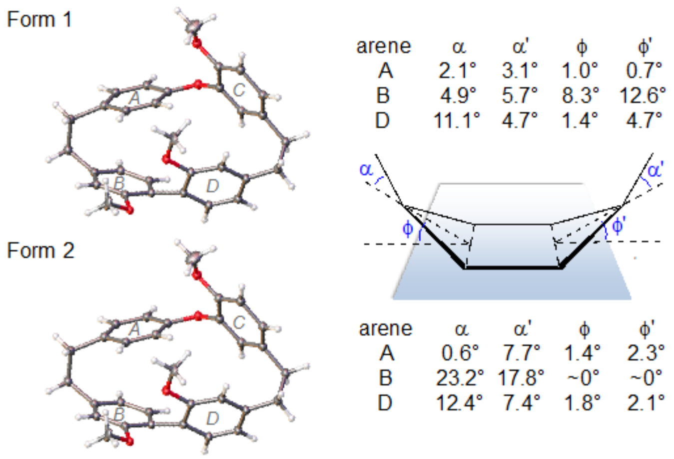
[a] Almalki, F. A.; Sun, W.; Light, M. E.; Wells, N.; Harrowven, D. C.; **2017**, unpublished results. The programme used for the calculation is Gaussian G09W and the level of computational theory is B3LYP/6-31G(d,p).

within the biaryl subunit. Curiously, arene B in one form adopted a clear boat-like conformation while in the other it is flat and linked to two out-of-plane benzylic carbons.

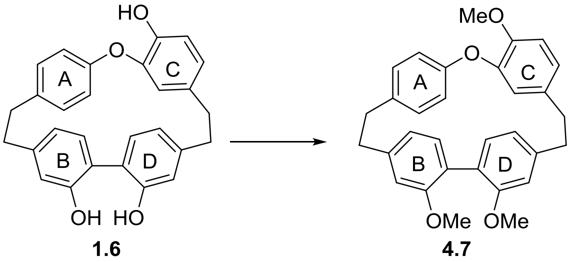


arene	α	α'	ϕ	ϕ'
A	2.1°	3.1°	1.0°	0.7°
B	4.9°	5.7°	8.3°	12.6°
D	11.1°	4.7°	1.4°	4.7°

arene	α	α'	ϕ	ϕ'
A	0.6°	7.7°	1.4°	2.3°
B	23.2°	17.8°	~0°	~0°
D	12.4°	7.4°	1.8°	2.1°

Figure 4.3: The two independent forms of polymorphatin A-trimethyl ether **4.7** revealed by X-ray crystallographic analysis

Surprisingly, the ^{1}H NMR spectrum of polymorphatin A-trimethyl ether **4.7**, prepared by methylation of polymorphatin A **1.6** (Scheme 4.6), did not give the appearance of a pure sample (Figure 4.4). We expended considerable effort attempting to purify the product, but each time the isolation sample produced identical NMR spectra. To test the purity of the synthetic sample, we dissolved the crystal of polymorphatin A-trimethyl ether **4.7** that had been analysed by X-ray crystallography and found its ^{1}H NMR spectra also matched those recorded previously. From this we were sure that our sample was pure and that it existed in two distinct forms in DMSO-*d*$_6$ solution at RT (See Section 1.6).



Reagents and conditions: MeI, DBU, 65%.

Scheme 4.6: Methylation reaction of polymorphatin A **1.6**

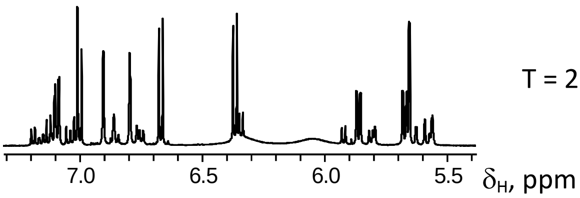


Figure 4.4: ^{1}H NMR for aromatic region of **4.7**

VT NMR experiments confirmed this as the two distinct rotamers were seen to interconvert at 373 K (Figure 4.5).

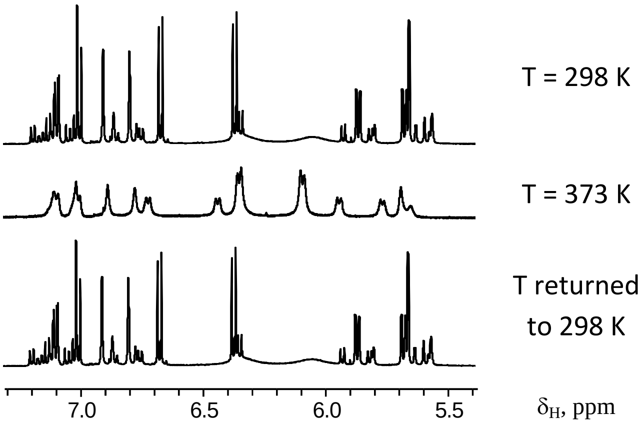


Figure 4.5: Extracts from VT ^{1}H NMR spectral recorded on polymorphatin A-trimethyl ether **4.7** in *d*$_6$-DMSO confirming the presence of rotamers in solution

The NMR spectrum of our sample of polymorphatin A-trimethyl ether **4.7** was compared with the data reported by Speicher *et al.*[46] on their synthetic sample and these did not concur (Table 4.2). Firstly, they make no mention of the existence of rotamers in any of their NMR spectra. Additionally, the ^{1}H NMR of their synthetic sample did not show the characteristic upfield shift for the isolated proton in arene C to ~5.8 ppm (See Section 1.4.5).[46] It therefore seems likely that they formed a dimer in their macrocyclisation reaction rather than a precursor to polymorphatin A.

^{1}H NMR data of our synthetic sample and Speicher *et al.*'s synthetic sample of **4.7** (CDCl$_3$)	
Our sample **4.7** data (400 MHz)	Sample **4.7** data by Speicher *et al*. (400 MHz)
7.04 (dd, *J*=8.1, 2.1 Hz, 2H, 2 x Ar**H**),	7.11 (dd, *J*=8.4, 2.0 Hz, 1H, Ar**H**),
6.87 (d, *J*=8.3 Hz, 1H, Ar**H**),	7.07 (d, *J*=7.7 Hz, 1H, Ar**H**),
6. 81(d, *J*=7.7 Hz, 2H, 2 x Ar**H**),	7.04 (d, *J*=7.5 Hz, 1H, Ar**H**),
6.80-6.68 (m, 2H, 2 x Ar**H**),	7.02 (d, *J*=8.5 Hz, 2H, 2 x Ar**H**),
6.58 (d, *J*=7.8 Hz, 1H, Ar**H**),	7.01 (d, *J*=8.4 Hz, 1H, Ar**H**),
5.99 (dd, *J*=7.9, 1.0 Hz, 1H, Ar**H**),	6.84 (dd, *J*=7.7, 1.5 Hz, 1H, Ar**H**),
5.82 (br. d, *J*=2.1 Hz, 2H, 2 x Ar**H**),	6.80 (d, *J*=1.5 Hz, 1H, Ar**H**),
5.70 (d, *J* = 2.2 Hz, 1H, Ar**H**),	6.61 (d, *J*=8.5 Hz, 2H, 2 x Ar**H**),
5.68-5.60 (m, 1H, Ar**H**),	6.55 (dd, *J*=7.5, 1.5 Hz, 1H, Ar**H**),
-	6.52 (d, *J*=1.5 Hz, 1H, Ar**H**),
-	6.48 (d, *J*=2.0 Hz, 1H, Ar**H**),
3.81 (s, 3H, OC**H**$_3$),	3.82 (s, 3H, OC**H**$_3$),
3.80 (s, 3H, OC**H**$_3$),	3.71 (s, 3H, OC**H**$_3$),
3.65 (s, 3H, OC**H**$_3$),	3.62 (s, 3H, OC**H**$_3$),
3.16-2.44 (m, 8H, 2 x C**H**$_2$C**H**$_2$).	2.98-2.81 (m, 8H, 2 x C**H**$_2$C**H**$_2$).
^{13}C NMR data of our synthetic sample and Speicher *et al.*'s synthetic sample of **4.7** (CDCl$_3$)	
156.5, 156.2, 156.1, 150.6, 141.3, 140.5, 140.2, 134.2, 132.7, 131.9, 131.4, 129.3 (x 2), 126.1, 126.0, 125.9, 125.1, 123.1, 122.2, 113.4, 112.5, 112.3, 111.8, 110.5, 56.2 (O**C**H$_3$), 55.8 (O**C**H$_3$), 55.7 (O**C**H$_3$), 38.3 (**C**H$_2$), 38.2 (**C**H$_2$), 37.1 (**C**H$_2$), 36.6 (**C**H$_2$).	157.00, 156.43, 156.43, 149.79, 143.47, 142.52, 141.23, 135.31, 134.39, 131.67, 131.22, 129.27, 125.43, 125.20, 124.78, 123.78, 120.94, 119.97, 115.95, 113.36, 111.79, 111.26, 56.29 (O**C**H$_3$), 55.60 (O**C**H$_3$), 55.46 (O**C**H$_3$), 38.41 (**C**H$_2$), 38.24 (**C**H$_2$), 36.90 (**C**H$_2$), 36.53 (**C**H$_2$).

Table 4.2: The ^{1}H and ^{13}C NMR of **4.7**

4.8 NMR analysis for polymorphatin A 1.6

When we compared the NMR data of our synthetic sample of polymorphatin A **1.6** with the data reported by Lou *et al*. and Speicher *et al*., we noted significant discrepancies with both data sets (Table 4.3).[32.46] ^{1}H NMR data recorded on our synthetic sample of polymorphatin A **1.6** showed a doublet at 5.65 ppm with the characteristic upfield shift expected for the isolated proton in arene C. A similar signal was reported by Lou *et al*. at 5.88 ppm. In stark contrast, the data reported by Speicher *et al*. had no such signal supporting our earlier suggestion that the structural assigned to their synthetic sample was wrong.

^{1}H NMR data of isolation polymorphatin A **1.6** and synthetic polymorphatin A **1.6** (acetone-d_6)		
Polymorphatin A **1.6** data by Speicher *et al*. (400MHz)[46]	Polymorphatin A **1.6** data by Lou *et al*. (600 MHz)[32]	Our sample **1.6** data (400 MHz)
8.58 (br. s),	8.01 (s),	8.64 (br. s, 1H, O**H**),
8.29 (br. s),	7.82 (s),	8.36 (br. s, 1H, O**H**),
7.89 (br. s),	7.65 (s),	7.67 (s, 1H, O**H**),
7.22 (d, *J*=7.9, 1H, Ar**H**),	7.17 (dd, *J*=8.2, 2.1, 1H, Ar**H**),	7.00 (br. d, *J*=7.9 Hz, 1H, Ar**H**),
7.17 (d, *J*=7.8, 1H, Ar**H**),	7.00 (dd, *J*=8.3, 2.1, 1H, Ar**H**),	6.94 (dd, *J*=8.3, 2.1 Hz, 1H, Ar**H**),
7.09 (dd, *J*=8.3,2.0, 1H, Ar**H**),	6.89 (dd, *J*=8.2, 2.2, 1H, Ar**H**),	6.83 (dd, *J*=9.2, 2.6 Hz, 1H, Ar**H**),
7.02 (d, *J*=8.8, 1H, Ar**H**),	6.88 (d, *J*=8.2, 1H, Ar**H**),	6.81 (d, *J*=8.2 Hz, 1H, Ar**H**),
7.02 (d, *J*=8.8, 1H, Ar**H**),	6.77 (dd, *J*=8.3, 2.2, 1H, Ar**H**),	6.60 (br. d, *J*=7.7 Hz, 1H, Ar**H**),
7.01 (d, *J*=8.3, 1H, Ar**H**),	6.77 (d, *J*=7.6, 1H, Ar**H**),	6.51 (br. m, 1H, Ar**H**),
6.94 (d, *J*=1.6, 1H, Ar**H**),	6.76 (d, *J*=2.6, 1H, Ar**H**),	6.43 (br. d, *J*=0.3 Hz, 1H, Ar**H**),
6.90 (dd, *J*=7.9,1.6, 1H, Ar**H**),	6.72 (d, *J*=8.1, 1H, Ar**H**),	6.34 (br. d, *J*=6.1 Hz, 1H, Ar**H**),
6.67 (dd, *J*=7.8,1.6, 1H, Ar**H**),	6.66 (dd, *J*=8.1, 1.9, 1H, Ar**H**),	6.32 (br. d, *J*=7.3 Hz, 2H, 2 x Ar**H**),
6.59 (d, *J*=1.6, 1H, Ar**H**),	6.62 (dd, *J*=8.2, 2.6, 1H, Ar**H**),	-
6.56 (d, *J*=8.8, 1H, Ar**H**),	6.55 (dd, *J*=7.6, 1.4, 1H, Ar**H**),	6.12 (br. d, *J*=6.6 Hz, 1H, Ar**H**),
6.56 (d, *J*=8.8, 1H, Ar**H**),	6.44 (d, *J*=1.4, 1H, Ar**H**),	6.10 (d, *J*=7.2 Hz, 1H, Ar**H**),
6.37 (d, *J*=2.0, 1H, Ar**H**),	5.88 (d, *J*=1.9, 1H, Ar**H**),	5.65 (d, *J*=2.0 Hz, 1H, Ar**H**),
2.94-2.68 (m, 8**H**).	3.06-2.32 (m, 8**H**).	2.96-2.70 (m, 8**H**).
^{13}C NMR data of isolation and synthetic polymorphatin A **1.6** (acetone-d_6)		
157.60, 155.09, 154.41, 148.46, 144.33, 143.13, 142.76, 136.74, 133.01, 132.84, 134.25, 130.50, 130.50, 126.41, 125.36, 124.95, 124.36, 122.83, 121.89, 118.69, 118.69, 117.97, 117.08, 117.08, 38.92, 38.84, 37.82, 37.42.	157.6, 155.6, 155.1, 149.7, 145.6, 143.3, 141.9, 135.4, 135.4, 135.4, 131.8, 131.7, 131.6, 131.0, 127.1, 122.6, 122.3, 121.2, 122.1, 117.4, 117.0, 116.6, 116.5, 116.3, 38.7, 38.1, 37.3, 36.2.	157.4, 154.4, 154.3, 149.4, 142.8, 142.7, 141.5, 134.3, 133.7, 132.9, 132.2, 130.7, 130.6, 127.4, 126.2, 126.0, 125.4, 123.9, 122.9, 118.9, 118.7, 118.1, 118.0, 114.9, 39.4, 38.6, 37.7, 37.6.

Table 4.3: The ^{1}H and ^{13}C NMR of **1.6**

The differences between our data and those attained by Lou *et al*. were also significant. It is plausible that this is due to different levels of water in the acetone-d_6 used in the analyse of each sample. However, they made no mention of the existence of rotamers, which our synthetic sample exhibited. The VT ^{1}H NMR experiments confirmed that two distinct rotamers were seen to interconvert at 373 K (Figure 4.6). It is therefore difficult to say whether the paper of Lou *et al*. describes the isolation of polymorphatin A **1.6** or not. In contrast to both Lou and Speicher, our data is supported by an X-ray crystal structure for polymorphatin A trimethyl ether **4.7**.

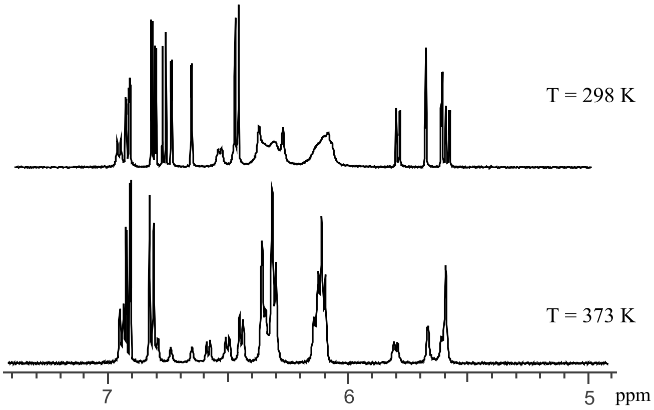


Figure 4.6: Extracts from VT ^{1}H NMR spectral recorded on polymorphatin A **1.6** in d_6-DMSO confirming the presence of rotamers in solution

4.9 Conclusion and future work

In conclusion, we have completed the first total synthesis of polymorphatin A **1.6** using a nickel-mediated cross-coupling reaction to effect the critical macrocyclisation step. Of the many strategies investigated, this was the only one found to achieve connection of the strained biaryl linkage. Our approach provides a concise method of preparing this macrocyclic bisbibenzyl. Data exhibited by our synthetic sample of polymorphatin A **1.6** is very different to that reported for a synthetic sample prepared within the Speicher research group casting severe doubt on their claim. Though our data shows some consistency with that reported by Lou *et al*. in the isolation paper, the discrepancies are such that we are unable to support conclusively their structural assignment.[32,46]

We hope that other researchers try to isolate polymorphatin A **1.6** from nature and find a way to crystalise the natural product. To date, the biology activity of polymorphatin A **1.6** has not been tested. The method of synthesis we have developed readily leads to polymorphatin A **1.6** as it is based on the rapid assembly the four subunits that are easily prepared from simple starting materials. Therefore, future research can extend this work to other natural products in the macrocyclic bisbibenzyl family.

Chapter 5: Experimental part

5.1 General methods

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

All commercial compounds and regents were purchased from Acros Organics, Sigma-Aldrich, Alfa Aesar, Fluorochem or Apollo Chemicals and were used as received unless otherwise stated.

Solvents were purchased from Fischer Scientific and Rathburn or used as received unless stated as dry. In which case, diethyl ether, and tetrahydrofuran were freshly distilled over sodium / benzophenone under argon and dichloromethane was distilled over calcium hydride immediately prior to use. Toluene was distilled from sodium under argon.

All air and water sensitive reactions were carried out under an argon atmosphere.

All reactions were monitored by TLC on precoated plates (Merck silica gel 60 F_{254}) and the products were visualized with 254 nm UV light followed most commonly by PMA, DNPH or $KMnO_4$ stains as appropriate.

Purification by flash column chromatography was accomplished using silica (Sigma Aldrich 60, 40-63 µm) with the stated solvent system.

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Bruker DPX400 spectrometer at 298 K unless otherwise stated. Data for proton NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singulet, d = doublet, t = triplet, q = quartet, m = multiplet or a combination of the above), coupling constant *J* (Hz), integration and attribution.

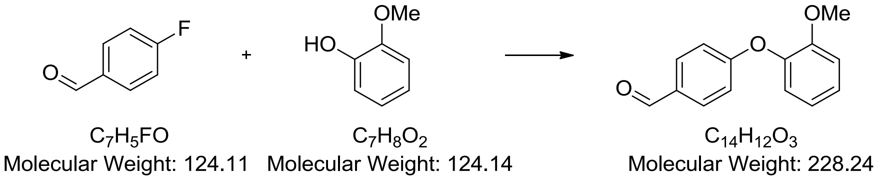
Infrared spectra (IR) were recorded on a Nicolet 380 FT-IR spectrometer. Absorptions are described as s (strong), m (medium), w (weak) or br (broad) and reported in cm^{-1}.

Electrospray mass spectrometry was performed on a directly injected Waters quadrupole MSD using ESI+ or ESI- ionisation with MeOH or MeCN as solvent. Electron ionisation and chemical ionisation mass spectrometry were carried out using a Finnigan 2000 Series GC/MS using a Zebron ZB5 30 m x 0.25 mm x 0.25 µm column run from 40 °C to 200 °C over 18 minutes. High resolution mass spectra were recorded on either a Bruker Apex III FT-ICR mass spectrometer equipped with a 4.7 T actively shielded superconducting magnet and Apollo ESI ion source or a Bruker maXis ESI-ToF coupled to a Dionex Ultimate 3000 HPLC and Apollo ESI ion source. High resolution mass spectra were recorded by Dr John Langley and/or Ms. Julie Herniman at the University of

Southampton. Samples indicated as (EI-Direct) were analysed by electron ionisation *via* direct insertion probe on the Thermo Mat 900 XP double focusing high resolution mass spectrometer system.

5.2 Experimental Section

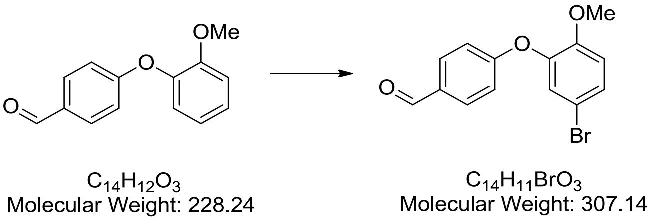
4-(2-Methoxyphenoxy)benzaldehyde (1.147)



To a stirred solution of 2-methoxyphenol **1.145** (10 g, 80.6 mmol) and 4-fluorobenzaldehyde **1.146** (10.99 g, 88.6 mmol) in DMF (450 mL) was added K_2CO_3 (13.37 g, 96.7 mmol). After 13 h at reflux, water (300 mL) was added to the reaction mixture and the aqueous phase was extracted with Et_2O (3 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% Et_2O/PE) to give the title compound **1.147** as a yellow solid (17.68 g, 96%). These data are accordance with those reported in the literature.[50]

MP	67-68 °C (Et_2O/PE) [Lit. 56-56.5 °C (PE)][50]
IR (υ_{max})	2919 (w), 2843 (w) 1691 (m), 1597 (m), 1579 (m), 1496 (s), 1456 (w), 1390 (w), 1302 (s), 1260 (s), 1225 (s), 1173 (s), 1152 (m), 1107 (s), 1040 (s), 1020 (w), 937 (w), 875 (m), 825 (s), 744 (s), 652 (s), 618 (m), 535 (s), 499(m), 468 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	9.91 (s, 1H, C**H**O), 7.82 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 7.28-7.22 (m, 1H, Ar**H**), 7.11 (dd, *J*=8.0, 1.6 Hz, 1H, Ar**H**), 7.05 (dd, *J*=8.3, 1.2 Hz, 1H, Ar**H**), 7.03-7.00 (m, 1H, Ar**H**), 6.99 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 3.80 (s, 3H, OC**H$_3$**).
δ_C (100 MHz, $CDCl_3$)	190.7 (**C**HO), 163.5 (**C**), 151.7 (**C**), 142.9 (**C**), 131.8 (2 x **C**H), 130.9 (**C**), 126.4 (**C**H), 122.5 (**C**H), 121.3 (**C**H), 116.2 (2 x **C**H), 113.1 (**C**H), 55.9 (**C**H_3).
LRMS (EI+, m/z)	228 $[M]^+$ (100%).

4-(5-Bromo-2-methoxyphenoxy)benzaldehyde (2.3)



To a stirred solution of ether **1.147** (4.00 g, 17.5 mmol) in MeCN (35 mL) was added *N*–bromosuccinimide (3.43 g, 19.3 mmol). After 22 h at reflux, a saturated solution of $Na_2S_2O_3$ (50 mL) and water (50 mL) were added and the aqueous phase was extracted with Et_2O (2 x 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (10-20% Et_2O/PE) to give the title compound **2.3** as a creamy solid (5.13 g, 95%).

These data are accordance with those reported in the literature.[63]

MP 70-72 °C (Et_2O/PE) [Lit. 76-78 °C (PE/EA)][63]

IR (υ_{max}) 2836 (w), 2736 (w), 1691 (s), 1601 (s), 1576 (s), 1488 (s), 1439 (m), 1397 (m), 1353 (w), 1217 (s), 1294 (s), 1263 (s), 1217 (s), 1176 (m), 1152 (s), 1130 (s), 1105 (m), 1022 (m), 899 (m), 829 (s), 803 (s) 651 (s), 502 (m), 435 (w) cm^{-1}.

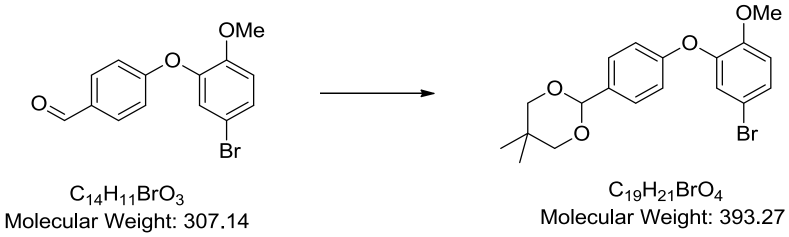
δ_H (400 MHz, $CDCl_3$) 9.92 (s, 1H, C**H**O),
7.84 (d, *J*=8.9 Hz, 2H, 2 x Ar**H**),
7.35 (dd, *J*=8.6, 2.4 Hz, 1H, Ar**H**),
7.24 (d, *J*=2.2 Hz, 1H, Ar**H**),
7.00 (d, *J*=8.4 Hz, 2H, 2 x Ar**H**),
6.92 (d, *J*=8.8, 1H, Ar**H**),
3.78 (s, 3H, OC**H**$_3$).

δ_C (100 MHz, $CDCl_3$) 190.7 (**C**HO), 162.8 (**C**), 151.0 (**C**), 143.7 (**C**), 131.9 (2 x **C**H), 131.3 (**C**), 129.1 (**C**H), 125.5 (**C**H), 116.4 (2 x **C**H), 114.3 (**C**H), 112.5 (**C**Br), 56.1 (**C**H$_3$).

LRMS (EI+, m/z) 306 $[M(^{79}Br)]^+$ (100%), 308 $[M(^{81}Br)]^+$ (90%).

HRMS (ESI+, m/z) calcd for $C_{14}H_{12}{}^{79}BrO_3$ $[M+H]^+$ requires 306.9964; found: 306.9971.

2-(4-(5-Bromo-2-methoxyphenoxy)phenyl)-5,5-dimethyl-1,3-dioxane (1.230)

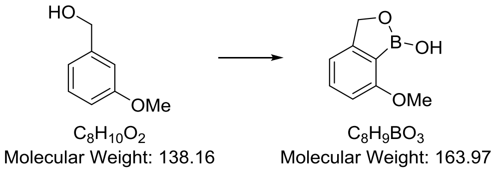


To a stirred solution of aldehyde **2.3** (2.00 g, 6.53 mmol) in toluene (65 mL) was added neopentylglycol (2.04 g, 19.6 mmol) and *p*-toluenesulfonic acid (37.0 mg, 0.20 mmol). After 3 h at reflux under a Dean Stark apparatus, the reaction mixture was diluted with Et_2O (70 mL) and the organic phase was washed with saturated $NaHCO_3$ (50 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (15% Et_2O/PE) to afford the title compound **1.230** as a beige solid (2.38 g, 92%).

These data are accordance with those reported in the literature.[63]

MP	155-157 °C (Et_2O/PE) [Lit. 155-157 °C (PE/EA)][63]
IR (υ_{max})	2953 (w), 2843 (w), 1613 (w), 1582 (w), 1507 (m), 1492 (s), 1439 (m), 1388 (m), 1296 (m), 1264 (s), 1222 (s), 1176 (w), 1132 (w), 1099 (s), 1018 (w), 989 (w), 962 (w), 900 (m), 829 (w) 803 (w), 622 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.49 (d, *J*=8.4 Hz, 2H, 2 x Ar**H**), 7.21 (dd, *J*=8.6, 2.4 Hz, 1H, Ar**H**), 7.04 (d, *J*=2.6 Hz, 1H, Ar**H**), 6.98 (d, *J*=8.8 Hz, 2H, 2 x Ar**H**), 6.86 (d, *J*=8.8 Hz, 1H, Ar**H**), 5.39 (s, 1H, OC**H**O), 3.82 (s, 3H, OC$\mathbf{H}_3$), 3.78 (d, *J*=11.2 Hz, 2H, 2 X OC**H**H), 3.66 (d, *J*=10.6 Hz, 2H, 2 X OCH**H**), 1.31 (s, 3H, C$\mathbf{H}_3$), 0.81 (s, 3H, C$\mathbf{H}_3$).
δ_C (100 MHz, $CDCl_3$)	157.3 (**C**), 150.3 (**C**), 146.2 (**C**), 133.7 (**C**), 127.7 (2 x **C**H), 127.1 (**C**H), 123.1 (**C**H), 117.7 (2 x **C**H), 113.9 (**C**H), 112.4 (**C**), 101.3 (**C**H), 77.6 (2 x **C**H_2), 56.1 (**C**H_3), 30.2 (**C**), 23.0 (**C**H_3), 21.8 (**C**H_3)
LRMS (EI+, m/z)	392 [M (^{79}Br)]$^+$ (60%), 394 [M(^{81}Br)]$^+$ (57%), 306 (100%).

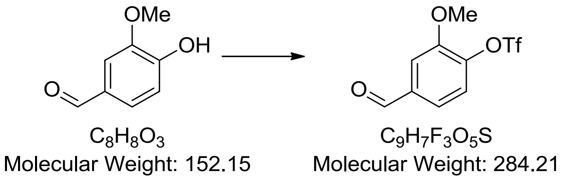
7-Methoxybenzo[c][1,2]oxaborol-1(3*H*)-ol (2.4)



To a stirred solution of 3-methoxybenzyl alcohol **1.226** (10.0 mL, 72.4 mmol) in Et_2O (360 mL) at 0 °C was added *n*-BuLi (66.4 mL, 159.24 mmol, 2.4 M in hexanes) dropwise over 15 min. The reaction mixture was warmed to RT for 6 h then a $B(OMe)_3$ (22.56 g, 217.14 mmol) was added at -78 °C. After 13 h at RT, 2M HCl (100 mL) was added. After 10 min the aqueous phase was separated at extracted with EtOAc (3 x 100 mL). The organic phases were combined and washed with 2M NaOH (3 x 100 mL) then the combined aqueous phases were acidified with 3M HCl until pH=2 and extracted with EtOAc (3 x 100 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound **2.4** as an orange solid (6.45 g, 54%).

MP	136-138 °C (EtOAc)
IR (υ_{max})	3221 (br. m), 3012 (m), 2932 (w), 2840 (w), 1712 (w), 1605 (s), 1580 (m), 1454 (s), 1411 (s), 1367 (s), 1305 (s), 1257 (s), 1197 (m), 1073 (s), 1044 (m), 968 (s), 770 (s) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.45 (t, *J*=7.9 Hz, 1H, Ar**H**), 6.95 (d, *J*=7.7 Hz, 1H, Ar**H**), 6.77 (d, *J*=8.4 Hz, 1H, Ar**H**), 5.38 (s, 1H, O**H**), 5.07 (s, 2H, OC**H₂**), 3.90 (s, 3H, OC**H₃**).
δ_C (100 MHz, $CDCl_3$)	162.2 (**C**), 156.0 (**C**), 133.5 (**C**H), 113.8 (**C**H), 108.0 (**C**H), 71.1 (O**C**H₂), 55.2 (O**C**H₃). One C not observed.
LRMS (EI+, m/z)	163 (50%), 121 (100%).
HRMS (ESI+, m/z)	calcd for $C_8H_{10}{}^{11}BO_3$ $[M+H]^+$ requires 165.0719; found: 165.0719.

2-Methoxy-4-formyl-phenyl-trifluoromethane sulfonate (2.5)

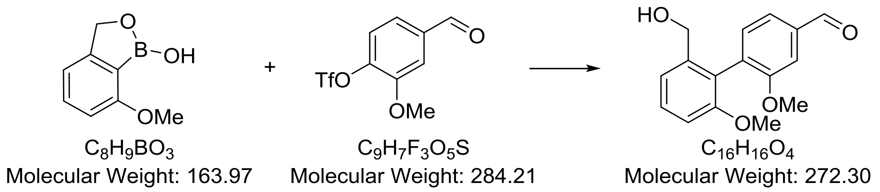


To a stirred solution of vanillin **1.149** (10.0 g, 65.8 mmol) and pyridine (10.6 mL, 131.5 mmol) in DCM (131 mL) at 0 °C was added Tf_2O (14.38 mL, 85.5 mmol) dropwise over 15 min. The reaction mixture was warmed to RT and after 2 h a saturated solution of sat. $NaHCO_3$ (150 mL) was added followed by water (150 mL). The aqueous phase was extracted with Et_2O (3 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (10-25% DCM/PE) to afford the title compound **2.5** as a colourless oil (15.11 g, 80%).

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

IR (υ_{max})	2839 (w), 1703 (m), 1604 (s), 1499 (m), 1465 (s), 1420 (s), 1388 (w), 1317 (m), 1277 (s), 1246 (s), 1203 (s) 1135 (s), 1102 (s), 1027 (m), 956 (w), 931 (s), 869 (s), 821 (m), 778 (m) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	9.96 (s, 1H, C**H**O), 7.55 (d, *J*=1.8 Hz, 1H, Ar**H**), 7.50 (dd, *J*=8.4, 1.8 Hz, 1H, Ar**H**), 7.40 (d, *J*=8.1 Hz, 1H, Ar**H**), 3.98 (s, 3H, OC$\mathbf{H_3}$).
δ_C (100 MHz, $CDCl_3$)	190.3 (**C**HO), 152.1 (**C**), 142.6 (**C**), 136.8 (**C**), 123.9 (**C**H), 123.1 (**C**H), 118.6 (q, $J_{C\text{-}F}$=320.7 Hz, **C**-F), 111.8 (**C**H), 56.4 (**C**H_3).
LRMS (EI+, m/z)	284 $[M]^+$ (62%), 151 (100%).
HRMS (ESI+, m/z)	calcd for $C_9H_8F_3O_5S$ $[M+H]^+$ requires 285.0039; found: 285.0041

<u>2'-(Hydroxymethyl)-2,6'-dimethoxybiphenyl-4-carbaldehyde (2.6)</u>



To a stirred solution of triflate **2.5** (10.0 g, 35.2 mmol) and boronic acid **2.4** (6.56 g, 38.7 mmol) in a mixture of PhMe/EtOH/water (110/55/55 mL) was added Cs_2CO_3 (22.93 g, 70.4 mmol). The resulting mixture was degassed under argon for 30 min then $Pd(PPh_3)_4$ (4.06 g, 3.52 mmol) was added. After 13 h at reflux, water (100 mL) was added. The aqueous phase was separated and extracted with EtOAc (3 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (25% EtOAc/PE) to afford the title compound **2.6** as a yellow foamy solid (4.76 g, 49%).

MP	140-143 °C (EtOAc/PE)
IR (υ_{max})	3429 (br. w), 2938 (w), 2837 (w), 2359 (w), 1685 (s), 1603 (m), 1575 (m), 1506 (s), 1465 (s), 1414 (m), 1387 (m), 1258 (s), 1189 (m), 1154 (w), 1125 (w), 1083 (m), 1034 (m), 1003 (w), 904 (w), 866 (w), 826 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	10.04 (s, 1H, C**H**O),

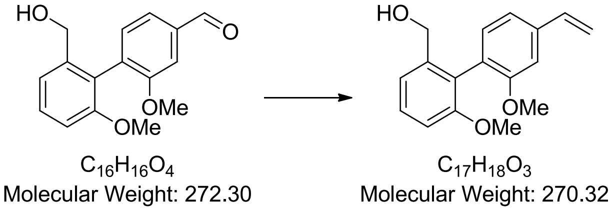
7.55 (dd, *J*=7.5, 1.5 Hz, 1H, Ar**H**),
7.53 (d, *J*=1.1, 1H, Ar**H**),
7.42 (t, *J*=8.0 Hz, 1H, Ar**H**),
7.33 (d, *J*=7.5 Hz, 1H, Ar**H**),
7.20 (dd, *J*=7.7, 0.4 Hz, 1H, Ar**H**),
6.97 (dd, *J*=8.3,0.6 Hz, 1H, Ar**H**),
4.36 (d, *J*=12.5 Hz 1H, OC**H**H),
4.31 (d, *J*=12.5 Hz 1H, OCH**H**),
3.83 (s, 3H, OC**H**$_3$),
3.73 (s, 3H, OC**H**$_3$),
1.69 (br. s, 1H, O**H**).

δ$_C$ (100 MHz, CDCl$_3$) 191.8 (**C**HO), 157.6 (**C**), 156.7 (**C**), 140.4 (**C**), 137.2 (**C**), 132.5 (**C**H), 129.4 (**C**H), 125.0 (**C**), 124.2 (**C**H), 120.5 (**C**H), 110.4 (**C**H), 109.6 (**C**H), 63.4 (**C**H$_2$), 55.9 (**C**H$_3$) 55.8 (**C**H$_3$). One C not observed.

LRMS (EI+, m/z) 272 [M]$^+$ (90%), 136 (100%).

HRMS (ESI+, m/z) calcd for $C_{16}H_{16}NaO_4$ [M+Na]$^+$ requires 295.0941; found: 295.0946.

(2',6-Dimethoxy-4'-vinylbiphenyl-2-yl)methanol (2.7)



To a stirred suspension of methyltriphenylphosphonium bromide (13.39 g, 37.5 mmol) in THF (130 mL) at 0 °C was added KO^{t}Bu (4.20 g, 37.5 mmol). After 15 min, a solution of aldehyde **2.6** (3.40 g, 12.5 mmol) in THF (31 mL) was added. After 12 h at RT, water (70 mL) was added and the reaction mixture was extracted with EtOAc (3 x 100 mL). The organic phases were combined, washed with sat. NH$_4$Cl (70 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (25% EtOAc/PE) to afford the title compound **2.7** as a colourless oil (2.91 g, 86%).

IR (υ_{max}) 3387 (br. m), 2935 (w), 2834 (w), 1596 (m), 1578 (m), 1559 (w), 1509 (s), 1463 (s), 1407 (m), 1390 (m), 1253 (s), 1160 (m), 1133 (w), 1082 (s), 1031 (s), 1001 (m), 906 (m), 780 (s) cm^{-1}.

δ$_H$ (400 MHz, CDCl$_3$) 7.39 (t, *J*=8.1 Hz, 1H, Ar**H**),
7.19 (d, *J*=7.3 Hz, 1H, Ar**H**),
7.15-7.05 (m, 3H, 3 x Ar**H**),
6.96 (d, *J*=8.1 Hz, 1H, Ar**H**),

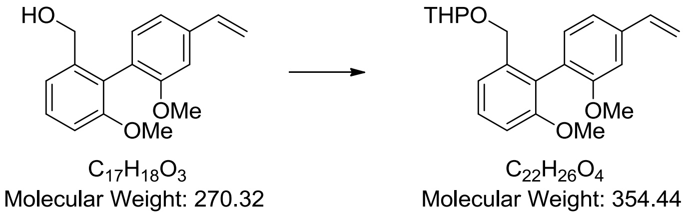
6.78 (dd, *J*=17.6, 11.0 Hz, 1H, C**H**=CH$_2$),
5.82 (dd, *J*=17.6, 0.7 Hz, 1H, CH**H**=CH),
5.31 (dd, *J*=10.9, 0.7 Hz, 1H, C**H**H=CH),
4.38 (d, *J*=12.3 Hz 1H, OC**H**H),
4.32 (d, *J*=12.3 Hz 1H, OCH**H**),
3.78 (s, 3H, OC**H**$_3$),
3.74 (s, 3H, OC**H**$_3$),
2.03 (br. s, 1H, O**H**).

δ$_C$ (100 MHz, CDCl$_3$) 157.1 (**C**), 156.9 (**C**), 141.9 (**C**), 138.5 (**C**), 136.8 (**C**H), 131.8 (**C**H), 128.8 (**C**H), 125.9 (**C**), 124.9 (**C**), 120.6 (**C**H), 119.0 (**C**H), 114.0 (**C**H$_2$=CH), 110.4 (**C**H), 109.1 (**C**H), 63.6 (**C**H$_2$), 55.9 (**C**H$_3$), 55.7 (**C**H$_3$).

LRMS (EI+, m/z) 270 [M]$^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{17}H_{18}NaO_3$ [M+Na]$^+$ requires 293.1148; found: 293.1155.

2-((2',6-Dimethoxy-4'-vinylbiphenyl-2-yl)methoxy)tetrahydro-2*H*-pyran (1.231)



To a stirred solution of alcohol **2.7** (1.20 g, 4.80 mmol) in DCM (50 mL), was added *p*-TsOH·H$_2$O (0.10 g, 0.48 mmol) then 3,4-dihydro-2*H*-pyran (1.31 mL, 14.4 mmol). After 4 h, a solution of saturated NaHCO$_3$ (30 mL) was added. The aqueous phase was separated and extracted with DCM (3 x 30 mL). The organic phases were combined, dried over MgSO$_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (15% EtOAc/PE) to afford the title compound **1.231** as a colourless oil (1.54 g, 90%) as an inseparable mixture of diastereomers.

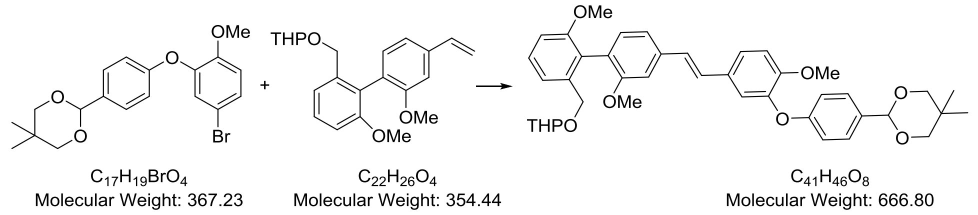
IR (υ_{max}) 2938 (m), 2868 (w), 1581 (w), 1560 (w), 1510 (m), 1464 (m), 1407 (m), 1390 (w), 1256 (s), 1200 (w), 1159 (m), 1122 (m), 1075 (s), 1053 (s), 1026 (s), 973 (m), 904 (m), 816 (m), 781 (w) cm^{-1}.

δ$_H$ (400 MHz, CDCl$_3$) 7.40 (t, *J*=8.1 Hz, 1H, Ar**H**),
7.26 (d, *J*=7.3 Hz, 1H, Ar**H**),
7.16-7.09 (m, 2H, 2 x Ar**H**),
7.08 (s, 1H, Ar**H**),
6.96 (d, *J*=8.4 Hz, 1H, Ar**H**),
6.81 (dd, *J*=17.6, 10.6 Hz, 1H, C**H**=CH$_2$),

5.83 (d, *J*=17.6 Hz, 1H, C**H**H=CH),
5.32 (d, *J*=10.6 Hz, 1H, CH**H**=CH),
4.63 (d, *J*=12.1 Hz, 0.5H, OC**H**HC),
4.59 (t, *J*=3.3 Hz, 0.5H, OC**H**OCH$_2$),
4.54 (d, *J*=12.4 Hz, 0.5H, OC**H**HC),
4.49 (t, *J*=3.3 Hz, 0.5H, OC**H**OCH$_2$),
4.27 (d, *J*=12.4 Hz, 0.5H, OCH**H**C),
4.19 (d, *J*=12.4 Hz, 0.5H, OCH**H**C),
3.79 (s, 3H, OC**H**$_3$),
3.75 (s, 3H, OC**H$_3$**),
3.68-3.37 (m, 2H, OC**H**$_2$CH$_2$),
1.97-1.80 (m, 1H, C**H**HCH$_2$O),
1.70-1.48 (m, 5H, C**H$_2$**C**H$_2$**C**H**HCH$_2$O).

δ$_C$ (100 MHz, CDCl$_3$)	157.3 (**C**), 157.1 & 157.0 (**C**), 138.6 & 138.5 (**C**), 138.2(**C**), 137.0 (**C**H), 131.7 & 131.6 (**C**H), 128.4 (**C**H), 126.4 & 126.3 (**C**), 125.0 (**C**), 120.3 & 120.2 (**C**H), 118.7 & 118.6 (**C**H), 113.61 & 113.6 (CH=**C**H$_2$), 110.2 & 110.1 (**C**H), 108.5 & 108.4 (**C**H), 98.1 & 98.0 (O**C**HO), 67.1 & 67.0 (O**C**H$_2$Ar), 61.7 & 61.5 (O**C**H$_2$), 55.9 (O**C**H$_3$), 55.6 & 55.5 (O**C**H$_3$), 30.5 & 30.4 (**C**H$_2$), 25.4 (**C**H$_2$), 19.2 & 19.1 (**C**H$_2$).
LRMS (EI+, m/z)	354 [M]$^+$ (18%), 254 [M-OTHP]$^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{22}H_{26}NaO_4$ [M+Na]$^+$ requires 377.1723; found: 377.1730.

(*E*)-2-(4-(5-(2-(2,2'-Dimethoxy-6'-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-[1,1'-biphenyl]-4-yl)vinyl)-2-methoxyphenoxy)phenyl)-5,5-dimethyl-1,3-dioxane (2.2)



To a stirred solution of aryl bromide **1.230** (2.05 g, 5.21 mmol) and biaryl **1.231** (2.21 g, 6.25 mmol) in DMA (39 mL) was added Cy$_2$NMe (1.67 mL, 8.45 mmol) and TBAC (140 mg, 0.56 mmol). The reaction mixture was degassed for 10 min under argon and then PdCl$_2$(dtbpf) (68 mg, 1.04 mmol) was added. The reaction mixture was heated at reflux for 18 h then cooled to RT and the solvent removed *in vacuo*. The residue was diluted with Et$_2$O (50 mL) and purified by flash column chromatography (20-35% Et$_2$O/cyclohexane) to afford the title compound **2.2** as a white solid (2.76 g, 79%) as an inseparable mixture of diastereomers.

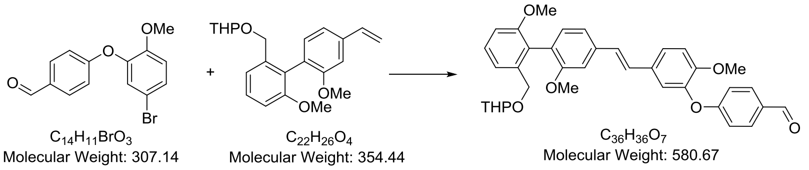
MP	94-95 °C (Et$_2$O/cyclohexane)
IR (υ_{max})	2951 (m), 2847 (w), 2360 (m), 2339 (w), 1599 (w), 1579 (w), 1508 (s), 1463 (s), 1388 (w), 1264 (s), 1223 (w), 1164 (w), 1096 (s), 1023 (s), 976 (w), 906 (w), 866 (w), 724 (s), 664 (w), 646 (m), 542 (w) cm^{-1}.
δ_H (400 MHz, CDCl$_3$)	7.50 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 7.36 (t, *J*=7.8 Hz, 1H, Ar**H**), 7.29 (dd, *J*=8.4, 2.08 Hz, 1H, Ar**H**), 7.21 (d, *J*=7.6 Hz, 1H, Ar**H**), 7.17 (d, *J*=2.0 Hz, 1H, Ar**H**) 7.14-7.09 (m, 2H, Ar**H**, ArC**H**=C) 7.09-7.06 (m, 1H, Ar**H**) 7.03 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 7.02-6.98 (m, 3H, 2 x Ar**H**, ArC**H**=C), 6.98 (d, *J*=12.4 Hz, 1H, ArC=C**H**) 6.95-6.90 (m, 1H, Ar**H**) 5.41 (s, 1H, OC**H**O) 4.59 (d, *J*=12.1 Hz, 0.5H, OC**H**HC), 4.54 (t, *J*=3.3 Hz, 0.5H, OC**H**OCH$_2$), 4.49 (d, *J*=12.5 Hz, 0.5H, OC**H**HC), 4.44 (t, *J*=3.4 Hz, 0.5H, OC**H**OCH$_2$), 4.23 (d, *J*=12.5 Hz, 0.5H, OCH**H**C), 4.14 (d, *J*=12.2 Hz, 0.5H, OCH**H**C), 3.87 (s, 3H, OC**H**$_3$), 3.83-3.78 (m, 2H, 2 x CCH**H**O), 3.79 (s, 3H, OC**H**$_3$), 3.73 (s, 3H, OC**H**$_3$), 3.68 (d, *J*=10.6 Hz, 2H, 2 x CC**H**HO) 3.56-3.34 (m, 2H, OC**H**$_2$CH$_2$), 1.86-1.43 (m, 6H, C**H**$_2$C**H**$_2$C**H**$_2$CH$_2$O), 1.33 (s, 3H, C**H**$_3$), 0.82 (s, 3H, C**H**$_3$).

δ_C (100 MHz, $CDCl_3$) 158.1 (**C**), 157.3 (**C**), 157.1 (**C**), 150.8 (**C**), 145.3 & 145.3 (**C**), 138.6 & 138.5 (**C**), 138.0 (**C**), 133.0 (**C**), 131.7 & 131.6 (**C**H), 130.9 (**C**), 128.4 (**C**H), 127.6 & 127.5 (2 x **C**H), 127.4 & 127.3 (**C**H), 126.5 (**C**), 126.4 (**C**H), 124.7 & 124.6 (**C**), 123.0 (**C**H), 120.4 & 120.3 (**C**H), 118.8 & 118.7 (**C**H), 118.3 (**C**H), 117.4 (2 x **C**H), 112.7 (**C**H), 110.2 & 110.1 (**C**H), 108.6 & 108.5 (**C**H), 101.5 (**C**H), 98.1 & 98.0 (**C**H), 77.7 (2 x **C**H$_2$), 67.1 & 67.0 (**C**H$_2$), 61.7 & 61.5 (**C**H$_2$), 56.1 (**C**H$_3$), 55.9 (**C**H$_3$), 55.6 & 55.5 (**C**H$_3$), 30.5 & 30.4 (**C**H$_2$), 30.2 (**C**H$_2$), 25.4 (**C**H$_2$), 23.0 (**C**H$_3$), 21.9 (**C**H$_3$), 19.2 & 19.0 (**C**H$_2$).

LRMS (**ESI+, m/z**) 689 $[M+Na]^+$ (15%), 684 (100%).

HRMS (ESI+, m/z) calcd for $C_{41}H_{46}NaO_8$ $[M+Na]^+$ requires 689.3085; found: 689.3080.

(*E*)-4-(5-(2-(2,2'-Dimethoxy-6'-((tetrahydro-2H-pyran-2-yloxy)methyl)biphenyl-4-yl)vinyl)-2-methoxyphenoxy)benzaldehyde (2.9)



To a stirred solution of ether **2.3** (700 mg, 1.97 mmol) and biaryl **1.231** (1.39 g, 3.94 mmol) in 1.4-dioxane (15 mL) was added Et_3N (1.34 mL, 7.88 mmol). The reaction mixture was degassed for 30 min under argon and then $Pd(OAc)_2$ (40 mg, 0.19 mmol) was added. After 13 h at reflux, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography column (25-50% EtOAC/PE) to afford the title compound **2.9** as a yellow solid (301 mg, 26%) as an inseparable mixture of diastereomers.

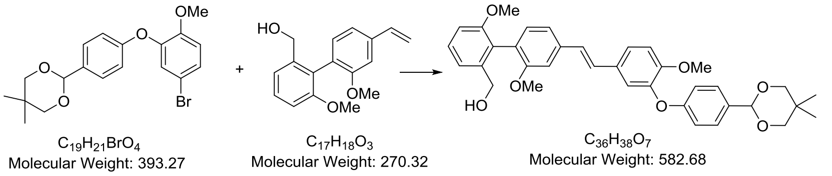
MP 86-88 °C (EtOAc/PE)

IR (υ_{max}) 2961 (m), 2857 (w), 2186 (w), 2159 (w), 1692 (w), 1596 (m), 1580 (w), 1503 (m), 1461 (m),1421 (w), 1268 (s), 1227 (s), 1154 (s), 1121 (m), 1074 (s), 1054 (w), 1025 (s), 963 (m), 902 (m), 862 (w), 815 (m), 782 (w) cm^{-1}.

δ_H (300 MHz, $CDCl_3$)
9.93 (s, 1H, C**H**O),
7.87 (d, *J*=6.4, 2.0 Hz, 2H, 2 x Ar**H**),
7.41 (dd, *J*=2.2 Hz, 1H, Ar**H**),

	7.38 (d, *J*=3.7 Hz, 1H, Ar**H**), 7.34 (d, *J*=1.8 Hz, 1H, Ar**H**), 7.21 (d, *J*=7.7 Hz, 1H, Ar**H**), 7.14-7.11 (m, 2H, 2 x Ar**H**), 7.08-7.03 (m, 6H, 4 x Ar**H** + C**H**=C**H**), 6.93 (d, *J*=8.1 Hz, 1H, Ar**H**), 4.58 (d, *J*=12.4 Hz, 0.5H, OC**H**HC), 4.54 (t, *J*=3.3 Hz, 0.5H, OC**H**OCH$_2$), 4.49 (d, *J*=12.4 Hz, 0.5H, OC**H**HC), 4.44 (t, *J*=3.3 Hz, 0.5H, OC**H**OCH$_2$), 4.23 (d, *J*=12.8 Hz, 0.5H, OCH**H**C), 4.14 (d, *J*=12.1 Hz, 0.5H, OCH**H**C), 3.83 (s, 3H, OC**H**$_3$), 3.78 (s, 3H, OC**H**$_3$), 3.73 (s, 3H, OC**H**$_3$), 3.69-3.46 (m, 2H, OC**H**$_2$CH$_2$), 1.88-1.40 (m, 6H, C**H**$_2$C**H**$_2$C**H**$_2$O).
δ$_C$ (75 MHz, CDCl$_3$)	190.8 (**C**HO), 163.5 (**C**), 157.4 (**C**), 157.1 (**C**), 151.2 (**C**), 143.1 (**C**), 138.6 (**C**), 138.5 (**C**), 137.8 (**C**), 131.9 (2 x **C**H), 131.8 (**C**H), 131.4 (**C**), 131.0 (**C**), 128.4 (**C**H), 128.1 (**C**H), 127.1 (**C**H), 126.3 (**C**), 124.9 (**C**H), 120.2 (**C**H), 120.0 (**C**H), 118.8 (**C**H), 116.2 (2 x **C**H), 113.1 (**C**H), 110.1 (**C**H), 108.6 (**C**H), 98.1 (**C**H), 67.1 (**C**H$_2$), 61.7 (**C**H$_2$), 56.0 (O**C**H$_3$), 55.9 (O**C**H$_3$), 55.6 (O**C**H$_3$), 30.5 (**C**H$_2$), 25.5 (**C**H$_2$), 19.1 (**C**H$_2$).
LRMS (ESI+, m/z)	603 [M+Na]$^+$ (100%)

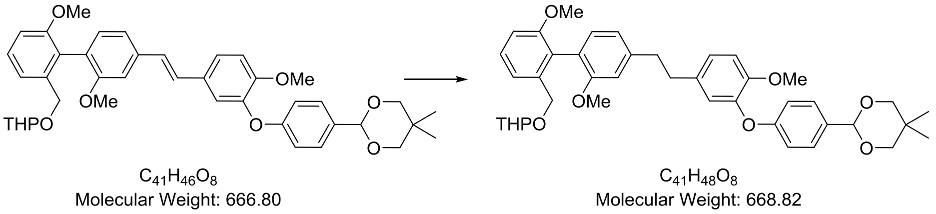
(*E*)-(4'-(3-(4-(5,5-Dimethyl-1,3-dioxan-2-yl)phenoxy)-4-methoxystyryl)-2',6-dimethoxybiphenyl-2-yl)metanol (2.8)



To a stirred solution of ether **1.230** (400 mg, 1.02 mmol) and biaryl **2.6** (330 mg, 1.22 mmol) in DMA (10 mL) was added K$_3$PO$_4$ (430 mg, 2.04 mmol). The reaction mixture was degassed for 30 min under argon and then Pd(OAc)$_2$ (20 mg, 0.10 mmol) was added. After 12 h at reflux, water (50 mL) was added and the aqueous phase was separated and extracted with EtOAc (3 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (25% EtOAc/PE) to afford the title compound **2.8** as a brown soild (180 mg, 30%).

MP	105-108 °C (EtOAc/PE)
IR (υ_{max})	3430 (br. w), 2922 (s), 2851 (m), 1732 (w), 1609 (w), 1506 (s), 1462 (s), 1386 (m), 1258 (s), 117 (s), 1164 (m), 1095 (s), 1034 (m), 1014 (m), 987 (w), 925 (w) cm^{-1}.
δ_H (300 MHz, $CDCl_3$)	7.51 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 7.42-7.34 (m, 2H, 2 x Ar**H**), 7.29 (dd, *J*=8.3, 1.9 Hz, 1H, Ar**H**), 7.22-6.91 (m, 10H, 10 x Ar**H**), 5.41 (s, 1H, OC**H**O), 4.45-4.27 (m, 2H, OC**H**$_2$Ar), 3.86 (s, 3H, OC**H**$_3$), 3.79 (s, 2H, OC**H**$_2$), 3.78 (s, 3H, OC**H**$_3$), 3.73 (s, 3H, OC**H**$_3$), 3.70-3.65 (m, 2H, OC**H**$_2$), 2.18 (br. s, 1H, O**H**), 1.33 (s, 3H, C**H**$_3$), 0.81 (s, 3H, C**H**$_3$).
δ_C (75 MHz, $CDCl_3$)	158.1 (**C**), 157.2 (2 x **C**), 157.0 (**C**), 150.8 (**C**), 145.2 (**C**), 140.8 (**C**), 138.2 (**C**), 133.0 (**C**), 131.9 (2**C**H), 130.7 (**C**), 128.8 (**C**), 128.4 (**C**H), 127.7 (**C**H), 127.6 (**C**H), 127.2 (**C**H), 125.9 (**C**H), 124.4 (**C**), 123.1 (**C**H), 120.5 (**C**H), 119.1 (**C**H), 118.3 (**C**H), 1217.3 (**C**H), 112.7 (**C**H), 110.3 (**C**H), 109.1 (**C**H), 101.5 (**C**H), 77.6 (**C**H$_2$), 63.5 (2 x **C**H$_2$), 56.0 (**C**H$_3$), 55.8 (**C**H$_3$), 55.7 (**C**H$_3$), 30.1 (**C**H), 23.0 (**C**H$_3$), 21. 8 (**C**H$_3$).
LRMS (ESI+, m/z)	605 $[M+Na]^+$ (100%)

2-(4-(5-(2-(2,2'-Dimethoxy-6'-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-[1,1'-biphenyl]-4-yl)ethyl)-2-methoxyphenoxy)phenyl)-5,5-dimethyl-1,3-dioxane (2.13)



To a solution of alkene **2.2** (2.61 g, 3.91 mmol) in EtOH (150 mL) and DCM (150 mL) was added PtO_2 (260 mg, 1.17 mmol) and Et_3N (5.93 mL, 58.7 mmol). The flask was evacuated/purged with argon three times then evacuated/purged with hydrogen twice. After 6 h stirred vigorously under an atmosphere of H_2 at RT. The mixture filtered through Celite$^{©}$ and the solvent was removed *in vacuo*. The residue was purified by flash chromatography column (40-50% Et_2O/cyclohexane) to afford the title compound **2.13** as a while solid (2.49 g, 95%) and an inseparable mixture of diastereomers.

MP	60-62 °C (Et_2O/cyclohexane)
IR (υ_{max})	2945 (m), 2839 (w), 2360 (m), 2339 (w), 1611 (w), 1579 (w), 1509 (s), 1465 (s), 1417 (m), 1388 (w), 1263 (s), 1225 (w), 1164 (w), 1099 (s), 1032 (s), 976 (w), 815 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.46 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 7.34 (t, *J*=7.9 Hz 1H, Ar**H**), 7.20 (d, *J*=8.6 Hz, 1H, Ar**H**), 7.04 (d, *J*=7.6 Hz, 1H, Ar**H**), 7.02 (d, *J*=7.6 Hz, 1H, Ar**H**), 6.97 (d, *J*=8.8 Hz, 1H, Ar**H**), 6.96-6.90 (m, 3H, 3 x Ar**H**), 6.88 (d, *J*=1.7 Hz, 1H, Ar**H**), 6.83 (d, *J*=7.5 Hz, 1H, Ar**H**), 6.75 (m, 1H, Ar**H**), 5.38 (s, 1H, OC**H**O), 4.55 (d, *J*=12.2 Hz, 0.5H, OC**H**HC), 4.52 (t, *J*=3.3 Hz, 0.5H, OC**H**OCH_2), 4.46 (d, *J*=12.3 Hz, 0.5H, OC**H**HC), 4.41 (t, *J*=3.4 Hz, 0.5H, OC**H**OCH_2), 4.20 (d, *J*=12.3 Hz, 0.5H, OCH**H**C), 4.11 (d, *J*=12.1 Hz, 0.5H, OCH**H**C), 3.82 (s, 3H, OC**H**$_3$),

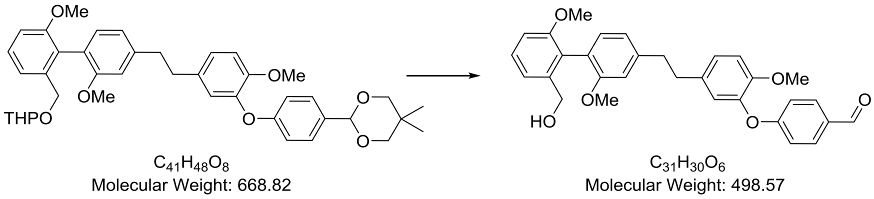
3.78 (d, *J*=11.1 Hz, 2H, 2 x $OCH\mathbf{H}C$),
3.71 (s, 3H, $OC\mathbf{H}_3$),
3.70 (s, 3H, $OC\mathbf{H}_3$),
3.66 (d, *J*=10.6 Hz, 2H, 2 x $CC\mathbf{H}HO$),
3.62-3.30 (m, 2H, $OC\mathbf{H}_2CH_2$),
2.88 (s, 4H, $ArC\mathbf{H}_2C\mathbf{H}_2Ar$),
1.94-1.50 (m, 6H, $C\mathbf{H}_2C\mathbf{H}_2C\mathbf{H}_2CH_2O$),
1.31 (s, 3H, $C\mathbf{H}_3$),
0.81 (s, 3H, $C\mathbf{H}_3$).

δ_C (100 MHz, $CDCl_3$) 158.3 (**C**), 157.2 & 157.1 (**C**), 156.9 & 156.8 (**C**), 149.5 (**C**), 144.9 (**C**), 142.3 (**C**), 138.7 & 138.6 (**C**), 135.01 & 135.0 (**C**), 132.8 (2 x **C**), 131.4 & 131.3 (**C**H), 128.2 (**C**H), 127.5 (2 x **C**H), 124.5 (**C**H), 122.8 & 122.7 (**C**), 120.8 & 120.7 (**C**H), 120.4 & 120.4 (**C**H), 120.3 & 120.2 (**C**H), 117.2 (2 x **C**H), 112.7 (**C**H), 111.3 & 111.2 (**C**H), 110.2 & 110.1 (**C**H), 101.6 (**C**H), 98.2 & 98.1 (**C**H), 77.7 (2 x $\mathbf{C}H_2$), 67.2 & 67.1 ($\mathbf{C}H_2$), 61.7 & 61.4 ($\mathbf{C}H_2$), 56.1 ($\mathbf{C}H_3$), 56.0 ($\mathbf{C}H_3$), 55.6 & 55.5 ($\mathbf{C}H_3$), 38.3 ($\mathbf{C}H_2$), 37.0 ($\mathbf{C}H_2$), 30.5 & 30.4 ($\mathbf{C}H_2$), 30.2 ($\mathbf{C}H_2$), 25.5 ($\mathbf{C}H_2$), 23.1 (**C**H), 21.9 (**C**H), 19.2 & 19.1 ($\mathbf{C}H_2$).

LRMS (**ESI+, m/z**) 691 $[M+Na]^+$ (15%), 686 (100%).

HRMS (ESI+, m/z) calcd for $C_{41}H_{48}NaO_8$ $[M+Na]^+$ requires 691.3241; found: 691.3257.

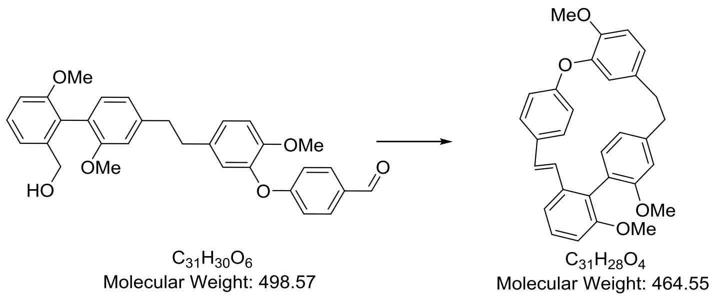
4-(5-(2-(2'-(Hydroxymethyl)-2,6'-dimethoxybiphenyl-4-yl)ethyl)-2-methoxyphenoxy)benzaldehyde (1.229)



To a stirred solution of protecting compound **2.13** (1.97 g, 3.98 mmol) in THF (200 mL) was added 2M HCl (60 mL) and water (5 mL). After 24 h at RT, a solution of saturated $NaHCO_3$ (150 ml) was added to the mixture. The aqueous phase was extracted with Et_2O (3 x 100 mL) and the resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography column (40-60% Et_2O/cyclohexane) to afford the title compound **1.229** as a white foamy solid (1.51 g, 76%).

MP	73-75 °C (Et_2O/cyclohexane)
IR (υ_{max})	3426 (br), 2927 (m), 2836 (m), 2360 (w), 1687 (m), 1597 (s), 1577 (s), 1504 (s), 1462 (m), 1412 (m), 1257 (s), 1226 (s), 1154 (s), 1122 (s), 1033 (m), 1004 (w), 909 (w), 855 (w) 730 (s), 562 (m), 503 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	9.81 (s, 1H, C**H**O), 7.73 (d, *J*=8.6 Hz, 2H, 2 x Ar**H**), 7.29 (t, *J*=7.8 Hz, 1H, Ar**H**), 7.07 (d, *J*=7.6 Hz, 1H, Ar**H**), 6.99 (dd, *J*=8.3, 2 Hz, 1H, Ar**H**), 6.94 (d, *J*=7.6 Hz, 1H, Ar**H**), 6.90 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 6.86 (d, *J*=8.3 Hz, 1H, Ar**H**) 6.92-6.87 (m, 2H, 2 x Ar**H**), 6.75 (dd, *J*=7.7, 1 Hz, 1H, Ar**H**), 6.70 (s, 1H, Ar**H**), 4.23 (d, *J*=12.2 Hz, 1H, C**H**HOH), 4.19 (d, *J*=12.3 Hz, 1H, CH**H**OH), 3.79 (s, 3H, OC**H**$_3$), 3.62 (s, 6H, 2 x OC**H**$_3$), 2.87 (m, 4H, ArC**H**$_2$C**H**$_2$Ar), 1.93 (br. s, 1H, O**H**).
δ_C (100 MHz, $CDCl_3$)	190.7 (**C**H), 163.6 (**C**), 157.2 (**C**), 156.6 (**C**), 149.9 (**C**), 142.6 (**C**), 142.4 (**C**), 141.0 (**C**), 135.1 (**C**), 131.8 (2 x **C**H), 131.6 (**C**H), 130.8 (**C**), 128.7 (**C**), 126.2 (**C**H), 126.1 (**C**), 122.8 (**C**H), 122.6 (**C**H), 120.9 (**C**H), 120.7 (**C**H), 116.1 (2 x **C**H), 113.0 (**C**H), 111.9 (**C**H), 110.5 (**C**H), 63.7 (**C**H$_2$), 56.0 (**C**H$_3$), 55.9 (**C**H$_3$), 55.8 (**C**H$_3$), 38.1 (**C**H$_2$), 36.7 (**C**H$_2$).
LRMS (ESI+, m/z)	521 [M+Na]$^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{31}H_{30}NaO_6$ [M+Na]$^+$ requires 521.1935; found: 521.1943.

Dehydroriccardin D trimethyl ether (2.1)



To a stirred solution of benzyl alcohol **1.229** (70 mg, 0.14 mmol) in toluene (7 mL) at 0 °C was added PBr_3 (110 mg, 0.42 mmol) dropwise over 3 min. After 15 h at RT, a solution of saturated $NaHCO_3$ (30 mL) was added and the reaction mixture was extracted with Et_2O (3 x 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The residue was then dissolved in toluene (11 mL) and PPh_3 (60 mg, 0.21 mmol) was added to the mixture. After 16 h at reflux, the reaction mixture was concentrated *in vacuo.* The residue was dissolved in DCM (14 mL) and added dropwise over 30 min to a stirred solution of KO^tBu (30 mg, 0.28 mmol) in DCM (3 mL) at RT. After 18 h at reflux, the reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (10-20% Et_2O/PE) to afford the title compound **2.1** as a white solid (33 mg, 50%).

MP	78-79 °C (Et_2O/PE)
IR (υ_{max})	2925 (s), 2854 (m), 2360 (s), 2339 (s), 1570 (m), 1508 (s), 1465 (m), 1412 (w), 1261 (s), 1228 (s), 1160 (m), 1126.79 (m), 1070 (w), 964 (w), 909 (w), 874 (w), 810 (m) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.36 (t, *J*=7.9 Hz, 1H, Ar**H**), 7.19-7.12 (m, 2H, 2 x Ar**H**), 7.10 (d, *J*=7.6 Hz, 1H, Ar**H**), 6.99-6.91 (m, 3H, 3 x Ar**H**), 6.87(d, *J*=7.5 Hz, 1H, Ar**H**), 6.85 (d, *J*=8.4 Hz, 1H, Ar**H**), 6.79 (dd, *J*=8.2, 1.5 Hz, 1H, Ar**H**), 6.68 (d, *J*=7.5 Hz, 1H, Ar**H**), 6.61 (d, *J*=16.4 Hz, 1H, =C**H**), 5.58 (d, *J*=2.1 Hz, 1H, Ar**H**), 5.88 (d, *J*=16.1 Hz, 1H, =C**H**), 5.77 (d, *J*=1.2 Hz, 1H, Ar**H**), 3.97 (s, 3H, OC**H**$_3$), 3.78 (s, 3H, OC**H**$_3$),

3.66 (s, 3H, OC**H**$_3$),

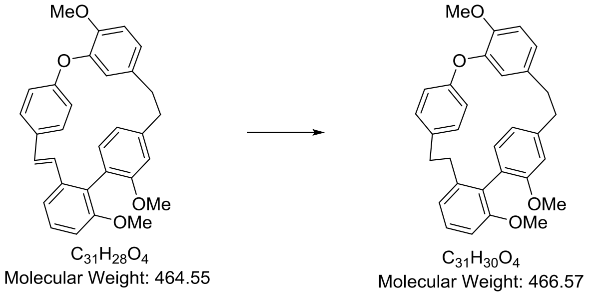
3.09-2.72 (m, 4H, ArC**H**$_2$C**H**$_2$Ar).

δ$_C$ (100 MHz, CDCl$_3$) 157.1 (**C**), 156.8 (**C**), 155.3 (**C**), 150.4 (**C**), 147.4 (**C**), 142.5 (**C**), 139.6 (**C**), 138.9 (**C**), 138.6 (**C**H), 136.0 (**C**), 131.8 (**C**H), 130.1 (**C**H), 128.5 (**C**H), 127.4 (**C**), 127.0 (**C**H), 126.9 (**C**H), 123.6 (**C**), 122.6 (**C**H), 122.5 (**C**H), 122.4 (**C**H), 119.8 (**C**H), 117.3 (**C**H), 115.8 (**C**H), 111.8 (**C**H), 110.8 (**C**H), 110.1 (**C**H), 56.2 (**C**H$_3$), 55.9 (**C**H$_3$), 55.6 (**C**H$_3$), 36.3 (**C**H$_2$), 33.5 (**C**H$_2$).

LRMS (ESI+, m/z) 951 [2M+Na]$^+$ (70%), 487 [M+Na]$^+$ (35%), 465 [M+H]$^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{31}H_{28}NaO_4$ [M+Na]$^+$ requires 487.1880; found: 487.1866.

Riccardin D trimethyl ether (2.15)



To a stirred solution of alkene **2.1** (160 mg, 0.34 mmol) in MeOH (10 mL) and DCM (10 mL) was added 10% Pd/C (36 mg, 0.34 mmol). The flask was evacuated/purged with argon three times then evacuated/purged with hydrogen twice. After 2 h stirred vigorously under an atmosphere of H_2 at RT, the reaction filtered thought Celite© and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (20-25% Et_2O/cyclohexane) to afford the title compound **2.15** as white solid (150 mg, 94%).

MP 76-78 °C (Et_2O/cyclohexane)

IR (υ_{max}) 2955 (m), 2925 (s), 2854 (m), 2358 (w), 2160 (w), 2028 (w), 2008 (w), 1735 (m), 1508 (m), 1462 (m), 1258 (s), 1230 (w), 1164 (w), 1128 (w), 1077 (w), 1039 (w) cm^{-1}.

δ$_H$ (400 MHz, CDCl$_3$) 7.36 (t, *J*=8.0 Hz, 1H, Ar**H**),

7.08 (d, J=7.8 Hz, 1H, Ar**H**),

6.91 (d, *J*=8.1 Hz 2H, 2 x Ar**H**),

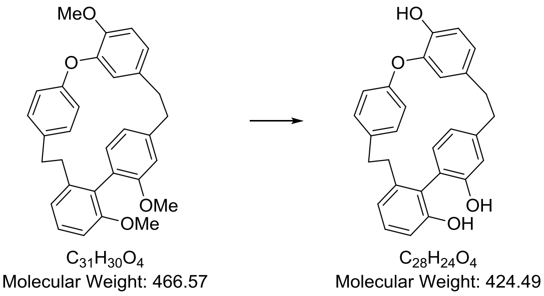
6.87 (d, *J*=7.6 Hz, 2H, 2 x Ar**H**),

6.84 (d, *J*=8.4 Hz, 1H, Ar**H**),

6.80 (d, *J*=8.2 Hz, 2H,2 x Ar**H**),

	6.76 (d, *J*=8.1 Hz 1H, Ar**H**),
	6.42 (d, *J*=8.6 Hz, 1H, Ar**H**),
	6.40 (s, 1H, Ar**H**),
	5.49 (d, *J*=1.7 Hz, 1H, Ar**H**),
	3.97 (s, 3H, OC**H**$_3$),
	3.69 (s, 3H, OC**H**$_3$),
	3.67 (s, 3H, OC**H**$_3$),
	3.00-2.61 (m, 8H, 2 x ArC**H**$_2$C**H**$_2$Ar).
δ_C (100 MHz, CDCl$_3$)	157.3 (**C**), 156.7 (**C**), 152.9 (**C**), 149.1(**C**), 146.9(**C**), 143.7 (**C**), 141.5 (**C**), 140.2 (**C**), 134.3 (**C**), 132.6 (**C**H), 129.4 (**C**H), 129.2 (**C**H), 128.4 (**C**H), 127.1 (**C**), 122.6 (**C**H) 122.4 (**C**H), 122.3 (**C**H), 122.2 (**C**H), 121.4 (**C**H), 120.8 (**C**H), 116.6 (**C**H), 111.9 (**C**H), 111.8 (**C**H), 108.2 (**C**H), 56.1 (**C**H$_3$), 55.8 (**C**H$_3$), 55.3 (**C**H$_3$), 38.1 (**C**H$_2$), 37.7 (**C**H$_2$), 36.9 (**C**H$_2$), 34.8 (**C**H$_2$).
LRMS (ESI+, m/z)	955 $[2M+H]^+$ (100%), 489 (13%), 467 (51%).
HRMS (ESI+, m/z)	calcd for $C_{31}H_{30}NaO_4$ $[M+Na]^+$ requires 489.2036; found: 489.2050.

Riccardin D (1.1)



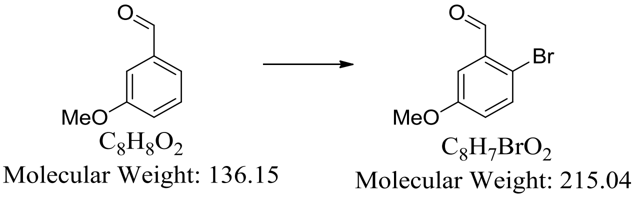
To a stirred solution of riccardin D trimethyl ether **2.15** (120 mg, 0.26 mmol) in DCM (21 mL) at 0°C was added boron tribromide (3 mL, 1 M solution in DCM, 2.6 mmol) dropwise over 5 min. After 3 h at 0 °C, ice water (20 mL) was added. The aqueous phase was separated and extracted with DCM (5 x 30 mL), and then the resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (40-50% Et_2O/hexane) afforded the title compound **1.1** as a white solid (68 mg, 61%).

These data are accordance with those reported in the literature.[46]

MP	172-174 °C (Et_2O/hexane) [Lit. 173 °C, no solvent given][46]
IR (υ_{max})	3484 (br. s), 2927 (w), 2856 (w), 1604 (w), 1563 (w), 1504 (s), 1446 (m), 1267 (m), 1223 (s), 1186 (m), 1161 (m), 1110 (w),

	1017 (w), 978 (w), 907 (s), 850 (m), 794 (w) 729 (s), 650 (w) 527 (w) 449 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.35 (t, *J*=8.0 Hz, 1H, Ar**H**), 7.08 (dd, *J*=7.7, 1.0 Hz, 1H, Ar**H**), 6.94 (d, *J*=8.1 Hz, 2H, 2 x Ar**H**), 6.91 (d, *J*=1.0 Hz, 1H, Ar**H**), 6.79-6.88 (m, 3H, 3 x Ar**H**), 6.76 (dd, *J*=8.1, 1.9 Hz, 1H, Ar**H**), 6.69-6.69 (m, 1H, Ar**H**), 6.53 (d, *J*=1.5 Hz, 1H, Ar**H**), 6.34 (dd, *J*=7.8, 1.5 Hz, 1H, Ar**H**), 5.63 (s, 1H, O**H**), 5.44 (d, *J*=2.0 Hz, 1H, Ar**H**), 4.90-4.95 (m, 1H, O**H**), 4.85 (s, 1H, O**H**), 2.56-3.05 (m, 8H, 2x $ArC\mathbf{H}_2C\mathbf{H}_2Ar$).
δ_C (100 MHz, $CDCl_3$)	153.6 (**C**), 152.9 (**C**), 152.7 (**C**), 146.5 (**C**), 143.9 (**C**), 143.8 (**C**), 143.4 (**C**), 140.3 (**C**), 133.0 (**C**), 131.5 (**C**H), 130.2 (**C**H), 129.4 (**C**H), 129.2 (**C**H), 122.8 (**C**H), 122.6 (**C**H), 122.6 (**C**H), 122.2 (**C**H), 122.2 (**C**H), 121.5 (**C**), 117.2 (**C**H), 117.1 (**C**), 116.0 (**C**H), 115.1 (**C**H), 113.4 (**C**H), 37.8 (**C**H_2), 37.7 (**C**H_2), 36.6 (**C**H_2), 35.0 (**C**H_2).
LRMS (ESI-, m/z)	423 $[M-1]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{28}H_{25}O_4$ $[M+H]^+$ requires 425.1747; found: 425.1759.

2-Bromo-5-methoxybenzaldehyde (3.4)



To a stirred solution of *m*-anisaldehyde **3.1** (15.0 g, 110.17 mmol) in glacial acetic acid (370 mL) was added bromine (22.89 g, 143.22 mmol) dropwise over 20 min. After 13 h water (400 mL) was added and the reaction left for 13 h without stirring to allow precipitation of the product. The product was collected by filtration then dried in a desiccator for one day to yield the title compound **3.4** as a cream solid (21.94 g, 92%).

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

MP 63-65 °C (Water) [Lit. 60–62 °C (Water)][50]

IR (υ_{max}) 3006 (w), 2943 (w), 2874 (w), 2841 (w), 1672 (s), 1643 (w), 1598 (m), 1569 (s), 1469 (s), 1439 (m), 1417 (m), 1382 (m), 1300 (m), 1278 (s), 1241 (s), 1197 (m), 1169 (m), 1134 (w), 1060 (w), 1013 (m), 930 (s), 865 (m), 819 (s), 754 (m), 647 (m), 598 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$)
10.31 (s, 1H, C**H**O),
7.52 (d, *J*=8.8 Hz, 1H, Ar**H**),
7.42 (d, *J*=3.2 Hz, 1H, Ar**H**),
7.04 (dd, *J*=8.8, 3.2 Hz, 1H, Ar**H**),
3.84 (s, 3H, OC**H**$_3$).

δ_C (100 MHz, $CDCl_3$) 191.7 (**C**H) 159.3 (**C**) 134.5 (**C**H) 134.0 (**C**) 123.1 (**C**H) 117.9 (**C**Br) 112.7 (**C**H) 55.7 (**C**H$_3$)

LRMS (ESI+, m/z) 215 [M+H (^{79}Br)]$^+$ (100%), 217 [M+H (^{81}Br)]$^+$ (70%).

2-(2-Bromo-5-methoxyphenyl)-1,3-dioxolane (3.5)

To a stirred solution of 2-bromo-5-methoxybenzaldehyde **3.4** (21.49 g, 99.83 mmol) in toluene (300 mL) was added ethylene glycol (27.84 ml, 499.18 mmol) and PPTS (1.02 g, 3.99 mmol). The reaction mixture was heated at reflux under a Dean and Stark apparatus for 3 h then cooled to RT, diluted with diethyl ether (50 mL) and washed with saturated aqueous $NaHCO_3$ (50 mL) and water (100 mL). The aqueous phase was extracted with Et_2O (3 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the title compound **3.5** as a colourless oil (25.62 g, 99%).

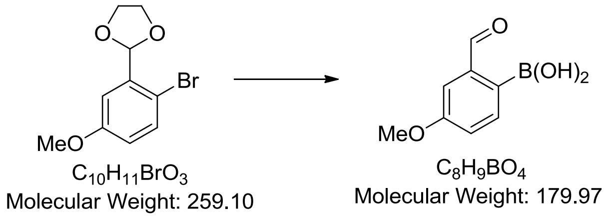
These data are accordance with those reported in the literature.[50]

IR (υ_{max}) 2958 (w), 2888 (w), 1595 (w), 1574 (m), 1471 (s), 1419 (m), 1391 (s), 1291 (s), 1270 (s), 1232 (s), 1194 (m), 1167 (s), 1139 (m), 1124 (m), 1082 (s), 1051 (s), 1015 (s), 945 (s), 878 (m), 865 (m), 809 (m), 773 (w), 732 (m), 696 (w), 688 (w), 605 (m), 511 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.42 (d, *J*=8.8 Hz, 1H, Ar**H**),

	7.15 (d, *J*=3.2 Hz, 1H, Ar**H**), 6.76 (dd, *J*=8.7, 3.1 Hz, 1H, Ar**H**), 6.02 (s, 1H, ArC**H**), 3.96-4.18 (m, 4H, 2 x C**H**$_2$), 3.76 (s, 3H, OC**H**$_3$).
δ_C (100 MHz, CDCl$_3$)	158.7 (**C**), 137.2 (**C**), 133.3 (**C**H), 116.3 (**C**H), 112.9 (**C**H), 112.8 (**C**), 102.2 (**C**H), 65.2 (2 x **C**H$_2$), 55.2 (**C**H$_3$).
LRMS (ESI+, m/z)	259 [M+H (^{79}Br)]$^+$ (100%), 261 [M+H (^{81}Br)]$^+$ (88%).

(2-Formyl-4-methoxyphenyl)boronic acid (1.152)



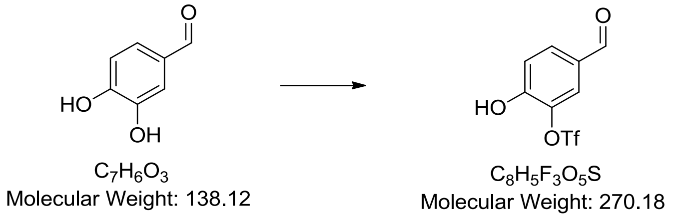
To a stirred solution of dioxolane **3.5** (20.26 g, 78.19 mmol) in THF (200 mL) at -78 °C was added *n*-butyllithium (37.07 mL, 86.00 mmol, 2.32 M solution in hexanes) dropwise over 10 min. After 1 h at –78 °C, tri-*n*-butyl borate (27.43 ml, 101.64 mmol) was added dropwise over 10 min. The reaction mixture was warmed to RT over 3 h, then HCl (40 mL, 2 M) was added. After 1 h, the biphasic mixture was extracted with NaOH (3 X 50 mL, 3 M) and this extract acidified with HCl (approx. 150 mL, 2 M). A white precipitate formed which was collected by filtration to afford the title compound **1.152** as a white crystalline solid (11.97 g, 85%).

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

MP	186-189 °C (water) [Lit. 190–192 °C (Water)][50]
IR (υ_{max})	3350 (w), 3116 (w), 2977 (w), 1671 (m), 1599 (s), 1559 (s), 1500 (w), 1482 (s), 1426 (m), 1407 (w), 1354 (s), 1315 (w), 1268 (s), 1252 (s), 1196 (w), 1160 (w), 1120 (w), 1105 (m), 1085 (s), 1050 (m), 1026 (m), 981 (w), 924 (m), 880 (w), 841 (w), 760 (m), 669 (m), 633 (m), 576 (w), 510 (w) cm^{-1}.
δ_H (400 MHz, CDCl$_3$)	9.88 (s, 1H, C**H**O) 8.24 (d, *J*=8.4 Hz, 1H, Ar**H**) 7.44 (d, *J*=2.1 Hz, 1H, Ar**H**) 7.20 (dd, *J*=8.4, 2.1 Hz, 1H, Ar**H**) 6.97 (s, 2H, ArB(O**H**)$_2$) 3.94 (s, 3H, OC**H**$_3$)

LRMS (EI+, m/z) 136 $[M-B(OH)_2]^+$ (100%), 135 (93%), 91 (15%), 77 (57%).

4-Formyl-2-hydroxyphenyl trifluoromethanesulfonate (3.6)



To a stirred solution of **3.2** (10.0 g, 72.4 mmol) and pyridine (7.03 mL, 86.88 mmol) in DCM (240 mL) at 0 °C was added Tf_2O (12.18 mL, 72.4 mmol) dropwise over 15 minutes. The reaction mixture was warmed to RT and after 13 h a saturated solution of NH_4Cl (100 mL) and water (100 mL) were added to the mixture. The aqueous phase was extracted with DCM (3 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (50% Et_2O/cyclohexane) to afford the title compound **3.6** as a colourless oil (14.65 g, 74%).

IR (υ_{max}) 3528 (w), 2979 (w), 1605 (w), 1499 (w), 1417 (s), 1205 (s), 1134 (s), 1096 (m), 1069 (w), 907 (s), 864 (s), 816 (w), 774 (w), 731 (m), 651 (w), 614 (s), 509 (w) cm^{-1}.

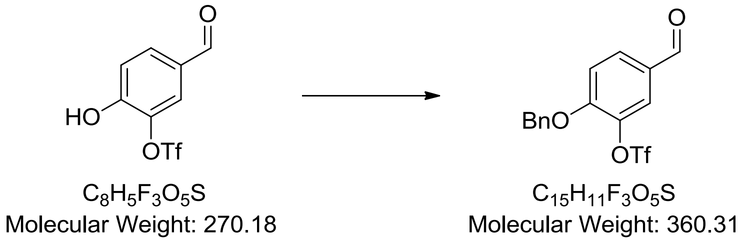
δ_H (400 MHz, $CDCl_3$) 10.03 (s, 1H, C**H**O),
8.04 (dd, *J*=8.4, 2.0 Hz, 1H, Ar**H**),
8.01 (d, *J*=1.8 Hz, 1H, Ar**H**),
7.72 (d, *J*=8.4 Hz, 1H Ar**H**).

δ_C (100 MHz, $CDCl_3$) 188.3 (**C**HO), 144.2 (**C**), 141.2 (**C**), 136.9 (**C**), 130.7 (**C**H), 124.5 (**C**H), 123.7 (**C**H), 118.5 (q, *J*=320.6 Hz, **C**F_3).

δ_F (376 MHz, $CDCl_3$) -73.83 (C**F**$_3$)

LRMS (EI+, m/z) 270 $[M]^+$ (4%), 149 (87%), 69 (100%).

2-(Benzyloxy)-5-formylphenyl trifluoromethanesulfonate (3.7)



To a solution of **3.6** (22.5 g, 83.28 mmol) in MeCN (200 mL) were added potassium carbonate (17.26 g, 124.92 mmol) and benzyl bromide (11.89 mL, 99.94 mmol). After 13 h, water (100 mL) was added and the product was extracted by Et_2O (3 x 50 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (20-25% Et_2O/PE) to afford the title compound **3.7** as an orange oil (21.71 g, 72%).

IR (υ_{max}) 1697 (m), 1607 (m), 1577 (w), 1508 (m), 1455 (w), 1423 (s), 1318 (s), 1278 (m), 1247 (m), 1209 (s), 1137 (s), 1090 (m), 974 (w), 955 (w), 905 (s), 832 (m), 769 (w), 725 (s), 695 (m), 649 (m), 597 (w), 505 (w) cm^{-1}.

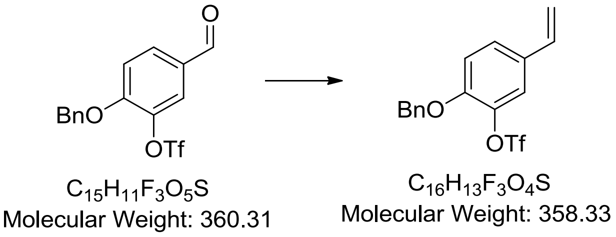
δ_H (400 MHz, $CDCl_3$) 9.89 (s, 1H, C**H**O),
7.85 (dd, *J*=8.5, 1.9 Hz, 1H, Ar**H**),
7.79 (d, *J*=1.9 Hz, 1H, Ar**H**),
7.49-7.35 (m, 5H, 5 x Ar**H**),
7.22 (d, *J*=8.5 Hz, 1H, Ar**H**),
5.29 (s, 2H, ArC**H**$_2$O) .

δ_C (100 MHz, $CDCl_3$) 189.0 (**C**), 155.4 (**C**), 139.3 (**C**), 134.5 (**C**), 131.8 (**C**H), 130.1 (**C**), 128.8 (2 x **C**H), 128.6 (**C**), 127.3 (2 x **C**H), 123.0 (**C**H), 114.2 (**C**H), 118.6 (q, *J*=320.6 Hz,**C**F$_3$), 71.6 (**C**H$_2$).

LRMS (ESI+, m/z) 361 $[M+H]^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{15}H_{11}F_3NaO_5S$ $[M+Na]^+$ requires 383.0171; found: 383.0180.

2-(Benzyloxy)-5-vinylphenyl trifluoromethanesulfonate (3.8)



To a solution of aldehyde **3.7** (18.5 g, 51.43 mmol) in THF (470 mL) was added sodium hydride (6.17 g, 154.28 mmol). Then methyltriphenylphosphonium bromide (27.6 g, 77.15 mmol) at 0 °C was slowly added. The reaction mixture was warmed to RT. After 18 h, the residue was purified by flash column chromatography (10% Et_2O/PE) to afford the title compound **3.8** as a yellow oil (15.83 g, 85%).

IR (υ_{max}) 2953 (w), 1615 (w), 1509 (s), 1455 (w), 1419 (s), 1295 (w), 1270 (m), 1247 (m), 1201 (s), 1137 (s), 1092 (s), 987 (w), 942 (s), 909 (w), 816 (m), 785 (m), 763 (m), 734 (s), 711 (w), 694 (m), 598 (s), 503 (m) cm^{-1}.

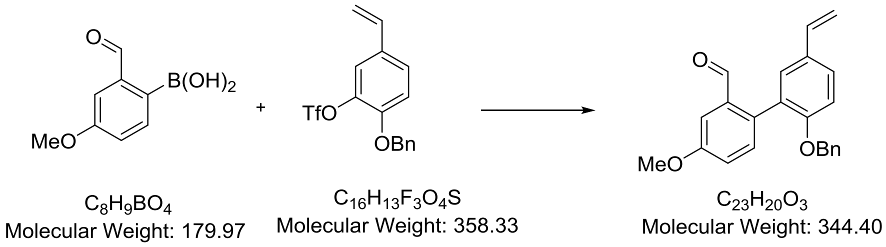
δ$_H$ (400 MHz, CDCl$_3$) 7.50 (d, *J*=7.2 Hz, 2H, 2 x Ar**H**),
7.44 (t, *J*=7.5 Hz, 2H, 2 x Ar**H**),
7.39 (d, *J*=7.1 Hz, 1H, Ar**H**),
7.35-7.30 (m, 2H, 2 x Ar**H**),
7.04 (d, *J*=8.8 Hz, 1H, Ar**H**),
6.65 (dd, *J*=17.5, 10.9 Hz, 1H, ArC**H**=),
5.69 (d, *J*=17.6 Hz, 1H, =C**H**H),
5.29 (d, *J*=10.9 Hz, 1H, =CH**H**),
5.20 (s, 2H, ArOC**H**$_2$).

δ$_C$ (100 MHz, CDCl$_3$) 149.9 (**C**), 139.0 (**C**), 135.6 (**C**), 134.6 (=**C**H), 131.5 (**C**), 128.6 (2 x **C**H), 128.2 (**C**H), 127.2 (2 x **C**H), 126.9 (**C**H), 119.8 (**C**H), 114.4 (**C**H), 114.0 (=**C**H$_2$), 118.7 (q, *J*=320.6 Hz, **C**F$_3$), 71.0 (**C**H$_2$).

LRMS (EI+, m/z) 358 M$^+$ (10%), 91 (100%).

HRMS (ESI+, m/z) calcd for $C_{16}H_{13}F_3NaO_4S$ [M+Na]$^+$ requires 381.0379; found: 381.0389.

2'-(Benzyloxy)-4-methoxy-5'-vinyl-[1,1'-biphenyl]-2-carbaldehyde (1.236)



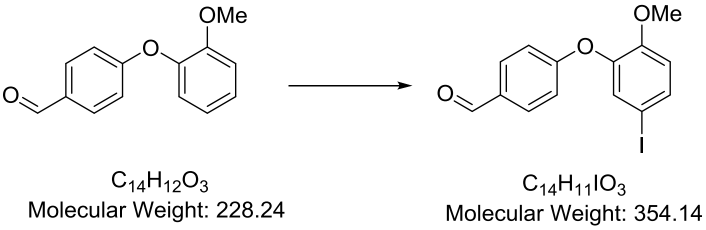
To a stirred solution of triflate **3.8** (2.49 g, 6.95 mmol) and boronic acid **1.152** (1.5 g, 8.38 mmol) in a mixed solvent system of PhMe (150 mL), EtOH (75 mL), and water (75 mL) was added Cs_2CO_3 (4.53 g, 13.9 mmol). The resulting mixture was degassed under argon for 20 min then $Pd(PPh_3)_4$ (0.52 g, 0.45 mmol) was added. After 14 h at reflux, water (100 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (10-15% Et_2O/cyclohexane) to afford the title compound **1.236** as a yellow oil (2.11 g, 88%).

IR (υ_{max}) 2927 (w), 2854 (w), 1698 (s), 1603 (s), 1489 (s), 1455 (m), 1419 (m), 1393 (m), 1315 (m), 1269 (s), 1225 (s), 1188 (w), 1161 (m), 1148 (m), 1043 (m), 1016 (m), 937 (w), 901 (w), 819 (w), 761 (w), 735 (w), 696 (w), 668 (w) cm^{-1}.

δ$_H$ (400 MHz, CDCl$_3$) 9.81 (s, 1H, C**H**O),
7.48 (d, *J*=2.8 Hz, 1H, Ar**H**),

	7.36 (dd, *J*=8.5, 2.3 Hz, 1H, Ar**H**),
	7.31-7.21 (m, 5H, 5 x Ar**H**),
	7.18 (dd, *J*=8.5, 2.8 Hz, 1H, Ar**H**),
	7.16-7.10 (m, 2H, 2 x Ar**H**),
	6.94 (d, *J*=8.4 Hz, 1H, Ar**H**),
	6.66 (dd, *J*=17.6, 10.9 Hz, 1H, =C**H**),
	5.62 (dd, *J*=17.6, 0.6 Hz, 1H,=C**H**H),
	5.16 (dd, *J*=10.9, 0.6 Hz, 1H, =CH**H**),
	5.00 (br. s, 2H, OC$\mathbf{H_2}$),
	3.87 (s, 3H, OC$\mathbf{H_3}$) .
δ_C (100 MHz, $CDCl_3$)	192.4 (**C**HO), 159.2 (**C**), 155.6 (**C**), 136.5 (**C**), 135.7 (**C**H), 134.9 (**C**), 134.7 (**C**), 132.5 (**C**H), 130.9 (**C**), 129.6 (**C**H), 128.4 (2 x **C**H), 127.8 (**C**H), 127.4 (**C**H), 127.4 (**C**), 126.9 (2 x **C**H), 121.2 (**C**H), 112.8 (**C**H), 112.7 (**C**H_2), 109.4 (**C**H), 70.5 (**C**H_2), 55.6 (**C**H_3).
LRMS (ESI+, m/z)	367 $[M+Na]^+$ (100%).

4-(5-Iodo-2-methoxyphenoxy)benzaldehyde (1.148)



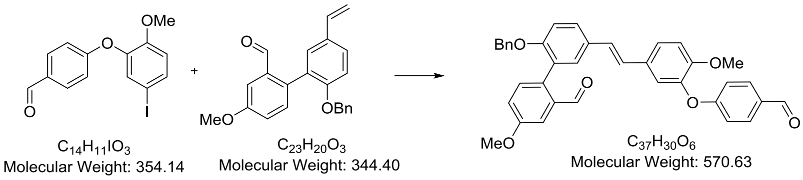
To a stirred solution of 4-(methoxyphenoxy)benzaldehyde **1.147** (100 mg, 0.44 mmol) in MeCN (3 mL) were added trifluoroacetic acid (0.009 ml, 0.13mmol) and *N*-Iodosuccinimide (0.11 g, 0.48 mmol). The reaction mixture was heated at 50 °C for 13 h then cooled to RT. Ice water (2 mL) was added and the product was extracted by Et_2O (3 x 5 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (10-20% Et_2O/PE) to afford the title compound **1.148** as an orange gum which crystallised on standing (0.14 g, 90%).

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

MP	48-49 °C (Et_2O/PE) [lit. 48 °C (DCM)][50]
IR (υ_{max})	2838 (w), 1694 (m), 1600 (s), 1582 (m), 1571 (m), 1489 (s), 1462 (w), 1439 (m), 1393 (w), 1292 (m), 1263 (s), 1224 (s), 1177 (w), 1154 (s), 1132 (m), 1024 (m), 905 (s), 891 (s), 850 (w), 831 (m), 804 (w), 723 (s), 648 (w), 502 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$)	9.81 (s, 1H, C**H**O), 7.74 (d, *J*=8.8 Hz, 2H, 2 x Ar**H**), 7.43 (dd, *J*=8.7, 2.2 Hz, 1H, Ar**H**), 7.31 (d, *J*=2.2 Hz, 1H, Ar**H**), 6.91 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 6.73 (d, *J*=8.7 Hz, 1H Ar**H**), 3.67 (s, 3H, OC**H**$_3$).
δ_C (100 MHz, $CDCl_3$)	190.2 (**C**) 162.4 (**C**) 151.4 (**C**) 143.3 (**C**) 134.8 (**C**H) 131.5 (2 x **C**H) 130.8 (**C**) 130.7 (**C**H) 115.9 (2 x **C**H) 114.7 (**C**H) 81.6 (**C**-I) 55.6 (**C**H$_3$).
LRMS (ESI+, m/z)	355 $[M+H]^+$ (100%).

(*E*)-2'-(Benzyloxy)-5'-(3-(4-formylphenoxy)-4-methoxystyryl)-4-methoxy-[1,1'-biphenyl]-2-carbaldehyde (3.9)

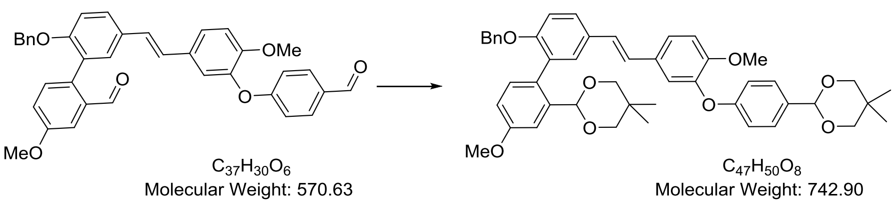


To a stirred solution of biaryl **1.236** (5.09 g, 14.78 mmol) and ether **1.148** (4.36 g, 12.32 mmol) in *N*,*N*-dimethylacetamide (40 mL) was added potassium phosphate (3.66 g, 17.24 mmol). The reaction mixture was degassed with sonication for 20 min under argon then $Pd(OAc)_2$ (138 mg, 0.61 mmol) was added. The reaction mixture was heated at reflux for 13 h then cooled to RT and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (50-60% Et_2O/PE) to afford the title compound **3.9** as a white solid (5.13 g, 72%).

MP	102-103°C (Et_2O/PE)
IR (υ_{max})	2933 (w), 2838 (w), 2159 (w), 2015 (w), 1689 (s), 1598 (m), 1581 (m), 1570 (w), 1506 (s), 1456 (w), 1441 (w), 1424 (w), 1271 (s), 1227 (s), 1154 (m), 1123 (m), 1046 (w), 1023 (m), 961 (w), 939 (w), 858 (m), 756 (m), 696 (w), 667 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	9.93 (s, 1H, C**H**O), 9.88 (s, 1H, C**H**O), 7.86 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 7.54 (d, *J*=2.8 Hz, 1H, Ar**H**), 7.46 (dd, *J*=8.5, 2.1 Hz, 1H, Ar**H**), 7.43 (d, *J*=2.1 Hz, 1H, Ar**H**), 7.36 (d, *J*=8.4 Hz, 1H, Ar**H**),

	7.35 (dd, *J*=8.5, 2.1 Hz, 1H, Ar**H**), 7.26-7.32 (m, 4H, 4 x Ar**H**) , 7.24 (d, *J*=2.8 Hz, 1H, Ar**H**), 7.18-7.23 (m, 2H, 2 x Ar**H**), 7.05 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 7.05-7.00 (m, 2H, 2 x Ar**H**), 6.96 (s, 2H, ArC**H**=C**H**), 5.06 (d, *J*=3.1 Hz, 2H, OC$\mathbf{H}_2$), 3.92 (s, 3H, OC$\mathbf{H}_3$), 3.82 (s, 3H, OC$\mathbf{H}_3$).
δ_C (100 MHz, $CDCl_3$)	192.3 (**C**HO), 190.7 (**C**HO), 163.7 (**C**), 159.2 (**C**), 155.5 (**C**), 151.0 (**C**), 143.1 (**C**), 136.4 (**C**), 134.9 (**C**), 134.5 (**C**), 132.4 (**C**H), 131.8 (2 x **C**H), 131.3 (**C**), 130.9 (**C**), 130.5 (**C**), 129.6 (**C**H), 128.4 (2 x **C**H), 127.8 (**C**H), 127.6 (**C**H), 127.5 (**C**), 126.9 (2 x **C**H), 126.8 (**C**H), 126.1 (**C**H), 124.6 (**C**H), 121.1 (**C**H), 119.8 (**C**H), 116.2 (2 x **C**H), 113.1 (**C**H), 112.9 (**C**H), 109.5 (**C**H), 70.5 (**C**H_2), 55.9 (**C**H_3), 55.5 (**C**H_3).
LRMS (ESI+, m/z)	593 $[M+Na]^+$(100%).
HRMS (ESI+, m/z)	calcd for $C_{37}H_{30}NaO_6$ $[M+Na]^+$ requires 593.1935; found: 593.1941.

(*E*)-2-(4-(5-(2-(6-(Benzyloxy)-2'-(5,5-dimethyl-1,3-dioxan-2-yl)-4'-methoxy-[1,1'-biphenyl]-3-yl)vinyl)-2-methoxyphenoxy)phenyl)-5,5-dimethyl-1,3-dioxane (3.10)



To a stirred solution of **3.9** (1.48 g, 2.59 mmol) in toluene (75 mL) was added neopentylglycol (1.35 g, 17.96 mmol) and pyridinium *p*-toluenesulfonate (169 mg, 0.67 mmol). After 13 h at reflux under a Dean Stark apparatus, was cooled to RT. Water (50 mL) and sat. $NaHCO_3$ (50 mL) were added. The product was extracted by Et_2O (3 x 50 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (45% Et_2O/PE) to afford the title compound **3.10** as a white solid (1.89 g, 98 %).

MP	94-96 °C (Et_2O/PE)
IR (υ_{max})	2954 (w), 2840 (w), 1608 (s), 1507 (s), 1463 (m), 1426 (w), 1390 (m), 1270 (s), 1224 (s), 1166 (m), 1092 (w), 1013 (w), 986 (m), 963

(w), 906 (s), 813 (m), 725 (w), 696 (m), 667 (w), 647 (m), 496 (w) cm^{-1}.

δ_H (400 MHz, CDCl$_3$)

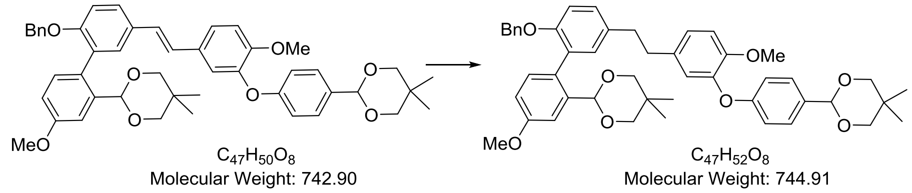
7.47 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**),
7.47 (d, *J*=2.3 Hz, 1H, Ar**H**),
7.44 (d, *J*=2.7 Hz, 1H, Ar**H**),
7.33 (dd, *J*=8.6, 2.3 Hz, 1H, Ar**H**),
7.29 (d, *J*=1.7 Hz, 1H, Ar**H**),
7.23-7.26 (m, 5H, 3 x Ar**H**+ ArC**H**C**H**),
7.19 (dd, *J*=8.4, 2.1 Hz, 1H, Ar**H**),
7.14 (d, *J*=2.1 Hz, 1 H, Ar**H**),
6.98 (d, *J*=8.4 Hz, 2H, 2 x Ar**H**),
6.95 (d, *J*=8.4 Hz, 1 H, Ar**H**),
6.96 (d, *J*=2.2 Hz, 1 H, Ar**H**),
6.93 (d, *J*=2.3 Hz, 1H, Ar**H**),
6.87 (d, *J*=1.0 Hz, 2H, Ar**H**),
5.38 (s, 1H, CC**H**O),
5.20 (s, 1H, CC**H**O),
5.05 (s, 2H, ArOC**H**$_2$),
3.90 (s, 3H, OC**H**$_3$),
3.81 (s, 3H, OC**H**$_3$),
3.77 (d, *J*=11.3 Hz, 2H, 2 x CC**H**HO),
3.65 (d, *J*=11.4 Hz, 4H, 4 x CCH**H**O),
3.41 (d, *J*=11.1 Hz, 1H, CC**H**HO),
3.37 (d, *J*=11.1 Hz, 1H, CC**H**HO),
1.33 (s, 3H, C**H**$_3$),
1.31 (s, 3H, C**H**$_3$),
0.80 (s, 3H, C**H**$_3$),
0.68 (s, 3H, C**H**$_3$).

δ_C (100 MHz, CDCl$_3$)

159.1 (**C**), 158.1 (**C**), 155.3 (**C**), 150.7 (**C**), 145.0 (**C**), 137.7 (**C**), 137.2 (**C**), 132.9 (**C**), 131.7 (**C**), 131.2 (**C**), 129.8 (**C**), 129.7 (**C**H), 129.5 (**C**), 129.3 (**C**H), 128.3 (2 x **C**H), 127.5 (2 x **C**H), 127.4 (**C**H), 126.9 (**C**H), 126.7 (**C**H), 126.6 (2 x **C**H), 125.8 (**C**H), 123.1 (**C**H), 118.1 (**C**H), 117.0 (2 x **C**H), 114.8 (**C**H), 113.2 (**C**H), 112.7 (**C**H), 110.6 (**C**H), 101.4 (**C**H), 99.9 (**C**H), 77.6 (2 x **C**H$_2$), 77.5 (**C**H$_2$), 77.2 (**C**H$_2$), 70.2 (**C**H$_2$), 56.0 (**C**H$_3$), 55.3 (**C**H$_3$), 30.1 (**C**), 30.1 (**C**), 23.1 (**C**H$_3$), 23.0 (**C**H$_3$), 21.8 (**C**H$_3$), 21.7 (**C**H$_3$).

LRMS (ESI+, m/z)	765 $[M+Na]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{47}H_{50}NaO_8$ $[M+Na]^+$ requires 765.3398; found: 765.3381.

2-(4-(5-(2-(6-(Benzyloxy)-2'-(5,5-dimethyl-1,3-dioxan-2-yl)-4'-methoxy-[1,1'-biphenyl]-3-yl)ethyl)-2-methoxyphenoxy)phenyl)-5,5-dimethyl-1,3-dioxane (3.11)



To a stirred solution of **3.10** (47 mg, 0.063 mmol) in 1:1 v/v THF and water (6 mL each) was added *P*-toluenesulfonylhydrazide (110 mg, 0.63 mmol) and NaOAc (50 mg, 0.63 mmol). The reaction mixture was heated at reflux for 2.5 days, then cooled to RT and saturated aqueous K_2CO_3 (10 mL) and water (10 ml) added. The reaction mixture was extracted with Et_2O (3 x 15 mL), then the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (30-50% Et_2O/PE) afforded the title compound **3.11** as a white foamy solid (36 mg, 76%).

MP	67-69 °C (Et_2O/PE)
IR (υ_{max})	2923 (w), 2838 (w), 1687 (s), 1600 (s), 1578 (m), 1540 (m), 1501 (s), 1489 (s), 1455 (m), 1422 (w), 1393 (w), 1271 (s), 1226 (s), 1154 (m), 1123 (w), 1047 (w), 1025 (w), 937 (w), 856 (w), 832 (m), 813 (w), 735 (w), 696 (w), 668 (w), 581 (w), 472 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.44 (d, *J*=8.6 Hz, 2H, 2 x Ar**H**), 7.39 (d, *J*=2.8 Hz, 1H, Ar**H**), 7.31-7.22 (m, 6H, 6 x Ar**H**), 7.19 (d, *J*=8.4 Hz, 1H, Ar**H**), 7.07 (d, *J*=2.2 Hz, 1H, Ar**H**), 7.01 (dd, *J*=8.4, 2.3 Hz, 1H, Ar**H**), 6.95-6.91 (m, 2H, 2 x Ar**H**), 6.91 (d, *J*=1.8 Hz, 2H, 2 x Ar**H**), 6.87 (d, *J*=8.3 Hz, 1H, Ar**H**), 6.78 (s, 1H, Ar**H**), 5.36 (s, 1H, ArC**H**O), 5.17 (s, 1H, ArC**H**O),

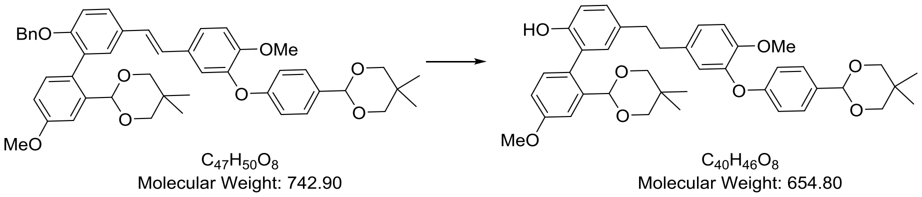
5.00 (s, 2H, OC**H**$_2$),
3.90 (s, 3 H, OC**H**$_3$),
3.80 (s, 3 H, OC**H**$_3$),
3.76 (d, *J*=11.2 Hz, 2H, 2 x CC**H**HO),
3.64 (d, *J*=10.6 Hz, 4H, 4 x CCH**H**O),
3.39 (d, *J*=10.9, 1H, CC**H**HO),
3.32 (d, *J*=10.9, 1H, CC**H**HO),
2.93-2.67 (m, 4H, ArC**H**$_2$C**H**$_2$Ar),
1.32 (s, 3H C**H**$_3$),
1.30 (s, 3H, C**H**$_3$),
0.80 (s, 3H, C**H**$_3$),
0.68 (s, 3H, C**H**$_3$).

δ$_C$ (100 MHz, CDCl$_3$) 159.0 (**C**), 158.3 (**C**), 154.0 (**C**), 149.5 (**C**), 144.6 (**C**), 137.7 (**C**), 137.5 (**C**), 134.9 (**C**), 133.5 (**C**), 132.7 (**C**), 132.3 (**C**H), 131.7 (**C**H), 129.6 (**C**), 129.4 (**C**), 128.3 (**C**H), 128.3 (2 x **C**H), 127.5 (2 x **C**H), 127.3 (**C**H), 126.7 (2 x **C**H), 124.5 (**C**H), 121.1 (**C**H), 117.0 (2 x **C**H), 114.8 (**C**H), 113.2 (**C**H), 112.7 (**C**H), 110.6 (**C**H), 101.5 (Ar**C**HO), 100.0 (Ar**C**HO), 77.6 (2 x **C**CH$_2$O), 77.5 (C**C**H$_2$O), 77.4 (C**C**H$_2$O), 70.4 (ArO**C**H$_2$), 56.0 (O**C**H$_3$), 55.3 (O**C**H$_3$), 37.1 (Ar-**C**H$_2$), 37.1 (Ar-**C**H$_2$), 30.2 (**C**), 30.1 (**C**), 23.2 (**C**H$_3$), 23.0 (**C**H$_3$), 21.9 (**C**H$_3$), 21.7 (**C**H$_3$).

LRMS (ESI+, m/z) 767 [M+Na]$^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{47}H_{52}NaO_8$ [M+Na]$^+$ requires 767.3554; found: 767.3563.

2'-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-(3-(4-(5,5-dimethyl-1,3-dioxan-2-yl)phenoxy)-4-methoxyphenethyl)-4'-methoxy-[1,1'-biphenyl]-2-ol (3.14)



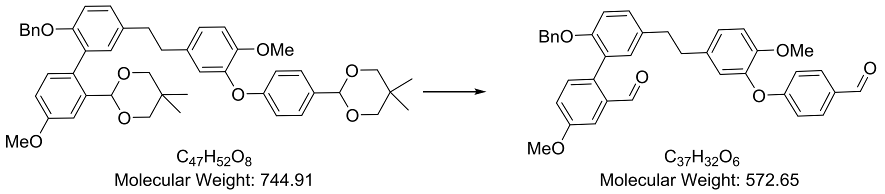
To a solution of alkene **3.10** (1.61 g, 2.17 mmol) in EtOH (80 mL) and DCM (80 mL) was added PtO$_2$ (210 mg, 0.76 mmol) and Et$_3$N (4.54 mL, 32.56 mmol). The flask was evacuated/purged with argon three times then evacuated/purged with hydrogen twice. After 13 h stirred vigorously under an atmosphere of H$_2$ at RT. the mixture filtered thought Celite© and the solvent was removed *in* *vacuo*. The residue was purified by flash chromatography column (50% Et$_2$O/PE) to afford the title compound **3.14** as a while solid (1.07 g, 75%).

MP	65-67 °C (Et$_2$O/PE)
IR (υ_{max})	3358 (w), 2953 (w), 2851 (w), 1609 (m), 1508 (s), 1466 (m), 1423 (m), 1390 (w), 1269 (s), 1226 (s), 1166 (w), 1092 (s), 1035 (m), 1013 (m), 987 (m), 927 (w), 826 (w) cm^{-1}.
δ_H (400 MHz, CDCl$_3$)	7.44 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 7.37 (d, *J*=2.7 Hz, 1H, Ar**H**), 7.09 (d, *J*=8.4 Hz, 1H, Ar**H**), 7.04 (dd, *J*=8.3, 2.2 Hz, 1H Ar**H**), 6.98 (dd, *J*=8.4, 2.8 Hz, 1H, Ar**H**), 6.95-6.91 (m, 2H, 2 x Ar**H**), 6.90 (s, 3H, 3 x Ar**H**), 6.86 (d, *J*=2.1 Hz, 1H, Ar**H**), 6.76 (s, 1H, Ar**H**), 6.00 (s, 1H, ArO**H**), 5.37 (s, 1H, OC**H**O), 5.16 (s, 1H, OC**H**O), 3.89 (s, 3H, OC**H**$_3$), 3.81 (s, 3H, OC**H**$_3$), 3.77 (d, *J*=11.1 Hz, 2H, 2 x OC**H**HC), 3.74-3.61 (m, 4H, 4x OCH**H**C), 3.48 (d, *J*=4.0 Hz, 1H, OC**H**HC), 3.45 (d, *J*=4.0 Hz, 1H, OC**H**HC), 2.81 (d, *J*=2.7 Hz, 4H, ArC**H**$_2$C**H**$_2$Ar), 1.30 (s, 3H, C**H**$_3$), 1.31 (s, 3H, C**H**$_3$), 0.81 (s, 3H, C**H**$_3$), 0.72 (s, 3H, C**H**$_3$).
δ_C (100 MHz, CDCl$_3$)	159.6 (**C**), 158.2 (**C**), 151.8 (**C**), 149.4 (**C**), 144.8 (**C**), 137.6 (**C**), 134.8 (**C**), 133.2 (**C**), 132.8 (**C**), 132.3 (**C**H), 131.3 (**C**H), 129.2 (**C**H), 128.2 (**C**), 127.5 (2 x **C**H), 126.9 (**C**), 124.5 (**C**H), 120.9 (**C**H), 117.2 (2 x **C**H), 116.6 (**C**H), 115.7 (**C**H), 112.6 (**C**H), 110.7 (**C**H), 101.5 (**C**H), 99.7 (**C**H), 77.6 (3 x **C**H$_2$), 77.4 (**C**H$_2$), 56.0 (**C**H$_3$), 55.4 (**C**H$_3$), 37.1 (**C**H$_2$), 37.0 (**C**H$_2$), 30.2 (2 X **C**), 23.1 (**C**H$_3$), 23.0 (**C**H$_3$), 21.8 (**C**H$_3$), 21.6 (**C**H$_3$).

LRMS (ESI+, m/z) 677 [M+Na]$^+$ (90%), 551 (100%).

HRMS (ESI+, m/z) calcd for $C_{40}H_{46}NaO_8$ [M+Na]$^+$ requires 677.3085; found: 677.3074.

2'-(Benzyloxy)-5'-(3-(4-formylphenoxy)-4-methoxyphenethyl)-4-methoxy-[1,1'-biphenyl]-2-carbaldehyde (3.12)



To a stirred solution of protecting aldehyde **3.11** (1.4 g, 1.88 mmol) in acetone (160 mL) was added pyridinium *p*-toluenesulfonate (2.36 g, 9.4 mmol) water (40 mL). The reaction mixture was heated at reflux for 13 h, then cooled to RT. A solution of saturated $NaHCO_3$ (50 ml) and water (60 ml) were added to the mixture. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography column (40-50% Et_2O/PE) to afford the title compound **3.12** as a colourless oil (910 mg, 84%).

IR (υ_{max}) 2955 (m), 2868 (w), 1609 (m), 1508 (s), 1454 (w), 1424 (w), 1390 (s), 1269 (s), 1224 (s), 1165 m(), 1091 (s), 1035 (s), 1013 (m), 986 (m), 879 (w), 808 (w), 736 (w), 668 (w) cm^{-1}.

δ_H (400 MHz, CDCl$_3$)
9.89 (s, 1H, C**H**O),
9.78 (s, 1H, C**H**O),
7.79 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**),
7.51 (d, *J*=2.8 Hz, 1H, Ar**H**),
7.31-7.24 (m, 4H, 4 x Ar**H**),
7.22-7.17 (m, 3H, 3 x Ar**H**),
7.14 (dd, *J*=8.4, 2.3 Hz, 1H, Ar**H**),
7.02-6.97 (m, 3H, 3 x Ar**H**),
6.96 (d, *J*=1.7 Hz, 2H, 2 x Ar**H**),
6.94 (d, *J*=2.1 Hz, 1H, Ar**H**),
6.90 (d, *J*=1.8 Hz, 1H, Ar**H**),
5.00 (d, *J*=3.2 Hz, 2H, OC**H**$_2$),
3.92 (s, 3H, OC**H**$_3$),
3.79 (s, 3H, OC**H**3),
2.91 (s, 4H, ArC**H**$_2$C**H**$_2$Ar).

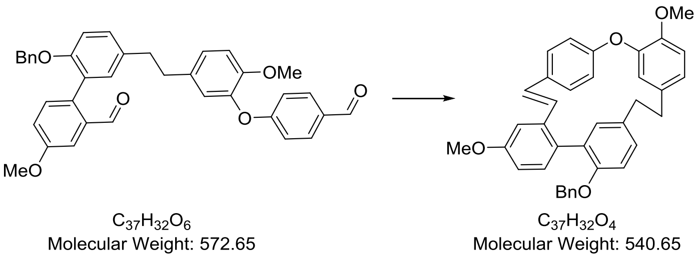
δ_C (100 MHz, CDCl$_3$) 192.4 (**C**HO), 190.7 (**C**HO), 163.5 (**C**), 159.1 (**C**), 154.1 (**C**), 149.8

(**C**), 142.5 (**C**), 136.7 (**C**), 134.9 (**C**), 134.8 (**C**), 134.8 (**C**), 134.0 (**C**), 132. 5 (**C**H), 132.0 (**C**H), 131.8 (2 x **C**H), 130.8 (**C**), 129.4 (**C**H), 128.4 (2 x **C**H), 127.7 (**C**H), 127.0 (**C**), 126.8 (2 x **C**H), 126.2 (**C**H), 122.5 (**C**H), 121.1 (**C**H), 116.1 (2 x **C**H), 112.9 (**C**H), 112.8 (**C**H), 109.3 (**C**H), 70.6 (**C**H_2), 55.9 (**C**H_3), 55.5 (**C**H_3), 36.9 (**C**H_2), 36.8 (**C**H_2).

LRMS (ESI+, m/z) 595 $[M+Na]^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{37}H_{32}NaO_6$ $[M+Na]^+$ requires 595.2091; found: 595.2096.

13,14-Dihydro-18-benzyloxy-9,23-dimethoxy-3,6-etheno-8,12;15,19-bis(metheno)-7-oxabenzo[*t*]cycloeicosadecaene (3.13)



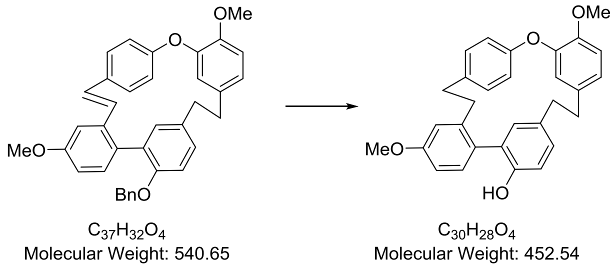
To a cooled aliquot of THF (10 mL) at -78 °C containing magnesium (117 mg, 7.0 mmol) was added titanium tetrachloride (1.39 g, 7.35 mmol, 0.81 mL) dropwise over 5 min. The reaction mixture was allowed to warm to RT and stirred for 3 h. The resultant black solution was cooled to -78 °C and a solution of tetraaromatic **3.12** (200 mg, 0.35 mmol) in THF (25 mL) was added dropwise over 10 min. After 5 h at RT the reaction mixture was warmed at reflux for 13 h, then cooled to RT. Water (20 mL) was added to the mixture. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purifica232tion by flash column chromatography (20-25% Et_2O/PE) afforded the title compound **3.13** as a colourless oil (51 mg, 26%).

IR (υ_{max}) 2929 (m), 2855 (w), 2360 (w), 2342 (w), 1602 (m), 1582 (w), 1560 (w), 1499 (s), 1478 (s), 1454 (m), 1290 (m), 1253 (s), 1224 (s), 1160 (m), 1125 (m), 1094 (m), 1034 (m), 963 (w), 874 (w), 814 (w), 735 (w), 696 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.55 (d, *J*=8.6 Hz, 1H, Ar**H**),
7.37 (d, *J*=8.3 Hz, 2H, 2 x Ar**H**),
7.34 (d, *J*=0.9 Hz, 1H, Ar**H**),
7.32 (d, *J*=2.0 Hz, 2H, 2 x Ar**H**),
7.30 (br. s., 1H, Ar**H**),

	7.18 (d, *J*=2.7 Hz, 1H, Ar**H**), 7.07 (d, *J*=8.4 Hz, 2H, 2 x Ar**H**), 7.00 (d, *J*=8.6 Hz, 1H, Ar**H**), 6.99-6.96 (m, 2H, 2 x Ar**H**), 6.91 (dd, *J*=8.7, 2.7 Hz, 2H, 2 x Ar**H**), 6.80 (d, *J*=8.1 Hz, 1H, Ar**H**), 6.74 (d, *J*=1.8 Hz, 1H, Ar**H**), 6.72-6.70 (m, 1H, ArC**H**), 6.38 (d, *J*=15.8 Hz, 1H, ArC**H**), 5.46 (d, *J*=1.8 Hz, 1H, Ar**H**), 5.04 (s, 2H, OC$\mathbf{H_2}$), 3.97 (s, 3H, OC$\mathbf{H_3}$), 3.93 (s, 3H, OC$\mathbf{H_3}$), 2.94-2.68 (m, 4H, ArC$\mathbf{H_2}$C$\mathbf{H_2}$Ar).
δ_C (100 MHz, CDCl$_3$)	158.8 (**C**), 156.3 (**C**), 154.0 (**C**), 151.7 (**C**), 146.6 (**C**), 139.1 (**C**), 138.3 (**C**H), 137.6 (**C**), 137.4 (**C**), 135.0 (**C**), 134.6 (**C**), 133.9 (**C**H), 132.9 (**C**H), 130.9 (**C**H), 130.0 (**C**), 128.75 (**C**), 128.4 (2 x **C**H) 128.3 (**C**H), 128.3 (**C**H), 127.6 (2 x **C**H), 126.9 (2 x **C**H), 126.1 (**C**H), 121.0 (2 x **C**H), 115.3 (**C**H), 114.2 (**C**H), 113.1 (**C**H), 111.3 (**C**H), 109.9 (**C**H), 70.8 (**C**H$_2$), 56.2 (**C**H$_3$), 55.4 (**C**H$_3$), 34.2 (**C**H$_2$), 33.2 (**C**H$_2$).
LRMS (ESI+, m/z)	563 [M+Na]$^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{37}H_{32}NaO_4$ [M+Na]$^+$ requires 563.2193; found: 563.2208.

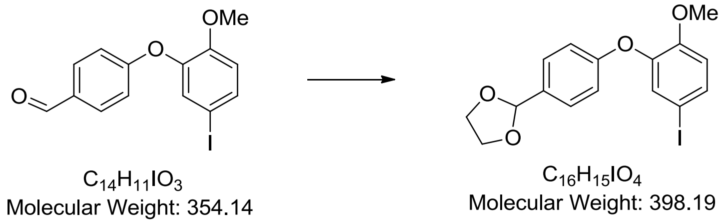
1,2,13,14-Tetrahydro-18-hydroxy-9,23-dimethoxy-3,6-etheno-8,12;15,19-bis(metheno)-7-oxabenzo[*t*]cycloeicosadecaene (1.232)



To a solution of alkene **3.13** (90 mg, 0.166 mmol) in EtOH (6 mL) and DCM (6 mL) was added 10% Pd/C (75.96 mg, 0.71 mmol). The reaction mixture was stirred vigorously under an atmosphere of H_2 at RT for 5 h then filtered thought Celite© and the solvent was removed *in vacuo*. The residue was purified by flash chromatography column (30-40% Et$_2$O/PE) to afford the title compound **1.232** as a white solid (54 mg, 71%).

MP	85-87 °C (Et$_2$O/PE)
IR (υ_{max})	3447 (br. w), 2956 (s), 2924 (s), 2854 (m), 2360 (w), 2340 (w), 1727 (s), 1605 (w), 1505 (s), 1463 (m), 1420 (w), 1378 (w), 1269 (s), 1230 (s), 1165 (w), 1128 (m), 1072 (w), 1037 (w), 850 (w), 815 (w), 742 (w), 668 (w) cm^{-1}.
δ_H (400 MHz, CDCl$_3$)	7.10 (d, *J*=2.6 Hz, 1H, Ar**H**), 7.05 (d, *J*=8.6 Hz, 2H, 2 x Ar**H**), 6.88 (dd, *J*=8.6, 2.7 Hz, 2H, 2 x Ar**H**), 6.84 (d, *J*=7.3 Hz, 1H, Ar**H**), 6.80 (d, *J*=8.1 Hz, 1H, Ar**H**), 6.77-6.70 (m, 3H, 3 x Ar**H**), 6.62 (d, *J*=1.8 Hz, 1H, Ar**H**), 6.33 (br. s., 1H, Ar**H**), 6.29 (d, *J*=2.0 Hz, 1H, Ar**H**), 4.62 (s, 1H, ArO**H**), 3.92 (s, 6H, OC**H**$_3$), 3.18 (br. dd, *J*=13.5, 3.9 Hz, 1**H**, ArCH$_2$CH**H**Ar) 3.07-2.85 (m, 5H, ArC**H**$_2$C**H**$_2$Ar, ArCH$_2$C**H**HAr), 2.73-2.49 (m, 2H, ArC**H**$_2$CH$_2$Ar).
δ_C (100 MHz, CDCl$_3$)	159.7 (**C**), 153.7 (**C**), 150.1 (**C**), 149.8 (**C**), 147.0 (**C**), 141.0 (**C**), 137.6 (**C**), 136.3 (**C**), 134.8 (**C**), 133.1 (2 x **C**H), 130.4 (**C**H), 129.9 (**C**H), 129.3 (**C**H), 129.2 (**C**), 128.5 (**C**H), 126.8 (**C**), 121.5 (**C**H), 121.0 (**C**H), 115.4 (**C**H), 114.9 (**C**H), 114.8 (**C**H), 113.0 (**C**H), 111.6 (**C**H), 56.2 (**C**H$_3$), 55.3 (**C**H$_3$), 37.8 (**C**H$_2$), 35.2 (**C**H$_2$), 34.9 (**C**H$_2$), 33.4 (**C**H$_2$).
LRMS (ESI+, m/z)	475 [M+Na]$^+$ (100%).
HRMS (ESI+, m/z)	calcd for C$_{30}$H$_{28}$NaO$_4$ [M+Na]$^+$ requires 475.1880; found: 475.1879.

2-(4-(5-Iodo-2-methoxyphenoxy)phenyl)-1,3-dioxolane (3.23)



To a stirred solution of aldehyde **1.148** (16.16 g, 45.6 mmol) in toluene (150 mL) was added ethylene glycol (14.16 g, 228.15 mmol) and pyridinium *p*-toluenesulfonate (460 mg, 1.82 mmol). After 5 h at reflux under a Dean Stark apparatus, water (100 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O/PE) to afford the title compound **3.23** as a white solid (11.64 g, 64%).

MP 89-90 °C (Et_2O/PE)

IR (υ_{max}) 2935 (w), 2859 (w), 1695 (m), 1610 (m), 1508 (m), 1488 (s), 1431 (m), 1387 (m), 1295 (m), 1262 (s), 1224 (s), 1196 (m), 1130 (s), 1074 (s), 1021 (s), 960 (m), 892 (m), 825 (s), 793 (s), 762 (m), 721 (w), 669 (w), 613 (m), 585 (w) cm^{-1}.

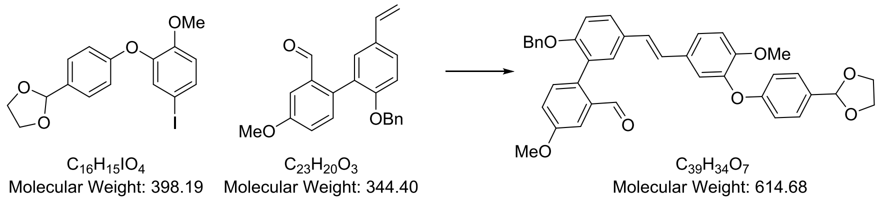
δ_H (400 MHz, $CDCl_3$)
7.44 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**),
7.41 (dd, *J*=8.2, 2.0 Hz, 1H, Ar**H**),
7.24 (d, *J*=2.1 Hz, 1H, Ar**H**),
6.95 (d, *J*=8.6 Hz, 2H, 2 x Ar**H**),
6.75 (d, *J*=8.6 Hz, 1H, Ar**H**),
5.79 (s, 1H, OC**H**O),
4.20-4.00 (m, 4H, OC**H**$_2$C**H**$_2$O),
3.81 (s, 3H, OC**H**$_3$).

δ_C (100 MHz, $CDCl_3$) 158.0 (**C**), 151.4 (**C**), 145.9 (**C**), 133.6 (**C**), 132.5 (**C**H), 129.4 (**C**H), 128.0 (2 x **C**H), 117.3 (2 x **C**H), 114.7 (**C**H), 103.4 (**C**H), 81.9 (**C**I), 65.3 (2 x **C**H$_2$), 56.0 (**C**H$_3$).

LRMS (ESI+, m/z) 399 $[M+H]^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{16}H_{15}INaO_4$ $[M+Na]^+$ requires 420.9907; found: 420.9915.

(*E*)-5'-(3-(4-(1,3-Dioxolan-2-yl)phenoxy)-4-methoxystyryl)-2'-(benzyloxy)-4-methoxy-[1,1'-biphenyl]-2-carbaldehyde (3.24)

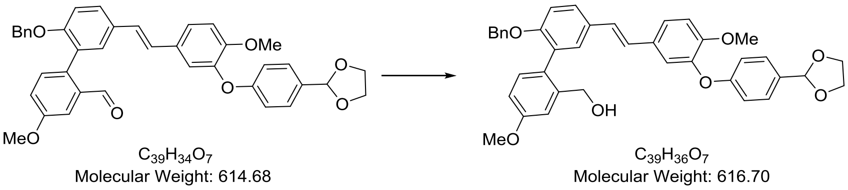


To a stirred solution of biaryl **1.236** (7.95 g, 23.08 mmol) and ether **3.23** (8.36 g, 20.99 mmol) in DMA (21 mL) was added potassium phosphate (6.24 g, 29.38 mmol). The reaction mixture was degassed with sonication for 30 min under argon then $Pd(OAc)_2$ (230 mg, 1.05 mmol) was added. The reaction mixture was heated at reflux for 18 h then cooled to RT. Water (100 mL) was added. The product was extracted by Et_2O (3 x 100 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (50% Et_2O/PE) to afford the title compound **3.24** as a white solid (10.64 g, 82%).

MP	78-79 °C (Et_2O/PE)
IR (υ_{max})	2884 (w), 1686 (m), 1604 (s), 1571 (w), 1505 (s), 1487 (s), 1453 (m), 1424 (m), 1389 (m), 1268 (s), 1222 (s), 1162 (s), 1123 (m), 1076 (s), 1021 (s), 961 (s), 961 (s), 939 (s), 885 (m), 812 (s), 737 (s), 695 (s), 657 (w), 632 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	9.87 (s, 1H, C**H**O), 7.53 (d, *J*=2.8 Hz, 1H, Ar**H**), 7.45 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 7.44-7.40 (m, 2H, 2 x Ar**H**), 7.35 (d, *J*=8.4 Hz, 1H, Ar**H**), 7.30 (d, *J*=7.2 Hz, 2H, 2 x Ar**H**), 7.29-7.17 (m, 6H, 6 x Ar**H**), 7.01 (d, *J*=8.7 Hz, 2H, 2 X Ar**H**), 7.00 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 6.91 (s, 2H, ArC**H**C**H**Ar), 5.80 (s, 1H, OC**H**O), 5.05 (d, *J*=3.8 Hz, 2H, ArC**H**$_2$O), 4.21-4.01 (m, 4H, OC**H**$_2$C**H**$_2$O), 3.93 (s, 3H, OC**H**$_3$), 3.86 (s, 3H, OC**H**$_3$).
δ_C (100 MHz, $CDCl_3$)	192.4 (**C**HO), 159.2 (**C**), 158.6 (**C**), 155.4 (**C**), 150.9 (**C**), 145.0 (**C**), 136.5 (**C**), 134.9 (**C**), 134.7 (**C**), 132.5(**C**H), 131.9 (**C**), 131.0

	(**C**), 130.7 (**C**), 129.5 (**C**H), 128.4 (2 x **C**H), 128.0 (2 x **C**H), 127.8 (**C**H), 127.6 (**C**H), 127.6 (**C**), 126.9 (2 x **C**H), 126.5 (**C**H), 126.4 (**C**H), 123.3 (**C**H), 121.2 (**C**H), 118.5 (**C**H), 117.0 (2 x **C**H), 113.0 (**C**H), 112.9 (**C**H), 109.4 (**C**H), 103.6 (**C**H), 70.6 (**C**H_2), 65.3 (2 x **C**H_2), 56.1 (**C**H_3), 55.6 (**C**H_3).
LRMS (ESI+, m/z)	637 $[M+Na]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{39}H_{34}NaO_7$ $[M+Na]^+$ requires 637.2197; found: 637.2196.

(*E*)-(5'-(3-(4-(1,3-Dioxolan-2-yl)phenoxy)-4-methoxystyryl)-2'-(benzyloxy)-4-methoxy-[1,1'-biphenyl]-2-yl)methanol (3.25)

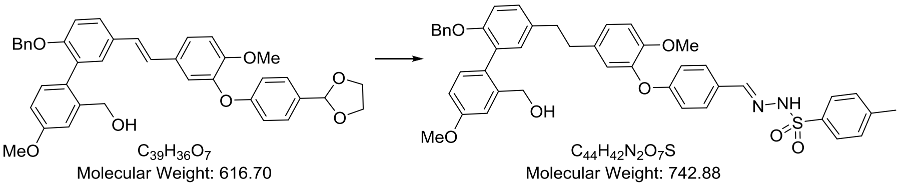


To a suspension of aldehyde **3.24** (1.01 g, 1.64 mmol) in methanol (6 mL) and DCM (6 mL) at 0 °C was added $NaBH_4$ (120 mg, 3.28 mmol). Then, the reaction mixture warmed to RT. After 1 h, water (10 mL) was added. The product was extracted by Et_2O (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (60% Et_2O/PE) to afford the title compound **3.25** as a white solid (940 mg, 92%).

MP	75-77 °C (Et_2O/PE)
IR (υ_{max})	3560 (br. w), 2925 (w), 1603 (m), 1578 (w), 1505 (s), 1454 (m), 1422 (m), 1365 (w), 1269 (s), 1226 (s), 1184 (w), 1161 (s), 1123 (m), 1025 (m), 955 (w), 909 (m), 812 (m), 731 (s), 696 (w), 665 (w), 581 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.45 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 7.40 (dd, *J*=2.3, 8.5 Hz, 1H, Ar**H**), 7.35 (d, *J*=2.2 Hz, 1H, Ar**H**), 7.33-7.27 (m, 3H, 3 x Ar**H**), 7.25 (dd, *J*=2.0, 8.5 Hz, 1H, Ar**H**), 7.19 (d, *J*=8.4 Hz, 3H, 3 x Ar**H**), 7.17 (d, *J*=2.1 Hz, 1H, Ar**H**), 7.14 (d, *J*=2.7 Hz, 1H, Ar**H**), 7.04-6.97 (m, 4H, 4 x Ar**H**), 6.94 (dd, *J*=2.7, 8.4 Hz, 1H, Ar**H**),

	6.90 (s, 2H, ArC**H**C**H**Ar), 5.80 (s, 1H, OC**H**O), 5.03 (d, *J*=6.8 Hz, 2H, ArC**H**$_2$O), 4.61-4.31 (m, 2H, ArC**H**$_2$O), 4.20-4.01 (m, 4H, OC**H**$_2$C**H**$_2$O), 3.90 (s, 3H, OC**H**$_3$), 3.85 (s, 3H, OC**H**$_3$), 2.17 (br. s., 1H, O**H**).
δ$_C$ (100 MHz, CDCl$_3$)	159.3 (**C**), 158.6 (**C**), 155.3 (**C**), 150.8 (**C**), 144.9 (**C**), 140.7 (**C**), 136.4 (**C**), 131.8 (**C**), 131.3 (**C**H), 131.1 (**C**), 130.9 (**C**), 130.8 (**C**), 129.5 (**C**), 129.3 (**C**H), 128.5 (2 x **C**H), 127.9 (2 x **C**H), 127.9 (**C**H), 127.1 (2 x **C**H), 126.9 (**C**H), 126.6 (**C**H), 126.3 (**C**H), 123.3 (**C**H), 118.5 (**C**H), 116.9 (2 x **C**H), 113.9 (**C**H), 113.4 (**C**H), 113.2 (**C**H), 112.8 (**C**H), 103.5 (**C**H), 71.2 (**C**H$_2$), 65.2 (2 x **C**H$_2$), 63.7 (**C**H$_2$), 56.0 (**C**H$_3$), 55.3 (**C**H$_3$).
LRMS (ESI+, m/z)	599 [MH-H$_2$O]$^+$ (100%), 639 [M+Na]$^+$ (84%)
HRMS (ESI+, m/z)	calcd for $C_{39}H_{36}NaO_7$ [M+Na]$^+$ requires 639.2353; found: 639.2346.

(*E*)-*N*'-(4-(5-(2-(6-(Benzyloxy)-2'-(hydroxymethyl)-4'-methoxy-[1,1'-biphenyl]-3-yl)ethyl)-2-methoxyphenoxy)benzylidene)-4-methylbenzenesulfonohydrazide (3.26)



To a stirred solution of stilbene **3.25** (760 mg, 1.23 mmol) in 1:1 v/v THF and water (20 mL each) was added tosylhydrazone (2.29 g, 12.32 mmol) and NaOAc (1.01 g, 12.32 mmol). The reaction mixture was heated at reflux for 18 h, then cooled to RT and water (50 mL) added. The reaction mixture was extracted with Et$_2$O (3 x 50 mL), then the combined organic phases were dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography (70% Et$_2$O/hexane) afforded the title compound **3.26** as a white solid (510 g, 55%).

MP	98-100 °C (Et$_2$O/hexane)
IR (υ_{max})	3499 (br. w), 3191 (w), 2931 (w), 1603 (m), 1578 (w), 1505 (s), 1487 (m), 1453 (m), 1442 (w), 1364 (w), 1300 (m), 1269 (s), 1227 (s), 1161 (s), 1122 (m), 1093 (m), 1047 (m), 953 (w), 811

(s), 737 (w), 696 (m), 664 (s), 579 (s), 546 (s), 518 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$)

7.51 (d, *J*=8.3 Hz, 2H, 2 x Ar**H**),
7.47 (br. s, 1H, NC**H**),
7.09 (d, *J*=8.8 Hz, 2H, 2 x Ar**H**),
6.95 (d, *J*=7.9 Hz, 2H, 2 x Ar**H**),
6.93-6.87 (m, 3H, 3 x Ar**H**),
6.79 (dd, *J*=7.5, 1.9 Hz, 2H, 2 x Ar**H**),
6.77-6.67 (m, 3H, 3 x Ar**H**),
6.60-6.56 (m, 3H, 3 x Ar**H**),
6.54 (d, *J*=2.0 Hz, 1H, Ar**H**),
6.53 (dd, *J*=8.7, 2.6 Hz, 1H, Ar**H**),
6.46 (d, *J*=8.8 Hz, 2H, 2 x Ar**H**),
6.43 (d, *J*=1.6 Hz, 1H, Ar**H**),
4.58 (d, *J*=11.9 Hz, 2H, ArC**H**$_2$O),
4.09-3.87 (m, 2H, ArC**H**$_2$O),
3.51 (s, 3H, OC**H**$_3$),
3.42 (s, 3H, OC**H**$_3$),
2.49 (s, 4H, ArC**H**$_2$C**H**$_2$Ar),
2.06 (s, 3H, ArC**H**$_3$),
1.87 (t, *J*=6.3 Hz, 1H, O**H**),
1.27 (s, 1H, N**H**).

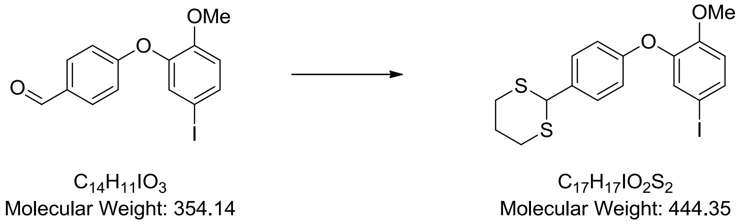
δ_C (100 MHz, $CDCl_3$)

160.2 (**C**), 159.2 (**C**), 154.0 (**C**), 149.7 (**C**), 147.8 (**C**H), 144.1 (**C**), 143.4 (**C**), 140.7 (**C**), 136.7 (**C**), 135.4 (**C**), 134.8 (**C**), 134.5 (**C**), 131.8 (**C**H), 131.2 (**C**H), 130.5 (**C**), 129.8 (**C**), 129.6 (2 x **C**H), 128.9 (2 x **C**H), 128.6 (**C**H), 128.5 (2 x **C**H), 127.9 (2 x **C**H), 127.9 (**C**H), 127.2 (**C**), 127.1 (2 x **C**H), 125.5 (**C**H), 122.1 (**C**H), 116.5 (2 x **C**H), 114.0 (**C**H), 113.4 (**C**H), 113.3 (**C**H), 112.9 (**C**H), 71.4 (**C**H$_2$), 63.7 (**C**H$_2$), 56.0 (**C**H$_3$), 55.3 (**C**H$_3$), 36.9 (2 x **C**H$_2$), 21.6 (**C**H$_3$).

LRMS (ESI+, m/z) 765 [M+Na]$^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{44}H_{42}N_2NaO_7S$ [M+Na]$^+$ requires 765.2605; found: 765.2590.

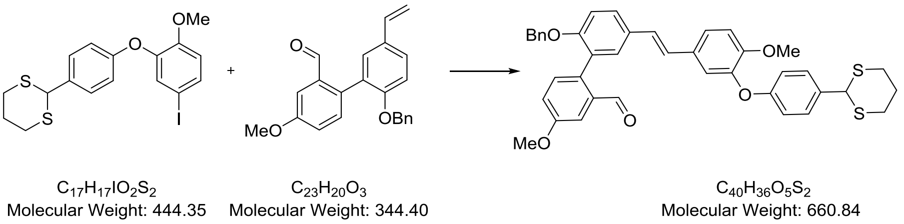
2-(4-(5-Iodo-2-methoxyphenoxy)phenyl)-1,3-dithiane (3.19)



To a stirred solution of aldehyde **1.148** (4.55 g, 12.84 mmol) in DCM (140 mL) was added 1,3-propanedithiol (1.68 mL, 16.7 mmol) and PPTS (760 mg, 2.95 mmol). The reaction mixture was heated at reflux for 24 h and cooled to RT. Purification by column chromatography (20% Et_2O:PE) afforded the title compound **3.19** as a white solid (4.66 g, 81%).

MP	131-133 °C (Et_2O/PE)
IR (υ_{max})	2935 (w), 2895 (w), 1605 (w), 1572 (w), 1502 (s), 1487 (s), 1460 (m), 1438 (w), 1419 (w), 1393 (w), 1292 (m), 1262 (s), 1218 (s), 1175 (s), 1164 (s), 1132 (m), 1103 (w), 1023 (m), 907 (m), 890 (s), 802 (m), 764 (w), 726 (s), 674 (w), 610 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.45 (dd, *J*=8.6, 2.1 Hz, 1H, Ar**H**), 7.44-7.40 (d, *J*=8.8 Hz, 2H, 2 x Ar**H**), 7.28 (d, *J*=2.2 Hz, 1H, Ar**H**), 6.90 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 6.77 (d, *J*=8.7 Hz, 1H, Ar**H**), 5.17 (s, 1H, SC**H**S), 3.82 (s, 3H, OC**H**$_3$), 3.14-3.02 (m, 2H, 2 x SC**H**HC), 2.93 (dt, *J*=13.6, 4 Hz, 2H, 2 X SCH**H**C), 2.26-2.12 (m, 1H, CH**H**CH$_2$), 2.02-1.87 (m, 1H, C**H**HCH$_2$).
δ_C (100 MHz, $CDCl_3$)	157.4 (**C**), 151.6 (**C**), 145.5 (**C**), 133.9 (**C**H), 133.5 (**C**), 129.9 (**C**H), 129.1 (2 x **C**H), 117.2 (2 x **C**H), 114.7 (**C**H), 81.9 (**C**I), 56.0 (**C**H$_3$), 50.7 (**C**H), 32.1 (2 x **C**H$_2$), 25.0 (**C**H$_2$).
LRMS (ESI+, m/z)	445 $[M+H]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{17}H_{18}IO_2S_2$ $[M+H]^+$ requires 444.9787; found: 444.9794.

(*E*)-5'-(3-(4-(1,3-Dithian-2-yl)phenoxy)-4-methoxystyryl)-2'-(benzyloxy)-4-methoxy-[1,1'-biphenyl]-2-carbaldehyde (3.36)



To a stirred solution of biaryl **1.236** (81 mg, 0.23 mmol) and ether **3.19** (94 mg, 0.21 mmol) in DMA (2 mL) was added potassium phosphate (62 mg, 0.29 mmol). The reaction mixture was degassed with sonication for 30 min under argon then $Pd(OAc)_2$ (2.4 mg, 0.01 mmol) was added. The reaction mixture was heated at reflux for 18 h then cooled to RT. The residue was purified by flash column chromatography (50-60% Et_2O/PE) to afford the title compound **3.36** as a yellow solid (54 g, 38%).

MP	88-90 °C (Et_2O/PE)
IR (υ_{max})	2928 (w), 2899 (w), 1687 (m), 1602 (m), 1500 (s), 1453 (w), 1419 (w), 1392 (w), 1268 (s), 1221 (s), 1163 (m), 1124 (w), 1045 (w), 1021 (m), 960 (w), 909 (w), 881 (w), 815 (m), 763 (m), 737 (m), 695 (m), 5674 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	9.85 (s, 1H, C**H**O), 7.51 (d, *J*=2.8 Hz, 1H, Ar**H**), 7.44-7.38 (m, 4H, 4 x Ar**H**), 7.33 (d, *J*=8.4 Hz, 1H, Ar**H**), 7.29 (d, *J*=7.1 Hz, 2H, 2 x Ar**H**), 7.24 (d, *J*=2.2 Hz, 1H, Ar**H**), 7.22 (d, *J*=2.9 Hz, 1H, Ar**H**), 7.21-7.17 (m, 4H, 4 x Ar**H**), 6.99 (dd, *J*=8.4,0.9 Hz, 2H, 2 x Ar**H**), 6.92 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 6.90 (s, 2H, ArC**H**C**H**Ar), 5.16 (s, 1H, SC**H**S), 5.04 (d, *J*=4.8 Hz, 2H, ArC**H**$_2$O), 3.91 (s, 3H, OC**H**$_3$), 3.85 (s, 3H, OC**H**$_3$), 3.13-3.00 (m, 2H, SC**H**$_2$CH$_2$), 2.91 (dt, *J*=14.0, 3.9 Hz, 2H, SC**H**$_2$CH$_2$),

2.22-2.13 (m, 1H, $SCH_2CH\mathbf{H}$),

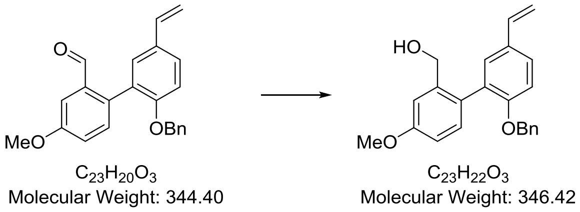
1.98-1.87 (m, 1H, $SCH_2C\mathbf{H}H$).

δ_C (100 MHz, $CDCl_3$) 192.5 (**C**HO), 159.2 (**C**), 158.0 (**C**), 155.3 (**C**), 151.1 (**C**), 144.6 (**C**), 136.5 (**C**), 134.9 (**C**), 134.7 (**C**), 133.0 (**C**), 132.5 (**C**H), 131.0 (**C**), 130.7 (**C**), 129.5 (**C**H), 129.0 (2 x **C**H), 128.4 (2 x **C**H), 127.8 (**C**H), 127.6 (**C**H), 127.5 (**C**), 126.9 (2 x **C**H), 126.4 (**C**H), 126.4 (**C**H), 123.5 (**C**H), 121.2 (**C**H), 118.9 (**C**H), 117.0 (2 x **C**H), 112.9 (**C**H), 112.8 (**C**H), 109.4 (**C**H), 70.5 (**C**H_2), 56.1 (**C**H_3), 55.6 (**C**H_3), 50.8 (**C**H), 32.2 (2 x **C**H_2), 25.0 (**C**H_2).

LRMS (ESI+, m/z) 683 $[M+Na]^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{40}H_{36}NaO_5S_2$ $[M+Na]^+$ requires 683.1896; found: 683.1891.

(2'-(Benzyloxy)-4-methoxy-5'-vinyl-[1,1'-biphenyl]-2-yl)methanol (3.21)



To a suspension of **1.236** (11.85 g, 34.4 mmol) in methanol (140 mL) and DCM (140 mL) at 0 °C was added $NaBH_4$ (2.60 g, 68.8 mmol). Then, the reaction mixture warmed to RT. After 2 h, Water (100 mL) was added. The product was extracted by Et_2O (3 x 250 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (30-40% Et_2O/PE) to afford the title compound **3.21** as a colourless oil (11.9 g, 99%).

IR (υ_{max}) 3450 (br. s), 2939 (w), 1604 (m), 1489 (m), 1455 (w), 1381 (w), 1266 (m), 1228 (s), 1185 (w), 11185 (w), 1149 (w), 1104 (w), 1012 (m), 904 (s), 724 (s), 695 (m), 647 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$) 7.38 (dd, *J*=8.5, 2.3 Hz, 1H, Ar**H**),

7.34-7.27 (m, 4H, 4 x ArH),

7.22-7.18 (m, 3H, 3 x Ar**H**),

7.16 (d, *J*=2.7 Hz, 1H, Ar**H**),

7.02 (d, *J*=8.6 Hz, 1H, Ar**H**),

6.95 (dd, *J*=8.3, 2.7 Hz, 1H, Ar**H**),

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

5.68 (d, *J*=17.6 Hz, 1H,=C**H**H),

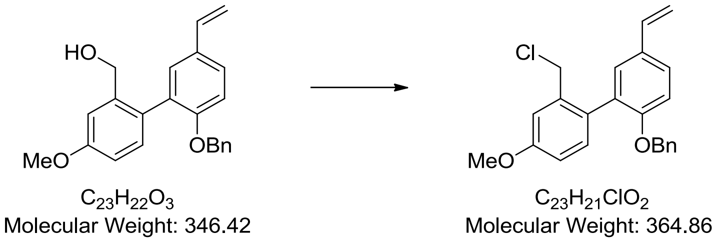
5.21 (d, *J*=11.0 Hz, 1H, =CH**H**),
5.03 (br., 2H, OC$\mathbf{H}_2$),
4.56-4.36 (br., 2H,OC$\mathbf{H}_2$),
3.90 (s, 3H, OC$\mathbf{H}_3$),
2.24 (br. s, 1H, O**H**).

δ_C (100 MHz, CDCl$_3$) 159.3 (**C**), 155.5 (**C**), 140.7 (**C**), 136.4 (**C**), 135.9 (**C**H), 131.2 (**C**H), 131.2 (**C**), 130.6 (**C**), 129.4 (**C**), 129.3 (**C**H), 128.5 (2 x **C**H), 127.9 (**C**H), 127.0 (2 x **C**H), 126.6 (**C**H), 113.7 (**C**H), 113.3 (**C**H), 113.2 (**C**H), 112.4 (**C**H$_2$), 71.1 (**C**H$_2$), 63.6 (**C**H$_2$), 55.3 (**C**H$_3$).

LRMS (ESI+, m/z) 369 [M+Na]$^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{23}H_{22}NaO_3$ [M+Na]$^+$ requires 369.1461; found: 369.1469.

2'-(Benzyloxy)-2-(chloromethyl)-4-methoxy-5'-vinyl-1,1'-biphenyl (3.20)



To a stirred solution of mixture of benzyl alcohol **3.21** (190 mg, 0.54 mmol) in DCM (25 mL), DBU (0.24 mL, 1.64 mmol) were added. The methanesulfonyl chloride (0.12 mL, 1.64 mmol) was added at 0 °C. After 18 h at RT, the mixture was concentrated *in vacuo*. Purification by flash column chromatography (25% Et$_2$O/PE) afforded the title compound **3.20** as colourless oil (190 mg, 96%).

IR (υ_{max}) 2921 (m), 2852 (w), 1626 (w), 1603 (s), 1572 (w), 1489 (w), 1453 (m), 1380 (w), 1271 (s), 1230 (s), 1188 (m), 1147 (w), 1108 (w), 1079 (w), 1044 (m), 1021 (m), 989 (m), 934 (w), 901 (m), 865 (w), 815 (s), 779 (s), 734 (s), 694 (s), 601 (m) cm^{-1}.

δ_H (400 MHz, CDCl$_3$) 7.37 (br. d, *J*=6.1 Hz, 1H, Ar**H**),
7.35 (d, *J*=6.1 Hz, 1H, Ar**H**),
7.29 (d, *J*=7.2 Hz, 2H, 2 x Ar**H**),
7.27-7.17 (m, 4H, 4 x Ar**H**),
7.13 (d, *J*=2.7 Hz, 1H, Ar**H**),
6.96 (d, *J*=9.3 Hz, 1H, Ar**H**),
6.93 (dd, *J*=8.4, 2.7 Hz, 1H, Ar**H**),
6.69 (dd, *J*=17.6, 10.9 Hz, 1H, ArC**H**CH$_2$),
5.66 (dd, *J*=17.5, 0.8 Hz, 1H, ArCHCH**H**),

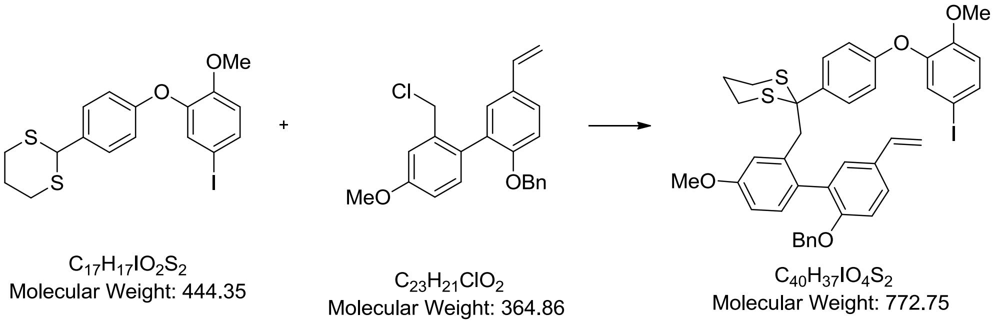
5.17 (dd, *J*=10.9, 0.7 Hz, 1H, ArCHC**H**H),
5.05 (s, 2H, ArC**H**$_2$Cl),
4.56-4.34 (m, 2H, ArC**H**$_2$O),
3.88 (s, 3H, OC**H**$_3$).

δ$_C$ (100 MHz, CDCl$_3$) 159.1 (**C**), 155.5 (**C**), 137.1 (**C**), 137.0 (**C**), 136.0 (**C**H), 131.7 (**C**H), 130.7 (**C**), 130.3 (**C**), 129.7 (**C**), 129.4 (**C**H), 128.4 (2 x **C**H), 127.6 (**C**H), 126.9 (**C**H), 126.6 (2 x **C**H), 114.4 (**C**H), 114.0 (**C**H), 113.0 (**C**H), 112.3 (**C**H$_2$), 70.4 (**C**H$_2$), 55.3 (**C**H$_3$), 44.7 (**C**H$_2$).

LRMS (ESI+, m/z) 365 [M(^{35}Cl)+H]$^+$ (100%), 367 [M(^{37}Cl)+H]$^+$ (20%).

HRMS (ESI+, m/z) calcd for $C_{23}H_{21}ClNaO_2$ [M+Na]$^+$ requires 387.1122; found: 387.1129.

2-((2'-(Benzyloxy)-4-methoxy-5'-vinyl-[1,1'-biphenyl]-2-yl)methyl)-2-(4-(5-iodo-2-methoxyphenoxy)phenyl)-1,3-dithiane (3.52)



To a stirred solution of mixture of compound **3.20** (390 mg, 0.84 mmol) and ether **3.19** (350 mg, 0.96 mmol) in THF (90 mL) at -78 °C was added LDA (0.43 mL, 0.87 mmol, 2 M in THF). The reaction mixture was warmed to RT for 5 h. sat. NH$_4$Cl (20 mL) and water (10 mL) was added. The organic phase was extracted with Et$_2$O (3 x 100 mL), then the combined organic phases were dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography (40% Et$_2$O/PE) afforded the title compound **3.52** as a colourless oil (120 mg, 18%).

IR (υ_{max}) 2925 (m), 2152 (w), 1604 (w), 1490 (s), 1457 (w), 1264 (m), 1225 (m), 1175 (w), 1133 (w), 1024 (w), 893 (w), 814 (w), 735 (w), 669 (m) cm^{-1}.

δ$_H$ (400 MHz, CDCl$_3$) 7.45 (dd, *J*=2.1, 8.7 Hz, 2H, 2 x Ar**H**),
7.42 (d, *J*=8.8 Hz, 2H, 2 x Ar**H**),
7.33-7.28 (m, 3H, 3 x Ar**H**),
7.24 (d, *J*=6.7 Hz, 1H, Ar**H**),
7.20 (d, *J*=1.0 Hz, 2H, 2 x Ar**H**),
6.98 (d, *J*=8.4 Hz, 1H, Ar**H**),

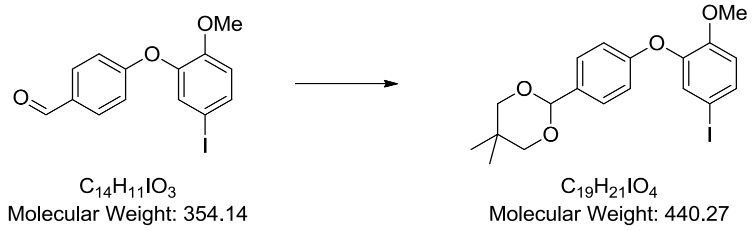
6.87 (d, *J*=8.4 Hz, 1H, Ar**H**),
6.81-6.75 (m, 3H, Ar**H**),
6.72 (d, *J*=8.8 Hz, 2H, Ar**H**),
6.69 (d, *J*=2.6 Hz, 1H, Ar**H**),
6.64 (dd, *J*=11.0, 17.7 Hz, 1H, ArC**H**CH$_2$),
5.61 (d, *J*=17.4 Hz, 1H, ArCHCH**H**),
5.13 (d, *J*=11.4 Hz, 1H, ArCHC**H**H),
4.99 (d, *J*=5.3 Hz, 2H, ArC**H**$_2$O),
3.83 (s, 3H, OC**H**$_3$),
3.73 (s, 3H, OC**H**$_3$),
3.46-3.36 (m, 1H, ArC**H**HC),
3.31-3.22 (m, 1H, ArCH**H**C),
2.65-2.46 (m, 4H, 2 x SC**H**$_2$CH$_2$),
1.90-1.75 (m, 2H, SCH$_2$C**H**$_2$).

δ_C (100 MHz, CDCl$_3$) 157.8 (**C**), 156.2 (**C**), 156.0 (**C**), 151.7 (**C**), 145.7 (**C**), 136.4 (**C**H), 135.5 (**C**), 135.3 (**C**), 134.9 (**C**), 133.7 (**C**H), 132.0 (**C**), 131.1 (**C**), 130.8 (**C**), 130.7 (**C**H), 130.4 (2 x **C**H), 129.9 (**C**H), 129.9 (**C**), 129.8 (**C**H), 128.4 (2 x **C**H), 127.5 (**C**H), 126.6 (2 x **C**H), 125.8 (**C**H), 116.4 (2 x **C**H), 116.0 (**C**H), 114.7 (**C**H), 112.8 (**C**H), 112.5 (**C**H), 111.8 (**C**H$_2$), 95.7 (**C**I), 70.2 (**C**H$_2$), 56.3 (**C**), 55.9 (**C**H$_3$), 55.1 (**C**H$_3$), 47.6 (**C**H$_2$), 22.6 (2 x **C**H$_2$), 22.5 (**C**H$_2$).

LRMS (ESI+, m/z) 795 $[M+Na]^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{40}H_{37}INaO_4S_2$ $[M+Na]^+$ requires 795.1070; found: 795.1085.

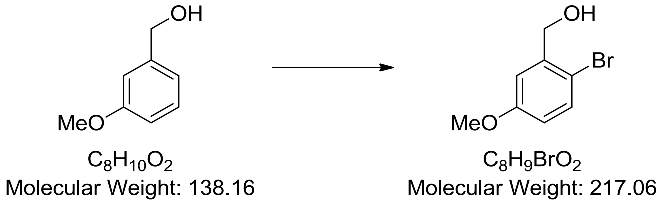
2-(4-(5-Iodo-2-methoxyphenoxy)phenyl)-5,5-dimethyl-1,3-dioxane (3.32)



To a stirred solution of aldehyde **1.148** (22.5 g, 63.55 mmol) in toluene (320 mL) was added neopentylglycol (19.86 g, 190.65 mmol) and *p*-toluenesulfonic acid (480 mg, 1.91 mmol). After 7 h at reflux under a Dean Stark apparatus, water (150 mL) and sat. NaHCO$_3$ (50 mL) were added. The organic phase was extracted with Et$_2$O (3 x 100 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% Et_2O/PE) to afford the title compound **3.32** as a white solid (26.19 g, 93%).

MP	83-84 °C (Et_2O/PE)
IR (υ_{max})	2936 (w), 1687 (w), 1605 (m), 1503 (s), 1460 (m), 1423 (w), 1419 (w), 1269 (s), 1224 (s), 1165 (m), 1124 (m), 1023 (m), 962 (w), 904 (s), 815 (m), 723 (s), 647 (m), 513 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.48 (d, *J*=8.6 Hz, 2H, 2 x Ar**H**), 7.41 (dd, *J*=8.6, 2.1 Hz, 1H, Ar**H**), 7.20 (d, *J*=2.1 Hz, 1H, Ar**H**), 6.97 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 6.74 (d, *J*=8.6 Hz, 1H, Ar**H**), 5.39 (s, 1H, OC**H**O), 3.81 (s, 3H, OC$\mathbf{H}_3$), 3.78 (d, *J*=11.1 Hz, 2H, C$\mathbf{H}_2$), 3.66 (d, *J*=10.9 Hz, 2H, C$\mathbf{H}_2$), 1.31 (s, 3H, C$\mathbf{H}_3$), 0.81 (s, 3H, C$\mathbf{H}_3$).
δ_C (100 MHz, $CDCl_3$)	157.4 (**C**), 151.2 (**C**), 146.2 (**C**), 133.6 (**C**), 133.3 (**C**H), 128.9 (**C**H), 127.7 (2 x **C**H), 117.6 (2 x **C**H), 114.5 (**C**H), 101.4 (**C**H), 81.8 (**C**I), 77.7 (2 x **C**H_2), 56.0 (**C**H_3), 30.2 (**C**), 23.0 (**C**H_3), 21.9 (**C**H_3).
LRMS (ESI+, m/z)	441 $[M+H]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{19}H_{22}IO_4$ $[M+H]^+$ requires 441.0557; found: 441.0555.

(2-Bromo-5-methoxyphenyl)metanol (1.228)

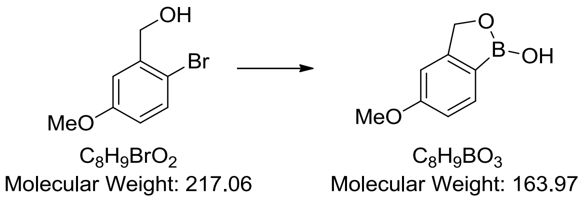


To a stirred solution of *m*-anisyl alcohol **1.226** (2.22 g, 16.1 mmol) in MeCN (40 mL) was added *N*–bromosuccinimide (3.44 g, 19.3 mmol). After 18 h at reflux, a saturated solution of $Na_2S_2O_3$ (20 mL) and water (10 mL) were added and the aqueous phase was extracted with Et_2O (3 x 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O/PE) to give the title compound **1.228** as a white solid (3.16 g, 90%).

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

MP	47-49 °C (Et_2O/PE) [Lit. 45-48 °C (PE)][50]
IR (υ_{max})	3255 (br. m), 2936 (w), 2895 (w), 2835 (w), 1591 (m), 1574 (m), 1504 (w), 1469 (s), 1459 (s), 1440 (s), 1416 (m), 1409 (m), 1376 (w), 1294 (s), 1269 (s), 1251 (s), 1190 (w), 1157 (s), 1130 (s), 1064 (m), 1049 (s), 1012 (s), 982 (w), 983 (w), 852 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.34 (d, *J*=8.8 Hz, 1H, Ar**H**), 7.01 (d, *J*=2.2 Hz, 1H, Ar**H**), 6.65 (dd, *J*=8.6, 2.4 Hz, 1H, Ar**H**), 4.61 (d, *J*=5.7 Hz, 2H, ArC$\mathbf{H_2}$), 3.74 (s, 3H, OC$\mathbf{H_3}$), 3.41 (t, *J*=5.7 Hz, 1H, O**H**).
δ_C (100 MHz, $CDCl_3$)	158.9 (**C**), 140.6 (**C**), 132.8 (**C**H), 114.4 (**C**H), 113.8 (**C**H), 112.1 (**C**Br), 64.4 (**C**H_2), 55.3 (**C**H_3).
LRMS (ESI+, m/z)	199 $[MH(^{79}Br)-H_2O]^+$ (100%), 201 $[MH(^{81}Br)-H_2O]^+$ (80%).
HRMS (ESI+, m/z)	calcd for C_8H_8BrO $[MH-H_2O]^+$ requires 198.9753; found: 198.9753.

5-Methoxybenzo[c][1,2]oxaborol-1(3H)-ol (3.31)

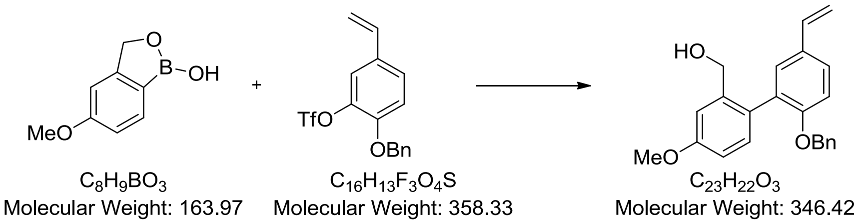


To a stirred solution of 2-bromo-5-methoxybenzyl alcohol **1.228** (410 g, 1.89 mmol) in THF (15 mL) was added sodium hydride (60% in mineral oil; 90 mg, 3.78 mmol). After 5 min the mixture was cooled to -78°C and *n*-BuLi (0.85 mL, 2.07 mmol, 2.4 M in hexanes) was added. After 20 min a $B(OMe)_3$ (0.23 g, 2.26 mmol) was added. After 4 h at RT, 2M HCl (10 mL) was added. After 30 min the product was extracted with Et_2O (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (20% Et_2O/PE) to afford the title compound **3.31** as a brown solid (180 mg, 57%). These data are in accordance with those reported in the literature.[63,115]

MP	126-128 °C (Et_2O/PE) [Lit. 124-128 °C (hexane)][63]
IR (υ_{max})	3360 (br. m), 3005 (w), 2922 (w), 2842 (w), 1605 (s), 1571 (w), 1509 (w) 1462 (w), 1418 (s), 1363 (m), 1319 (w), 1255 (s), 1160 (m), 1080 (w), 1042 (s), 966 (s), 846 (m), 713 (s), 651 (w), 633 (s)

	cm^{-1}.
δ_H (400 MHz, acetone-d_6)	7.87 (s, 1H, O**H**), 7.63 (d, *J*=8.1 Hz, 1H, Ar**H**), 6.96 (d, *J*=1.5 Hz, 1H, Ar**H**), 6.90 (dd, *J*=2.2, 8.1 Hz, 1H, Ar**H**), 4.96 (s, 2H, OC**H**$_2$), 3.83 (s, 3H, OC**H**$_3$).
δ_C (100 MHz, acetone-d_6)	163.4 (**C**), 157.9 (**C**), 132.4 (**C**H), 115.3 (**C**H), 106.6 (**C**H), 71.1 (**C**H$_2$), 55.7 (**C**H$_3$).
LRMS (ESI+, m/z)	164 $[M+H]^+$ (100%).

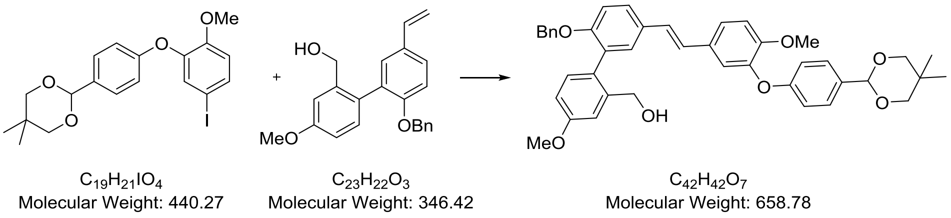
(2'-(Benzyloxy)-4-methoxy-5'-vinyl-[1,1'-biphenyl]-2-yl)methanol (3.21)



To a stirred solution of triflate **3.38** (4.81 g, 13.41 mmol) and boronic acid **3.31** (2.42 g, 14.76 mmol) in a mixed solvent system of PhMe (46 mL), EtOH (23 mL), and water (23 mL) was added Cs_2CO_3 (8.75 g, 26.84 mmol). The resulting mixture was degassed under argon for 30 min then $Pd(PPh_3)_4$ (1.55 g, 1.34 mmol) was added. After 18 h at reflux, water (20 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 x 50 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (30-40% Et_2O/PE) to afford the title compound **3.21** as a colourless oil (2.25 g, 48%).

The data were identical to those previously reported (See P.133).

(*E*)-(2'-(Benzyloxy)-5'-(3-(4-(5,5-dimethyl-1,3-dioxan-2-yl)phenoxy)-4-methoxystyryl)-4-methoxy-[1,1'-biphenyl]-2-yl)methanol (3.33)



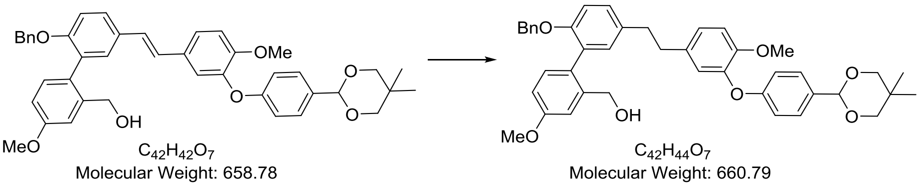
To a stirred solution of biaryl **3.21** (1.68 g, 4.85 mmol) and ether **3.32** (1.94 g, 4.41 mmol) in DMA (5 mL) was added potassium phosphate (1.31 g, 6.17 mmol). The reaction mixture was degassed with sonication for 30 min under argon then $Pd(OAc)_2$ (99 mg, 0.44 mmol) was added. The reaction mixture was heated at reflux for 18 h then cooled to RT. Water (20 mL) was added. The product was extracted by EtOAc (3 x 50 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (65% Et_2O/PE) to afford the title compound **3.33** as a white solid (1.73 g, 59%).

MP	97-99 °C (Et_2O/PE)
IR (υ_{max})	3459 (br. w), 2953 (w), 2838 (w), 1606 (m), 1572 (w), 1506 (s), 1488 (m), 1462 (m), 1441 (w), 1425 (m), 1386 (m), 1269 (s), 1223 (s), 1164 (m), 1096 (s), 1014 (m), 988 (w), 963 (w), 909 (m), 814 (m), 731 (s), 696 (w), 663 (w), 647 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.49 (d, *J*=8.6 Hz, 2H, 2 x Ar**H**), 7.40 (dd, *J*=8.6, 2.2 Hz, 1H, Ar**H**), 7.34 (d, *J*=2.2 Hz, 1H, Ar**H**), 7.32-7.26 (m, 3H, 3 x Ar**H**), 7.23 (dd, *J*=8.4, 2.1 Hz, 1H, Ar**H**), 7.21-7.18 (m, 3H, 3 x Ar**H**), 7.14 (d, *J*=2.3 Hz, 2H, 2 x Ar**H**), 7.01 (d, *J*=8.7 Hz, 3H, 3 x Ar**H**), 6.98 (d, *J*=8.6 Hz, 1H, Ar**H**), 6.94 (dd, *J*=8.4, 2.7 Hz, 1H, Ar**H**), 6.89 (s, 2H, ArC**H**C**H**Ar), 5.41 (s, 1H, OC**H**O), 5.02 (d, *J*=7.0 Hz, 2H, ArC$\mathbf{H}_2$), 4.54-4.38 (m, 2H, ArC$\mathbf{H}_2$), 3.89 (s, 3H, OC$\mathbf{H}_3$), 3.85 (s, 3H, OC$\mathbf{H}_3$), 3.80 (d, *J*=11.2 Hz, 2H, CC$\mathbf{H}_2$O), 3.69 (d, *J*=10.8 Hz, 2H, CC$\mathbf{H}_2$O), 2.19 (br. s., 1H, O**H**), 1.33 (s, 3H, C$\mathbf{H}_3$), 0.83 (s, 3H, C$\mathbf{H}_3$).
δ_C (100 MHz, $CDCl_3$)	159.3 (**C**), 158.1 (**C**), 155.3 (**C**), 150.7 (**C**), 145.2 (**C**), 140.7 (**C**), 136.4 (**C**), 133.0 (**C**), 131.3 (**C**H), 131.0 (**C**), 131.0 (**C**), 130.8 (**C**), 129.5 (**C**), 129.3 (**C**H), 128.5 (2 x **C**H), 127.9 (**C**H), 127.5 (2 x **C**H), 127.0 (2 x **C**H), 126.8 (**C**H), 126.5 (**C**H), 126.4 (**C**H), 123.0 (**C**H), 118.1 (**C**H), 117.2 (2 x **C**H), 113.9 (**C**H), 113.4 (**C**H), 113.2 (**C**H), 112.7 (**C**H), 101.5 (**C**H), 77.6 (2 x $\mathbf{C}H_2$), 71.2 ($\mathbf{C}H_2$), 63.6 ($\mathbf{C}H_2$),

56.0 (**C**H_3), 55.3 (**C**H_3), 30.1 (**C**), 23.0 (**C**H_3), 21.8 (**C**H_3).

LRMS (ESI+, m/z)	681 $[M+Na]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{42}H_{42}NaO_7$ $[M+H]^+$ requires 681.2823; found: 681.2825.

(2'-(Benzyloxy)-5'-(3-(4-(5,5-dimethyl-1,3-dioxan-2-yl)phenoxy)-4-methoxyphenethyl)-4-methoxy-[1,1'-biphenyl]-2-yl)methanol (3.34)

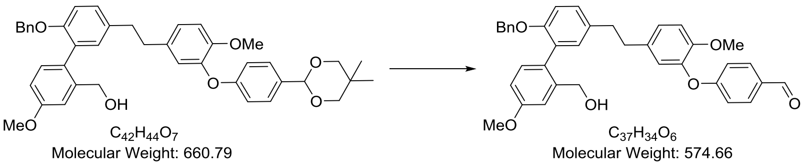


To a stirred solution of stilbene **3.33** (1.60 g, 2.43 mmol) in 1:1 v/v THF and water (150 mL each) was added tosylhydrazone (4.52 g, 24.30 mmol) and NaOAc (1.99 g, 24.30 mmol). The reaction mixture was heated at reflux for 36 h, then cooled to RT. water (50 mL) was added. The reaction mixture was extracted with Et_2O (3 x 100 mL), then the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (60% Et_2O/PE) afforded the title compound **3.34** as a yellow solid (1.32 g, 82%).

MP	87-89°C (Et_2O/PE)
IR (υ_{max})	3223 (w), 2922 (w), 1595 (w), 1433 (w), 1386 (m), 1363 (m), 1330 (s), 1308 (m), 1290 (w), 1157 (s), 1121 (m), 1086 (s), 1032 (w), 1008 (s), 923 (m), 810 (s), 703 (m), 664 (s), 633 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.43 (d, *J*=8.3 Hz, 2H, 2 x Ar**H**), 7.30 (d, *J*=7.3 Hz, 3H, 3 x Ar**H**), 7.19 (d, *J*=6.8 Hz, 2H, 2 x Ar**H**), 7.13 (d, *J*=8.3 Hz, 2H, 2 x Ar**H**), 7.05 (d, *J*=8.3 Hz, 1H, Ar**H**), 6.86-6.98 (m, 7H, 7 x Ar**H**), 6.74 (s, 1H, Ar**H**), 5.36 (s, 1H, OC**H**O), 4.97 (d, *J*=9.0 Hz, 2H, ArC**H**$_2$), 4.37 (d, *J*=19.8 Hz, 2H, ArC**H**$_2$), 3.89 (s, 3H, OC**H**$_3$), 3.82 (s, 3H, OC**H**$_3$), 3.78 (d, *J*=10.6 Hz, 2H, OC**H**$_2$C), 3.65 (d, *J*=10.9 Hz, 2H, OC**H**$_2$C), 2.84 (s, 4H, ArC**H**$_2$C**H**$_2$Ar),

	2.37 (br. s., 1H, O**H**), 1.31 (s, 3H, C**H**$_3$), 0.82 (s, 3H, C**H**$_3$).
δ$_C$ (100 MHz, CDCl$_3$)	159.2 (**C**), 158.2 (**C**), 154.0 (**C**), 149.4 (**C**), 144.6 (**C**), 140.8 (**C**), 136.7 (**C**), 134.6 (**C**), 134.5 (**C**), 132.7 (**C**), 131.8 (**C**H), 131.2 (**C**H), 130.4 (**C**), 129.6 (**C**), 128.6 (**C**H), 128.4 (2 x **C**H), 127.7 (**C**H), 127.5 (2 x **C**H), 127.1 (2 x **C**H), 124.5 (**C**H), 121.0 (**C**H), 117.0 (2 x **C**H), 113.9 (**C**H), 113.2 (**C**H), 113.0 (**C**H), 112.7 (**C**H), 101.5 (**C**H), 77.6 (2 x **C**H$_2$), 71.3 (**C**H$_2$), 63.5 (**C**H$_2$), 56.0 (**C**H$_3$), 55.3 (**C**H$_3$), 37.0 (**C**H$_2$), 37.0 (**C**H$_2$), 30.1 (**C**), 23.0 (**C**H$_3$), 21.8 (**C**H$_3$).
LRMS (ESI+, m/z)	683 [M+Na]$^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{42}H_{44}NaO_7$ [M+Na]$^+$ requires 683.2979; found: 683.2985.

4-(5-(2-(6-(Benzyloxy)-2'-(hydroxymethyl)-4'-methoxy-[1,1'-biphenyl]-3-yl)ethyl)-2-methoxyphenoxy)benzaldehyde (3.35)



To a stirred solution of protecting aldehyde **3.34** (1.03 g, 1.56 mmol) in THF (30 mL) was added 2M HCl 4 mL). After 2 h at RT, water (10 ml) was added to the mixture. The aqueous phase was extracted with Et$_2$O (3 x 50 mL) and the resulting organic phases were combined, dried over MgSO$_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography column (50% Et$_2$O/PE) to afford the title compound **3.35** as a white foam (520 mg, 58%).

IR (υ_{max})	3463 (br. w), 2923 (w), 2854 (w), 1686 (m), 1598 (m), 1577 (m), 1501 (s), 1488 (m), 1441 (w), 1423 (w), 1269 (s), 1226 (s), 1184 (w), 1153 (s), 1121 (m), 1024 (m), 909 (m), 857 (w), 831 (m), 812 (m), 731 (s), 696 (w), 620 (w) cm^{-1}.
δ$_H$ (400 MHz, CDCl$_3$)	9.89 (s, 1H, C**H**O), 7.79 (d, *J*=8.8 Hz, 2H, 2 x Ar**H**), 7.34 -7.27 (m, 3H, 3 x Ar**H**), 7.18 (d, *J*=2.0 Hz, 2H, 2 x Ar**H**), 7.13-7.08 (m, 3H, 3 x Ar**H**), 7.00-6.89 (m, 8H, 8 x Ar**H**),

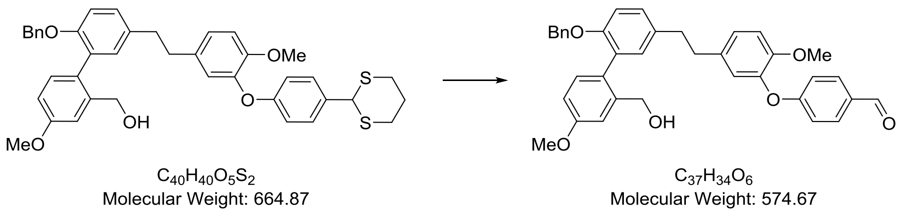
4.96 (d, *J*=8.7 Hz, 2H, ArC**H**$_2$),
4.50-4.20 (m, 2H, ArC**H**$_2$),
3.89 (s, 3H, OC**H**$_3$),
3.79 (s, 3H, OC**H**$_3$),
2.89 (s, 4H, ArC**H**$_2$C**H**$_2$Ar),
2.22 (t, *J*=6.4 Hz, 1H, O**H**).

δ_C (100 MHz, CDCl$_3$) 190.7 (**C**HO), 163.5 (**C**), 159.2 (**C**), 154.1 (**C**), 149.8 (**C**), 142.5 (**C**), 140.7 (**C**), 136.6 (**C**), 134.9 (**C**), 134.4 (**C**), 131.8 (2 x **C**H), 131.2 (**C**H), 130.8 (**C**), 130.5 (**C**), 129.7 (**C**), 128.5 (**C**H), 128.5 (2 x **C**H), 127.8 (**C**H), 127.1 (2 x **C**H), 127.1 (**C**H), 126.3 (**C**H), 122.6 (**C**H), 116.1 (2 x **C**H), 114.0 (**C**H), 113.4 (**C**H), 113.3 (**C**H), 112.9 (**C**H), 71.4 (**C**H$_2$), 63.7 (**C**H$_2$), 56.0 (**C**H$_3$), 55.3 (**C**H$_3$), 36.9 (2 x **C**H$_2$).

LRMS (ESI+, m/z) 597 [M+Na]$^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{37}H_{34}NaO_6$ [M+Na]$^+$ requires 597.2248; found: 597.2253.

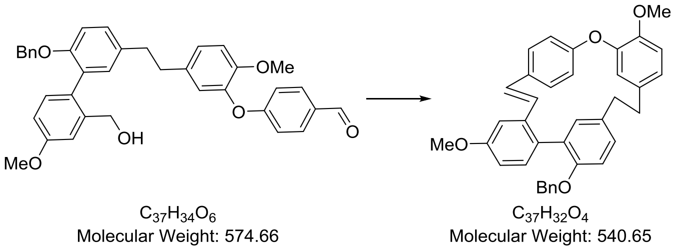
4-(5-(2-(6-(Benzyloxy)-2'-(hydroxymethyl)-4'-methoxy-[1,1'-biphenyl]-3-yl)ethyl)-2-methoxyphenoxy)benzaldehyde (3.35)



To a stirred solution of protected aldehyde **3.29** (41 mg, 0.06 mmol) in MeCN (3 mL) and water (3 mL) was added CaCO$_3$ (67 mg, 0.67 mmol) and methyl iodide (180 mg, 1.30 mmol). The reaction mixture was heated at reflux for 18 h, then cooled to RT and diluted it with Et$_2$O (10 mL) and water (10 mL). The reaction mixture was extracted with Et$_2$O (3 x 20 mL), then the combined organic phases were dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography (75% Et$_2$O/hexane) afforded the title compound **3.35** as a white foam (31 mg, 87%).

The data were identical to those previously reported (See P.142).

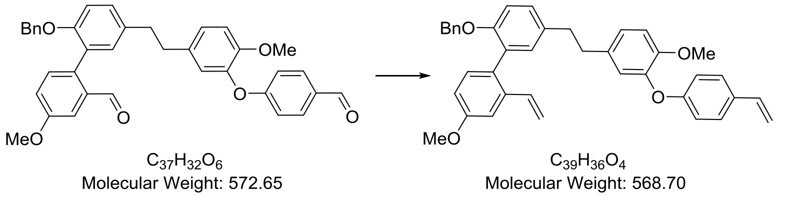
13,14-Dihydro-18-benzyloxy-9,23-dimethoxy-3,6-etheno-8,12;15,19-bis(metheno)-7-oxabenzo[*t*]cycloeicosadecaene (3.13)



To a stirred solution of benzyl alcohol **3.35** (2.40 g, 4.17 mmol) in MeCN (25 mL) was added PPh_3.HBr (1.58 g, 4.59 mmol). The reaction mixture was heated at reflux for 18 h. The reaction mixture was concentrated *in vacuo.* The residue was then dissolved in DCM (150 mL) and a solution of KO^{t}Bu (940 mg, 8.35 mmol) in (150 mL) was added to the mixture. After 18 h at reflux, the reaction mixture was concentrated i*n vacuo.* The residue was purified by flash column chromatography (15-20% Et_2O/PE) to afford the *title compound* **3.13** as a white solid (230 mg, 10%).

The data were identical to those previously reported (See P.123).

2'-(Benzyloxy)-4-methoxy-5'-(4-methoxy-3-(4-vinylphenoxy)phenethyl)-2-vinyl-1,1'-biphenyl (3.18)

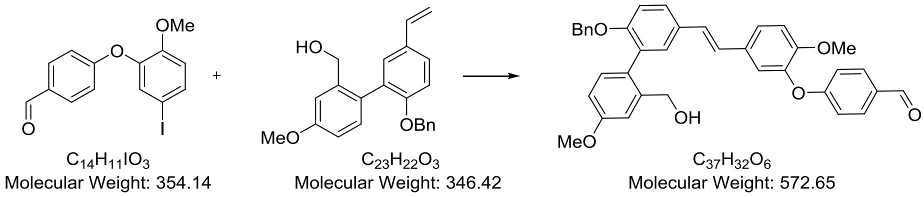


To a solution of methyltriphenylphosphonium bromide (1.12 g, 3.15 mmol) in THF (10 mL) at 0 °C was added KO^{t}Bu (420 mg, 3.78 mmol). After 15 min, a solution of bis-aldehyde **3.12** (720 mg, 1.26 mmol) in THF (1.5 mL) was added. The reaction mixture was warmed to RT. After 4 h, sat. NH_4Cl (5 mL) was added. The organic phase was extracted with Et_2O (3 x 20 mL), then the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% Et_2O/PE) to afford the title compound **3.18** as a colourless oil (520 mg, 72%).

IR (υ_{max})	2928 (w), 1603 (m), 1562 (w), 1503 (s), 1485 (m), 1454 (m), 1422 (w), 1269 (s), 1225 (s), 1166 (s), 1124 (m), 1025 (m), 990 (w), 908 (w), 837 (w), 811 (w), 737 (w), 696 (m) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.22 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 7.20-7.12 (m, 5H, 5 x Ar**H**), 7.11 (d, *J*=2.6 Hz, 1H, Ar**H**),

	7.06 (d, *J*=8.4 Hz, 1H, Ar**H**), 6.94 (dd, *J*=2.3, 8.3 Hz, 1H, Ar**H**), 6.83 (d, *J*=2.3 Hz, 1H, Ar**H**), 6.82-6.74 (m, 6H, 6 x Ar**H**), 6.70 (s, 1H, Ar**H**), 6.57 (dd, *J*=10.9, 17.6 Hz, 1H, ArC**H**), 6.43 (dd, *J*=10.9, 17.5 Hz, 1H, ArC**H**), 5.57 (d, *J*=12.8 Hz, 1H, =CH**H**), 5.53 (d, *J*=13.0 Hz, 1H, =CH**H**), 5.06 (d, *J*=11.0 Hz, 1H, =C**H**H), 5.02 (d, *J*=10.8 Hz, 1H, =C**H**H), 4.89 (s, 2H, ArC**H**$_2$O), 3.80 (s, 3H, OC**H**$_3$), 3.72 (s, 3H, OC**H**$_3$), 2.74 (s, 4H, ArC**H**$_2$C**H**$_2$Ar).
δ$_C$ (100 MHz, CDCl$_3$)	158.9 (**C**), 157.8 (**C**), 154.3 (**C**), 149.5 (**C**), 144.4 (**C**), 143.1 (**C**H), 137.5 (**C**), 137.4 (**C**), 136.1 (**C**H), 135.8 (**C**H), 134.8 (**C**), 133.7 (**C**), 132.2 (**C**H), 131.9 (**C**), 131.7 (**C**H), 130.5 (**C**), 130.1 (**C**), 128.3 (**C**H), 128.2 (2 x **C**H), 127.4 (2 x **C**H), 126.7 (2 x **C**H), 124.7 (**C**H), 121.3 (**C**H), 117.0 (2 x **C**H), 114.0 (**C**H$_2$), 113.2 (**C**H), 113.2 (**C**H), 112.7 (**C**H), 112.3 (**C**H$_2$), 109.6 (**C**H), 70.5 (**C**H$_2$), 56.1 (**C**H$_3$), 55.3 (**C**H$_3$), 37.1 (**C**H$_2$), 37.0 (**C**H$_2$).
LRMS (ESI+, m/z)	591 [M+Na]$^+$ (40%).
HRMS (ESI+, m/z)	calcd for $C_{39}H_{36}NaO_4$ [M+Na]$^+$ requires 591.2506; found: 591.2504.

<u>(*E*)-4-(5-(2-(6-(Benzyloxy)-2'-(hydroxymethyl)-4'-methoxy-[1,1'-biphenyl]-3-yl)vinyl)-2-methoxyphenoxy)benzaldehyde (3.27)</u>

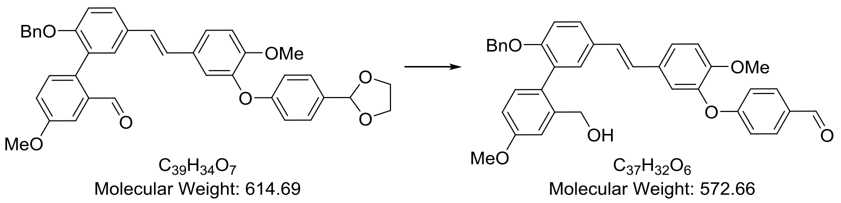


To a stirred solution of iodide **1.148** (4.78 g, 13.4 mmol) and styrene **3.21** (5.14 g, 14.8 mmol) in DMA (55 mL) was added potassium phosphate (4.01 g, 18.8 mmol). The reaction mixture was degassed with sonication for 20 min under argon then Pd(OAc)$_2$ (150 mg, 0.67 mmol) was added. The reaction mixture was heated at reflux for 18 h then cooled to RT. Water (100 mL) was added.

The product was extracted by EtOAc (3 x 50 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (65% Et_2O/PE) to afford the title compound **3.27** as a white solid (5.84 g, 76%).

MP	70-71 °C (Et_2O/PE)
IR (υ_{max})	3438 (br. s), 2933 (w), 2836 (w), 1689 (m), 1596 (m), 1581 (m), 1501 (s), 1454 (m), 1424 (w), 1269 (s), 1225 (s), 1153 (s), 1120 (w), 1046 (w), 906 (w), 813 (w), 725 (s), 725 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	9.91 (s, 1H, C**H**O), 7.84 (d, *J*=8.8 Hz, 2H, 2 x Ar**H**), 7.40 (dd, *J*=8.6, 2.3 Hz, 1H, Ar**H**), 7.34 (d, *J*=2.3 Hz, 1H, ArH), 7.33-7.26 (m, 5H, 5 x Ar**H**), 7.20-7.16 (m, 3H, 3 x Ar**H**), 7.12 (d, *J*=2.7 Hz, 1H,Ar**H**), 7.04-6.98 (m, 4H, 4 x Ar**H**), 6.94-6.90 (m, 3H, Ar**H** , ArC**H**C**H**Ar), 5.02 (br., 2H, ArOC**H**$_2$), 4.35-4.51 (br., 2H, ArC**H**$_2$), 3.88 (s, 3H, OC**H**$_3$), 3.81 (s, 3H, OC**H**$_3$), 2.15 (s, 1H, O**H**).
δ_C (100 MHz, $CDCl_3$)	190.8 (**C**HO), 163.4 (**C**), 159.4 (**C**), 155.4 (**C**), 151.0 (**C**), 143.1 (**C**), 140.7 (**C**), 136.4 (**C**), 131.9 (2 x **C**H), 131.4 (**C**), 131.3 (**C**H), 130.9 (**C**), 130.9 (**C**), 130.7 (**C**), 129.4 (**C**), 129.4 (**C**H), 128.5 (2 **C**H), 127.9 (**C**H), 127.1 (2 x **C**H), 127.0 (**C**), 126.9 (**C**H), 126.0 (**C**H), 124.7 (**C**H), 119.7 (**C**H), 116.2 (2 x **C**H), 113.9 (**C**H), 113.4 (**C**H), 113.3 (**C**H), 113.1 (**C**H), 71.2 (**C**H$_2$), 63.7 (**C**H$_2$), 56.0 (**C**H$_3$), 55.3 (**C**H$_3$).
LRMS (ESI+, m/z)	595 $[M+Na]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{37}H_{32}NaO_6$ $[M+Na]^+$ requires 595.2091; found: 595.2082

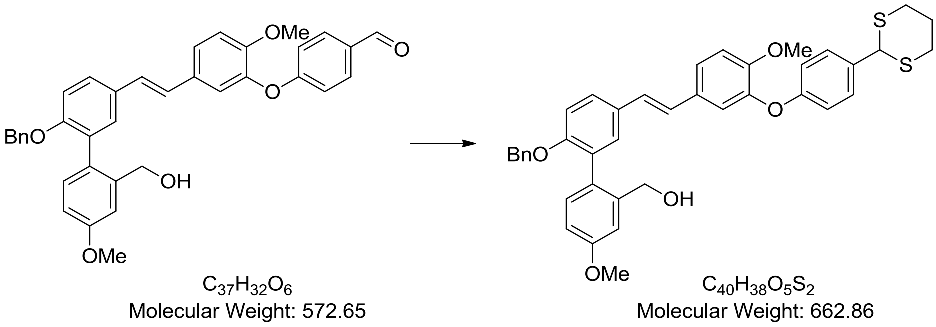
(*E*)-4-(5-(2-(6-(Benzyloxy)-2'-(hydroxymethyl)-4'-methoxy-[1,1'-biphenyl]-3-yl)vinyl)-2-methoxyphenoxy)benzaldehyde (3.27)



To a suspension of aldehyde **3.24** (1.3 g, 2.11 mmol) in methanol (8 mL) and DCM (8 mL) at 0 °C was added $NaBH_4$ (160 mg, 4.23 mmol). Then, the reaction mixture warmed to RT. After 1 h, water (5 mL) and 2M HCl (10 mL) were added. After 24 h at RT, water (20 mL) was added to the mixture. The product was extracted by Et_2O (3 x 50 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (65% Et_2O/PE) to afford the title compound **3.27** as a white solid (1.01 g, 83%).

The data were identical to those previously reported (See P.145).

(*E*)-(5'-(3-(4-(1,3-Dithian-2-yl)phenoxy)-4-methoxystyryl)-2'-(benzyloxy)-4-methoxy-[1,1'-biphenyl]-2-yl)methanol (3.28)



To a stirred solution of arene **3.27** (4.53 g, 7.93 mol) in DCM (88 mL) was added propan-1,3-dithiol (2.58 g, 23.8 mmol) and PPTS (490 mg, 1.90 mmol). The reaction mixture was heated at reflux for 18 h and cooled to RT. Water (30 mL) and saturated aqueous $NaHCO_3$ (100 mL) was added. The aqueous phase was extracted with Et_2O (60 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (70% Et_2O/PE) afforded the title compound **3.28** as a white foamy solid (4.79 g, 91%).

MP	85-87 °C (Et_2O/PE)
IR (υ_{max})	3445 (br. s), 2933 (w), 2897 (w), 1605 (m), 1572 (w), 1501 (s), 1454 (m), 1441 (m), 1422 (m), 1381 (w), 1268 (s), 1222 (s), 1166 (m), 1124 (m), 1023 (m), 962 (w), 907 (m), 727 (s) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.43-7.36 (m, 3H, 3 x Ar**H**), 7.33 (d, *J*=2.2 Hz, 1H, Ar**H**), 7.30-7.25 (m, 3H, 3 x Ar**H**),

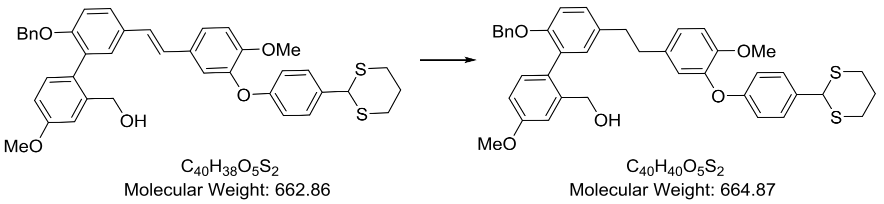
7.24 (dd, *J*=8.5, 2.2 Hz, 1H, Ar**H**),
7.19-7.15 (m, 4H, 4 x Ar**H**),
7.12 (d, *J*=2.7 Hz, 1H, Ar**H**),
6.99 (t, *J*=8.1 Hz, 2H, 2 x Ar**H**),
6.94-6.87 (m, 5H, 3 x Ar**H**, 2 x ArC**H**C**H**Ar),
5.16 (s, 1H, ArC**H**S),
5.01 (br., 2H, ArOC**H**$_2$),
4.55-4.35 (br., 2H, ArC**H**$_2$),
3.88 (s, 3H, OC**H**$_3$),
3.84 (s, 3H, OC**H**$_3$),
3.11-3.01 (m, 2H, SC**H**$_2$CH$_2$),
2.91 (dt, *J*=14.0, 3.7 Hz, 2H, SC**H**$_2$CH$_2$),
2.21-2.11 (m, 1H, SCH$_2$CH**H**),
1.97-1.86 (m, 1H, SCH$_2$C**H**H).

δ_C (100 MHz, $CDCl_3$) 159.3 (**C**), 158.0 (**C**), 155.3 (**C**), 151.0 (**C**), 144.5 (**C**), 140.7 (**C**), 136.4 (**C**), 133.0 (**C**), 131.3 (**C**H), 131.1 (**C**), 130.9 (**C**), 130.8 (**C**), 129.5 (**C**), 129.3 (**C**H), 129.0 (2 x **C**H), 128.5 (2 x **C**H), 127.1 (**C**H), 126.9 (2 x **C**H), 126.8 (**C**H), 126.6 (**C**H), 126.2 (**C**H), 123.5 (**C**H), 118.9 (**C**H), 116.9 (2 x **C**H), 113.9 (**C**H), 113.4 (**C**H), 113.2 (**C**H), 112.9 (**C**H), 71.2 (**C**H$_2$), 63.7 (**C**H$_2$), 56.0 (**C**H$_3$), 55.3 (**C**H$_3$), 50.7 (**C**H), 32.1 (2 x **C**H$_2$), 25.0 (**C**H$_2$).

LRMS (ESI+, m/z) 685 $[M+Na]^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{40}H_{38}NaO_5S_2$ $[M+Na]^+$ requires 685.2053; found: 685.2058.

<u>(5'-(3-(4-(1,3-Dithian-2-yl)phenoxy)-4-methoxyphenethyl)-2'-(benzyloxy)-4-methoxy-[1,1'-biphenyl]-2-yl)methanol (3.29)</u>

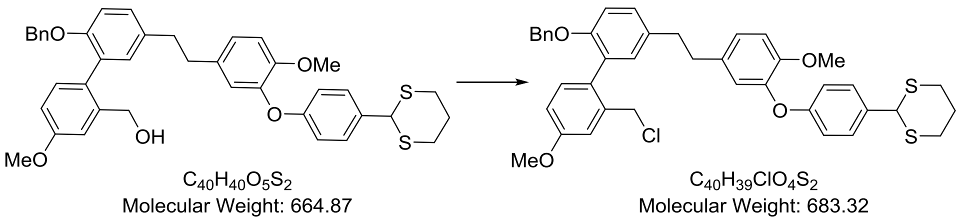


To a stirred solution of stilbene **3.28** (1.50 g, 2.26 mmol) in a mixture (1:1, v/v) of THF (30 mL) and water (30 mL) was added tosylhydrazone (4.21 g, 22.62 mmol) and NaOAc (1.86 g, 22.62 mmol). The reaction mixture was heated at reflux for 18 h, then cooled to RT and saturated aqueous K_2CO_3 (50 mL) and water (10 mL) added. The reaction mixture was extracted with Et_2O (3 x 100 mL), then the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*.

Purification by flash column chromatography (50% Et$_2$O/PE) afforded the title compound **3.29** as a white solid (1.37 g, 91%).

MP	90-92 °C (Et$_2$O/PE)
IR (υ_{max})	3447 (br. s), 2933 (w), 1605 (m), 1501 (s), 1454 (w), 1422 (w), 1269 (s), 1223 (s), 1164 (s), 1123 (m), 1024 (m), 906 (s), 849 (m), 725 (s) cm^{-1}.
δ$_H$ (400 MHz, CDCl$_3$)	7.37 (d, J=8.7 Hz, 2H, 2 x Ar**H**), 7.31-7.27 (m, 3H, 3 x Ar**H**), 7.20-7.15 (m, 2H, 2 x Ar**H**), 7.13-7.10 (m, 2H, 2 x Ar**H**), 7.08 (dd, J=8.3, 2.2 Hz, 1H, Ar**H**), 6.95 (d, J=8.4 Hz, 1H, Ar**H**), 6.93-6.89 (m, 4H, 4 x Ar**H**), 6.85 (d, J=8.8 Hz, 2H, 2 x Ar**H**), 6.81 (br. s, 1H, Ar**H**), 5.14 (s, 1H, ArC**H**S), 4.98 (br., 2H, ArOC**H**$_2$), 4.48-4.29 (br., 2H, ArC**H**$_2$O), 3.89 (s, 3H, OC**H**$_3$), 3.81 (s, 3H, OC**H**$_3$), 3.14-2.98 (m, 2H, SC**H**$_2$CH$_2$), 2.90 (dt, J=14.1, 3.7 Hz, 2**H**, SC**H**$_2$CH$_2$), 2.86 (br. s, 4H, 4 x ArC**H**$_2$C**H**$_2$Ar), 2.31 (t, J=6.2 Hz, 1H, O**H**), 2.17 (m, 1H, SCH$_2$CH**H**), 1.92 (m, 1H, SCH$_2$C**H**H).
δ$_C$ (100 MHz, CDCl$_3$)	159.2 (**C**), 158.1 (**C**), 154.0 (**C**), 149.7 (**C**), 143.9 (**C**), 140.7 (**C**), 136.7 (**C**), 134.6 (**C**), 134.5 (**C**), 132.7 (**C**), 131.8 (**C**H), 131.2 (**C**H), 130.4 (**C**), 129.7 (**C**), 128.9 (2 x **C**H), 128.5 (**C**H), 128.4 (2 x **C**H), 127.8 (**C**H), 127.1 (2 x **C**H), 125.0 (**C**H), 121.8 (**C**H), 116.6 (2 x **C**H), 113.9 (**C**H), 113.3 (**C**H), 113.1 (**C**H), 112.7 (**C**H), 71.3 (**C**H$_2$), 63.6 (**C**H$_2$) 56.0 (**C**H$_3$), 55.3 (**C**H$_3$), 50.7 (**C**H), 36.9 (**C**H$_2$), 36.9 (**C**H$_2$), 32.1 (2 x **C**H$_2$), 24.8 (**C**H$_2$).
LRMS (ESI+, m/z)	687 [M+Na]$^+$ (100%).
HRMS (ESI+, m/z)	calcd for C$_{40}$H$_{40}$NaO$_5$S$_2$ [M+Na]$^+$ requires 687.2209; found: 687.2203

2-(4-(5-(2-(6-(Benzyloxy)-2'-(chloromethyl)-4'-methoxy-[1,1'-biphenyl]-3-yl)ethyl)-2-methoxyphenoxy)phenyl)-1,3-dithiane (3.38)



To a stirred solution of mixture of benzyl alcohol **3.29** (760 mg, 1.14 mmol) in 55 mL DCM, DBU (520 mg, 3.42 mmol) and LiCl (53 mg, 1.25 mmol) were added. The MsCl (390 mg, 3.42 mmol) was added in an ice-water bath. After 18 h at RT, the mixture was concentrated *in vacuo*. Purification by flash column chromatography (30% Et_2O/PE) afforded the title compound **3.38** as a colourless oil (690 mg, 88%).

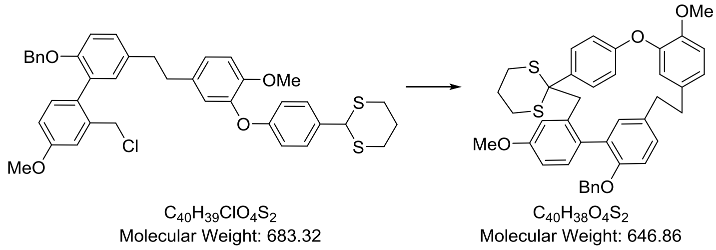
IR (υ_{max})	2930 (w), 1605 (w), 1503 (m), 1456 (w), 1369 (w), 1270 (m), 1225 (m), 1165 (m), 1123 (w), 1026 (w), 905 (s), 812 (w), 724 (s), 648 (m) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.35 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**),
	7.31-7.23 (m, 3H, 3 x Ar**H**),
	7.20-7.17 (m, 2H, 2 x Ar**H**),
	7.15 (d, *J*=8.4 Hz, 1H, Ar**H**),
	7.10 (d, *J*=2.6 Hz, 1H, Ar**H**),
	7.05 (dd, *J*=8.3,2.3 Hz, 1H, Ar**H**),
	7.01 (d, *J*=2.2 Hz, 1H, Ar**H**),
	6.93-6.87 (m, 4H, 4 x Ar**H**),
	6.85-6.80 (m, 3H, 3 x Ar**H**),
	5.11 (s, 1H, ArC**H**S)
	5.00 (s, 2H, ArOC**H**$_2$),
	4.44 (d, *J*=11.7 Hz, 1H, ArC**H**HO),
	4.35 (d, *J*=11.3 Hz, 1H, ArCH**H**O),
	3.88 (s, 3H, OC**H**$_3$),
	3.80 (s, 3H, OC**H**$_3$),
	3.09-2.98 (m, 2H, SC**H**$_2$CH$_2$),
	2.89 (dt, *J*=14.1, 3.8 Hz, 2H, SC**H**$_2$CH$_2$),
	2.84 (s, 4H, 4 x ArC**H**$_2$C**H**$_2$Ar),
	2.16 (m, 1H, SCH$_2$CH**H**),
	1.90 (m, 1H, SCH$_2$C**H**H).

δ_C (100 MHz, CDCl$_3$) 159.0 (**C**), 158.2 (**C**), 154.0 (**C**), 149.7 (**C**), 143.9 (**C**), 137.3 (**C**), 137.1 (**C**), 134.8 (**C**), 134.0 (**C**), 132.7 (**C**), 131.9 (**C**H), 131.7 (**C**H), 130.6 (**C**), 129.2 (**C**), 128.9 (2 x **C**H), 128.8 (**C**H), 128.3 (2 x **C**H), 127.5 (**C**H), 126.7 (2 x **C**H), 125.1 (**C**H), 121.9 (**C**H), 116.7 (2 x **C**H), 114.4 (**C**H), 113.9 (**C**H), 113.1 (**C**H), 112.8 (**C**H), 70.5 (**C**H$_2$), 56.1 (**C**H$_3$), 55.4 (**C**H$_3$), 50.8 (**C**H), 44.8 (**C**H$_2$), 37.0 (**C**H$_2$), 36.9 (**C**H$_2$), 32.1 (2 x **C**H), 25.0 (**C**H$_2$).

LRMS (ESI+, m/z) 705 [M(^{35}Cl)+Na]$^+$ (100%), 707 [M(^{37}Cl)+Na]$^+$ (40%).

HRMS (ESI+, m/z) calcd for $C_{40}H_{39}ClNaO_4S_2$ [M+Na]$^+$ requires 705.1870; found: 705.1858.

22-Benzyloxy-2,3,4,17,18,30-hexahydro-13,27-dimethoxy-7,10-etheno-12,16;19,23-bis(metheno)-11-oxa-1,5-dithiabenzo-[x]spiro[5,20]hexacosatridecaene (3.39)



To a stirred solution of mixture of compound **3.38** (0.20 g, 0.29 mmol) in 30 mL THF at -78 °C was added *n*-BuLi (0.13 mL, 0.32 mmol, 2.44 M in hexanes) dropwise over 3 min. The reaction mixture was warmed to RT for 18 h. sat. NH_4Cl (10 mL) and water (5 mL) was added. After 5 min the aqueous phase was separated at extracted with Et_2O (3 x 20 mL), then the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (40-50 % Et_2O/PE) afforded the title compound **3.39** as a white solid (91.9 mg, 48%).

MP 118-120 °C (Et_2O/PE)

IR (υ_{max}) 2925 (m), 2852 (w), 1605 (m), 1582 (w), 1513 (m), 1496 (s), 1463 (m), 1421 (w), 1270 (s), 1230 (s), 1166 (m), 1128 (m), 1027 (w), 910 (w), 803 (w), 734 (m), 696 (w) cm^{-1}.

δ_H (400 MHz, CDCl$_3$)
7.55 (br. s, 1H, Ar**H**),
7.42 (d, *J*=2.7 Hz, 1H, Ar**H**),
7.37-7.23 (m, 7H, 7 x Ar**H**),
7.06 (dd, *J*=8.4, 2.1 Hz, 1H, Ar**H**),
6.94 (d, *J*=8.6 Hz, 1H, Ar**H**),
6.89-6.78 (m, 4H, 4 x Ar**H**),
6.80 (d, *J*=1.9 Hz, 1H, Ar**H**),

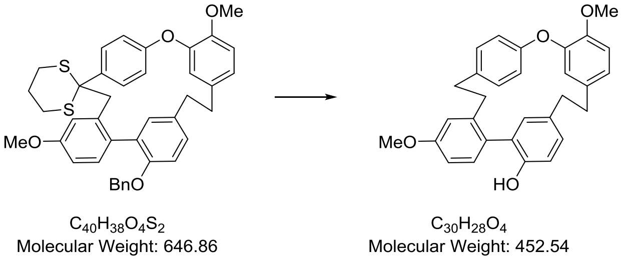
6.76 (d, *J*=2.1 Hz, 1H, Ar**H**),
6.63 (d, *J*=1.8 Hz, 1H, Ar**H**),
4.95 (d, *J*=12.2 Hz, 1H, ArC**H**HO),
4.85 (d, *J*=12.0 Hz, 1H, ArCH**H**O),
3.91 (s, 6H, OC**H**$_3$),
3.62 (d, *J*=14.2 Hz, 1H, ArC**H**HC),
3.52 (d, *J*=14.0 Hz, 1H, ArCH**H**C),
3.19-2.95 (m, 3H, SC**H**HCH$_2$, SC**H**$_2$CH$_2$),
2.72-2.55 (m, 4H, 4 x ArC**H$_2$**C**H$_2$**Ar),
2.47 (m, 1H, SCH**H**CH$_2$),
1.98-1.87 (m, 2H, SCH$_2$C**H**$_2$).

δ_C (100 MHz, CDCl$_3$) 157.6 (**C**), 154.6 (**C**), 153.1 (**C**), 148.8 (**C**), 147.2 (**C**), 137.2 (**C**), 136.3 (**C**), 135.6 (**C**), 134.8 (**C**), 134.6 (**C**), 133.4 (**C**H), 131.9 (**C**), 131.7 (**C**H), 130.8 (**C**), 128.4 (2 x **C**H), 127.6 (**C**H), 127.2 (**C**H), 127.2 (2 x **C**H), 127.1 (2 x **C**H), 122.0 (**C**H), 117.5 (**C**H), 116.1 (**C**H), 113.8 (2 x **C**H), 113.0 (**C**H), 112.1 (2 x **C**H), 71.1 (**C**H$_2$), 59.7 (**C**), 56.3 (**C**H$_3$), 55.3 (**C**H$_3$), 49.5 (**C**H$_2$), 34.0 (**C**H$_2$), 31.8 (**C**H$_2$), 28.2 (**C**H$_2$), 27.5 (**C**H$_2$), 25.2 (**C**H$_2$).

LRMS (ESI+, m/z) 669 [M+Na]$^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{40}H_{38}NaO_4S_2$ [M+Na]$^+$ requires 669.2104; found: 669.2103.

1,2,13,14-Tetrahydro-18-hydroxy-9,23-dimethoxy-3,6-etheno-8,12;15,19-bis(metheno)-7-oxabenzo[*t*]cycloeicosadecaene (1.232)

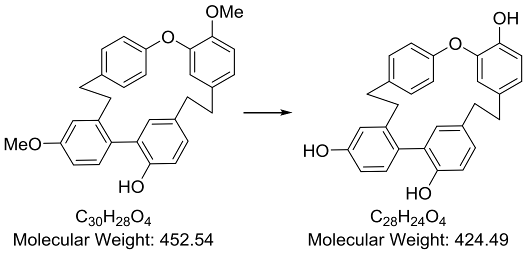


To a stirred solution of mixture of NiCl$_2$.6H$_2$O (310 mg, 1.28 mmol) in 1 mL DMF, solution of the compound **3.39** (52 mg, 0.08 mmol) in 2 mL THF at 0 °C was added NaBH$_4$ (96 mg, 2.56 mmol). The reaction mixture was warmed to RT for 18 h. The mixture filtered through Celite© and the solvent was removed *in vacuo*. Water (10 mL) was added. The aqueous phase was separated at extracted with Et$_2$O (3 x 15 mL), then the combined organic phases were dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography (30 % Et$_2$O/PE) afforded the residue as a white solid (25 mg, 0.047 mmol, 59%). To a solution of residue in EtOH (3 mL) and

DCM (3 mL) was added 10% Pd/C (10 mg, 0.094 mmol). The flask was evacuated/purged with argon three times then evacuated/purged with hydrogen twice. After 6 h stirred vigorously under an atmosphere of H_2 at RT, the mixture filtered through Celite© and the solvent was removed *in vacuo*. The residue was purified by flash chromatography column (50-70% Et_2O/hexane) to afford the title compound **1.232** as a white solid (15.8 mg, 74%).

The data were identical to those previously reported (See P.124).

1,2,13,14-Tetrahydro-9,18,23-trihydroxy-3,6-etheno-8,12;15,19-bis(metheno)-7-oxabenzo[*t*]cycloeicosadecaene (1.3)



To a stirred solution of macrocyclic bis(bibenzyl) **1.232** (150 mg, 0.33 mmol) in DCM (33 mL) at 0°C was added boron tribromide (3.31 mL, 1 M solution in DCM, 3.31 mmol). After 5 h at RT, water (10 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 x 30 mL), and then the resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% Et_2O/hexane) afforded the title compound **1.3** as a white solid (130 mg, 92%).

MP	154-155 °C (Et_2O/hexane)
IR (υ_{max})	3363 (br. s), 2954 (m), 2923 (s), 2853 (m), 1603 (w), 1505 (s), 1456 (w), 1445 (m), 1375 (w), 1287 (w), 1222 (s), 1163 (m), 1111 (w), 976 (w), 910 (w), 851 (w), 731 (w), 6690 (w) cm^{-1}.
δ_H (400 MHz, MeOD)	6.93 (d, *J*=2.6 Hz, 1H, Ar**H**), 6.89 (dd, *J*=8.4, 2.1 Hz, 1H, Ar**H**), 6.80 (d, *J*=8.4 Hz, 1H, Ar**H**), 6.74 (d, *J*=1.2 Hz, 1H, Ar**H**), 6.69 (d, *J*=8.1 Hz, 1H, Ar**H**), 6.66-6.62 (m, 2H, 2 x Ar**H**), 6.61-6.56 (m, 3H, 3 x Ar**H**), 6.51 (d, *J*=2.2 Hz, 1H, Ar**H**), 6.32 (br. s, 1H, Ar**H**), 6.22 (d, *J*=2.0 Hz, 1H, Ar**H**), 3.04 (dd, *J*=12.9, 4.8 Hz, 1H, ArC**H**HCH_2Ar),

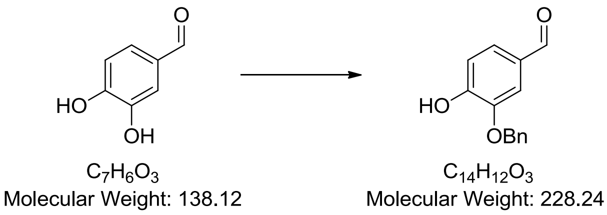
2.96-2.65 (m, 6H, ArC**H**$_2$CH**H**Ar),
2.43 (m, 1H, ArCH**H**C**H**$_2$Ar).

δ_C (100 MHz, MeOD) 157.9 (**C**), 155.6 (**C**), 152.8 (**C**), 149.6 (**C**), 145.5 (**C**), 143.4 (**C**), 139.8 (**C**), 136.6 (**C**), 135.0 (**C**), 133.4 (**C**H), 132.8 (**C**H), 132.4 (**C**), 130.7 (**C**H), 129.7 (**C**), 128.5 (**C**H), 122.7 (br. 2 x **C**H), 121.6 (br. 2 x **C**H), 116.9 (**C**H), 116.8 (**C**H), 116.8 (**C**H), 116.3 (**C**H), 114.4 (**C**H), 38.8 (**C**H$_2$), 37.1 (**C**H$_2$), 36.0 (**C**H$_2$), 34.5 (**C**H$_2$).

LRMS (ESI-, m/z) 447 [M+1]$^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{28}H_{25}O_4$ [M+H]$^+$ requires 425.1747; found: 425.1743.

3-(Benzyloxy)-4-hydroxybenzaldehyde (3.48)

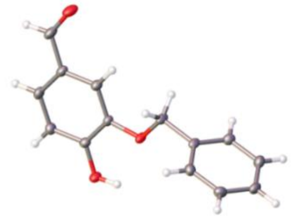


To a stirred solution of sodium hydride (60% in mineral oil; 579 mg, 4.48 mmol) in anhydrous DMF (14 mL) were added dropwise in the ice bath with a solution of 3,4-dihydroxybenzaldehyde **3.2** (1.00 g, 7.24 mmol) in anhydrous DMF (7 mL). The mixture was stirred at RT for 1 h and re-cooled on an ice bath. Benzyl chloride (1.04 mL, 1.05 mmol) was added and the mixture allowed to warm to RT for 18 h. Ice water (30 mL) was added and acidified with 2M HCl (20 mL). The mixture was extracted with Et_2O (3 X 100 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (25% Et_2O/PE) to afford the title compound **3.48** as white solid (1.20 g, 72%).

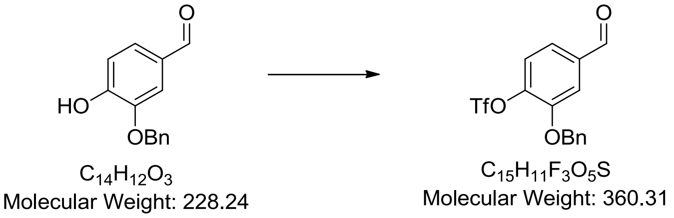
MP 115- 116 °C (Et_2O/PE) [Lit. 117-118 °C (PE)][102]

IR (υ_{max}) 3231 (br.w), 2969 (m), 1701 (m), 1666 (s), 1587 (s), 1509 (m), 1487 (w), 1436 (s), 1385 (m), 1297 (m), 1265 (s), 1151 (s), 1114 (m), 1078 (w), 1005 (m), 918 (w), 872 (w), 771 (w), 740 (m), 682 (s), 631 (s), 587 (w), 559 (w) cm^{-1}.

δ_H (400 MHz, CDCl$_3$) 9.81 (s, 1H, C**H**O),
7.52 (d, *J*=1.7 Hz, 1H, Ar**H**),
7.45 (d, *J*=1.8 Hz, 1H, Ar**H**),
7.44-7.42 (m, 4H, 4 X Ar**H**),
7.41-7.39 (m, 1H, Ar**H**),
7.07 (d, *J*=8.1 Hz, 1H, Ar**H**),

	6.39 (s, 1H, O**H**), 5.17 (s, 2H, ArC**H**$_2$O).
δ$_C$ (100 MHz, CDCl$_3$)	190.7 (**C**HO), 151.8 (**C**), 146.3 (**C**), 135.4 (**C**), 129.8 (**C**), 128.8 (2 x **C**H), 128.7(**C**H), 128.0(2 x **C**H), 127.5(**C**H), 114.6 (**C**H), 110.2 (**C**H), 71.3 (**C**H$_2$).
LRMS (ESI+, m/z)	229 [M+H]$^+$ (100%).
HRMS (EI, Direct)	calcd for $C_{14}H_{12}O_3$ [M]$^+$ requires 228.0781; found: 228.0792.
X-ray	

2-(Benzyloxy)-4-formylphenyl trifluoromethanesulfonate (3.49)



To a stirred solution of 3-benzyloxy-4-hydroxybenzaldehyde **3.48** (110 mg, 0.48 mmol) and pyridine (0.046 mL, 0.57 mmol) in DCM (2 mL) at 0 °C was added Tf_2O (0.088 mL, 0.52 mmol). The reaction mixture was warmed to RT for 5 h. The residue was purified by flash column chromatography (20% Et_2O/PE) to afford the title compound **3.49** as a colourless oil (120 mg, 70%).

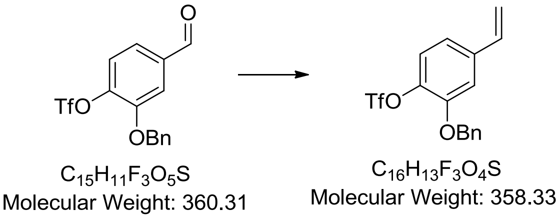
IR (υ_{max})	2838 (w), 1701 (s), 1602 (m), 1497 (m), 1423 (s), 1381 (m), 1316 (w), 1274 (w), 1246 (w), 1205 (m), 1136 (s), 1100 (s), 1007 (m), 871 (s), 820 (w), 736 (s), 696 (m), 610 (s), 587 (w), 512 (w) cm^{-1}.
δ$_H$ (400 MHz, CDCl$_3$)	9.97 (s, 1H, C**H**O), 7.64 (d, *J*=1.7 Hz, 1H, Ar**H**), 7.53 (dd, *J*=8.1, 1.8 Hz, 1H, Ar**H**), 7.51-7.47 (m, 2H, 2 x Ar**H**), 7.44 (d, *J*=8.2 Hz, 1H, Ar**H**), 7.46-7.35 (m, 3H, 3 x Ar**H**), 5.26 (s, 2H, ArC**H**$_2$O).
δ$_C$ (100 MHz, CDCl$_3$)	190.2 (**C**HO), 151.3 (**C**), 142.8 (**C**), 136.7 (**C**), 134.8 (**C**), 128.7 (2 X **C**), 128.5 (**C**H), 127.4 (2 X **C**H), 124.1 (**C**H), 123.2 (**C**H), 118.6 (q, *J*=320.6 Hz, **C**F$_3$), 113.1 (**C**H), 71.4 (**C**H$_2$).

δ_F (376 MHz, CDCl$_3$) -73.83 (C**F**$_3$)

LRMS (EI+, m/z) 360 [M]$^+$ (2%), 108 (5%), 108 (30%), 91 (100%).

HRMS (EI, Direct) calcd for $C_{15}H_{11}O_5F_3S$ [M]$^+$ requires 360.02738; found: 360.02703.

<u>**2-(Benzyloxy)-4-vinylphenyl trifluoromethanesulfonate (3.47)**</u>



To a solution of aldehyde **3.49** (8.25 g, 22.89 mmol) in THF (230 mL) was added sodium hydride (60% in mineral oil; 2.75 g, 68.69 mmol). Then methyltriphenylphosphonium bromide (12.26 g, 34.33 mmol) at 0 °C was slowly added. The reaction mixture was warmed to RT. After 18 h, the residue was purified by flash column chromatography (10% Et$_2$O/PE) to afford the title compound **3.47** as a colourless oil (7.20 g, 87%).

IR (υ_{max}) 3035 (w), 1596 (m), 1502 (m), 1455 (w), 1418 (s), 1291 (w), 1275 (m), 1247 (m), 1203 (s), 1179 (m), 1137 (s), 1101 (s), 1010 (m), 988 (w), 912 (w), 869 (s), 736 (m), 695 (m), 683 (w), 614 (m) cm^{-1}.

δ_H (400 MHz, CDCl$_3$)
7.51 (br. d, *J*=8.7 Hz, 2H, 2 x Ar**H**),
7.46-7.34 (m, 3H, 3 x Ar**H**),
7.22 (d, *J*=8.3 Hz, 1H, Ar**H**),
7.13 (d, *J*=2.0 Hz, 1H, Ar**H**),
7.04 (dd, *J*=8.4, 1.8 Hz, 1H, Ar**H**),
6.68 (dd, *J*=17.5, 10.9 Hz, 1H, =C**H**),
5.74 (d, *J*=17.5 Hz, 1H, =C**H**H),
5.35 (d, *J*=10.9 Hz, 1H, =CH**H**),
5.21 (s, 2H, ArOC**H**$_2$).

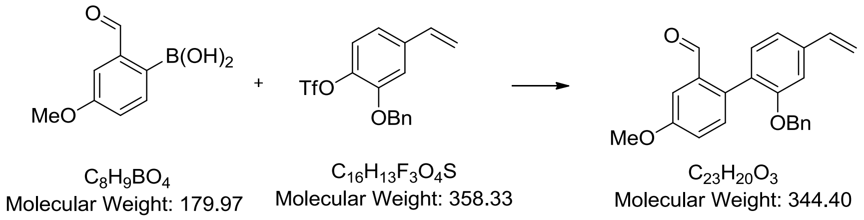
δ_C (100 MHz, CDCl$_3$) 150.5 (**C**HO), 138.9 (**C**), 138.3 (**C**), 135.6 (**C**), 135.4 (**C**H), 128.6 (2 X **C**H), 128.2, 127.3 (2 X **C**H), 122.4 (**C**H), 119.1 (**C**H), 115.9 (=**C**H$_2$), 118.7 (q, *J*=320.6 Hz, **C**F$_3$), 111.9 (**C**H), 71.0 (**C**H$_2$).

δ_F (376 MHz, CDCl$_3$) -73.95 (C**F**$_3$)

LRMS (EI+, m/z) 358 M$^+$ (12%), 91 (100%).

HRMS (EI, Direct) calcd for $C_{16}H_{13}O_4F_3S$ [M]$^+$ requires 358.04812; found: 358.04732.

2'-(Benzyloxy)-4-methoxy-4'-vinyl-[1,1'-biphenyl]-2-carbaldehyde (3.50)

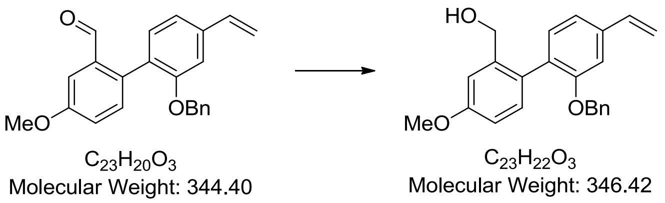


To a stirred solution of triflate **3.47** (100 mg, 0.27 mmol) and boronic acid **1.152** (98.9 mg, 0.55 mmol) in 1,4-dioxane (2 mL) was added Cs_2CO_3 (340 mg, 1.06 mmol), LiCl (110 mg, 2.67 mmol) and SPhos (43 mg, 0.1 mmol). The resulting mixture was degassed under argon for 15 min then $Pd(OAc)_2$ (2.4 mg, 0.01 mmol) was added and the reaction heated at reflux for 3 h. The reaction was cooled to RT, and then water (5 mL) was added. The aqueous phase was separated and extracted with EtOAc (3 x 10 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% Et_2O/PE) to afford the title compound **3.50** as a white solid (74 mg, 75%).

MP	76-77 °C (Et_2O/PE)
IR (υ_{max})	2932 (w), 2851 (w), 1687 (s), 1603 (s), 1510 (w), 1486 (s), 1458 (m), 1416 (m), 1393 (m), 1316 (m), 1271 (s), 1241 (m), 1162 (m), 1136 (m), 1038 (m), 999 (w), 935 (w), 824 (w), 734 (w), 696 (w), 668 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	9.86 (s, 1H, C**H**O), 7.52 (d, *J*=2.8 Hz, 1H, Ar**H**), 7.34-7.31 (m, 2H, 2 X Ar**H**), 7.30-7.28 (m, 2H, 2 x Ar**H**), 7.25 (d, *J*=7.8 Hz, 1H, Ar**H**), 7.23-7.19 (m, 3H, 3 X Ar**H**), 7.15 (dd, *J*=7.8, 1.4 Hz, 1H, Ar**H**), 7.10 (d, *J*=1.3 Hz, 1H, Ar**H**), 6.75 (dd, *J*=17.6, 10.9 Hz, 1H, =C**H**), 5.79 (d, *J*=17.6 Hz, 1H,=C**H**H), 5.33 (d, *J*=10.9 Hz, 1H, =CH**H**), 5.07 (s, 2H, OC**H**$_2$), 3.92 (s, 3H, OC**H**$_3$).

δ_C (100 MHz, CDCl$_3$)	192.4 (**C**HO), 159.2 (**C**), 156.1 (**C**), 139.2 (**C**), 136.5 (**C**), 136.4 (**C**H), 135.0 (**C**), 134.6 (**C**), 132.5 (**C**H), 131.9 (**C**H), 128.5 (2 x **C**H), 127.8 (**C**H), 126.9 (2 x **C**H), 126.9 (**C**), 121.1 (**C**H), 119.4 (**C**H), 114.7 (**C**H$_2$), 110.4 (**C**H), 109.5 (**C**H), 70.6 (**C**H$_2$), 55.6 (**C**H$_3$).
LRMS (EI+, m/z)	344 [M]$^+$ (3%), 237 (35%), 91 (100%).
HRMS (EI, Direct)	calcd for $C_{23}H_{20}O_3$ [M]$^+$ requires 344.14070; found: 344.14146.

(2'-(Benzyloxy)-4-methoxy-4'-vinyl-[1,1'-biphenyl]-2-yl)methanol (1.234)

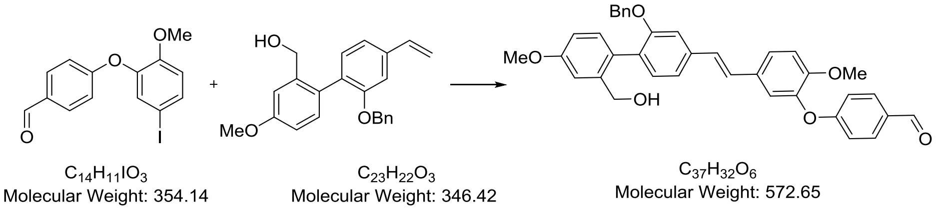


To a suspension of **3.50** (1.69 g, 4.91 mmol) in methanol (25 mL) and DCM (25 mL) at 0 °C was added NaBH$_4$ (370 mg, 9.82 mmol). Then, the reaction mixture warmed to RT. After 4 h, water (20 mL) was added. The aqueous phase was separated and extracted with Et$_2$O (3 x 50 mL). The organic phases were combined, dried over MgSO$_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (40% Et$_2$O/PE) to afford the title compound **1.234** as a colourless oil (1.60 g, 94%).

IR (υ_{max})	3420 (br. s), 3008 (w), 2937 (w), 1604 (m), 1485 (m), 1414 (w), 1391 (w), 1271 (m), 1232 (s), 1160 (w), 1134 (w), 1104 (w), 999 (m), 908 (s), 749 (s), 623 (m), 460 (m) cm^{-1}.
δ_H (400 MHz, CDCl$_3$)	7.37-7.29 (m, 3H, 3 x Ar**H**), 7.25-7.14 (m, 7H, 7 x Ar**H**), 6.96 (dd, *J*=8.3, 2.7 Hz, 1H, Ar**H**), 6.78 (dd, *J*=17.5, 10.8 Hz, 1H, =C**H**), 5.81 (d, *J*=17.5 Hz, 1H, =C**H**H), 5.34 (d, *J*=10.9 Hz, 1H, =CH**H**), 5.05 (s, 2H, ArC**H**$_2$O), 4.47 (br., 2H, ArC**H**$_2$OH), 3.91 (s, 3H, OC**H**$_3$), 2.24 (br. s, 1H, O**H**).
δ_C (100 MHz, CDCl$_3$)	159.3 (**C**), 155.9 (**C**), 140.8 (**C**),138.3 (**C**) 136.5 (**C**H), 136.4 (**C**), 131.7 (**C**H), 131.3 (**C**H), 130.3 (**C**), 129.4 (**C**), 128.5 (2 x **C**H), 127.9 (**C**H), 127.1 (2 x **C**H), 119.8 (**C**H), 114.2 (**C**H$_2$), 113.4 (**C**H),

	113.2 (**C**H), 111.5 (**C**H), 71.2 (**C**H$_2$), 63.6 (**C**H$_2$), 55.3 (**C**H$_3$).
LRMS (EI+, m/z)	346 [M]$^+$ (5%) 239 (70%) 91 (100%).
HRMS (EI, Direct)	calcd for $C_{23}H_{22}O_3$ [M]$^+$ requires 346.15635; found: 346.15576.

(*E*)-4-(5-(2-(2-(Benzyloxy)-2'-(hydroxymethyl)-4'-methoxy-[1,1'-biphenyl]-4-yl)vinyl)-2-methoxyphenoxy)benzaldehyde (3.51)



To a stirred solution of styrene **1.234** (1.51 g, 4.36 mmol) and iodide **1.148** (1.40 g, 3.96 mmol) in DMA (5 mL) was added potassium phosphate (1.18 g, 5.54 mmol). The reaction mixture was degassed with sonication for 20 min under argon then Pd(OAc)$_2$ (44 mg, 0.19 mmol) was added. The reaction mixture was heated at 110 ^{0}C for 18 h then cooled to RT. The residue was purified by flash column chromatography (50% Et$_2$O/PE) to afford the title compound **3.51** as a white solid (1.53 g, 67 %).

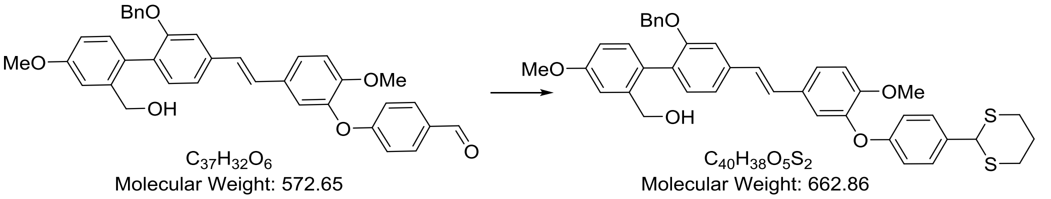
MP	66-67 °C (Et$_2$O/PE)
IR (υ_{max})	3447 (br. s), 2925 (w), 2852 (w), 1690 (m), 1598 (s), 1573 (m), 1503 (s), 1460 (m), 1423 (m), 1271 (s), 1227 (s), 1155 (s), 1123 (m), 1024 (m), 963 (w), 909 (w), 860 (w), 732 (m) cm^{-1}.
δ$_H$ (400 MHz, CDCl$_3$)	9.95 (s, 1H, C**H**O), 7.88 (d, *J*=8.8 Hz, 2H, 2 x Ar**H**), 7.40 (dd, *J*=8.5, 2.0 Hz, 1H, Ar**H**), 7.35 (d, *J*=2.0 Hz, 1H, Ar**H**), 7.31-7.27 (m, 3H, 3 x Ar**H**), 7.23-7.16 (m, 5H, 5 x Ar**H**), 7.14 (d, *J*=2.7 Hz, 1H, Ar**H**), 7.09-7.01 (m, 5H, 3 x Ar**H**, ArC**H**C**H**Ar), 6.97 (d, *J*=8.3 Hz, 1H, Ar**H**), 6.94 (dd, *J*=8.4, 2.7 Hz, 1H, Ar**H**), 5.05 (s, 2H, ArOC**H**$_2$), 4.46 (br. s, 2H, ArC**H**$_2$), 3.90 (s, 3H, OC**H**$_3$), 3.85 (s, 3H, OC**H**$_3$), 2.16 (t, *J*=6.4 Hz, 1H, O**H**).

δ_C (100 MHz, CDCl$_3$) 190.7 (**C**HO), 163.4 (**C**), 159.3 (**C**), 156.1 (**C**), 151.3 (**C**), 143.1 (**C**), 140.8 (**C**), 138.0 (**C**), 136.4 (**C**), 131.9 (3 x **C**H), 131.3 (**C**H), 131.1 (**C**), 131.0 (**C**), 130.1 (**C**), 129.4 (**C**), 128.5 (2 x **C**H), 127.9 (**C**H), 127.6 (**C**H), 127.4 (**C**H), 127.1 (2 x **C**H), 125.0 (**C**H), 120.0 (**C**H), 119.9 (**C**H), 116.2 (2 x **C**H), 113.4 (**C**H), 113.3 (**C**H), 113.1 (**C**H), 111.6 (**C**H), 71.3 (**C**H_2), 63.7 (**C**H_3), 56.0 (**C**H_2), 55.3 (**C**H_3).

LRMS (ESI+, m/z) 595 $[M+Na]^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{37}H_{32}NaO_6$ $[M+Na]^+$ requires 595.2091; found: 595.2077.

(*E*)-(4'-(3-(4-(1,3-Dithian-2-yl)phenoxy)-4-methoxystyryl)-2'-(benzyloxy)-4-methoxy-[1,1'-biphenyl]-2-yl)methanol (3.42)



To a stirred solution of arene **3.51** (1.31 g, 2.28 mmol) in DCM (35 mL) was added propan-1,3-dithiol (0.69 mL, 6.84 mmol) and PPTS (130 mg, 0.54 mmol). The reaction mixture was heated at reflux for 18 h and cooled to RT. Purification by column chromatography (60% Et$_2$O/PE) afforded the title compound **3.42** as a white solid (1.39 g, 91%).

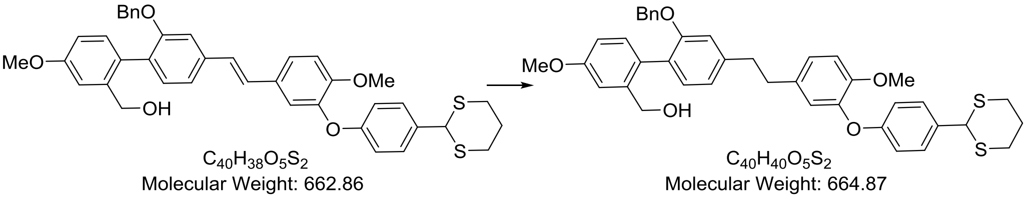
MP 72-73 °C (Et$_2$O/PE)

IR (υ_{max}) 3437 (br. s), 2933 (w), 1602 (m), 1572 (w), 1503 (s), 1462 (w), 1441 (m), 1422 (m), 1272 (s), 1227 (s), 1167 (m), 1126 (w), 1025 (m), 963 (w), 911 (w), 734 (m) cm^{-1}.

δ_H (400 MHz, CDCl$_3$) 7.43 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**),
7.34-7.25 (m, 4H, 4 x Ar**H**),
7.23 (d, *J*=2.1 Hz, 1H, Ar**H**),
7.20-7.13 (m, 6H, 6 x Ar**H**),
7.11 (d, *J*=2.6 Hz, 1H, Ar**H**),
7.06-6.97 (m, 3H, 3 x Ar**H**),
6.97-6.93 (m, 2H, 2 x Ar**H**),
6.91 (dd, *J*=8.4, 2.7 Hz, 1H, Ar**H**),
5.18 (s, 1H, ArC**H**S),
5.03 (br. s, 2H, ArOC**H**$_2$),
4.43 (br. s, 2H, ArC**H**$_2$),

	3.88 (s, 3H, OC**H**$_3$), 3.86 (s, 3H, OC**H**$_3$), 3.12-3.03 (m, 2H, SC**H**$_2$CH$_2$), 2.92 (dt, *J*=14.0, 3.8 Hz, 2H, SC**H**$_2$CH$_2$), 2.19 (m, 1H, SCH$_2$CH**H**), 2.09 (t, *J*=6.1 Hz, 1H, O**H**), 1.93 (m, 1H, SCH$_2$C**H**H).
δ_C (100 MHz, CDCl$_3$)	159.3 (**C**), 158.0 (**C**), 156.0 (**C**), 151.4 (**C**), 144.6 (**C**), 140.8 (**C**), 138.2 (**C**), 136.5 (**C**), 133.1 (**C**), 131.8 (**C**H), 131.3 (**C**H), 130.8 (**C**), 129.9 (**C**), 129.5 (**C**), 129.1 (2 x **C**H), 128.5 (2 x **C**H), 128.0 (**C**H), 127.9 (**C**H), 127.2 (2 x **C**H), 127.1 (**C**H), 123.8 (**C**H), 119.9 (**C**H), 119.2 (**C**H), 116.9 (2 x **C**H), 113.4 (**C**H), 113.3 (**C**H), 112.9 (**C**H), 111.6 (**C**H), 71.3 (**C**H$_2$), 63.8 (**C**H$_2$), 56.1 (**C**H$_3$), 55.3 (**C**H$_3$), 50.8 (**C**H), 32.2 (2 x **C**H$_2$), 25.0 (**C**H$_2$).
LRMS (ESI+, m/z)	685 [M+Na]$^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{40}H_{38}NaO_5S_2$ [M+Na]$^+$ requires 685.2053; found: 685.2061.

(4'-(3-(4-(1,3-Dithian-2-yl)phenoxy)-4-methoxyphenethyl)-2'-(benzyloxy)-4-methoxy-[1,1'-biphenyl]-2-yl)metanol (1.233)

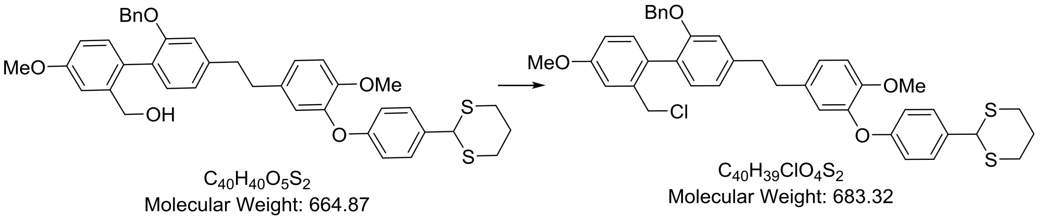


To a stirred solution of stilbene **3.42** (100 mg, 0.15 mmol) in 1:1 v/v THF and water (2 mL each) was added tosylhydrazone (290 mg, 1.57 mmol) and NaOAc (130 g, 1.57 mmol). The reaction mixture was heated at reflux for 18 h, then cooled to RT and water (5 mL) and HCl (2M, 2 mL) added. The reaction mixture was extracted with Et$_2$O (3 x 10 mL), then the combined organic phases were dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash column chromatography (30% EtOAc/PE) afforded the title compound **1.233** as a white solid (62 mg, 62%).

MP	78-79 °C (EtOAc/PE)
IR (υ_{max})	3437 (br. s), 2933 (w), 1602 (m), 1503 (s), 1462 (w), 1441 (w), 1422 (m), 1272 (s), 1227 (s), 1167 (s), 1126 (m), 1025 (m), 963 (w), 911 (w), 850 (w), 734 (m) cm^{-1}.

δ_H (400 MHz, $CDCl_3$)	7.40 (d, J=8.6 Hz, 2H, 2 x Ar**H**), 7.30-7.26 (m, 3H, 3 x Ar**H**), 7.18-7.06 (m, 5H, 5 x Ar**H**), 6.99-6.81 (m, 8H, Ar**H**) 5.15 (s, 1H, ArC**H**S), 4.95 (br. s, 2H, ArOC$\mathbf{H}_2$), 4.40 (br. s, 2H, ArC$\mathbf{H}_2$O), 3.89 (s, 3H, OC$\mathbf{H}_3$), 3.82 (s, 3H, OC$\mathbf{H}_3$), 3.07 (br. t, J=13.1 Hz, 2H, SC$\mathbf{H}_2$CH$_2$), 2.97-2.84 (m, 6H, SC$\mathbf{H}_2$CH$_2$, ArC$\mathbf{H}_2$C$\mathbf{H}_2$Ar), 2.21 (br. s, 1H, O**H**), 2.15 (m, 1H, SCH$_2$CH**H**), 1.95 (m, 1H, SCH$_2$C**H**H).
δ_C (100 MHz, $CDCl_3$)	159.2 (**C**), 158.2 (**C**), 155.7 (**C**), 149.9 (**C**), 144.0 (**C**), 142.4 (**C**), 140.8 (**C**), 136.6 (**C**), 134.7 (**C**), 132.8 (**C**), 131.4 (**C**H), 131.4 (**C**H), 129.7 (**C**), 129.0 (2 x **C**H), 128.5 (2 x **C**H), 128.3 (**C**), 127.8 (**C**H), 127.2 (2 x **C**H), 125.0 (**C**H), 121.9 (**C**H), 121.8 (**C**H), 116.7 (2 x **C**H), 114.3 (**C**H), 113.4 (**C**H), 113.3 (**C**H), 112.9 (**C**H), 71.3 (**C**H$_2$), 63.8 (**C**H$_2$), 56.1 (**C**H$_3$), 55.3 (**C**H$_3$), 50.8 (**C**H), 37.9 (**C**H$_2$), 36.8 (**C**H$_2$), 32.2 (2 x **C**H$_2$), 25.1 (**C**H$_2$).
LRMS (ESI+, m/z)	687 $[M+Na]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{40}H_{40}NaO_5S_2$ $[M+Na]^+$ requires 687.2209; found: 687.2201.

2-(4-(5-(2-(2-(Benzyloxy)-2'-(chloromethyl)-4'-methoxy-[1,1'-biphenyl]-4-yl)ethyl)-2-methoxyphenoxy)phenyl)-1,3-dithiane (3.41)



To a stirred solution of mixture of benzyl alcohol **1.233** (75 mg, 0.11 mmol) in 5 mL DCM, pyridine (0.013 mL, 0.16 mmol) was added. The thionyl chloride (0.012 mL, 0.16 mmol) was added in an ice-water bath. After 18 h at RT, water (5 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 x 10 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (30% Et_2O/PE) afforded the title compound **3.41** as a white solid (51 mg, 67%).

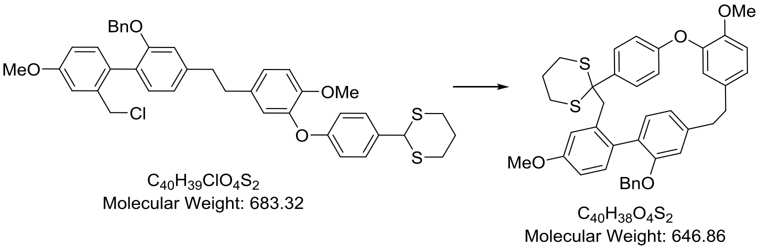
Alternative:

To a stirred solution of mixture of benzyl alcohol **1.233** (250 mg, 0.37 mmol) in 18 mL DCM, DBU (170 mg, 1.12 mmol) and LiCl (157 mg, 0.37 mmol) were added. The MsCl (120 mg, 1.12 mmol) was added in an ice-water bath. After 18 h at RT, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (30 % Et_2O/PE) to give the title compound **3.41** as a white solid (160 mg, 63 %).

MP	59-60 °C (Et_2O/PE)
IR (υ_{max})	2932 (w), 1605 (m), 1577 (w), 1501 (s), 1454 (w), 1441 (w), 1380 (w), 1270 (s), 1223 (s), 1166 (s), 1124 (w), 1027 (w), 908 (m), 816 (m), 729 (s) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.40 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 7.31-7.24 (m, 3H, 3 x Ar**H**), 7.19-7.13 (m, 4H, 4 x Ar**H**), 7.11 (d, *J*=2.7 Hz, 1H, Ar**H**), 6.96-6.82 (m, 7H, 7 x Ar**H**), 6.79 (d, *J*=0.8 Hz, 1H, Ar**H**), 5.15 (s, 1H, ArC**H**S), 4.98 (s, 2H, ArC**H**$_2$), 4.44 (br., 2H, ArC**H**$_2$O), 3.88 (s, 3H, OC**H**$_3$), 3.81 (s, 3H, OC**H**$_3$), 3.12-3.01 (m, 2H, SC**H**$_2$CH$_2$), 2.95-2.83 (m, 6H, SC**H**$_2$CH$_2$, ArC**H$_2$**C**H**$_2$Ar), 2.18 (m, 1H, SCH$_2$CH**H**), 1.91 (m, 1H, SCH$_2$C**H**H).
δ_C (100 MHz, $CDCl_3$)	159.0 (**C**), 158.2 (**C**), 155.6 (**C**), 149.9 (**C**), 144.1 (**C**), 142.6 (**C**), 137.2 (**C**), 137.1 (**C**), 134.7 (**C**), 132.8 (**C**), 131.9 (**C**H), 131.5 (**C**H), 130.5 (**C**), 129.0 (2 x **C**H), 128.4 (2 x **C**H), 127.5 (**C**H), 127.1 (**C**), 126.7 (2 x **C**H), 125.0 (**C**H), 121.9 (**C**H), 121.2 (**C**H), 116.7 (2 x **C**H), 114.4 (**C**H), 113.9 (**C**H), 113.5 (**C**H), 112.8 (**C**H), 70.3 (**C**H$_2$), 56.1 (**C**H$_3$), 55.3 (**C**H$_3$), 50.8 (**C**H), 44.8 (**C**H$_2$), 37.9 (**C**H$_2$), 36.8 (**C**H$_2$), 32.2 (2 x **C**H$_2$), 25.1(**C**H$_2$).
LRMS (ESI+, m/z)	705 $[M(^{35}Cl)+Na]^+$ (100%), 707 $[M(^{37}Cl)+Na]^+$ (40%).
HRMS (ESI+, m/z)	calcd for $C_{40}H_{39}ClNaO_4S_2$ $[M+Na]^+$ requires 705.1870; found:

705.1857.

21-Benzyloxy-1,2,3,17,18,29-hexahydro-13,26-dimethoxy-7,10;19,22-bis(etheno)-12,16-metheno-11-oxa-1,5-dithiabenzo[w]spiro[5,19]pentacosadodecaene (3.40)

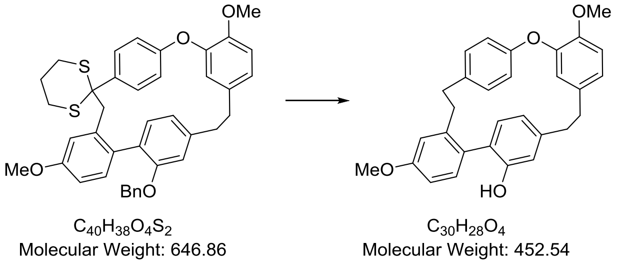


To a stirred solution of mixture of compound **3.41** (120 mg, 0.18 mmol) in 15 mL THF at -78 °C was added *n*-BuLi (0.1 mL, 0.22 mmol, 2.44 M in hexanes). The reaction mixture was warmed to RT for 18 h. sat. NH_4Cl (5 mL) and water (10 mL) was added. After 5 min the aqueous phase was separated at extracted with Et_2O (3 x 20 mL), then the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (30% Et_2O/PE) afforded the title compound **3.40** as a white solid (39 mg, 33%).

MP	83-85 °C (Et_2O/PE)
IR (υ_{max})	2926 (m), 1604 (m), 1582 (w), 1513 (m), 1494 (s), 1463 (w), 1420 (m), 1261 (s), 1230 (s), 1165 (m), 1128 (m), 1043 (w), 908 (w), 858 (w), 733 (m), 696 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.73 (br. s, 1H, Ar**H**), 7.55 (br. s, 1H, Ar**H**), 7.33-7.24 (m, 4H, 4 x Ar**H**), 7.21-7.17 (m, 2H, 2 x Ar**H**), 7.00 (d, *J*=8.4 Hz, 1H, Ar**H**), 6.90 (d, *J*=8.6 Hz, 1H, Ar**H**), 6.88-6.78 (m, 5H, 5 x Ar**H**), 6.52 (d, *J*=1.3 Hz, 1H, Ar**H**), 6.34 (dd, *J*=7.6, 1.6 Hz, 1H, Ar**H**), 5.69 (d, *J*=2.1 Hz, 1H, Ar**H**), 4.87 (br., 2H, ArC**H**$_2$O), 3.95 (s, 3H, OC**H**$_3$), 3.93 (s, 3H, OC**H**$_3$), 3.48 (s, 2H, ArC**H**$_2$C), 2.90-2.77 (br., 2H, SC**H**$_2$CH$_2$), 2.76-2.63 (br., 2H, SC**H**$_2$CH$_2$),

	2.61-2.45 (br., 4H, 4 x ArC**H$_2$**C**H$_2$**Ar),
	2.19-1.88 (br., 2H, SCH$_2$C**H$_2$**).
δ_C (100 MHz, CDCl$_3$)	157.5 (**C**), 154.8 (**C**), 153.3 (**C**), 147.6 (**C**), 147.1 (**C**), 141.2 (**C**), 139.4 (**C**), 137.1 (**C**), 133.8 (**C**), 133.7 (**C**), 133.4 (**C**), 132.1 (**C**H), 131.7 (**C**H), 130.3 (**C**H), 129.5 (**C**H), 128.4 (**C**), 128.3 (2 x **C**H), 127.5 (**C**H), 126.8 (2 x **C**H), 122.5 (**C**H), 122.1 (**C**H), 122.1 (**C**H), 121.6 (**C**H), 118.5 (**C**H), 116.7 (**C**H), 113.5 (**C**H), 113.3 (**C**H), 112.0 (**C**H), 70.1 (**C**H$_2$), 58.6 (**C**), 56.2 (**C**H$_3$), 55.4 (**C**H$_3$), 49.8 (**C**H$_2$), 37.6 (**C**H$_2$), 36.4 (**C**H$_2$), 28.7 (**C**H$_2$), 28.1 (**C**H$_2$), 25.1 (**C**H$_2$).
LRMS (ESI+, m/z)	669 $[M+Na]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{40}H_{38}NaO_4S_2$ $[M+Na]^+$ requires 669.2104; found: 669.2098.

Dimethylriccardin C (1.177)



To a stirred solution of mixture of $NiCl_2.6H_2O$ (170 mg, 0.74 mmol) in 1 mL DMF, solution of the compound **3.40** (30 mg, 0.046 mmol) in 1 mL THF at 0 °C was added $NaBH_4$ (55 mg, 1.47 mmol). The reaction mixture was warmed to RT for 18 h. The mixture filtered through Celite©. Water (5 mL) was added. The aqueous phase was separated at extracted with Et_2O (3 x 10 mL), then the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude was dissolved in EtOH (3 mL) and DCM (3 mL). Then 10% Pd/C (48 mg, 0.016 mmol) was added. The flask was evacuated/purged with argon three times then evacuated/purged with hydrogen twice. After 18 h stirred vigorously under an atmosphere of H_2 at RT, the mixture filtered through Celite© and the solvent was removed *in vacuo*. The residue was purified by flash chromatography column (35% Et_2O/hexane) to afford the title compound **1.177** as a white solid (15 mg, 71%)

MP	140-141 °C (Et_2O/ hexane) [ref.[52] Oil]
IR (υ_{max})	3467 (br. w), 2927 (m), 2853 (w), 1605 (m), 1506 (s), 1441 (w), 1420 (m), 1260 (m), 1229 (s), 1164 (w), 1127 (m), 1044 (w), 981 (w), 907 (w), 851 (w), 808 (w), 730 (w) cm^{-1}.
δ_H (400 MHz, CDCl$_3$)	7.11 (d, *J*=8.4 Hz, 1H, Ar**H**), 7.03 (d, *J*=2.6 Hz, 1H, Ar**H**),

6.92-6.78 (m, 5H, 5 x Ar**H**),

6.89 (d, *J*=7.9 Hz, 1H, Ar**H**),

6.82 (d, *J*=7.6 Hz, 1H, Ar**H**),

6.78 (dd, *J*=8.4, 1.5 Hz, 1H, Ar**H**),

6.44 (d, *J*=0.7 Hz, 1H, Ar**H**),

6.30 (d, *J*=7.6 Hz, 1H, Ar**H**),

5.44 (d, *J*=1.5 Hz, 1H, Ar**H**),

4.79 (s, 1H, ArO**H**),

3.95 (s, 3H, OC**H**$_3$),

3.91 (s, 3H, OC**H**$_3$),

3.15-3.02 (m, 1H, ArC**H**HC**H**$_2$Ar),

3.02-2.83 (m, 2H, ArCH$_2$C**H**$_2$Ar),

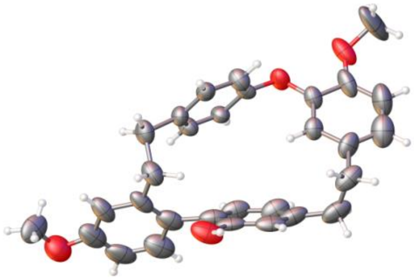
2.83-2.58 (m, 5H, ArC**H**$_2$CH$_2$Ar, ArCH**H**C**H**$_2$Ar).

δ_C (100 MHz, CDCl$_3$) 159.9 (**C**), 153.0 (**C**), 151.9 (**C**), 148.6 (**C**), 146.9 (**C**), 143.6 (**C**), 142.0 (**C**), 139.3 (**C**), 133.8 (**C**), 132.5 (**C**H), 131.5 (**C**H), 129.3 (**C**H), 129.3 (**C**H), 128.0 (**C**), 124.5 (**C**), 122.7 (**C**H), 122.5 (**C**H), 121.6 (**C**H), 121.4 (**C**H), 116.6 (**C**H), 116.3 (**C**H), 115.9 (**C**H), 112.6 (**C**H), 111.8 (**C**H), 56.1 (**C**H$_3$), 55.3 (**C**H$_3$), 38.2 (**C**H$_2$), 37.7 (**C**H$_2$), 37.0 (**C**H$_2$), 35.2 (**C**H$_2$).

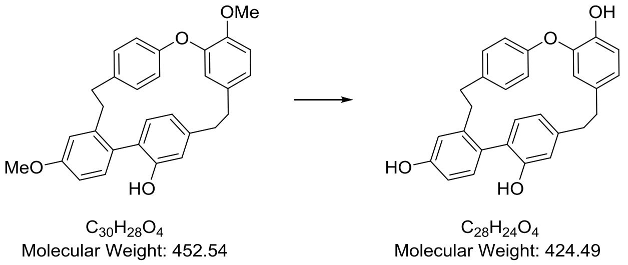
LRMS (ESI+, m/z) 453 $[M+H]^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{30}H_{29}O_4$ $[M+H]^+$ requires 453.2060; found: 453.2060.

X-Ray



Riccardin C (1.2)



To a stirred solution of dimethylriccardin C **1.177** (7.5 mg, 0.016 mmol) in DCM (2 mL) at 0°C was added boron tribromide (0.16 mL, 1 M solution in DCM, 0.16 mmol). After 5 h at RT, water (5 mL) was added. The aqueous phase was separated and extracted with Et_2O (3 x 10 mL), and then the resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (60% Et_2O/PE) afforded the title compound **1.2** as a white solid (4.9 mg, 71%).

These data are accordance with those reported in the literature.[47,50]

MP	193-195 °C (Et_2O/PE) [Lit. 194 °C (hexane)][47]
IR (υ_{max})	3409 (br. s), 2924 (s), 2854 (m), 1605 (m), 1505 (s), 1434 (m), 1338 (w), 1270 (m), 1224 (s), 1189 (m), 1163 (m), 1110 (w), 919 (m), 851 (w), 814 (m), 733 (m), 647 (w) cm^{-1}.
δ_H (500 MHz, $CDCl_3$)	7.05 (d, *J*=8.3 Hz, 1H, Ar**H**), 6.98 (d, *J*=2.7 Hz, 1H, Ar**H**), 6.92 (d, *J*=8.1 Hz, 1H, Ar**H**), 6.82 (d, *J*=2.7 Hz, 2H, 2 x Ar**H**), 6.80 (m, 1H, Ar**H**), 6.79 (d, *J*=7.7 Hz, 2H, 2 x Ar**H**), 6.75 (dd, *J*=8.1, 2.0 Hz, 2H, 2 x Ar**H**), 6.40 (d, *J*=1.6 Hz, 1H, Ar**H**), 6.24 (dd, *J*=7.7, 1.7 Hz, 1H, Ar**H**), 5.58 (s, 1H, O**H**), 5.37 (d, *J*=2.0 Hz, 1H, Ar**H**), 4.89 (s, 1H, O**H**), 4.76 (s, 1H, O**H**), 3.16-2.59 (m, 8H, 2 x ArC**H**$_2$C**H**$_2$Ar).
δ_C (126 MHz, $CDCl_3$)	155.8 (**C**), 152.5 (**C**), 151.8 (**C**), 146.3 (**C**), 143.8 (**C**), 143.3 (**C**), 142.0 (**C**), 139.8 (**C**), 133.0 (**C**), 132.9 (**C**H), 131.4 (**C**H), 129.4 (**C**H), 129.2 (**C**H), 128.3 (**C**), 124.3 (**C**), 122.5 (2 x **C**H), 122.1 (**C**H), 121.7 (**C**H), 117.5 (**C**H), 116.0 (**C**H), 116.0 (**C**H), 114.9

	(**C**H), 114.3 (**C**H), 38.1 (**C**H_2), 37.8 (**C**H_2), 37.1 (**C**H_2), 35.0 (**C**H_2).
LRMS (ESI+, m/z)	425 $[M+H]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{28}H_{25}O_4$ $[M+H]^+$ requires 425.1747; found: 425.1741.

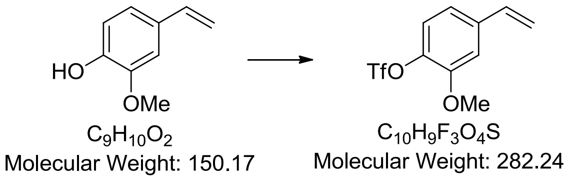
2-Methoxy-4-vinylphenol (3.44)

To a stirred suspension of methyltriphenylphosphonium bromide (52.82g, 147.9 mmol) in THF (750 mL) at 0 °C was added KO^tBu (33.19 g, 295.8 mmol). After 30 min, a aldehyde **1.149** (15 g, 98.6 mmol) was added. After 3 h at RT, water (300 mL) and NH_4Cl (200 mL) was added and the reaction mixture was extracted with Et_2O (2 x 200 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (20% Et_2O/PE) to afford the title compound **3.44** as a pale yellow gum (14.76 g, 99%).

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

IR (υ_{max})	3426 (w), 2936 (w), 1602 (m), 1509 (s), 1462 (m), 1429 (m), 1364 (w), 1265 (s), 1232 (s), 1204 (s), 1152 (s), 1121 (s), 1030 (s), 990 (w), 902 (w), 854 (m), 818 (m), 790 (m), 563 (w), 555 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	6.97 (s, 1H, Ar**H**), 6.94 (d, *J*=2.0 Hz, 1H, Ar**H**), 6.91 (d, *J*=8.0 Hz, 1H, Ar**H**), 6.67 (dd, *J*=18.0, 11.0 Hz, 1H, ArC**H=**), 5.63 (d, *J*=17.0 Hz, 1H, =C**H**H), 5.45-5.59 (1H, s, ArO**H**), 5.16 (d, *J*=11.0 Hz, 1H, =CH**H**), 3.91 (s, 3H, OC**H**$_3$).
δ_C (100 MHz, $CDCl_3$)	146.6 (**C**), 145.6 (**C**), 136.5 (**C**H), 130.2 (**C**), 120.0 (**C**H), 114.3 (**C**H), 111.3 (**C**H_2), 108.0 (**C**H), 55.8 (**C**H_3).
LRMS (EI+, m/z)	150 $[M]^+$ (2%), 91 (100%), 77 (7%).

2-Methoxy-4-vinylphenyl trifluoromethanesulfonate (3.43)

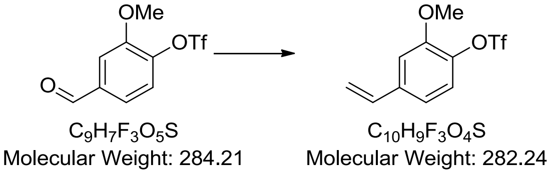


To a stirred solution of 2-methoxy-4-vinylphenol **3.44** (9.0 g, 59.9 mmol) and pyridine (9.69 mL, 119.9 mmol) in DCM (120 mL) at 0 °C was added Tf_2O (13.11 mL, 77.91 mmol) dropwise over 15 minutes. The reaction mixture was warmed to RT for 13 h. The residue was purified by flash column chromatography (15% Et_2O/PE) to afford the title compound **3.43** as colourless oil (15.47 g, 91%).

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

IR (υ_{max})	2944 (w), 1597 (m), 1502 (s), 1464 (w), 1413 ()s, 1313 (s), 1292 (m), 1278 (m), 1247 (m), 1201 (s), 1178 (s), 1136 (s), 1103 (s), 1029 (m), 987 (w), 922 (m), 865 (s), 820 (m), 773 (w), 746 (w), 722 (s), 684 (m), 615 (s), 573 (w), 541 (w), 502 (m) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.18 (d, *J*=8.4 Hz, 1H, Ar**H**), 7.07 (d, *J*=1.0 Hz, 1H, Ar**H**), 7.01 (dd, *J*=8.3, 1.6 Hz, 1H, Ar**H**), 6.69 (dd, *J*=17.6, 10.9 Hz, 1H, ArC**H=**), 5.77 (d, *J*=17.5 Hz, 1H, =C**H**H), 5.36 (d, *J*=10.9 Hz, 1H, =CH**H**), 3.92 (s, 3H, OCH_3) .
δ_C (100 MHz, $CDCl_3$)	151.3 (**C**), 139.0 (**C**), 138.1 (**C**), 135.5 (**C**H), 122.3 (**C**H), 118.8 (q, *J*=320.58 Hz, CF_3), 118.7 (**C**H), 115.8 (CH_2), 110.6(**C**H), 56.0 (CH_3).
LRMS (EI+, m/z)	282 $[M]^+$ (71%), 149 (100%), 77 (32%).

2-Methoxy-4-vinylphenyl trifluoromethanesulfonate (3.43)

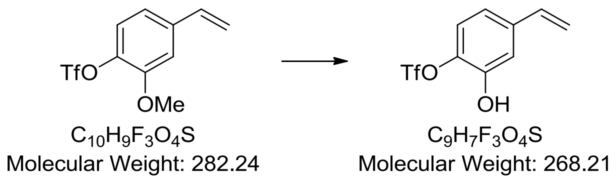


To a stirred suspension of methyltriphenylphosphonium bromide (41.14 g, 115.17 mmol) in THF (50 mL) at 0 °C was added KO^tBu (26.52 g, 236.3 mmol). After 15 min, a solution of aldehyde **2.5**

(21.8 g, 76.8 mmol) in THF (31 mL) was added. After 3 h at 0 °C, water (100 mL) and (100 mL) were added and the reaction mixture was extracted with Et_2O (3 x 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (15-20% Et_2O/cyclohexane) to afford the title compound **3.43** as a colourless oil (4.01 g, 18%).

The data were identical to those previously reported (See P.169).

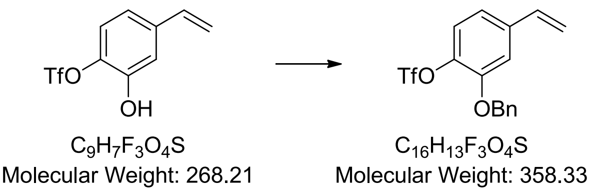
2-Hydroxy-4-vinylphenyl trifluoromethanesulfonate (3.46)



To a stirred solution of 2-methoxy-4-vinylphenyl trifluoromethanesulfonate **3.43** (8 g, 28.3 mmol) in DCM (300 mL) at 0 °C was added boron tribromide (36.84 mL, 1 M solution in DCM, 36.8 mmol) dropwise over 10 min. After 3 h at 0 °C, ice water (100 mL) was added. The aqueous phase was separated and extracted with DCM (3 x 100 mL), and then the resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (30% diethyl ether/cyclohexane) afforded the title compound **3.46** as grey oil (2.97 g, 39%).

IR (υ_{max})	3528 (w), 2979 (w), 1605 (w), 1499 (w), 1417 (s), 1300 (w), 1269 (m), 1247 (w), 1205 (s), 1134 (s), 1096 (m), 933 (m), 907 (w), 864 (s), 816 (w), 774 (w), 731 (m), 700 (w), 651 (w), 614 (s), 509 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.19 (d, *J*=9.0 Hz, 1H, Ar**H**), 7.06 (d, *J*=2.0 Hz, 1H, Ar**H**), 6.99 (dd, *J*=8.0, 2.0 Hz, 1H, Ar**H**), 6.62 (dd, *J*=17.0, 11.0 Hz, 1H, ArC**H**=), 5.72 (d, *J*=17.0 Hz, 1H, =C**H**H), 5.33 (d, *J*=11.0 Hz, 1H, =CH**H**), 5.17-5.28 (br. s, 1H, ArO**H**).
δ_C (100 MHz, $CDCl_3$)	147.6 (**C**), 139.1 (**C**), 136.8 (**C**), 135.0 (**C**H), 122.3 (**C**H), 119.3 (**C**H), 118.7 (q, *J*=320.58 Hz, **C**F_3), 116.1 (**C**H_2), 115.5 (**C**H).
LRMS (EI+, m/z)	268 $[M]^+$ (43%), 134 (100%), 77 (79%).

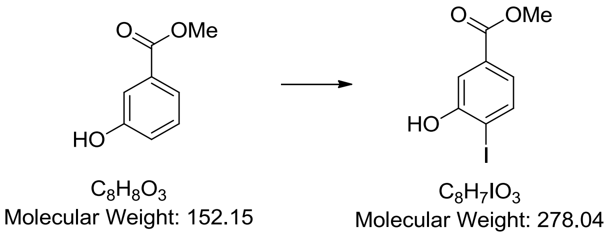
2-(Benzyloxy)-4-vinylphenyl trifluoromethanesulfonate (3.47)



To a solution of **3.46** (2.90 g, 10.8 mmol) in MeCN (15 mL) were added potassium carbonate (2.24 g, 16.2 mmol) and benzyl bromide (1.53 mL, 12.9 mmol). After 13 h, water (15 mL) was added and the product was extracted by Et_2O (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (20% Et_2O/cyclohexane) to afford the title compound **3.47** (3.33 g, 86%) as a yellow oil.

The data were identical to those previously reported (See P.156).

Methyl 3-hydroxy-4-iodobenzoate (4.2)



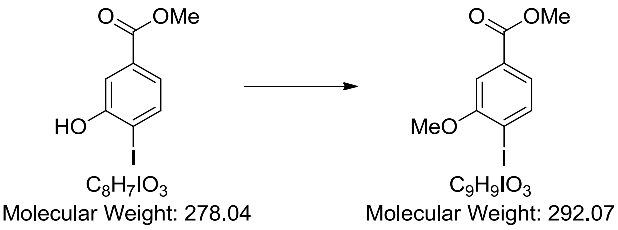
To a stirred suspension of methyl 3-hydroxybenzoate **4.1** (10 g, 65.7 mmol) in sat. aq. Na_2CO_3 (300 mL) and water (100 mL) was added iodine (16.6 g, 65.7 mmol) and the mixture was stirred at RT. After 20 h, the product was collected by filtration, washed with water then dried in a desiccator for 5 h to yield the title compound **4.2** as a cream solid (14.3 g, 78%).

These data are in accordance with those reported in the literature.[116]

MP	155-157 °C (water) [lit. 145-148 °C (water)][116]
IR (υ_{max})	3270 (m), 2950 (m), 1686 (s), 1579 (m), 1433 (m), 1406 (m), 1296 (s), 1239 (s), 1192 (s), 1106 (s), 1016 (m), 976 (m), 906 (w), 880 (m), 797 (w) cm^{-1}.
δ_H (400 MHz, acetone-d_6)	7.52 (d, *J* = 8.1 Hz, 1H, Ar**H**), 7.15 (d, *J*=2.2 Hz, 1H, Ar**H**), 6.60 (dd, *J*=8.1, 2.2 Hz, 1H, Ar**H**), 3.70 (s, 3H, OC**H**$_3$), 3.44 (br. s, 1H, O**H**).
δ_C (100 MHz, acetone-d_6)	167.1 (**C**), 158.0 (**C**), 140.9 (**C**H), 133.0 (**C**), 123.2 (**C**H), 116.3 (**C**H), 91.3 (**C**I), 52.9 (**C**H$_3$).

LRMS (ESI+, m/z)	279 $[M+H]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_8H_8IO_3$ $[M+H]^+$ requires 278.9509; found: 278.9513

Methyl 4-iodo-3-methoxybenzoate (4.3)

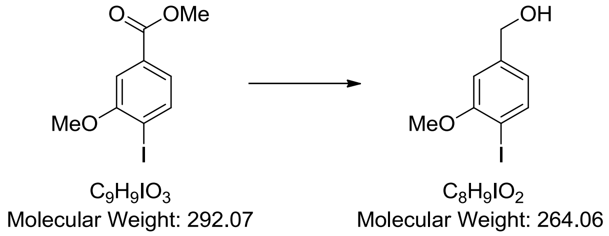


To a stirred solution of methyl 3-hydroxy-4-iodobenzoate **4.2** (13.8 g, 49.6 mmol) in acetone (500 mL) was added K_2CO_3 (20.7 g, 149.8 mmol) and iodomethane (12.4 mL, 199 mmol) and the mixture was stirred at RT. After 18 h it was filtered on Celite®, the solid was washed with acetone (200 mL). The filtrate was concentrated *in vacuo*. The residue was partitioned between water (50 mL) and dichloromethane (100 mL). The aqueous phase was extracted with dichloromethane (3 x 100 mL), combined organic phases were dried over $MgSO_4$, filtered, concentrated *in vacuo* to afford the title compound **4.3** as a yellow solid (9.54 g, 66%).

These data are in accordance with those reported in the literature.[117]

MP	59-60 °C (DCM) [Lit. 50-52 °C (EA)][117]
IR (υ_{max})	2948 (w), 1716 (s), 1584 (m), 1570 (m), 1460 (m), 1432 (m), 1395 (s), 1285 (s), 1229 (s), 1182 (s), 1105 (s), 1036 (m), 1014 (s), 984 (m), 874 (m), 829 (w), 786 (m), 754 (s), 677 (w), 589 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.84 (d, *J*= 8.1 Hz, 1H, Ar**H**), 7.44 (d, *J*=1.8 Hz, 1H, Ar**H**), 7.36 (dd, *J*=8.1, 1.8 Hz, 1H, Ar**H**), 3.93 (s, 3H, $OC\mathbf{H}_3$), 3.91 (s, 3H, $OC\mathbf{H}_3$).
δ_C (100 MHz, $CDCl_3$)	166.5 (**C**), 158.1 (**C**), 139.4 (**C**H), 131.5 (**C**), 123.2 (**C**H), 111.1 (**C**H), 92.6 (**C**I), 56.4 ($O\mathbf{C}H_3$), 52.3 ($O\mathbf{C}H_3$).
LRMS (ESI+, m/z)	293 $[M+H]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_9H_9INaO_3$ $[M+Na]^+$ requires 314.9492; found: 314.9489.

(4-Iodo-3-methoxyphenyl)methanol (4.4)

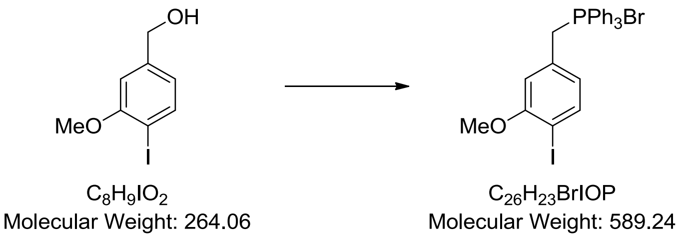


To a stirred solution of methyl 4-iodo-3-methoxybenzoate **4.3** (8.40 g, 28.7 mmol) in DCM (300 mL) at -78 °C was slowly added diisobutylaluminium hydride (66.1 mL, 66.1 mmol, 1 M in hexanes) dropwise over 30 min. The mixture was warmed to RT for 4 h then cooled to -78 °C. MeOH (50 mL) then sat. Rochelle's salt solution (200 mL) were added cautiously and after 5 h at RT the phases were separated. The aqueous phase was extracted with DCM (3 x 100 mL) then the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (20-50% Et_2O/PE) to afford the title compound **4.4** as a pale yellow oil (5.54 g, 73%).

These data are in accordance with those reported in the literature.[118]

IR (υ_{max})	3322 (br. m), 2936 (w), 2863 (w), 1574 (m), 1476 (s), 1459(s), 1403 (s), 1278 (s), 1254 (m), 1166 (m), 1131 (w), 1037 (s), 1011 (s), 907 (m), 851 (w), 806 (m), 727 (s), 582 (w), 547 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.68 (d, *J*=7.9 Hz, 1H, Ar**H**), 6.79 (d, *J*=1.7 Hz, 1H, Ar**H**), 6.64 (dd, *J*=7.9, 1.8 Hz, 1H, Ar**H**), 4.57 (d, *J*=5.7 Hz, 2H, ArC**H**$_2$), 3.83 (s, 3H, OC**H**$_3$), 2.62 (s, 1H, O**H**).
δ_C (100 MHz, $CDCl_3$)	158.0 (**C**), 142.8 (**C**), 139.1 (**C**H), 120.6 (**C**H), 109.3(**C**H), 84.4 (**C**I), 64.4 (**C**H$_2$), 56.2 (O**C**H$_3$).
LRMS (EI+, m/z)	264 (M^+, 100%), 247 (45%), 77 (55%), 51 (17%).
LRMS (ESI+, m/z)	247 $[MH-H_2O]^+$ (100%).
HRMS (ESI+, m/z)	calcd for C_8H_8IO $[MH-H_2O]^+$ requires 246.9610; found: 246.9614.

(4-Iodo-3-methoxybenzyl)triphenylphosphonium bromide (1.139)

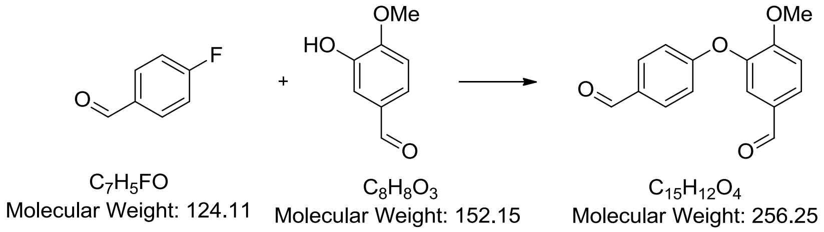


To a solution of 4-Iodo-3-methoxyphenyl alcohol **4.4** (3.61 g, 13.7 mmol) and triphenyl phosphine (4.30 g, 16.4 mmol) in THF (35 mL) at 0 ℃was added *N*-bromosuccinimide (2.92 g, 16.4 mmol). After 1 h at RT, the solution was filtered through silica gel (washing through with 25% Et_2O/PE, 100 mL). The filtrate was concentrated *in vacuo* then dissolved in toluene (35 mL). Triphenylphosphine (3.58 g, 13.7 mmol) added then the solution was heated at reflux for 18 h, then cooled to RT. The resultant precipitate was collected by filtration to give the title compound **1.139** as a beige solid (6.82 g, 84%).

These data are in accordance with those reported in the literature.[63]

MP	> 300 ℃(PhMe)
IR (υ_{max})	2988 (w), 1771 (w), 1701 (m), 1650 (w), 1558(w), 1541 (m), 1508 (m), 1437 (m), 1399 (m), 1289 (w), 1111 (m), 1032 (m), 1010(w), 745 (m), 717 (s), 688 (s), 634 (m), 541(m), 515 (s), 504 (s), 487 (m) cm^{-1}.
δ_H (400 MHz, DMSO-d_6)	7.97-7.88 (m, 3H, 3 x Ar**H**), 7.81-7.55 (m, 13H, 13 x Ar**H**), 6.52-6.43 (m, 2H, 2 x Ar**H**), 5.17 (d, *J*=15.8 Hz, 2H, ArC$\mathbf{H}_2$), 3.41 (s, 3H, OC$\mathbf{H}_3$).
δ_C (100 MHz, DMSO-d_6)	157.5 (d, *J*=2.9 Hz, **C**), 139.2 (d, *J*=2.9 Hz, **C**H), 135.1 (d, *J*=2.9 Hz, 3 x **C**H), 134.1 (d, *J*=9.5 Hz, 6 x **C**H), 130.1 (d, *J* = 12.5 Hz, 6 x **C**H), 129.7 (d, *J* = 7.8 Hz, **C**), 124.8 (d, *J* = 5.9 Hz, **C**H), 118.0 (s, **C**H), 117.6 (s, **C**), 113.9 (d, *J*=5.1 Hz, **C**H), 86.3 (d, *J*=5.1 Hz, **C**I), 55.9 (s, **C**H_3), 28.1 (d, *J*=46.2 Hz, **C**H_2).
δ_p (162 MHz, DMSO-d6)	24.0 (s, 1P).
LRMS (ESI+, m/z)	509 $[M-Br]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{26}H_{23}IOP$ $[M-Br]^+$ requires 509.0525; found: 509.0526.

3-(4-Formylphenoxy)-4-methoxybenzaldehyde (1.138)

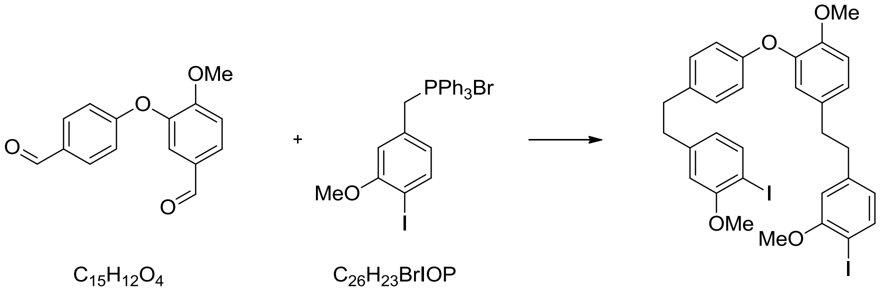


To a solution of isovanillin **1.128** (5.0 g, 32.8 mmol) and 4-fluorobenzaldehyde **1.146** (3.9 mL, 36.3 mmol) in DMF (20 mL) was added K_2CO_3 (5.45 g, 39.4 mmol). The solution was heated at reflux for 18 h then cooled, diluted with water (50 mL) and extracted with EtOAc (3 x 80 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (25-75% Et_2O/PE) to afford the title compound **1.138** as a white solid (8.42 g, 100%).

These data are in accordance with those reported in the literature.[119]

MP	78-79 °C (Et_2O/PE) [Lit. 83-85 °C (EA/hexane)][119]
IR (υ_{max})	2838 (w), 2736 (w), 1685 (s), 1597 (s), 1576 (s), 1501 (s), 1431 (m), 1391 (m), 1273 (s), 1210 (s), 1152 (s), 1108 (s), 1015 (m), 958 (w), 855 (m), 814 (s), 772 (w), 727 (s), 656 (w), 633 (m), 506 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	9.92 (s, 1H, C**H**O), 9.88 (s, 1H, C**H**O), 7.84 (d, *J*=8.8 Hz, 2H, 2 x Ar**H**), 7.78 (dd, *J*=8.4, 2.0 Hz, 1H, Ar**H**), 7.62 (d, *J*=2.0 Hz, 1H, Ar**H**), 7.16 (d, *J*=8.4 Hz, 1H, Ar**H**), 7.00 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**), 3.89 (s, 3H, OCH_3).
δ_C (100 MHz, $CDCl_3$)	190.6 (**C**), 189.9 (**C**), 162.6 (**C**), 156.7 (**C**), 143.7 (**C**), 131.9 (2 x **C**H), 131.4 (**C**), 130.4 (**C**), 129.5 (**C**H), 122.2 (**C**H), 116.5 (2 x **C**H), 112.5 (**C**H), 56.2 (O**C**H_3).
LRMS (ESI+, m/z)	257 $[M+H]^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{15}H_{13}O_4$ $[M+H]^+$ requires 257.0802; found: 257.0808.

1-Iodo-4-(4-(5-(4-iodo-3-methoxyphenethyl)-2-methoxyphenoxy)phenethyl)-2-methoxybenzene (1.137)



$C_{15}H_{12}O_4$
Molecular Weight: 256.25

$C_{26}H_{23}BrIOP$
Molecular Weight: 589.24

$C_{31}H_{30}I_2O_4$
Molecular Weight: 720.38

To a solution of (4-Iodo-3-methoxybenzyl)triphenylphosphonium bromide **1.139** (6.40 g, 10.8 mmol) in THF (50 mL) at 0 ℃ was added sodium hydride (60 % in mineral oil; 566 mg, 14.16 mmol). After 30 min, dialdehyde **1.138** (1.21 g, 4.72 mmol) in THF (10 mL) was added and the mixture was allowed to warm up to RT. After 18 h, water (60 mL) was added and the mixture was extracted with Et_2O (3 X 100 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (20-100% Et_2O/PE) to afford a yellow gum that was dissolved in THF (60 mL). Water (60 mL), tosyl hydrazide (8.79 g, 47.2 mmol) and sodium acetate (3.87 g, 47.2 mmol) were added then the reaction mixture was heated at reflux for 18 h. On cooling to RT, further water (20 mL) was added then the solution was extracted with Et_2O (3 x 100 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (20-35% Et_2O/PE) to afford the title compound **1.137** as a white foam (3.35 g, 98%).

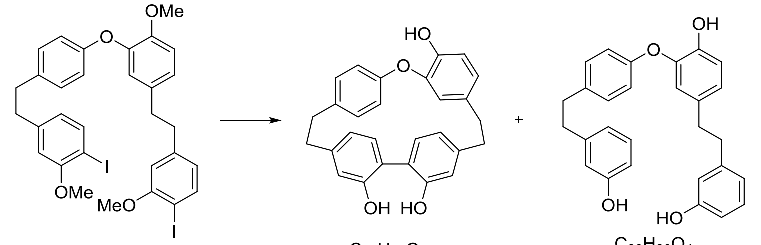
These data are in accordance with those reported in the literature.[63]

IR (υ_{max}) 2931 (w), 2856 (w), 1572 (w), 1503 (s), 1467 (m), 1460 (m), 1403 (m), 1267 (s), 1220 (s), 1168 (m), 1124 (m), 1040 (s), 1014 (s), 907 (m), 847 (w), 808 (m), 728 (s), 645 (w), 502 (w), 451 (w) cm^{-1}.

δ_H (400 MHz, $CDCl_3$)
7.65 (d, *J*=7.9 Hz, 1H, Ar**H**),
7.62 (d, *J*=7.8 Hz, 1H, Ar**H**),
7.09 (d, *J*=8.6 Hz, 2H, 2 x Ar**H**),
6.95-6.90 (m, 2H, 2 x Ar**H**),
6.81 (d, *J*=8.6 Hz, 2H, 2 x Ar**H**),
6.72 (d, *J*=1.7 Hz, 1H, Ar**H**),
6.60 (d, *J*=1.8 Hz, 1H, Ar**H**),
6.56 (dd, *J*=7.8, 1.8 Hz, 1H, Ar**H**),
6.54 (d, *J*=1.7 Hz, 1H, Ar**H**),
6.49 (dd, *J*=7.9, 1.9 Hz, 1H, Ar**H**),

	3.83 (s, 6H, 2 x OC**H**$_3$),
	3.80 (s, 3H, OC**H**$_3$),
	2.90 (s, 4H, 2 x ArC**H**$_2$),
	2.84 (s, 4H, 2 x ArC**H**$_2$).
δ_C (100 MHz, CDCl$_3$)	157.8 (**C**), 157.8 (**C**), 155.9 (**C**), 149.5 (**C**), 144.9 (**C**), 143.7 (**C**), 143.4 (**C**), 139.0 (**C**H), 139.0 (**C**H), 135.2 (**C**), 134.1 (**C**), 129.4 (2 x **C**H), 124.2 (**C**H), 122.7 (**C**H), 122.7 (**C**H), 120.8 (**C**H), 117.1 (2 x **C**H), 112.7 (**C**H), 111.6 (**C**H), 111.5 (**C**H), 82.5 (**C**I), 82.5 (**C**I), 56.1 (**C**H$_3$), 56.1 (**C**H$_3$), 56.1 (**C**H$_3$), 37.8 (**C**H$_2$), 37.6 (**C**H$_2$), 36.8 (**C**H$_2$), 36.6 (**C**H$_2$).
LRMS (ESI+, m/z)	743 [M+Na]$^+$ (100%).
HRMS (ESI+, m/z)	calcd for $C_{31}H_{30}I_2NaO_4$ [M+Na]$^+$ requires 743.0126; found: 743.0120.

Polymorphatin A (1.6) and Perrottetin E (1.21)



$C_{31}H_{30}I_2O_4$
Molecular Weight: 720.38

$C_{28}H_{24}O_4$
Molecular Weight: 424.49
Polymorphatin A (**1.6**)

$C_{28}H_{26}O_4$
Molecular Weight: 426.50
Perrottetin E (**1.21**)

To a solution of NiCl$_2$(Ph$_3$P)$_2$ (6.95 g, 10.6 mmol) and PPh$_3$ (5.62 g, 21.4 mmol) in dry DMF (280 mL) was added Zn powder (770 mg, 11.8 g-atom). The reaction mixture was stirred under argon at 55 ℃ for 1 h, then added a solution of 12,12'-diiodoperrottetin E trimethyl ether **1.132** (3.19 g, 4.42 mmol) at the same temperature. After 1 h, the temperature was increased to 100 °C for 18 h; the mixture was allowed to cool down to RT and added slowly HCl (300 mL, 2M), extracted with Et$_2$O (5 x 100 mL). The combined organic phases were dried over MgSO$_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (25-35% Et$_3$O/PE) to afford a colourless gum that was dissolved in DCM (150 mL) at 0°C was added boron tribromide (44.2 mL, 1 M solution in DCM, 44.2 mmol). After 18 h at RT, water (100 mL) was added. The aqueous phase was separated and extracted with Et$_2$O (5 x 100 mL), and then the resulting organic phases were combined, dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20-25% EtOAc/Hexane) afforded firstly polymorphatin A **1.6** (503 mg, 26%) as a white solid and secondly perrottetin E **1.21** (120 mg, 6%) as a colourless oil.

Polymorphatin A (1.6)

MP	160-161 °C (EtOAc/Hexane) [Lit. 234 – 235 °C (MeOH)][32]
IR (υ_{max})	3333 (br. w) 2925 (w), 2856 (w), 1560 (w), 1503 (s), 1440 (m), 1420 (m), 1334 (w), 1285 (m), 1268 (w), 1210 (m), 1167 (m), 1107 (w), 910 (s), 819 (m), 784 (w), 735 (s), 669 (w), 647 (w) cm^{-1}.
δ_H (400 MHz, acetone-d_6)	8.64 (br. s, 1H, O**H**), 8.36 (br. s, 1H, O**H**), 7.67 (s, 1H, O**H**), 7.00 (br. d, *J*=7.9 Hz, 1H, Ar**H**), 6.94 (dd, *J*=8.3, 2.1 Hz, 1H, Ar**H**), 6.83 (dd, *J*=9.2, 2.6 Hz, 1H, Ar**H**), 6.81 (d, *J*=8.2 Hz, 1H, Ar**H**), 6.60 (br. d, *J*=7.7 Hz, 1H, Ar**H**), 6.51 (br. m, 1H, Ar**H**), 6.43 (br. d, *J*=0.3 Hz, 1H, Ar**H**), 6.34 (br. d, *J*=6.1 Hz, 1H, Ar**H**), 6.32 (br. d, *J*=7.3 Hz, 2H, 2 x Ar**H**), 6.12 (br. d, *J*=6.6 Hz, 1H, Ar**H**), 6.10 (d, *J*=7.2 Hz, 1H, Ar**H**), 5.65 (d, *J*=2.0 Hz, 1H, Ar**H**), 2.96-2.70 (m, 8**H**, 2 x $ArC\mathbf{H}_2C\mathbf{H}_2Ar$).
δ_C (100 MHz, acetone)	157.4 (**C**), 154.4 (**C**), 154.3 (**C**), 149.4 (**C**), 142.8 (**C**), 142.7 (**C**), 141.5 (**C**), 134.3 (**C**), 133.7 (**C**), 132.9 (**C**H), 132.2 (**C**H), 130.7 (**C**H), 130.6 (**C**H), 127.4 (**C**H), 126.2 (**C**), 126.0 (**C**H), 125.4 (**C**), 123.9 (**C**H), 122.9 (**C**H), 118.9 (**C**H), 118.7 (**C**H), 118.1 (**C**H), 118.0 (**C**H), 114.9 (**C**H), 39.4 ($\mathbf{C}H_2$), 38.6 ($\mathbf{C}H_2$), 37.7 ($\mathbf{C}H_2$), 37.6 ($\mathbf{C}H_2$).
LRMS (ESI+, m/z)	425 $[M+H]^+$ (100%)
HRMS (ESI+, m/z)	calcd for $C_{28}H_{25}O_4$ $[M+H]^+$ requires 425.1747; found: 425.1749.

Perrottetin E (1.21)

IR (υ_{max}) 3350 (br. w) 2925 (w), 2858 (w), 1588(m), 1504 (s), 1455 (m), 1435 (m), 1342 (w), 1272 (m), 1216 (s), 1156 (s), 1108 (w), 908 (m), 821 (w), 779 (m), 729 (m), 692 (m), 648 (w) cm^{-1}.

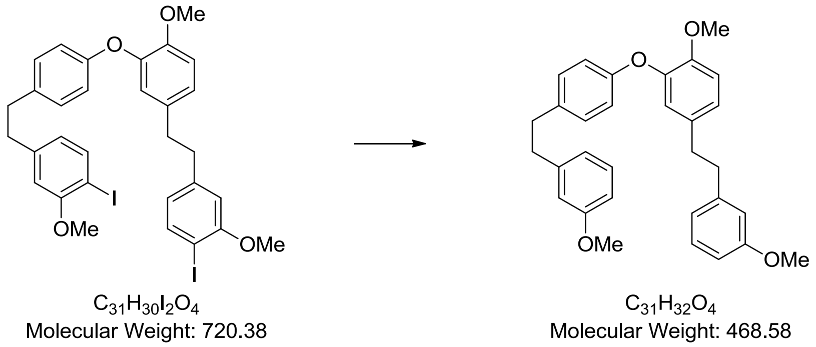
δ_H (400 MHz, CDCl$_3$)
7.16 (t, *J*=7.8 Hz, 1H, Ar**H**),
7.12 (t, *J*=7.8 Hz, 1H, Ar**H**),
7.11 (d, *J*=8.7 Hz, 2H,2 x Ar**H**),
6.96 (d, *J*=8.2 Hz, 1H, Ar**H**),
6.87 (d, *J*=8.7 Hz, 2H, 2 x Ar**H**),
6.84 (dd, *J*=8.0, 2.0 Hz, 1H, Ar**H**),
6.77 (d, *J*=7.6 Hz, 1H, Ar**H**),
6.70-6.63 (m, 4H, 4 x Ar**H**),
6.63 (d, *J*=2.1 Hz, 1H, Ar**H**),
6.59 (dd, *J*=2.5,1.5 Hz, 1H, Ar**H**),
5.48 (s, 1H, O**H**),
4.89 (br.s, 1H, O**H**),
4.85 (br.s.,1H, O**H**),
2.95-2.83 (m, 4H, 2 x ArC**H$_2$**),
2.78 (s, 4H, 2 x ArC**H$_2$**).

δ_C (100 MHz, CDCl$_3$) 155.4 (**C**), 155.4 (**C**), 154.8 (**C**), 145.3 (**C**), 143.5 (**C**), 143.4 (**C**), 143.2 (**C**), 136.8 (**C**), 134.1 (**C**), 129.8 (2 x **C**H), 129.5 (**C**H), 129.4 (**C**H), 124.3 (**C**H), 121.0 (2 x **C**H), 118.7 (**C**H), 117.8 (2 x **C**H), 115.8 (**C**H), 115.5 (**C**H), 115.4 (**C**H), 112.9 (**C**H), 112.8 (**C**H), 37.8 (**C**H$_2$), 37.7 (**C**H$_2$), 36.8 (**C**H$_2$), 36.7 (**C**H$_2$).

LRMS (ESI+, m/z) 427 [M+H]$^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{28}H_{27}O_4$ [M+H]$^+$ requires 427.1904; found: 427.1914.

1-Methoxy-4-(3-methoxyphenethyl)-2-(4-(3-methoxyphenethyl)phenoxy)benzene (4.6)

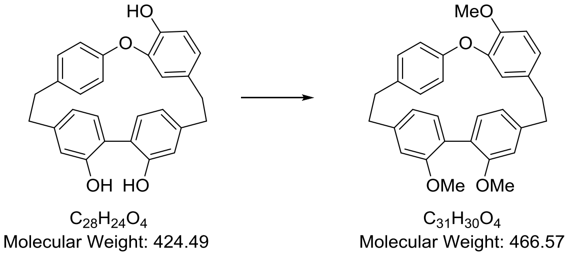


To a stirred solution of **1.137** (410 mg, 0.56 mmol) in THF (55 mL) at -78 °C was added *n*-BuLi (0.47 mL, 1.17 mmol, 2.5 M in hexanes). The reaction mixture was stirring at the same temperature for 1 h then a CuCN (0.12 g, 1.40 mmol) was added. After 18 h at RT, water (20 mL) was added. After 10 min, the aqueous phase was separated at extracted with Et_2O (3 x 100 mL). The resulting organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (35% Et_2O/Hexane) afforded the title compound **4.6** as colourless oil (120 mg, 45%).

IR (υ_{max})	2934 (w), 2835 (w), 1601 (m), 1584 (m), 1505 (s), 1454 (m), 1438 (m), 1313 (w), 1261 (s), 1223 (s), 1166 (m), 1151 (m), 1050 (m), 826 (w), 777 (m), 694 (m) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.20 (td, *J*=7.8, 10.6 Hz, 2H, Ar**H**), 7.11 (d, *J*=8.6 Hz, 2H, Ar**H**), 6.92 (d, *J*=1.1 Hz,2H, Ar**H**), 6.85 (d, *J*=8.6 Hz, 2H, Ar**H**), 6.81-6.72 (m, 6H, Ar**H**), 6.71-6.67 (m, 1H, Ar**H**), 3.84 (s, 3H, $OC\mathbf{H}_3$), 3.80 (s, 3H, $OC\mathbf{H}_3$), 3.78 (s, 3H, $OC\mathbf{H}_3$), 2.91 (s, 4H, 2 x $ArC\mathbf{H}_2$), 2.84 (s, 4H, 2 x $ArC\mathbf{H}_2$).
δ_C (100 MHz, $CDCl_3$)	159.6 (**C**), 159.6 (**C**), 156.0 (**C**), 149.5 (**C**), 145.1 (**C**), 143.4 (**C**), 143.1 (**C**), 135.7 (**C**), 134.7 (**C**), 129.4 (2 x **C**H), 129.2 (**C**H), 129.2 (**C**H), 124.2(**C**H), 120.9 (2 x **C**H), 120.8 (**C**H), 117.2 (2 x **C**H), 114.2 (**C**H), 114.2 (**C**H), 112.7 (**C**H), 111.2 (**C**H), 111.2 (**C**H), 56.1 ($\mathbf{C}H_3$), 55.1 ($\mathbf{C}H_3$), 55.1 ($\mathbf{C}H_3$), 38.0 ($\mathbf{C}H_2$), 37.9 ($\mathbf{C}H_2$), 37.0 ($\mathbf{C}H_2$), 36.8 ($\mathbf{C}H_2$).
LRMS (ESI+, m/z)	469 $[M+H]^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{28}H_{27}O_4$ $[M+H]^+$ requires 491.2193; found: 491.2184.

Polymorphatin A trimethyl ether (4.7)



To a stirred solution of polymorphatin A **1.6** (35 mg, 0.082 mmol) in acetone (2 mL) was added at 0 °C DBU (0.073 mL, 0.49 mmol) and iodomethane (0.03 mL, 0.49 mmol). The mixture was stirred at room temperature. After 24 h it was filtered on Celite®. The filtrate was concentrated *in vacuo*. Purification by flash column chromatography (25% Et_2O/Hexane) afforded the title compound **4.7** as white solid (25 mg, 65%).

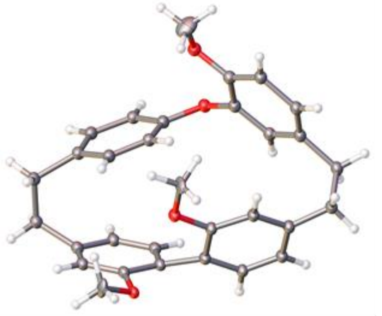
MP	130-133 °C (Et_2O/Hexane)
IR (υ_{max})	2928 (m), 2854 (s), 1605 (m), 1503 (s), 1462 (m), 1403 (m), 1337 (w), 1269 (s), 1220 (m), 1166 (m), 1122 (m), 1099 (w), 1039 (s), 1004 (w), 907 (w), 799 (w) 648 (w) cm^{-1}.
δ_H (400 MHz, $CDCl_3$)	7.04 (dd, *J*=8.1, 2.1 Hz, 2H, 2 x Ar**H**), 6.87 (d, *J*=8.3 Hz, 1H, Ar**H**), 6. 81(d, *J*=7.7 Hz, 2H, 2 x Ar**H**), 6.80-6.68 (m, 2H, 2 x Ar**H**), 6.58 (d, *J*=7.8 Hz, 1H, Ar**H**), 5.99 (dd, *J*=7.9, 1.0 Hz, 1H, Ar**H**), 5.82 (br. d, *J*=2.1 Hz, 2H, 2 x Ar**H**), 5.70 (d, *J* = 2.2 Hz, 1H, Ar**H**), 5.68-5.60 (m, 1H, Ar**H**), 3.81 (s, 3 H, OC**H**$_3$), 3.80 (s, 3 H, OC**H**$_3$), 3.65 (s, 3 H, OC**H**$_3$), 3.16-2.44 (m, 8 H, 2 x C**H**$_2$C**H**$_2$).
δ_C (100 MHz, $CDCl_3$)	156.5 (**C**), 156.2 (**C**), 156.1 (**C**), 150.6 (**C**), 141.3 (**C**), 140.5 (**C**), 140.2 (**C**), 134.2 (**C**), 132.7 (**C**), 131.9 (**C**H), 131.4 (**C**H), 129.3 (2 X **C**), 126.1 (**C**H), 126.0 (**C**H), 125.9 (**C**H), 125.1 (**C**H), 123.1 (**C**H), 122.2 (**C**H), 113.4 (**C**H), 112.5 (**C**H), 112.3 (**C**H), 111.8

(**C**H), 110.5 (**C**H), 56.2 (O**C**H$_3$), 55.8 (O**C**H$_3$), 55.7 (O**C**H$_3$), 38.3 (**C**H$_2$), 38.2 (**C**H$_2$), 37.1 (**C**H$_2$), 36.6 (**C**H$_2$).

LRMS (ESI+, m/z) 467 $[M+H]^+$ (100%).

HRMS (ESI+, m/z) calcd for $C_{31}H_{30}NaO_4$ $[M+Na]^+$ requires 489.2036; found: 489.2044.

X-ray



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2016sot0014_R_100K

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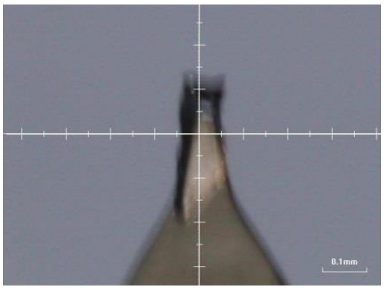
groupsite.soton.ac.uk/Research/xray/ | light@soton.ac.uk | 02380 599429



Submitted by: **Faisal Almalki**
Supervisor: **David Harrowven**
Solved by: **Mark Edward Light**
Sample ID: **FA(7694/87)**

CCDC1455092

Crystal Data and Experimental

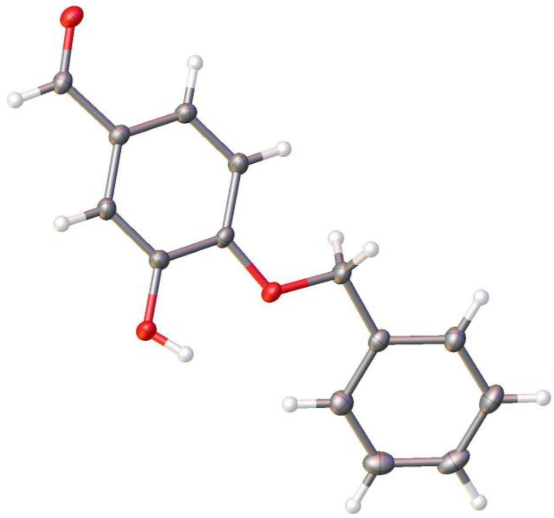


Figure 1: Thermal ellipsoids drawn at the 50% probability level.

Experimental. Single clear colourless block-shaped crystals of (**2016sot0014-R-100K**) were recrystallised from --- by slow evaporation. A suitable crystal (0.21×0.08×0.04) was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku AFC12 FRE-VHF diffractometer. The crystal was kept at T = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Direct Methods solution method. The model was refined with ShelXL (Sheldrick, 2015) using Least Squares minimisation.

Crystal Data. $C_{14}H_{12}O_3$, $M_r = 228.24$, orthorhombic, $P2_12_12_1$ (No. 19), a = 6.45565(16) Å, b = 10.9910(3) Å, c = 15.7263(4) Å, $\alpha = \beta = \gamma = 90^\circ$, $V = 1115.84(5)$ Å^3, $T = 100(2)$ K, $Z = 4$, $Z' = 1$, $\mu(\text{MoK}_\alpha) = 0.095$, 10548 reflections measured, 2874 unique ($R_{int} = 0.0197$) which were used in all calculations. The final wR_2 was 0.0850 (all data) and R_1 was 0.0311 (I > 2(I)).

References

Compound	**2016sot0014-R-100 K**
Formula	$C_{14}H_{12}O_3$
$D_{calc.}$/ g cm^{-3}	1.359
μ/mm^{-1}	0.095
Formula Weight	228.24
Colour	clear colourless
Shape	block
Max Size/mm	0.21
Mid Size/mm	0.08
Min Size/mm	0.04
T/K	100(2)
Crystal System	orthorhombic
Flack Parameter	-0.4(3)
Hooft Parameter	-0.42(19)
Space Group	$P2_12_12_1$
a/Å	6.45565(16)
b/Å	10.9910(3)
c/Å	15.7263(4)
α/°	90
β/°	90
γ/°	90
V/Å^3	1115.84(5)
Z	4
Z'	1
Θ_{min}/°	3.185
Θ_{max}/°	28.687
Measured Refl.	10548
Independent Refl.	2874
Reflections Used	2778
R_{int}	0.0197
Parameters	158
Restraints	0
Largest Peak	0.302
Deepest Hole	-0.192
GooF	1.028
wR_2 (all data)	0.0850
wR_2	0.0842
R_1 (all data)	0.0322
R_1	0.0311

Structure Quality Indicators

Reflections:	d min	0.74	I/σ	52.7	Rint	1.97%	complete at 2θ=61°	100%
Refinement:	Shift	0.001	Max Peak	0.3	Min Peak	-0.2	GooF	1.028

A clear colourless block-shaped crystal with dimensions 0.21×0.08×0.04 was mounted on a MITIGEN holder in perfluoroether oil. Data were collected using a Rigaku AFC12 FRE-VHF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at T = 100(2) K.

Data were measured using profile data from scans of 1.0° per frame for 10.0 s using MoK$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was Θ = 28.687.

Cell parameters were retrieved using the CrysAlisPro (Agilent) software and refined using CrysAlisPro (Agilent) on 7519 reflections, 71 of the observed reflections.

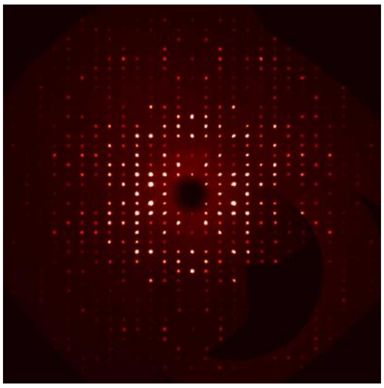
Data reduction was performed using the CrysAlisPro (Agilent) software, which corrects for Lorentz polarisation. The final completeness is 99.80 out to 28.687 in Θ. The absorption coefficient (μ) of this material is 0.095 and the minimum and maximum transmissions are 0.80406 and 1.00000.

The structure was solved in the space group $P2_12_12_1$ (# 19) by Direct Methods using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using ShelXL (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model; the OH hydrogen was freely refined.

There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

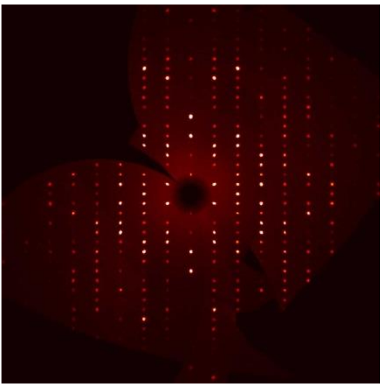
The Flack parameter was refined to -0.4(3). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in -0.42(19). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

Generated precession images



0kl

5



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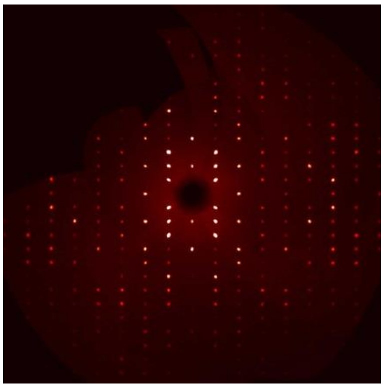
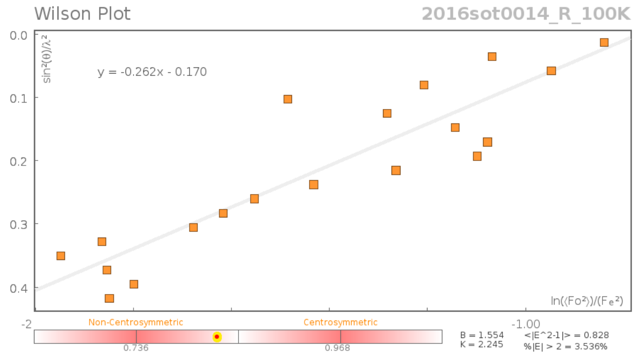
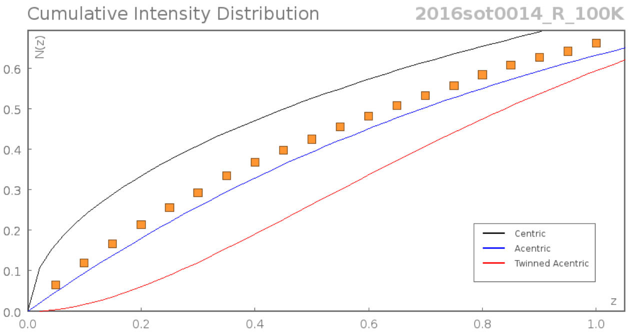


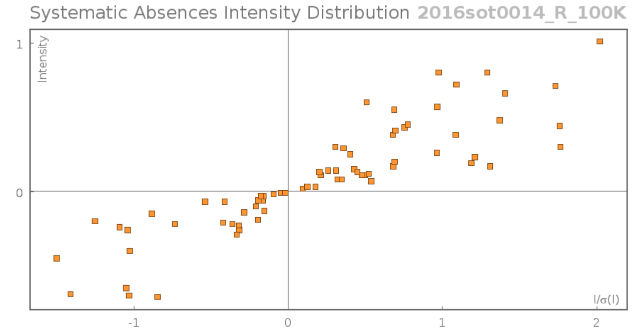
hk0

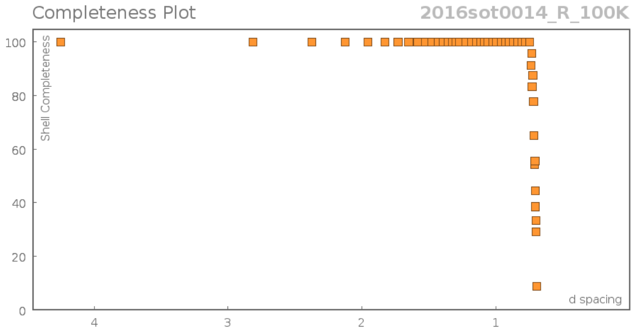
Appendix

Data Plots: Diffraction Data

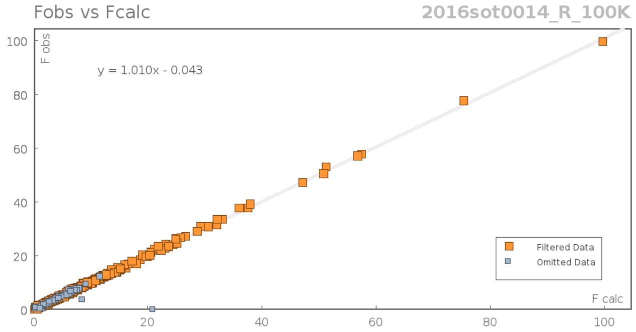


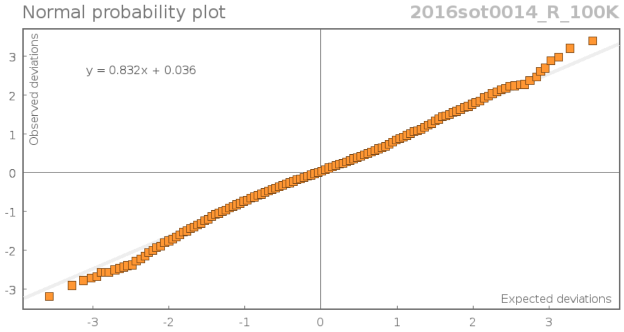






Data Plots: Refinement and Data





Reflection Statistics

Total reflections (after filtering)	10630	Unique reflections	2874
Completeness	0.999	Mean I/σ	52.72
hklsub>max</sub> collected	(9, 15, 22)	hklsub>min</sub> collected	(-8, -15, -22)
hkl$_{max}$ used	(8, 14, 21)	hkl$_{min}$ used	(-8, 0, 0)
Lim d$_{max}$ collected	7.0	Lim d$_{min}$ collected	0.74

d_{max} used	6.46	d_{min} used	0.74
Friedel pairs	2845	Friedel pairs merged	0
Inconsistent equivalents	38	R_{int}	0.0197
R_{sigma}	0.0145	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	12
Multiplicity	(5966, 2059, 302, 23)	Maximum multiplicity	11
Removed systematic absences	70	Filtered off (Shel/OMIT)	452

Table 1: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **2016sot0014_R_100K.** U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
O1	5418.9(17)	4997.6(11)	2277.8(6)	22.2(2)
O2	9699.2(17)	5506.6(12)	5606.0(7)	24.5(3)
O3	6080.2(16)	6302.1(10)	6226.2(6)	19.6(2)
C1	6844(2)	5127.1(13)	2778.6(8)	17.9(3)
C2	6565(2)	5408.9(12)	3681.5(9)	16.7(3)
C3	8265(2)	5332.1(13)	4229.3(9)	17.9(3)
C4	8044(2)	5609.8(13)	5082.6(9)	17.5(3)
C5	6105(2)	6009.5(13)	5384.7(8)	16.1(3)
C6	4396(2)	6059.0(13)	4845.0(9)	18.1(3)
C7	4630(2)	5749.9(13)	3995.2(9)	18.2(3)
C8	4128(2)	6636.4(13)	6593.6(9)	18.6(3)
C9	4492(2)	7135.9(12)	7472.6(8)	17.1(3)
C10	6379(2)	7639.5(13)	7719.3(10)	21.5(3)
C11	6612(3)	8131.7(14)	8531.8(11)	26.7(3)
C12	4968(3)	8130.5(14)	9093.8(10)	27.1(4)
C13	3078(3)	7639.0(15)	8850.9(10)	26.1(3)
C14	2844(2)	7134.6(14)	8046.6(9)	21.6(3)

Table 2: Anisotropic Displacement Parameters (×10^4) **2016sot0014_R_100K.** The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11}+ \ldots +2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	23.3(5)	29.0(5)	14.3(4)	-1.4(4)	-0.2(4)	-0.7(4)
O2	15.2(5)	45.0(7)	13.2(5)	1.4(4)	-0.6(4)	2.8(5)
O3	17.3(5)	29.4(5)	12.0(4)	-2.0(4)	0.8(4)	3.2(4)
C1	20.6(6)	17.8(6)	15.3(6)	-0.6(5)	3.2(5)	-0.1(5)
C2	19.6(7)	16.6(6)	13.8(6)	0.9(5)	0.3(5)	-0.5(5)
C3	16.0(6)	21.7(6)	16.0(6)	1.1(5)	2.3(5)	0.8(5)
C4	15.9(6)	21.5(7)	15.0(6)	2.0(5)	-0.7(5)	-0.7(5)
C5	19.2(6)	18.0(6)	11.0(5)	1.7(5)	1.8(5)	0.6(5)
C6	16.5(6)	21.8(6)	16.0(6)	1.6(5)	0.8(5)	3.3(5)
C7	18.1(6)	21.3(6)	15.2(6)	1.2(5)	-1.9(5)	1.4(5)
C8	18.0(7)	22.9(6)	15.0(6)	-1.9(5)	2.4(5)	2.4(5)
C9	21.7(7)	14.9(6)	14.7(6)	1.2(5)	0.9(5)	1.4(5)
C10	23.7(7)	19.3(6)	21.6(7)	1.0(5)	0.9(6)	-1.9(5)
C11	31.0(8)	20.7(7)	28.4(8)	-2.2(6)	-8.6(7)	-2.5(6)
C12	44.4(10)	19.5(6)	17.2(6)	-3.8(5)	-5.0(6)	4.9(7)
C13	34.9(8)	26.1(7)	17.4(6)	-2.1(6)	5.8(6)	3.5(7)
C14	22.9(7)	22.8(7)	19.1(6)	-1.2(6)	3.4(6)	-0.5(6)

Table 3: Bond Lengths in Å for **2016sot0014_R_100K.**

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C1	1.2195(18)	O2	C4	1.3536(17)

Atom	Atom	Length/Å
O3	C5	1.3619(16)
O3	C8	1.4343(17)
C1	C2	1.4643(18)
C2	C3	1.3978(19)
C2	C7	1.395(2)
C3	C4	1.3836(19)
C4	C5	1.4089(19)
C5	C6	1.3933(19)
C6	C7	1.3872(19)
C8	C9	1.5058(18)
C9	C10	1.393(2)
C9	C14	1.3953(19)
C10	C11	1.396(2)
C11	C12	1.381(2)
C12	C13	1.388(3)
C13	C14	1.389(2)

Table 4: Bond Angles in ° for **2016sot0014_R_100K**.

Atom	Atom	Atom	Angle/°
C5	O3	C8	117.55(11)
O1	C1	C2	123.94(13)
C3	C2	C1	119.24(12)
C7	C2	C1	120.66(13)
C7	C2	C3	120.10(12)
C4	C3	C2	120.23(13)
O2	C4	C3	119.33(13)
O2	C4	C5	121.49(12)
C3	C4	C5	119.18(13)
O3	C5	C4	114.32(12)
O3	C5	C6	124.98(12)
C6	C5	C4	120.69(12)
C7	C6	C5	119.41(13)
C6	C7	C2	120.28(13)
O3	C8	C9	109.03(11)
C10	C9	C8	122.47(13)
C10	C9	C14	119.15(13)
C14	C9	C8	118.33(13)
C9	C10	C11	120.21(14)
C12	C11	C10	120.17(15)
C11	C12	C13	119.99(14)
C12	C13	C14	120.11(15)
C13	C14	C9	120.37(15)

Table 5: Torsion Angles in ° for **2016sot0014_R_100K**.

Atom	Atom	Atom	Atom	Angle/°
O1	C1	C2	C3	169.03(14)
O1	C1	C2	C7	-10.9(2)
O2	C4	C5	O3	1.5(2)
O2	C4	C5	C6	-177.15(13)
O3	C5	C6	C7	179.25(14)
O3	C8	C9	C10	23.83(18)
O3	C8	C9	C14	-158.77(12)
C1	C2	C3	C4	179.15(13)
C1	C2	C7	C6	-177.60(13)
C2	C3	C4	O2	178.70(13)
C2	C3	C4	C5	-2.1(2)
C3	C2	C7	C6	2.4(2)
C3	C4	C5	O3	-177.59(13)
C3	C4	C5	C6	3.7(2)
C4	C5	C6	C7	-2.2(2)
C5	O3	C8	C9	-169.98(11)
C5	C6	C7	C2	-0.9(2)
C7	C2	C3	C4	-0.9(2)
C8	O3	C5	C4	-175.79(12)
C8	O3	C5	C6	2.8(2)

Atom	**Atom**	**Atom**	**Atom**	**Angle/˚**
C8	C9	C10	C11	177.57(13)
C8	C9	C14	C13	-176.92(14)
C9	C10	C11	C12	-0.5(2)
C10	C9	C14	C13	0.6(2)
C10	C11	C12	C13	0.0(2)
C11	C12	C13	C14	0.8(2)
C12	C13	C14	C9	-1.1(2)
C14	C9	C10	C11	0.2(2)

Table 6: Hydrogen Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **2016sot0014_R_100K**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H1	8218	5040	2571	21
H3	9577	5088	4015	21
H6	3082	6302	5057	22
H7	3467	5771	3625	22
H8A	3211	5916	6625	22
H8B	3443	7259	6236	22
H10	7511	7648	7333	26
H11	7905	8469	8699	32
H12	5130	8466	9646	32
H13	1943	7647	9235	31
H14	1554	6787	7887	26
H2	9320(40)	5450(20)	6117(16)	44(7)

Table 7: Hydrogen Bond information for **2016sot0014_R_100K**.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/deg
O2	H2	O1[1]	0.84(3)	1.90(3)	2.6879(15)	155(3)

----

[1] 3/2-X,1-Y,1/2+Z

Citations

CrystalClear, Rigaku,

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

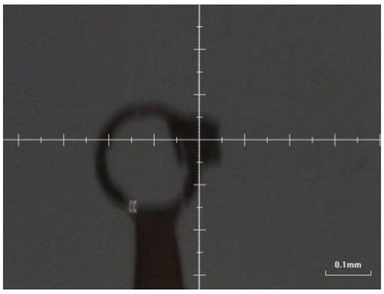
Sheldrick, G.M., ShelXT, *Acta Cryst.*, (2014), **A71**, 3-8.

Appendix

```
#==============================================================================
# PLATON/CHECK-(251013) versus check.def version of 211013   for Entry: 2016sot0
# Data: 2016sot0014_R_100K.cif - Type: CIF       Bond Precision   C-C = 0.0021 A
# Refl: 2016sot0014_R_100K.fcf - Type: LIST4                        Temp = 100 K
#                                                X-Ray         Nref/Npar =  10.6
# Cell 6.45565(16)  10.9910(3)  15.7263(4)           90           90          90
# Wavelength 0.71073    Volume Reported    1115.84(5)   Calculated    1115.85(5)
# SpaceGroup from Symmetry P 21 21 21 Hall: P 2ac 2ab
#                 Reported P 21 21 21       P 2ac 2ab
# MoietyFormula C14 H12 O3
#      Reported C14 H12 O3
#    SumFormula C14 H12 O3
#      Reported C14 H12 O3
# Mr        =    228.24[Calc],    228.24[Rep]
# Dx,gcm-3  =     1.359[Calc],     1.359[Rep]
# Z         =         4[Calc],         4[Rep]
# Mu (mm-1) =     0.095[Calc],     0.095[Rep]
# F000      =     480.0[Calc],     480.0[Rep]  or F000' =    480.26[Calc]
# Reported   T Limits: Tmin=0.804             Tmax=1.000  AbsCorr=MULTI-SCAN
# Calculated T Limits: Tmin=0.991 Tmin'=0.980  Tmax=0.996
# Reported   Hmax=  8, Kmax= 14, Lmax= 21, Nref=   2874        , Th(max)= 28.687
# Obs in FCF Hmax=  8, Kmax= 14, Lmax= 21, Nref=   2874[  1672], Th(max)= 28.687
# Calculated Hmax=  8, Kmax= 14, Lmax= 21, Nref=   2878[  1674], Ratio=1.72/1.00
# Reported   Rho(min) = -0.19, Rho(max) =  0.30 e/Ang**3 (From CIF)
# Calculated Rho(min) = -0.20, Rho(max) =  0.30 e/Ang**3 (From CIF+FCF data)
# w=1/[sigma**2(Fo**2)+(0.0562P)**2+  0.1736P], P=(Fo**2+2*Fc**2)/3
# R= 0.0311(  2778), wR2= 0.0850(  2874), S = 1.028      (From CIF+FCF data)
# R= 0.0311(  2778), wR2= 0.0850(  2874), S = 1.028      (From FCF data only)
# R= 0.0311(  2778), wR2= 0.0850(  2874), S = 1.028, Npar = 158, Flack   -0.4(3)
# Number Bijvoet Pairs = 1202 (100%)     ( 1141 Selected for:  Parsons -0.40(19)
# P2(tr) 1.000, P3(tr) 0.999, P3(tw) 0.001,  Student-T Nu 13.62, Hooft   -0.4(2)
#==============================================================================
For Documentation: http://www.platonsoft.nl/CIF-VALIDATION.pdf
#==============================================================================

#==============================================================================
>>> The Following Improvement and Query ALERTS were generated - (Acta-Mode) <<<
#==============================================================================
Format: alert-number_ALERT_alert-type_alert-level text

032_ALERT_4_G Std. Uncertainty on Flack Parameter Value High .      0.300
910_ALERT_3_G Missing # of FCF Reflections Below Th(Min) .....          2 Why ?
#==============================================================================

#==============================================================================
!! Congratulations !! : No (A,B,C) ALERT Conditions were Detected

#==============================================================================
```

2016sot0031_K1_100K

UNIVERSITY OF Southampton
groupsite.soton.ac.uk/Research/xray/ | light@soton.ac.uk | 02380 599429



Submitted by: **Faisal Almalki**
Supervisor: **David Harrowven**
Solved by: **Mark Light**
Sample ID: **(7865/5)**

CCDC1480749

Crystal Data and Experimental

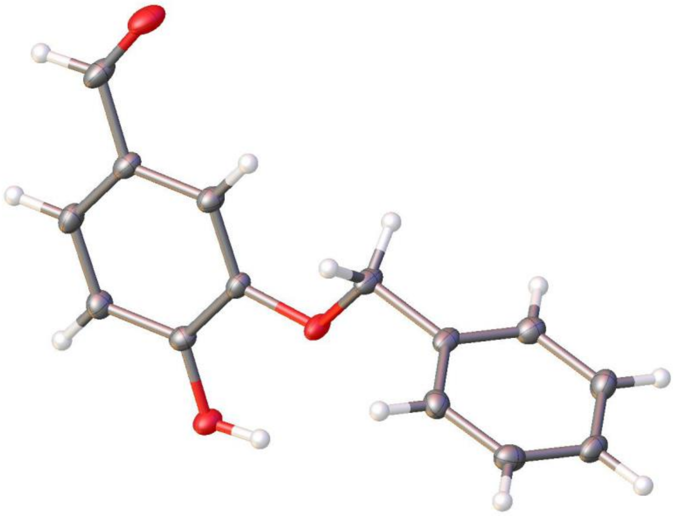


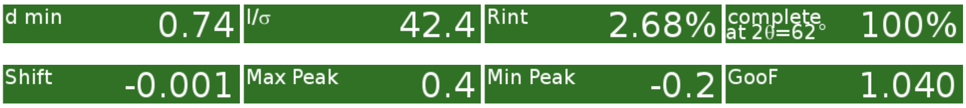
Figure 2: Thermal ellipsoids drawn at the 50% probability level.

Experimental. Single clear colourless prism-shaped crystals of (**2016sot0031_K1_100K**) were recrystallised from --- by slow evaporation. A suitable crystal (0.12×0.07×0.05) mm^3 was selected and mounted on a MITIGEN holder silicon oil on a Rigaku AFC12 FRE-HF diffractometer. The crystal was kept at T = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Direct Methods solution method. The model was refined with version 2014/7 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

Crystal Data. $C_{14}H_{12}O_3$, M_r = 228.24, monoclinic, P2$_1$/c (No. 14), a = 7.60836(13) Å, b = 16.4739(2) Å, c = 9.30104(16) Å, β = 95.5631(16)°, $\alpha = \gamma$ = 90°, V = 1160.30(3) Å^3, T = 100(2) K, Z = 4, Z' = 1, μ(MoK$_\alpha$) = 0.092, 23066 reflections measured, 2993 unique (R_{int} = 0.0268) which were used in all calculations. The final wR_2 was 0.0976 (all data) and R_1 was 0.0384 (I > 2(I)).

Compound	**2016sot0031_K_100 K**
Formula	$C_{14}H_{12}O_3$
$D_{calc.}$/ g cm^{-3}	1.307
μ/mm^{-1}	0.092
Formula Weight	228.24
Colour	clear colourless
Shape	prism
Size/mm^3	0.12×0.07×0.05
T/K	100(2)
Crystal System	monoclinic
Space Group	$P2_1/c$
a/Å	7.60836(13)
b/Å	16.4739(2)
c/Å	9.30104(16)
α/°	90
β/°	95.5631(16)
γ/°	90
V/Å^3	1160.30(3)
Z	4
Z'	1
Wavelength/Å	0.71073
Radiation type	MoK_α
Θ_{min}/°	2.961
Θ_{max}/°	28.689
Measured Refl.	23066
Independent Refl.	2993
Reflections Used	2704
R_{int}	0.0268
Parameters	158
Restraints	0
Largest Peak	0.385
Deepest Hole	-0.198
GooF	1.040
wR_2 (all data)	0.0976
wR_2	0.0943
R_1 (all data)	0.0431
R_1	0.0384

Structure Quality Indicators



Reflections:	d min 0.74	I/σ 42.4	Rint 2.68%	complete at 2θ=62° 100%
Refinement:	Shift -0.001	Max Peak 0.4	Min Peak -0.2	GooF 1.040

A clear colourless prism-shaped crystal with dimensions 0.12×0.07×0.05 was mounted on a MITIGEN holder silicon oil. Data were collected using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at T = 100(2) K.

Data were measured using profile data from ω-scans of 1.0° per frame for 10.0 s using MoK$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was Θ = 28.689.

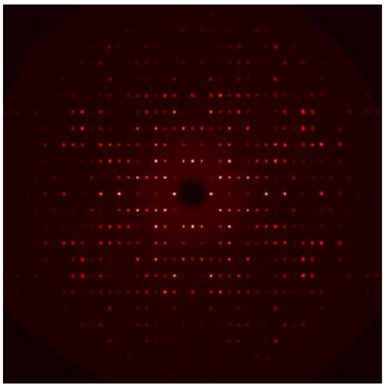
Cell parameters were retrieved using the **CrysAlisPro** (Rigaku, V1.171.38.41, 2015) software and refined using **CrysAlisPro** (Rigaku, V1.171.38.41, 2015) on 15793 reflections, 68 of the observed reflections.

Data reduction was performed using the **CrysAlisPro** (Rigaku, V1.171.38.41, 2015) software, which corrects for Lorentz polarisation. The final completeness is 99.80 out to 28.689 in Θ. The absorption coefficient μ of this material is 0.092 at this wavelength (λ = 0.71073) and the minimum and maximum transmissions are 0.95492 and 1.00000.

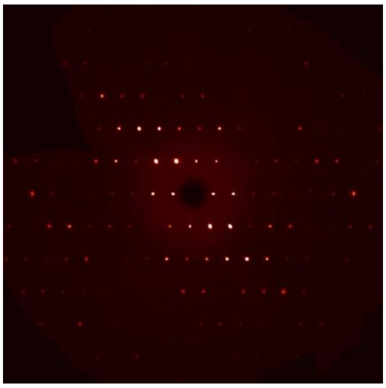
The structure was solved in the space group P2$_1$/c (# 14) by Direct Methods using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2014/7 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

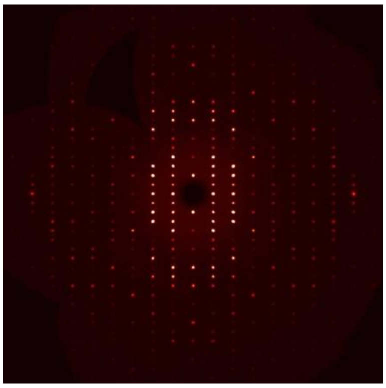
Generated precession images



0kl



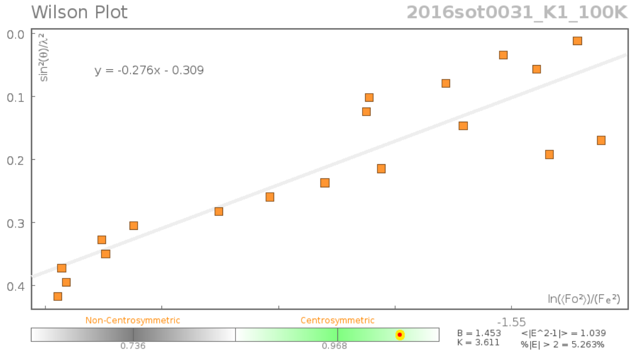
h0l

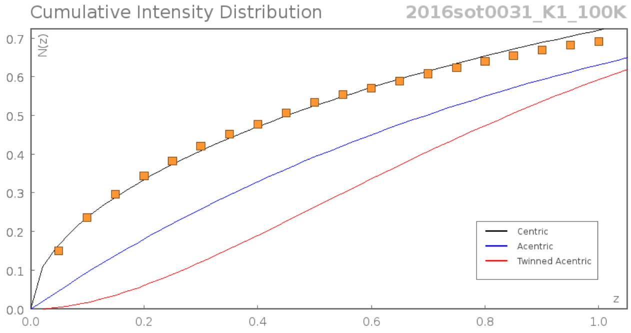


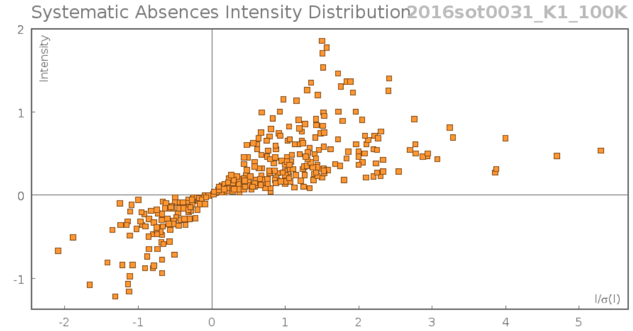
hk0

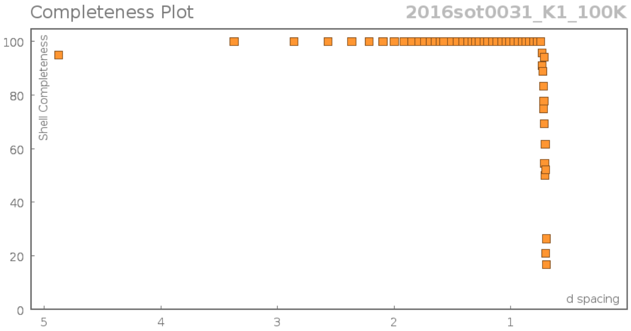
Appendix

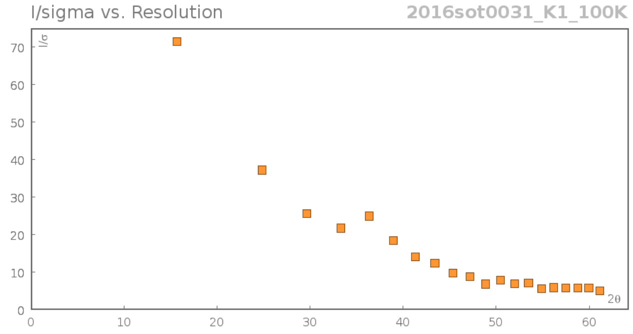
Data Plots: Diffraction Data



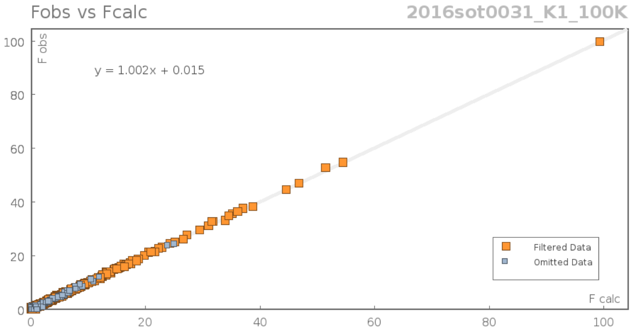


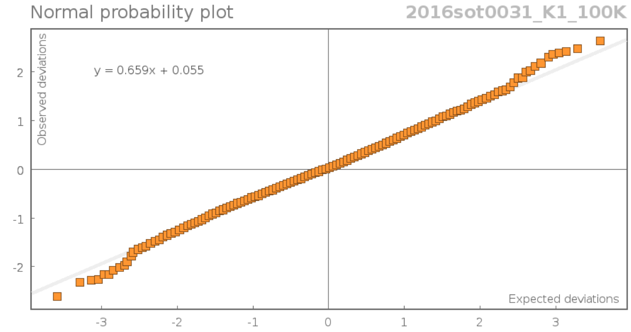






Data Plots: Refinement and Data





Reflection Statistics

Total reflections (after filtering)	23538	Unique reflections	2993
Completeness	1.0	Mean I/σ	42.45
hkl$_{max}$ collected	(10, 23, 13)	hkl$_{min}$ collected	(-10, -23, -13)
hkl$_{max}$ used	(10, 22, 12)	hkl$_{min}$ used	(-10, 0, 0)
Lim d$_{max}$ collected	7.0	Lim d$_{min}$ collected	0.74
d$_{max}$ used	6.88	d$_{min}$ used	0.74
Friedel pairs	5384	Friedel pairs merged	1
Inconsistent equivalents	5	R$_{int}$	0.0268
R$_{sigma}$	0.014	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	0
Multiplicity	(4777, 4032, 1723, 1061, 307, 127, 19, 1)	Maximum multiplicity	23
Removed systematic absences	472	Filtered off (Shel/OMIT)	1154

Table 8: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **2016sot0031_K1_100K.** U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	**x**	**y**	**z**	U_{eq}
O1	3415.1(10)	5944.5(4)	1043.4(9)	19.62(17)
O2	6107.7(9)	5397.6(4)	2866.3(8)	17.84(17)
O3	5069.9(11)	2279.0(5)	2814.4(10)	28.3(2)
C1	3618.2(13)	5141.6(6)	1255.7(11)	15.8(2)
C2	2433.4(14)	4619.4(6)	497.4(11)	18.6(2)
C3	2589.2(14)	3786.0(6)	689.4(12)	19.4(2)
C4	3928.6(13)	3473.2(6)	1655.4(11)	17.8(2)
C5	5149.6(13)	3995.6(6)	2414.3(11)	17.2(2)
C6	5002.0(13)	4823.9(6)	2212.2(11)	15.3(2)
C7	4020.3(14)	2600.2(6)	1916.1(13)	22.2(2)
C8	7679.3(14)	5088.1(6)	3669.1(12)	21.0(2)
C9	8828.3(13)	5792.8(6)	4171.1(12)	17.4(2)
C10	10062.6(14)	6104.9(6)	3307.6(12)	19.9(2)
C11	11137.5(14)	6751.4(7)	3789.5(12)	21.5(2)
C12	10980.8(14)	7094.3(6)	5136.0(12)	20.8(2)
C13	9753.4(14)	6783.6(6)	6002.0(12)	21.4(2)
C14	8689.7(14)	6133.0(6)	5524.3(12)	19.6(2)

Table 9: Anisotropic Displacement Parameters (×10^4) **2016sot0031_K1_100K.** The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + ... + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	19.3(4)	13.0(3)	25.4(4)	0.7(3)	-4.1(3)	0.9(3)
O2	15.6(3)	11.8(3)	24.6(4)	-0.9(3)	-6.2(3)	-0.4(3)
O3	25.6(4)	13.7(4)	43.8(5)	1.7(3)	-5.3(4)	0.1(3)
C1	15.3(4)	13.4(4)	18.8(5)	0.0(3)	2.1(4)	0.8(3)
C2	15.9(5)	19.0(5)	20.1(5)	-0.5(4)	-2.6(4)	0.7(4)
C3	17.4(5)	17.4(5)	22.8(5)	-3.9(4)	-1.1(4)	-3.0(4)
C4	17.1(5)	13.2(4)	23.0(5)	-1.9(4)	1.5(4)	-1.0(3)
C5	15.3(5)	14.0(4)	21.9(5)	-0.1(4)	-1.1(4)	0.3(3)
C6	13.5(4)	13.6(4)	18.5(5)	-1.9(3)	0.2(4)	-1.7(3)
C7	19.2(5)	13.9(5)	33.0(6)	-3.3(4)	-0.1(4)	-2.1(4)
C8	18.0(5)	13.4(4)	29.2(5)	1.2(4)	-9.3(4)	0.0(4)
C9	14.8(4)	12.1(4)	23.8(5)	1.0(4)	-6.2(4)	1.6(3)
C10	21.0(5)	19.0(5)	18.8(5)	-0.7(4)	-2.8(4)	2.4(4)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C11	18.3(5)	20.7(5)	24.8(5)	4.8(4)	-1.0(4)	-1.9(4)
C12	18.1(5)	15.0(4)	27.7(5)	0.3(4)	-6.0(4)	-2.6(4)
C13	22.6(5)	18.2(5)	22.5(5)	-3.8(4)	-1.7(4)	0.5(4)
C14	17.0(5)	17.1(5)	24.2(5)	1.0(4)	-0.2(4)	0.0(4)

Table 10: Bond Lengths in Å for **2016sot0031_K1_100K**.

Atom	Atom	Length/Å
O1	C1	1.3440(12)
O2	C6	1.3681(11)
O2	C8	1.4402(12)
O3	C7	1.2192(14)
C1	C2	1.3882(14)
C1	C6	1.4114(14)
C2	C3	1.3880(14)
C3	C4	1.3906(15)
C4	C5	1.4052(14)
C4	C7	1.4591(14)
C5	C6	1.3806(13)
C8	C9	1.5003(14)
C9	C10	1.3919(15)
C9	C14	1.3910(15)
C10	C11	1.3904(15)
C11	C12	1.3895(16)
C12	C13	1.3888(16)
C13	C14	1.3897(14)

Table 11: Bond Angles in ° for **2016sot0031_K1_100K**.

Atom	Atom	Atom	Angle/°
C6	O2	C8	115.46(7)
O1	C1	C2	118.39(9)
O1	C1	C6	121.71(9)
C2	C1	C6	119.89(9)
C3	C2	C1	120.30(10)
C2	C3	C4	119.85(9)
C3	C4	C5	120.33(9)
C3	C4	C7	119.53(9)
C5	C4	C7	120.10(9)
C6	C5	C4	119.72(9)
O2	C6	C1	114.40(8)
O2	C6	C5	125.72(9)
C5	C6	C1	119.88(9)
O3	C7	C4	124.00(10)
O2	C8	C9	108.47(8)
C10	C9	C8	120.77(10)
C14	C9	C8	120.02(10)
C14	C9	C10	119.20(9)
C11	C10	C9	120.37(10)
C12	C11	C10	120.19(10)
C13	C12	C11	119.61(10)
C12	C13	C14	120.15(10)
C13	C14	C9	120.47(10)

Table 12: Torsion Angles in ° for **2016sot0031_K1_100K**.

Atom	Atom	Atom	Atom	Angle/°
O1	C1	C2	C3	-179.68(9)
O1	C1	C6	O2	-1.08(14)
O1	C1	C6	C5	179.12(9)
O2	C8	C9	C10	-88.64(12)
O2	C8	C9	C14	92.51(11)
C1	C2	C3	C4	0.59(16)
C2	C1	C6	O2	178.38(9)
C2	C1	C6	C5	-1.42(15)
C2	C3	C4	C5	-1.44(16)
C2	C3	C4	C7	176.34(10)
C3	C4	C5	C6	0.85(15)
C3	C4	C7	O3	-174.73(11)
C4	C5	C6	O2	-179.20(9)
C4	C5	C6	C1	0.57(15)
C5	C4	C7	O3	3.06(17)

Atom	Atom	Atom	Atom	Angle/°
C6	O2	C8	C9	173.78(9)
C6	C1	C2	C3	0.84(15)
C7	C4	C5	C6	-176.91(10)
C8	O2	C6	C1	-170.75(9)
C8	O2	C6	C5	9.03(14)
C8	C9	C10	C11	-179.17(9)
C8	C9	C14	C13	179.71(9)
C9	C10	C11	C12	-0.34(16)
C10	C9	C14	C13	0.85(15)
C10	C11	C12	C13	0.47(16)
C11	C12	C13	C14	0.06(16)
C12	C13	C14	C9	-0.73(16)
C14	C9	C10	C11	-0.32(15)

Table 13: Hydrogen Fractional Atomic Coordinates ($\times10^4$) and Equivalent Isotropic Displacement Parameters (Å$^2\times10^3$) for **2016sot0031_K1_100K**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ}.

Atom	x	y	z	U_{eq}
H2	1512	4833	-156	22
H3	1783	3430	162	23
H5	6073	3780	3064	21
H7	3213	2261	1351	27
H8A	8320	4726	3049	25
H8B	7361	4771	4510	25
H10	10171	5875	2384	24
H11	11981	6959	3196	26
H12	11709	7539	5462	25
H13	9641	7016	6923	26
H14	7862	5919	6126	23
H1	4260(20)	6230(10)	1532(18)	40(4)

Table 14: Hydrogen Bond information for **2016sot0031_K1_100K**.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/deg
O1	H1	O3[1]	0.887(17)	1.885(17)	2.6558(11)	144.2(15)

----

[1] 1-X,1/2+Y,1/2-Z

Citations

CrysAlisPro Software System, Rigaku Oxford Diffraction, (2015).

CrystalClear, Rigaku,

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., Crystal structure refinement with ShelXL, *Acta Cryst.*, (2015), **C27**, 3-8.

Sheldrick, G.M., ShelXT-Integrated space-group and crystal-structure determination, *Acta Cryst.*, (2015), **A71**, 3-8.

Appendix

```
#===============================================================================
# PLATON/CHECK-(251013) versus check.def version of 211013   for Entry: 2016sot0
# Data: 2016sot0031_K1_100K.cif - Type: CIF      Bond Precision   C-C = 0.0015 A
# Refl: 2016sot0031_K1_100K.fcf - Type: LIST4                       Temp = 100 K
#                                                X-Ray         Nref/Npar =  18.9
# Cell 7.60836(13)  16.4739(2) 9.30104(16)           90  95.5631(16)          90
# Wavelength 0.71073    Volume Reported    1160.30(3)   Calculated    1160.30(3)
# SpaceGroup from Symmetry P 21/c     Hall: -P 2ybc
#                 Reported P 1 21/c 1       -P 2ybc
# MoietyFormula C14 H12 O3
#      Reported C14 H12 O3
#    SumFormula C14 H12 O3
#      Reported C14 H12 O3
# Mr        =    228.24[Calc],    228.24[Rep]
# Dx,gcm-3  =     1.307[Calc],     1.307[Rep]
# Z         =         4[Calc],         4[Rep]
# Mu (mm-1) =     0.092[Calc],     0.092[Rep]
# F000      =     480.0[Calc],     480.0[Rep]  or F000' =    480.26[Calc]
# Reported   T Limits: Tmin=0.955              Tmax=1.000  AbsCorr=MULTI-SCAN
# Calculated T Limits: Tmin=0.992 Tmin'=0.989  Tmax=0.995
# Reported   Hmax= 10, Kmax= 22, Lmax= 12, Nref=   2993        , Th(max)= 28.689
# Obs in FCF Hmax= 10, Kmax= 22, Lmax= 12, Nref=   2993[  2993], Th(max)= 28.689
# Calculated Hmax= 10, Kmax= 22, Lmax= 12, Nref=   2996        , Ratio  =  0.999
# Reported   Rho(min) = -0.20, Rho(max) =  0.38 e/Ang**3 (From CIF)
# Calculated Rho(min) = -0.19, Rho(max) =  0.37 e/Ang**3 (From CIF+FCF data)
# w=1/[sigma**2(Fo**2)+(0.0438P)**2+  0.4918P], P=(Fo**2+2*Fc**2)/3
# R= 0.0384(  2703), wR2= 0.0976(  2993), S = 1.041      (From CIF+FCF data)
# R= 0.0384(  2703), wR2= 0.0976(  2993), S = 1.040      (From FCF data only)
# R= 0.0384(  2704), wR2= 0.0976(  2993), S = 1.040, Npar = 15
#===============================================================================
For Documentation: http://www.platonsoft.nl/CIF-VALIDATION.pdf
#===============================================================================

#===============================================================================
>>> The Following Improvement and Query ALERTS were generated - (Acta-Mode) <<<
#===============================================================================
Format: alert-number_ALERT_alert-type_alert-level text

906_ALERT_3_C Large K value in the Analysis of Variance ......      2.319 Check
913_ALERT_3_C Missing # of Very Strong Reflections in FCF ....          1
#===============================================================================
910_ALERT_3_G Missing # of FCF Reflections Below Th(Min) .....          3 Why ?
#===============================================================================

ALERT_Level and ALERT_Type Summary
==================================
2 ALERT_Level_C = Check. Ensure it is Not caused by an Omission or Oversight
1 ALERT_Level_G = General Info/Check that it is not Something Unexpected

3 ALERT_Type_3 Indicator that the Structure Quality may be Low.
#===============================================================================

0 Missing  Experimental  Info Issue(s) (Out of  53 Tests) -  100 % Satisfied
0 Experimental  Data  Related Issue(s) (Out of  28 Tests) -  100 % Satisfied
1 Structural  Model   Related Issue(s) (Out of 116 Tests) -   99 % Satisfied
2 Unresolved or to be Checked Issue(s) (Out of 222 Tests) -   99 % Satisfied

#===============================================================================
```

2015sot0063_K_100K

UNIVERSITY OF Southampton

groupsite.soton.ac.uk/Research/xray/ | light@soton.ac.uk | 02380 599429

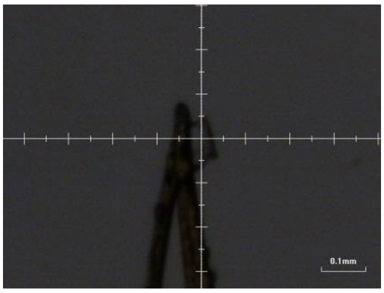
Submitted by: **Faisal Almalki**

Supervisor: **David Harrowven**

Solved by: **Mark Edward Light**

Sample ID: **FA(75U3/89)**

CCDC1438902



Crystal Data and Experimental

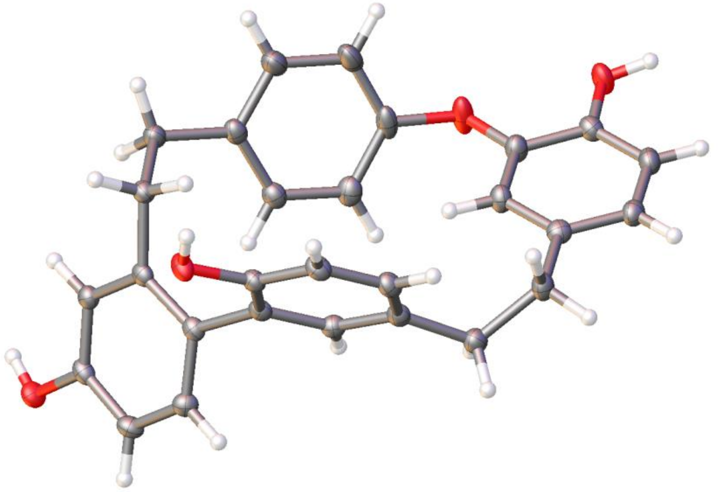


Figure 3: Thermal ellipsoids drawn at the 50% probability level.

Experimental. Single clear colourless prism-shaped crystals of (**2015sot0063-K-100K**) were recrystallised from --- by slow evaporation. A suitable crystal (0.09×0.05×0.04) was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku AFC12 FRE-HF diffractometer. The crystal was kept at T = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Direct Methods solution method. The model was refined with **ShelXL** (Sheldrick, 2008) using Least Squares minimisation.

Crystal Data. $C_{28}H_{24}O_4$, M_r = 424.47, triclinic, P-1 (No. 2), a = 8.8755(3) Å, b = 10.7962(3) Å, c = 12.1943(4) Å, α = 72.714(3)°, β = 89.774(3)°, γ = 69.733(3)°, V = 1040.22(6) Å^3, T = 100(2) K, Z = 2, Z' = 1, μ(MoK$_\alpha$) = 0.090, 15432 reflections measured, 5355 unique (R_{int} = 0.0233) which were used in all calculations. The final wR_2 was 0.1408 (all data) and R_1 was 0.0531 (I > 2(I)).

Compound	**2015sot0063-K-100K**
Formula	$C_{28}H_{24}O_4$
$D_{calc.}$/ g cm^{-3}	1.355
μ/mm^{-1}	0.090
Formula Weight	424.47
Colour	clear colourless
Shape	prism
Max Size/mm	0.09
Mid Size/mm	0.05
Min Size/mm	0.04
T/K	100(2)
Crystal System	triclinic
Space Group	P-1
a/Å	8.8755(3)
b/Å	10.7962(3)
c/Å	12.1943(4)
α/°	72.714(3)
β/°	89.774(3)
γ/°	69.733(3)
V/Å^3	1040.22(6)
Z	2
Z'	1
Θ_{min}/°	2.912
Θ_{max}/°	28.696
Measured Refl.	15432
Independent Refl.	5355
Reflections Used	4398
R_{int}	0.0233
Parameters	301
Restraints	0
Largest Peak	1.209
Deepest Hole	-0.225
GooF	1.023
wR_2 (all data)	0.1408
wR_2	0.1328
R_1 (all data)	0.0653
R_1	0.0531

Appendix

Structure Quality Indicators

Reflections:	d min 0.74	I/σ 23.9	Rint 2.33%	complete at 2θ=61° 100%
Refinement:	Shift 0.000	Max Peak 1.2	Min Peak -0.2	GooF 1.023

A clear colourless prism-shaped crystal with dimensions 0.09×0.05×0.04 was mounted on a MITIGEN holder in perfluoroether oil. Data were collected using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at T = 100(2) K.

Data were measured using profile data from scans of 10.0° per frame for 1.0 s using MoK$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was Θ = 28.696.

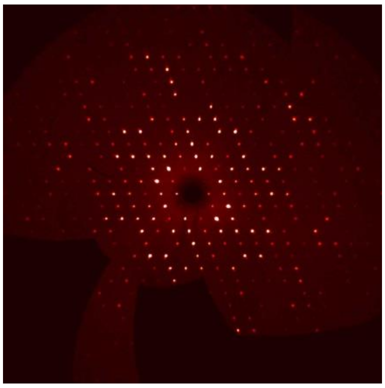
Cell parameters were retrieved using the CrysAlisPro (Agilent) software and refined using CrysAlisPro (Agilent) on 9980 reflections, 65 of the observed reflections.

Data reduction was performed using the CrysAlisPro (Agilent) software that corrects for Lorentz polarisation. The final completeness is 99.80 out to 28.696 in Θ. The absorption coefficient (μ) of this material is 0.090 and the minimum and maximum transmissions are 0.82213 and 1.00000.

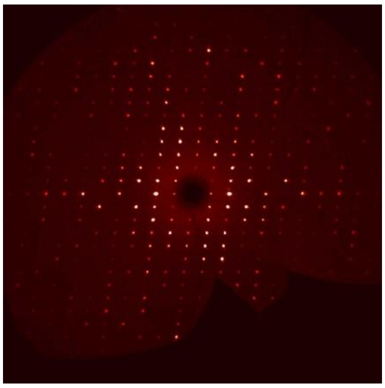
The structure was solved in the space group P-1 (# 2) by Direct Methods using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using **ShelXL** (Sheldrick, 2008). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model, except the)-H which were freely refined.

There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 2 and Z' is 1.

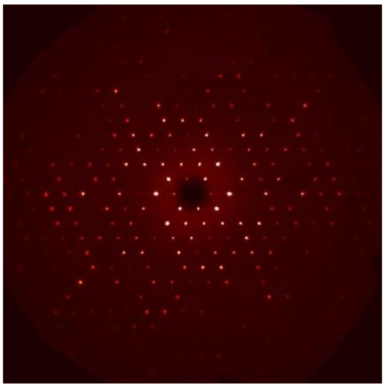
Generated precession images



0kl

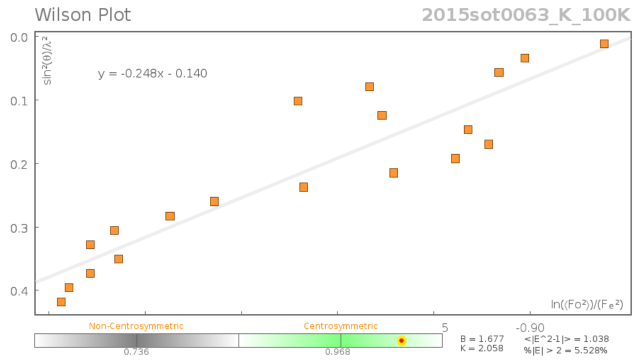


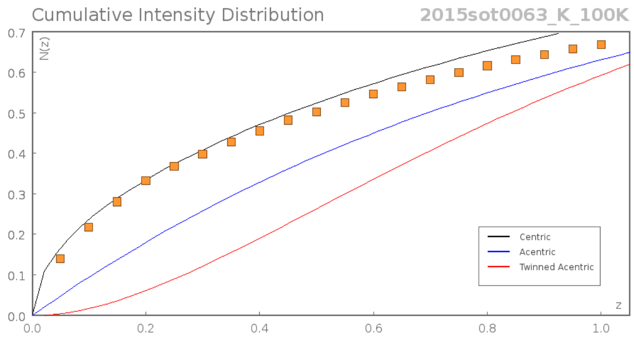
h0l

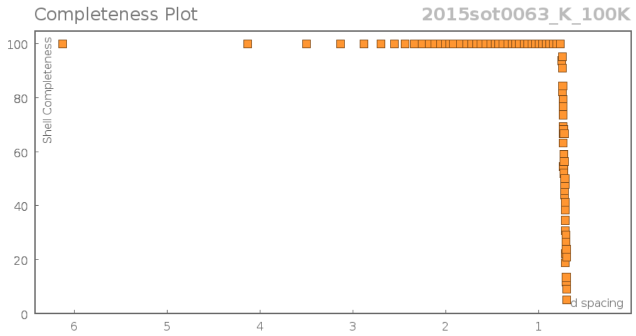


hk0

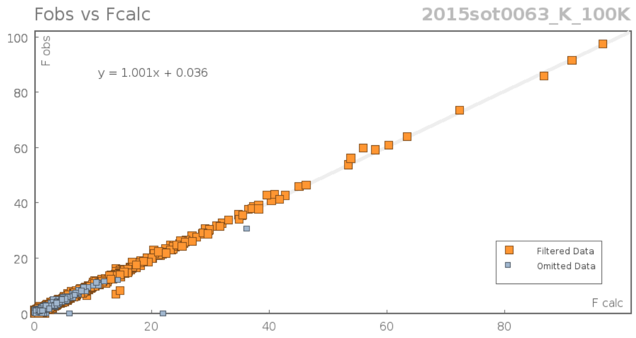
Data Plots: Diffraction Data

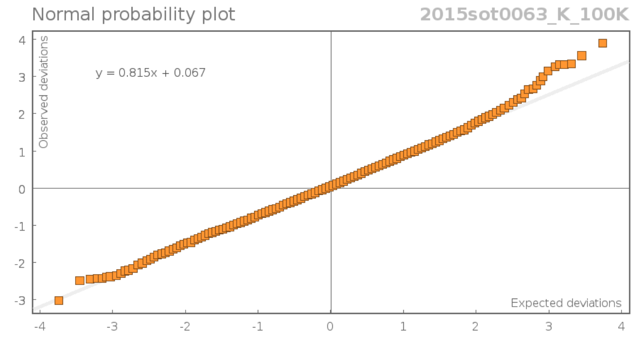






Data Plots: Refinement and Data





Reflection Statistics

Total reflections (after filtering)	15441	Unique reflections	5355
Completeness	0.999	Mean I/σ	23.92
hklsub>max</sub> collected	(12, 14, 17)	hklsub>min</sub> collected	(-12, -15, -16)
hkl$_{max}$ used	(11, 14, 16)	hkl$_{min}$ used	(-11, -13, 0)
Lim d$_{max}$ collected	7.0	Lim d$_{min}$ collected	0.74
d$_{max}$ used	6.99	d$_{min}$ used	0.74
Friedel pairs	3888	Friedel pairs merged	1
Inconsistent equivalents	17	R$_{int}$	0.0233
R$_{sigma}$	0.0271	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	9
Multiplicity	(5014, 3475, 1010, 245, 42, 9)	Maximum multiplicity	10
Removed systematic absences	0	Filtered off (Shel/OMIT)	797

Table 15: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **2015sot0063_K_100K**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
O1	2336.8(13)	6043.9(13)	451.2(10)	21.3(2)
O2	9054.8(13)	7165.6(12)	482.5(10)	21.4(2)
O3	7512.2(15)	6695.0(13)	8794.5(10)	25.8(3)
O4	7179.5(18)	6038.1(13)	6948.4(10)	32.5(3)
C1	6269.2(17)	5994.1(15)	1482.2(12)	17.0(3)
C2	5067.8(18)	5539.9(15)	1207.5(13)	17.9(3)
C3	3558.6(17)	6473.9(16)	676.8(13)	18.4(3)
C4	3242.3(18)	7891.5(16)	342.7(13)	20.2(3)
C5	4409.4(18)	8350.9(16)	638.1(13)	20.0(3)
C6	5916.5(17)	7427.5(15)	1226.5(12)	17.0(3)
C7	7007.6(17)	8037.0(15)	1617.1(12)	17.3(3)
C8	8523.8(18)	7914.0(16)	1236.6(13)	18.3(3)
C9	9450.3(18)	8562.3(16)	1594.4(13)	21.1(3)
C10	8868.0(19)	9352.8(16)	2317.0(13)	21.7(3)
C11	7351.6(18)	9516.4(16)	2710.4(13)	19.5(3)
C12	6460.4(18)	8841.2(15)	2352.3(13)	18.6(3)
C13	6634.4(19)	10488.7(16)	3406.4(14)	21.9(3)
C14	7738(2)	10394.1(17)	4425.3(14)	22.8(3)
C15	7667.8(18)	9421.4(16)	5588.0(14)	20.3(3)
C16	7787.1(19)	9766.1(17)	6583.7(14)	22.1(3)
C17	7763.0(19)	8865.6(17)	7665.7(14)	22.6(3)
C18	7581.3(18)	7616.7(16)	7763.5(13)	21.1(3)
C19	7420(2)	7275.8(16)	6763.6(14)	22.2(3)
C20	7481.5(19)	8160.0(16)	5692.5(14)	21.9(3)
C21	7289(2)	5521.6(18)	6014.8(14)	26.4(4)
C22	8592(2)	4350.7(18)	6064.6(15)	31.4(4)
C23	8717(2)	3796.5(18)	5159.4(15)	27.7(4)
C24	7562.3(19)	4421.4(16)	4204.7(13)	20.7(3)
C25	6237.1(19)	5596.7(17)	4192.7(14)	22.2(3)
C26	6085(2)	6149.2(17)	5093.4(14)	24.9(3)
C27	7778.7(19)	3848.3(16)	3203.8(13)	20.2(3)
C28	7885.4(17)	4896.1(15)	2063.6(13)	18.6(3)

Table 16: Anisotropic Displacement Parameters (×10^4) **2015sot0063_K_100K**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + \ldots + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	18.2(5)	25.2(6)	23.4(6)	-8.5(5)	0.7(4)	-10.7(4)
O2	17.1(5)	32.5(6)	19.5(5)	-13.6(5)	4.8(4)	-10.3(4)
O3	37.9(7)	30.5(6)	14.9(5)	-8.3(5)	2.3(5)	-18.5(5)
O4	62.4(9)	31.4(6)	16.0(6)	-9.0(5)	7.2(6)	-30.6(6)
C1	17.4(6)	22.3(7)	12.2(6)	-6.5(5)	3.6(5)	-7.3(5)
C2	19.5(7)	19.9(7)	15.6(7)	-6.9(5)	2.9(5)	-7.7(5)
C3	16.5(7)	27.0(7)	14.8(7)	-8.2(6)	3.5(5)	-10.4(6)
C4	15.8(6)	24.1(7)	17.9(7)	-3.2(6)	0.5(5)	-6.7(6)
C5	19.8(7)	20.1(7)	19.2(7)	-3.8(6)	3.3(6)	-8.1(6)
C6	16.5(6)	22.1(7)	14.2(7)	-6.1(5)	4.1(5)	-8.8(5)
C7	17.2(6)	18.7(7)	14.7(7)	-2.9(5)	0.8(5)	-7.0(5)
C8	18.1(7)	21.4(7)	15.0(7)	-5.2(5)	1.5(5)	-7.2(5)
C9	17.9(7)	27.0(8)	19.7(7)	-6.1(6)	2.3(6)	-10.6(6)
C10	22.8(7)	24.1(7)	20.4(7)	-5.9(6)	0.0(6)	-12.0(6)
C11	21.9(7)	19.3(7)	16.5(7)	-3.9(5)	0.9(5)	-7.9(6)
C12	18.1(7)	18.5(7)	18.3(7)	-4.1(5)	3.2(5)	-6.9(5)
C13	23.8(7)	20.4(7)	22.0(8)	-6.5(6)	1.1(6)	-8.7(6)
C14	29.0(8)	23.3(7)	21.2(8)	-8.9(6)	4.1(6)	-14.0(6)
C15	17.5(7)	21.7(7)	22.1(8)	-6.7(6)	3.0(6)	-7.8(6)
C16	22.1(7)	22.2(7)	25.5(8)	-10.4(6)	1.8(6)	-9.7(6)
C17	23.6(7)	25.7(8)	21.6(8)	-11.5(6)	1.1(6)	-9.3(6)
C18	21.0(7)	24.7(7)	18.4(7)	-6.5(6)	2.0(6)	-9.7(6)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C19	27.4(8)	22.4(7)	20.6(8)	-8.0(6)	3.4(6)	-12.7(6)
C20	26.8(8)	24.5(7)	19.1(7)	-9.7(6)	5.1(6)	-12.5(6)
C21	46.1(10)	27.1(8)	15.2(7)	-7.1(6)	5.4(7)	-23.8(7)
C22	46.4(10)	27.8(8)	19.4(8)	-3.5(7)	-8.4(7)	-16.1(8)
C23	34.1(9)	23.5(8)	22.8(8)	-4.5(6)	-5.3(7)	-9.4(7)
C24	26.6(8)	21.4(7)	16.0(7)	-3.9(6)	1.3(6)	-12.6(6)
C25	25.5(8)	24.9(8)	17.6(7)	-5.7(6)	2.2(6)	-11.6(6)
C26	31.7(8)	26.4(8)	20.8(8)	-8.6(6)	7.8(6)	-14.6(7)
C27	23.5(7)	18.3(7)	18.1(7)	-4.7(6)	-0.3(6)	-7.6(6)
C28	17.8(7)	20.3(7)	17.2(7)	-6.5(6)	0.9(5)	-6.0(5)

Table 17: Bond Lengths in Å for **2015sot0063_K_100K**.

Atom	Atom	Length/Å
O1	C3	1.3763(17)
O2	C8	1.3765(18)
O3	C18	1.3685(19)
O4	C19	1.3783(19)
O4	C21	1.3983(19)
C1	C2	1.397(2)
C1	C6	1.403(2)
C1	C28	1.515(2)
C2	C3	1.383(2)
C3	C4	1.386(2)
C4	C5	1.383(2)
C5	C6	1.399(2)
C6	C7	1.493(2)
C7	C8	1.397(2)
C7	C12	1.400(2)
C8	C9	1.393(2)
C9	C10	1.382(2)
C10	C11	1.398(2)
C11	C12	1.392(2)
C11	C13	1.513(2)
C13	C14	1.542(2)
C14	C15	1.509(2)
C15	C16	1.386(2)
C15	C20	1.397(2)
C16	C17	1.392(2)
C17	C18	1.383(2)
C18	C19	1.395(2)
C19	C20	1.384(2)
C21	C22	1.372(3)
C21	C26	1.385(2)
C22	C23	1.391(2)
C23	C24	1.387(2)
C24	C25	1.396(2)
C24	C27	1.508(2)
C25	C26	1.383(2)
C27	C28	1.536(2)

Table 18: Bond Angles in ° for **2015sot0063_K_100K**.

Atom	Atom	Atom	Angle/°
C19	O4	C21	117.17(12)
C2	C1	C6	118.85(13)
C2	C1	C28	117.62(13)
C6	C1	C28	123.52(13)
C3	C2	C1	121.30(14)
O1	C3	C2	122.05(14)
O1	C3	C4	117.84(13)
C2	C3	C4	120.11(13)
C5	C4	C3	118.83(14)
C4	C5	C6	122.00(14)
C1	C6	C7	123.98(13)
C5	C6	C1	118.63(13)
C5	C6	C7	117.24(13)
C8	C7	C6	123.40(13)
C8	C7	C12	117.63(13)
C12	C7	C6	118.87(13)
O2	C8	C7	118.31(13)
O2	C8	C9	121.21(13)
C9	C8	C7	120.47(14)
C10	C9	C8	120.28(14)
C9	C10	C11	121.25(14)
C10	C11	C13	121.64(13)
C12	C11	C10	117.27(14)
C12	C11	C13	120.86(14)
C11	C12	C7	123.08(14)
C11	C13	C14	117.14(13)
C15	C14	C13	116.21(13)
C16	C15	C14	120.31(14)
C16	C15	C20	118.34(15)
C20	C15	C14	121.35(14)
C15	C16	C17	121.04(14)
C18	C17	C16	120.32(14)
O3	C18	C17	123.54(14)
O3	C18	C19	117.37(14)
C17	C18	C19	119.07(15)
O4	C19	C18	114.63(14)
O4	C19	C20	124.99(14)
C20	C19	C18	120.37(14)
C19	C20	C15	120.83(14)
C22	C21	O4	117.80(15)
C22	C21	C26	121.49(15)
C26	C21	O4	120.67(16)
C21	C22	C23	119.12(16)
C24	C23	C22	121.07(16)
C23	C24	C25	118.25(15)
C23	C24	C27	119.96(15)
C25	C24	C27	121.78(14)
C26	C25	C24	121.34(15)
C25	C26	C21	118.69(16)
C24	C27	C28	113.24(12)

C1	C28	C27	114.02(12)

Table 19: Hydrogen Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **2015sot0063_K_100K**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
H2A	5292	4570	1389	21
H4	2242	8537	-82	24
H5	4180	9323	435	24
H9	10487	8461	1341	25
H10	9511	9793	2551	26
H12	5433	8930	2619	22
H13A	5667	10315	3714	26
H13B	6262	11455	2873	26
H14A	8868	10097	4237	27
H14B	7454	11338	4492	27
H16	7887	10631	6527	27
H17	7872	9110	8340	27
H20	7396	7906	5020	26
H22	9398	3924	6709	38
H23	9608	2977	5195	33
H25	5424	6026	3553	27
H26	5172	6944	5080	30
H27A	6859	3560	3100	24
H27B	8777	3010	3391	24
H28A	8605	5364	2218	22
H28B	8385	4382	1525	22
H1	2590(30)	5190(20)	774(19)	28(5)
H2	10080(30)	6950(20)	490(20)	38(6)
H3	7860(30)	6900(30)	9380(20)	46(7)

Table 20: Hydrogen Bond information for **2015sot0063_K_100K**.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/deg
O1	H1	O3^1	0.84(2)	1.98(2)	2.7781(17)	160(2)
O2	H2	O1^2	0.86(2)	1.91(2)	2.7451(16)	165(2)
O3	H3	O2^3	0.89(3)	1.87(3)	2.7377(16)	167(2)

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^{1}1-X,1-Y,1-Z; ^{2}1+X,+Y,+Z; ^{3}+X,+Y,1+Z

Citations

CrystalClear, Rigaku,

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., A short history of ShelX, *Acta Cryst.*, (2008), **A64**, 339-341.

Sheldrick, G.M., ShelXT, *Acta Cryst.*, (2014), **A71**, 3-8.

Appendix

```
#==============================================================================
# PLATON/CHECK-(251013) versus check.def version of 211013   for Entry: 2015sot0
# Data: 2015sot0063_K_100K.cif - Type: CIF       Bond Precision   C-C = 0.0021 A
# Refl: 2015sot0063_K_100K.fcf - Type: LIST4                        Temp = 100 K
#                                                X-Ray         Nref/Npar =  17.8
# Cell   8.8755(3)  10.7962(3)  12.1943(4)    72.714(3)    89.774(3)   69.733(3)
# Wavelength 0.71073    Volume Reported    1040.22(6)   Calculated    1040.22(6)
# SpaceGroup from Symmetry P -1        Hall: -P 1
#                 Reported P -1              -P 1
# MoietyFormula C28 H24 O4
#      Reported C28 H24 O4
#    SumFormula C28 H24 O4
#      Reported C28 H24 O4
# Mr         =    424.47[Calc],    424.47[Rep]
# Dx,gcm-3   =     1.355[Calc],     1.355[Rep]
# Z          =         2[Calc],         2[Rep]
# Mu  (mm-1) =     0.090[Calc],     0.090[Rep]
# F000       =     448.0[Calc],     448.0[Rep]  or F000' =    448.22[Calc]
# Reported   T Limits: Tmin=0.822               Tmax=1.000  AbsCorr=MULTI-SCAN
# Calculated T Limits: Tmin=0.995 Tmin'=0.992  Tmax=0.996
# Reported   Hmax= 11, Kmax= 14, Lmax= 16, Nref=   5355         , Th(max)= 28.696
# Obs in FCF Hmax= 11, Kmax= 14, Lmax= 16, Nref=   5355[  5355], Th(max)= 28.695
# Calculated Hmax= 11, Kmax= 14, Lmax= 16, Nref=   5368         , Ratio  =  0.998
# Reported   Rho(min) = -0.22, Rho(max) =  1.21 e/Ang**3  (From CIF)
# Calculated Rho(min) = -0.21, Rho(max) =  1.25 e/Ang**3  (From CIF+FCF data)
# w=1/[sigma**2(Fo**2)+(0.0665P)**2+  0.6979P], P=(Fo**2+2*Fc**2)/3
# R= 0.0532(  4398), wR2= 0.1407(  5355), S = 1.023       (From CIF+FCF data)
# R= 0.0532(  4398), wR2= 0.1408(  5355), S = 1.023       (From FCF data only)
# R= 0.0531(  4398), wR2= 0.1408(  5355), S = 1.023, Npar = 30
#==============================================================================
For Documentation: http://www.platonsoft.nl/CIF-VALIDATION.pdf
#==============================================================================

#==============================================================================
>>> The Following Improvement and Query ALERTS were generated - (Acta-Mode) <<<
#==============================================================================
Format: alert-number_ALERT_alert-type_alert-level text

094_ALERT_2_B Ratio of Maximum / Minimum Residual Density ....       5.37
097_ALERT_2_B Large Reported Max.  (Positive) Residual Density       1.21 eA-3
#==============================================================================
906_ALERT_3_C Large K value in the Analysis of Variance ......      3.282 Check
910_ALERT_3_C Missing # of FCF Reflections Below Th(Min) .....          6 Why ?
911_ALERT_3_C Missing # FCF Refl Between THmin & STh/L=  0.600          2
#==============================================================================
154_ALERT_1_G The su's on the Cell Angles are Equal ..........    0.00300 Deg.
760_ALERT_1_G CIF Contains no Torsion Angles ..................         ? Info
912_ALERT_4_G Missing # of FCF Reflections Above STh/L=  0.600          5
#==============================================================================

ALERT_Level and ALERT_Type Summary
==================================
2 ALERT_Level_B = A Potentially Serious Problem - Consider Carefully
3 ALERT_Level_C = Check. Ensure it is Not caused by an Omission or Oversight
3 ALERT_Level_G = General Info/Check that it is not Something Unexpected

2 ALERT_Type_1 CIF Construction/Syntax Error, Inconsistent or Missing Data.
2 ALERT_Type_2 Indicator that the Structure Model may be Wrong or Deficient.
3 ALERT_Type_3 Indicator that the Structure Quality may be Low.
1 ALERT_Type_4 Improvement, Methodology, Query or Suggestion.
#==============================================================================

0 Missing  Experimental  Info Issue(s) (Out of  53 Tests) -  100 % Satisfied
0 Experimental  Data  Related Issue(s) (Out of  28 Tests) -  100 % Satisfied
3 Structural  Model    Related Issue(s) (Out of 116 Tests) -   97 % Satisfied
5 Unresolved or to be Checked Issue(s) (Out of 222 Tests) -   98 % Satisfied

#==============================================================================
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2016sot0045_K1_100K

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Solved by: **Mark Edward Light**

Sample ID: **Key (FA(7865/36)**

Note: Not for publication – very poor quality structure. CCDC1565196

Crystal Data and Experimental

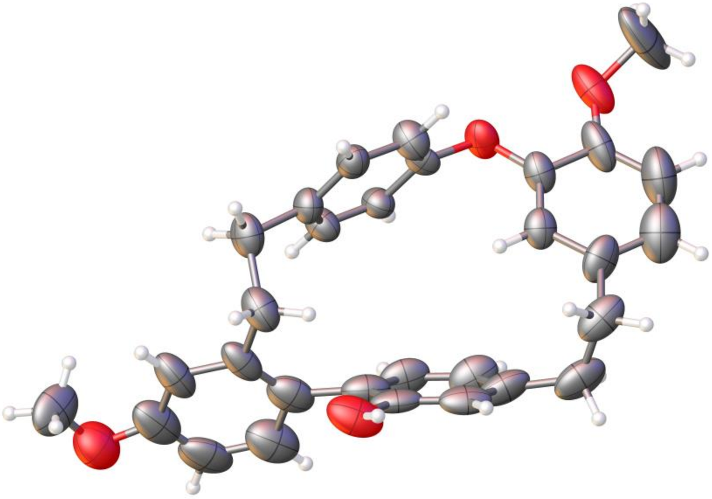


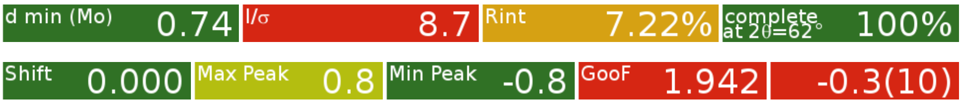
Figure 4: Thermal ellipsoids drawn at the 50% probability level.

Experimental. Single clear colourless rod-shaped crystals of (**2016sot0045_K1_100K**) were recrystallised from --- by slow evaporation. A suitable crystal (0.40×0.05×0.04) mm^3 was selected and mounted on a MITIGEN holder with silicon oil on a Rigaku AFC12 FRE-HF diffractometer. The crystal was kept at T = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version 2014/7 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

Crystal Data. $C_{30}H_{28}O_4$, M_r = 452.52, orthorhombic, $P2_12_12_1$ (No. 19), a = 9.7042(10) Å, b = 15.0491(13) Å, c = 16.3428(15) Å, $\alpha = \beta = \gamma = 90^\circ$, V = 2386.7(4) Å^3, T = 100(2) K, Z = 4, Z' = 1, $\mu(\mathrm{MoK}_\alpha)$ = 0.083, 23086 reflections measured, 6137 unique (R_{int} = 0.0722) which were used in all calculations. The final wR_2 was 0.5538 (all data) and R_1 was 0.2170 (I > 2(I)).

Compound	**2016sot0045_K_100 K**
Formula	$C_{30}H_{28}O_4$
$D_{calc.}$/ g cm^{-3}	1.259
μ/mm^{-1}	0.083
Formula Weight	452.52
Colour	clear colourless
Shape	rod
Size/mm^3	0.40×0.05×0.04
T/K	100(2)
Crystal System	orthorhombic
Flack Parameter	-0.3(10)
Hooft Parameter	0.8(8)
Space Group	$P2_12_12_1$
a/Å	9.7042(10)
b/Å	15.0491(13)
c/Å	16.3428(15)
α/°	90
β/°	90
γ/°	90
V/Å^3	2386.7(4)
Z	4
Z'	1
Wavelength/Å	0.71073
Radiation type	MoK$_\alpha$
Θ_{min}/°	2.980
Θ_{max}/°	28.700
Measured Refl.	23086
Independent Refl.	6137
Reflections Used	3559
R_{int}	0.0722
Parameters	274
Restraints	273
Largest Peak	0.818
Deepest Hole	-0.836
GooF	1.942
wR_2 (all data)	0.5538
wR_2	0.5318
R_1 (all data)	0.2679
R_1	0.2170

Structure Quality Indicators



Reflections:	d min (Mo)	0.74	I/σ	8.7	Rint	7.22%	complete at 2θ=62°	100%	
Refinement:	Shift	0.000	Max Peak	0.8	Min Peak	-0.8	GooF	1.942	-0.3(10)

A clear colourless rod-shaped crystal with dimensions 0.40×0.05×0.04 was mounted on a MITIGEN holder with silicon oil. Data were collected using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at T = 100(2) K.

Data were measured using profile data from ω-scans of 1.0° per frame for 10.0 s using MoK$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrystalClear** (Rigaku). The actually achieved resolution was Θ = 28.700.

Cell parameters were retrieved using the **CrysAlisPro** (Rigaku, V1.171.38.41, 2015) software and refined using **CrysAlisPro** (Rigaku, V1.171.38.41, 2015) on 7156 reflections, 31 of the observed reflections.

Data reduction was performed using the **CrysAlisPro** (Rigaku, V1.171.38.41, 2015) software, which corrects for Lorentz polarisation. The final completeness is 99.20 out to 28.700 in Θ. The absorption coefficient μ of this material is 0.083 at this wavelength (λ = 0.71073) and the minimum and maximum transmissions are 0.27489 and 1.00000.

The structure was solved in the space group $P2_12_12_1$ (# 19) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2014/7 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

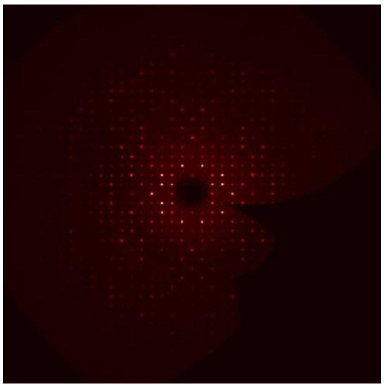
There is a single molecule in the asymmetric unit, which is represented by the reported sum formula. In other words: Z is 4 and Z' is 1.

The Flack parameter was refined to -0.3(10). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in 0.8(8). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

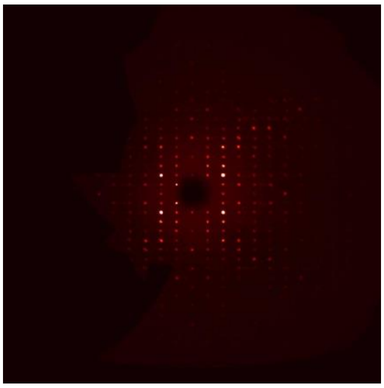
_refine_special_details: The crystal quality and diffraction pattern was very poor, this structure provides connectivity information only.

Generated precession images

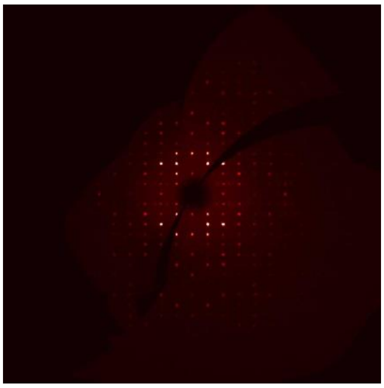
Appendix



0kl

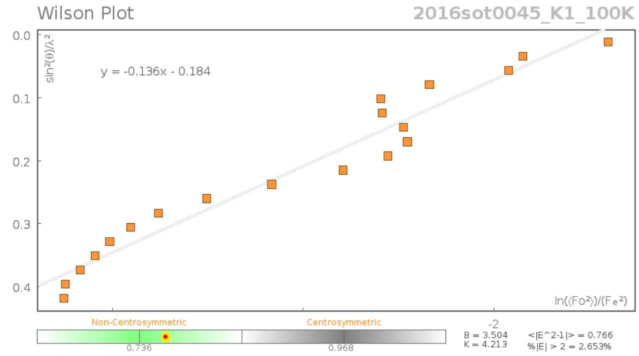


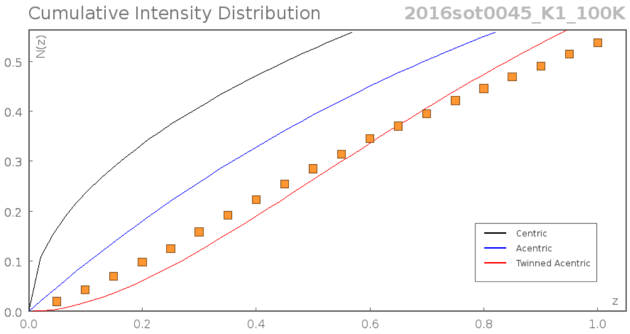
h0l

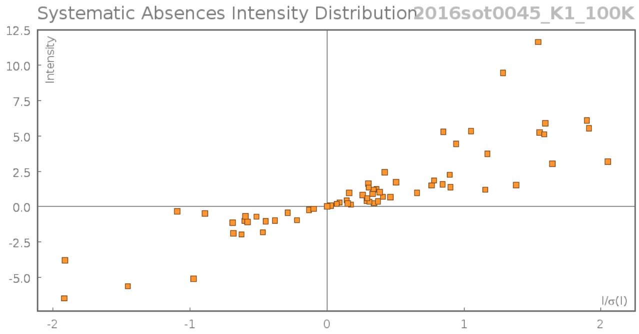


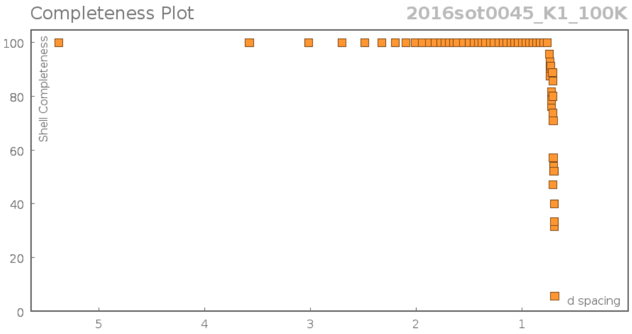
hk0

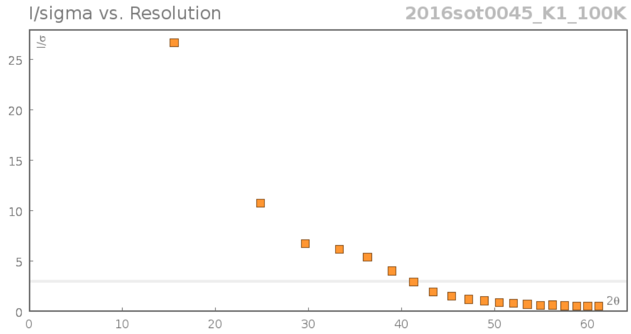
Data Plots: Diffraction Data



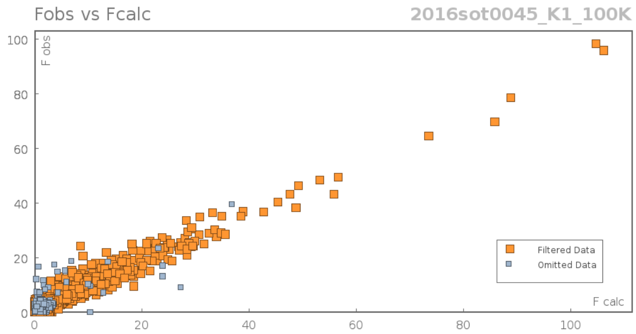


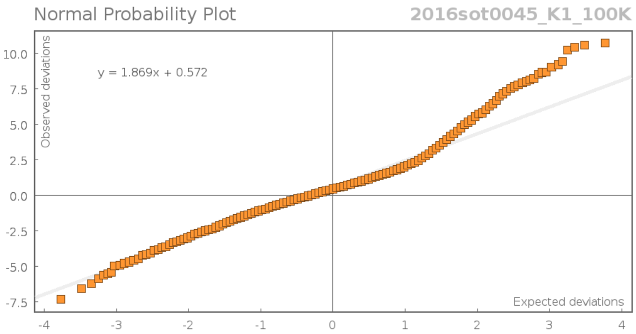






Data Plots: Refinement and Data





Reflection Statistics

Total reflections (after filtering)	23276	Unique reflections	6137
Completeness	0.996	Mean I/σ	8.65
hkl$_{max}$ collected	(13, 20, 23)	hkl$_{min}$ collected	(-8, -21, -22)
hkl$_{max}$ used	(13, 20, 22)	hkl$_{min}$ used	(-13, 0, 0)
Lim d$_{max}$ collected	7.0	Lim d$_{min}$ collected	0.74
d$_{max}$ used	6.83	d$_{min}$ used	0.74
Friedel pairs	3444	Friedel pairs merged	0
Inconsistent equivalents	10	R$_{int}$	0.0722
R$_{sigma}$	0.0785	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	120
Multiplicity	(8052, 5587, 1531, 126, 22)	Maximum multiplicity	13
Removed systematic absences	70	Filtered off (Shel/OMIT)	1157

Table 21: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **2016sot0045_K1_100K.** U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
O1	-7158(17)	-3143(9)	-7463(7)	94(4)
O2	-6556(10)	-2931(6)	-1424(5)	57(2)
O3	-5582(14)	-2549(7)	7(6)	78(3)
O4	-5382(15)	-5841(7)	-4832(7)	89(3)
C1	-8470(20)	-3378(12)	-7560(14)	93(6)
C2	-6833(14)	-3433(6)	-6720(4)	88(4)
C3	-7616(11)	-3927(7)	-6172(5)	78(4)
C4	-7039(11)	-4211(6)	-5439(4)	63(3)
C5	-5680(11)	-4001(6)	-5253(5)	72(3)
C6	-4897(10)	-3507(7)	-5801(7)	93(5)
C7	-5473(13)	-3223(6)	-6535(6)	88(4)
C8	-7903(19)	-4725(11)	-4843(9)	72(3)
C9	-9014(16)	-4165(10)	-4368(8)	64(3)
C10	-8446(12)	-3834(8)	-3568(7)	49(3)
C11	-8754(13)	-4242(9)	-2797(8)	52(3)
C12	-8100(15)	-3929(9)	-2085(8)	58(3)
C13	-7219(12)	-3239(6)	-2147(7)	41(2)

Atom	**x**	**y**	**z**	***U***
C14	-6924(12)	-2795(8)	-2900(7)	47(2)
C15	-7522(13)	-3071(8)	-3588(7)	52(3)
C21	-4893(9)	-4135(5)	-1602(4)	53(3)
C16	-5455(9)	-3435(5)	-1160(5)	54(3)
C17	-4905(12)	-3206(6)	-403(5)	72(3)
C18	-3793(13)	-3679(8)	-89(5)	100(5)
C19	-3232(11)	-4379(7)	-532(7)	98(5)
C20	-3782(10)	-4607(6)	-1289(6)	67(3)
C22	-5640(40)	-2463(15)	892(10)	147(12)
C23	-3250(15)	-5445(9)	-1763(12)	78(4)
C24	-2365(17)	-5098(10)	-2449(12)	81(4)
C30	-3310(10)	-3941(5)	-3415(6)	75(4)
C29	-4150(10)	-3682(4)	-4062(6)	71(3)
C28	-4847(9)	-4320(5)	-4518(5)	64(3)
C27	-4704(9)	-5215(5)	-4327(5)	62(3)
C26	-3864(9)	-5473(4)	-3681(6)	65(3)
C25	-3167(9)	-4836(6)	-3225(6)	75(3)

Table 22: Anisotropic Displacement Parameters (×10^4) **2016sot0045_K1_100K**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + \ldots + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	117(7)	85(8)	81(6)	16(5)	6(6)	-2(7)
O2	78(5)	45(4)	48(4)	-13(3)	-11(4)	6(4)
O3	125(8)	68(5)	42(4)	4(4)	-5(5)	-38(5)
O4	130(9)	54(5)	82(6)	4(5)	37(6)	-18(6)
C1	90(8)	59(8)	130(14)	51(9)	-1(8)	8(7)
C2	146(9)	50(7)	66(6)	6(5)	15(6)	23(7)
C3	132(10)	57(7)	44(5)	-1(5)	-2(6)	4(7)
C4	113(7)	36(5)	38(5)	-2(4)	7(5)	5(5)
C5	105(7)	46(6)	65(6)	-9(5)	20(5)	6(5)
C6	135(11)	57(8)	88(8)	6(6)	27(7)	6(8)
C7	134(9)	55(7)	73(7)	-10(6)	39(6)	20(7)
C8	95(8)	69(7)	54(6)	4(5)	-8(6)	-14(6)
C9	78(7)	55(7)	58(6)	-2(5)	-20(5)	-10(6)
C10	49(5)	51(5)	47(5)	0(4)	-9(4)	-1(5)
C11	50(6)	52(6)	53(5)	-5(4)	-4(4)	5(5)
C12	74(7)	46(5)	53(5)	0(5)	-4(5)	-12(5)
C13	56(5)	28(4)	39(4)	-12(3)	6(4)	3(4)
C14	47(6)	53(6)	42(4)	-1(4)	4(4)	-4(5)
C15	61(6)	52(5)	43(5)	-3(4)	2(5)	-11(5)
C21	63(6)	39(4)	58(6)	8(4)	-12(5)	-7(4)
C16	73(6)	40(5)	47(5)	3(4)	-14(5)	-8(4)
C17	111(8)	61(6)	44(5)	4(4)	-25(5)	-27(6)
C18	127(11)	90(9)	85(9)	10(7)	-49(8)	-12(8)
C19	115(11)	71(8)	109(9)	15(7)	-40(8)	-19(8)
C20	64(6)	40(5)	98(8)	17(5)	-19(6)	3(5)
C22	300(40)	99(14)	42(7)	12(7)	-8(9)	60(20)
C23	55(7)	43(6)	135(9)	9(6)	-3(7)	-4(5)
C24	61(7)	44(6)	139(9)	2(6)	13(6)	12(6)
C30	70(8)	39(5)	115(9)	-1(6)	10(7)	-4(5)
C29	72(7)	33(5)	107(8)	-1(5)	22(6)	3(5)
C28	66(6)	44(5)	82(6)	-2(4)	33(5)	-1(5)
C27	58(6)	42(5)	88(7)	-4(4)	46(5)	-4(4)
C26	69(6)	39(5)	88(7)	5(5)	45(5)	-8(5)
C25	53(6)	45(5)	128(8)	0(5)	24(6)	8(5)

Table 23: Bond Lengths in Å for **2016sot0045_K1_100K**.

Atom	Atom	Length/Å
O1	C1	1.33(2)
O1	C2	1.329(14)
O2	C13	1.423(13)
O2	C16	1.379(11)
O3	C17	1.363(15)
O3	C22	1.45(2)
O4	C27	1.415(14)
C2	C3	1.3900
C2	C7	1.3900
C3	C4	1.3900
C4	C5	1.3900
C4	C8	1.499(17)
C5	C6	1.3900
C5	C28	1.526(11)
C6	C7	1.3900
C8	C9	1.57(2)
C9	C10	1.504(17)
C10	C11	1.433(18)
C10	C15	1.458(18)

Atom	Atom	Length/Å
C11	C12	1.406(18)
C12	C13	1.349(17)
C13	C14	1.429(16)
C14	C15	1.332(16)
C21	C16	1.3900
C21	C20	1.3900
C16	C17	1.3900
C17	C18	1.3900
C18	C19	1.3900
C19	C20	1.3900
C20	C23	1.567(18)
C23	C24	1.50(2)
C24	C25	1.54(2)
C30	C29	1.3900
C30	C25	1.3900
C29	C28	1.3900
C28	C27	1.3900
C27	C26	1.3900
C26	C25	1.3900

Table 24: Bond Angles in ° for **2016sot0045_K1_100K**.

Atom	Atom	Atom	Angle/°
C2	O1	C1	104.4(14)
C16	O2	C13	115.6(7)
C17	O3	C22	125.0(15)
O1	C2	C3	129.4(11)
O1	C2	C7	110.5(11)
C3	C2	C7	120.0
C2	C3	C4	120.0
C3	C4	C8	119.6(9)
C5	C4	C3	120.0
C5	C4	C8	120.4(9)
C4	C5	C6	120.0
C4	C5	C28	127.1(7)
C6	C5	C28	112.7(7)
C5	C6	C7	120.0
C6	C7	C2	120.0
C4	C8	C9	115.3(12)
C10	C9	C8	110.8(12)
C11	C10	C9	123.1(11)
C11	C10	C15	119.0(11)
C15	C10	C9	117.8(11)
C12	C11	C10	119.4(11)
C13	C12	C11	118.8(12)
O2	C13	C14	118.2(9)
C12	C13	O2	118.4(10)
C12	C13	C14	123.5(11)
C15	C14	C13	119.6(11)
C14	C15	C10	119.6(11)

Atom	Atom	Atom	Angle/°
C16	C21	C20	120.0
O2	C16	C21	123.9(6)
O2	C16	C17	116.1(6)
C17	C16	C21	120.0
O3	C17	C16	115.6(8)
O3	C17	C18	124.3(8)
C16	C17	C18	120.0
C19	C18	C17	120.0
C18	C19	C20	120.0
C21	C20	C23	119.0(8)
C19	C20	C21	120.0
C19	C20	C23	120.8(8)
C24	C23	C20	106.1(11)
C23	C24	C25	114.5(13)
C29	C30	C25	120.0
C30	C29	C28	120.0
C29	C28	C5	117.6(6)
C27	C28	C5	122.3(6)
C27	C28	C29	120.0
C28	C27	O4	117.9(8)
C28	C27	C26	120.0
C26	C27	O4	122.0(8)
C25	C26	C27	120.0
C30	C25	C24	118.9(8)
C26	C25	C24	120.7(8)
C26	C25	C30	120.0

Table 25: Torsion Angles in ° for **2016sot0045_K1_100K**.

Atom	Atom	Atom	Atom	Angle/˚
O1	C2	C3	C4	176.0(11)
O1	C2	C7	C6	-176.7(9)
O2	C13	C14	C15	179.6(11)
O2	C16	C17	O3	4.1(10)
O2	C16	C17	C18	180.0(9)
O3	C17	C18	C19	175.5(11)
O4	C27	C26	C25	177.0(9)
C1	O1	C2	C3	4.2(17)
C1	O1	C2	C7	-179.6(12)
C2	C3	C4	C5	0.0
C2	C3	C4	C8	178.5(10)
C3	C2	C7	C6	0.0
C3	C4	C5	C6	0.0
C3	C4	C5	C28	-174.4(9)
C3	C4	C8	C9	-73.3(12)
C4	C5	C6	C7	0.0
C4	C5	C28	C29	-130.2(7)
C4	C5	C28	C27	53.7(10)
C4	C8	C9	C10	-92.5(14)
C5	C4	C8	C9	105.2(12)
C5	C6	C7	C2	0.0
C5	C28	C27	O4	-1.1(10)
C5	C28	C27	C26	176.0(8)
C6	C5	C28	C29	55.0(7)
C6	C5	C28	C27	-121.1(6)
C7	C2	C3	C4	0.0
C8	C4	C5	C6	-178.5(10)
C8	C4	C5	C28	7.0(12)
C8	C9	C10	C11	-101.3(15)
C8	C9	C10	C15	77.7(15)
C9	C10	C11	C12	175.4(12)
C9	C10	C15	C14	-175.4(12)
C10	C11	C12	C13	1.3(19)
C11	C10	C15	C14	3.6(18)
C11	C12	C13	O2	-179.6(10)
C11	C12	C13	C14	0.9(19)
C12	C13	C14	C15	-0.9(18)
C13	O2	C16	C21	7.6(12)
C13	O2	C16	C17	-172.4(8)
C13	C14	C15	C10	-1.5(18)
C15	C10	C11	C12	-3.5(18)
C21	C16	C17	O3	-175.9(10)
C21	C16	C17	C18	0.0
C21	C20	C23	C24	80.2(12)
C16	O2	C13	C12	78.3(14)
C16	O2	C13	C14	-102.1(11)
C16	C21	C20	C19	0.0
C16	C21	C20	C23	174.7(10)
C16	C17	C18	C19	0.0
C17	C18	C19	C20	0.0
C18	C19	C20	C21	0.0
C18	C19	C20	C23	-174.6(11)
C19	C20	C23	C24	-105.1(12)
C20	C21	C16	O2	180.0(10)
C20	C21	C16	C17	0.0
C20	C23	C24	C25	-84.8(14)
C22	O3	C17	C16	151(2)
C22	O3	C17	C18	-25(2)

Atom	Atom	Atom	Atom	Angle/°
C23	C24	C25	C30	108.0(11)
C23	C24	C25	C26	-65.1(13)
C30	C29	C28	C5	-176.2(8)
C30	C29	C28	C27	0.0
C29	C30	C25	C24	-173.1(10)
C29	C30	C25	C26	0.0
C29	C28	C27	O4	-177.1(9)
C29	C28	C27	C26	0.0
C28	C5	C6	C7	175.2(8)
C28	C27	C26	C25	0.0
C27	C26	C25	C24	173.0(10)
C27	C26	C25	C30	0.0
C25	C30	C29	C28	0.0

Table 26: Hydrogen Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **2016sot0045_K1_100K**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	**x**	**y**	**z**	U_{eq}
H4	-5336	-6347	-4616	133
H1A	-8875	-3034	-8008	140
H1B	-8977	-3261	-7053	140
H1C	-8519	-4013	-7690	140
H3	-8545	-4071	-6299	93
H6	-3968	-3363	-5675	112
H7	-4938	-2886	-6909	105
H8A	-7284	-5008	-4438	87
H8B	-8380	-5207	-5144	87
H9A	-9302	-3653	-4708	77
H9B	-9836	-4538	-4264	77
H11	-9393	-4719	-2767	62
H12	-8276	-4199	-1570	70
H14	-6304	-2307	-2910	57
H15	-7348	-2771	-4089	62
H21	-5269	-4291	-2120	64
H18	-3417	-3523	428	121
H19	-2472	-4702	-317	118
H22A	-4741	-2615	1126	221
H22B	-6343	-2867	1109	221
H22C	-5876	-1850	1036	221
H23A	-2704	-5832	-1396	93
H23B	-4034	-5791	-1983	93
H24A	-1681	-5559	-2595	97
H24B	-1852	-4572	-2250	97
H30	-2833	-3505	-3104	90
H29	-4247	-3070	-4192	85
H26	-3766	-6085	-3550	79

Citations

CrysAlisPro Software System, Rigaku Oxford Diffraction, (2015).

CrystalClear, Rigaku,

O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., Crystal structure refinement with ShelXL, *Acta Cryst.*, (2015), **C27**, 3-8.

Sheldrick, G.M., ShelXT-Integrated space-group and crystal-structure determination, *Acta Cryst.*, (2015), **A71**, 3-8.

Appendix

```
#===============================================================================
# PLATON/CHECK-(251013) versus check.def version of 211013   for Entry: 2016sot0
# Data: 2016sot0045_K1_100K.cif - Type: CIF        Bond Precision  C-C = 0.0156 A
# Refl: 2016sot0045_K1_100K.fcf - Type: LIST4                       Temp = 100 K
#                                                X-Ray         Nref/Npar =  12.6
# Cell  9.7042(10) 15.0491(13) 16.3428(15)           90            90          90
# Wavelength 0.71073    Volume Reported     2386.7(4)   Calculated     2386.7(4)
# SpaceGroup from Symmetry P 21 21 21 Hall: P 2ac 2ab
#                 Reported P 21 21 21       P 2ac 2ab
# MoietyFormula C30 H28 O4
#      Reported C30 H28 O4
#    SumFormula C30 H28 O4
#      Reported C30 H28 O4
# Mr        =    452.52[Calc],    452.52[Rep]
# Dx,gcm-3  =     1.259[Calc],     1.259[Rep]
# Z         =         4[Calc],         4[Rep]
# Mu (mm-1) =     0.083[Calc],     0.083[Rep]
# F000      =     960.0[Calc],     960.0[Rep]  or F000' =    960.45[Calc]
# Reported   T Limits: Tmin=0.275              Tmax=1.000  AbsCorr=MULTI-SCAN
# Calculated T Limits: Tmin=0.995 Tmin'=0.967  Tmax=0.997
# Reported   Hmax= 13, Kmax= 20, Lmax= 22, Nref=   6137        , Th(max)= 28.700
# Obs in FCF Hmax= 13, Kmax= 20, Lmax= 22, Nref=   6137[  3445], Th(max)= 28.700
# Calculated Hmax= 13, Kmax= 20, Lmax= 22, Nref=   6169[  3467], Ratio=1.77/0.99
# Reported   Rho(min) = -0.84, Rho(max) =  0.82 e/Ang**3 (From CIF)
# Calculated Rho(min) = -0.82, Rho(max) =  0.87 e/Ang**3 (From CIF+FCF data)
# w=1/[sigma**2(Fo**2)+(0.2000P)**2], P=(Fo**2+2*Fc**2)/3
# R= 0.2170(  3558), wR2= 0.5540(  6137), S = 1.943      (From CIF+FCF data)
# R= 0.2170(  3558), wR2= 0.5538(  6137), S = 1.942      (From FCF data only)
# R= 0.2170(  3559), wR2= 0.5538(  6137), S = 1.942, Npar = 274, Flack  -0.3(10)
# Number Bijvoet Pairs = 2692 (100%)     ( 1073 Selected for:  Parsons    0.1(7)
# P2(tr) 0.404, P3(tr) 0.256, P3(tw) 0.366,  Student-T Nu 81.51, Hooft    0.8(9)
#===============================================================================
For Documentation: http://www.platonsoft.nl/CIF-VALIDATION.pdf
#===============================================================================

#===============================================================================
>>> The Following Improvement and Query ALERTS were generated - (Acta-Mode) <<<
#===============================================================================
Format: alert-number_ALERT_alert-type_alert-level text

082_ALERT_2_A High R1 Value ..................................       0.22
084_ALERT_3_A High wR2 Value (i.e. > 0.25) ...................       0.55
#===============================================================================
097_ALERT_2_B Large Reported Max.  (Positive) Residual Density       0.82 eA-3
098_ALERT_2_B Large Reported Min.  (Negative) Residual Density      -0.84 eA-3
340_ALERT_3_B Low Bond Precision on  C-C Bonds ...............     0.0156 Ang.
412_ALERT_2_B Short Intra XH3 .. XHn     H1B    ..  H3      ..       1.78 Ang.
934_ALERT_3_B Number of (Iobs-Icalc)/SigmaW > 10 Outliers ....          3 Check
#===============================================================================
019_ALERT_1_C Check _diffrn_measured_fraction_theta_full/_max      0.998
220_ALERT_2_C Large Non-Solvent    C     Ueq(max)/Ueq(min) ...        3.6 Ratio
241_ALERT_2_C High      Ueq as Compared to Neighbors for .....        C18 Check
242_ALERT_2_C Low       Ueq as Compared to Neighbors for .....         O3 Check
790_ALERT_4_C Centre of Gravity not Within Unit Cell: Resd.  #          1
C30 H28 O4
906_ALERT_3_C Large K value in the Analysis of Variance ......     14.477 Check
906_ALERT_3_C Large K value in the Analysis of Variance ......      4.578 Check
906_ALERT_3_C Large K value in the Analysis of Variance ......      2.715 Check
910_ALERT_3_C Missing # of FCF Reflections Below Th(Min) .....          7 Why ?
911_ALERT_3_C Missing # FCF Refl Between THmin & STh/L=  0.600         14
918_ALERT_3_C Reflection(s) # with I(obs) much smaller I(calc)          2 Check
#===============================================================================
003_ALERT_2_G Number of Uiso or Uij Restrained non-H Atoms ...         34
007_ALERT_5_G Number of Unrefined Donor-H Atoms ..............          1 Why ?
032_ALERT_4_G Std. Uncertainty on Flack Parameter Value High .      1.000
```

```
072_ALERT_2_G SHELXL First  Parameter in WGHT Unusually Large.       0.20
795_ALERT_4_G C-Atom in CIF Coordinate List out of Sequence ..        C16
860_ALERT_3_G Number of Least-Squares Restraints ............         273 Note
916_ALERT_2_G Hooft y and Flack x Parameter values differ by .       1.10 Check
#==============================================================================

ALERT_Level and ALERT_Type Summary
==================================
2 ALERT_Level_A = Most Likely a Serious Problem - Resolve or Explain
5 ALERT_Level_B = A Potentially Serious Problem - Consider Carefully
11 ALERT_Level_C = Check. Ensure it is Not caused by an Omission or Oversight
7 ALERT_Level_G = General Info/Check that it is not Something Unexpected

1 ALERT_Type_1 CIF Construction/Syntax Error, Inconsistent or Missing Data.
10 ALERT_Type_2 Indicator that the Structure Model may be Wrong or Deficient.
10 ALERT_Type_3 Indicator that the Structure Quality may be Low.
3 ALERT_Type_4 Improvement, Methodology, Query or Suggestion.
1 ALERT_Type_5 Informative Message, Check.
#==============================================================================

0 Missing  Experimental  Info Issue(s) (Out of  53 Tests) -  100 % Satisfied
1 Experimental  Data  Related Issue(s) (Out of  28 Tests) -   96 % Satisfied
15 Structural  Model   Related Issue(s) (Out of 116 Tests) -   87 % Satisfied
8 Unresolved or to be Checked Issue(s) (Out of 222 Tests) -   96 % Satisfied

#==============================================================================
```

2016sot0088_R1_100K

UNIVERSITY OF Southampton
groupsite.soton.ac.uk/Research/xray/ | light@soton.ac.uk | 02380 599429

Submitted by: **Faisal Almalki**
Supervisor: **David Harrowven**
Solved by: **Mark Edward Light**
Sample ID: **FA(7865/72)**

CCDC1517765

Crystal Data and Experimental

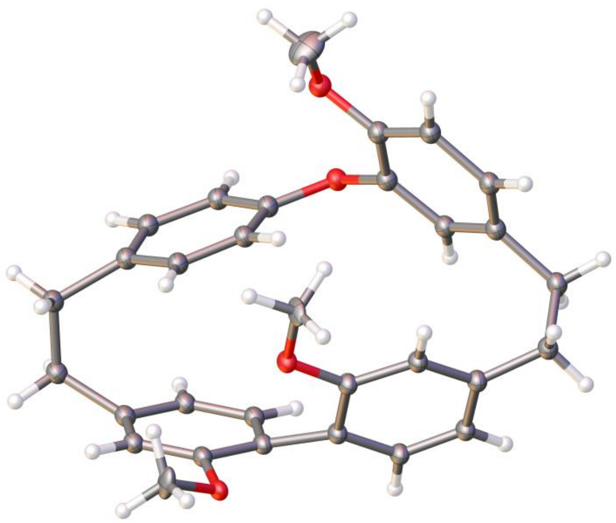


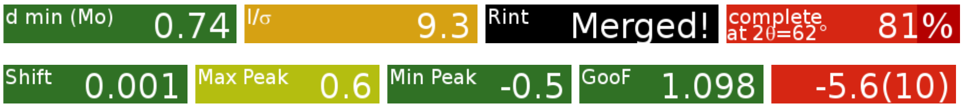
Figure 1. Thermal ellipsoids drawn at the 50% probability level (2nd molecule omitted for clarity).

Experimental. Single clear colourless block-shaped crystals of (**2016sot0088_R1_100K**) were recrystallised from a mixture of CDCl3 and hexane by slow evaporation. A suitable crystal (0.12×0.03×0.02) mm^3 was selected and mounted on a MITIGEN holder silicon oil on a Rigaku AFC12 FRE-VHF diffractometer. The crystal was kept at T = 100(2) K during data collection. Using **Olex2** (Dolomanov et al., 2009), the structure was solved with the **ShelXT** (Sheldrick, 2015) structure solution program, using the Intrinsic Phasing solution method. The model was refined with version 2016/6 of **ShelXL** (Sheldrick, 2015) using Least Squares minimisation.

Compound	**2016sot0088_R_100 K**
Formula	$C_{31}H_{30}O_4$
$D_{calc.}$/ g cm^{-3}	1.269
μ/mm^{-1}	0.083
Formula Weight	466.55
Colour	clear colourless
Shape	block
Size/mm^3	0.12×0.03×0.02
T/K	100(2)
Crystal System	monoclinic
Flack Parameter	-0.3(10)
Hooft Parameter	0.4(10)
Space Group	$P2_1$
a/Å	8.3656(6)
b/Å	11.0874(7)
c/Å	26.366(2)
α/°	90
β/°	93.127(6)
γ/°	90
V/Å^3	2441.9(3)
Z	4
Z'	2
Wavelength/Å	0.71073
Radiation type	MoK$_\alpha$
Θ_{min}/°	2.959
Θ_{max}/°	28.696
Measured Refl.	11110
Independent Refl.	11110
Reflections Used	4686
R_{int}	.
Parameters	626
Restraints	1027
Largest Peak	0.658
Deepest Hole	-0.472
GooF	1.103
wR_2 (all data)	0.2670
wR_2	0.2158
R_1 (all data)	0.2543
R_1	0.1233

Crystal Data. $C_{31}H_{30}O_4$, M_r = 466.55, monoclinic, $P2_1$ (No. 4), a = 8.3656(6) Å, b = 11.0874(7) Å, c = 26.366(2) Å, β = 93.127(6)°, $\alpha = \gamma$ = 90°, V = 2441.9(3) Å^3, T = 100(2) K, Z = 4, Z' = 2, μ(MoK$_\alpha$) = 0.083, 11110 reflections measured, 11110 unique (R_{int} = .) which were used in all calculations. The final wR_2 was 0.2670 (all data) and R_1 was 0.1233 (I > 2(I)).

Structure Quality Indicators



Reflections:	d min (Mo) 0.74	I/σ 9.3	Rint Merged!	complete at 2θ=62° 81%	
Refinement:	Shift 0.001	Max Peak 0.6	Min Peak -0.5	GooF 1.098	-5.6(10)

A clear colourless block-shaped crystal with dimensions $0.12\times0.03\times0.02$ mm^3 was mounted on a MITIGEN holder silicon oil. X-ray diffraction data were collected using a Rigaku AFC12 FRE-VHF diffractometer equipped with a Oxford Cryosystems low-temperature device, operating at T = 100(2) K.

Data were measured using profile data from ω-scans of 1.0 ° per frame for 20.0 s using MoK$_\alpha$ radiation (Rotating Anode, 45.0 kV, 55.0 mA). The total number of runs and images was based on the strategy calculation from the program **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015).The maximum resolution achieved was Θ = 28.696°.

Cell parameters were retrieved using the **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) software and refined using **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) on 5142 reflections, 46 % of the observed reflections. Data reduction was performed using the **CrysAlisPro** (Rigaku, V1.171.39.9g, 2015) software, which corrects for Lorentz polarisation. The final completeness is 99.70 out to 28.696 in Θ. The absorption coefficient μ of this material is 0.083 at this wavelength (λ = 0.71073) and the minimum and maximum transmissions are 0.48971 and 1.00000.

The structure was solved in the space group P2$_1$ (# 4) by Intrinsic Phasing using the **ShelXT** (Sheldrick, 2015) structure solution program and refined by Least Squares using version 2016/6 of **ShelXL** (Sheldrick, 2015). All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

The value of Z' is 2. This means that there are two independent molecules in the asymmetric unit.

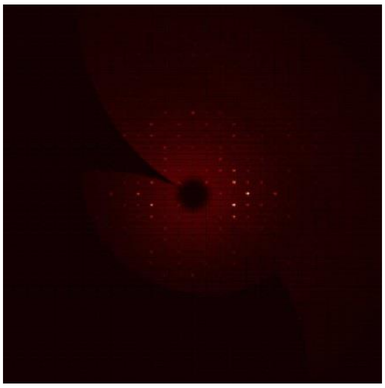
The Flack parameter was refined to -0.3(10). Determination of absolute structure using Bayesian statistics on Bijvoet differences using the Olex2 results in 0.4(10). Note: The Flack parameter is used to determine chirality of the crystal studied, the value should be near 0, a value of 1 means that the stereochemistry is wrong and the model should be inverted. A value of 0.5 means that the crystal consists of a racemic mixture of the two enantiomers.

_refine_special_details: The crystal was a non-merohedral twin and the HKLF5 (merged) reflection file generated using PLATON. The data set was also weak. The structure also possesses pseudo-symmetry.

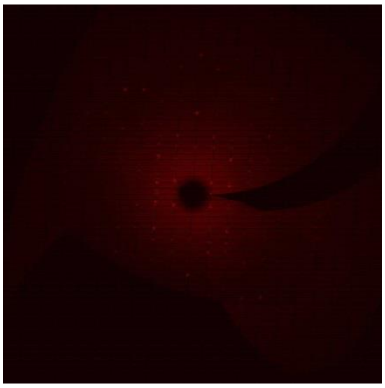
_exptl_absorpt_process_details: CrysAlisPro 1.171.39.9g (Rigaku Oxford Diffraction, 2015) Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm.

Generated precession images

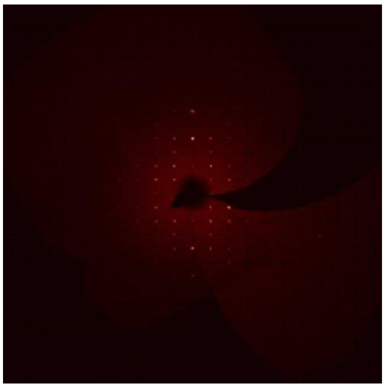
Appendix



0kl

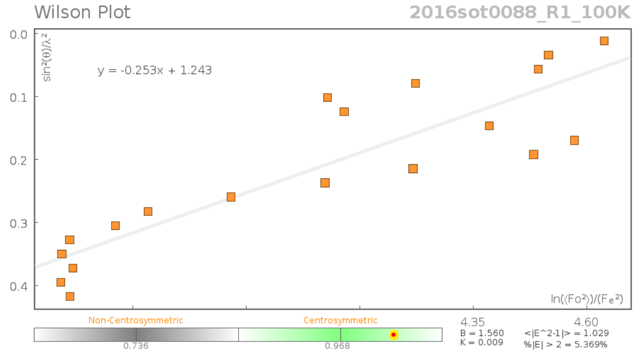


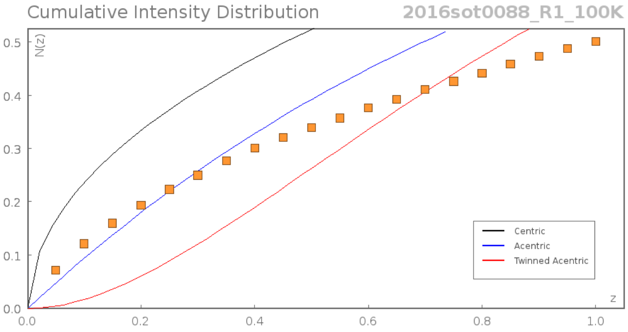
h0l

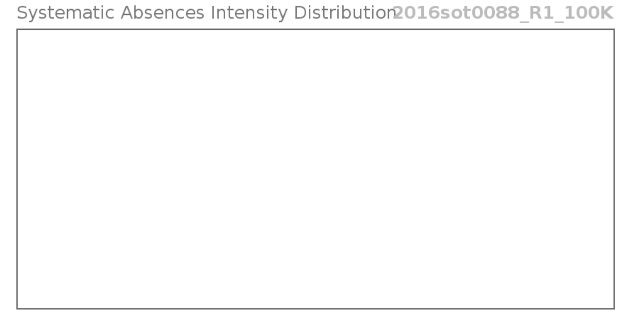


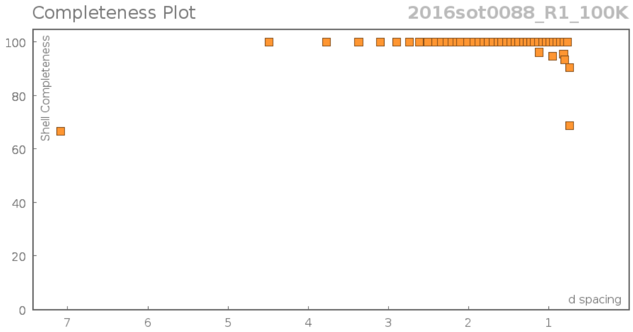
hk0

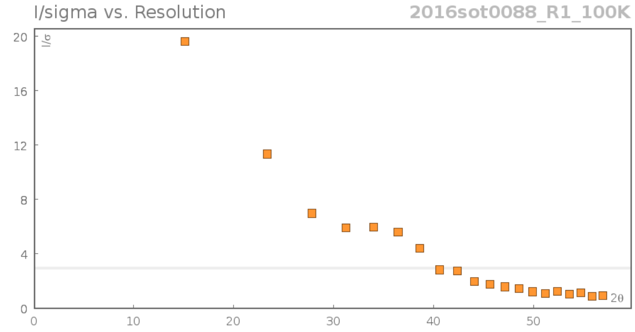
Data Plots: Diffraction Data



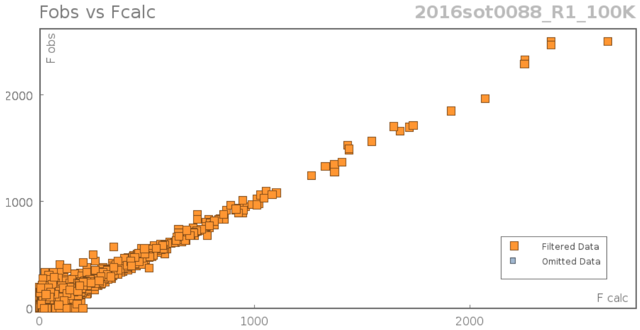


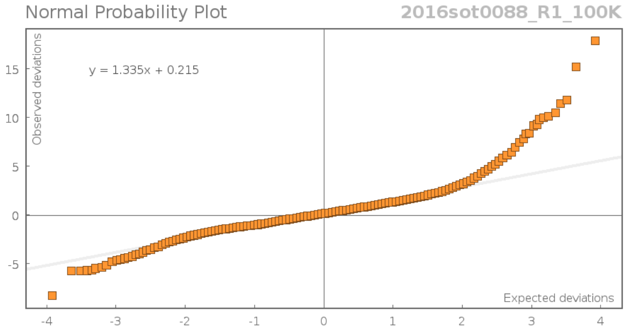






Data Plots: Refinement and Data





Reflection Statistics

Total reflections (after filtering)	14831	Unique reflections	11590
Completeness	0.92	Mean I/σ	3.53
hkl$_{max}$ collected	(11, 14, 35)	hkl$_{min}$ collected	(-11, -14, -2)
hkl$_{max}$ used	(11, 14, 35)	hkl$_{min}$ used	(-11, -14, 0)
Lim d$_{max}$ collected	7.0	Lim d$_{min}$ collected	0.74
d$_{max}$ used	6.89	d$_{min}$ used	0.74
Friedel pairs	3	Friedel pairs merged	0
Inconsistent equivalents	0	R$_{int}$	0.0
R$_{sigma}$	0.2167	Intensity transformed	0
Omitted reflections	0	Omitted by user (OMIT hkl)	0
Multiplicity	(11110,)	Maximum multiplicity	0
Removed systematic absences	0	Filtered off (Shel/OMIT)	1

Table 27: Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **2016sot0088_R1_100K.** U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	x	y	z	U_{eq}
O101	10094(12)	2215(9)	8856(3)	19.8(9)
O102	8533(12)	48(9)	8833(4)	21.1(11)
O103	4406(12)	3724(8)	8457(3)	18.4(10)
O104	3241(11)	5876(8)	8762(3)	17.6(10)
C101	7380(20)	-966(16)	8809(7)	42(4)
C102	8493(17)	680(13)	8378(5)	20.3(9)
C103	7904(17)	294(13)	7926(5)	20.2(10)
C104	8028(17)	1058(12)	7481(5)	20(1)
C105	8748(17)	2099(13)	7502(5)	19.8(9)
C106	9453(18)	2472(13)	7961(5)	19.7(9)
C107	9285(18)	1770(12)	8389(5)	19.8(8)
C108	8854(18)	2913(13)	7038(5)	19.8(9)
C109	7309(17)	3579(13)	6891(5)	19.5(9)
C110	6697(17)	4203(13)	7324(5)	18.7(9)
C111	7421(17)	5371(12)	7476(5)	18.6(9)
C112	7033(16)	5899(13)	7904(5)	18.2(9)
C113	6056(17)	5406(12)	8252(5)	18.1(8)
C114	5316(17)	4229(13)	8109(5)	18.1(9)
C115	5629(17)	3694(13)	7640(5)	18.3(9)
C116	3655(19)	2534(12)	8316(5)	25(3)
C117	1820(17)	5438(15)	8979(5)	27(3)
C119	4785(8)	5840(8)	9596(3)	19.1(9)
C120	6281(10)	5897(8)	9852(2)	19.7(9)

Atom	x	y	z	U_{eq}
C121	7657(7)	5928(9)	9579(3)	19.2(9)
C122	7537(8)	5903(9)	9051(3)	18.6(9)
C123	6041(9)	5846(8)	8796(2)	18.1(8)
C118	4665(7)	5815(8)	9068(3)	18.2(9)
C124	6377(18)	5383(12)	10385(5)	20.6(9)
C125	6262(18)	4069(12)	10430(5)	20.6(9)
C126	7288(19)	3399(13)	10032(5)	20.0(9)
C127	8919(18)	3283(12)	10085(6)	20.1(10)
C128	9904(18)	2905(12)	9701(5)	19.9(10)
C129	9066(18)	2584(13)	9228(5)	19.4(9)
C130	7456(18)	2656(13)	9194(6)	19.3(10)
C131	6506(18)	3046(12)	9557(5)	19.5(10)
O201	9(12)	7202(9)	6144(4)	21.7(9)
O202	1499(12)	5085(9)	6176(4)	22.5(11)
O203	5618(12)	8719(9)	6533(4)	21.7(10)
O204	6808(11)	10801(9)	6170(3)	23.4(11)
C201	2336(17)	4005(12)	6152(6)	23(3)
C202	1439(17)	5702(13)	6618(5)	21.8(9)
C203	2176(18)	5314(13)	7096(5)	21.6(10)
C204	2041(17)	5927(13)	7510(5)	21.4(10)
C205	1190(18)	7095(13)	7498(6)	21.3(9)
C206	624(18)	7506(13)	7022(5)	21.2(9)
C207	664(19)	6820(12)	6584(6)	21.4(9)
C208	1106(18)	7837(13)	7973(5)	21.6(9)
C209	2743(18)	8477(13)	8112(5)	21.8(9)
C210	3238(18)	9254(13)	7652(6)	21.8(9)
C211	2592(18)	10286(12)	7537(5)	21.8(9)
C212	2897(17)	10839(13)	7053(5)	21.9(9)
C213	3955(18)	10285(12)	6726(5)	22.0(8)
C214	4668(17)	9254(13)	6883(6)	21.6(9)
C215	4337(18)	8736(13)	7334(5)	21.6(9)
C216	6293(19)	7646(12)	6665(6)	27(3)
C217	8100(20)	10245(15)	5937(6)	36(4)
C218	5356(15)	10771(12)	5924(5)	23.3(9)
C219	5264(16)	10774(12)	5389(5)	23.6(10)
C220	3810(16)	10739(12)	5129(5)	23.9(9)
C221	2453(16)	10889(12)	5393(5)	23.7(10)
C222	2564(16)	10898(12)	5921(5)	23.1(10)
C223	3982(16)	10692(11)	6197(5)	22.7(9)
C224	3544(18)	10423(12)	4560(5)	24.1(10)
C225	3668(18)	8911(12)	4564(5)	23.7(10)
C226	2711(19)	8405(14)	4962(6)	22.8(9)
C227	1077(18)	8347(12)	4906(6)	22.6(10)
C228	234(18)	7899(12)	5299(6)	22.2(10)
C229	943(18)	7565(13)	5749(6)	21.8(9)
C230	2624(18)	7620(13)	5835(6)	21.9(10)
C231	3427(19)	8042(13)	5410(5)	22.2(10)

Table 28: Anisotropic Displacement Parameters (×10^4) **2016sot0088_R1_100K**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2} \times U_{11} + \ldots + 2hka^* \times b^* \times U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O101	22.4(18)	19.0(17)	18.3(17)	-0.7(16)	4.0(15)	2.0(16)
O102	24(2)	19(2)	20(2)	0.3(19)	3.9(19)	0.3(19)
O103	20(2)	17(2)	18(2)	-0.1(19)	6.2(18)	-1.9(18)
O104	19.0(19)	17(2)	18(2)	1(2)	7.8(17)	2.6(19)
C101	45(7)	35(6)	45(10)	10(7)	1(7)	-19(6)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C102	23.0(18)	19.2(18)	19.1(18)	-0.3(16)	4.3(16)	1.1(16)
C103	22.5(19)	19.5(19)	19.1(18)	-0.6(17)	4.5(17)	1.1(17)
C104	22.0(19)	19.8(19)	18.7(18)	-0.9(17)	4.9(17)	1.3(17)
C105	21.6(18)	19.5(17)	18.6(17)	-0.8(16)	5.0(15)	1.6(16)
C106	21.6(18)	19.1(18)	18.7(17)	-0.6(16)	4.6(16)	1.9(16)
C107	22.2(17)	19.1(17)	18.6(16)	-0.5(15)	4.3(15)	1.7(15)
C108	21.8(18)	19.5(18)	18.5(18)	-0.8(16)	5.2(16)	1.0(16)
C109	21.7(18)	18.8(18)	18.4(18)	-0.3(17)	5.4(16)	0.6(16)
C110	20.9(17)	17.8(17)	18.1(17)	0.2(16)	5.7(15)	0.3(16)
C111	20.8(18)	17.2(18)	18.2(18)	0.5(17)	6.1(16)	0.2(17)
C112	20.6(18)	16.4(18)	18.2(18)	0.5(17)	6.2(16)	-0.1(17)
C113	20.4(16)	16.1(16)	18.3(16)	0.2(16)	6.2(14)	0.0(15)
C114	20.3(17)	16.6(17)	18.0(17)	0.2(16)	5.9(15)	-0.8(16)
C115	20.5(18)	17.0(18)	17.8(18)	0.0(17)	5.5(16)	-0.3(16)
C116	30(7)	20(4)	26(7)	-3(5)	20(6)	-11(5)
C117	20(4)	44(8)	18(6)	6(6)	10(5)	0(5)
C119	21.9(17)	16.5(18)	19.3(17)	-0.5(17)	6.1(15)	1.8(17)
C120	23.0(17)	17.0(17)	19.4(17)	-1.2(17)	5.1(15)	1.5(17)
C121	22.2(18)	16.3(18)	19.6(18)	-1.0(18)	5.1(16)	1.1(18)
C122	21.2(17)	15.7(18)	19.3(17)	-0.4(18)	5.9(16)	0.6(17)
C123	20.6(16)	15.6(16)	18.7(16)	0.1(16)	6.5(14)	0.6(16)
C118	20.4(17)	15.9(17)	18.8(17)	0.4(17)	6.8(15)	1.8(16)
C124	24.6(18)	18.5(18)	19.1(18)	-1.4(17)	4.2(16)	1.7(17)
C125	24.9(18)	18.8(18)	18.3(18)	-0.9(17)	3.7(16)	1.9(17)
C126	24.1(18)	18.4(18)	17.6(18)	-0.4(17)	3.6(16)	1.8(16)
C127	24.0(19)	18.7(19)	17.7(19)	0.0(18)	3.2(17)	1.9(17)
C128	23.6(19)	18.5(19)	17.7(18)	0.3(18)	3.4(17)	2.0(17)
C129	22.8(17)	18.2(17)	17.6(17)	-0.2(16)	3.8(15)	2.0(16)
C130	22.9(19)	17.8(19)	17.4(19)	-0.3(18)	3.7(17)	1.9(17)
C131	23.5(19)	18.0(19)	17.4(19)	-0.2(18)	3.8(17)	1.6(17)
O201	23.4(18)	17.4(17)	24.3(18)	0.4(16)	-0.4(16)	-0.3(16)
O202	25(2)	17(2)	26(2)	-0.4(19)	-0.3(19)	0.6(19)
O203	22(2)	18(2)	25(2)	1.6(19)	-0.7(18)	-0.5(19)
O204	23(2)	20(2)	27(2)	2(2)	-0.9(18)	-2(2)
C201	26(6)	15(4)	30(8)	1(4)	8(6)	-1(4)
C202	23.4(19)	16.9(18)	24.9(18)	0.5(17)	-0.1(16)	0.0(16)
C203	23(2)	16.9(19)	24.9(19)	1.4(18)	0.1(17)	-0.1(17)
C204	22.5(19)	16.9(19)	24.9(19)	1.5(18)	0.2(17)	-0.2(17)
C205	22.2(18)	17.1(17)	24.6(18)	1.0(16)	0.0(16)	-0.6(16)
C206	22.1(18)	16.9(18)	24.4(18)	0.7(17)	-0.2(16)	-0.4(16)
C207	22.7(18)	17.0(17)	24.4(17)	0.6(16)	-0.1(15)	-0.3(15)
C208	22.4(18)	17.5(18)	24.8(18)	0.8(17)	-0.3(17)	-0.9(17)
C209	22.6(18)	17.8(18)	24.9(19)	0.6(17)	-0.7(16)	-1.3(17)
C210	22.3(18)	17.8(17)	24.9(18)	0.5(16)	-1.1(15)	-1.9(16)
C211	22.4(19)	17.7(18)	25.2(19)	0.4(17)	-1.0(17)	-2.2(17)
C212	22.4(18)	17.6(18)	25.5(19)	0.5(17)	-1.1(16)	-2.2(17)
C213	22.5(17)	17.6(17)	25.4(17)	0.7(16)	-1.4(15)	-1.7(15)
C214	21.8(18)	17.8(17)	24.9(18)	0.9(17)	-1.2(16)	-1.4(16)
C215	21.9(18)	17.7(18)	24.7(19)	0.7(17)	-1.4(16)	-1.5(17)
C216	26(7)	17(4)	36(8)	-1(5)	-9(6)	0(4)
C217	29(6)	41(8)	39(8)	-10(7)	0(5)	5(5)
C218	24.0(18)	18.6(18)	26.9(18)	1.6(18)	-1.8(16)	-2.0(17)
C219	25.1(18)	18.5(19)	26.9(19)	1.7(18)	-2.0(16)	-1.7(18)
C220	26.2(18)	18.2(18)	26.8(18)	1.6(17)	-2.6(16)	-1.5(17)
C221	25.6(19)	18.1(19)	26.9(19)	1.6(19)	-3.0(17)	-1.5(18)
C222	24.5(18)	17.7(19)	26.6(19)	1.6(18)	-2.9(16)	-1.3(18)
C223	23.7(17)	17.8(17)	26.2(17)	1.2(16)	-2.1(15)	-1.5(16)
C224	27.1(19)	18.7(18)	26.3(19)	1.4(18)	-2.0(17)	-1.0(17)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C225	27.0(19)	18.4(18)	25.4(19)	0.5(18)	-1.3(17)	-0.5(17)
C226	25.9(18)	17.5(18)	24.6(19)	-0.3(17)	-0.9(16)	0.2(17)
C227	25.6(19)	17.5(19)	24(2)	-0.7(18)	-1.2(17)	0.3(18)
C228	24.8(19)	17.2(19)	24.3(19)	-0.7(18)	-1.1(17)	0.3(18)
C229	24.0(18)	17.1(17)	24.1(18)	-0.3(17)	-0.5(16)	0.2(16)
C230	24.4(19)	17.0(19)	24(2)	-0.1(18)	-0.6(17)	0.4(17)
C231	25(2)	17.0(19)	24(2)	-0.4(18)	-0.4(17)	0.5(18)

Table 29: Bond Lengths in Å for **2016sot0088_R1_100K**.

Atom	**Atom**	**Length/Å**
O101	C107	1.459(16)
O101	C129	1.400(16)
O102	C101	1.479(18)
O102	C102	1.389(16)
O103	C114	1.347(15)
O103	C116	1.499(16)
O104	C117	1.431(16)
O104	C118	1.404(11)
C102	C103	1.336(18)
C102	C107	1.377(19)
C103	C104	1.454(18)
C104	C105	1.302(19)
C105	C106	1.380(19)
C105	C108	1.527(19)
C106	C107	1.385(18)
C108	C109	1.52(2)
C109	C110	1.453(18)
C110	C111	1.476(19)
C110	C115	1.376(18)
C111	C112	1.326(17)
C112	C113	1.377(17)
C113	C114	1.483(19)
C113	C123	1.515(14)
C114	C115	1.408(18)
C119	C120	1.3900
C119	C118	1.3900
C120	C121	1.3900
C120	C124	1.515(14)
C121	C122	1.3900
C122	C123	1.3900
C123	C118	1.3900
C124	C125	1.465(18)
C125	C126	1.579(18)
C126	C127	1.37(2)
C126	C131	1.44(2)
C127	C128	1.405(18)
C128	C129	1.441(19)
C129	C130	1.35(2)
C130	C131	1.347(18)

Atom	**Atom**	**Length/Å**
O201	C207	1.326(16)
O201	C229	1.394(17)
O202	C201	1.390(15)
O202	C202	1.356(16)
O203	C214	1.384(17)
O203	C216	1.354(16)
O204	C217	1.415(18)
O204	C218	1.346(16)
C202	C203	1.437(19)
C202	C207	1.399(19)
C203	C204	1.297(18)
C204	C205	1.477(19)
C205	C206	1.394(19)
C205	C208	1.502(19)
C206	C207	1.385(19)
C208	C209	1.57(2)
C209	C210	1.561(19)
C210	C211	1.294(19)
C210	C215	1.40(2)
C211	C212	1.453(18)
C212	C213	1.409(19)
C213	C214	1.344(19)
C213	C223	1.468(18)
C214	C215	1.363(19)
C218	C219	1.409(17)
C218	C223	1.391(17)
C219	C220	1.365(17)
C220	C221	1.373(17)
C220	C224	1.543(18)
C221	C222	1.390(16)
C222	C223	1.377(17)
C224	C225	1.680(18)
C225	C226	1.47(2)
C226	C227	1.37(2)
C226	C231	1.36(2)
C227	C228	1.38(2)
C228	C229	1.348(19)
C229	C230	1.41(2)
C230	C231	1.415(19)

Table 30: Bond Angles in ° for **2016sot0088_R1_100K**.

Atom	**Atom**	**Atom**	**Angle/°**
C129	O101	C107	114.5(11)

Atom	**Atom**	**Atom**	**Angle/°**
C102	O102	C101	111.2(12)

Atom	Atom	Atom	Angle/˚
C114	O103	C116	116.2(10)
C118	O104	C117	116.8(9)
C103	C102	O102	126.9(14)
C103	C102	C107	117.0(13)
C107	C102	O102	115.8(13)
C102	C103	C104	119.6(14)
C105	C104	C103	122.3(14)
C104	C105	C106	118.6(14)
C104	C105	C108	122.4(14)
C106	C105	C108	119.0(13)
C105	C106	C107	119.2(14)
C102	C107	O101	121.0(12)
C102	C107	C106	123.1(14)
C106	C107	O101	115.8(12)
C109	C108	C105	113.9(12)
C110	C109	C108	111.2(12)
C109	C110	C111	118.4(12)
C115	C110	C109	123.3(13)
C115	C110	C111	117.8(12)
C112	C111	C110	120.2(13)
C111	C112	C113	125.0(14)
C112	C113	C114	115.7(12)
C112	C113	C123	122.6(12)
C114	C113	C123	120.0(10)
O103	C114	C113	115.8(12)
O103	C114	C115	124.2(13)
C115	C114	C113	120.0(12)
C110	C115	C114	121.1(13)
C120	C119	C118	120.0
C119	C120	C121	120.0
C119	C120	C124	115.7(8)
C121	C120	C124	119.1(8)
C120	C121	C122	120.0
C123	C122	C121	120.0
C122	C123	C113	114.8(7)
C118	C123	C113	122.0(7)
C118	C123	C122	120.0
C119	C118	O104	126.0(6)
C123	C118	O104	113.7(6)
C123	C118	C119	120.0
C125	C124	C120	116.7(11)
C124	C125	C126	111.9(12)
C127	C126	C125	123.4(14)
C127	C126	C131	117.9(13)
C131	C126	C125	118.1(13)
C126	C127	C128	125.0(15)
C127	C128	C129	114.9(13)
O101	C129	C128	112.9(12)
C130	C129	O101	128.4(14)
C130	C129	C128	118.7(13)
C131	C130	C129	126.8(15)
C130	C131	C126	116.6(14)
C207	O201	C229	121.6(12)
C202	O202	C201	121.2(12)
C216	O203	C214	116.9(12)
C218	O204	C217	118.1(11)
O202	C202	C203	124.6(13)
O202	C202	C207	115.5(13)
C207	C202	C203	119.8(13)
C204	C203	C202	121.8(14)
C203	C204	C205	120.4(14)
C204	C205	C208	120.5(13)
C206	C205	C204	116.4(13)
C206	C205	C208	122.8(13)
C207	C206	C205	123.3(14)
O201	C207	C202	120.5(13)
O201	C207	C206	121.8(13)
C206	C207	C202	117.7(14)
C205	C208	C209	111.2(12)
C210	C209	C208	109.5(12)
C211	C210	C209	123.0(14)
C211	C210	C215	120.1(14)
C215	C210	C209	116.7(13)
C210	C211	C212	119.2(14)
C213	C212	C211	120.0(13)
C212	C213	C223	119.4(13)
C214	C213	C212	117.8(14)
C214	C213	C223	121.6(13)
C213	C214	O203	115.0(13)
C213	C214	C215	121.3(14)
C215	C214	O203	123.5(13)
C214	C215	C210	121.4(14)
O204	C218	C219	118.7(11)
O204	C218	C223	120.2(11)
C223	C218	C219	121.1(12)
C220	C219	C218	120.1(12)
C219	C220	C221	118.7(12)
C219	C220	C224	124.9(12)
C221	C220	C224	116.1(12)
C220	C221	C222	119.8(12)
C223	C222	C221	122.4(12)
C218	C223	C213	124.5(12)
C222	C223	C213	119.7(12)
C222	C223	C218	115.4(12)
C220	C224	C225	102.5(10)
C226	C225	C224	110.4(12)
C227	C226	C225	121.4(15)
C231	C226	C225	120.4(14)
C231	C226	C227	118.1(15)
C226	C227	C228	119.0(15)
C229	C228	C227	122.8(15)
O201	C229	C230	119.1(13)
C228	C229	O201	119.9(14)
C228	C229	C230	121.0(14)
C229	C230	C231	113.5(14)
C226	C231	C230	125.5(15)

Table 31: Torsion Angles in ˚ for **2016sot0088_R1_100K**.

Atom	Atom	Atom	Atom	Angle/°
O101	C129	C130	C131	-178.2(13)
O102	C102	C103	C104	-177.2(13)
O102	C102	C107	O101	-0.4(18)
O102	C102	C107	C106	175.5(13)
O103	C114	C115	C110	-173.4(14)
C101	O102	C102	C103	-18.5(19)
C101	O102	C102	C107	168.2(13)
C102	C103	C104	C105	2(2)
C103	C102	C107	O101	-174.4(12)
C103	C102	C107	C106	1(2)
C103	C104	C105	C106	2(2)
C103	C104	C105	C108	-178.9(12)
C104	C105	C106	C107	-4(2)
C104	C105	C108	C109	76.2(17)
C105	C106	C107	O101	178.8(12)
C105	C106	C107	C102	3(2)
C105	C108	C109	C110	51.2(17)
C106	C105	C108	C109	-104.4(15)
C107	O101	C129	C128	174.3(11)
C107	O101	C129	C130	-5(2)
C107	C102	C103	C104	-3.9(19)
C108	C105	C106	C107	176.4(13)
C108	C109	C110	C111	79.7(16)
C108	C109	C110	C115	-91.4(17)
C109	C110	C111	C112	-172.0(14)
C109	C110	C115	C114	167.1(14)
C110	C111	C112	C113	5(2)
C111	C110	C115	C114	-4(2)
C111	C112	C113	C114	-4(2)
C111	C112	C113	C123	161.0(13)
C112	C113	C114	O103	177.7(13)
C112	C113	C114	C115	0(2)
C112	C113	C123	C122	-51.8(15)
C112	C113	C123	C118	148.4(11)
C113	C114	C115	C110	4(2)
C113	C123	C118	O104	-27.0(10)
C113	C123	C118	C119	158.8(9)
C114	C113	C123	C122	112.9(11)
C114	C113	C123	C118	-46.9(14)
C115	C110	C111	C112	0(2)
C116	O103	C114	C113	-179.9(12)
C116	O103	C114	C115	-2(2)
C117	O104	C118	C119	-27.3(13)
C117	O104	C118	C123	158.9(9)
C119	C120	C121	C122	0.0
C119	C120	C124	C125	71.0(13)
C120	C119	C118	O104	-173.4(10)
C120	C119	C118	C123	0.0
C120	C121	C122	C123	0.0
C120	C124	C125	C126	43.1(17)
C121	C120	C124	C125	-83.3(13)
C121	C122	C123	C113	-160.3(8)
C121	C122	C123	C118	0.0
C122	C123	C118	O104	174.2(9)
C122	C123	C118	C119	0.0
C123	C113	C114	O103	12.0(18)
C123	C113	C114	C115	-166.0(12)

Atom	Atom	Atom	Atom	Angle/°
C118	C119	C120	C121	0.0
C118	C119	C120	C124	-154.1(9)
C124	C120	C121	C122	153.2(9)
C124	C125	C126	C127	77.1(18)
C124	C125	C126	C131	-93.7(16)
C125	C126	C127	C128	-167.2(13)
C125	C126	C131	C130	169.6(13)
C126	C127	C128	C129	-2(2)
C127	C126	C131	C130	-2(2)
C127	C128	C129	O101	180.0(12)
C127	C128	C129	C130	-1(2)
C128	C129	C130	C131	3(3)
C129	O101	C107	C102	-70.9(16)
C129	O101	C107	C106	112.9(14)
C129	C130	C131	C126	-1(2)
C131	C126	C127	C128	4(2)
O201	C229	C230	C231	-177.9(12)
O202	C202	C203	C204	-178.1(14)
O202	C202	C207	O201	2(2)
O202	C202	C207	C206	-177.6(13)
O203	C214	C215	C210	-173.3(14)
O204	C218	C219	C220	179.7(12)
O204	C218	C223	C213	-19(2)
O204	C218	C223	C222	168.1(13)
C201	O202	C202	C203	-1(2)
C201	O202	C202	C207	175.3(12)
C202	C203	C204	C205	-4(2)
C203	C202	C207	O201	178.5(13)
C203	C202	C207	C206	-1(2)
C203	C204	C205	C206	-3(2)
C203	C204	C205	C208	-176.8(14)
C204	C205	C206	C207	8(2)
C204	C205	C208	C209	75.2(16)
C205	C206	C207	O201	174.9(14)
C205	C206	C207	C202	-6(2)
C205	C208	C209	C210	56.0(16)
C206	C205	C208	C209	-98.4(16)
C207	O201	C229	C228	177.2(13)
C207	O201	C229	C230	-5(2)
C207	C202	C203	C204	6(2)
C208	C205	C206	C207	-178.5(14)
C208	C209	C210	C211	76.5(18)
C208	C209	C210	C215	-98.1(15)
C209	C210	C211	C212	-168.3(13)
C209	C210	C215	C214	170.1(14)
C210	C211	C212	C213	-4(2)
C211	C210	C215	C214	-5(2)
C211	C212	C213	C214	-1(2)
C211	C212	C213	C223	166.4(13)
C212	C213	C214	O203	176.4(13)
C212	C213	C214	C215	2(2)
C212	C213	C223	C218	143.2(14)
C212	C213	C223	C222	-44.0(19)
C213	C214	C215	C210	0(2)
C214	C213	C223	C218	-50(2)
C214	C213	C223	C222	122.7(16)
C215	C210	C211	C212	6(2)
C216	O203	C214	C213	-176.7(13)

Atom	Atom	Atom	Atom	Angle/˚
C216	O203	C214	C215	-3(2)
C217	O204	C218	C219	-31.5(18)
C217	O204	C218	C223	146.2(13)
C218	C219	C220	C221	10.0(19)
C218	C219	C220	C224	-164.0(13)
C219	C218	C223	C213	158.8(13)
C219	C218	C223	C222	-14.3(18)
C219	C220	C221	C222	-9.3(19)
C219	C220	C224	C225	79.2(16)
C220	C221	C222	C223	-4(2)
C220	C224	C225	C226	46.5(15)
C221	C220	C224	C225	-94.9(14)
C221	C222	C223	C213	-158.2(13)
C221	C222	C223	C218	15.3(19)
C223	C213	C214	O203	10(2)
C223	C213	C214	C215	-164.5(14)
C223	C218	C219	C220	2(2)
C224	C220	C221	C222	165.2(12)
C224	C225	C226	C227	75.8(18)
C224	C225	C226	C231	-100.6(16)
C225	C226	C227	C228	-177.9(13)
C225	C226	C231	C230	175.3(14)
C226	C227	C228	C229	3(2)
C227	C226	C231	C230	-1(2)
C227	C228	C229	O201	175.3(13)
C227	C228	C229	C230	-2(2)
C228	C229	C230	C231	0(2)
C229	O201	C207	C202	-71.0(17)
C229	O201	C207	C206	108.3(16)
C229	C230	C231	C226	2(2)
C231	C226	C227	C228	-1(2)

Table 32: Hydrogen Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for **2016sot0088_R1_100K**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{ij}.

Atom	**x**	**y**	**z**	U_{eq}
H10A	7672.41	-1532.14	8543.32	63
H10B	6301.75	-656.84	8730.21	63
H10C	7417.15	-1383.02	9137.18	63
H103	7406.67	-474.55	7894.43	24
H104	7566.66	787.51	7163.85	24
H106	10046.93	3202.58	7982.8	24
H10D	9715.16	3512.6	7107.69	24
H10E	9156.26	2416.08	6746.56	24
H10F	7506.69	4169.5	6619.97	23
H10G	6497.61	2995.59	6755.02	23
H111	8167.89	5744.51	7267.73	22
H112	7462.6	6678.17	7974.52	22
H115	5092.41	2969.67	7540.64	22
H11A	2903.73	2640.61	8021.43	37
H11B	3079.85	2225.07	8603.06	37
H11C	4490.88	1959.98	8232.34	37
H11D	950.17	5396.78	8715.16	41
H11E	1517.62	5985.43	9249.21	41
H11F	2021.04	4631.55	9120.68	41
H119	3844.8	5817.78	9782.18	23
H121	8679.87	5967.32	9753.82	23
H122	8477.86	5925.16	8865.31	22
H12A	7404.94	5641.71	10554.65	25
H12B	5508.01	5747.01	10574.1	25
H12C	5127.04	3823.09	10378.04	25
H12D	6638.24	3824.03	10777.71	25
H127	9422.67	3472.08	10407.1	24
H128	11036.12	2864.31	9748.66	24
H130	6937.3	2404.92	8882.64	23
H131	5375.56	3085.12	9500.53	23
H20A	2288.44	3713.1	5800.31	35
H20B	1853.94	3404.46	6369.52	35
H20C	3455.36	4134.76	6268.05	35
H203	2778.89	4587.44	7107.97	26
H204	2491.59	5622.91	7822.91	26
H206	190.54	8297.1	6997.24	25
H20D	823.68	7309.21	8257.62	26
H20E	254.65	8452.08	7922.71	26
H20F	2640.05	8998.27	8412.72	26
H20G	3577.67	7864.37	8195.34	26
H211	1926.29	10676.7	7767.36	26
H212	2382.3	11573.87	6955.7	26
H215	4862.75	8008.53	7434.72	26
H21A	7044.64	7409.41	6410.66	40
H21B	5455.44	7032.07	6682.72	40
H21C	6867.74	7720.62	6997.64	40
H21D	8500.81	10786.48	5678.22	54
H21E	7737.37	9489.27	5776.09	54
H21F	8961.99	10075.19	6193.74	54
H219	6216.88	10801.66	5208.87	28
H221	1442.48	10986.36	5215.02	28
H222	1625.52	11051.46	6097.61	28
H22A	4383.44	10785.34	4357.93	29
H22B	2480.39	10697.65	4423.58	29

Atom	**x**	**y**	**z**	***U_{eq}***
H22C	3275.3	8591.35	4229.01	28
H22D	4799.58	8663.55	4623.49	28
H227	531.91	8611.16	4600.51	27
H228	-895.42	7821.98	5251.7	27
H230	3163.8	7396.35	6146.77	26
H231	4562.53	8071.84	5441.54	27

Citations

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O.V. Dolomanov and L.J. Bourhis and R.J. Gildea and J.A.K. Howard and H. Puschmann, Olex2: A complete structure solution, refinement and analysis program, *J. Appl. Cryst.*, (2009), **42**, 339-341.

Sheldrick, G.M., Crystal structure refinement with ShelXL, *Acta Cryst.*, (2015), **C27**, 3-8.

Sheldrick, G.M., ShelXT-Integrated space-group and crystal-structure determination, *Acta Cryst.*, (2015), **A71**, 3-8.

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#===============================================================================
# PLATON/CHECK-(120716) versus check.def version of 160712 for Entry: 2016sot008
# Data: 2016sot0088_R1_100K.cif - Type: CIF      Bond Precision   C-C = 0.0185 A
# Refl: 2016sot0088_R1_100K.fcf - Type: LIST4                      Temp = 100 K
# X-ray MoKa                R(int) = 0.000,  wR2/R(int) =  0.0,  Nref/Npar =  10.5
# Cell    8.3656(6)  11.0874(7)   26.366(2)           90    93.127(6)          90
# Wavelength 0.71073    Volume Reported     2441.9(3)   Calculated     2441.9(3)
# SpaceGroup from Symmetry P 21       Hall: P 2yb                monoclinic
#                 Reported P 1 21 1         P 2yb                monoclinic
# MoietyFormula C31 H30 O4
#      Reported C31 H30 O4
#    SumFormula C31 H30 O4
#      Reported C31 H30 O4
# Mr          =    466.55[Calc],    466.55[Rep]
# Dx,gcm-3    =     1.269[Calc],     1.269[Rep]
# Z           =         4[Calc],         4[Rep]
# Mu (mm-1)   =     0.083[Calc],     0.083[Rep]
# F000        =     992.0[Calc],     992.0[Rep]  or F000' =    992.46[Calc]
# Reported    T Limits: Tmin=0.490              Tmax=1.000  AbsCorr = MULTI-SCAN
# Calculated T Limits: Tmin=0.997 Tmin'=0.990  Tmax=0.998
# Reported    Hmax= 11, Kmax= 14, Lmax= 35, Nref=  11110        , Th(max)= 28.696
# Obs in FCF Hmax= 11, Kmax= 14, Lmax= 35, Nref=  11110[  6603], Th(max)= 28.696
# Calculated Hmax= 11, Kmax= 14, Lmax= 35, Nref=  12610[  6622], Ratio=1.68/0.88
# Reported    Rho(min) = -0.47, Rho(max) =  0.66 e/Ang**3 (From CIF)
# w=1/[sigma**2(Fo**2)+(0.0213P)**2+  9.7905P], P=(Fo**2+2*Fc**2)/3
# R= 0.1233(  4686), wR2= 0.2670( 11110), S = 1.103       (From FCF data only)
# R= 0.1233(  4686), wR2= 0.2670( 11110), S = 1.103, Npar=  626, Flack  -0.3(10)
#===============================================================================
For Documentation: http://http://www.platonsoft.nl/CIF-VALIDATION.pdf
#===============================================================================

#===============================================================================
>>> The Following Improvement and Query ALERTS were generated - (Acta-Mode) <<<
#===============================================================================
Format: alert-number_ALERT_alert-type_alert-level text

881_ALERT_1_A Missing datum for _diffrn_reflns_av_R_equivalents .. Please Check
#===============================================================================
110_ALERT_2_B ADDSYM Detects Potential Lattice Translation ...          ? Check
112_ALERT_2_B ADDSYM Detects New (Pseudo) Symm. Elem.      c/2        100 %Fit
113_ALERT_2_B ADDSYM Suggests Possible Pseudo/New  Space Group        P21 Check
Note: (Pseudo) Lattice Translation Implemented
340_ALERT_3_B Low Bond Precision on  C-C Bonds ...............    0.01847 Ang.
#===============================================================================
026_ALERT_3_C Ratio Observed / Unique Reflections (too) Low ..         42 %
082_ALERT_2_C High R1 Value ..................................       0.12 Report
084_ALERT_3_C High wR2 Value (i.e. > 0.25) ...................       0.27 Report
097_ALERT_2_C Large Reported Max.  (Positive) Residual Density       0.66 eA-3
334_ALERT_2_C Small Average Benzene  C-C Dist. C102    -C107         1.37 Ang.
361_ALERT_2_C Long   C(sp3)-C(sp3) Bond   C224   -    C225   ..      1.68 Ang.
906_ALERT_3_C Large K value in the Analysis of Variance ......     13.532 Check
906_ALERT_3_C Large K value in the Analysis of Variance ......      3.748 Check
906_ALERT_3_C Large K value in the Analysis of Variance ......      2.317 Check
910_ALERT_3_C Missing # of FCF Reflection(s) Below Theta(Min)           9 Note
911_ALERT_3_C Missing # FCF Refl Between THmin & STh/L=  0.600          2 Report
#===============================================================================
003_ALERT_2_G Number of Uiso or Uij Restrained non-H Atoms ...         70 Report
032_ALERT_4_G Std. Uncertainty on Flack Parameter Value High .      1.000 Report
083_ALERT_2_G SHELXL Second Parameter in WGHT  Unusually Large       9.79 Why ?
178_ALERT_4_G The CIF-Embedded .res File Contains SIMU Records          1 Report
187_ALERT_4_G The CIF-Embedded .res File Contains RIGU Records          1 Report
335_ALERT_2_G Check Large C6 Ring     C-C Range C102    -C107        0.16 Ang.
335_ALERT_2_G Check Large C6 Ring     C-C Range C110    -C115        0.15 Ang.
335_ALERT_2_G Check Large C6 Ring     C-C Range C202    -C207        0.18 Ang.
335_ALERT_2_G Check Large C6 Ring     C-C Range C210    -C215        0.16 Ang.
860_ALERT_3_G Number of Least-Squares Restraints ............        1027 Note
870_ALERT_4_G ALERTS Related to Twinning Effects Suppressed ..          ! Info
908_ALERT_2_G Max. Perc. Data with I > 2*s(I) per Res.Shell .       72.51 %
```

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912_ALERT_4_G Missing # of FCF Reflections Above STh/L=  0.600          9 Note
931_ALERT_5_G Found Twin Law ( 0 0  1)[       ] Estimated BASF       0.31 Check
#===============================================================================

ALERT_Level and ALERT_Type Summary
==================================
1 ALERT_Level_A = Most Likely a Serious Problem - Resolve or Explain
4 ALERT_Level_B = A Potentially Serious Problem - Consider Carefully
11 ALERT_Level_C = Check. Ensure it is Not caused by an Omission or Oversight
14 ALERT_Level_G = General Info/Check that it is not Something Unexpected

1 ALERT_Type_1 CIF Construction/Syntax Error, Inconsistent or Missing Data.
14 ALERT_Type_2 Indicator that the Structure Model may be Wrong or Deficient.
9 ALERT_Type_3 Indicator that the Structure Quality may be Low.
5 ALERT_Type_4 Improvement, Methodology, Query or Suggestion.
1 ALERT_Type_5 Informative Message, Check.
#===============================================================================

1 Missing  Experimental  Info Issue(s) (Out of  62 Tests) -   98 % Satisfied
1 Experimental  Data  Related Issue(s) (Out of  28 Tests) -   96 % Satisfied
16 Structural  Model   Related Issue(s) (Out of 127 Tests) -   87 % Satisfied
11 Unresolved or to be Checked Issue(s) (Out of 248 Tests) -   96 % Satisfied

#============================================================================
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